Development of Highly Active Nucleophilic Catalyst for Enantioselective Transformations

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Seiji Suga at the Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University during 2013–2018.

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1-1. Organocatalyst

The term organocatalysis is put forward by MacMillan[1] in 2000 and also attracted a great deal of attention as List and coworkers[2] reported aldol reaction using proline. Organocatalyst enable the reaction control by precise molecular design and have some advantages: (i) easy to prepare inexpensively in significant quantities; (ii) easy to synthesize highly tunable catalyst structure; (iii) chemically stable molecule compared with metal and enzymatic catalyst; (iv) less toxic waste. Recently, a number of organocatalyst have been developed by many groups (Figure 1).

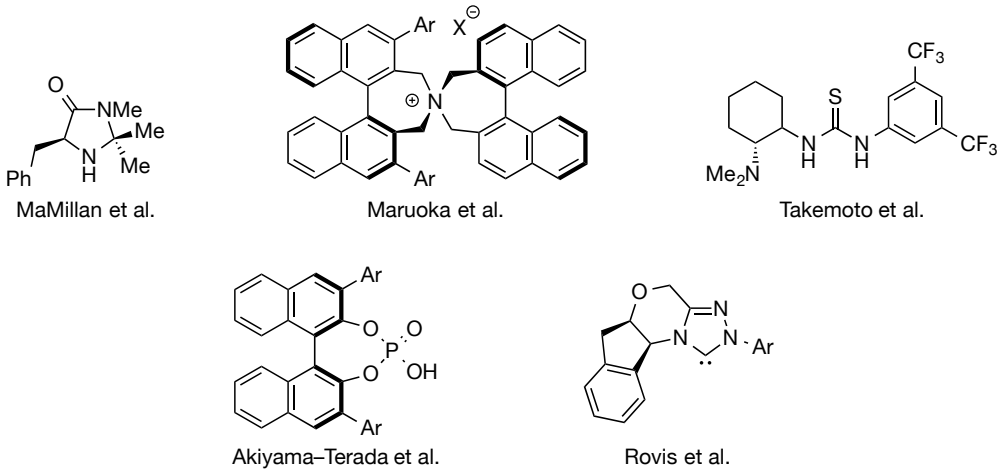


Figure 1. Various organocatalysts

1-2. Nucleophilic Catalyst

Nucleophilic catalyst is classified one of the organocatalyst and has been studied decades ago. One particularly useful reaction with nucleophilic catalyst is acylation of alcohols, amine, and thiols. There are some types of nucleophilic catalyst such as pyridine, phosphine, or diamine based nucleophilic catalyst. These catalysts work through similar reaction mechanism but show various reactivity.

On the other hand, Mayr and coworkers proposed a new linear free energy relationship, demonstrating that one parameter for electrophiles (*E*) and two parameters for nucleophiles (*N* and *s*) are sufficient to describe quantitatively the reaction rates of a large variety of electrophile-nucleophile combinations, namely, where s is a nucleophile specific slope parameter and *N* and *E* are the nucleophilicity and electrophilicity parameters, respectively. [3,4] These authors proved that eq 1, seems to be applicable for a wide variety of electrophile-nucleophile combinations.

$$\log k = s(N + E) \qquad (1)$$

Based on eq 1 Mayr and coworkers determined the reactivity (nucleophilicity) of various nucleophilic catalysts (Figure 2).[3,4] Next section, I will introduce the phosphine, diamine, and pyridine based catalyst as traditional nucleophilic catalyst.

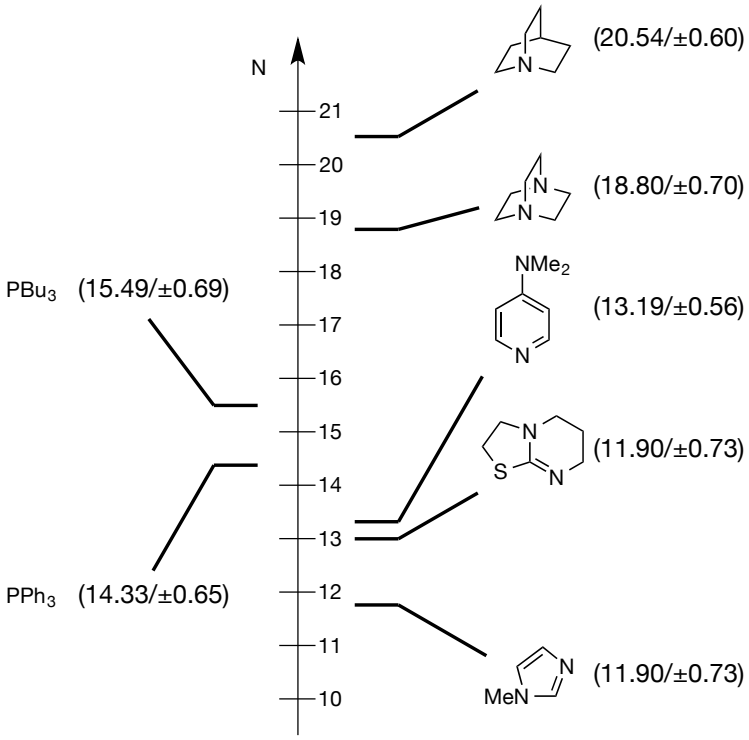
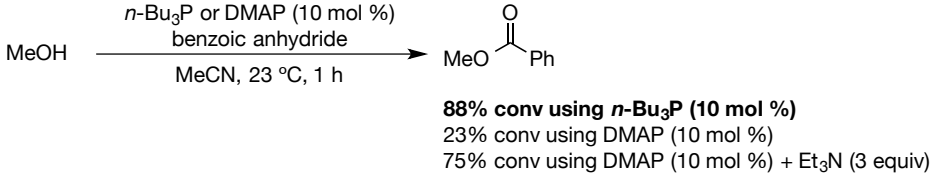


Figure 2. Nucleophilicity parameters of various nucleophilic

1-2-1. Phosphine Based Nucleophilic Catalyst

Studies on nucleophilicity of trialkyl phosphines have been enthusiastically carried out since the 1960's,[5] however, it was used firstly as catalyst for acylation catalyst in 1990. In 1993, Vedejs and coworkers firstly reported that tributylphosphine acts as a nucleophilic catalyst in acylation reaction of alcohols (Scheme 1).[6] An interesting result is that the catalytic activity of tributylphosphine is higher than that of *N,N*-dimethyl-4-aminopyridine (DMAP) (88% conversion with *n*-Bu_3P vs 23% conversion with DMAP). This is well shown a characteristic of phosphine that basicity is weak but nucleophilicity is high.

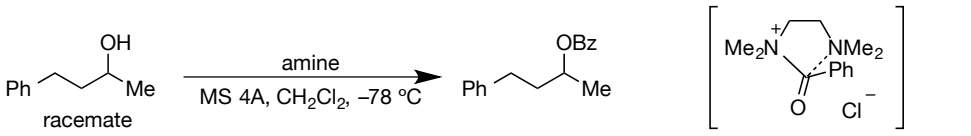
Scheme 1. First report of phosphine as nucleophilic catalyst in acylation of alcohol



1-2-2. Diamine Based Nucleophilic Catalyst

Diamine behaves as a nucleophilic catalyst as well as DMAP and phosphine, and it has a unique feature. In 1999, Oriyama and coworkers reported *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) exhibited much higher catalytic activity than 1,4-diazabicyclo[2.2.2]octane (DABCO) (very strong nucleophile) in the benzoylation reaction of alcohol despite its nucleophilicity lower than DABCO (Table 1).[7] In this reaction, it is considered that benzoyl chloride–TMEDA complex brought about such catalytic activity. After this paper, Oriyama developed ordinal chiral diamine catalyst and applied to various enantioselective benzoylation of alcohols.

Table 1. First repot of acceleration effect using diamine in benzoylation of alcohol.



entry	amine (equiv)	BzCl (equiv)	time (h)	yield (%)
1	none	1.5	3	0
2	**TMEDA (0.6)**	**1.1**	**0.67**	**97**
3	Et_3N (1.1)	1.5	3	2
4	Pyridine (1.0)	1.5	5	48
5	1,4-dimetylpiperazine (1.1)	1.5	3	26
6	DABCO (1.1)	1.6	3	88
7	$Me_2NCH_2NMe_2$ (0.6)	1.1	3	2
8	$Me_2(CH_2)_3NMe_2$ (0.6)	1.1	3	22
9	$Me_2(CH_2)_4NMe_2$ (0.6)	1.1	3	16

1-2-3. Pyridine Based Nucleophilic Catalyst

Among various nucleophilic catalysts, pyridine based nucleophilic catalysts such as DMAP or 4-pyrolidinopyridine (PPY) are the most studied nucleophilic catalysts. Its utility in acylation (as mediator) was first reported by Litvinenko and Kirichenko in 1967.[8] They found that one equivalent of DMAP shows 10^4-fold rate acceleration compered with pyridine in benzoylation of *m*-chloroaniline (Figure 3).

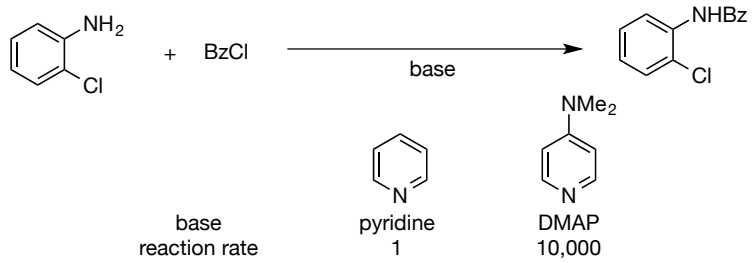


Figure 3. First report of acceleration effect of DMAP in acylation reaction.

In 1969, Steglich reported that DMAP act as catalyst by trapping side product of acid with additional base (Figure 4).[9] As a result of this report, DMAP became widely known as a useful acylation catalyst.

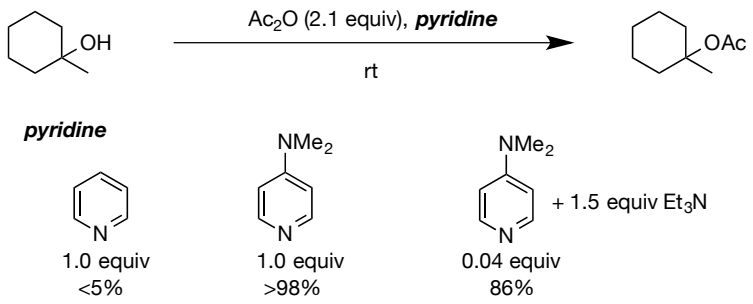


Figure 4. First report of DMAP as nucleophilic catalyst in acylation reaction.

The catalytic acylation with DMAP has been investigated in detail by computational chemistry, and the reaction mechanism has been proposed by Zipse and coworkers as follows (Figure 5).[10] Step 1: DMAP attacked to an acylating reagent to form a stable ion pair **I**. Step 2: The reaction substrate (alcohol) reacts with the ion pair **I**, and the product (ester) is obtained by deprotonation of alcohol by counteranion ($^{-}$OAc) in transition state **II**. Step 3: The conjugate acid of DMAP is neutralized with base and DMAP regenerates.

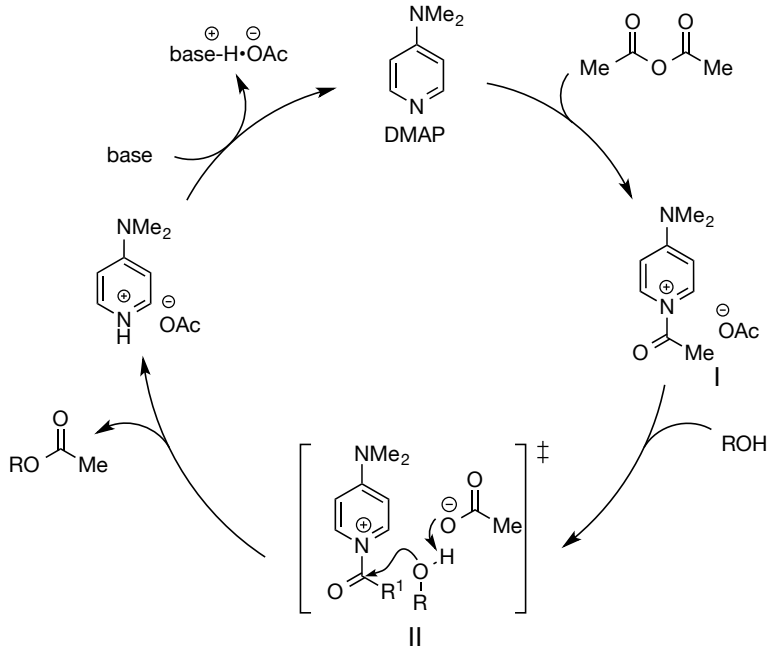


Figure 5. Proposed mechanism of acylation reaction using DMAP.

Many research groups have attempted to synthesize chiral DMAP derivatives and have accomplished various types of enantioselective reaction systems. I describe a history of chiral DMAP derivatives and its current problems on the following section. In describing the kinetic

resolution, an index of enantioselectivity called selectivity factor (*s* value)[11] is used, which is the value of the ratio of the reaction rate of two enantiomer, and the accomplishing of a reaction system in which the *s* value exceeds 20 is a synthetically valuable. The selectivity factor was defined as following equations (2–5).

$$s = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]} = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} = \frac{k_{fast}}{k_{slow}} \quad (2)$$

$$ee = \textit{enantiomeric excess measured for the starting material} \quad (3)$$

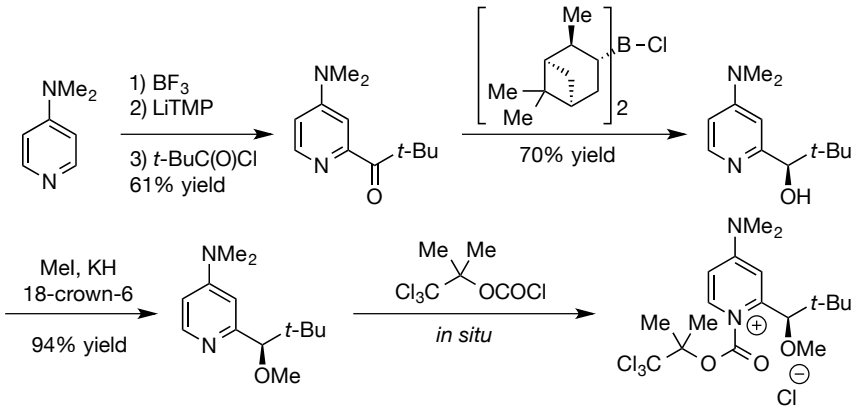
$$ee' = \textit{enantiomeric excess measured for the product} \quad (4)$$

$$C = \frac{ee}{ee + ee'}100 = \textit{conversion} \quad (5)$$

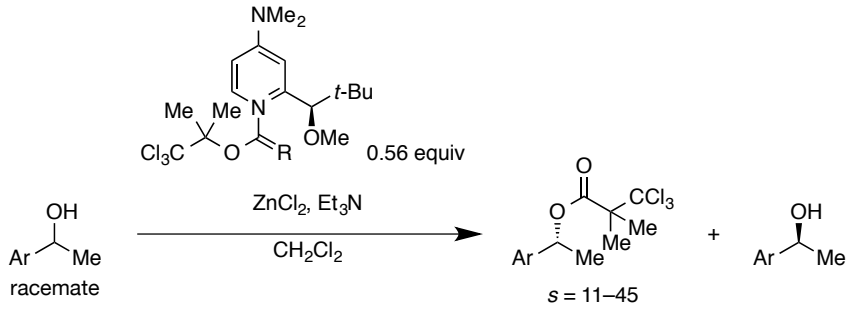
1-2-4. Chiral DMAP derivatives

In 1996, Vedejs and coworkers reported the development of the first chiral DMAP derivative (Scheme 1).[12] It worked as a good enantioselective acylating "regent", however, did not work as a "catalyst" due to deactivation effect of a bulky substituent of chiral source introduced at the 2-position of the pyridine ring. They demonstrated the kinetic resolution of aryl alkyl carbinols with the synthesized acylation reagent (Scheme 2).

Scheme 1. Synthesis of Vedejs' acylation reagent.



Scheme 2. Kinetic resolution of secondary alcohols using Vedejs' acylation reagent.



In the same year, Fu and coworkers developed the ferrocene-based nucleophilic catalyst.[13] They tried to solve the problems of catalytic activity and selectivity by approach that improves nucleophilicity by electronic tuning (using electron rich ferrocene skeleton) and builds a bulky and robust chiral scaffold in the vicinity of the reaction point. Fu's approach utilized the unique electron rich ferrocene character and planar chirality. Planer chirality was introduced by different substituent vertically and horizontally one by one on the two mirror planes of DMAP (mirror plane **a** and **b**, Figure 6). In addition, high catalytic activity (nucleophilicity) was provided by electron-rich π complex. This catalyst was used in kinetic resolution of secondary alcohols which is the fist report of the chiral DMAP derivatives "catalyzed" enantioselective reaction. During past two decades, Fu's catalyst was applied to a numerous reactions such as acylative desymmetrization of diols,[14] dynamic kinetic resolution by alcoholysis of azlactones,[15] Steglich type rearrangement,[16,17] Staudinger reaction,[18-20] [3+2] cycloaddition,[21] *C*-acylation of silyl enol ether and silyl ketene imine,[22-24] alcoholysis of ketenes.[25-27] However, Fu's catalyst have also several drawbacks: (i) Preparative chiral HPLC purification is needed for synthesis of catalyst (at present, optical resolution conditions are reported); (ii) long catalyst synthesis (7 steps) and low total yield (2.1% yield, Scheme 3).

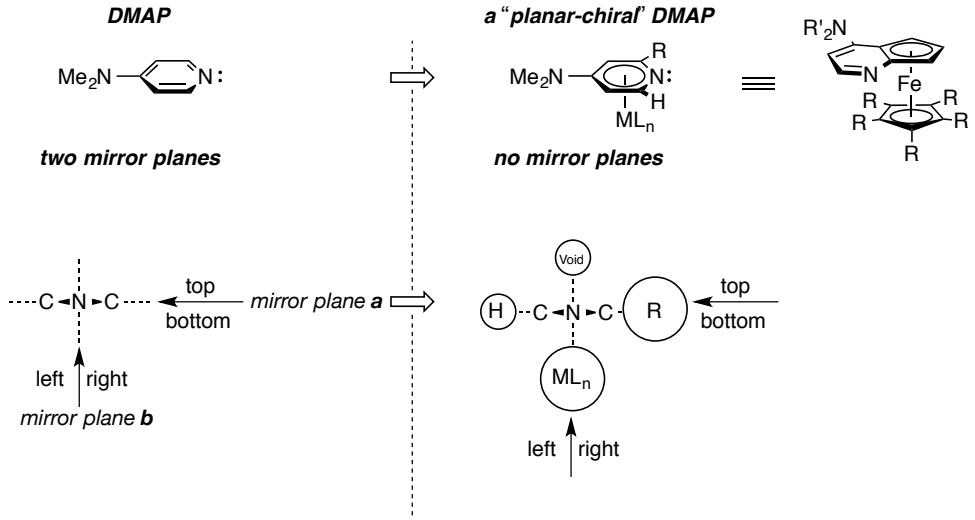
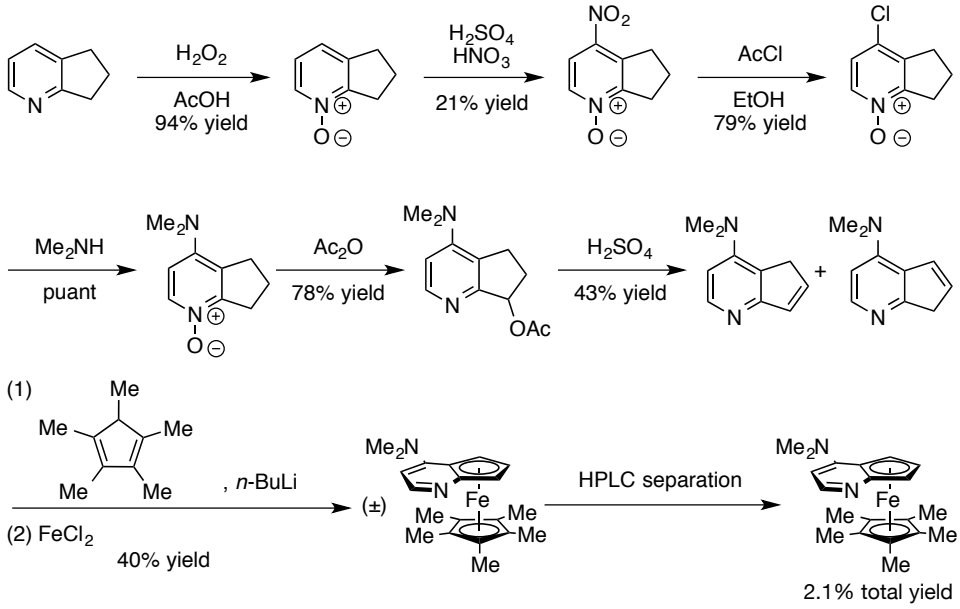


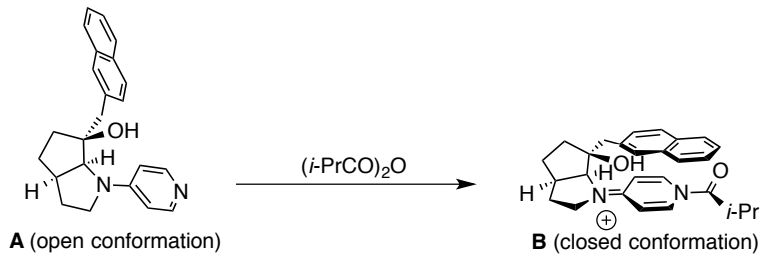
Figure 6. Design of a "planar-chiral" derivative of DMAP.

Scheme 3. Synthesis of planner-chiral DMAP derivatives



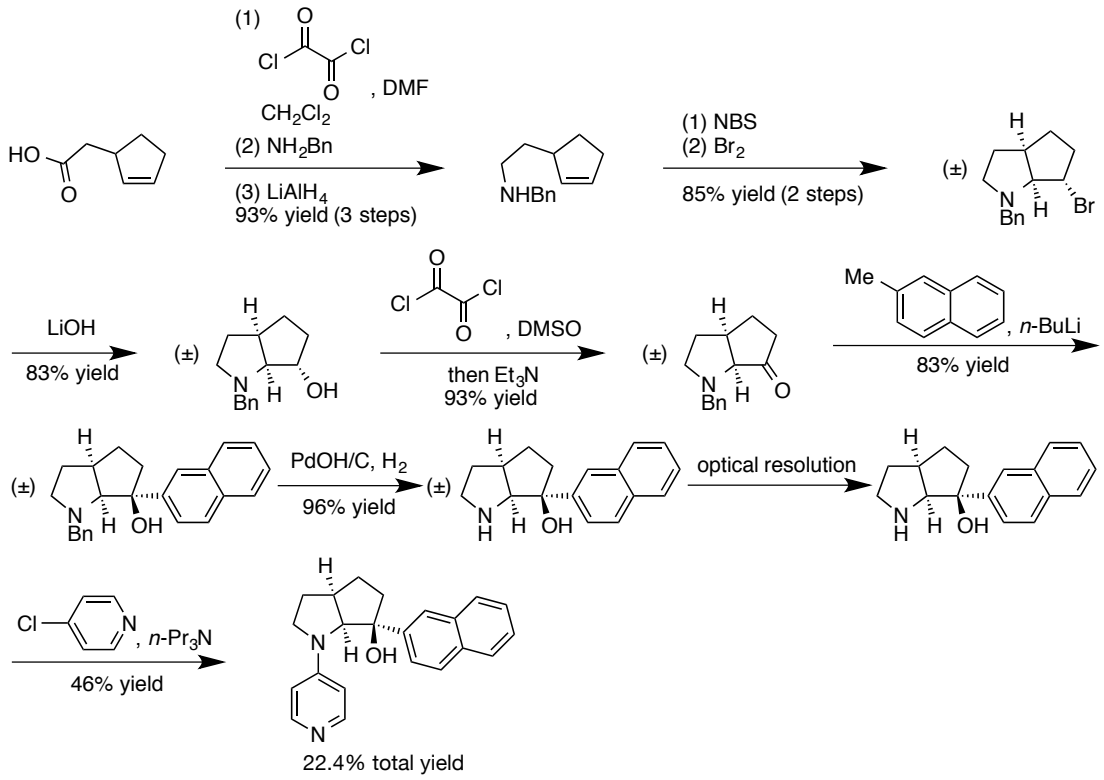
On the other hand, Kawabata and coworkers worked on another approach to resolve "the problem of catalytic activity and selectivity". That is chiral recognition from a remote location without loss of the nucleophilicity of the catalyst in DMAP catalyzed possesses. In 1997, they have developed a chiral PPY derivatives utilizing remote chiral induction based on attractive π-π interaction strategy.[28] Although the naphthalene ring does not interact with the pyridine ring in the ground state (**A**), the structure is changed by cation-π interaction to form the closed conformation (**B**) when PPY part reacts with the acylating reagent to form *N*-acylpyridinium ion intermediate (Scheme 4). However, there were several disadvantages as follows: (i) The narrow substrate scope of this catalysis (ii) catalyst was synthesized via optical resolution in low yield (22.4% yield in 11 steps, Scheme 5).

Scheme 4. Concept of induce-fit model based on attractive π-π interaction.



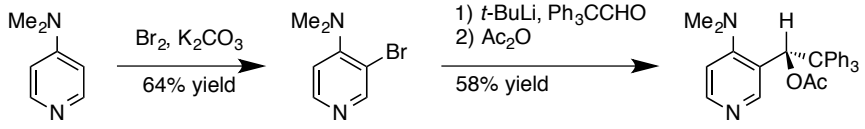
A (open conformation) **B** (closed conformation)

Scheme 5. Synthesis of Kawabata's catalyst expressed attractive π-π interaction.

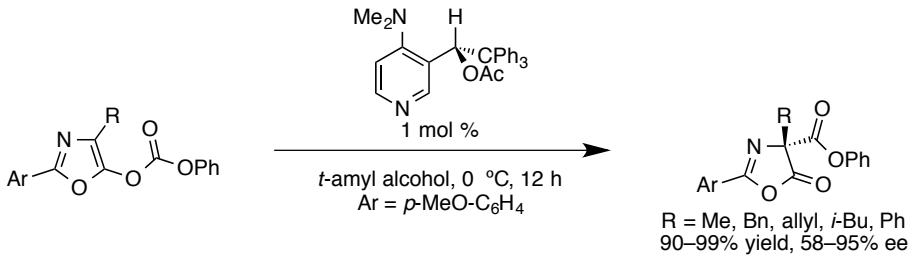


In 2003, Vedejs and coworkers reported a chiral DMAP derivative in which an chiral source was introduced at the 3-position of the pyridine ring (Scheme 6).[29,30] The result showed that the chiral DMAP derivative acts as a chiral "catalyst". Although high enantioselectivity was shown, the reaction took long time (12 h) in the Steglich rearrangement of *O*-acylated azlactones (Scheme 7). In addition, the selectivity factor was moderate (s = 4.4) in the acylative kinetic resolution of (±)-1-naphthyl-1-ethanol.

Scheme 6. Synthesis of Vedejs' DMAP derivative.

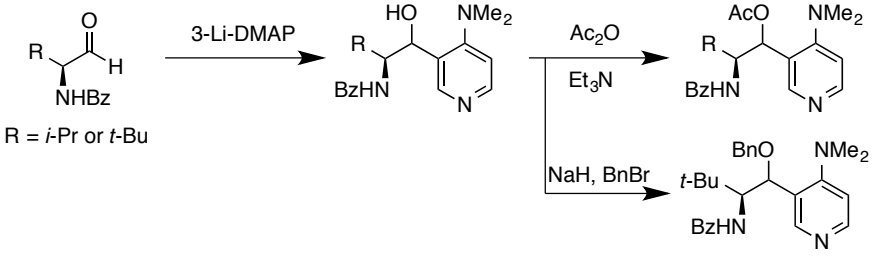


Scheme 7. Steglich rearrangement using Vedejs' DMAP derivative.

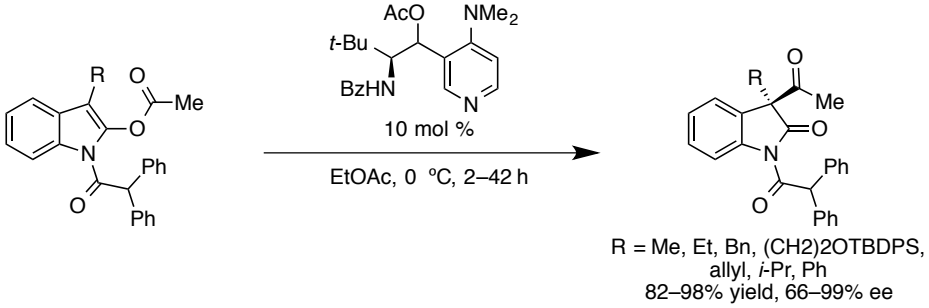


Furthermore, in 2009, Vedejs and coworkers reported another chiral DMAP derivatives allowed to synthesize many catalyst library in a short process (Scheme 8).[31] The chiral DMAP derivative can catalyze the enantioselective Steglich rearrangement with high enantioselectivity in high yield (Scheme 9).

Scheme 8. Synthesis of new Vedejs' DMAP derivatives.



Scheme 9. Steglich rearrangement of oxindoles using Vedejs' DMAP derivative.



After these pioneering reports of Vedejs, Fu, and Kawabata, various chiral DMAP derivatives have been developed (Figure 7).[32-42] Some of these catalysts showed relatively good enantioselectivity although fundamental weakness of chiral DMAP, which is the problem of catalytic activity and selectivity, is not completely solved. Therefore, for the advancement of the field of chiral nucleophilic catalyst, new concept for high catalytic activity and high selectivity are required.

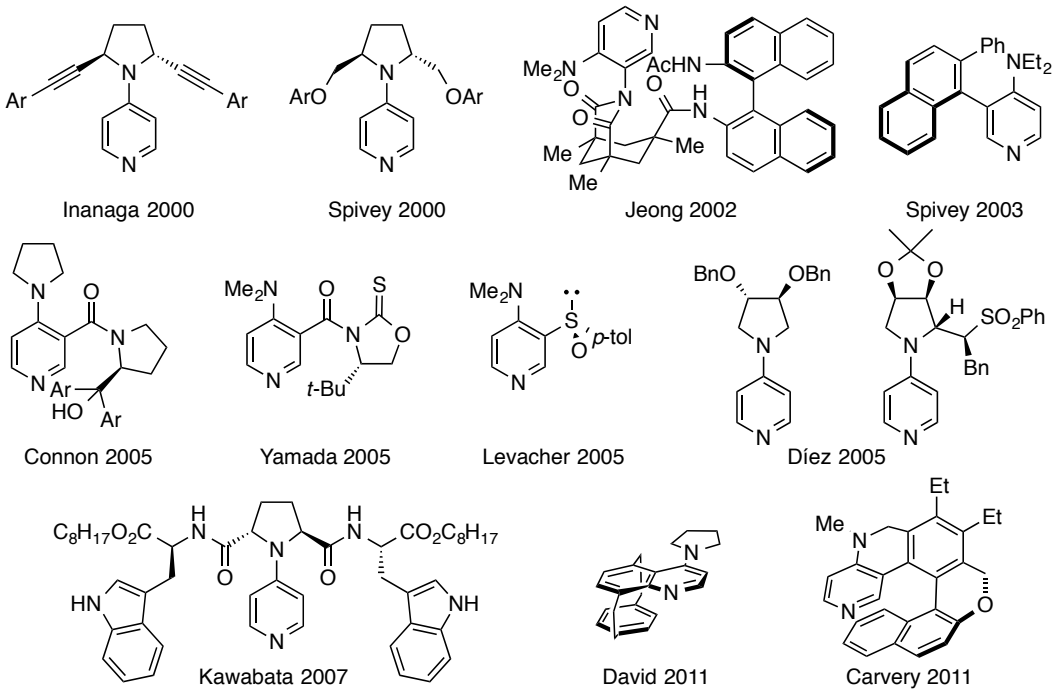


Figure 7. Developed DMAP derivatives in 20 decades

1-3. The Electrostatic Interaction in Small-Molecule Catalysis

Recently, reaction control by electrostatic interaction rather than simple steric hindrance from chiral scaffold (conventional approach) was focused in field of organocatalysts. Some organocatalysts with electrostatic interactions (such as hydrogen bondings,[40,42,43] ionic bonds,[44] and Brønsted acid and base combination catalytic systems[45]). In the recent nucleophilic catalyst, reaction control by electrostatic interaction is being achieved to get the high catalytic activity and selectivity. The next section introduces the nucleophilic catalysis controlled by electrostatic interaction in recent years.

1-3-1. Selectivity and Rate Enhancement controlled by Attractive Interactions

In 1998, Miller and coworkers developed the chiral peptide-based *N*-methylimidazole (NMI) catalyst which was developed based on biomimetic peptide–substrate interaction strategy (Figure 8).[43] This catalyst showed rate enhancement in the enantioselective acylation of α-hydroxy amide. In fact, the competitive experiment manifested the effect of rate enhancement of particular transformation (Table 2). When 1 equiv of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol **a**, and 1 equiv of naphthyl methyl carbinol **b** were treated with chiral NMI catalyst and acetic anhydride, the corresponding acetate **a-Ac** and **b-Ac** were observed in a 6:1 ratio. As the control, when the use of normal NMI under the same reaction conditions, **a-Ac** and **b-Ac** were formed in equal quantities. This observation might be caused by stabilization of transition states through hydrogen bonding between catalyst and substrate.

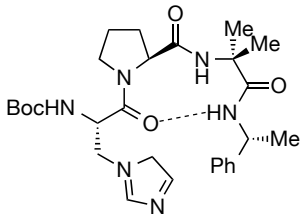
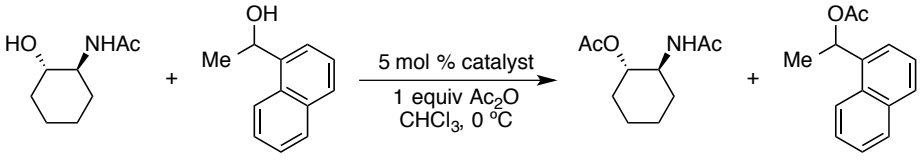
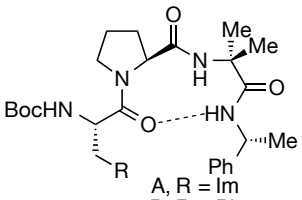


Figure 8. Miller's peptide based NMI catalyst

Table 2. Competitive acylation experiments



	Catalyst	Product Distribution **a**-Ac	**b**-Ac
 A, R = Im B, R = Ph	**NMI**	1	1
	A	6	1
	B	no reaction	

Kawabata and coworkers reported the enantioselective acylation with chiral PPY utilizing attractive π-π interaction (see the previous section 1-2-4.) in 1997. Moreover, they achieved the excellent regioselective acylation of monosaccharides with newly developed PPY derivatives in 2007 (Figure 9).[40] This catalyst can perform regioselective acylation to hydroxyl group at 4-position of D-glucose which is inherently lowest reactivity. The reaction mechanism was proposed that after forming the complex through hydrogen bonding between hydroxyl groups at 3- and 6-positions of D-glucose and indol moieties of catalyst structure, free hydroxy group of 4-position was selectively acylated (Figure 9). In this reaction system, the notion of accelerative acylation was supported experimentally by the competitive acylation between octyl-D-glucopyranoside and a primary alcohol or a secondary alcohol (Scheme 10a and b). When a 1:1 mixture of octyl-D-glucopyranoside and 2-phenylethanol was conducted to the reaction under the conditions similar to regioselective acylation, the 4-*O*-isobutyrate of octyl-D-glucopyranoside was selectively obtained with 99% regioselectivity in 98% yield for monoacylation. Similarly, competitive acylation between octyl-D-glucopyranoside and racemic 1-phenylethanol gave only 4-*O*-isobutyrate of octyl-D-glucopyranoside with >99% regioselectivity in 99% yield for monoacylation in spite of that

1-phenylethanol is more reactive primary alcohol. However, this catalyst achieved excellent results in regioselective acylation of polyols, thre are some problems as follows: (i) Low enantioselectivity in other enantioselective reaction due to remote chiral control; (ii) To achieve the selectivity, it was needed hydrogen bonding point at substrate structure; (iii) Low total yield of the catalyst synthesis (8.4% yield in 6 steps, scheme 10).

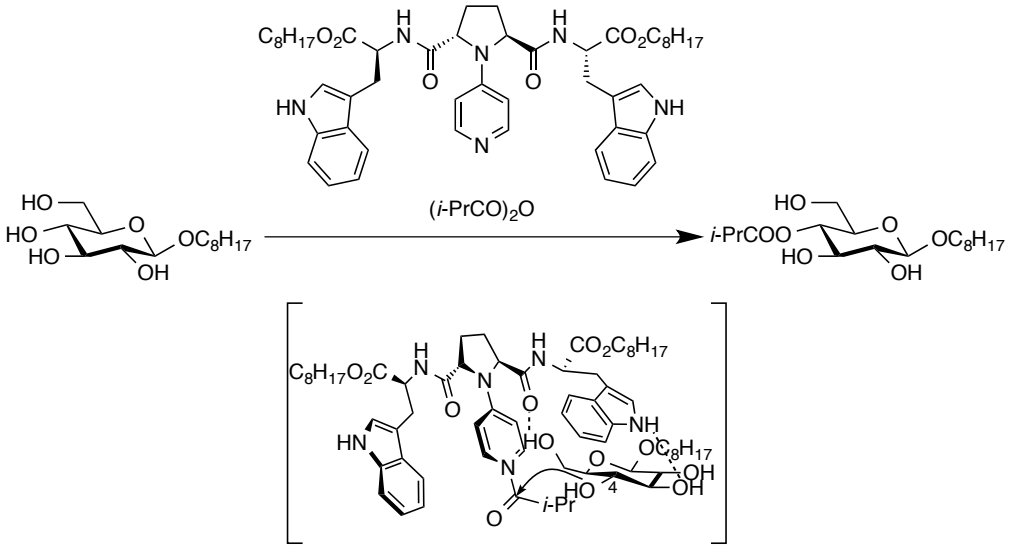


Figure 9. Chemo- and regioselective acylation of monosaccharides using Kawabata's PPY derivative.

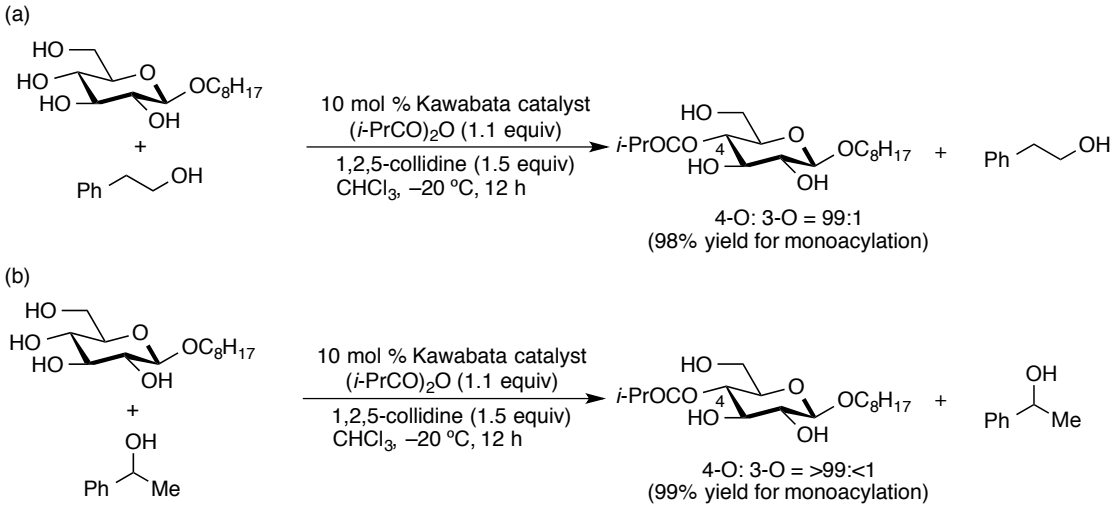
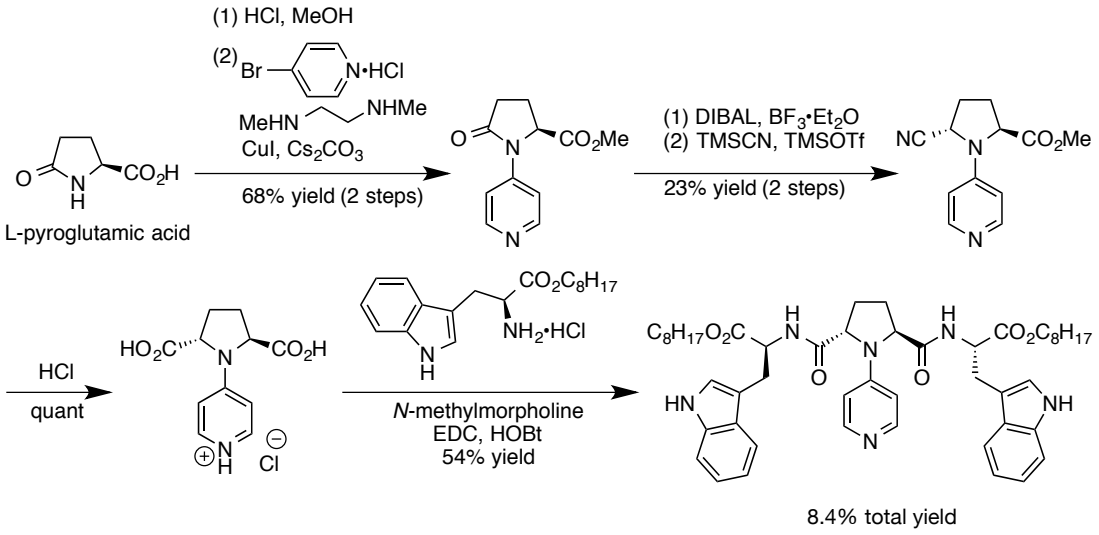
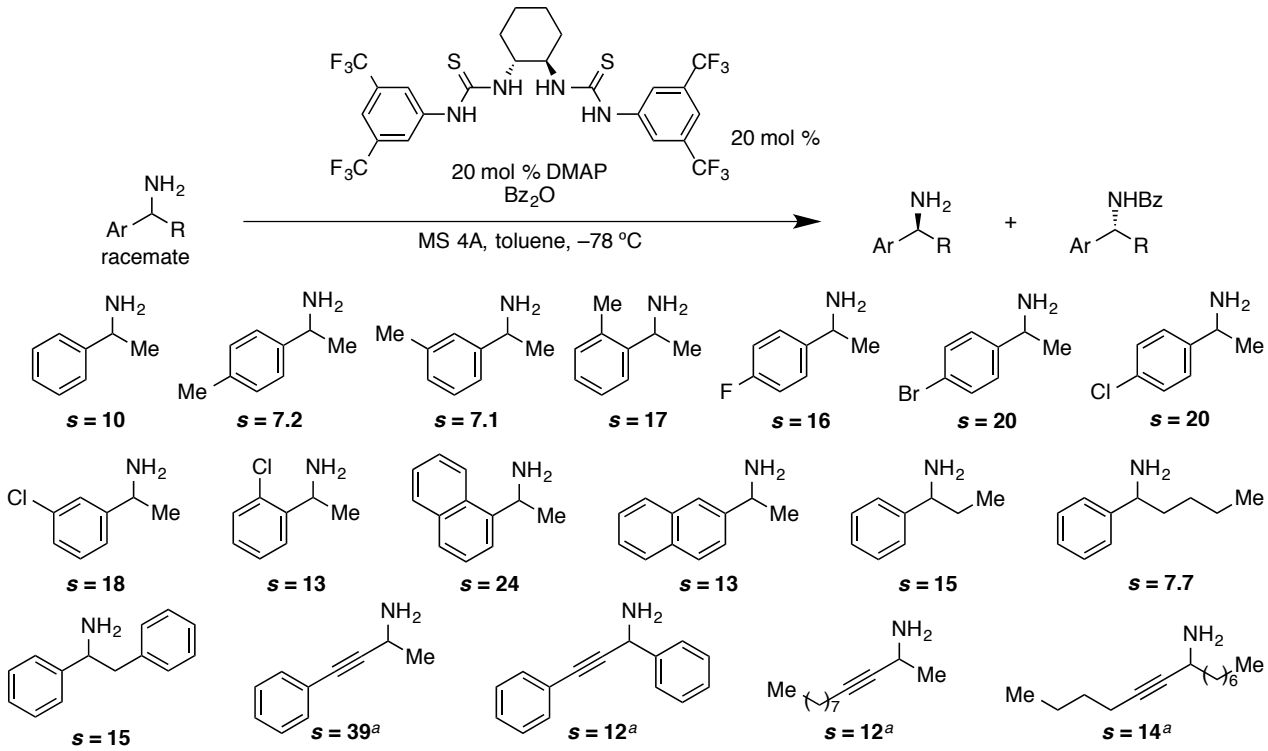


Figure 10. Competitive experiments with Kawabata's catalyst

Scheme10. Synthesis of Kawabata's PPY derivative.

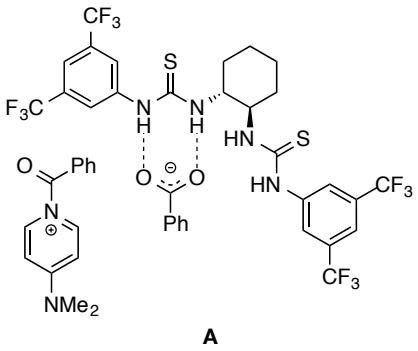


In 2009, Seidel and coworkers reported kinetic resolution of secondary amine with DMAP and thiourea co-catalytic system (Figure 11).[45] This system realized both the rate enhancement and high enantioselectivity. High selectivity factors were shown in this reaction in spite of that the chirality of catalyst is only placed on the side of thiourea catalyst. This reaction did not proceed with only DMAP catalyst (<2% conv) and shown very low selectivity factor in the case of using only chiral thiourea catalyst (40% conv, s = 1.4). They proposed active intermediate **A** in the presence of benzoic anhydride, DMAP, and chiral thiourea (Figure 12). Binding of benzoate to chiral thiourea may have an effect on the equilibrium concentrations of DMAP and its corresponding acyl pyridinium salt, which is a factor that is likely playing an important role in the overall process.



[a] 5 mol % catlyst and 5 mol % of DMAP was used.

Figure 11. Kinetic resolution of amines using thiourea and DMAP co-catalyst system.



A

Figure 12. Kinetic resolution.

1-4. Enantioselective Acylation

• Chiral DMPA catalyst

Non-enzymatic acylative kinetic resolution of secondary alcohols was first reported by Vedejs and coworkers in 1996 (Figure 13).[12] However, it succeeded with good enantioselectivity, but stoichiometric amount of chiral acylating regent was required.

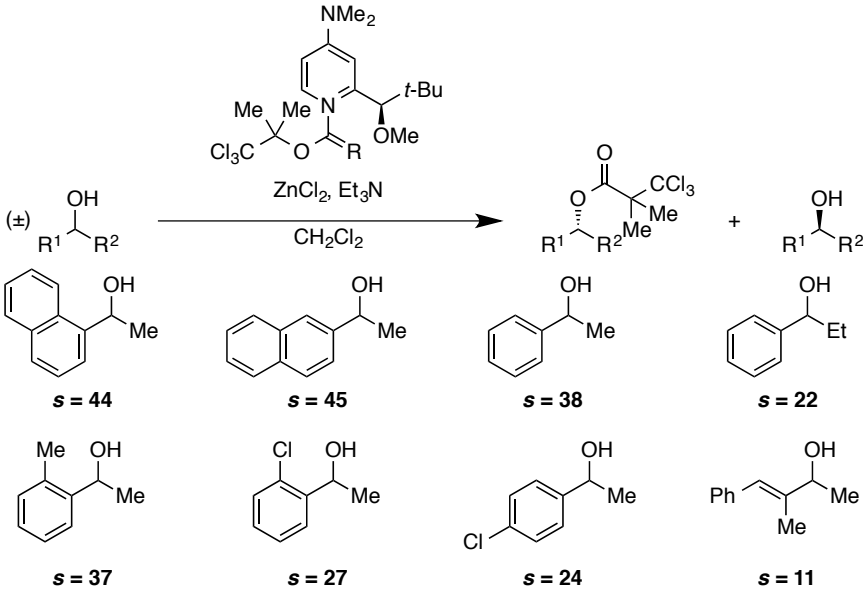


Figure 13. First report of kinetic resolution of alcohols using DMAP derivatives.

The first "catalytic" kinetic resolution of secondary alcohols with chiral DMAP derivatives was reported by Fu and coworkers in 1996 (Figure 14).[13] In this reaction, the wide substrate generality with high selectivity factor was reported. After first reporting the catalytic kinetic resolution, Fu and coworkers reported that selectivity factor was improved when *t*-amino alcohol was used as a solvent.[14] Furthermore, this catalyst was applied to the kinetic resolution of propargyl alcohol.[46]

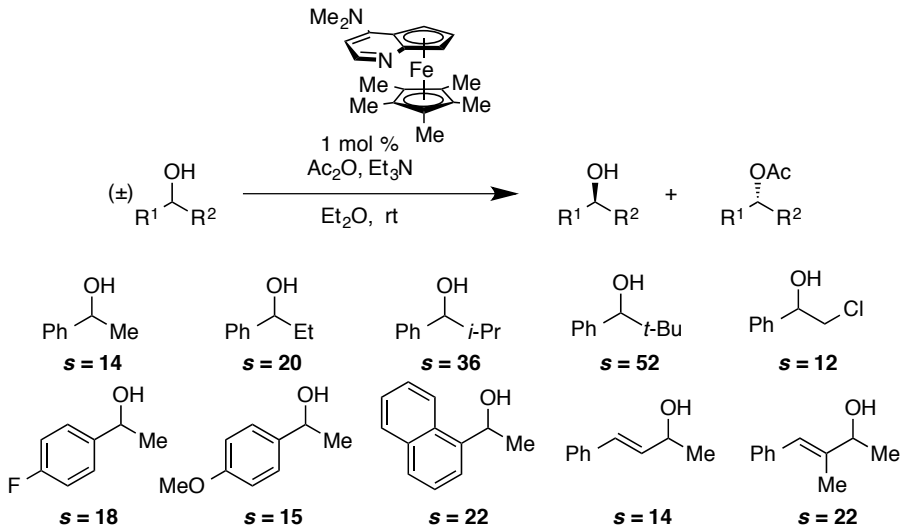


Figure 14. First report of catalytic kinetic resolution of alcohols using DMAP derivatives.

In 1997, Kawabata and coworkers developed kinetic resolution of cyclic mono protected *cis*-diols with the PPY derivative which was developed based on the concept of attractive π-π interaction strategy (Figure 15).[28] However, in this reaction, 6-membered ring as a reaction substrate showed high selectivity factors, although the use of the other reaction substrates resulted in moderate selectivity factors. This catalyst could be applied to kinetic resolution of cyclic *cis*-amide alcohol (Figure 16).[47] When a *trans*-amino alcohol is used as a substrate, it showed the same reaction rate as PPY but that of *cis*-amino alcohol shows about 20 times higher the reaction rate than that of PPY.[48]

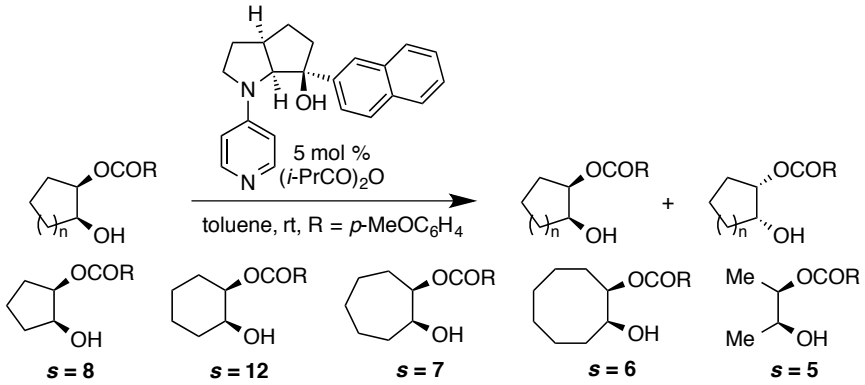


Figure 15. Kinetic resolution of cyclic *cis*-alcohols using Kawabata's catalyst.

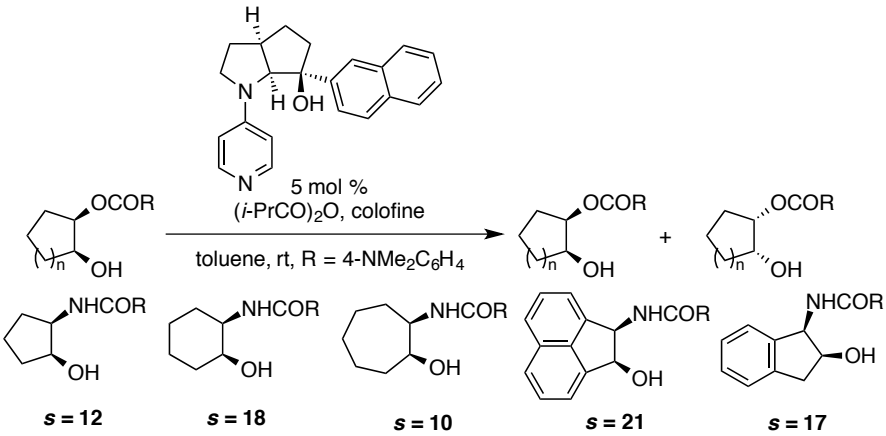


Figure 16. Kinetic resolution of cyclic *cis*-amidealcohols using Kawabata's catalyst.

• Chiral phosphine catalyst

In 1996, Vedejs and coworkers reported the acylative kinetic resolution of secondary alcohols with chiral phosphines for the first time and then repeatedly improved and developed a variety of the phosphine catalysts.[49-53] Among them, chiral phosphine reported in 2003 offered the highest enantioselectivities and broad substrate scope (Figure 17).[52]

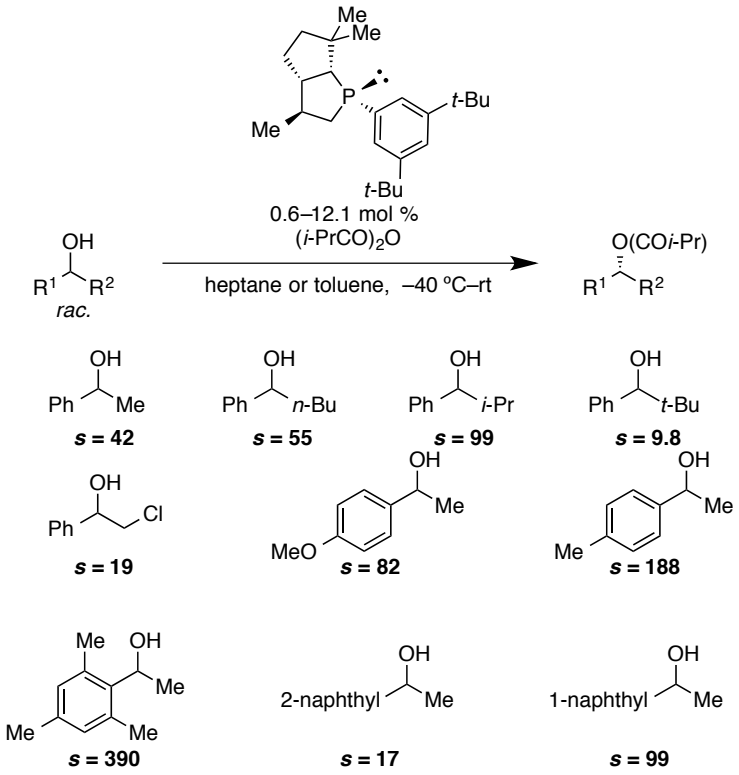


Figure 17. Kinetic resolution of *sec.* alcohols using chiral phosphine catalyst.

• Chiral diamine catalyst

In 1998, Oriyama and coworkers reported the acylative desymmetrization of *meso*-diols with chiral diamine (Figure 18).[54] The catalytic activity was very high and required only 0.5 mol % of catalyst. This catalyst could be applied to acylative desymmetrization of 1,3-*meso*-diols.[55]

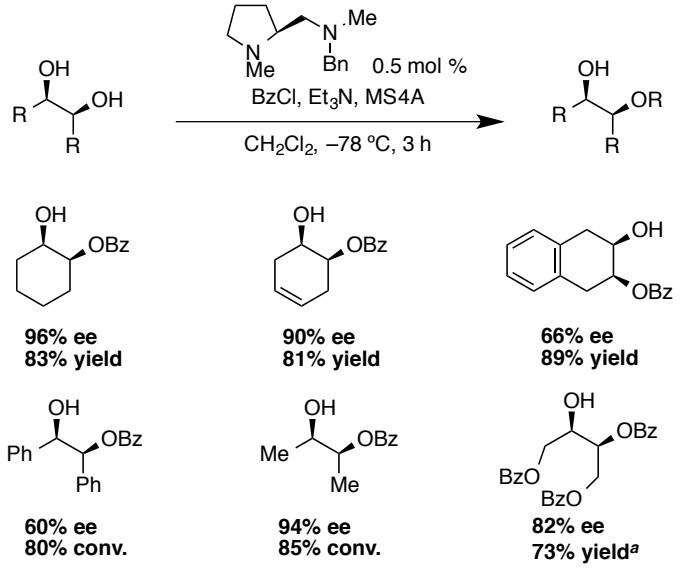


Figure 18. Desymmetrization of 1,2-diols Oriyama's diamine catalyst

In 1999, Oriyama and coworkers reported the kinetic resolution of secondary alcohols with chiral diamine catalyst (Figure 19).[56] Chiral diamine gives a very high selectivity factor for cyclic secondary alcohols, but moderate selectivity factor in the case of using acyclic alcohol as substrate.

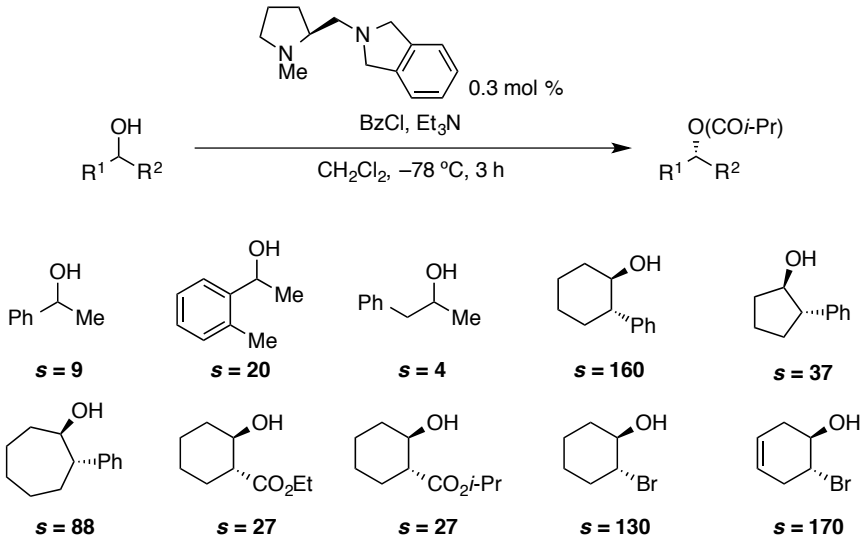
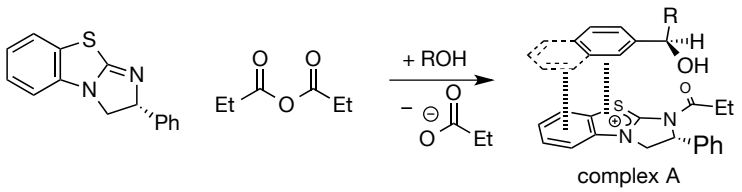


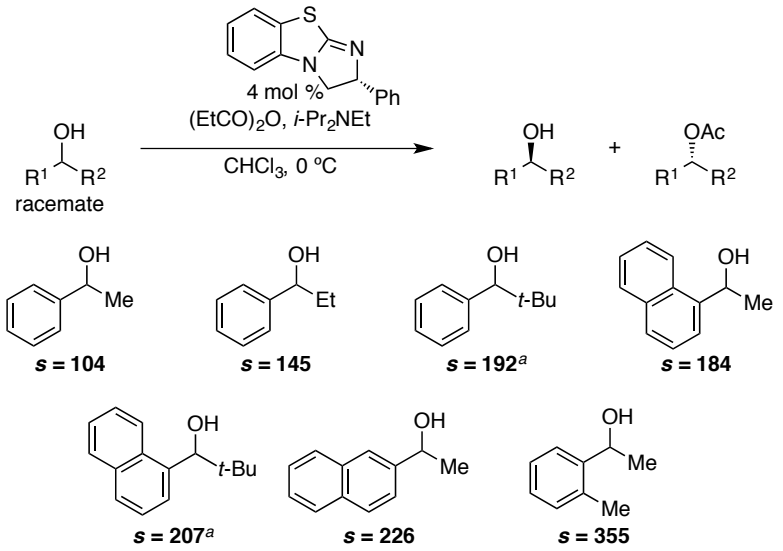
Figure 19. Kinetic resolution of *sec.* alcohols using Oriyama's chiral diamine catalyst

• Chiral isothiourea catalyst

In 2006, Birman and coworkers developed the newly very active isothiourea based catalyst. The origin of the enantioselectivity derived from complex **A** which formed π-π and cation-π interactions between the acylated catalyst and the substrate molecule (Scheme 11).[57] The kinetic resolution of secondary carbinols with this catalyst offered extremely high selectivity factor in most cases (Figure 20). These results showed the highest selectivity factor in the non-enzymatic acylative kinetic resolution. When the use of substrate without ary substituent, the enantioselectivity was significantly reduced due to the lack of π-π and cation-π interactions between the acylated catalyst and the substrate.



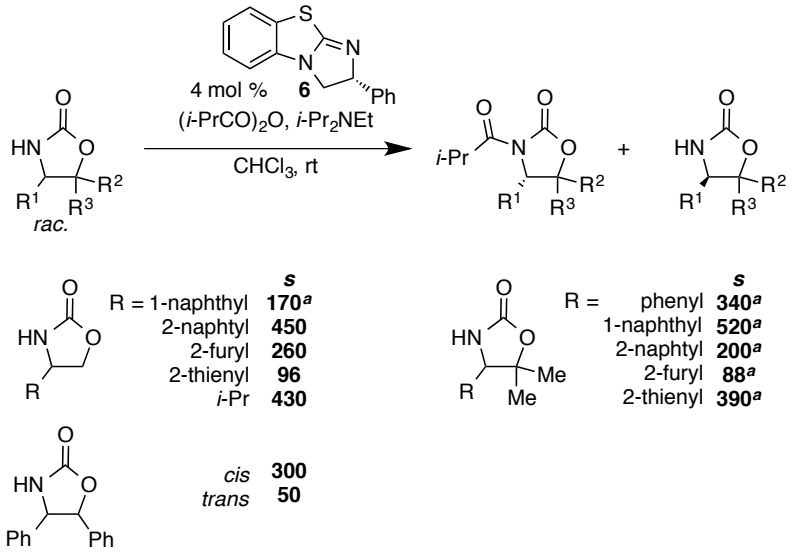
Scheme 11. Kinetic resolution of *sec.* alcohols using Oriyama's chiral diamine catalyst.



a 8 mol % of catalyst was used.

Figure 20. Kinetic resolution of *sec.* alcohols using chiral isothiourea catalyst.

Birman's catalyst could be applied to kinetic resolution of 2-oxazolidinone (Figure 21). The selectivity factor was also excellent value. Contrary to kinetic resolution of secondary carbinols, the reactions using aliphatic substrate proceed uneventfully with high selectivity factor.



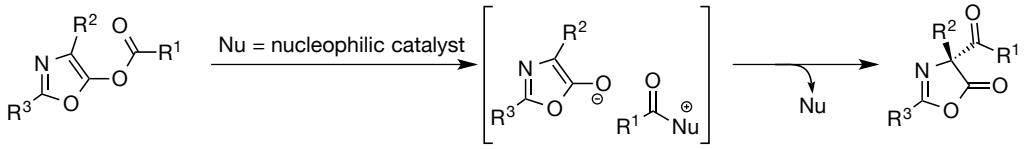
a 8 mol % of catalyst was used.

Figure 21. Kinetic resolution of oxazoline derivatives using isothiourea catalyst.

1-5. Acyl Migrations

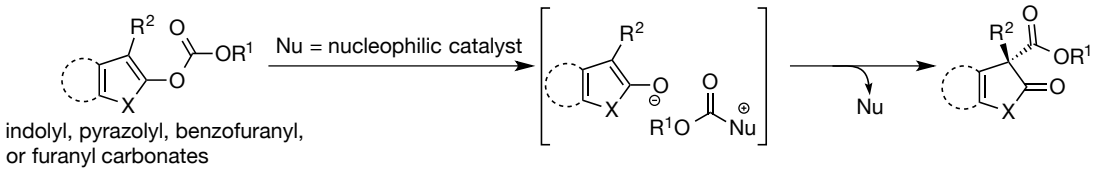
The Steglich rearrangement reaction was reported by Steglich and Höfle in 1969, which is known as the acyl migration through *O*-acylated compound to *C*-acylated compound to construct a all-carbon quaternary stereogenic center at α-position of heterocyclic compounds such as azlactone (Scheme 12).[58]

Scheme 12. Steglich rearrangement of azlactone



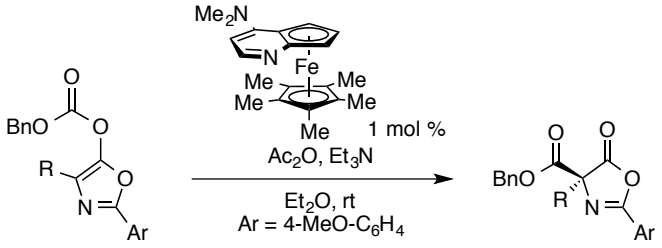
In 1986, Black reported that acyl migration was occurred by the use of benzofuranyl carbonate as substrate (Scheme 13).[9,59,60] This type of reaction was easy way to synthesis of heterocyclic which have all-carbon quaternary stereo center on its 3-position.[17,29,30,61-65]

Scheme 13. Steglich type rearrangement of heterocyclic compounds (Black rearrangement)



The first enantioselective Steglich type reaction of *O*-acylated azlactone was developed with ferrocene-based DMAP catalyst (see previous section 1-2-4.) by Fu and coworkers in 1998,[16] and showed high enantioselectivity and yield.

Table 3. Enantioselective rearrangement of O-acylated azlactones with Fu's PPY



entry	R	ee (%)	yield (%)
1	Me	91	94
2	Et	90	93
3	Bn	90	93
4	Allyl	91	93
5	*i*-Pr	92	95
6	CH_2CH_2SMe	88	94

After Fu's pioneering works, many groups reported this type of the reaction their original developed nucleophilic catalysts (Figure 22).[29,44,61,66-73]

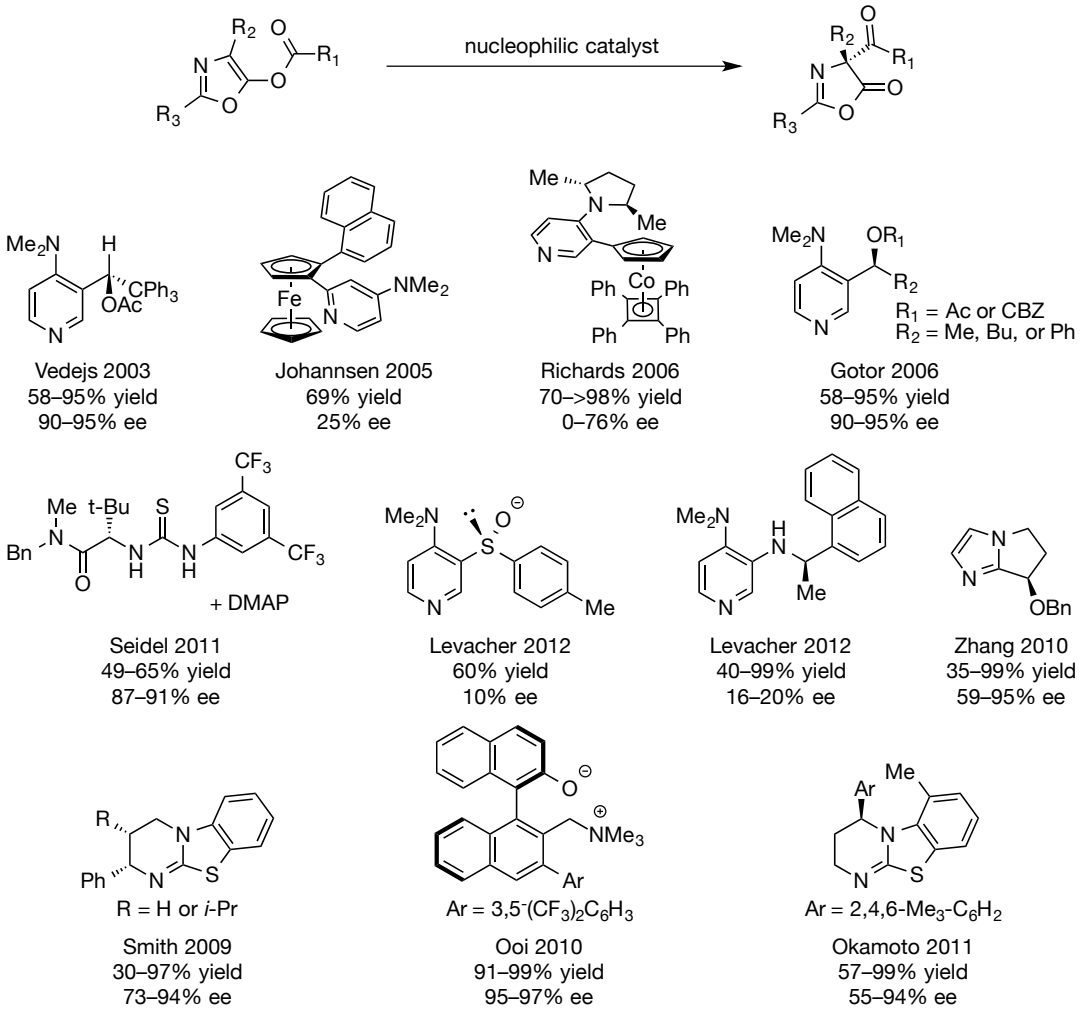


Figure 22. Summary of reported enantioselective Steglich rearrangements

Attractive point of Steglich rearrangement is that it allows access to complex natural or bioactive compounds (Figure 23). Among them, synthesis of oxindole and benzofuranone derivatives with all-carbon quaternary stereo center at 3-position of oxindole is very useful method in the organic chemistry.

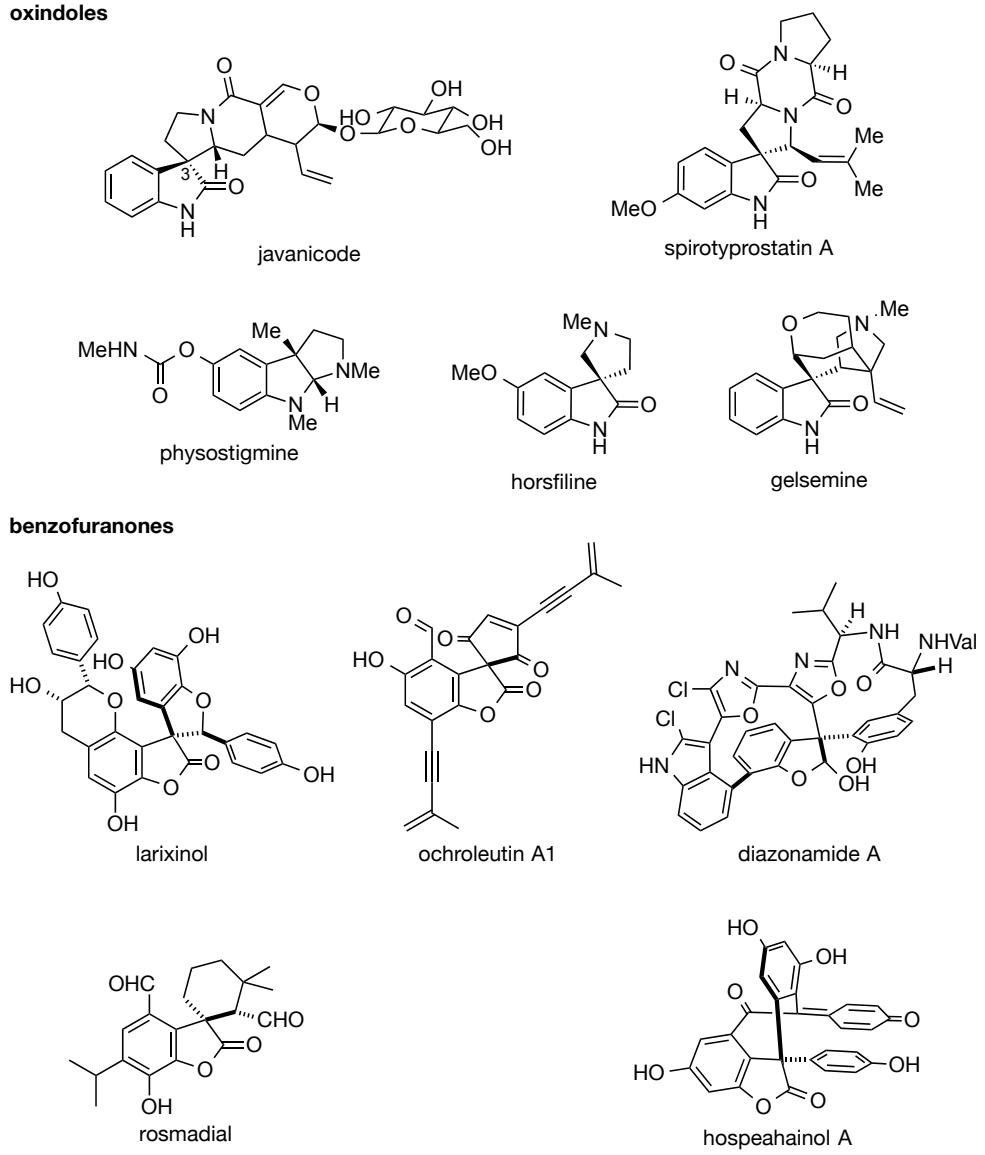


Figure 23. Natural compounds of oxindoles and benzofuranones

In 2003, Fu and coworkers reported the first enantioselective Steglich type (Black) rearrangement of indolyl and benzofuranyl carbonates (Figure 24).[17] All of the products was obtained with high enantiomeric ratio in good yield.

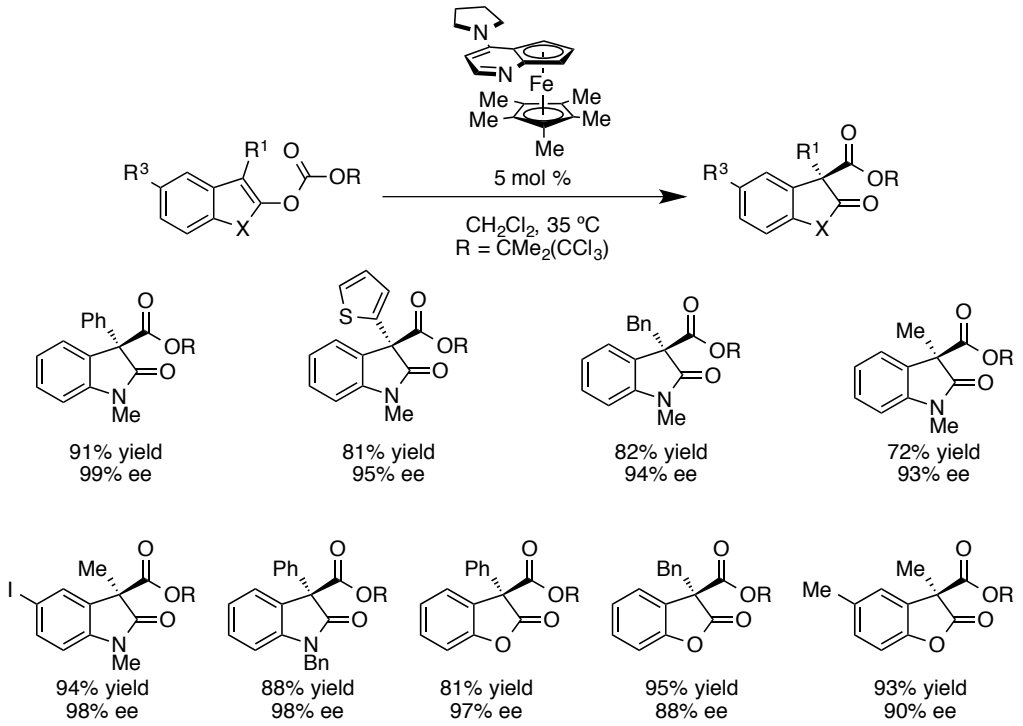
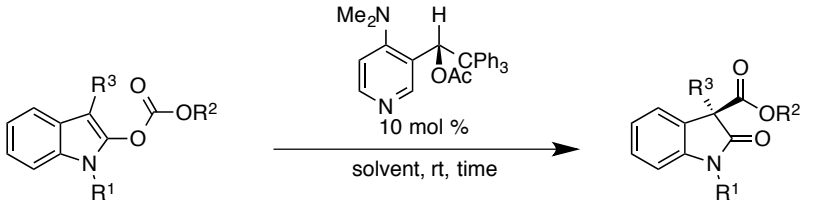


Figure 24. Enantioselective Steglich rearrangement of oxindoles using Fu's catalyst.

In 2003, Vedejs also reported enantioselective Steglich type rearrangement with TADMAP (see previous section 1-2-4.).[29] Compered with Fu's reaction, Vedejs' reaction needed for a long reaction time and showed moderate enantioselectivities (Table 4 and 5).

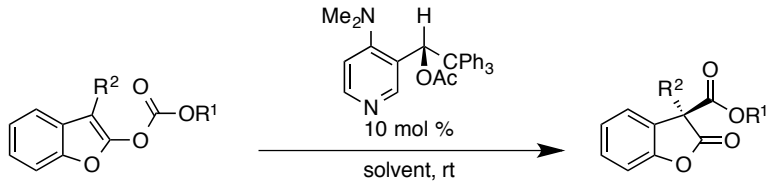
Table 4. Enantioselective Steglich rearrangement of oxindoles using Vedejs' catalyst.



entry	R^1	R^2	R^3	solvent	time	ee (%)
1	CO_2Ph	Ph	Me	THF	35 d	55
2	allyl	Ph	Me	CH_2Cl_2	8 d	37
3	Bn	Ph	Me	THF	8 d	18
4	4-MeO-C_6H_4	Ph	Me	THF	28 d	50
5	Me	Ph	Me	THF	24 h	23
6	Me	Me	Me	THF	24 h	<1
7	Me	CH_2CCl_3	Me	CH_2Cl_2	24 h	10
8	Me	$C(Me)_2CCl_3$	Me	*t*-amyl alcohol	24 h	49
9[b]	CO_2Ph	Ph	Ph	*t*-amyl alcohol	18 h	86

[a]Time required for >95% conversion. [b]The reaction was conducted at 40 °C.

Table 5. Enantioselective Steglich rearrangement of benzofuranones using Vedejs' catalyst.



entry	R^1	R^2	solvent	temp (°C)	yield (%)	ee (%)
1	Ph	Me	Et_2O	23	92	92
2	CH_2CCl_3	Ph	CH_2Cl_2	–40	92	86

In 2009, Vedejs and coworkers reported an enantioselective Steglich rearrangement of indolyl carbonates with AcOLeDMAP (Figure 25, see the previous section 1-2-4).[31] While the reaction proceeded with high enantioselectivities in high yields, the catalyst loading was 10 mol % and long time reaction in the case of using bulky substrates.

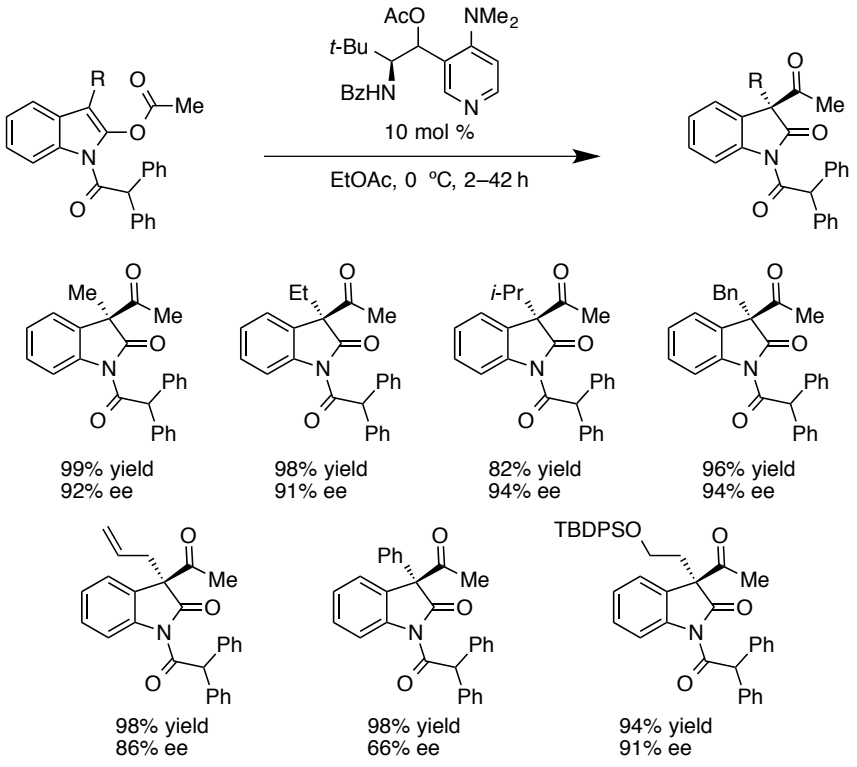
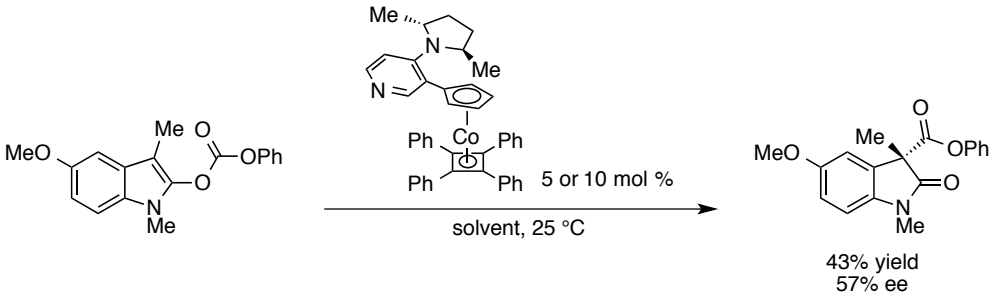


Figure 25. Enantioselective Steglich rearrangement of oxindoles using new Vedejs' catalyst.

In 2009, Richards and coworkers reported same reaction with cobaltocene-derived chiral DMAP catalyst, but both enantioselectivities and yields were still low (Scheme 14, up to 57% ee).[74]



Scheme 14. Enantioselective Steglich rearrangement of oxindoles using new Richards's catalyst.

In 2014, Zhang and coworkers reported same reaction with chiral imidazole based catalyst (Figure 26). Although the 16 examples of substrate were examined, simple alkyl substituted substrates were only used in this reaction. For this reason, functional group tolerance of this reaction is unclear.

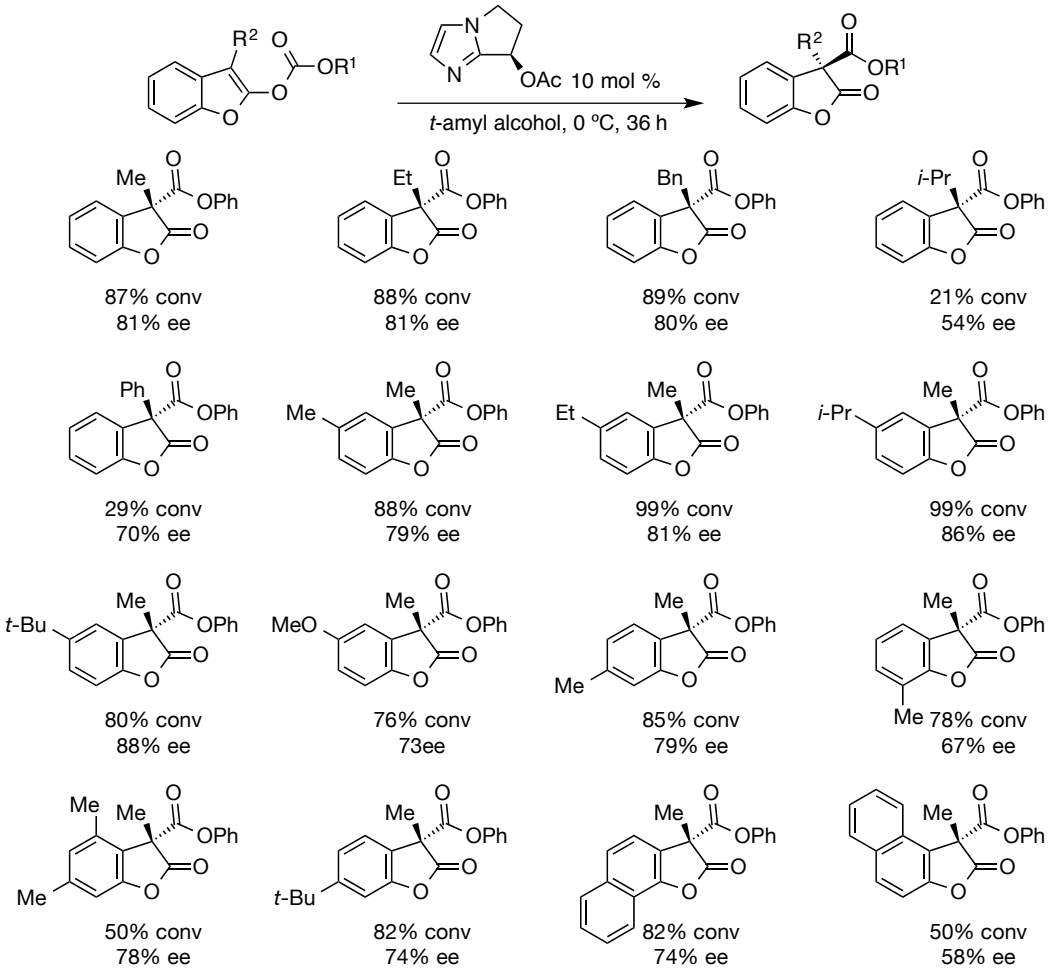


Figure 26. Enantioselective Steglich rearrangement of benzofuranone using Zhang's Imidazole catalyst

1-6. Objectives

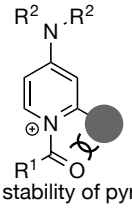
Zipse and coworkers estimate the important reaction intermediate (*N*-acylpyridinium ion) by computational calculations. According to Zipse's calculations, catalytic activity of DMAP increase when alkyl groups introduce on amino group at 4-position of pyridine ring or directly 3-position of pyridine ring. However, electric tuning of catalytic activity of DMAP causes significant restriction of catalyst structure, therefore, it is difficult to develop the chiral catalyst with extremely high catalytic activity. For that reason, all of the existing chiral DMAP catalyst shows low catalytic activity. Thus, development of a catalyst with a wide range of reaction scope, high catalytic activity and selectivity is strongly desired. We designed the highly active catalyst based on strategy utilizing electrostatic interaction such as hydrogen bonding and/or dipole interaction between catalyst and substrate. We believe that a working hypothesis would bring about dramatic rate acceleration

1-6-1. Catalyst Design

A conventional strategy for development of chiral DMAP catalyst includes the deactivating factor by introducing chiral scaffold or substituents (Figure 27a). Therefor, we envisioned that strategy based on remote-control recognition of substrate by utilizing electrostatic interaction to form the suitable transition state (Figure 27b). With this strategy, the inherent reactivity of DMAP do not decrease due to avoiding deactivation by steric repulsion of chiral scaffold. Specifically, polar functional groups such as a hydroxyl group or an ester group of catalyst structure activate the reaction substrate via hydrogen bonding, or dipole interaction to achieve high enantioselectivity and catalytic activity. In order to achieve this strategy, the best catalyst skeleton is 1,1´-binaphthol. We reasoned that this design would have several noteworthy advantages. First, either enantiomeric form of 1,1´-bi-2-naphthol (BINOL) is inexpensively available, thus obviating resolution procedures during a catalyst synthesis. Second, the catalyst platform allows synthesis and screening of C1- and C2-symmetric variants from a common intermediate. Third, it is easy to access an array of catalysts through steric and/or electronic modification by the use of well-established protocols. Finally, the absence of substituents at the C2 or C3 sites of the pyridyl ring would ensure that efficiency levels remain high.

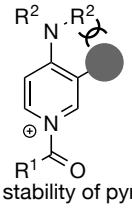
a conventional approach

***C-2* position**



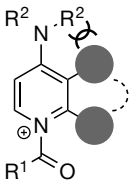
- Decrease stability of pyridinium salt
- Almost no catalytic activity
- Require stoichometric amount
- Few examples

***C-3* position**



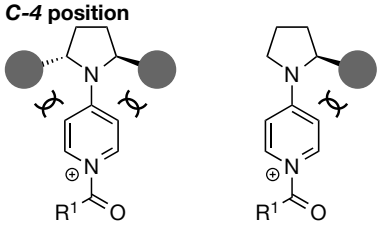
- Decrease stability of pyridinium salt
- Hamper efficient lone-pair/π-orbital overlap between 4-dialkyl amino moiety and pyridine rong
- Many examples

***C-2 and 3* positions**



- Decrease stability of pyridinium salt
- Hamper efficient lone-pair/π-orbital overlap between 4-dialkyl amino moiety and pyridine rong
- Few examples

***C-4* position**



- Chirality is far from reaction site.
- Hamper efficient lone-pair/π-orbital overlap between 4-dialkyl amino moiety and pyridine rong
- Many examples

b our strategy

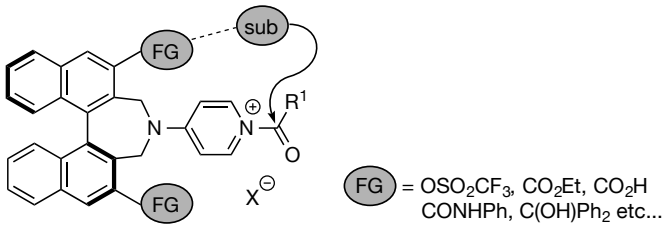


Figure 27. (a) Previously employed strategies involving structural alteration of DMAP-containing molecules to generate enantioselective acyl transfer catalysts (b) Stabilization of *N*-acyl pyridinium ion intermediate by intermolecular interaction

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Chapter 2. Design and Synthesis of Binaphthyl-Based Nucleophilic Catalyst

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2-1. Abstract

We developed the binaphthyl based DMAP catalysts. The four types of 3,3´-disubstituted catalyst synthesized through 10 steps from (*S*)-BINOL. The key intermediate **1a** was obtained 41% overall yield through 9 steps from (*S*)-BINOL and converted to dicarboxylic acid **1b**, diamide **1c**, di-*tert*-alcohol type catalyst **1d** in good yields.

2-2. Introduction

N,N-4-dimethylaminopyridine (DMAP) is one of the common nucleophilic catalysts and efficiently promote the acylation reaction of alcohol in organic synthesis.[1] The mechanism of this reaction is generally explained as shown in Figure 1.[2,3] Reaction mechanism involves; Step 1: DMAP reacted with an acylating reagent to form a stable ion pair. Step 2: The reaction substrate (alcohol) reacts with the ion pair and the product (acylate) is delivered by the assistance of deprotonation by the counteranion ($^{-}$OAc). Step 3: The conjugate acid of DMAP is neutralized with base and DMAP regenerates. If the optically active DMAP is used in this reaction, in principle, the reaction becomes a kinetic resolution reaction of alcohol, and the unreacted reaction substrate can be recovered as optically active alcohol.[4] After reporting with optically active DMAP by Vedejs et al.[5] and Fu et al.[6] in 1996, many researchers reported enantioselective acylation with optically active DMAP and 4-pyrrolidinopyridine (PPY) derivatives.[7] However, in order to synthesize optically active DMAP and PPY derivatives, it is generally necessary to introduce an chiral environment into the DMAP or PPY skeletons. The synthesic process required longer and complicated operations such as optical resolution to obtain an optically active catalyst. In another problem, the introduction of an chiral environment into the pyridine ring of the nucleophilic catalyst destablizes the formation of the *N*-acylpyridinium salt **i** and/or the transition state **ii** shown in Figure 1 and then resulted in low catalytic activity. In particular, it is known that nucleophilicity (reactivity) of catalyst is impaired when a bulky substituent is introduced near the nitrogen of the pyridine ring (the nucleophilic site).[8] For this reason, in design of optically active DMAP or PPY analogues, a chiral environment should be arranged in a apropriate position in order to minimize the decrease in catalytic activity. Therfore, conflicting design are required to develop the catalyst with high enantioselectivity and high catalytic activity.

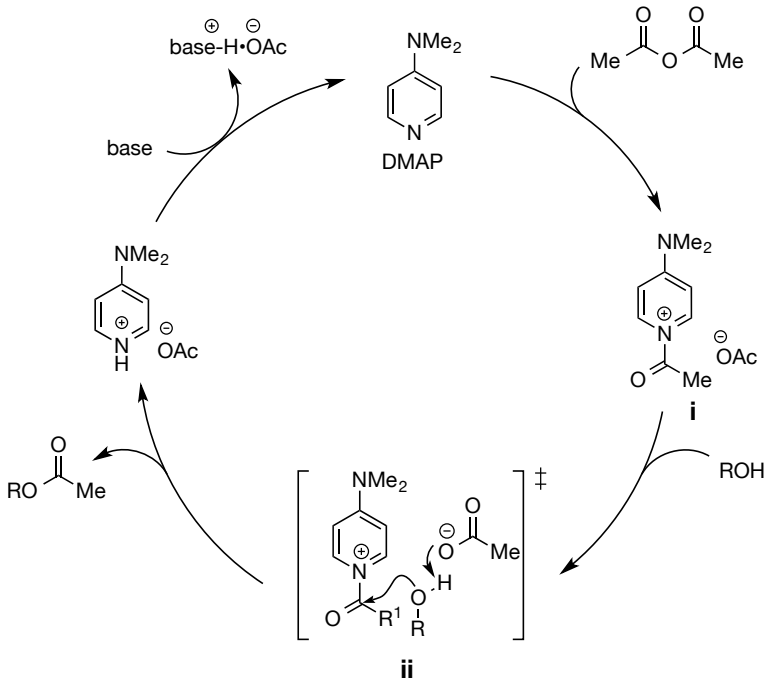
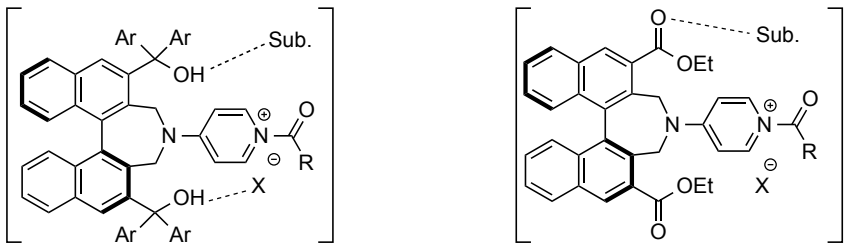


Figure 1. Mechanism of acylation reaction using DMAP.

2-3. Concept of Catalyst Design

Based on the background described preceding section, we design the binaphthyl based DMAP derivatives utilizing electrostatic interactions. For examples, *tert*-alcohol units may act as hydrogen bonding donor and ester units may act as hydrogen bonding donor (Figure 2). We expect the following advantages; (i) Both enantiomers of the starting material, optically active 1,1'-bi-2-naphthols (BINOL), are commercially available and the catalyst synthesis do not involve optical resolution. (ii) The large amount of catalyst can be synthesized and various derivatives can be accessed because there are many options for introducing substituent at 3,3′-position of binaphthyl group. (iii) Since there is no chiral environment in the vicinity of the reaction point of the catalyst (nitrogen of the pyridine ring), the deactivation of nucleophilicity may be avoided. (iv) Electrostatic interaction may stabilize the transition states and achieve the rate enhancement and high enantioselectivity.



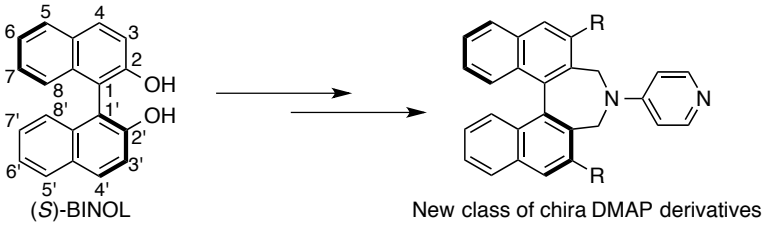
tert-Alcohol unit act as hydrogen bonding donor

Ester unit act as hydrogen bonding accepter

Figure 2. Concept of catalyst

In order to synthesize an array of catalyst that enable electrostatic interaction, we considered that the 1,1′-binaphthyl skeleton would be an ideal because there are many modification methods on its 3,3′-positions (Scheme 1).

Scheme 1. New class of chiral DMAP derivatives having axial chirality.



2-4. Synthesis of Catalyst

We selected the ester form **1a** as key intermediate and set synthetic route to amine **8** according to the reported methods by Maruoka et al.[9] and Liu et al.[10] (Scheme 2). Direct esterification through ortho-lithiation of MOM-protected (*S*)-BINOL **2** with *n*-BuLi and deprotection of MOM groups under acidic conditions gave the 3,3′-diester **3** in 98% yield over two steps in one pot manner without chromatographic purification (29.5 g, 79 mmol scale). Triflation of two hydroxy groups of **3** also proceeded in good yield without chromatographic purification (34 mmol scale). In the reported paper,[10] methylation of **4** was conducted by Negishi cross coupling reaction using dimethylzinc which is costly and pyrophoric reagent. Such reagent cannot be applied to s large-scale synthesis (>10 g) for cost and safety problems. Thus, we attempted the screening the various methylation methods (with trimethylboroxine, MeZnBr, $AlMe_3$). As the results of exploring the cross coupling, Migita-Kosugi-Stille cross coupling was only proceeded in low conversion including mono-methylated byproduct (Table 1, entries 1–8). Results of the screening and optimized the reaction conditions, reaction using a Pd nanoparticle catalyst generated *in situ* (use the tetra *n*-butyl ammonium chloride without ligand) only proceeded in full conversion (entry 10). We prefer Migita–Kosugi–Stille coupling reaction using a Pd nanoparticle than Negishi coupling reaction in large-scale reaction (**4**→**5**; 22.2 g; 32.0 mmol scale; Scheme 2). Next, the dibromination of **5** using *N*-bromosuccinimide in the presence of 2,2′-azodiisobutyronitrile gave the desired dibromide **6** in 97% yield. Allylamine was used to form the desired seven-membered ring amine **7** from dibromide **6**. After deprotection of allyl group using Pd catalyst, amine **8** was obtained in 95% yield. Buchwald-Hartwig cross coupling of amine **8** and 4-bromopyridine hydrochloride gave key intermediate **1a** in 70% yield. All transformations can be easily carried out in large scale (>10 g scale for **1a** from BINOL throughout the whole process), and overall yield of **1a** from (*S*)-BINOL was 41% (9 steps, >90% average yield for each step) with only 4 times of silica gel column chromatography purifications.

Scheme 2. Synthesis of key intermediate **1a**

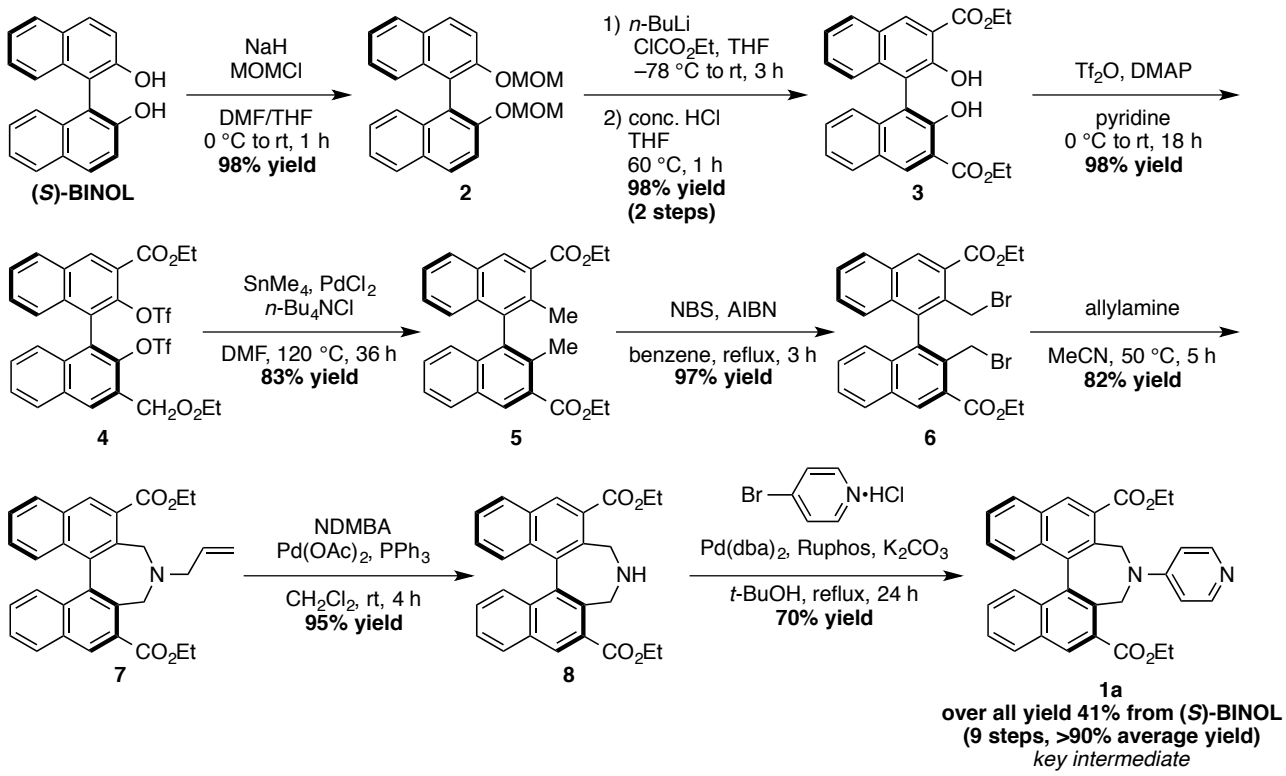
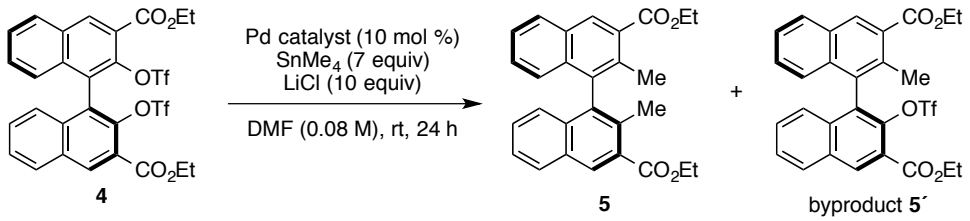


Table 1. Screening of Migita-Kosugi-Stille cross coupling



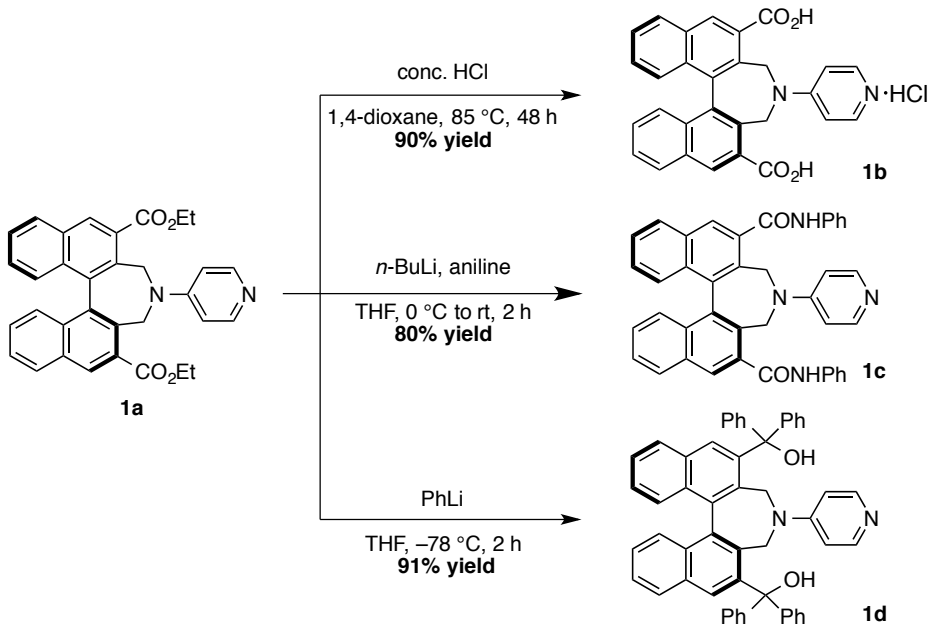
entry	catalyst	additive or ligand	**5** : **5´**[a]	conv (%)[a]
1	$Pd(PPh_3)_2Cl_2$	none	37:63	23
2	$Pd(dppf)Cl_2$	none	20:80	74
3	$Pd(dba)_2$	none	1:>99	96
4	$Pd[P(t\text{-}Bu)_3]_2$	none	>99:1	54
5	$Pd[P(t\text{-}Bu)_3]_2$	none	83:17	60
6	$PdCl_2$	PPh_3 (20 mol %)	82:18	63
8	$PdCl_2$	none	88:12	70
9	$PdCl_2$	$n\text{-}Bu_4NCl$	>99:1	>98
10[b]	$PdCl_2$	$n\text{-}Bu_4NCl$	>99:1	>98 (88)[c]

[a]Detemined by ^1H NMR. [b]3 equiv of Me_4Sn was used. [c]Yield of isolated material.

The key intermediate **1a** was easily converted to dicarboxylic acid type **1b**, diamide type **1c**, and di-*tert*-alcohol type catalyst **1d** in good yields (Scheme 3, 80–91% yield). We planned to conduct several enantioselective reactions based on these types of catalysts. The X-ray single crystal structure analyses of **1a** and **1d** were carried out (Figure 3). We expected that enantioselective

reactions might be possible because phenyl groups of catalyst **1d** were located at favorable position to construct appropriate chiral environments.

Scheme 3. Substituent conversion of catalyst



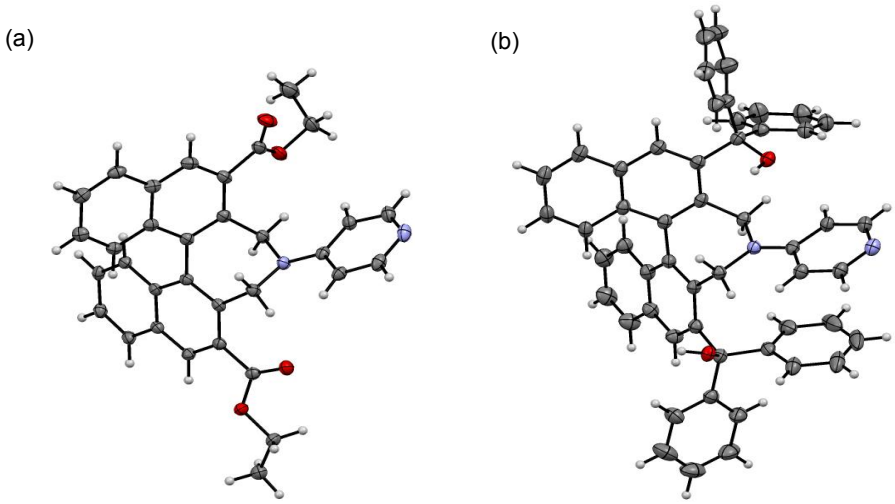


Figure 3. (a) X-ray crystal structural analysis of **1a**. (b) X-ray crystal structural analysis of **1d.**

2-5. Conclusion

We developed the new type of binaphthyl based DMAP derivatives as nucleophilic catalyst. The catalyst synthesized form (*S*)-BINOL in 10 steps via key intermediate **1a**. The key intermediate **1a** was obtained 41% overall yield from (*S*)-BINOL and converted to dicarboxylic acid **1b**, diamide **1c**, di-*tert*-alcohol type catalyst **1d** in good yields.

2-6. Experimental Section

General

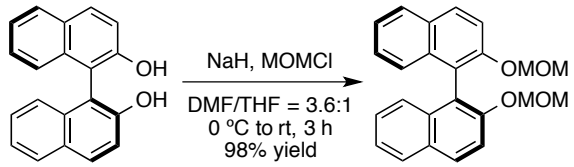
Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian 600 MR (^{1}H 600 MHz, ^{13}C 150 MHz), Varian 400 MR (^{1}H 400 MHz, ^{13}C 100 Mz) and JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 Mz) spectrometer. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin =quintet, sext = sextet, sep = septet, b = broad, m = multiplet), coupling constants, and integration. Chemical shifts for ^{13}C NMR were reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) with complete proton decoupling. Infrared (IR) spectra were recorded on JASCO FT/IR-4100 spectrophotometer and Varian 7000e FT-IR spectrometer, Vmax in cm^{-1}. High-resolution mass spectrometry was performed on a JEOL JMS-700 MStation (FAB-MS and EI-MS), Agilent 6520 Accurate Mass Q **-** TOF LC/MS (ESI-MS) and Thermo Fisher Scientific EXACTIVE Plus (ESI-MS). Optical rotations were measured on a JASCO DIP-1000. Melting point was recorded on a SANSYO SMP-300. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC) Shimadzu chromatograph (DAICEL CHIRALPAK® AS-3 (4.6 × 150 mm), DAICEL CHIRALPAK® AD-H (4.6 × 250 mm) in comparison with authentic racemic materials. Column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm) purchased from Kanto Chemical. All experiments were carried out under argon atmosphere unless otherwise noted.

Materials

All reagents were obtained commercial sources and used as received unless otherwise noted. acetonitrile [MeCN], and dichloromethane [CH_2Cl_2] were distilled over calcium hydride [CaH_2]. Dry tetrahydrofuran [THF], and dry diethyl ether [Et_2O], *N*-bromosuccinic imide [NBS], palladium chloride [PdCl], 4-bromopyridine hydrochloride, bis(dibenzylideneacetone)palladium (0) [$Pd(dba)_2$], , and palladium acetate [PdOAc] were purchased from Wako Pure Chemical Industries, Ltd. Dry dimethylformamide [DMF], pyridine, *N,N′*-Dimethylbarbituric acid [NDMBA], 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl [RuPhos], and tert-butyl alcohol [*t*-BuOH] were purchased from Sigma-ALDRICH Japan and used without further purification.

(*S*)-(-)-1,1′-Bi-2-naphthol [(*S*)-BINOL] (>99% ee), allyl amine, *n*-butyl lithium [*n*-BuLi], *N,N*-dimethyl-4-aminopyridine [DMAP] were purchased from KANTO CHEMICAL CO.,INC. Sodium hydride [NaH], triphenyl phosphine [PPh_3], trifluoromethane sulfonic anhydride [Tf_2O], aniline, phenyl lithium [PhLi], methoxymethyl chloride [MOMCl], ethyl chloroformate [$EtCO_2Cl$], and tetramethyltin [$SnMe_4$] were purchased from Tokyo Chemical Industry Co., Ltd. Potassium carbonate [K_2CO_3], 2,2'-azobis(isobutyronitrile) [AIBN], benzene, and 1,4-dioxane was purchased from NAKARAI TESQUE, INC.

Synthesis of 2[11]

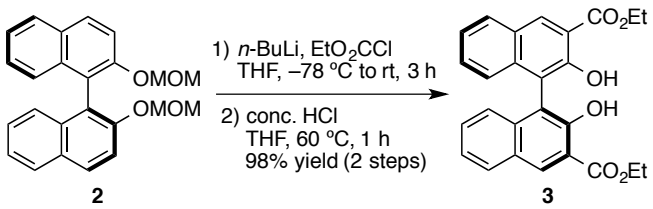


We modified solvent, substrate concentration, and purification method of known procedure.[11]

To a suspension of NaH (60% dispersion in paraffin liquid, 15.4 g, 385 mmol) in DMF (77.0 mL) was added dropwise solution of (*S*)-BINOL (50.0 g, 175 mmol) in THF (40.0 mL) and DMF (65.5 mL) for 10 min at 0 ºC. The resulting solution was warmed up to room temperature and stirred for 5 min at room temperature, then chloromethyl methyl ether [MOMCl] (29.2 mL, 384 mmol) was added dropwise for 40 min at room temperature. The reaction mixture was stirred for 3 h. After stirring for 3 h, the reaction mixture was poured into cold water (200 mL). The resulting solution was extracted with EtOAc (300 mL × 3), washed with brine (300 mL), dried over Mg_2SO_4 and concentrated *in vacuo*. The purification of the crude product by recrystallization from toluene/hexane gave **2** (64.5 g, 172 mmol, 98% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.35 (ddd, J = 8.3, 6.8, 1.3 Hz), 7.23 (ddd, J = 8.3, 6.8, 1.4 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 5.10 (d, J = 6.8 Hz, 2H), 4.99 (d, J = 6.8 Hz, 2H), 3.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 134.1, 130.0, 129.5, 128.0, 126.4, 125.7, 124.2, 121.4, 117.4, 95.3, 56.0; IR (KBr) 2952, 1622, 1593, 1507, 1478, 1241, 1089, 1041 cm^{-1}.

Synthesis of 3[10]

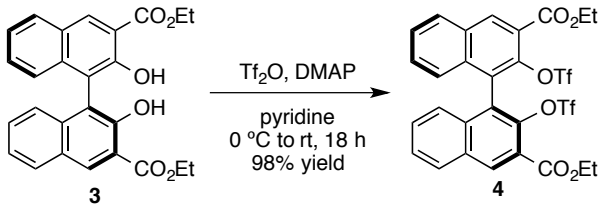


We modified substrate concentration and purification method of known procedure.[10]

To a solution of **2** (29.5 g, 78.8 mmol) in THF (200 mL) was added dropwise solution of *n*-BuLi (1.58 M, 125 mL, 197 mmol) in hexane for 10 min at –78 ºC. The reaction solution was warmed up to room temperature and stirred for 1 h. After stirring for 1 h, the reaction suspension was re-cooled to –78 ºC and Et_2CO_2Cl was carefully added dropwise for 20 min at –78 ºC. The reaction mixture was warmed up room temperature and stirred for 2 h, then water was carefully added to quench the reaction. After removal water using syringe from the mixture, 6 M aqueous HCl (200 mL, 1.20 mol) was added to resulting solution. The reaction solution was heated to 60 ºC and sirred for 1 h. Afetr being cooled to room temperature, the resulting solid was collected by filtration and washed with copious hexane. After drying of the solid, **3** (33.1 g, 76.9 mmol, 98% yield based on **2**) was isolated as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 2H), 8.69 (s, 2H), 7.94–7.92 (m, 2H), 7.36–7.32 (m, 4H), 7.16–7.14 (m, 2H), 4.49–4.55 (m, 4H), 1.56 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 154.2, 137.3, 132.9, 129.9, 129.5, 127.3, 124.8, 124.0, 117.1, 114.5, 62.0, 14.4; IR (KBr) 2921, 1840, 1665, 1580, 1072, 846, 680 cm^{-1}; $[\alpha]^{21}_D$ –112.9 (*c* 1.04, CH_2Cl_2, (*S*)-configuration) [lit.[10] $[\alpha]^{27}_D$ +168.5 (*c* 1.0, CH_2Cl_2, (*R*)-configuration)].

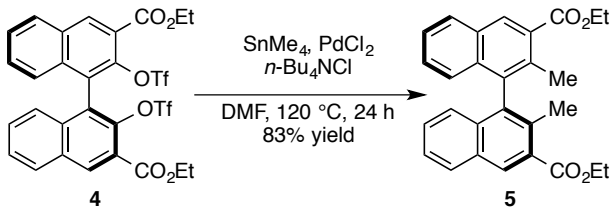
Synthesis of 4[10]



To a solution of **3** (14.6 g, 33.9 mmol) and DMAP (828 mg, 6.78 mmol) in pyridine (188 mL) was added dropwise trifluoromethanesulfonic anhydride [Tf_2O] (17.3 mL, 103 mmol) for 10 min at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 18 h at room temperature. The resulting solution was poured carefully into cold water and extracted with Et_2O

(200 mL × 3), washed with 6 M aqueous HCl (200 mL × 3), dried over $MgSO_4$, and concentration *in vacuo*. Subsequently, the resulting solid was subsequently thoroughly washed with MeOH. After filtration and drying of the solid, **4** (23.0 g, 33.1 mmol, 98% yield) was isolated as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 2H), 8.08 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 7.5 Hz, 2H), 7.45 (t, J = 7.7 Hz 2H), 7.19 (d, J = 8.6 Hz, 2H), 4.62–4.54 (m, 2H), 4.47–4.39 (m, 2H), 1.46 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 142.7, 135.8, 134.9, 131.5, 129.8, 129.6, 128.3, 127.7, 125.0, 124.1, 118.0 (q, $J_{C\text{-}F}$ = 1275.5), 62.6, 14.2; IR (KBr) 2900, 2359, 1987, 1836, 1750, 1587, 1498, 693 cm^{-1}; $[\alpha]^{21}_D$ +116.2 (*c* 1.03, CH_2Cl_2, (*S*)-configuration) [lit.[10] $[\alpha]^{27}_D$ –159.2 (*c* 1.0, CH_2Cl_2, (*R*)-configuration)].

Synthesis of 5[10]



Initially, Negishi cross coupling (with Me_2Zn) was conducted in according literature[10], but we modified this procedure to Migita-Kosugi-Stille cross coupling (with Me_4Sn) because Me_2Zn is costly and pyrophoric reagent, and unsuitable for scale up.

Small-scale reaction (2.00 mmol scale)

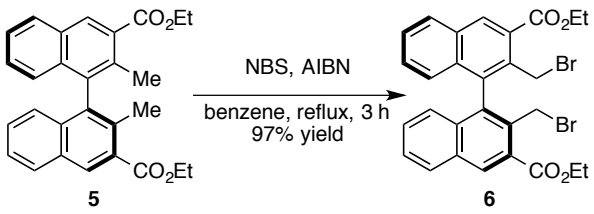
To a solution of **4**[10] (139 mg, 0.200 mmol), LiCl (86.5 mg, 2.04 mmol), *n*-Bu_4NCl (223 mg, 0.803 mmol) and Me_4Sn (83.0 μL, 0.600 mmol) in DMF (2.70 mL) was added $PdCl_2$ (3.70 mg, 20.9 μmol) at room temperature. The reaction mixture was heated at 120 ºC and stirred for 24 h, then the reaction mixture was under reduced pressure to removed excess Me_4Sn, and the resulting suspension was filtered through a short pad of silica gel with copious washing Et_2O. The resulting solution was extracted with Et_2O (10 mL × 3). The organic layer was washed with water (5 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 8/1, v/v) gave **20** (75.1 mg, 0.176 mmol, 88% yield) as a pale yellow solid.

Large-scale reaction (32.0 mmol scale)

To a solution of **4**[10] (22.2 g, 32.0 mmol), LiCl (6.85 g, 162 mmol), *n*-Bu_4NCl (25.3 g, 91.0 mmol) and Me_4Sn (9.00 mL, 65.0 mmol) in DMF (175 mL) was added $PdCl_2$ (397 mg, 2.24 mol) at room temperature. The reaction mixture was heated at 120 ºC and stirred for 20 h, then the reaction mixture was under reduced pressure to removed excess Me_4Sn, and the resulting suspension was filtered through a short pad of silica gel with copious washing Et_2O. The resulting solution was extracted with Et_2O (150 mL × 3). The organic layer was washed with water (150 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 5/1, v/v) gave **5** (11.3 g, 26.5 mmol, 83% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.29 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.47 (q, *J* = 7.2 Hz, 4H), 2.22 (s, 6H), 1.48 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 136.9, 134.2, 133.9, 131.2, 129.9, 129.1, 128.5, 126.0, 125.9, 61.3, 18.1, 14.4; IR (KBr) 2927, 1926, 1726, 1622, 1202, 1062, 905, 788 cm^{-1}; $[\alpha]^{23}_D$ −23.4 (*c* 0.76, CH_2Cl_2, (*S*)-configuration) [lit.[10] $[\alpha]^{27}_D$ +74.2 (*c* 0.76, CH_2Cl_2, (*R*)-configuration)].

Synthesis of 6[10]



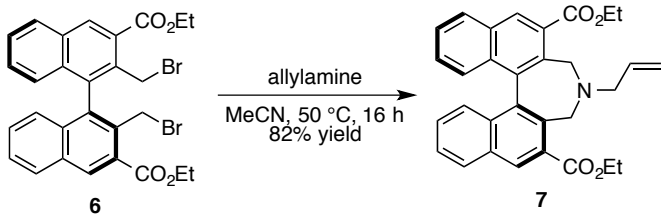
5 **6**

To a suspension of **5**[10] (11.3 g, 26.5 mmol), NBS (10.4 g, 58.4 mmol) in benzene (73.0 mL) was added AIBN (442 mg, 2.69 mmol) at room temperature. The reaction mixture was heated to refluxed temperature and stirred for 2 h, and then additional AIBN (218 mg, 1.22 mmol) was added to the reaction mixture at room temperature. After addition was completed, the reaction mixture was stirred for 1 h at refluxed temperature. After being cooled to room temperature, the reaction mixture was poured into water (100 mL) and extracted with Et_2O (100 mL × 3). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was passed through a short pad of silica gel (eluent: hexane/Et_2O = 3/1, v/v) to give a pale yellow solid (15.1 g, 25.8 mmol, 97% yield). This crude product was directly used for the following reaction without further purification. The analytical data of **6** was obtained by the purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 5/1 to 3/1, v/v)

as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 2H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.56 (ddd, *J* = 8.5, 7.2, 1.0 Hz, 2H), 7.36 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 4.80 (d, *J* = 9.8 Hz, 2H), 4.66 (d, *J* = 9.8 Hz, 2H), 4.52 (q, *J* = 7.2 Hz, 4H), 1.51 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 135.8, 133.5, 133.4, 133.2, 132.1, 129.0, 128.9, 128.4, 127.7, 127.1, 61.7, 30.0, 14.2; IR (KBr) 2980, 1716, 1425, 1242, 1057, 800, 752 cm^{-1}; $[\alpha]^{23}_D$ − 48.9 (*c* 0.64, CH_2Cl_2, (*S*)-configuration) [lit.[10] $[\alpha]^{24}_D$ +96.7 (*c* 0.64, CH_2Cl_2, (*R*)-configuration)].

Synthesis of 7[10]

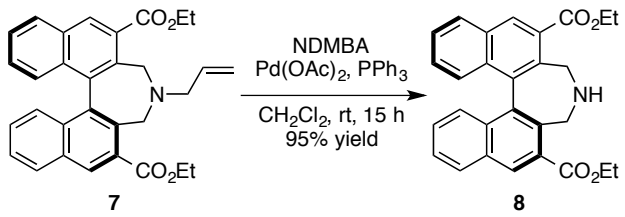


6 **7**

To a solution of **6**[10] (23.4 g, 40.0 mmol) in MeCN (400 mL) was added allylamine (8.90 mL, 119 mmol) at 0 ºC. The reaction mixture was heated to 50 ºC and stirred for 16 h, then poured into water (300 mL). The resulting solution was extracted with CH_2Cl_2 (100 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 9/2, v/v) gave **7** (15.7 g, 32.7 mmol, 82% yield) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.05-5.90 (m, 1H) 5.18-5.08 (m, 2H), 4.80 (d, *J* = 12.9 Hz, 2H), 4.53 (q, *J* = 7.1 Hz, 4H), 3.30 (dd, *J* = 13.1, 5.6 Hz, 1H), 3.01-2.89 (m, 3H), 1.49 (td, *J* = 7.1, 2.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 136.9, 136.5, 132.7, 132.0, 131.7, 129.3, 128.8, 128.0, 127.2, 126.3, 117.1, 61.4, 58.9, 49.8, 14.4; IR (KBr) 2979, 2790, 1721, 1443, 1241, 1204, 1056, 754 cm^{-1}; $[\alpha]^{22}_D$ +202.6 (*c* 1.00, CH_2Cl_2, (*S*)-configuration) (lit.[10] $[\alpha]^{27}_D$ −431.5 [*c* 1.0, CH_2Cl_2, (*R*)-configuration]).

Synthesis of 8

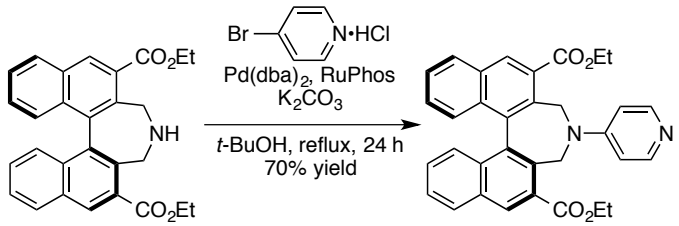


7 8

To a solution of **7**[10] (15.7 g, 32.7 mmol), NDMBA (10.3 g, 66.0 mmol) and Ph_3P (1.84 g, 7.02 mmol) in CH_2Cl_2 (110 mL) was added $Pd(OAc)_2$ (377 mg, 1.68 μmol) at room temperature. The reaction mixture was stirred for 15 h at room temperature, then water (100 mL) was added. The resulting solution was extracted with CH_2Cl_2 (100 mL × 3). The organic layer was washed saturated aqueous $NaHCO_3$ (100 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc to EtOAc/MeOH = 30/1, v/v) gave **8** (13.7 g, 31.2 mmol, 95% yield) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) d 8.58 (s, 2H), 8.01 (d, J = 8.0 Hz, 2H), 7.49 (dt, J = 8.0, 1.2 Hz, 2H), 7.31 (dt, J = 8.0, 1.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.78 (d, J = 12.5 Hz, 2H), 4.48 (qd, J = 7.1, 3.1 Hz, 4H), 3.22 (d, J = 12.5 Hz, 2H), 2.41 (bs, 1H), 1.48 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 136.7, 133.6, 132.7, 132.2, 131.7, 129.4, 128.5, 128.0, 127.3, 126.3, 61.5, 44.0, 14.5; IR (KBr) 2984, 1722, 1242, 1137, 1053, 909, 773, cm^{-1}; HRMS (FAB^+) calculated for $C_{28}H_{26}NO_4$ $[M+H]^+$ 440.1856, found 440.1857; $[\alpha]^{20}_D$ +433.4 (*c* 0.53, CH_2Cl_2, (*S*)-configuration).

Synthesis of 1a



8 1a

Small scale reaction (0.200 mmol scale)

To a suspension of **8** (87.9 mg, 0.200 mmol), 4-bromopyridine hydrochloride (77.7 mg, 0.400 mmol), RuPhos (7.70 mg, 16.5 mmol) and potassium carbonate (167 mg, 1.21 mmol) in *t*-BuOH (2.00 mL) was added $Pd(dba)_2$ (4.70 mg, 8.17 μmol) at room temperature. The reaction mixture was heated to refluxed temperature and vigorously stirred for 24 h, and then water (3 mL) was added

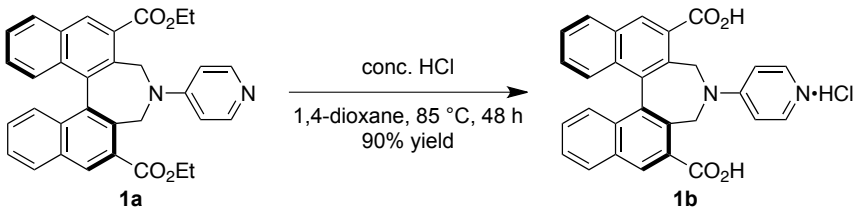
and filtered off. After filtrate was concentrated *in vacuo*, the resulting solution was extracted with CH_2Cl_2 (5 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc + 3% Et_3N) gave **1e** (80.0 mg, 0.155 mmol, 78% yield) as a pale yellow solid.

Large-scale reaction (31.2 mmol scale)

To a suspension of **8** (13.7 g, 31.2 mmol), 4-bromopyridine hydrochloride (12.2 g, 62.7 mmol), RuPhos (1.10 g, 2.36 mmol) and potassium carbonate (26.0 g, 188 mmol) in *t*-BuOH (313 mL) was added $Pd(dba)_2$ (721 mg, 1.25 mmol) at room temperature. The reaction mixture was heated to refluxed temperature and vigorously stirred for 24 h, and then water (100 mL) was added and filtered off. After filtrate was concentrated *in vacuo*, the resulting solution was extracted with CH_2Cl_2 (100 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc + 3% Et_3N) gave **1e** (11.2 g, 21.7 mmol, 70% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 2H), 8.22 (d, J = 5.7 Hz, 2H), 8.04 (d, J = 7.9 Hz, 2H), 7.55 (t, J = 7.9 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 6.78 (d, J = 5.7 Hz, 2H), 5.95 (d, J = 13.1 Hz, 2H), 4.46-4.32 (m, 4H), 3.53 (d, J = 13.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 153.5, 150.1, 137.0, 132.8, 132.7, 132.0, 131.2, 129.6, 128.6, 128.1, 127.4, 127.0, 109.1, 61.9, 44.3, 14.4; IR (KBr) 2963, 2501, 2352, 1972, 1726, 986, 754, 588 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{33}H_{29}N_2O_4$ $[M+H]^+$ 517.2121, found 517.2099; mp 195.5–196.6 ºC; $[\alpha]^{19}_D$ –388.9 (*c* 0.53, CH_2Cl_2, (*S*)-configuration).

Synthesis of 1b

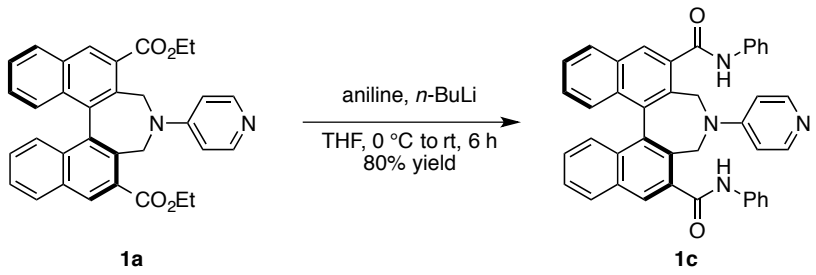


1a **1b**

To a solution of **1a** (25.8 mg, 0.0499 mmol) in 1,4-dioxane (0.125 mL) was added 12 M aqueous HCl (83 μL) at room temperature. The reaction mixture was heated to 85 °C and stirred for 48 h. The resulting solution was concentrated in *vacuo*. The resulting solid was subsequently thoroughly washed with Et_2O. After filtration and drying of the solid, **1b** (22.4 mg, 0.0451 μmol, 90% yield) was isolated as a pale yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (s, 2H), 8.14 (d, *J* = 8 Hz, 2H), 8.10 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8 Hz, 2H), 6.27 (d, *J* = 13.4 Hz, 2H), 3.53 (d, *J* = 13.4, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.3, 157.2, 140.0, 137.8, 134.6, 133.4, 130.8. 130.7, 129.7, 128.9, 128.4, 128.1, 110.0, 45.5; IR (KBr) 3509, 1961, 1705, 1645, 1533, 1246, 995, 922, 768 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{29}H_{21}N_2O_4$ $[M–Cl]^+$ 461.1501, found 461.1506; mp >280 ºC; $[\alpha]^{21}_D$ –346 (*c* 0.28, MeOH).

Synthesis of 1c

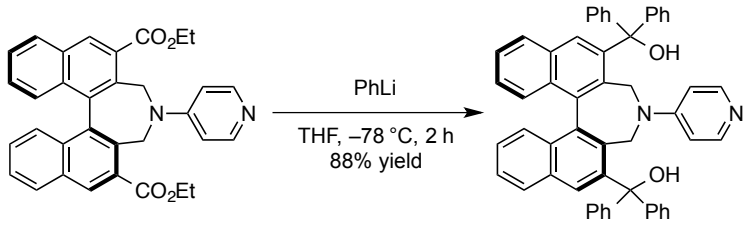


1a **1c**

To a solution of aniline (7.30 μL, 80.1 μmol) in THF (0.145 mL) was added a solution of *n*-BuLi in hexane (1.62 M, 99.0 μL, 160 μmol) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 1 h. After re-cooling to 0 °C, solution of **1a** (8.30 mg, 16.1 μmol) in THF (0.290 mL) was added dropwise to reaction mixture. The reaction mixture was warmed up to room temperature and stirred for 6 h. Then, the reaction mixture was poured into water (1 mL) and extracted with EtOAc (3 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc) gave **1c** (7.80 mg, 12.8 μmol, 80% yield) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (bs, 2H), 8.23 (s, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.59–7.21 (m, 14H), 7.11 (t, *J* = 7.2 Hz, 2H), 6.45 (d, *J* = 5.6 Hz, 2H), 5.28 (d, *J* = 13.2 Hz, 2H), 3.53 (d, *J* = 13.2 Hz, 2H), 2.44 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 153.4, 149.1, 137.9, 136.9, 134.4, 132.2, 131.8, 129.7, 129.2, 129.1, 129.0, 128.1, 127.5, 127.3, 125.0, 120.3, 109.4, 77.4, 45.9; IR (KBr) 3055, 2924, 1645, 1597, 1533, 1437, 1319, 1250, 901, 752 cm^{-1}; HRMS (EI$^+$) calculated for $C_{41}H_{30}N_4O_2$ $[M]^+$ 610.2363, found 610.2390; mp >280 ºC; $[\alpha]^{25}_D$ –208.0 (*c* 0.29, $CHCl_3$, (*S*)-configuration).

Synthesis of 1d



1a **1d**

To a solution of **1a** (103 mg, 0.200 mmol) in THF (2.00 mL) was added a solution of PhLi in *n*-Bu_2O (1.6 M, 750 μL, 1.20 mmol) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. Then, water (30 mL) was added to reaction mixture and extracted with $CHCl_3$ (10 mL × 3). The organic layer was washed with brine (10 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by recrystallization from $CHCl_3/Et_2O$ gave **1d** (130 mg, 0.176 mmol, 88% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 6.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.49–7.17 (m, 18H), 7.15-6.95 (m, 10H), 5.91 (d, J = 6.0 Hz, 2H), 5.23 (d, J = 13.2 Hz, 2H), 3.40 (d, J = 13.2 Hz, 2H), 3.34 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.9, 147.9, 147.6, 145.6, 142.5, 138.3, 132.3, 131.6, 131.2, 130.7, 128.8, 128.3, 127.9, 127.8, 127.5, 127.4, 127.2, 126.6, 126.2, 108.7, 83.2, 45.6; IR (KBr) 3057, 1597, 1447, 1396, 1242, 997, 748, 696 cm^{-1}; HRMS (ESI^+) calculated for $C_{53}H_{41}N_2O_2$ $[M+H]^+$ 737.3163, found 737.3130; mp >280 ºC; $[\alpha]^{19}_D$–260.5 (*c* 0.27, $CHCl_3$, (*S*)-configuration).

X-ray Crystallography of 1a and 1d

Details of the crystal data and a summary of the intensity data collection parameters for **1a** and **1d** are listed in Tables S1 and S4. Graphite-monochromated Mo Kα radiation (λ = 0.71075 Å) was used. The structures were solved by direct methods with SHELXS-97[12] or SIR2004.[13] and refined by full-matrix least-squares techniques against F (SHELXL-97). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. In the subsequent refinement, the function $\Sigma w(F_o^2 - F_c^2)^2$ was minimized, where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes, respectively. The agreement indices are defined as $R1 = \Sigma(||F_o|-|F_c||)/\Sigma|F_o|$ and $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_o^4)]^{1/2}$. All calculations were performed by using Yadokari-XG 2009[14] and illustrations were drawn by using ORTEP-3.

Table S1. Crystal data of **1a** and structure refinement for ydkr

Empirical formula	C33 H28 N2 O4	
Formula weight	516.57	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	orthorhombic	
Space group	$P2_12_12_1$ (#19)	
Unit cell dimensions	a = 7.537(3) Å	α= 90°.
	b = 14.252(5) Å	β= 90°.
	c = 23.552(9) Å	γ = 90°.
Volume	2529.9(16) $Å^3$	
Z	4	
Density (calculated)	1.356 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	1088	
Crystal size	0.10 x 0.09 x 0.05 mm^3	
Theta range for data collection	3.06 to 27.53°.	
Index ranges	-9<=h<=9, -18<=k<=18, -30<=l<=30	
Reflections collected	40951	
Independent reflections	5792 [R(int) = 0.0632]	
Completeness to theta = 27.53°	99.5 %	
Max. and min. transmission	0.9955 and 0.9911	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5792 / 6 / 358	
Goodness-of-fit on F^2	1.118	
Final R indices [I>2sigma(I)]	R_1 = 0.0528, wR_2 = 0.1099	
R indices (all data)	R_1 = 0.0564, wR_2 = 0.1116	
Absolute structure parameter	-0.3(11)	
Largest diff. peak and hole	0.219 and -0.208 e.$Å^{-3}$	

Table S2. Crystal data of **1d** and structure refinement for ydkr

Empirical formula	C62 H61 N5 O5	
Formula weight	956.16	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	hexagonal	
Space group	P65	
Unit cell dimensions	a = 24.664(4) Å	α= 90°.
	b = 24.664(4) Å	β= 90°.
	c = 13.930(2) Å	γ = 120°.
Volume	7339(2) $Å^3$	
Z	6	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	3048	
Crystal size	0.22 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.08 to 27.51°.	
Index ranges	-32<=h<=32, -32<=k<=32, -18<=l<=18	
Reflections collected	119646	
Independent reflections	11158 [R(int) = 0.0723]	
Completeness to theta = 27.51°	99.3 %	
Max. and min. transmission	0.9836 and 0.9820	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11158 / 72 / 630	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0548, wR2 = 0.1378	
R indices (all data)	R1 = 0.0576, wR2 = 0.1404	
Absolute structure parameter	-0.6(10)	
Largest diff. peak and hole	0.335 and -0.338 $e.Å^{-3}$	

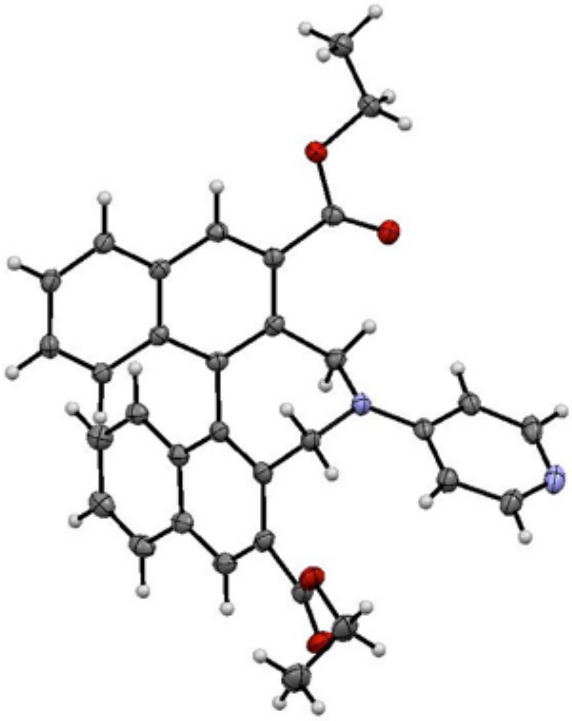


Figure S1. X-ray structure of catalyst **1a**

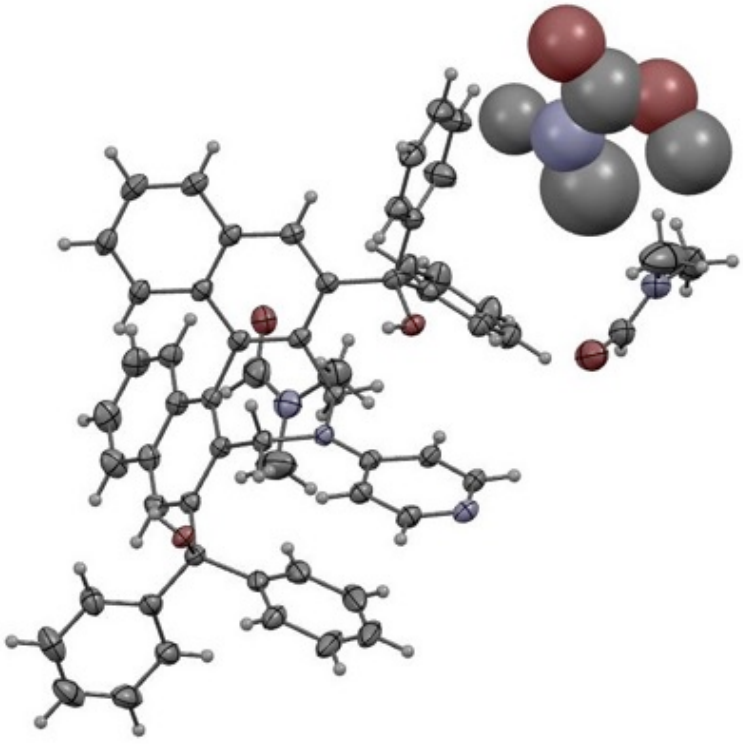


Figure S2. X-ray structure of catalyst **1d**

CCDC 1432805 (**1a**), 1432806 (**1a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Chapter 3. Enantioselective Steglich Rearrangement of Indolyl Carbonates with Binaphthyl-Based DMAP Derivatives

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3-1. Abstract

We achieved low-catalyst loading Steglich rearrangement of indolyl carbonate with binaphthyl-based active DMAP derivatives to give desired products having a all-carbon quaternary stereogenic center in all cases >98% yield with up to 99:1 er (13 examples). The reaction required only 0.5 mol % of catalyst and short reaction time (5 h). Several control experiments including kinetic studies and DFT calculation strongly supported that hydroxy groups of catalyst plays an important role in stabilization of transition state achieving high enantioselectivity.

3-2.Introduction

Oxindole alkaloids having an all-carbon quaternary stereogenic center on its 3-position are very important synthetic intermediates of pharmaceutical molecules and natural products. One option to make such compound is that the use of Steglich type rearrangement of corresponding oxindole derivative. This reaction was firstly reported by Steglich in 1969 as rearrangement of *O*-acylated compounds to *C*-acylated azlactone creating a new carbon-carbon bond at its α-position.[1] The enantioselective Steglich rearrangement of indolyl carbonates has been reported by Fu[2] and Vedjes.[3] However, these reactions required a long time to complete the reaction and showed poor substrate generality. On the other hand, our research group developed chiral nucleophilic catalysts derived from 1,1´-bi-2-naphthol (BINOL). To evaluate a catalytic activity and enantioselectivity of these catalysts, I selected Steglich type rearrangement (intramolecular reaction) as a model reaction. Here, I described the details of enantioselective Steglich rearrangement with our developed nucleophilic catalysts, and several key experiment to clarify the reaction mechanism.

3-3. Optimization of Reaction Conditions

Steglich rearrangement of indolyl carbonates **2a** was carried out with newly synthesized catalyst **1a**–**n** (5 mol %) under the reaction conditions at 0 °C in THF for 12 h (Figure 1). Reaction with **1k**, which have only DMAP core and binaphthyl skeleton, was efficient in conversion but obtained nearly racemic product (57:43 er). Methoxy substituted **1l** was almost same results as **1k** (54:46 er). Phenyl or naphtyl substituted **1m** and **1n** offered low reactivity due to more sterically hindered structure (**1m**: 37% conv, **1n**: 35% conv). The catalyst **1a** and **1c** showed moderate enantioselectivity but it was not satisfactory results (**1a**: 72:28 er, **1c**: 70:30 er). The surprising breakthrough came when we evaluated catalyst that contains tertiary alcohol units within their chiral binaphthyl moiety (**1d**). The use of catalyst **1d** led to the formation of the all-carbon quaternary stereogenic center not only with exceptional efficiency (>98% conv) but also high enantioselectivity (91:9 er). We tried to further optimize the catalyst structure of **1d**.

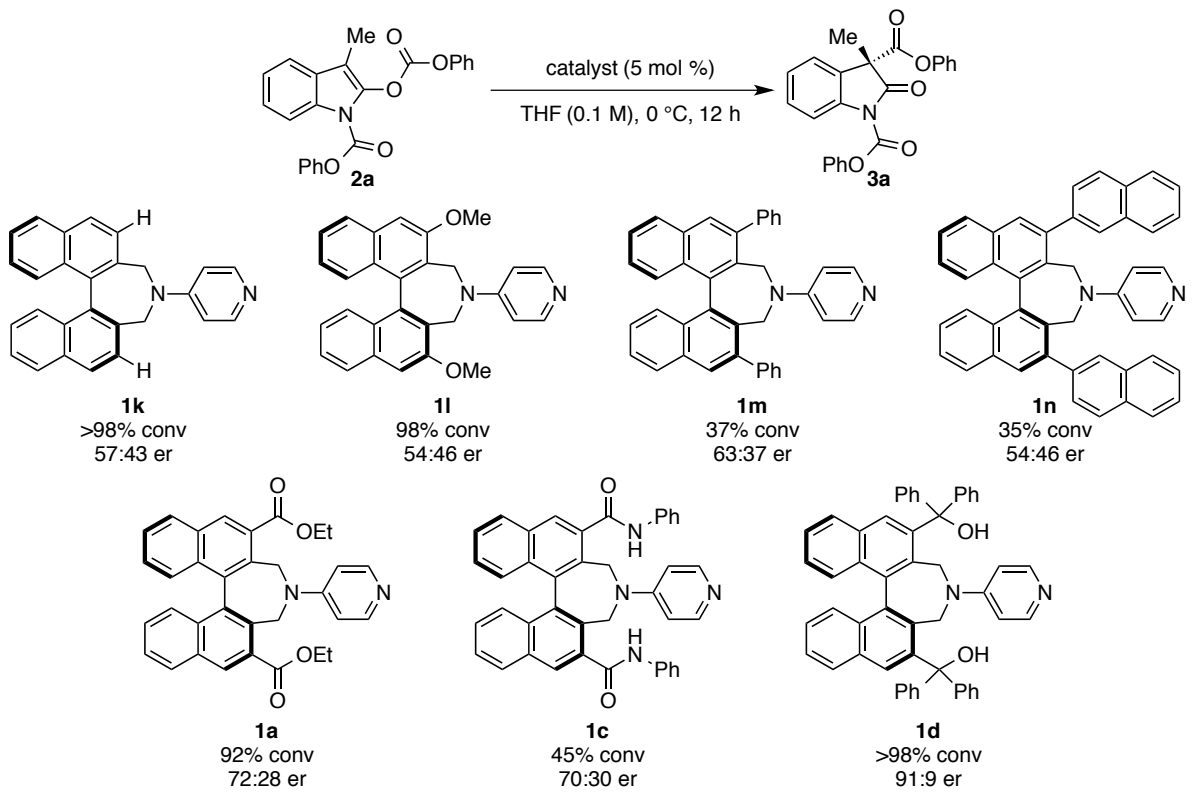


Figure 1. Catalyst screening of Steglich rearrangement

We synthesized additional seven analogues of **1d** and evaluated the enantioselectivity. Among them, catalyst **1g** having 4-*t*-BuC_6H_4 groups shows the highest enantioselectivity (98:2 er). On the other hand, catalyst **1i** and **1j**, which have 3,5-disubstituted aryl groups, offered very low enantioselectivities. We selected the catalyst **1g** as an optimal catalyst, and explored further optimization of reaction conditions with **1g**.

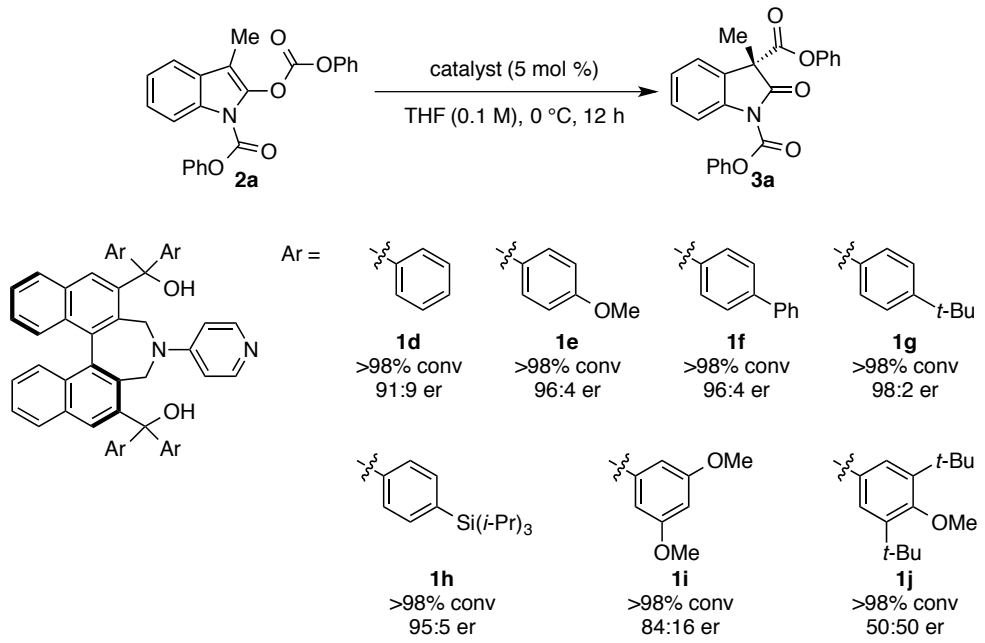
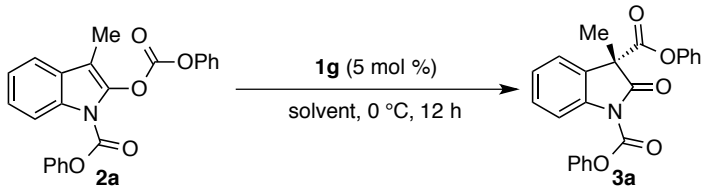


Figure 2. Structure tuning of *tert*-alcohol type catalysts

Firstly, we conducted the solvent screening (Table 1). Any solvent could be used in this reaction (entries 1–7), but the use of hexane gave low conversion with slightly decreased enantioselectivity (74% conv; 93:7 er; entry 8). When protic solvent was used in this reaction, enantioselectivity decreased than that of using aprotic solvent (88% conv; 64:36 er; entry 10). We considered that this observation caused by that the protic solvent inhibited the hydrogen bonding networks between catalyst and substrate forming in transition state. In consideration of solubility and wide range of operable reaction temperature, further optimizations of reaction conditions were carried out using THF as an optimal solvent.

Table 1. Solvent screening

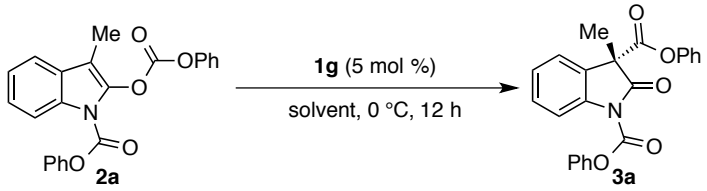


entry	solvent	conversion (%)[a]	er of **12a**[b]
1	THF	>98	98:2
2	Et_2O	>98	98:2
3	CPME	>98	97:3
4	acetone	>98	95:5
5	EtOAc	>98	98:2
6	CH_2Cl_2	>98	97:3
7	toluene	>98	98:2
8	hexane	74	93:7
9	*t*-amyl alcohol	88	64:36

[a]Determined by ^{1}H NMR analysis. [b]Determined by HPLC analysis.

Next, we also carried out the reaction at respective reaction temperature (Table 2). The reaction at above –40 °C proceeded smoothly (>98% conv; >96:4 er; entries 1–4), whereas below –60 °C decreased the reaction conversions with maintaining almost the same enantiomeric ratios (99:1 er, entries 5 and 6). Interestingly, synthetically useful enantioselectivity (96:4 er) was also maintained even if the reaction at 25 °C. The catalyst **1g** could be used and tolerated in various solvents and the reaction temperature to deliver the desired product **3a** with a high enantiomeric ratio. Judging from practicality and efficiency of the reaction, the reaction at –20 °C was determined to be optimal in the enantioselective Steglich rearrangement of indolyl carbonates.

Table 2. Solvent screening of reaction temperature

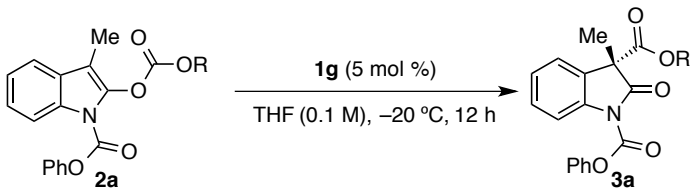


Entry	temp. (°C)	conv (%)[a]	er[b]
1	25	>98	96:4
2	0	>98	97:3
3	–20	>98	98:2
4	–40	>98	98:2
5	–60	97	99:1
6	–78	39	99:1

[a]Determined by ^{1}H NMR analysis. [b]Determined by HPLC analysis.

We carried out the reaction with different migrating group (Table 3). As a result, phenyl carbonate gave the best enantioselectivity (98:2 er, entry 1). Therefore, phenyl carbonate thought to be the optimal migrating group, and was used for further screening.

Table 3. The screening of the migrating and *N*-protected groups

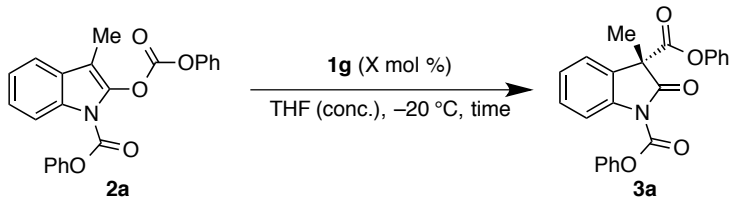


entry	product (R =)	conv (%)[b]	er[c]
1	**3a**: Ph	>98	98:2
2	**3n**: 4-MeO-C_6H_4	>98	98:2
3	**3o**: 4-F-C_6H_4	>98	96:4
4	**3p**: Bn	94	92:8
5	**3q**: Me	82	95:5
6	**3r**: *i*-Pr	<2	—

[a]Determined by ^{1}H NMR analysis. [b]Determined by HPLC analysis.

We conducted the screening of catalyst loading (Table 4, entries 1–6). The reaction with at least 0.5 mol % of catalyst **1g** also proceeded smoothly to give desired product **3a** in >98% conv with 98:2 er (entries 1–4). The use of less than 0.3 mol % of **1g** in the reaction decreased the conversion of **2a** after 12 h but still maintaining high enantioselectivities (entries 5 and 6). Further tuning of the reaction conditions (entries 7–9), concentration of substrate **2a** and reaction time, allowed finding the optimal reaction conditions to afford **3a** within 5 hours (>98% conv; 98:2 er; entry 9).

Table 4. Screening of other factors in Steglich rearrangement



2a **3a**

entry	X (mol %)	time (h)	conc. (M)	conversion (%)[a]	er of **3a**[b]
1	5	12	0.1	>98	98:2
2	3	12	0.1	>98	98:2
3	1	12	0.1	>98	98:2
4	0.5	12	0.1	>98	98:2
5	0.3	12	0.1	73	98:2
6	0.1	12	0.1	15	98:2
7	0.5	5	0.1	71	98:2
8	0.5	5	0.2	92	98:2
9	0.5	5	0.4	>98	98:2

[a]Determined by ^{1}H NMR analysis. [b]Determined by HPLC analysis.

3-4. Substrate Scope

With optimal reaction conditions in hand, we explored substrate scope in this reaction system (Figure 3). A variety of different substrates could be used in the enantioselective Steglich rearrangement process (Figure 3a). Thus, 3-alkyl-, 3-allyl- or 3-propargyl substituted oxindole products **3b**–**f** were isolated in quantitative yields and in 96:4–99:1 er. Higher catalyst loading (3.0 versus 0.5 mol %) and temperature (25 versus –20 °C) was required in the case of more sterically demanding isopropyl group (**3c**, >98% yield, 96:4 er). The absolute configuration of **3c** was determined to be *S* configuration by single-crystal X-ray structure analysis (Figure 3b). Substrates bearing amide (**2g**), silyl ether (**2h**) or cyano unit (**2i**) were converted to the corresponding products **3g**–**i** in quantitative yields and high enantioselectivity (91:9–97:3 er). Rearrangements of 3-phenyl (**2j**) or 3-thienyl substituted indolyl carbonates (**2k**) were lack of reactivity, therefore catalyst loading was increased at 3 mol % (**3j**: 84:16 er, **3k**: 79:21 er). Bromo substituted **3l** (>98% yield, 92:8 er) were also showed good results. Product **3m** protected by methyl group was obtain in somewhat low enantioselectivity (87:13 er). Detailed reasons for this observation are described in the following section 3-5-3.

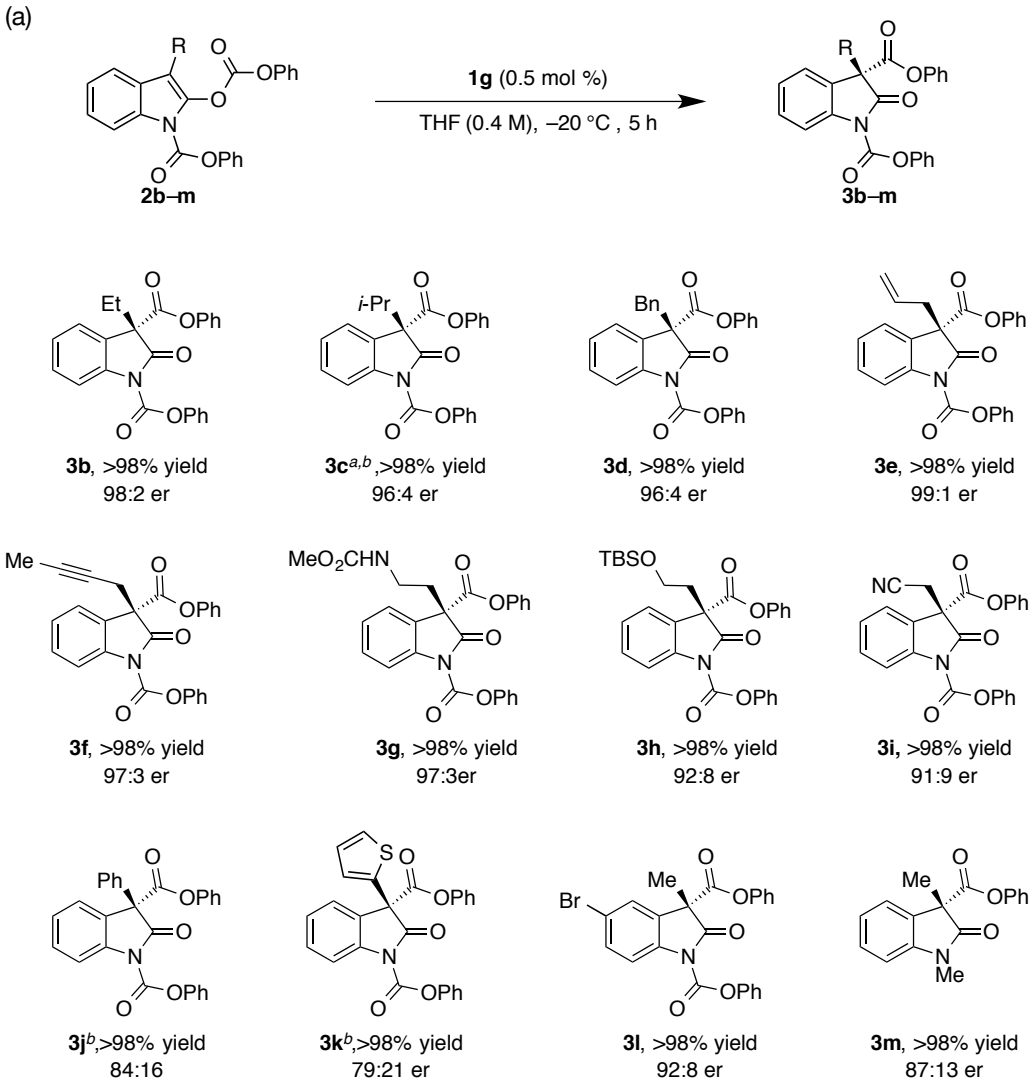


Figure 3. (a) Substrate scope (b) X-ray structure of product 3c

3-5. Application and Control Experiments

3-5-1. Multigram Scale Reaction and Investigation of the Recyclability of Catalyst

We conducted multigram scale reaction utilizing 15 g of substrate **2a** and 193 mg of catalyst **1g** under the optimal reaction conditions. Substrate **2a** delivered the desired product **3a** in quantitative yield (purification by standard silica gel chromatography) and 98:2 er (Figure 4a). Furthermore, catalyst **1g** could be recovered in 95% yield, and used in same reaction (0.2 mmol scale) to afford the desired product **3a** in >98% yield with 98:2 er without loss of any catalytic activity and enantioselectivity (Figure 4b).

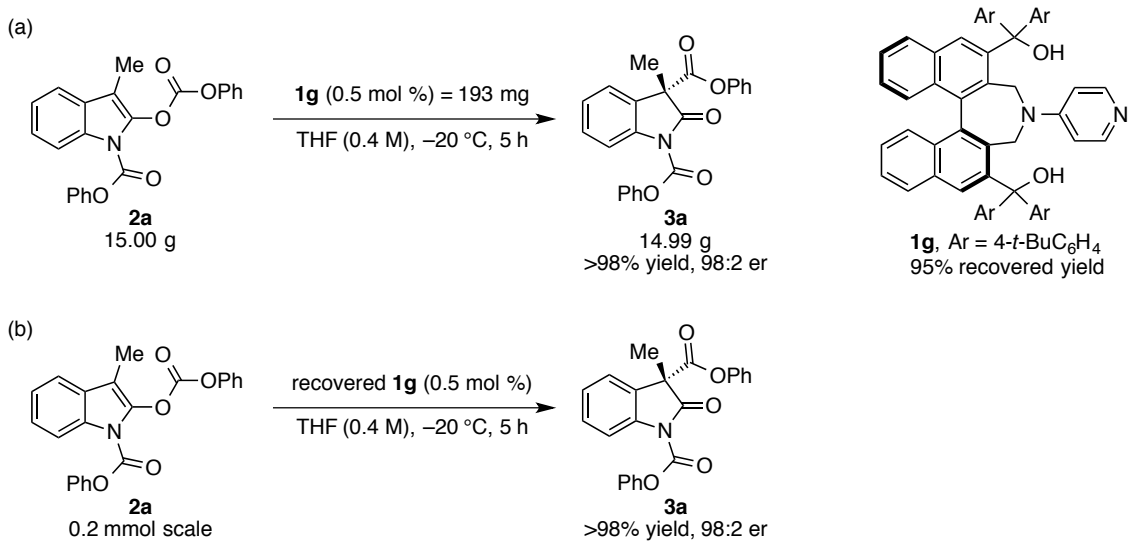


Figure 4. (a) Multigram scale experiment (b) Investigation of recyclability

3-5-2. Cross-over Experiment

To investigate the mechanism of the catalytic enantioselective rearrangement process, we performed a number of key experiments. First, cross-over studies (Figure 5) between two marked substrates **2a** and **2n** clearly indicated that reactions proceed via an ion pair complex, identifying the recovered starting material **2a** and **2n** (starting material); **2a´** and **2n´** (scrambled starting material) along with corresponding products **3a**, **3n**, **3a´** and **3n´**.[4] The crossover occurred in the substrate that means that there is a rapid equilibrium reaction between the substrate and the reaction intermediate (Figure 6, step 1). In addition, this observation suggested that stable *N*-acyl pyridinium intermediate generated in this reaction (Figure 6). Fu,[4] Smith,[5-7] and Suginome[8] conducted similar cross-over experiments. The scrambling was generally observed in Steglich rearrangement with DMAP derivative except for Suginome's helical polymer immobilized chiral DMAP derivatives. Suginome and coworkers suggested that the highly sterically demanding polymer scaffold protects the *N*-acylpyridinium intermediate from attack by the enolates generated on the other catalyst or promotes the intramolecular acyl transfer significantly.

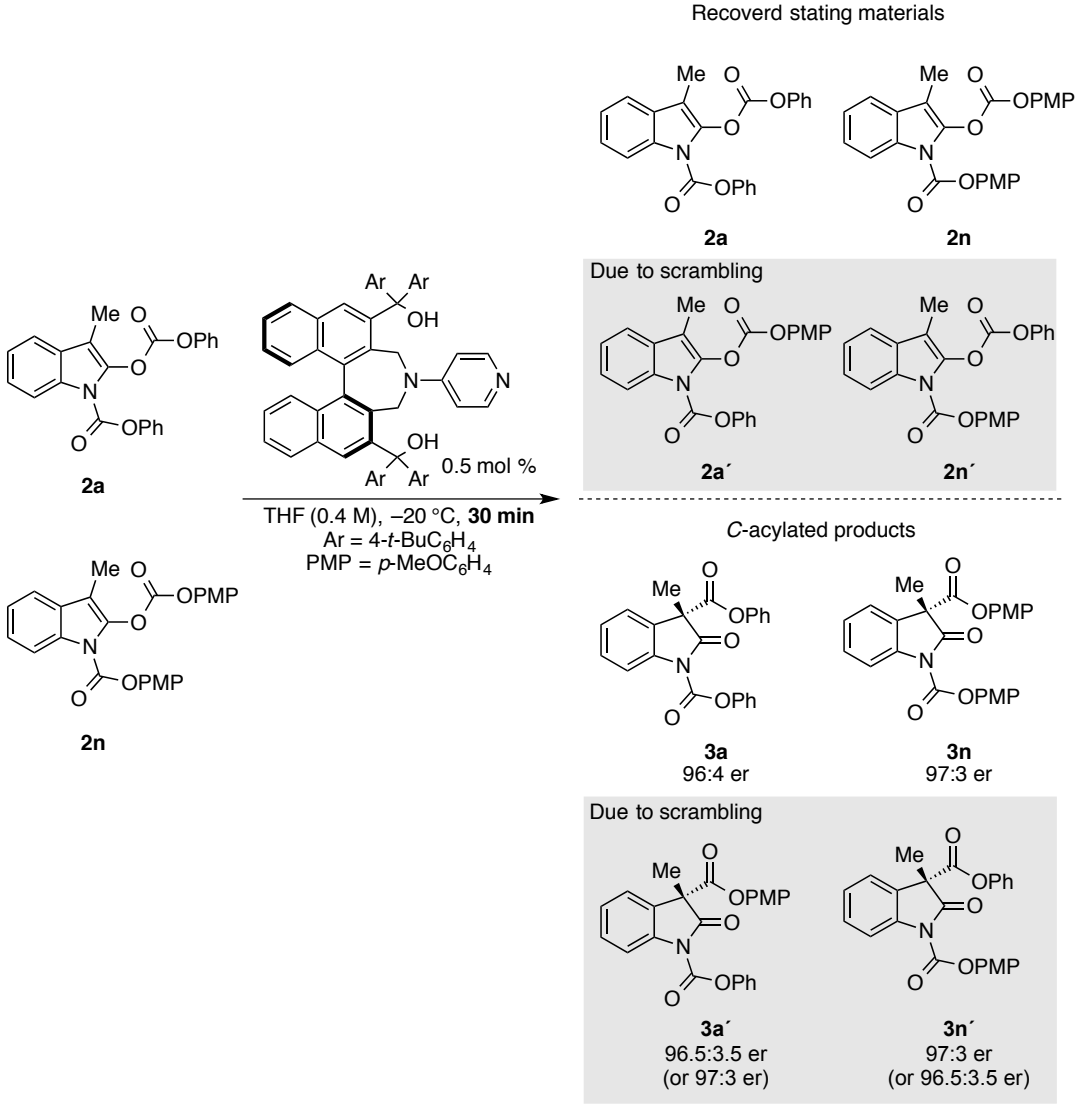


Figure 5. Cross-over studies of Steglich rearrangement of indolyl carbonates **2a** and **2n**

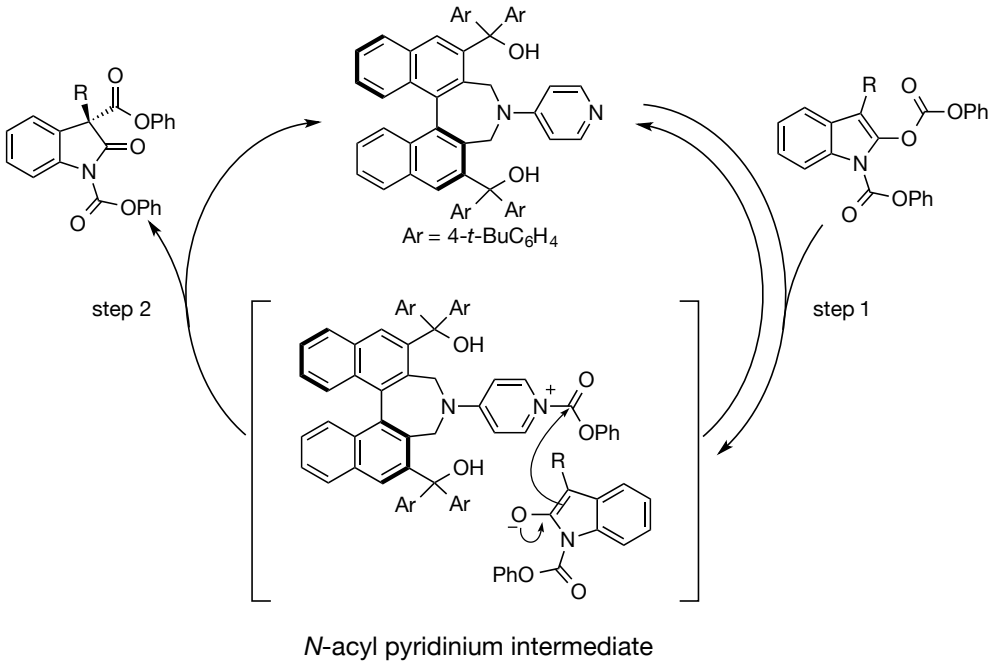


Figure 6. Proposed catalytic cycle of Steglich rearrangement of indolyl carbonates

3-5-3. Kinetic Experiments

To elucidate the role of *tert*-alcohol units of the catalyst **1g**, we conducted kinetic measurements (Figure 7) of this transformations promoted by catalyst **1g**, the corresponding bis-methyl ether **1g´**, and DMAP; indolyl carbonate **2a** served as the substrate under the optimal conditions (0.5 mol% catalyst, THF (0.4 M), –20 °C, 5 h). In all cases, the reactions were found to be first-order with respect to the substrate. Moreover, substantially higher activity was observed with catalyst **1g** ($k_{\mathbf{1g}}$ = 1.22 h^{-1}) versus its derived bis-methyl ether **1g´** ($k_{\mathbf{1g'}} = 2.62 \times 10^{-2}$ h^{-1}), or DMAP ($k_{DMAP} = 7.47 \times 10^{-2}$ h^{-1}). Thus, acyl rearrangement was nearly 50 times faster with **1g** compared with **1g´** and 16 times faster than DMAP. Additionally, whereas the desired product was obtained in 98:2 er when **1g** was used, there was hardly any enantiofacial selectivity when the hydroxy units were protected (66:34 er with **1g´**). The presence of tertiary alcohols clearly has a significant impact on the rate fo the reaction as well as enantioselectivity of the catalytic process.

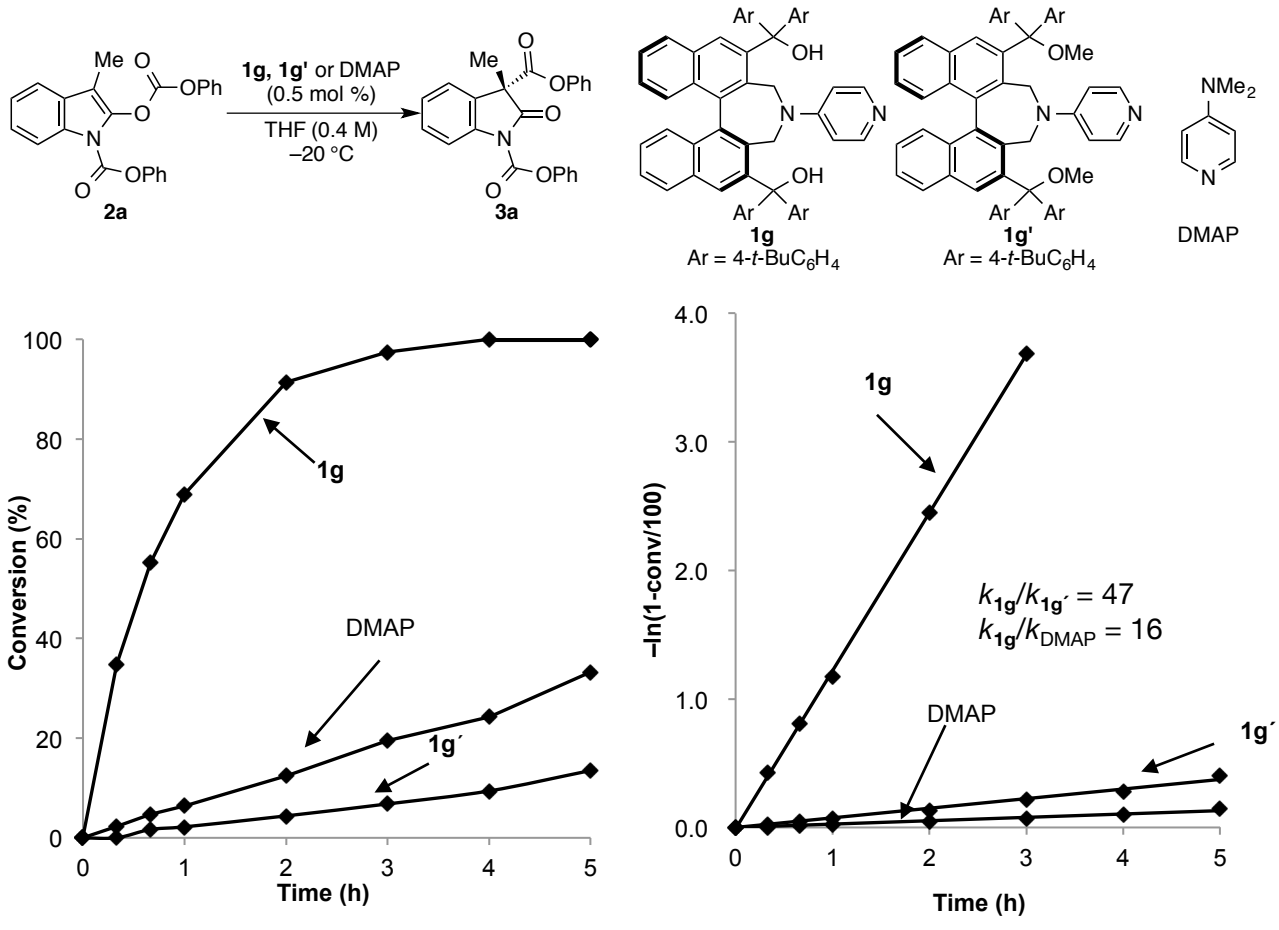


Figure 7. Kinetic studies in enantioselective Steglich rearrangement with **1g**, **1g´** and DMAP

3-5-4. DFT Calculations

To gain further insight regarding the role of the chiral catalyst's tertiary alcohol units, density functional theory (DFT) calculations were performed at the B3LYP/6-31G(d) level, with **2a** as the substrate and compound **1d** as the catalyst, which represent simplified catalyst of **1g**. These investigations point to two critical attractive interactions, which directly involve the tertiary alcohol moiety, between the chiral catalyst and counteranion (enolate) to form tight ion pair intermediate. In the lowest energy transition state **TS-I** (Figure 8), which consistent with the experimental observations leads to the observed major enantiomer, there appears to be a hydrogen bonding between the enolate oxygen of the ion pair and the catalyst's hydroxy unit; it is likely that the conformational rigidity imposed by the presence of the two aryl unit on the same carbon, forces the hydroxyl unit to be properly positioned to associate with the negatively charged oxygen. Additionally, there appears to be an additional electrostatic attraction[9,10] between the enolate and an ortho hydrogen of one of the aforementioned aryl units at the C3 site of the chiral catalyst. The second lowest mode of addition, as indicated by DFT calculations, is **TS-II** (Figure 8). While there appears to be similar electrostatic attractive forces operative here as well, **TS-II** seems to suffer from a significant steric repulsion between the substrates phenoxy unit and the backbone of the catalyst's biaryl moiety. Nevertheless, DFT calculations indicate that there is in all likelihood steric repulsion between phenyl unit and the tertiary hydroxyl fragment that is involved in attractive interactions with the enolate group (see transition state (TS)-I, Figure 8); this is supported by the findings that a catalyst with meta-(3,5)-substituted aryl groups give lower enantioselectivities in the reaction of **2a** (cf. **1l** or **1m** in Figure 2). Further, as indicated by the transformation that afforded **3m** (Figure 3) involving a more diminutive *N*-Me group, while less enantioselective than when a benzoate group is present (**2a**), there is still appreciable enantiofacial differentiation observed (98:2 er versus 87:13 er for **3a** and **3m**, respectively). This suggests that other, non-steric, factors are at play here as well. Towards this end, second order perturbation theory analysis in NBO at the M062X/6-31g** level indicates that C–H/enolate attraction might be notably stronger in the favored **TS-I**.

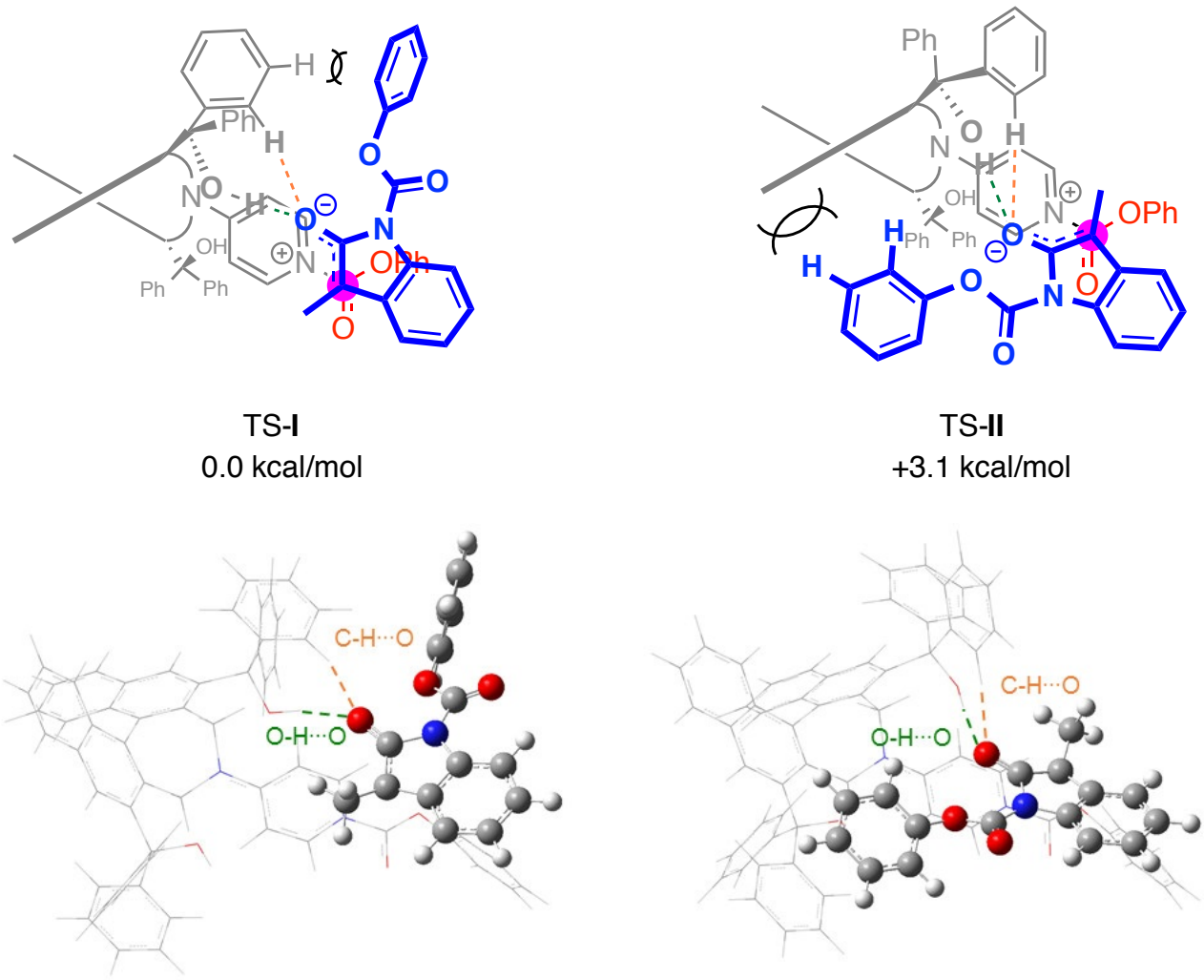


Figure 8. DFT calculations of two transition states TS-I and II in enantioselective Steglich rearrangement of **2a** with **1d**

3-6. Conclusion

We developed enantioselective Steglich rearrangement of indolyl carbonates with highly active DMAP derivatives. The reaction proceeds smoothly with low-loading of catalyst and offers wide substrate scope. Rate acceleration effect by **1g** showed 50 times higher than that of using methyl-capped analogue **1g′** and 16 times higher than that of using DMAP. DFT calculations figure out the origin of the enantioselectivity.

3-7. Experimental Section and Material Data

General

Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian 600 MR (^{1}H 600 MHz, ^{13}C 150 MHz), Varian 400 MR (^{1}H 400 MHz, ^{13}C 100 Mz) and JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 Mz) spectrometer. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin =quintet, sext = sextet, sep = septet, b = broad, m = multiplet), coupling constants, and integration. Chemical shifts for ^{13}C NMR were reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) with complete proton decoupling. Infrared (IR) spectra were recorded on JASCO FT/IR-4100 spectrophotometer and Varian 7000e FT-IR spectrometer, Vmax in cm^{-1}. High-resolution mass spectrometry was performed on a JEOL JMS-700 MStation (FAB-MS and EI-MS), Agilent 6520 Accurate Mass Q - TOF LC/MS (ESI-MS) and Thermo Fisher Scientific EXACTIVE Plus (ESI-MS). Optical rotations were measured on a JASCO DIP-1000. Melting point was recorded on a SANSYO SMP-300. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC) Shimadzu chromatograph (DAICEL CHIRALPAK® AS-3 (4.6 × 150 mm), DAICEL CHIRALPAK® AD-H (4.6 × 250 mm) in comparison with authentic racemic materials. Column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm) purchased from Kanto Chemical. All experiments were carried out under argon atmosphere unless otherwise noted.

Materials

All reagents were obtained commercial sources and used as received unless otherwise noted. Acetonitrile [MeCN], and dichloromethane [CH_2Cl_2] were distilled over calcium hydride [CaH_2]. Dry tetrahydrofuran [THF], and dry diethyl ether [Et_2O], *N*-bromosuccinic imide [NBS], palladium acetate [$Pd(OAc)_2$], benzene, 4-bromopyridine hydrochloride, bis(dibenzylideneacetone)palladium (0) [$Pd(dba)_2$], 2,2'-azobis(isobutyronitrile) [AIBN], *N,N,N′,N′*-tetramethylethylenediamine [TMEDA], 1,1'-bis(diphenylphosphino)ferrocene [dppf], tin(II)chloride (anhydrous) [$SnCl_2$], and methyl chloroformate were purchased from Wako Pure Chemical Industries, Ltd. *N,N′*-Dimethylbarbituric acid [NDMBA], 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl [RuPhos], 1-bromo-2-butyne, 4-methoxyphenyl chloroformate, and 4-fuluorophenyl chloroformate were purchased from Sigma-ALDRICH Japan. Allyl amine, *n*-butyl lithium [*n*-BuLi] and *N,N*-dimethyl-4-aminopyridine [DMAP] were purchased from KANTO CHEMICAL CO.,INC. Triphenyl phosphine [PPh_3], 4-bromoanisole, 4-bromobiphenyl, 1-bromo-4-tert-butylbenzene, phenyl chloroformate, isopropyl chloroformate, 1-bromo-3,5-dimethoxybenzene, 1-bromo-3,5-dimethoxybenzene, trifluoroacetic acid [TFA], and sodium *tert*-butoxide [NaO*t*-Bu]

were purchased from Tokyo Chemical Industry Co., Ltd. Methanol [MeOH] and acetic acid [AcOH] was purchased from NAKARAI TESQUE, INC.

General procedure fur enantioselective Steglich rearrangement under optimal conditions.

A solution of the catalyst in THF (50.0 mM) was prepared in advance using the following reaction. To a solution of substrate **9** (0.2 mmol) in THF (0.5 ml, 0.4 M) was added a solution of the catalyst (20 ml, 50 mM in THF) at –20 °C. The reaction mixture was stirred for 5 h and then 1 M aqueous HCl was added. The resulting mixture was extracted with EtOAc, dried over MgSO4 and concentrated in vacuo. The purification of the crude product by flash column chromatography on a short pad of silica gel (eluent: hexane/Et_2O = 1/1, v/v) gave the corresponding product **10** (>98% yield). For high-performance liquid chromatography analyses of the products descried after section.

Steglich rearrangement on multi-gram scale (Figure 4a)

To a solution of **2a**[11] (15.0 g, 42.0 mmol) in THF (95.5 mL) was added solution of **1g** (193.2 mg, 0.2 mmol) in THF (5.00 mL) at –20 ºC. The reaction mixture was stirred for 5 h at –20 ºC, then monitored by TLC. After checking of disappearance of **2a**, the reaction solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The purification of the crude product by flash column chromatography on a short pad of silica gel (eluent: hexane/Et2O = 1/1, v/v) gave the **3a**[11] (15.0 g, 42.0 mmol, >98% yield) and the catalyst **1g** was recovered by elution of polar solvent (Et2O/MeOH = 5/1, v/v): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 85/25, v/v, flow rate = 0.30 mL/min, 30 °C, UV = 254 nm), TR = 13.0 min (major) and TR = 14.0 min (minor), 98:2 er (Supplementary Figure 50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 1H), 7.51–7.27 (m, 10H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 167.6, 150.2, 150.1, 149.3, 139.1, 129.9, 129.6, 129.5, 128.6, 126.6, 126.4, 125.7, 123.0, 121.5, 121.1, 115.9, 55.9, 20.9; IR (KBr) 3069, 1802, 1741, 1724, 1591, 1477, 1341, 1209, 1092, 959, 758 cm^{-1}; $[\alpha]^{21}_D$ +74.1 (*c* 1.03, CH_2Cl_2, 98:2 er, (*S*)-configuration) [lit. $[\alpha]^{20}_D$ +34.0 (*c* 0.16, $CHCl_3$, 92:8 er, (*S*)-configuration)].

The Steglich rearrangement with the recovered catalyst 1g (Figure 4b)

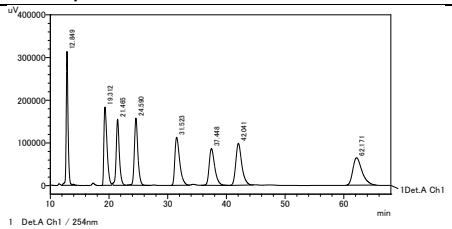
To a solution of recovered **2a**[11] (37.4 mg, 0.100 mmol) in THF (0.250 ml) was added solution of **1j** (50 mM, 10 μL, 2.50 μmol) in THF at –20 ºC. The reaction mixture was stirred for 5 h at –20 ºC and then 1 M aqueous HCl was added. The resulting mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on a short pad of silica gel (eluent: hexane/Et2O = 1/1, v/v) gave the **3a**[11] (36.9 mg, 98.9 μmol, 99% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 85/25, v/v, flow rate = 0.30 mL/min, 30 °C, UV = 254 nm), TR = 13.0 min (major) and TR = 14.0 min (minor), 98:2 er.

Considerations for the scrambling in Steglich rearrangement

Crossover experiment showed that treatment of 1:1 mixture of enol carbonates **2a** and **2n** using 0.5 mol % of **1g** gave **2a** and **2n**; unknown enol carbonates probable **2a´** with **2n´**; **3a** and **3n**; and **3a´**with **3n´** due to scrambling. This reaction quenched at 30 min and the conversion was 30% that determined by ^{1}H NMR analysis of unpurified reaction mixture (Scheme S1). Consequently, scrambling occurred initial rapid and reversible *O*-transcarboxylation process. Same scrambling results were reported in the Steglich rearrangement of azlactone.[4,6,7]

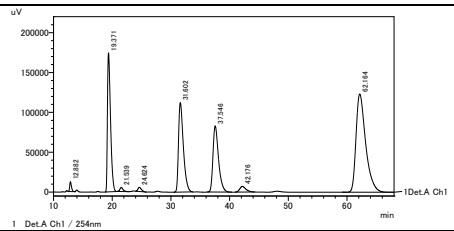
When the reaction quenched at 5 h, the conversion to products was >98% and the enantiomeric ratios of products were determined by HPLC analysis as 96:4 er (**3a**), 97:3 er (**3n**), 96.5:3.5 er and 97:3 er (**3a´**or **3n´**) respectively (see the following HPLC data). The enantiomeric ratio was determined by HPLC with CHIRALPAK AD-H® (hexane/*i*-PrOH = 92.5/7.5, v/v), flow rate = 1.00 mL/min, 30 °C, UV = 254 nm)

Racemic sample of **3a**, **3n**, **3a´**and **3n´**



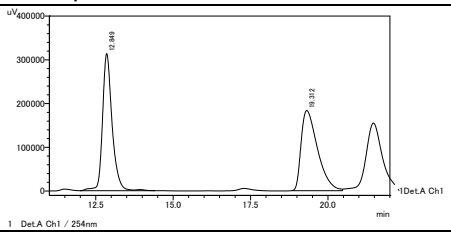
Peak #	Ret. Time	Area	Area %
1	12.849	6776862	13.088
2	19.312	6773022	13.081
3	21.465	5711902	11.032
4	24.590	6483558	12.522
5	31.523	6452442	12.462
6	37.448	5710356	11.029
7	42.041	6934043	13.392
8	62.171	6935636	13.395

(*S*)-**3a**, **3n**, **3a´** and **3n´**



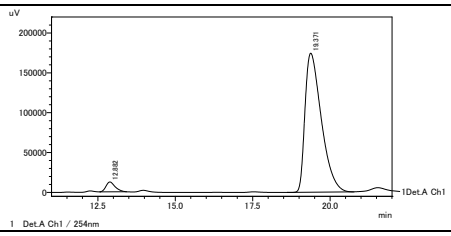
Peak #	Ret. Time	Area	Area %
1	12.882	260894	0.779
2	19.371	6386553	19.065
3	21.539	199224	0.595
4	24.624	212607	0.635
5	31.602	6433427	19.205
6	37.546	5450315	16.270
7	42.176	514876	1.537
8	62.164	14040320	41.914

Racemic sample of **3a**



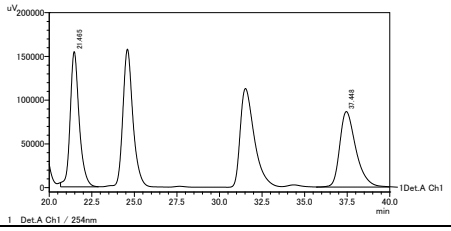
Peak #	Ret. Time	Area	Area %
1	12.849	6776862	50.014
2	19.312	6773022	49.986

(*S*)-**3a**



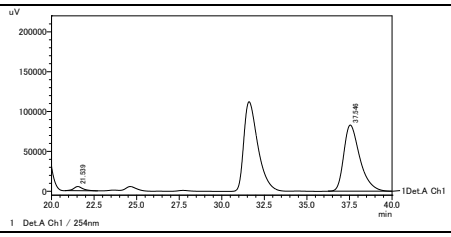
Peak #	Ret. Time	Area	Area %
1	12.882	251216	3.780
2	19.371	6394711	96.220

Racemic sample of **3a´** or **3n´**



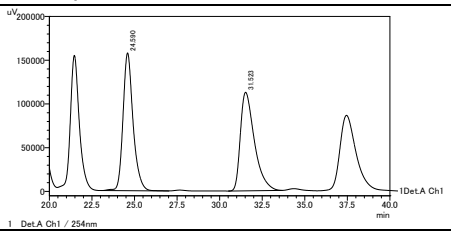
Peak #	Ret. Time	Area	Area %
1	21.465	5711902	50.007
2	37.448	5710356	49.993

(*S*)-**3a´** or **3n´**



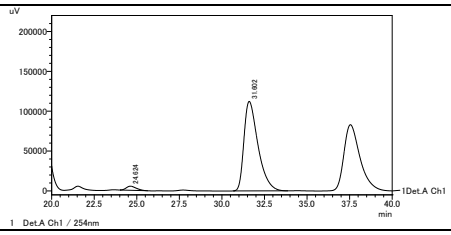
Peak #	Ret. Time	Area	Area %
1	21.539	197158	3.500
2	37.546	5436404	96.500

Racemic sample of **3a´** or **3n´**



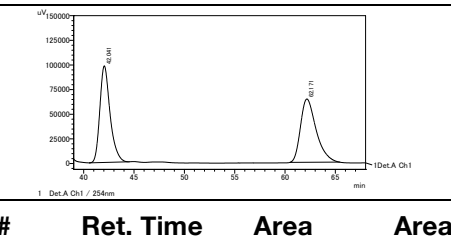
Peak #	Ret. Time	Area	Area %
1	24.590	6483558	50.120
2	31.523	6452442	49.880

(*S*)-**3a´** or **3n´**



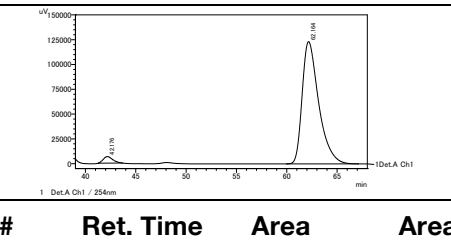
Peak #	Ret. Time	Area	Area %
1	24.624	208941	3.141
2	31.602	6442366	96.859

Racemic sample of **3n**



Peak #	Ret. Time	Area	Area %
1	42.041	6934043	49.994
2	62.171	6935636	50.006

(*S*)-**3n**



Peak #	Ret. Time	Area	Area %
1	42.176	435525	3.011
2	62.164	14027941	96.989

General procedure for kinetic experiment and data

To a solution of **3a** (112 mg, 0.299 mmol) in THF (0.750 mL) was added a solution of **1g**, **1g´**, or DMAP (50.0 mM, 2.50 μL, 1.50 μmol) in THF at −20 ºC. After stirring the indicated periods in Tables S3, the reaction mixture was sucked 100 μL by syringe, poured into 1 M aqueous HCl (2 mL), extracted with EtOAc (3 mL × 3), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was passed through a short pad of silica gel (eluent: hexane/Et_2O = 1/1, v/v) and ^1H NMR and HPLC were measured. The conversion was calculated by ^1H NMR analysis and the enantiomeric ratio was determined by HPLC analysis.

Table S1. The time course analysis of the enantioselective Steglich rearrangement of oxindole catalyzed by **1g**, **1g´**and DMAP.

catalyst **1g**

time (h)	0.33	0.67	1	2	3	4	5
conversion (%)	34.8	55.2	69.0	91.4	97.5	100	100
ln(1-conv/100)	0.428	0.803	1.17	2.45	3.69	–	–
kinetic constant (*k*, h^{-1})	1.22						

DMAP

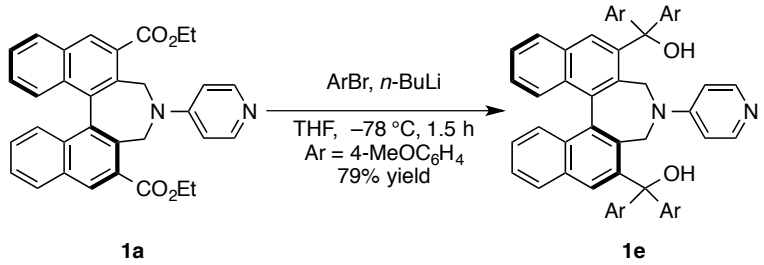
time (h)	0.33	0.67	1	2	3	4	5
conversion (%)	0	1.7	2.2	4.4	6.8	9.4	13.5
ln(1-conv/100)	0	0.0171	0.0222	0.0450	0.0704	0.0987	0.1450
kinetic constant (*k*, h^{-1})	7.47×10^{-2}						

catalyst **1g´**

time (h)	0.33	0.67	1	2	3	4	5
conversion (%)	2.3	4.7	6.4	12.4	19.5	24.3	33.2
ln(1-conv/100)	0.0233	0.0481	0.0661	0.132	0.217	0.278	0.404
kinetic constant (*k*, h^{-1})	2.62×10^{-2}						

Synthesis of catalyst 1e-n, 1g´

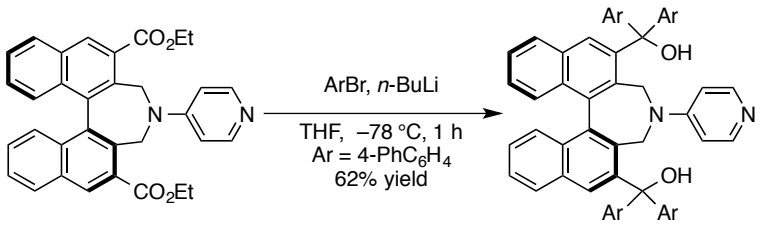
Synthesis of 1e



1a **1e**

To a solution of 4-bromoanisole (37.0 μL, 0.300 mmol) in THF (0.250 mL) was added dropwise a solution of *n*-BuLi in hexane (1.60 M, 190 μL, 0.304 mmol) at −78 °C and stirred for 20 min. After stirring for 20 min at −78 °C, a solution of **1a** (25.7 mg, 49.7 μmol) in THF (1.00 mL) was added to reaction mixture at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C. Then, additional solution of *n*-BuLi in hexane (1.60 M, 190 μL, 0.304 mmol) was added to reaction mixture to destroy 1-bromobutane which was generated in the reaction. The reaction mixture was warmed up to room temperature and stirred for 1 h, and then water (20 mL) was added. The resulting solution was extracted with $CHCl_3$ (10 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was subsequently thoroughly washed with Et_2O. After filtration and drying of the solid, **1e** (33.6 mg, 39.2 μmol, 79% yield) was isolated as a pale yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.56 (m, 4H), 7.36 (ddd, *J* = 7.9, 5.5, 2.5 Hz, 2H), 7.25-7.17 (m, 6H), 7.13 (d, *J* = 8.5 Hz, 4H), 6.91 (d, *J* = 8.5 Hz, 4H), 6.84 (d, *J* = 8.5 Hz, 4H), 6.47 (d, *J* = 8.5 Hz, 4H), 5.87 (d, *J* = 6.4 Hz, 2H), 5.35 (d, *J* = 13.2 Hz, 2H), 3.98 (bs, 1.4H), 3.80 (s, 6H), 3.60 (s, 6H), 3.37 (d, *J* = 13.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 ºC) δ 159.0, 158.8, 153.0, 147.8, 143.1, 140.7, 138.3, 138.3, 132.7, 131.7, 131.3, 130.5, 129.2, 128.9, 128.7, 127.5, 126.4, 126.1, 113.6, 113.1, 108.8, 82.8, 55.4, 55.1, 45.6; IR (KBr) 2363, 1603, 1506, 1248, 1175, 1031, 993, 829, 750 cm^{-1}; HRMS (ESI^+) calculated for $C_{57}H_{49}N_2O_6$ $[M+H]^+$ 857.3585, found 857.3549; mp 235 ºC dec; $[\alpha]^{24}_D$ –206.4 (*c* 0.29, $CHCl_3$).

Synthesis of 1f

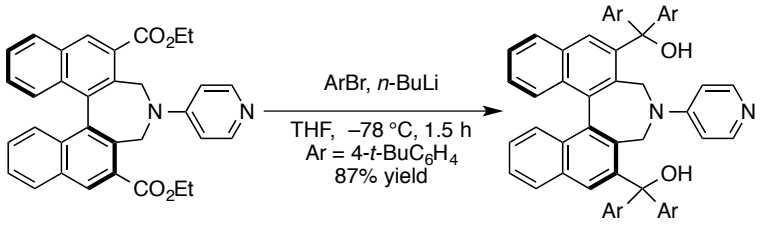


1a **1f**

To a solution of 4-bromobiphenyl (280 mg, 1.20 mmol) in THF (3.00 mL) was added dropwise a solution of *n*-BuLi in hexane (1.55 M, 775 μL, 1.20 mmol) at −78 °C and stirred for 20 min. After stirring for 20 min at −78 °C, a solution of **1a** (103 mg, 0.200 mmol) in THF (1.50 mL) was added to reaction mixture at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. Then, additional solution of *n*-BuLi in hexane (1.55 M, 775 μL, 1.20 mmol) was added to reaction mixture to destroy 1-bromobutane which was generated in the reaction. The reaction mixture was warmed up to room temperature and stirred for 1 h, and then water (20 mL) was added. The resulting mixture was extracted with $CHCl_3$ (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 30/1, v/v) gave **1f** (128 mg, 0.123 mmol, 62% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.64-7.54 (m, 10H), 7.47-7.54 (m, 36 H), 6.01 (d, *J* = 5.4 Hz, 2H), 5.43 (d, *J* = 12.9 Hz, 2H), 4.39 (bs, 1.2H), 3.46 (d, *J* = 12.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.0, 145.0, 142.5, 140.5, 140.4, 140.1, 140.1, 138.4, 132.4, 131.7, 131.2, 130.6, 128.9, 128.9, 128.2, 127.6, 127.3, 127.2, 127.2, 127.0, 126.6, 126.5, 126.2, 108.9, 83.0, 45.8; IR (KBr) 3055, 3028, 1593, 1508, 1485, 1398, 1242, 995, 893, 837, 748 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{77}H_{57}N_2O_2$ $[M+H]^+$ 1041.4415, found 1041.4385; mp 257 ºC dec; $[\alpha]^{23}_D$ −172.6 (*c* 0.26, $CHCl_3$).

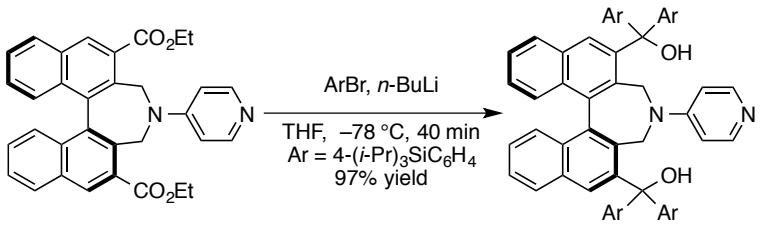
Synthesis of 1g



1e **1g**

To a solution of 1-bromo-4-tert-butylbenzene (497 µL, 2.88 mmol) in THF (3.00 mL) was added dropwise a solution of *n*-BuLi in hexane (1.60 M, 1.80 mL, 2.88 mmol) at −78 °C and stirred for 20 min. After stirring for 20 min at −78 °C, a solution of **1a** (311 mg, 0.602 mmol) in THF (6.00 mL) was added to reaction mixture at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C. Then, additional solution of *n*-BuLi in hexane (1.60 M, 1.80 mL, 2.88 mmol) was added to reaction mixture to destroy 1-bromobutane which was generated in the reaction. The reaction mixture was warmed up to room temperature and stirred for 1 h, and then water (30 mL) was added. The resulting mixture was extracted with $CHCl_3$ (50 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc + 3% Et_3N) gave **1g** (505.0 mg, 0.525 mmol, 87% yield) as a pale yellow solid.
^{1}H NMR (400MHz, $CDCl_3$) δ 7.77-7.62 (m, 6H), 7.49-6.97 (m, 22H), 6.37 (d, J = 7.2 Hz, 2H), 5.58 (d, J = 13.2 Hz, 2H), 3.60 (d, J = 13.2 Hz, 2H), 1.32 (s, 18H), 1,26 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.0, 149.8, 149.8, 147.6, 145.2, 143.6, 143.2, 138.1, 132.7, 131.6, 131.1, 130.3, 128.8, 127.7, 127.5, 127.4, 126.2, 125.8, 125.0, 124.5, 108.6, 82.6, 45.5, 34.6, 34.4, 31.5, 31.5; IR (KBr) 2961, 1595, 1508, 1398, 1233, 1107, 993, 829, 748 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{69}H_{73}N_2O_2$ $[M+H]^+$ 961.5667, found 961.5626; mp 231.0 ºC dec; $[\alpha]^{21}_D$ –280.4 (*c* 0.26, $CHCl_3$).

Synthesis of 1h



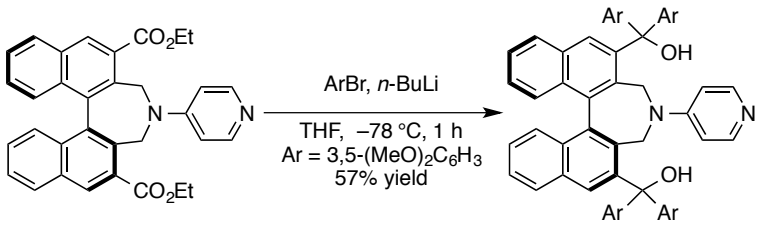
1a **1h**

To a solution of 1-bromo-4-[tris(1-methylethyl)silyl]-benzene[12] (175 µL, 0.603 mmol) in THF

(0.500 mL) was added dropwise a solution of *n*-BuLi in hexane (1.60 M, 375 μL, 0.600 mmol) at −78 °C and stirred for 20 min. After stirring for 20 min at −78 °C, a solution of **1a** (51.9 mg, 0.100 mmol) in THF (1.50 mL) was added to reaction mixture at −78 °C. The reaction mixture was stirred for 40 min at −78 °C. Then, additional solution of *n*-BuLi in hexane (1.60 M, 375 μL, 0.600 mmol) was added to reaction mixture to destroy 1-bromobutane which was generated in the reaction. The reaction mixture was warmed up to room temperature and stirred for 1 h, and then water (20 mL) was added. The resulting mixture was extracted with $CHCl_3$ (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: $CHCl_3$ to $CHCl_3$/MeOH = 4/1, v/v) gave **1h** (132 mg, 96.9 μmol, 97% yield) as a greenish yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J* = 6.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.50-7.35 (m, 12H), 7.33-7.23 (m, 8H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.08 (bs, 2H), 6.24 (bd, *J* = 6.0 Hz, 2H), 5.26 (bd, *J* = 12.6 Hz, 2H), 3.43 (bd, *J* = 12.6 Hz, 2H), 1.50-1.30 (m, 12H), 1.16-0.96 (m, 72H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 147.7, 146.9, 143.0, 138.2, 135.2, 134.9, 134.1, 132.2, 131.8, 131.2, 130.9, 128.8, 127.6, 127.3, 126.5, 126.4, 126.2, 109.2, 82.9, 46.2, 18.8, 10.9, 10.9; IR (KBr) 2943, 2864, 1595, 1464, 1242, 1101, 995, 883, 750 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{89}H_{121}N_2O_2Si_4$ $[M+H]^+$ 1361.8500, found 1361.8480; mp 250 ºC dec; $[\alpha]^{24}_D$ −172.8 (*c* 0.29, $CHCl_3$).

Synthesis of 1l



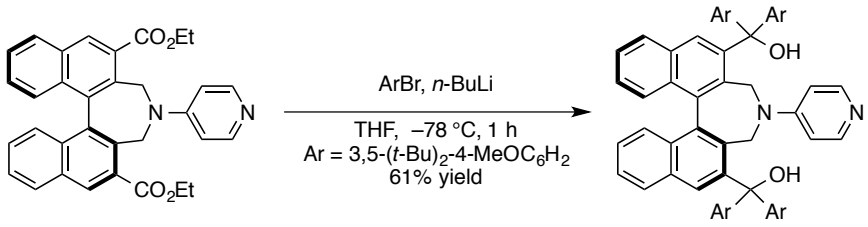
1a **1i**

To a solution of 1-bromo-3,5-dimethoxybenzene (522 mg, 2.40 mmol) in THF (2.00 mL) was added dropwise solution of *n*-BuLi in hexane (1.60 M, 1.50 mL, 2.40 mmol) at −78 °C and stirred for 20 min. After stirring for 20 min at −78 °C, a solution of **1a** (207 mg, 0.400 mmol) in THF (2.50 mL) was added to reaction mixture at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. Then, additional solution of *n*-BuLi in hexane (1.60 M, 1.50 mL, 2.40 mmol) was added to reaction mixture to destroy 1-bromobutane which was generated in the reaction. The reaction mixture was warmed up to room temperature and stirred for 1 h at room temperature, and then water (30 mL) was added. The resulting mixture was extracted with $CHCl_3$ (30 mL × 3), dried over $MgSO_4$ and

concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 20/1 + 3% Et_3N, v/v) gave **1i** (224 mg, 0.229 mmol, 57% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 4H), 7.39 (ddd, J = 7.1, 3.8, 2.9 Hz, 2H), 7.30 (s, 2H), 7.24-7.16 (m, 4H), 6.42 (s, 4H), 6.40 (s, 2H), 6.27 (s, 4H), 5.99-5.93 (m, 4H), 5.26 (d, J = 13.2 Hz, 2H), 3.70 (s, 12H), 3.59 (s, 12H), 3.46 (d, J = 13.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 160.4, 150.0, 147.5, 141.8, 138.2, 131.9, 131.7, 131.2, 130.7, 128.9, 127.4, 126.6, 126.2, 108.7, 106.6, 106.5, 99.4, 97.8, 83.3, 55.5, 55.2, 45.6; IR (KBr) 2935, 1597, 1458, 1204, 1155, 1057, 752 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{61}H_{57}N_2O_{10}$ $[M+H]^+$ 977.4008, found 977.3993; mp 242 ºC dec; $[\alpha]^{23}_D$ –212.1 (*c* 0.28, $CHCl_3$).

Synthesis of 1j



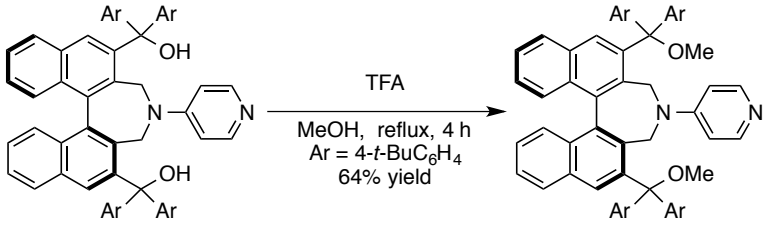
1a **1j**

To a solution of 4-bromo-2,6-di-tert-butylanisole[13] (178 mg, 0.595 mmol) in THF (1.00 mL) was added dropwise a solution of *n*-BuLi in hexane (1.60 M, 375 μL, 0.600 mmol) at −78 °C and stirred for 20 min. After stirring for 20 min at −78 °C, a solution of **1a** (51.7 mg, 0.100 mmol) in THF (1.50 mL) was added to the reaction mixture at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. Then, additional solution of *n*-BuLi in hexane (1.60 M, 375 μL, 0.600 mmol) was added to reaction mixture to destroy 1-bromobutane which was generated in the reaction. The reaction mixture was warmed up to room temperature and stirred for 1 h, and then water (10 mL) was added. The resulting mixture was extracted with $CHCl_3$ (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: Et_2O/MeOH = 30/1, v/v) gave **1j** (80.1 mg, 61.3 μmol, 61% yield) as a pale yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (bd, J = 5.4 Hz, 2H), 7.64 (d, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.23-6.85 (m, 14H), 6.35 (bd, J = 5.4 Hz, 2H), 5.30 (d, J = 13.2 Hz, 2H), 3.67 (s, 6H), 6.03 (s, 6H), 3.33 (d, J = 13.2 Hz, 2H), 3.02 (bs, 1H), 2.94 (bs, 1H), 1.30 (s, 36H), 1.22 (s, 36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.7, 158.7, 143.2, 143.0, 143.0, 141.4, 140.2, 138.4, 131.8, 131.0, 130.4, 128.8, 127.2, 127.0, 126.5, 126.4, 125.7, 124.1, 109.2, 83.0, 64.4, 64.3, 46.7, 36.0, 36.0, 32.3,

32.2; IR (KBr) 2961, 1645, 1595, 1539, 1227, 1115, 1012, 887, 748 cm^{-1}; HRMS (ESI^+) caluculated for $C_{89}H_{113}N_2O_6$ $[M+H]^+$ 1305.8593, found1305.8599; mp 202 ºC dec; $[\alpha]^{22}_D$ –218.6 (*c* 0.26, $CHCl_3$).

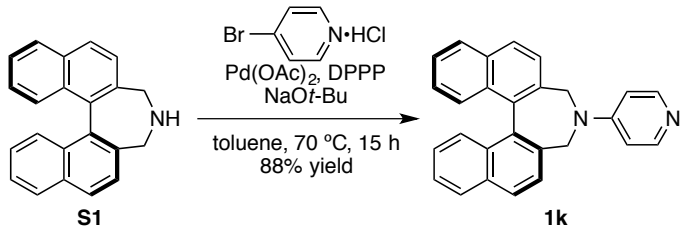
Synthesis of 1g'



1g **1g'**

To a solution of **1g** (172 mg, 0.179 mmol) in MeOH (2.00 mL) was added trifluoroacetic acid [TFA] (89.2 μL, 1.20 mmol) at room temperature. The reaction mixture was heated to refluxed temperature and stirred for 4 h, and then 2 M aqueous NaOH (5 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (5 mL × 3), dried over $MgSO_4$ and concentrated in *vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 1/1, v/v) gave **1g'** (113 mg, 0.114 mmol, 64% yield) as a pale yellow solid.
^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 8.09 (d, *J* = 5.4 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.49 (ddd, *J* = 8.1, 5.5, 2.5 Hz, 2H), 7.39-7.22 (m, 16H), 7.19 (d, *J* = 8.0 Hz, 4H), 6.08 (d, *J* = 5.4 Hz, 2H), 5.02 (d, *J* = 12.8 Hz, 2H), 3.12 (d, *J* = 12.8 Hz, 2H), 2.79 (s, 6H), 1.29 (s, 18H), 1,24 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, 40 ºC) δ 153.5, 149.5, 149.4, 149.0, 144.5, 140.3, 138.3, 138.2, 133.1, 132.1, 131.7, 131.5, 128.9, 128.1, 127.5, 126.7, 126.4, 126.1, 125.0, 124.8, 109.1, 87.8, 53.0, 45.1, 34.5, 31.5; IR (KBr) 2961, 1591, 1508, 1244, 1074, 750 cm^{-1}; HRMS (ESI^+) calculated for $C_{71}H_{77}N_2O_2$ $[M+H^+]$ 989.5980, found 989.5981; mp 221 ºC dec; $[\alpha]^{24}_D$ –78.7 (*c* 0.26, $CHCl_3$).

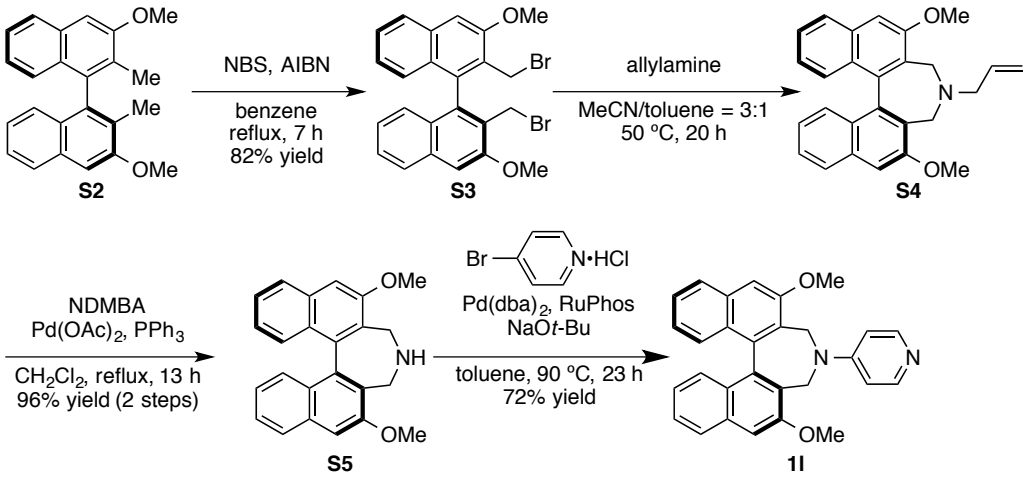
Synthesis of Catalyst 1k



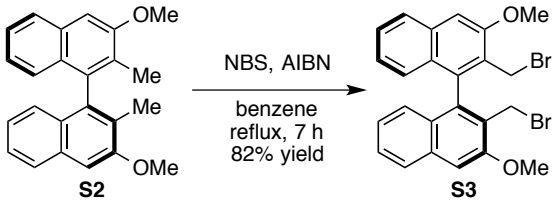
To a suspension of **S1**[14] (52.4 mg, 0.177 mmol), 4-bromopyridine hydrochloride (69.0 mg, 0.355 mmol), NaO*t*-Bu (68.0 mg, 0.708 mmol) and 1,3-bis(diphenylphosphino)propane [DPPP] (2.90 mg, 7.03 μmol) in toluene (1.61 mL) was added $Pd(OAc)_2$ (1.60 mg, 7.13 μmol) at room temperature. The reaction mixture was warmed up to 70 °C and stirred for 15 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ (30 mL) was added to reaction mixture and extracted with toluene (10 mL × 2). The organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL × 2), dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 5/1 to 2/1, v/v) gave **1k** (58.0 mg, 0.156 mmol, 88% yield) as a colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.6 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 4H), 7.57-7.47 (m, 6H), 7.32 (td, *J* = 7.8, 1.4 Hz, 2H), 6.80 (d, *J* = 6.6 Hz, 2H), 4.67 (d, *J* = 12.6 Hz, 2H), 3.89 (d, *J* = 12.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ153.5, 150.3, 135.0, 133.5, 132.9, 131.5, 129.4, 128.5, 127.6, 127.4, 126.3, 126.1, 108.6, 50.7; IR (KBr) 1593, 1505, 1232, 827, 760 cm^{-1}; HRMS (FAB^+) calculated for $C_{27}H_{21}N_2$ $[M+H]^+$ 373.1705, found 373.1699; mp 261.0-261.7 ºC; $[\alpha]^{22}_D$ –439.8 (*c* 1.15, $CHCl_3$).

An overview for synthesis of catalyst 1l



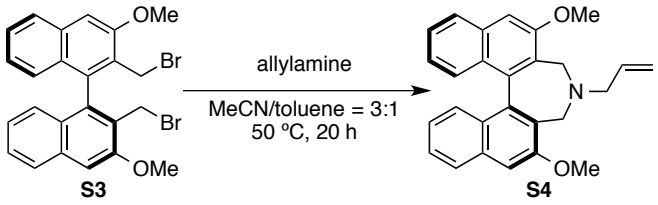
Synthesis of S3



To a solution of **S2**[15] (6.19 g, 18.1 mmol) and *N*-bromosuccinimide [NBS] (7.08 g, 39.8 mmol) in benzene (90.5 mL) was added azobisisobutyronitrile [AIBN] (297 mg, 1.81 mmol) at room temperature. The reaction mixture was warmed up to refluxed temperature and stirred for 7 h. After being cooled to room temperature, water (30 mL) was added to reaction mixture. The resulting solution was extracted with toluene (30 mL × 2), and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL × 2), and brine (20 mL × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by recrystallizition from CH_2Cl_2/hexane gave **S3** (7.39 g, 14.8 mmol, 82% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.44 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 2H), 7.33 (s, 2H), 7.11 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 2H), 6.99 (bd, *J* = 8.2 Hz, 2H), 4.34 (d, *J* = 9.4 Hz, 2H), 4.28 (d, *J* = 9.4 Hz, 2H), 4.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 136.5, 134.8, 127.8, 127.4, 127.4, 126.8, 124.3, 106.5, 56.0, 27.9; IR (KBr) 3060, 2935, 1599, 1170, 750 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{24}H_{21}Br_2O_2$ 500.9889, found 500.9881; mp 189.9-190.5 ºC; $[\alpha]^{20}_D$ +163.5 (*c* 0.22, $CHCl_3$).

Synthesis of S4

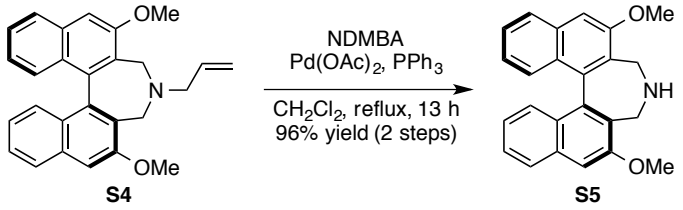


To a solution of **S3** (1.58 g, 3.16 mmol) in MeCN (31.6 mL) and toluene (10.5 mL) was added allylamine (781 μL, 10.4 mmol) at room temperature. The reaction mixture was warmed up to 50 °C and stirred for 20 h. After being cooled to room temperature, water (50 mL) was added to reaction mixture. The resulting solution was extracted with EtOAc (50 mL × 2), and the organic layer was washed with water (30 mL × 2) and brine (10 mL × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was directly used for the following reaction without

further purification. The analytical data of **S4** was obtained by the purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 3/1 to 2/1, v/v) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.41 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 2H), 7.10 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 6.08-5.98 (m, 1H), 5.23-5.14 (m, 2H), 4.36 (d, *J* = 12.4 Hz, 2H), 4.02 (s, 6H), 3.25 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.98 (dd, *J* = 13.2, 6.7 Hz, 1H), 2.78 (d, *J* = 12.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.1, 136.6, 134.2, 127.7, 127.2, 127.0, 126.3, 126.1, 123.5, 117.5, 105.6, 59.2, 55.6, 46.7; IR (KBr) 2950, 2827, 1596, 1226, 752 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{27}H_{26}NO_2$ $[M+H]^+$ 396.1964, found 396.1967; mp 158.0-158.7 °C; $[\alpha]^{20}_D$ +438.8 (*c* 0.23, $CHCl_3$).

Synthesis of S5

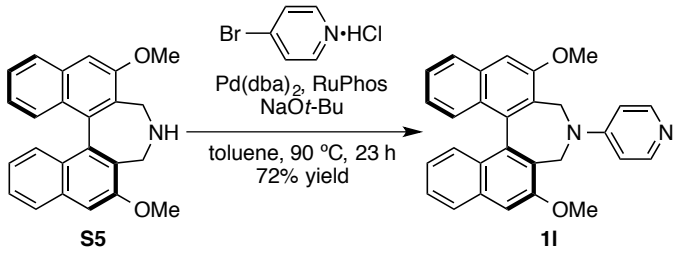


S4 **S5**

To a solution of **S4** (1.21 g, 3.06 mmol), *N*,*N*′-dimethylbarbituric acid [NDMBA] (1.43 g, 9.15 mmol), PPh_3 (160 mg, 0.608 mmol) in CH_2Cl_2 (30.4 mL) was added $Pd(OAc)_2$ (34.5 mg, 0.153 mmol) at room temperature. The reaction mixture was warmed up to refluxed temperature and stirred for 13 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ (30 mL) was added to reaction mixture. The resulting solution was extracted with EtOAc (30 mL × 2) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL × 2) and brine (10 mL × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc to EtOAc + 1% Et_3N) gave **S5** (1.08 g, 3.04 mmol, 96% yield based on **S3**) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.41 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.29 (s, 2H), 7.11 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H), 4.47 (d, *J* = 12.0 Hz, 2H), 4.03 (s, 6H), 3.04 (d, *J* = 12.0 Hz, 2H), 1.69 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 137.0, 134.1, 127.6, 127.4, 127.2, 127.0, 126.0, 123.5, 106.0, 55.6, 40.1; IR (KBr) 2934, 1595, 1231, 832, 748 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{24}H_{22}NO_2$ 356.1651, found 356.1661; mp 101.8-102.4 °C; $[\alpha]^{20}_D$ +388.5 (*c* 0.20, $CHCl_3$).

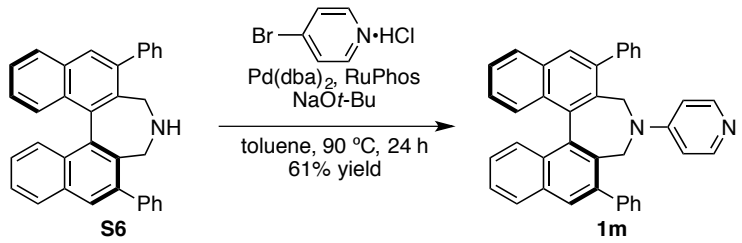
Synthesis of 1l



To a solution of **S5** (733 mg, 2.06 mmol), 4-bromopyridine hydrochloride (801 mg, 4.12 mmol), NaO*t*-Bu (1.19 g, 12.4 mmol), 2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl [RuPhos] (77.2 mg, 0.165 mmol) in toluene (20.6 mL) was added bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] (47.4 mg, 82.4 μmol) at room temperature. The reaction mixture was warmed up to 90 °C and stirred for 23 h. After being cooled to room temperature, water (20 mL) was added to reaction mixture, and passed through a short pad of celite. The resulting solution was extracted with toluene (30 mL × 2), and the organic layer was washed with brine (10 mL × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: EtOAc to EtOAc + 2% Et_3N) gave **1l** (639 mg, 1.48 mmol, 72% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 6.6 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.28 (s, 2H), 7.15 (t, J = 8.0 Hz, 2H), 6.85 (d, J = 6.6 Hz, 2H), 5.38 (d, J = 12.6 Hz, 2H), 3.96 (s, 6H), 3.36 (d, J = 12.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.0, 149.7, 137.2, 134.3, 127.7, 127.3, 126.9, 126.6, 125.4, 123.9, 108.9, 106.4, 55.8, 41.4; IR (KBr) 3421, 3003, 2937, 1507, 749 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{29}H_{25}N_2O_2$ [M+H]$^+$ 433.1916, found 433.1913; mp 154.3-155.3 °C; $[\alpha]^{20}_D$ −293.7 (*c* 0.20, $CHCl_3$).

Synthesis of 1m

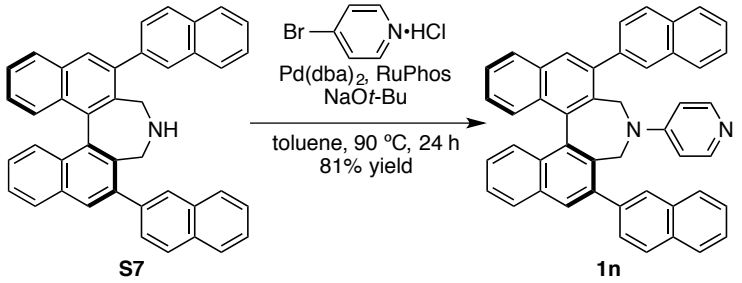


To a solution of **S6**[15] (58.0 mg, 0.130 mmol), 4-bromopyridine hydrochloride (50.9 mg, 0.262 mmol), NaO*t*-Bu (75.1 mg, 0.781 mmol), RuPhos (4.90 mg, 10.5 μmol) in toluene (1.30 mL) was

added $Pd(dba)_2$ (3.00 mg, 5.22 μmol) at room temperature. The reaction mixture was warmed up to 90 °C and stirred for 24 h. After being cooled to room temperature, water (2 mL) was added to reaction mixture, and then passed through a short pad of celite. The resulting solution was extracted with toluene (5 mL × 2) and the organic layer was washed with brine (5 mL × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 + 1% Et_3N to EtOAc + 1% Et_3N, v/v) gave **1m** (41.8 mg, 79.7 μmol, 61% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.93 (m, 6H), 7.56-7.49 (m, 4H), 7.43-7.27 (m, 12H), 6.16 (d, *J* = 6.8 Hz, 2H), 4.88 (d, *J* = 13.0 Hz, 2H), 3.66 (d, *J* = 13.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 149.6, 140.9, 140.0, 136.4, 132.9, 131.3, 130.8, 130.0, 129.8, 128.6, 128.5, 127.8, 127.6, 126.6, 126.3, 108.5, 45.9; IR (KBr) 3053, 2925, 2852, 2360, 1593, 703 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{39}H_{29}N_2$ $[M+H]^+$ 525.2331, found 525.2331; mp 143.5-144.0 °C; $[\alpha]^{20}_D$ −170.3 (*c* 0.20, $CHCl_3$).

Synthesis of 1n

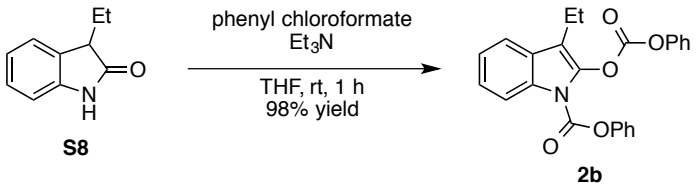


To a solution of **S7**[15] (201 mg, 0.367 mmol), 4-bromopyridine hydrochloride (143 mg, 0.734 mmol), NaO*t*-Bu (212 mg, 2.21 mmol), RuPhos (13.7 mg, 29.4 μmol) in toluene (3.70 mL) was added $Pd(dba)_2$ (8.60 mg, 15.0 μmol) at room temperature. The reaction mixture was warmed up to 90 °C and stirred for 24 h. After being cooled to room temperature, $CHCl_3$ (10 mL) and water (5 mL) was added to reaction mixture, and then passed through a short pad of celite. The resulting solution was extracted with $CHCl_3$ (5 mL × 2) and the organic layer was washed with brine (10 mL×2), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by recrystallization from $CHCl_3$/hexane gave **1n** (187 mg, 0.299 mmol, 81% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 4H), 7.83 (bd, *J* = 5.6 Hz, 4H), 7.57-7.49 (m, 10H), 7.36 (t, *J* = 7.4 Hz, 4H), 6.05 (d, *J* = 5.6 Hz, 2H), 4.97 (bd, *J* = 13.2 Hz, 2H), 3.79 (bd, *J* = 13.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 149.5, 139.9, 136.4, 133.3, 133.0, 132.6, 131.4, 130.9, 130.4, 128.9, 128.6, 128.2, 127.8, 126.8, 126.7, 126.5,

126.4, 108.6, 46.3; IR (KBr) 3053, 2866, 2359, 1589, 749 cm^{-1}; HRMS (FAB^+) calculated for $C_{47}H_{33}N_2$ $[M+H]^+$ 625.2644, found 625.2662; mp >280 °C; $[\alpha]^{20}_D$ −173.6 (*c* 0.20, $CHCl_3$).

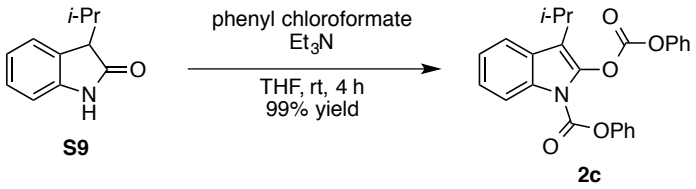
Synthesis of 2b



To a solution of **S8**[16] (239 mg, 1.48 mmol) and triethylamine (850 μL, 6.10 mmol) in THF (5.00 mL) was added phenyl chloroformate (753 μL, 6.00 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then 1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with EtOAc (10 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 10/1 to 8/1, v/v) gave **2b** (586 mg, 1.46 mmol, 98% yield) as a greenish yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 6.4 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.41-7.21 (m, 8H), 7.11 (d, *J* = 8.0 Hz, 2H), 2.77 (q, *J* = 7.7 Hz, 2H), 1.33 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 150.9, 149.9, 148.6, 136.6, 132.3, 129.7, 129.6, 127.3, 126.6, 126.5, 125.1, 123.7, 121.6, 120.7, 119.2, 115.7, 112.2, 16.0, 13.7; IR (KBr) 2965, 1792, 1753, 1458, 1204, 1015, 745 cm^{-1}; HRMS (FAB^+) calculated for $C_{24}H_{20}NO_5$ $[M+H]^+$ 402.1341, found 402.1328; mp 83.7-84.4 ºC.

Synthesis of 2c

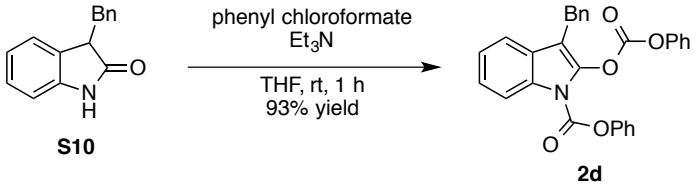


To a solution of **S9**[17] (262 mg, 1.50 mmol) and triethylamine (850 μL, 6.10 mmol) in THF (5.00 mL) was added phenyl chloroformate (753 μL, 6.00 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature, and then 1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with EtOAc (10mL × 3), dried over $MgSO_4$ and

concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 5/1, v/v) gave **2c** (619 mg, 1.49 mmol, 99% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.39-7.29 (m, 8H), 7.11 (d, *J* = 7.9 Hz, 2H), 3.27 (quin, *J* = 7.0 Hz, 1H), 1.46 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 150.9, 149.9, 148.6, 136.0, 132.4, 129.7, 129.6, 126.7, 126.6, 126.5, 124.9, 123.6, 121.6, 120.7, 119.9, 115.7, 115.7, 24.5, 21.6; IR (KBr) 2963, 1790, 1749, 1456, 1364, 1120, 748 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{25}H_{22}NO_5$ $[M+H]^+$ 416.1498, found 416.1511; mp 75.9-76.6 ºC.

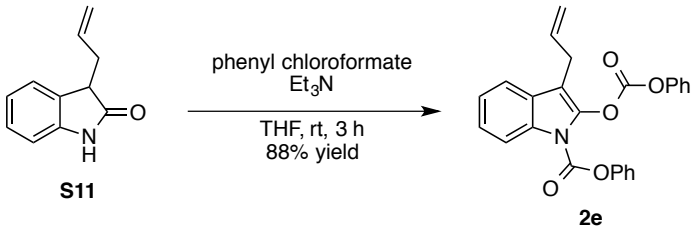
Synthesis of 2d



To a solution of **S10**[18] (670 mg, 3.00 mmol) and triethylamine (1.05 mL, 7.53 mmol) in THF (9.38 mL) was added phenyl chloroformate (945 μL, 7.53 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then 0.1 M aqueous HCl (20 mL) was carefully added. The resulting solution was extracted with EtOAc (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc 15/1 to 10/1 and hexane/EtOAc = 20/1, v/v) gave **2d** (1.30 g, 2.80 mmol, 93% yield) as a colorless solid.

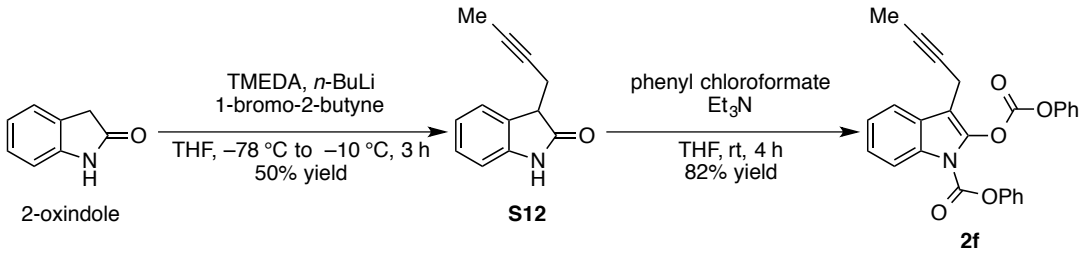
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.49-7.20 (m, 16H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 151.1, 150.9, 150.0, 148.7, 138.6, 137.9, 132.5, 129.8, 129.7, 128.7, 127.4, 126.8, 126.7, 125.3, 124.0, 121.7, 121.0, 120.1, 119.8, 115.8, 109.5, 28.9; IR (KBr) 3059, 1782, 1747, 1647, 1367, 1184, 752 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{29}H_{22}NO_5$ $[M+H]^+$ 464.1498, found 464.1488; mp 111.1-111.9 ºC.

Synthesis of 2e



To a solution of **S11**[16] (522 mg, 3.01 mmol) and triethylamine (920 μL, 6.60 mmol) in THF (9.38 mL) was added phenyl chloroformate (830 μL, 6.62 mmol) at room temperature. The reaction mixture was stirred for 2.5 h at room temperature, then additional triethylamine (139 μL, 1.00 mmol) and phenyl chloroformate (126 μL, 1.00 mmol) were added at room temperature because starting material was not disappeared. The reaction mixture was stirred for additional 30 min at room temperature, and then 0.1 M aqueous HCl (20 mL) was carefully added. The resulting solution was extracted with EtOAc (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 2/1, v/v) gave **2e** (1.10 g, 2.66 mmol, 88% yield) as a colorless solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.49-7.22 (m, 10H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.06-5.96 (m, 1H), 5.23 (d, *J* = 13.4 Hz, 1H), 5.14 (d, *J* = 13.4 Hz, 1H), 3.51 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 151.0, 150.0, 148.7, 137.6, 134.5, 132.4, 129.9, 129.7, 127.4, 126.8, 126.7, 126.4, 125.3, 123.9, 121.7, 121.0, 120.9, 119.6, 116.7, 115.8, 108.4, 27.1; IR (KBr) 3070, 1782, 1645, 1458, 1375, 748 cm^{-1}; HRMS (FAB^+) calculated for $C_{25}H_{20}NO_5$ $[M+H]^+$ 414.1341, found 414.1363; mp 79.2-80.1 ºC.

Synthesis of 2f



To a solution of 2-oxindole (2.10 g, 15.8 mmol) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine [TMEDA] (7.00 mL, 46.8 mmol) in THF (103 mL) was added dropwise a solution of *n*-BuLi (1.55 M, 22.0 mL, 34.1 mmol) in hexane at −78 °C and warmed up to −10 °C using ice/brine bath. The

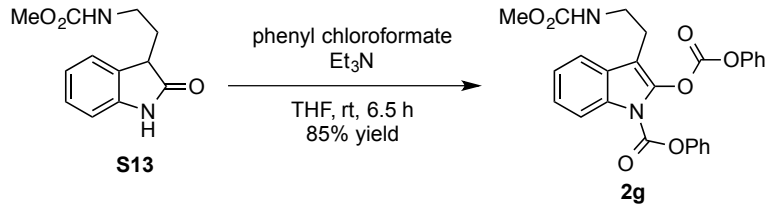
reaction mixture was stirred for 1 h at −10 °C, and then 1-bromo-2-butyne (1.65 mL, 18.8 mmol) was added. The reaction mixture was stirred for additional 3 h at −10 °C, and then saturated aqueous NH_4Cl (50 mL) was added. The resulting solution was extracted with EtOAc (50 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: toluene/EtOAc = 10/1 to 7/1 to 5/1, v/v) gave **S12** (1.42 g, 7.68 mmol, 50% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 3.53 (dd, *J* = 8.7, 4.5 Hz, 1H), 2.92 (ddq, *J* = 16.6, 4.5, 2.5 Hz, 1H), 2.57 (ddq, *J* = 16.6, 8.7, 2.5 Hz, 1H), 1.76 (t, *J* = 2.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 141.9, 129.0, 128.3, 124.5, 122.3, 110.0, 77.7, 75.2, 45.4, 20.6, 3.5; IR (KBr) 3034, 1697, 1470, 1319, 1236, 746 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{12}H_{12}NO$ $[M+H]^+$ 186.0919, found 186.0942; mp 146.4-146.7 ºC.

To a solution of **S12** (1.00 g, 5.40 mmol) and triethylamine (1.75 mL, 12.6 mmol) in THF (18.0 mL) was added phenyl chloroformate (1.60 mL, 12.8 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, then additional triethylamine (875 μL, 6.28 mmol) and phenyl chloroformate (800 μL, 6.38 mmol) was added at room temperature because starting material was not disappeared. The reaction mixture was stirred for additional 1 h at room temperature, and then 1 M aqueous HCl (20 mL) was carefully added. The resulting solution was extracted with Et_2O (30 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by recrystallization from EtOAc/hexane gave **2f** (1.88 g, 4.43 mmol, 82% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 6.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.44-7.21 (m, 8H), 7.13 (d, *J* = 7.6 Hz, 2H), 3.62 (dd, *J* = 5.0, 2.6 Hz, 2H), 1.80 (t, *J* = 2.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 150.0, 148.6, 137.1, 132.2, 129.8, 129.6, 126.8, 126.8, 126.6, 125.4, 123.9, 121.6, 120.7, 119.6, 115.7, 106.5, 77.0, 74.4, 13.1, 3.6; IR (KBr) 3059, 1782, 1741, 1649, 1460, 1368, 1206, 748 cm^{-1}; HRMS (EI$^+$) calculated for $C_{26}H_{19}NO_5$ $[M]^+$ 425.1263, found 425.1254; mp 134.8-135.7 ºC.

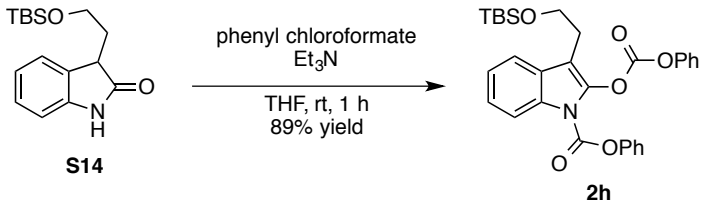
Synthesis of 2g



To a solution of **S13**[19] (470 mg, 2.00 mmol) and triethylamine (700 μL, 5.02 mmol) in THF (6.60 mL) was added phenyl chloroformate (640 μL, 5.10 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature, then additional triethylamine (350 μL, 2.51 mmol) and phenyl chloroformate (300 μL, 2.39 mmol) was added at room temperature because starting material was not disappeared. The reaction mixture was stirred for additional 4.5 h at room temperature, and then 1 M aqueous HCl (5 mL) was carefully added. The resulting solution was extracted with EtOAc (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1, v/v) gave **2g** (800 mg, 1.69 mmol, 85% yield) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.41-7.22 (m, 8H), 7.13 (d, J = 7.6 Hz, 2H), 4.96 (bs, 1H), 3.63 (s, 3H), 3.55 (dd, J = 12.6, 6.4 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 151.7, 150.9, 149.9, 148.6, 138.1, 132.5, 129.9, 129.7, 127.1, 126.9, 126.7, 125.5, 124.1, 121.7, 120.8, 119.2, 115.9, 107.8, 52.2, 40.1, 23.3; IR (KBr) 3331, 2926, 1784, 1738, 1682, 1649, 1593, 1528, 1495, 1381, 1330, 1250, 758 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{26}H_{23}N_2O_7$ $[M+H]^+$ 475.1505, found 475.1528; mp 109.6-110.7 ºC.

Synthesis of 2h

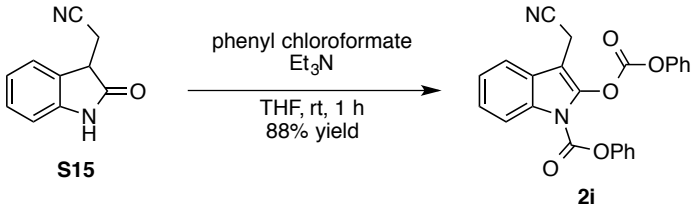


To a solution of **S14**[16] (3.09 g, 10.6 mmol) and triethylamine (4.44 mL, 31.8 mmol) in THF (35.0 mL) was added phenyl chloroformate (3.99 mL, 31.8 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then 1 M aqueous HCl (20 mL) was carefully added. The resulting solution was extracted with EtOAc (50 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography

on silica gel (eluent: hexane/Et_2O = 5/1 to 3/1, v/v) gave **2h** (5.02 g, 9.44 mmol, 89% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.43-7.21 (m, 8H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.90 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 151.0, 150.0, 148.7, 137.8, 132.4, 129.9, 129.7, 127.8, 126.8, 125.2, 123.8, 121.7, 120.9, 120.8, 119.7, 115.7, 107.9, 62.4, 26.7, 26.1, 18.5, −5.2; IR (KBr) 2897, 1750, 1628, 1589, 1457, 1365, 1223, 1082, 842, 748 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{30}H_{34}NO_6Si$ $[M+H]^+$ 532.2155, found 532.2135; mp 65.1-66.0 ºC.

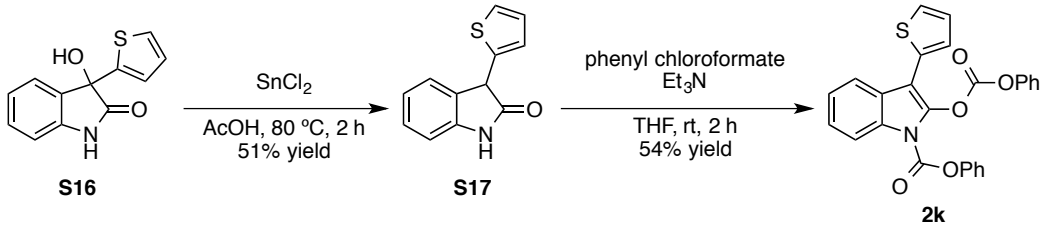
Synthesis of 2i



To a solution of **S15**[20] (600 mg, 3.49 mmol) and triethylamine (1.46 mL, 10.4 mmol) in THF (11.6 mL) was added phenyl chloroformate (1.31 mL, 10.4 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then 1 M aqueous HCl (5 mL) was carefully added. The resulting solution was extracted with EtOAc (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 3/1, v/v) and recrystallization from EtOAc/hexane gave **2i** (1.26 g, 3.06 mmol, 88% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.53-7.20 (m, 10H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 150.8, 149.8, 148.4, 138.5, 132.1, 130.0, 129.8, 127.1, 126.9, 126.2, 125.4, 124.6, 121.6, 120.8, 118.7, 116.0, 99.6, 12.1; IR (KBr) 3065, 2253, 1786, 1755, 1649, 1458, 1364, 1209, 750 cm^{-1}; HRMS (EI$^+$) calculated for $C_{24}H_{16}N_2O_5$ $[M]^+$ 412.1059, found 412.1085; mp 157.4-158.1 ºC.

Synthesis of 2k



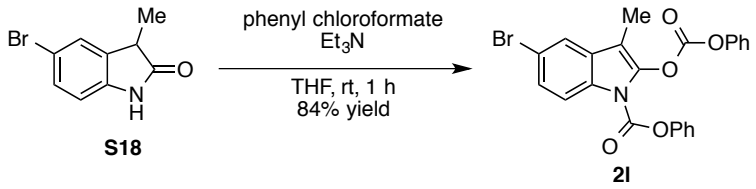
To a solution of **S16**[21] (1.94 g, 8.40 mmol) in AcOH (84.0 mL) was added $SnCl_2$ (3.20 g, 16.9 mmol) at room temperature. The reaction mixture was stirred for 2 h at 80 °C. Next, the solution was cooled to room temperature, concentrated *in vacuo*, and then diluted with EtOAc (50 mL). The solution was washed with water (10 mL × 3), saturated aqueous $NaHCO_3$ (10 mL × 3), and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 3/1, v/v) gave **S17** (927 mg, 4.31 mmol, 51% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.26-7.25 (m, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.03-6.99 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 4.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 141.5, 137.8, 128.9, 128.8, 127.2, 126.4, 125.5, 122.9, 110.3, 47.7; IR (KBr) 3213, 1717, 1470, 1327, 752 cm^{-1}, HRMS (EI^+) calculated for $C_{12}H_9NO_5S$ $[M]^+$ 215.0405, found 215.0376; mp 156.1-156.7 ºC.

To a solution of **S17** (901 mg, 4.18 mmol) and triethylamine (1.85 mL, 13.3 mmol) in THF (14.0 mL) was added phenyl chloroformate (1.73 mL, 13.8 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature, and then 0.1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with EtOAc (20 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 3/1, v/v) gave **2k** (1.04 g, 2.28 mmol, 54% yield) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.96 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.51-7.31 (m, 11H), 7.24-7.21 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 149.9, 148.6, 136.6, 132.3, 131.5, 129.9, 129.7, 127.7, 126.8, 126.5, 125.9, 125.8, 125.7, 124.5, 121.6, 120.9, 120.4, 115.9, 106.2; IR (KBr) 2917, 2183, 1791, 1758, 1520, 1110, 725 cm^{-1}; HRMS (FAB^+) calculated for $C_{26}H_{18}NO_5S$ $[M+H]^+$ 456.0906, found 456.0922; mp 152.9-153.1 ºC.

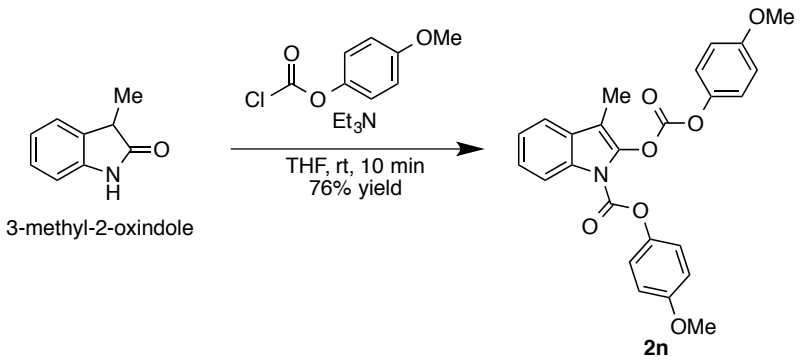
Synthesis of 2l



To a solution of **S18**[18] (680 mg, 3.01 mmol) and triethylamine (1.13 mL, 8.11 mmol) in THF (9.38 mL) was added phenyl chloroformate (1.02 mL, 8.13 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, and then 0.1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with EtOAc (10 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by recrystallization from CH_2Cl_2/hexane and flash column chromatography on a short pad of silica gel (eluent: CH_2Cl_2) gave **2l** (1.18 g, 2.53 mmol, 84% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.50-7.44 (m, 3H), 7.37-7.22 (m, 6H), 7.10 (d, J = 7.6 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ151.2, 150.9, 149.9, 148.4, 137.9, 131.0, 130.0, 129.9, 129.7, 128.1, 126.9, 126.8, 122.0, 121.6, 120.8, 117.2, 117.2, 106.0, 7.1; IR (KBr) 2916, 1782, 1749, 1649, 1494, 1458, 1363, 731 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{23}H_{17}BrNO_5$ $[M+H]^+$ 466.0290, found 466.0263; mp 163.1-163.7 ºC.

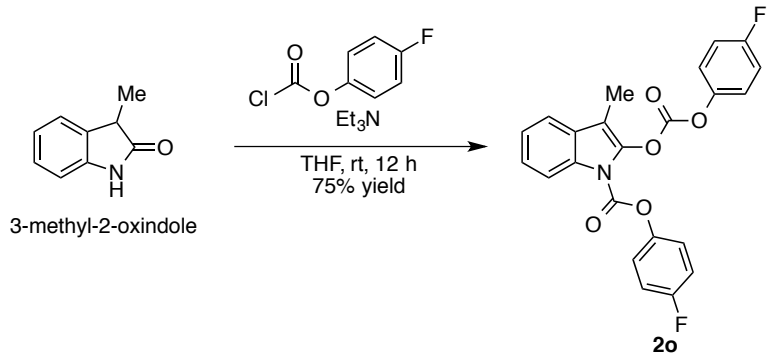
Synthesis of 2n



To a solution of 3-methyl-2-oxindole (1.49 g, 10.1 mmol) and triethylamine (3.2 mL, 23.0 mmol) in THF (30.0 mL) was added 4-methoxyphenyl chloroformate (3.00 mL, 20.2 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature, and then 1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with Et_2O (50 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 1/1, v/v) and recrystallization from

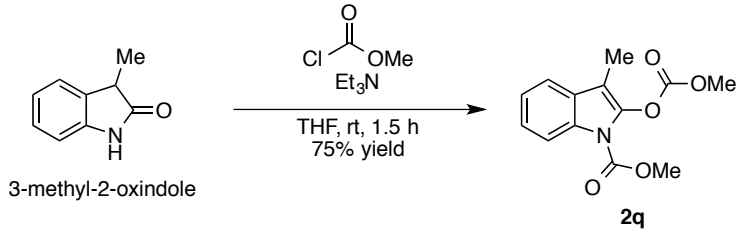
Et_2O/hexane gave **2n** (3.09 g, 7.66 mmol, 76% yield) as a colorless solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.40-7.29 (m, 2H), 7.21 (d, *J* = 9.2 Hz, 2H), 7.04 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 157.8, 151.6, 149.0, 144.6, 143.5, 137.3, 132.3, 128.2, 125.1, 123.7, 122.5, 121.7, 119.1, 115.6, 114.7, 114.6, 106.2, 55.7, 55.6, 7.0; IR (KBr) 2361, 1776, 1736, 1508, 1364, 1207, 748 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{25}H_{22}NO_7$ $[M+H]^+$ 448.1396, found 448.1373; mp 109.3-109.8 ºC.

Synthesis of 2o



To a solution of 3-methyl-2-oxindole (147 mg, 1.00 mmol) and triethylamine (310 μL, 2.22 mmol) in THF (30.0 mL) was added 4-fluorophenyl chloroformate (290 μL, 2.21 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then 0.1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with Et_2O (30 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 2/1, v/v) gave **2o** (317 mg, 0.748 mmol, 75% yield) as a colorless solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 6.8 Hz, 1H), 7.39-7.34 (m, 2H), 7.17-7.02 (m, 8H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (d, *J* = 245.3 Hz), 160.7 (d, *J* = 244.4 Hz), 151.4, 148.7, 146.8 (d, *J* = 2.9 Hz), 145.8 (d, *J* = 2.9 Hz), 137.1, 132.2, 128.2, 125.4, 124.0, 123.3 (d, *J* = 8.6 Hz), 122.4 (d, *J* = 8.6 Hz), 119.3, 116.6 (d, *J* = 22.9 Hz), 116.4 (d, *J* = 22.9 Hz), 115.6, 106.8, 7.2; IR (KBr) 3061, 1792, 1655, 1518, 1379, 1188, 837 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{23}H_{16}F_2NO_5$ $[M+H]^+$ 424.0997, found 424.1001; mp 123 ºC dec.

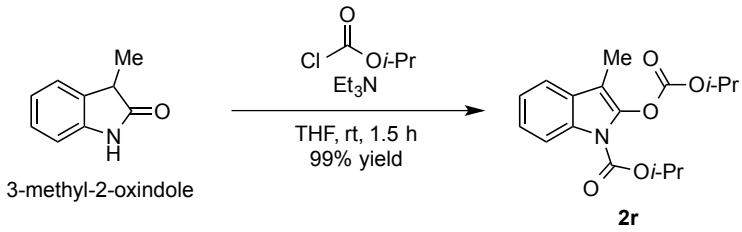
Synthesis of 2q



To a solution of 3-methyl-2-oxindole (1.47 g, 9.99 mmol) and triethylamine (5.60 mL, 40.2 mmol) in THF (30.0 mL) was added methyl chloroformate (3.10 mL, 40.1 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature, and then 1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with EtOAc (30 mL× 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 3/1 to 1/1, v/v) gave **2q** (1.97 g, 7.48 mmol, 75% yield) as a orange solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.33 (td, *J* = 7.7, 1.6 Hz, 1H), 7.28 (td, *J* = 7.7, 1.0 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 150.9, 137.6, 132.0, 128.1, 124.8, 123.4, 119.0, 115.4, 105.4, 56.3, 53.9, 7.0; IR (KBr) 2961, 1775, 1732, 1653, 1460, 1356, 1273, 1040, 934, 754 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{13}H_{14}NO_5$ $[M+H]^+$ 264.0872, found 264.0883; mp 51.3-51.9 ºC.

Synthesis of 2r



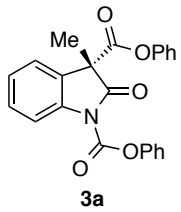
To a solution of 3-methyl-2-oxindole (1.47 g, 9.99 mmol) and triethylamine (5.60 mL, 40.2 mmol) in THF (30.0 mL) was added isopropyl chloroformate (5.50 mL, 40.0 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature, and then 1 M aqueous HCl (10 mL) was carefully added. The resulting solution was extracted with EtOAc (30 mL × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 6/1, v/v) gave **2r** (3.16 g, 9.90 mmol, 99%

yield) as a pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.31 (td, *J* = 7.8, 1.6 Hz, 1H), 7.28-7.22 (m, 1H), 5.26 (sep, *J* = 6.1 Hz, 1H), 5.02 (sep, *J* = 6.1 Hz, 1H), 2.15 (s, 3H), 1.43 (d, *J* = 6.2 Hz, 6H), 1.42 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.1, 150.0, 137.9, 132.2, 128.1, 124.5, 123.1, 118.8, 115.5, 74.3, 71.5, 22.0, 21.8, 7.0; IR (KBr) 2984, 1755, 1708, 1651, 1456, 1099, 912, 752 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{12}H_{22}NO_5$ $[M+H]^+$ 320.1498, found 320.1493.

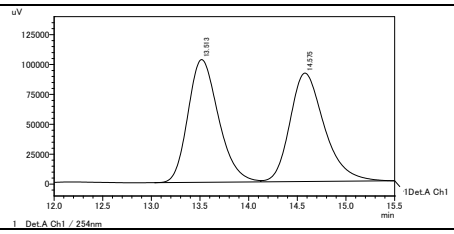
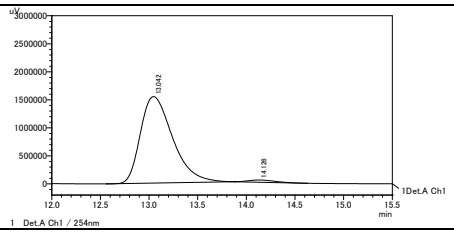
Analytical data for products 3a−3q of Steglich rearrangement

(*S*)-Diphenyl 3-methyl-2-oxoindoline-1,3-dicarboxylate (3a)[11]

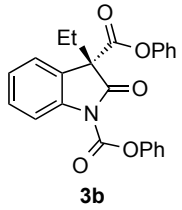


3a

According to general procedure, substrate **2a**[11] (77.3 mg, 0.200 mmol) with a solution of catalyst **1g** (20.0 μL, 50.0 mM in THF, 1.00 μmol) in THF (0.500 mL) at −20 ºC gave a pale yellow solid (77.2 mg, 0.199 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 85/15, v/v, flow rate = 0.300 mL/min, 30 °C, UV = 254 nm), T_R = 13.0 min (major) and T_R = 14.1 min (minor), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 1H), 7.51-7.27 (m, 10H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 167.6, 150.2, 150.1, 149.3, 139.1, 129.9, 129.6, 129.5, 128.6, 126.6, 126.4, 125.7, 123.0, 121.5, 121.1, 115.9, 55.9, 20.9; IR (KBr) 3069, 1802, 1741, 1724, 1591, 1477, 1341, 1209, 1092, 959, 758 cm^{-1}; $[\alpha]^{21}_D$ +74.1 (*c* 1.03, CH_2Cl_2, 98:2 er).

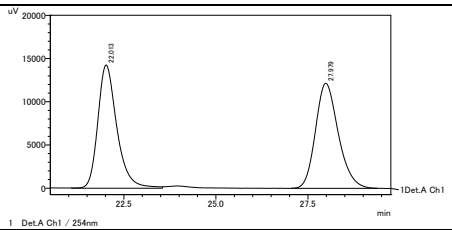
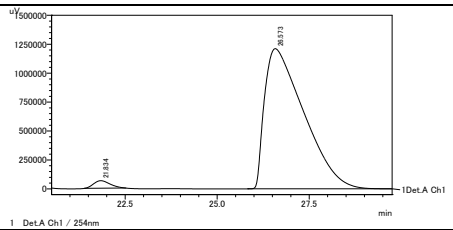
Racemic sample of **3a**				(*S*)-**3a**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	13.513	102652	50.170	1	13.042	35585727	97.899
2	14.575	90628	49.830	2	14.126	40017	2.101

(*S*)-Diphenyl 3-ethyl-2-oxoindoline-1,3-dicarboxylate (3b)

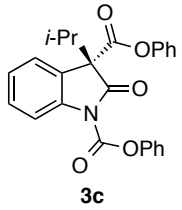


3b

According to general procedure, substrate **2b** (80.9 mg, 0.202 mmol) with a solution of catalyst **1g** (20.0 μL, 50.0 mM in THF, 1.00 μmol) in THF (0.500 mL) at −20 ºC gave a yellow solid (80.2 mg, 0.200 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 97.5/2.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 21.8 min (minor) and T_R = 26.6 min (major), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.50-7.39 (m, 4H), 7.38-7.27 (m, 6H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 2.56 (dq, *J* =13.9, 7.4 Hz, 2H), 2.42 (dq, *J* = 13.9, 7.4 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 167.5, 150.3, 150.2, 149.4, 140.0, 130.0, 129.8, 129.6, 126.7, 126.6, 126.5, 125.8, 123.3, 121.6, 121.3, 115.9, 60.9, 28.4, 8.3; IR (KBr) 3078, 2970, 1811, 1784, 1749, 1722, 1591, 1476, 1206 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{24}H_{20}NO_5$ $[M+H]^+$ 402.1341, found 402.1369; mp 133.1-133.7 ºC; $[\alpha]^{20}_D$ +60.3 (*c* 0.51, CH_2Cl_2, 98:2 er).

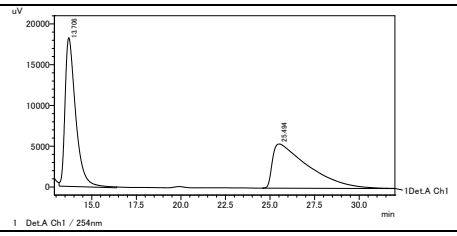
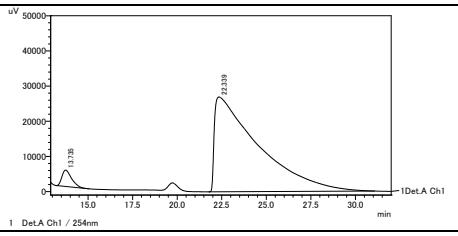
Racemic sample of **3b**				(*S*)-**3b**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	22.013	514169	49.559	1	21.834	2020595	2.198
2	27.979	523324	50.441	2	26.573	89913781	97.802

(*S*)-Diphenyl 3-isopropyl-2-oxoindoline-1,3-dicarboxylate (3c)

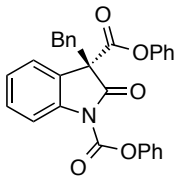


3c

According to general procedure, substrate **2c** (41.1 mg, 0.0989 mmol) with catalyst **1g** (3.00 mg, 3.12 μmol) in THF (0.250 mL) at 25 ºC gave a colorless solid (40.9 mg, 0.0984 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 99.3/0.7, v/v, flow rate = 1.50 mL/min, 30 °C, UV = 254 nm), T_R = 13.7 min (minor) and T_R = 22.3 min (major), 96:4 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.50-7.19 (m, 10H), 7.02 (d, *J* = 7.2 Hz, 2H), 2.96 (sep, *J* = 7.1 Hz, 1H), 1.31 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.2, 150.4, 150.2, 149.4, 139.7, 129.8, 129.7, 129.6, 126.7, 126.6, 126.5, 125.6, 123.9, 121.7, 121.4, 115.5, 63.8, 36.3, 17.5, 17.2; IR (KBr) 2968, 1811, 1748, 1489, 1207, 761 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{25}H_{22}NO_5$ $[M+H]^+$ 416.1492, found 416.1495; mp 153.1-154.1 ºC; $[\alpha]^{24}_D$ +30.0 (*c* 0.62, CH_2Cl_2, 96:4 er).

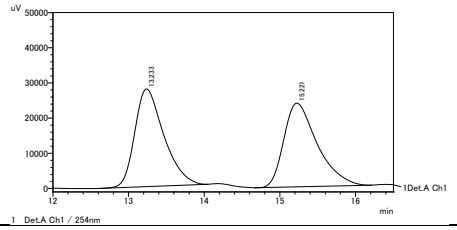
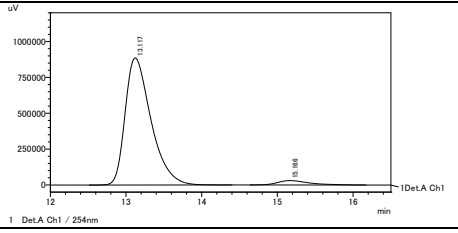
Racemic sample of **3c**				(*S*)-**3c**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	13.706	756612	49.881	1	13.735	175480	3.656
2	25.494	760216	50.119	2	22.339	4624284	96.344

(*S*)-Diphenyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (3d)

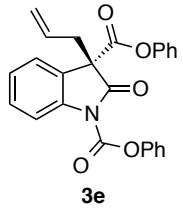


3d

According to general procedure, substrate **2d** (92.6 mg, 0.200 mmol) with a solution of catalyst **1g** (20.0 μL, 50.0 mM in THF, 1.00 μmol) in THF (0.500 mL) at −20 ºC gave a pale yellow solid (91.6 mg, 0.198 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 13.1 min (major) and T_R = 15.2 min (minor), 96:4 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.44-7.09 (m, 13H), 7.02 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 167.4, 150.4, 150.1, 148.9, 139.9, 133.4, 130.2, 130.1, 129.7, 129.6, 128.2, 127.5, 126.7, 126.6, 126.3, 125.5, 123.7, 121.6, 121.3, 115.8, 61.8, 41.1; IR (KBr) 3062, 1809, 1778, 1747, 1497, 1350, 1184, 744 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{29}H_{22}NO_5$ $[M+H]^+$ 464.1498, found 464.1479; mp 147.9-148.3 ºC; $[\alpha]^{24}_D$ +37.9 (*c* 0.45, CH_2Cl_2, 96:4 er).

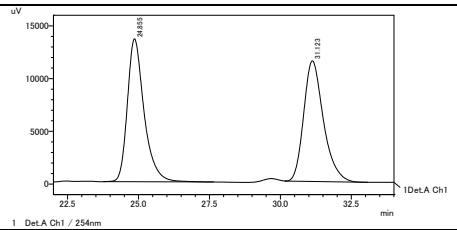
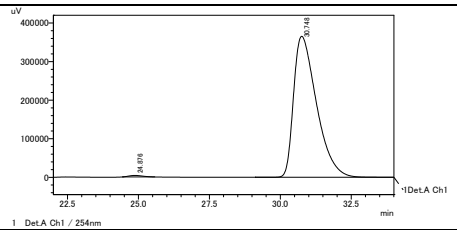
Racemic sample of **3d**				(*S*)-**3d**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	13.233	743275	50.426	1	13.117	21032544	95.986
2	15.221	730703	49.574	2	15.166	879600	4.014

(*S*)-Diphenyl 3-allyl-2-oxoindoline-1,3-dicarboxylate (3e)

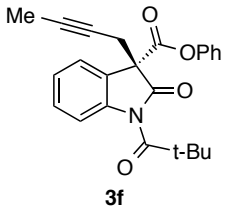


3e

According to general procedure, substrate **2e** (82.7 mg, 0.200 mmol) with a solution of catalyst **1g** (20.0 μL, 50.0 mM in THF, 1.00 μmol) in THF (0.500 mL) at −20 ºC gave a pale yellow solid (82.5 mg, 0.200 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 24.9 min (minor) and T_R = 30.7 min (major), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.47-7.40 (m, 4H), 7.37-7.20 (m, 7H), 6.99 (d, *J* = 8.4 Hz, 2H) 5.58-5.47 (m, 1H), 5.18 (dd, *J* = 13.6, 1.4 Hz, 1H), 5.09 (dd, *J* = 13.6, 1.4 Hz, 1H), 3.17 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 167.1, 150.3, 150.2, 149.3, 139.8, 130.1, 129.7, 129.6, 126.7, 126.5, 126.4, 126.3, 125.7, 123.6, 121.6, 121.3, 121.1, 115.9, 60.2, 39.2; IR (KBr) 3066, 1788, 1751, 1477, 1224, 1159, 750 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{25}H_{20}NO_5$ $[M+H]^+$ 414.1341, found 414.1335; mp 164.1-165.0 ºC; $[\alpha]^{24}_D$ +67.4 (*c* 0.76, CH_2Cl_2, 99:1 er).

Racemic sample of **3e**				(*S*)-**3e**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	24.855	555399	50.042	1	24.876	129407	0.627
2	31.123	554476	49.958	2	30.748	20522041	99.373

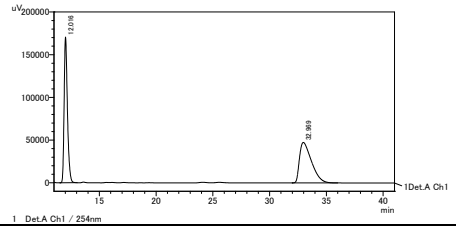
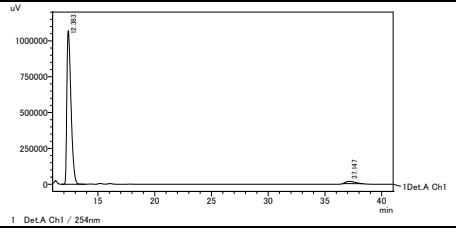
(*S*)-Diphenyl 3-(but-2-yn-1-yl)-2-oxoindoline-1,3-dicarboxylate (3f)



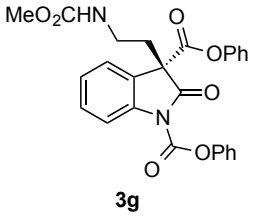
3f

According to general procedure, substrate **2f** (42.0 mg, 0.0987 mmol), THF (0.250 mL) with a solution of catalyst **1g** (10.0 μL, 50.0 mM in THF, 0.500 μmol) at −20 ºC gave a colorless solid (41.7 mg, 0.0980 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 85/15, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 12.4 min (major) and T_R = 37.1 min (minor), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.52-7.42 (m, 4H), 7.38-7.28 (m, 6H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 3.25 (dd, *J* = 2.3, 2.0 Hz, 2H), 1.64 (t, *J* = 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.5, 150.2, 150.2, 149.3, 140.1, 130.2, 129.7, 129.6, 126.7, 126.4, 125.7, 123.4, 121.6, 121.2, 115.8, 79.5, 71.8, 59.5, 25.8, 3.5; IR (KBr) 2627, 2359, 2340, 1778, 1748, 1732, 1348, 1217, 1157, 689 cm^{-1}; HRMS (EI$^+$) calculated for $C_{26}H_{19}NO_5$ $[M]^+$ 425.1263, found 425.1263; mp 99.3-100.2 ºC;

$[\alpha]^{24}_{D}$ +9.9 (*c* 0.85, CH_2Cl_2, 97:3 er).

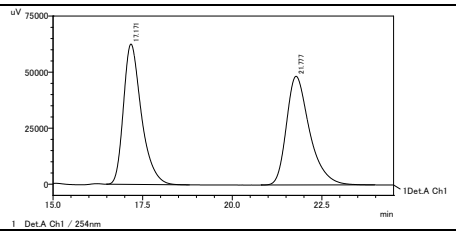
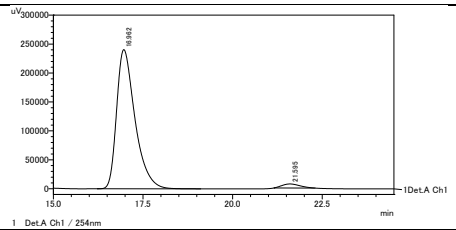
Racemic sample of **3f**				(*S*)-**3f**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	12.016	3434305	49.724	1	12.383	27117262	96.847
2	32.969	3472435	50.276	2	37.147	882922	3.153

(*R*)-Diphenyl 3-(2-((methoxycarbonyl)amino)ethyl)-2-oxoindoline-1,3-dicarboxylate (3g)

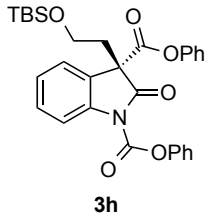


3g

According to general procedure, substrate **2g** (47.4 mg, 0.100 mmol), THF (0.250 mL) with a solution of catalyst **1g** (10.0 μL, 50.0 mM in THF, 0.500 μmol) at −20 ºC gave a pale yellow solid (47.2 mg, 0.0991 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 80/20, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 17.0 min (major) and T_R = 21.6 min (minor), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.55-7.40 (m, 4H), 7.39-7.27 (m, 6H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 4.81 (bs, 1H), 3.57 (s, 3H), 3.37-3.15 (m, 2H), 2.28-2.75 (m, 1H), 2.67-2.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 167.1, 156.7, 150.2, 150.1, 149.2, 139.7, 130.3, 129.7, 129.6, 126.7, 126.6, 126.0, 123.4, 121.6, 121.2, 116.2, 58.7, 52.3, 36.7, 34.6; IR (KBr) 3404, 2951, 1748, 1593, 1479, 1350, 1221, 910, 750 cm^{-1}; HRMS (EI^+) calculated for $C_{26}H_{22}N_2O_7$ $[M]^+$ 474.1427, found 474.1415; mp 54.3-55.0 ºC; $[\alpha]^{23}_{D}$ +68.7 (*c* 0.51, CH_2Cl_2, 97:3 er).

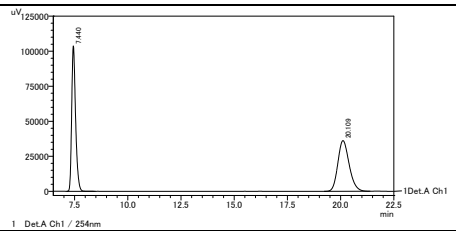
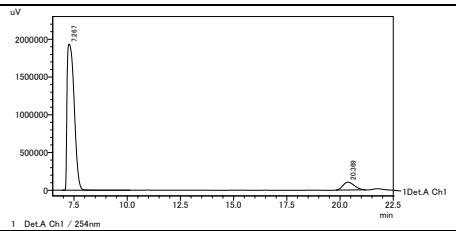
Racemic sample of **3g**				(*S*)-**3g**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	17.171	2182252	50.054	1	16.962	8578049	97.257
2	21.777	2177545	49.946	2	21.595	241908	2.743

(*S*)-diphenyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxoindoline-1,3-dicarboxylate (3h)

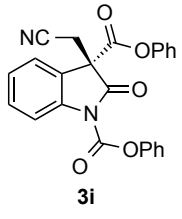


3h

According to general procedure, substrate **2h** (53.0 mg, 0.0997 mmol) with a solution of catalyst **1g** (10.0 μL, 50.0 mM in THF, 0.500 μmol) in THF (0.250 mL) at −20 ºC gave a colorless oil (52.7 mg, 0.0991 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 7.3 min (major) and T_R = 20.4 min (minor), 92:8 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.48-7.46 (m, 3H), 7.38-7.27 (m, 7H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 3.71 (ddd, *J* = 10.2, 4.8, 3.1 Hz, 1H), 3.41 (td, *J* = 10.2, 4.8 Hz, 1H), 2.89 (ddd, *J* = 14.9, 10.2, 4.8 Hz, 1H), 2.67 (dt, *J* = 14.9, 3.1 Hz, 1H), 0.76 (s, 9H), −0.12 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 167.8, 150.4, 150.3, 149.6, 140.5, 129.9, 129.6, 129.5, 126.5, 126.5, 125.9, 125.2, 123.5, 121.7, 121.3, 116.1, 58.9, 58.8, 36.2, 25.9, 18.4, −5.8, −5.8; IR (KBr) 2930, 1811, 1790, 1748, 1479, 1350, 1186, 752 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{30}H_{34}NO_6Si$ $[M+H]^+$ 532.2150, found 532.2134; $[\alpha]^{22}_D$ +29.4 (*c* 1.12, CH_2Cl_2, 92:8 er)

Racemic sample of **3h**				(*S*)-**3h**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	7.440	1325957	49.786	1	7.267	45012007	92.209
2	20.109	1337333	50.214	2	20.369	3803269	7.791

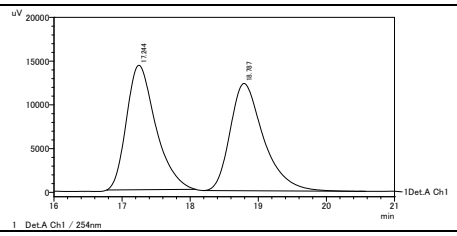
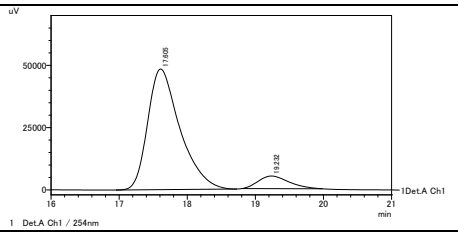
(*S*)-Diphenyl 3-(cyanomethyl)-2-oxoindoline-1,3-dicarboxylate (3i)



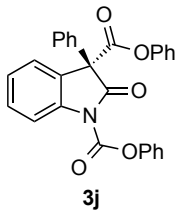
3i

According to general procedure, substrate **2i** (41.0 mg, 0.0994 mmol) with a solution of catalyst **1g** (10.0 μL, 50.0 mM in THF, 0.500 μmol) in THF (0.250 mL) at −20 ºC gave a pale yellow solid (40.8 mg, 0.0989 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 82/18, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 17.6 min (major) and T_R = 19.2 min (minor), 91:9 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.59-7.22 (m, 11H), 6.97 (d, *J* = 8.4 Hz, 2H), 3.51 (d, *J* = 16.8 Hz, 1H), 3.31 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.3, 150.0, 150.0, 148.9, 140.0, 131.5, 129.9, 129.8, 127.1, 127.0, 126.4, 124.1, 123.4, 121.5, 121.0, 116.7, 115.0, 56.8, 23.4; IR (KBr) 3059, 2978, 1809, 1782, 1755, 1602, 1481, 1348, 1217, 746, 689 cm^{-1}; HRMS (EI$^+$) calculated for

$C_{24}H_{16}N_2O_5$ $[M]^+$ 412.1059, found 412.1085; mp 130.0-130.9 ºC; $[\alpha]^{21}_D$ +35.2 (*c* 0.50, CH_2Cl_2, 91:9 er).

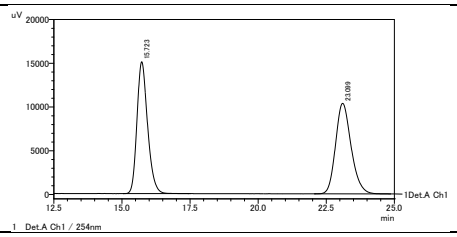
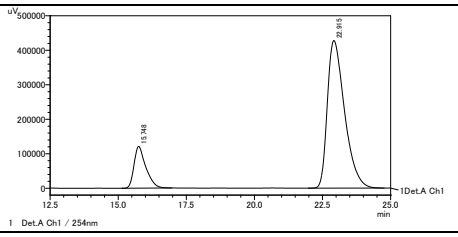
Racemic sample of **3i**				(*S*)-**3i**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	17.244	424561	50.356	1	17.605	1596012	90.985
2	18.787	418559	49.644	2	19.232	158136	9.015

(*S*)-Diphenyl 3-phenyl-2-oxoindoline-1,3-dicarboxylate (3j)[11]

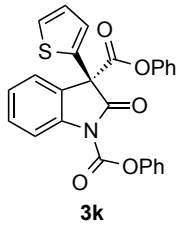


3j

According to general procedure, substrate **2j**[11] (45.2 mg, 0.101 mmol) with a catalyst **1g** (2.90 mg, 3.00 μmol) in THF (0.250 mL) at −20 ºC gave a colorless solid (45.0 mg, 0.100 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 15.7 min (minor) and T_R = 22.9 min (major), 84:16 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.56 (td, *J* = 7.8, 1.5 Hz, 1H), 7.48-7.20 (m, 14H), 7.04 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.2, 150.5. 150.2, 149.5, 140.2, 135.0, 130.6, 129.7, 129.6, 129.1, 129.0, 128.4, 126.7, 126.6, 126.0, 125.8, 125.6, 121.6, 121.2, 116.3, 64.8; IR (KBr) 3043, 2925, 1813, 1749, 1725, 1596, 1492, 1229, 841 cm^{-1};$[\alpha]^{22}_D$ +165.6 (*c* 0.27, CH_2Cl_2, 84:16 er).

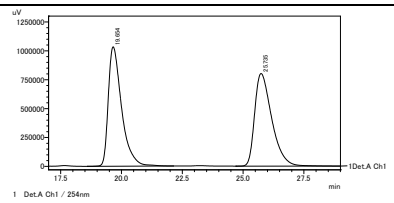
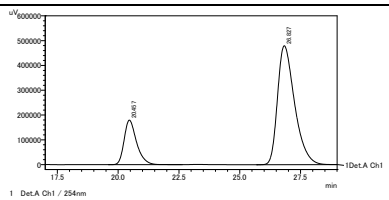
Racemic sample of **3j**				(*S*)-**3j**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	15.723	409768	49.925	1	15.748	3645897	16.244
2	23.099	410996	50.075	2	22.915	18798408	83.756

(*R*)-diphenyl 2-oxo-3-(thiophen-2-yl)indoline-1,3-dicarboxylate (3k)

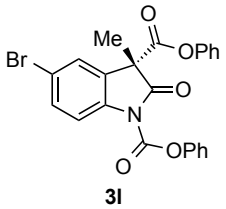


3k

According to general procedure, substrate **2k** (45.3 mg, 0.0995 mmol) with a catalyst **1g** (3.00 mg, 3.12 μmol) in THF (0.250 mL) at −20 ºC gave a brown solid (45.2 mg, 0.0992 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 20.5 min (minor) and T_R = 26.8 min (major), 79:21 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.2 Hz, 1H), 7.47-7.18 (m, 11H), 7.09-7.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.2, 150.4, 150.1, 149.3, 139.7, 136.6, 130.8, 129.7, 129.6, 128.3, 128.3, 127.5, 127.4, 127.1, 127.1, 126.7, 126.5, 125.8, 125.3, 121.5, 121.2, 116.2, 61.4; IR (KBr) 3108, 2929, 1813, 1749, 1722, 1600, 1491, 846 cm^{-1}; HRMS (ESI^+) calculated for $C_{26}H_{18}NO_5S$ $[M+H]^+$: 456.0827; found: 456.0917; mp 165.8-166.3 ºC; $[\alpha]_D^{21}$ +112.6 (*c* 0.51, CH_2Cl_2, 79:21 er).

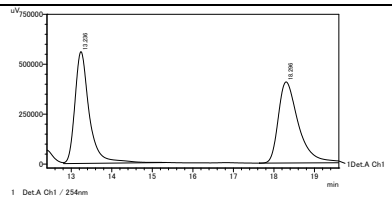
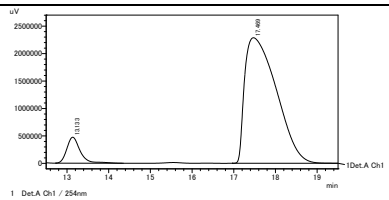
Racemic sample of **3k**				(*R*)-**3k**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	19.654	39311038	50.136	1	20.457	6376265	21.396
2	25.735	39098419	49.864	2	26.827	23424552	78.604

(*S*)-Diphenyl 5-bromo-3-methyl-2-oxoindoline-1,3-dicarboxylate (3l)

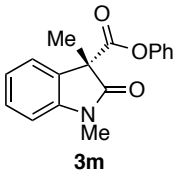


3l

According to general procedure, substrate **2l** (93.5 mg, 0.201 mmol) with a solution of catalyst **1g** (20.0 μL, 50.0 mM in THF, 1.00 μmol) in THF (0.500 mL) at −20 ºC gave a colorless solid (92.5 mg, 0.198 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 13.1 min (minor) and T_R = 17.5 min (major), 92:8 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.45 (t, *J* = 8.2 Hz, 2H), 7.38-7.22 (m, 5H), 7.00 (dd, *J* = 8.2, 0.8 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.1, 150.3, 150.0, 149.3, 138.2, 133.0, 130.5, 129.8, 129.7, 126.8, 126.7, 126.3, 121.5, 121.2, 118.7, 117.7, 55.9, 21.0; IR (KBr) 3072, 2630, 1813, 1782, 1739, 1475, 1340, 742 cm^{-1}; HRMS (FAB^+) calculated for $C_{23}H_{17}BrNO_5$ $[M+H]^+$ 464.1498, found 464.1488; mp 59.8-60.3 ºC; $[\alpha]^{24}_D$ +2.52 (*c* 0.52, CH_2Cl_2, 92:8 er).

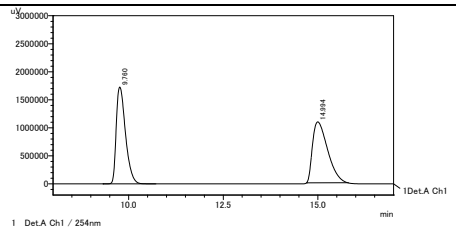
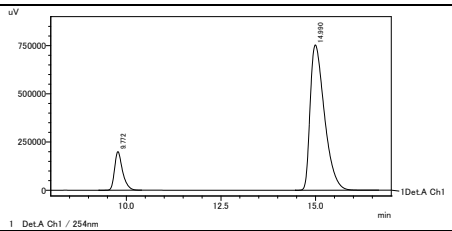
Racemic sample of **3l**				(*S*)-**3l**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	13.236	13821916	49.348	1	13.133	10516782	8.030
2	18.296	14187024	50.652	2	17.469	120452064	91.970

(*S*)-Phenyl 1,3-dimethyl-2-oxoindoline-3-carboxylate (3m)[11]

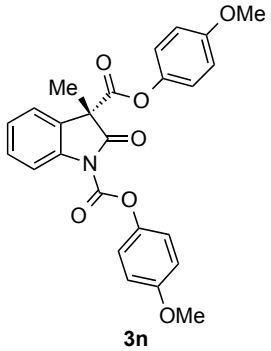


3m

According to general procedure, substrate **2m**[11] (27.9 mg, 0.100 mmol) with a solution of catalyst **1g** (10.0 μL, 50.0 mM in THF, 0.500 μmol) in THF (0.250 mL) at −20 ºC gave a colorless solid (27.9 mg, 0.100 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 9.8 min (minor) and T_R = 15.0 min (major), 87:13 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.22 (m, 4H), 7.21-7.09 (m, 2H), 6.97-6.88 (m, 3H), 3.29 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 168.6, 150.6, 143.9, 129.9, 129.5, 126.2, 123.2, 123.1, 121.4, 108.8, 55.3, 26.8, 20.1; IR (KBr) 1761, 1728, 1610, 1491, 1182, 1086, 743 cm^{-1}; $[\alpha]^{22}_D$ +28.4 (*c* 0.50, CH_2Cl_2, 87:13 er).

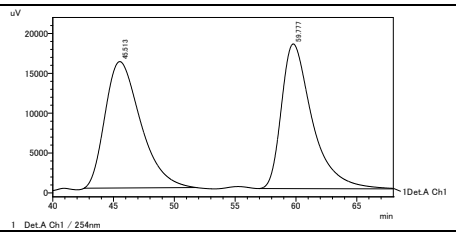
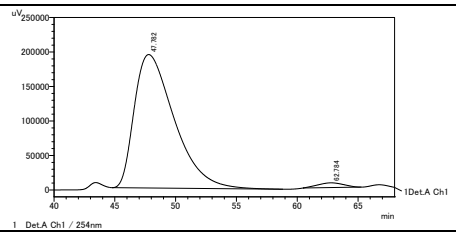
Racemic sample of **3m**				(*S*)-**3m**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	9.760	29335890	49.263	1	9.772	2945760	12.965
2	14.994	30213315	50.737	2	14.990	19774980	87.035

(*S*)-Bis(4-methoxyphenyl) 3-methyl-2-oxoindoline-1,3-dicarboxylate (3n)

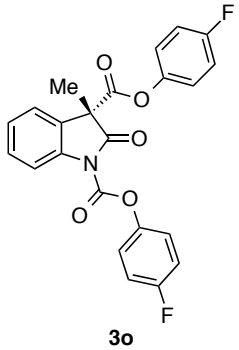


3n

According to general procedure, substrate **2n** (40.1 mg, 0.0993 mmol) with a catalyst **1g** (4.80 mg, 5.00 μmol) in THF (1.00 mL) at −20 ºC gave a brown oil (40.0 mg, 0.0991 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AS-3® (hexane/*i*-PrOH = 95/5, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 47.8 min (major) and T_R = 62.8 min (minor), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.47-7.38 (m, 2H), 7.32-7.16 (m, 3H), 6.98-6.80 (m, 6H), 3.83 (s, 3H), 3.77 (m, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.1, 157.9, 157.7, 149.8, 143.8, 143.7, 139.2, 129.9, 128.8, 125.8, 123.0, 122.4, 122.0, 116.0, 114.7, 114.5, 56.0, 55.7, 55.7, 21.0; IR (KBr) 2359, 1807, 1780, 1748, 1715, 1504, 1348, 1221, 1175, 1099, 764 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{25}H_{22}NO_7$ $[M+H]^+$ 448.1396, found 488.1423; $[\alpha]^{24}_D$ $[\alpha]^{21}_D$+103.3 (*c* 0.25, CH_2Cl_2, 98:2 er).

Racemic sample of **3n**				(*S*)-**3n**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	45.513	3232619	50.210	1	47.782	44320569	97.881
2	59.777	3205618	49.790	2	62.784	959339	2.119

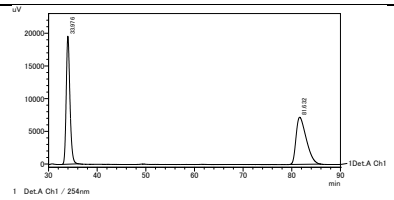
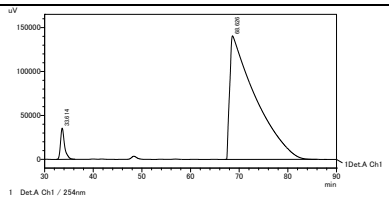
(*S*)-Bis(4-fluorophenyl) 3-methyl-2-oxoindoline-1,3-dicarboxylate (3o)



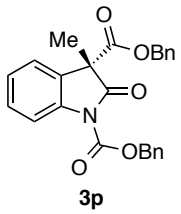
3o

According to general procedure, substrate **2o** (42.9 mg, 0.101 mmol) with a catalyst **1g** (5.00 mg, 5.20 μmol) in THF (1.00 mL) at −20 ºC gave a colorless solid (42.7 mg, 0.101 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 97.5/2.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 33.6 min (minor) and T_R = 68.6 min (major), 96:4 er; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.46 (td, *J* = 8.1, 1.3 Hz, 1H), 7.41 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.34-7.27 (m, 3H), 7.17-7.08 (m, 2H), 7.04-6.98 (m, 2H), 6.97-6.90 (m, 2H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 167.6, 160.6 (d, *J* = 244.4 Hz), 160.5 (d, *J* = 244.4 Hz), 149.2, 145.9 (d, *J* = 13.4 Hz), 138.9, 130.0, 128.6, 125.8, 123.0 (d, *J* = 8.6 Hz), 122.6 (d, *J* = 8.6 Hz), 116.4, 116.3, 116.2,

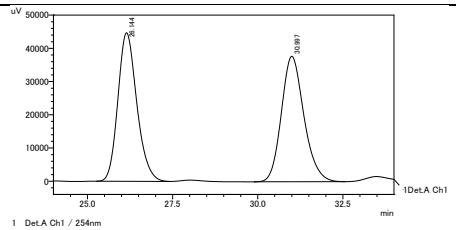
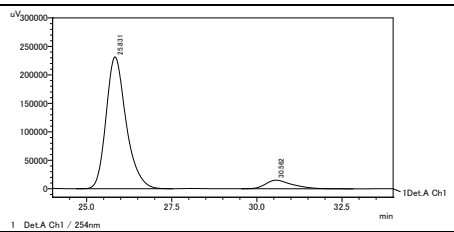
116.0, 115.9, 55.8, 20.9; IR (KBr) 1780, 1751, 1506, 1179, 831, 768 cm^{-1}; HRMS (FAB^+) calculated for $C_{23}H_{16}F_2NO_5$ $[M+H]^+$: 424.0997, found: 424.1001; mp 127.8-128.7 ºC; $[\alpha]^{24}_D$ +73.9 (*c* 0.58, CH_2Cl_2, 96:4 er).

Racemic sample of **3o**				(*S*)-**3o**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	33.976	1041862	49.883	1	33.614	2045765	3.826
2	81.632	1046766	50.117	2	68.626	51425941	96.174

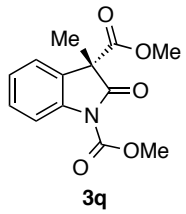
(*S*)-Dibenzyl 3-methyl-2-oxoindoline-1,3-dicarboxylate (3p)[22]


3p

According to general procedure, substrate **2p**[22] (37.1 mg, 0.100 mmol) with a catalyst **1g** (4.80 mg, 5.00 μmol) in THF (1.00 mL) at −20 ºC gave a colorless solid (36.9 mg, 94% conv): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 97.5/2.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 25.8 min (major) and T_R = 30.6 min (minor), 92:8 er; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.44-7.31 (m, 4H), 7.26-7.06 (m, 7H), 5.46 (s, 2H), 5.11 (s, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 168.8, 150.8, 139.3, 135.2, 134.9, 129.5, 128.8, 128.6, 128.6, 128.3, 128.2, 127.4, 125.2, 123.1, 115.7, 68.9, 67.6, 55.8, 20.7; IR (KBr) 2359, 1776, 1738, 1288, 1227, 696 cm^{-1}; $[\alpha]^{23}_D$ +26.9 (*c* 0.52, CH_2Cl_2, 92.5:7.5 er).

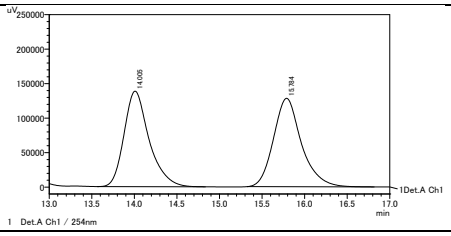
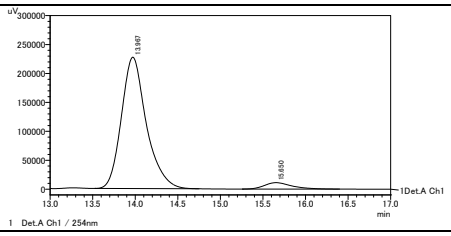
Racemic sample of **3p**				(*S*)-**3p**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	26.144	1729627	49.841	1	25.831	9461752	92.208
2	30.997	1740677	50.159	2	30.562	799572	7.792

(*S*)-dimethyl 3-methyl-2-oxoindoline-1,3-dicarboxylate (3q)



3q

According to general procedure, substrate **2q** (26.1 mg, 0.0991 mmol) with a catalyst **1g** (4.70 mg, 4.89 μmol) in THF (1.00 mL) at −20 ºC gave a colorless solid (25.8 mg, 88% conv): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK AD-H® (hexane/*i*-PrOH = 97.5/2.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 14.0 min (major) and T_R = 15.7 min (minor), 95:5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 1H), 7.38 (td, *J* = 7.7, 1.3 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 4.04 (s, 3H), 3.67 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 151.4, 139.2, 129.5, 128.9, 125.3, 123.0, 115.6, 55.6, 54.2, 53.4, 21.0; IR (KBr) 1801, 1778, 1742, 1439, 1350, 1244, 770 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{13}H_{14}NO_5$ $[M+H]^+$ 264.0872, found 264.0855; mp 89.3-89.9 ºC; $[\alpha]^{22}_D$ $[\alpha]_D^{21}$+80.3 (*c* 0.57, CH_2Cl_2, 93:7 er).

Racemic sample of **3q**				(*S*)-**3q**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	14.005	2832339	49.212	1	13.967	4624433	94.900
2	15.784	2923020	50.788	2	15.650	248504	5.100

X-ray Crystallography of 3c

Details of the crystal data and a summary of the intensity data collection parameters for **3c** is listed in Tables S2. Graphite-monochromated Mo Kα radiation (λ = 0.71075 Å) was used. The structures were solved by direct methods with SHELXS-97[23] or SIR2004.[24] and refined by full-matrix least-squares techniques against *F* (SHELXL-97). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. In the subsequent refinement, the function $\Sigma w(F_o^2 - F_c^2)^2$ was minimized, where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes, respectively. The agreement indices are defined as $R1 = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$ and $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_o^4)]^{1/2}$. All calculations were performed by using Yadokari-XG 2009[25] and illustrations were drawn by using ORTEP-3.

Table S2. Crystal data of **3c** and structure refinement for ydkr

Identification code	product **3c**	
Empirical formula	C25 H21 N O5	
Formula weight	415.43	
Temperature	93(2) K	
Wavelength	0.71075 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.850(3) Å	α= 90°.
	b = 8.0109(17) Å	β= 113.182(4)°.
	c = 12.135(3) Å	γ = 90°.
Volume	1059.0(4) $Å^3$	
Z	2	
Density (calculated)	1.303 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	436	
Crystal size	0.850 x 0.550 x 0.150 mm^3	
Theta range for data collection	3.086 to 27.487°.	
Index ranges	-15<=h<=15, -10<=k<=10, -15<=l<=15	
Reflections collected	16633	
Independent reflections	4829 [R(int) = 0.0320]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.93	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4829 / 1 / 280	
Goodness-of-fit on F^2	0.999	
Final R indices [I>2sigma(I)]	R1 = 0.0278, wR2 = 0.0699	
R indices (all data)	R1 = 0.0299, wR2 = 0.0706	
Absolute structure parameter	0.1(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.186 and -0.160 $e.Å^{-3}$	

Table S3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for product **3c** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-590(1)	11581(2)	2026(1)	20(1)
C(2)	799(1)	11567(2)	2779(1)	19(1)
C(3)	1336(1)	11830(2)	1850(1)	21(1)
C(4)	2553(1)	11863(2)	1981(2)	26(1)
C(5)	2811(2)	12107(2)	973(2)	33(1)
C(6)	1871(2)	12320(3)	-141(2)	35(1)
C(7)	641(2)	12299(2)	-290(2)	29(1)
C(8)	402(1)	12047(2)	725(1)	22(1)
C(9)	-1868(1)	12241(2)	-141(1)	23(1)
C(10)	-4004(1)	12372(2)	-655(1)	23(1)
C(11)	-4474(2)	11306(2)	-1620(2)	28(1)
C(12)	-5697(2)	11483(2)	-2384(2)	31(1)
C(13)	-6421(1)	12696(2)	-2173(2)	30(1)
C(14)	-5927(1)	13750(2)	-1201(2)	27(1)
C(15)	-4702(1)	13599(2)	-430(2)	25(1)
C(16)	1158(1)	12976(2)	3746(2)	24(1)
C(17)	731(2)	12608(2)	4758(1)	30(1)
C(18)	681(2)	14667(2)	3175(2)	34(1)
C(19)	1156(1)	9853(2)	3345(1)	19(1)
C(20)	2890(1)	8342(2)	4624(2)	22(1)
C(21)	3532(1)	7395(2)	4115(1)	26(1)
C(22)	4126(2)	5965(2)	4714(2)	32(1)
C(23)	4062(2)	5511(2)	5788(2)	32(1)
C(24)	3394(2)	6472(2)	6265(2)	32(1)
C(25)	2801(2)	7904(2)	5685(2)	26(1)
O(1)	-1387(1)	11350(2)	2386(1)	28(1)
O(2)	509(1)	8665(1)	3178(1)	25(1)
O(3)	2374(1)	9858(1)	4068(1)	26(1)
O(4)	-1958(1)	12542(2)	-1136(1)	37(1)
O(5)	-2805(1)	12179(2)	217(1)	31(1)

N(1)	-761(1)	11960(2)	827(1)	21(1)

Table S4. Bond lengths [Å] and angles [°] for product **3c**

C(1)-O(1)	1.2002(17)
C(1)-N(1)	1.4214(18)
C(1)-C(2)	1.537(2)
C(2)-C(3)	1.511(2)
C(2)-C(19)	1.519(2)
C(2)-C(16)	1.562(2)
C(3)-C(4)	1.387(2)
C(3)-C(8)	1.389(2)
C(4)-C(5)	1.387(2)
C(4)-H(1)	0.9500
C(5)-C(6)	1.383(3)
C(5)-H(2)	0.9500
C(6)-C(7)	1.397(2)
C(6)-H(3)	0.9500
C(7)-C(8)	1.383(2)
C(7)-H(4)	0.9500
C(8)-N(1)	1.4331(17)
C(9)-O(4)	1.1940(19)
C(9)-O(5)	1.3431(18)
C(9)-N(1)	1.3922(19)
C(10)-C(11)	1.378(2)
C(10)-C(15)	1.379(2)
C(10)-O(5)	1.4061(17)
C(11)-C(12)	1.386(2)
C(11)-H(5)	0.9500
C(12)-C(13)	1.385(3)
C(12)-H(6)	0.9500
C(13)-C(14)	1.379(3)
C(13)-H(7)	0.9500
C(14)-C(15)	1.389(2)

C(14)-H(8)	0.9500
C(15)-H(9)	0.9500
C(16)-C(18)	1.526(2)
C(16)-C(17)	1.530(2)
C(16)-H(10)	1.0000
C(17)-H(11)	0.9800
C(17)-H(12)	0.9800
C(17)-H(13)	0.9800
C(18)-H(14)	0.9800
C(18)-H(15)	0.9800
C(18)-H(16)	0.9800
C(19)-O(2)	1.1891(19)
C(19)-O(3)	1.3624(18)
C(20)-C(25)	1.378(2)
C(20)-C(21)	1.381(2)
C(20)-O(3)	1.4066(18)
C(21)-C(22)	1.390(2)
C(21)-H(17)	0.9500
C(22)-C(23)	1.384(3)
C(22)-H(18)	0.9500
C(23)-C(24)	1.384(2)
C(23)-H(19)	0.9500
C(24)-C(25)	1.384(2)
C(24)-H(20)	0.9500
C(25)-H(21)	0.9500

O(1)-C(1)-N(1)	126.21(13)
O(1)-C(1)-C(2)	126.47(13)
N(1)-C(1)-C(2)	107.31(11)
C(3)-C(2)-C(19)	109.78(12)
C(3)-C(2)-C(1)	102.89(12)
C(19)-C(2)-C(1)	108.55(12)
C(3)-C(2)-C(16)	112.93(12)
C(19)-C(2)-C(16)	111.63(13)
C(1)-C(2)-C(16)	110.65(12)

C(4)-C(3)-C(8)	120.02(14)
C(4)-C(3)-C(2)	129.88(14)
C(8)-C(3)-C(2)	110.10(12)
C(5)-C(4)-C(3)	118.81(16)
C(5)-C(4)-H(1)	120.6
C(3)-C(4)-H(1)	120.6
C(6)-C(5)-C(4)	120.50(15)
C(6)-C(5)-H(2)	119.8
C(4)-C(5)-H(2)	119.8
C(5)-C(6)-C(7)	121.53(16)
C(5)-C(6)-H(3)	119.2
C(7)-C(6)-H(3)	119.2
C(8)-C(7)-C(6)	117.09(16)
C(8)-C(7)-H(4)	121.5
C(6)-C(7)-H(4)	121.5
C(7)-C(8)-C(3)	122.06(14)
C(7)-C(8)-N(1)	128.63(14)
C(3)-C(8)-N(1)	109.32(13)
O(4)-C(9)-O(5)	125.35(14)
O(4)-C(9)-N(1)	124.37(14)
O(5)-C(9)-N(1)	110.24(12)
C(11)-C(10)-C(15)	122.46(14)
C(11)-C(10)-O(5)	121.47(14)
C(15)-C(10)-O(5)	115.87(14)
C(10)-C(11)-C(12)	118.11(16)
C(10)-C(11)-H(5)	120.9
C(12)-C(11)-H(5)	120.9
C(13)-C(12)-C(11)	120.59(16)
C(13)-C(12)-H(6)	119.7
C(11)-C(12)-H(6)	119.7
C(14)-C(13)-C(12)	120.15(15)
C(14)-C(13)-H(7)	119.9
C(12)-C(13)-H(7)	119.9
C(13)-C(14)-C(15)	120.16(16)
C(13)-C(14)-H(8)	119.9

C(15)-C(14)-H(8)	119.9
C(10)-C(15)-C(14)	118.54(15)
C(10)-C(15)-H(9)	120.7
C(14)-C(15)-H(9)	120.7
C(18)-C(16)-C(17)	110.83(14)
C(18)-C(16)-C(2)	110.96(13)
C(17)-C(16)-C(2)	112.67(13)
C(18)-C(16)-H(10)	107.4
C(17)-C(16)-H(10)	107.4
C(2)-C(16)-H(10)	107.4
C(16)-C(17)-H(11)	109.5
C(16)-C(17)-H(12)	109.5
H(11)-C(17)-H(12)	109.5
C(16)-C(17)-H(13)	109.5
H(11)-C(17)-H(13)	109.5
H(12)-C(17)-H(13)	109.5
C(16)-C(18)-H(14)	109.5
C(16)-C(18)-H(15)	109.5
H(14)-C(18)-H(15)	109.5
C(16)-C(18)-H(16)	109.5
H(14)-C(18)-H(16)	109.5
H(15)-C(18)-H(16)	109.5
O(2)-C(19)-O(3)	124.13(14)
O(2)-C(19)-C(2)	126.89(13)
O(3)-C(19)-C(2)	108.96(12)
C(25)-C(20)-C(21)	122.44(15)
C(25)-C(20)-O(3)	119.29(14)
C(21)-C(20)-O(3)	118.17(14)
C(20)-C(21)-C(22)	118.26(15)
C(20)-C(21)-H(17)	120.9
C(22)-C(21)-H(17)	120.9
C(23)-C(22)-C(21)	120.34(16)
C(23)-C(22)-H(18)	119.8
C(21)-C(22)-H(18)	119.8
C(22)-C(23)-C(24)	120.00(16)

C(22)-C(23)-H(19)	120.0
C(24)-C(23)-H(19)	120.0
C(25)-C(24)-C(23)	120.52(16)
C(25)-C(24)-H(20)	119.7
C(23)-C(24)-H(20)	119.7
C(20)-C(25)-C(24)	118.43(15)
C(20)-C(25)-H(21)	120.8
C(24)-C(25)-H(21)	120.8
C(19)-O(3)-C(20)	117.15(11)
C(9)-O(5)-C(10)	118.15(11)
C(9)-N(1)-C(1)	127.25(12)
C(9)-N(1)-C(8)	122.60(12)
C(1)-N(1)-C(8)	110.15(11)

Symmetry transformations used to generate equivalent atoms:

Table S5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for product **3c**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	19(1)	19(1)	22(1)	1(1)	8(1)	1(1)
C(2)	17(1)	18(1)	21(1)	3(1)	6(1)	0(1)
C(3)	21(1)	16(1)	26(1)	1(1)	11(1)	-1(1)
C(4)	20(1)	24(1)	35(1)	2(1)	11(1)	-1(1)
C(5)	23(1)	36(1)	46(1)	2(1)	20(1)	-2(1)
C(6)	35(1)	42(1)	39(1)	2(1)	26(1)	-4(1)
C(7)	28(1)	34(1)	28(1)	3(1)	15(1)	-3(1)
C(8)	20(1)	20(1)	27(1)	1(1)	11(1)	-1(1)
C(9)	21(1)	28(1)	21(1)	2(1)	8(1)	1(1)
C(10)	17(1)	32(1)	19(1)	6(1)	5(1)	1(1)
C(11)	30(1)	26(1)	29(1)	0(1)	14(1)	0(1)
C(12)	30(1)	36(1)	25(1)	-4(1)	9(1)	-11(1)
C(13)	19(1)	43(1)	25(1)	8(1)	6(1)	-4(1)
C(14)	22(1)	33(1)	28(1)	6(1)	12(1)	4(1)

C(15)	22(1)	31(1)	21(1)	-2(1)	9(1)	-3(1)
C(16)	23(1)	20(1)	26(1)	-1(1)	6(1)	0(1)
C(17)	32(1)	33(1)	24(1)	-3(1)	9(1)	3(1)
C(18)	42(1)	20(1)	37(1)	1(1)	11(1)	4(1)
C(19)	20(1)	20(1)	18(1)	1(1)	8(1)	0(1)
C(20)	17(1)	17(1)	28(1)	3(1)	4(1)	-1(1)
C(21)	25(1)	26(1)	27(1)	3(1)	11(1)	-1(1)
C(22)	30(1)	28(1)	41(1)	4(1)	18(1)	7(1)
C(23)	28(1)	28(1)	40(1)	14(1)	12(1)	8(1)
C(24)	33(1)	34(1)	29(1)	10(1)	14(1)	3(1)
C(25)	26(1)	24(1)	30(1)	0(1)	12(1)	1(1)
O(1)	20(1)	43(1)	24(1)	6(1)	11(1)	0(1)
O(2)	24(1)	19(1)	29(1)	1(1)	6(1)	-4(1)
O(3)	19(1)	18(1)	34(1)	6(1)	3(1)	-1(1)
O(4)	26(1)	62(1)	22(1)	9(1)	8(1)	-3(1)
O(5)	17(1)	53(1)	22(1)	6(1)	6(1)	5(1)
N(1)	19(1)	24(1)	20(1)	3(1)	9(1)	0(1)

Table S20. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for product **3c**.

	x	y	z	U(eq)
H(1)	3198	11721	2748	31
H(2)	3640	12130	1048	40
H(3)	2066	12483	-822	42
H(4)	-4	12450	-1056	34
H(5)	-3974	10474	-1759	33
H(6)	-6042	10766	-3058	37
H(7)	-7259	12803	-2699	36
H(8)	-6426	14580	-1059	33
H(9)	-4353	14324	239	30
H(10)	2075	13042	4112	29

H(11)	1047	11518	5112	45
H(12)	1040	13475	5374	45
H(13)	-168	12595	4436	45
H(14)	965	14878	2530	52
H(15)	-218	14666	2844	52
H(16)	990	15545	3783	52
H(17)	3567	7712	3375	31
H(18)	4577	5296	4384	38
H(19)	4477	4539	6198	39
H(20)	3342	6147	6996	38
H(21)	2343	8568	6011	31

Table S6. Torsion angles [°] for product **3c**.

O(1)-C(1)-C(2)-C(3)	176.93(16)
N(1)-C(1)-C(2)-C(3)	-4.49(15)
O(1)-C(1)-C(2)-C(19)	60.6(2)
N(1)-C(1)-C(2)-C(19)	-120.78(13)
O(1)-C(1)-C(2)-C(16)	-62.2(2)
N(1)-C(1)-C(2)-C(16)	116.40(14)
C(19)-C(2)-C(3)-C(4)	-61.6(2)
C(1)-C(2)-C(3)-C(4)	-176.99(16)
C(16)-C(2)-C(3)-C(4)	63.7(2)
C(19)-C(2)-C(3)-C(8)	117.94(14)
C(1)-C(2)-C(3)-C(8)	2.53(15)
C(16)-C(2)-C(3)-C(8)	-116.79(14)
C(8)-C(3)-C(4)-C(5)	-0.3(2)
C(2)-C(3)-C(4)-C(5)	179.15(16)
C(3)-C(4)-C(5)-C(6)	0.2(3)
C(4)-C(5)-C(6)-C(7)	0.1(3)
C(5)-C(6)-C(7)-C(8)	-0.3(3)
C(6)-C(7)-C(8)-C(3)	0.2(2)
C(6)-C(7)-C(8)-N(1)	-179.57(17)
C(4)-C(3)-C(8)-C(7)	0.1(2)

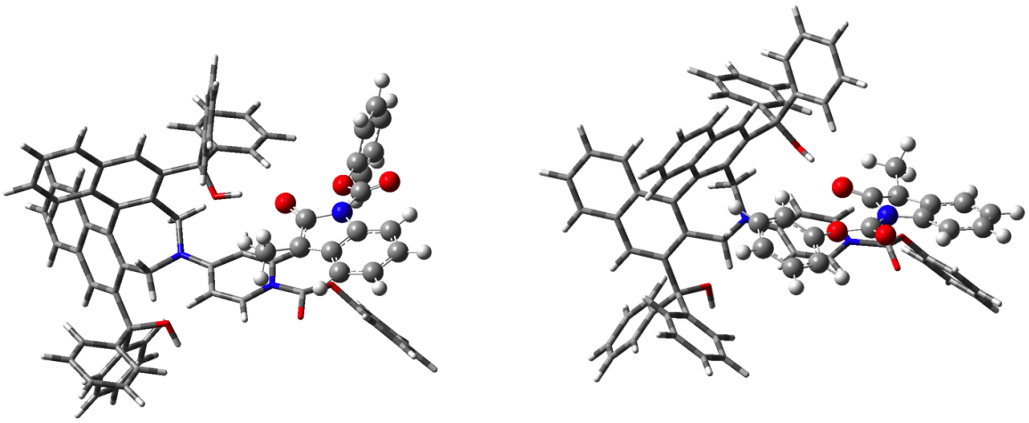
C(2)-C(3)-C(8)-C(7)	-179.47(15)
C(4)-C(3)-C(8)-N(1)	179.93(14)
C(2)-C(3)-C(8)-N(1)	0.36(17)
C(15)-C(10)-C(11)-C(12)	-0.3(2)
O(5)-C(10)-C(11)-C(12)	174.38(14)
C(10)-C(11)-C(12)-C(13)	-0.2(2)
C(11)-C(12)-C(13)-C(14)	0.4(3)
C(12)-C(13)-C(14)-C(15)	0.0(2)
C(11)-C(10)-C(15)-C(14)	0.6(2)
O(5)-C(10)-C(15)-C(14)	-174.31(14)
C(13)-C(14)-C(15)-C(10)	-0.5(2)
C(3)-C(2)-C(16)-C(18)	61.36(17)
C(19)-C(2)-C(16)-C(18)	-174.38(13)
C(1)-C(2)-C(16)-C(18)	-53.37(17)
C(3)-C(2)-C(16)-C(17)	-173.71(12)
C(19)-C(2)-C(16)-C(17)	-49.45(16)
C(1)-C(2)-C(16)-C(17)	71.56(16)
C(3)-C(2)-C(19)-O(2)	-106.55(18)
C(1)-C(2)-C(19)-O(2)	5.2(2)
C(16)-C(2)-C(19)-O(2)	127.44(17)
C(3)-C(2)-C(19)-O(3)	71.67(15)
C(1)-C(2)-C(19)-O(3)	-176.56(12)
C(16)-C(2)-C(19)-O(3)	-54.34(16)
C(25)-C(20)-C(21)-C(22)	-1.2(2)
O(3)-C(20)-C(21)-C(22)	174.90(14)
C(20)-C(21)-C(22)-C(23)	0.4(2)
C(21)-C(22)-C(23)-C(24)	0.7(3)
C(22)-C(23)-C(24)-C(25)	-1.0(3)
C(21)-C(20)-C(25)-C(24)	0.9(2)
O(3)-C(20)-C(25)-C(24)	-175.12(14)
C(23)-C(24)-C(25)-C(20)	0.2(2)
O(2)-C(19)-O(3)-C(20)	1.6(2)
C(2)-C(19)-O(3)-C(20)	-176.70(12)
C(25)-C(20)-O(3)-C(19)	-84.61(18)
C(21)-C(20)-O(3)-C(19)	99.16(16)

O(4)-C(9)-O(5)-C(10)	4.5(3)
N(1)-C(9)-O(5)-C(10)	-177.55(14)
C(11)-C(10)-O(5)-C(9)	58.8(2)
C(15)-C(10)-O(5)-C(9)	-126.19(16)
O(4)-C(9)-N(1)-C(1)	-179.32(17)
O(5)-C(9)-N(1)-C(1)	2.7(2)
O(4)-C(9)-N(1)-C(8)	1.7(3)
O(5)-C(9)-N(1)-C(8)	-176.33(14)
O(1)-C(1)-N(1)-C(9)	4.5(3)
C(2)-C(1)-N(1)-C(9)	-174.11(14)
O(1)-C(1)-N(1)-C(8)	-176.42(16)
C(2)-C(1)-N(1)-C(8)	4.99(16)
C(7)-C(8)-N(1)-C(9)	-4.5(3)
C(3)-C(8)-N(1)-C(9)	175.70(14)
C(7)-C(8)-N(1)-C(1)	176.37(16)
C(3)-C(8)-N(1)-C(1)	-3.45(17)

Symmetry transformations used to generate equivalent atoms:

Calculations of the ion pair intermediate

All calculations were performed with the Gaussian 03 program. Geometries were fully optimized and characterized by frequency calculation using the the B3LYP density functional theory (DFT) with the 6-31G(d) basis set. Free energies (298.15 K, 1 atm) were initially computed for the gas phase.



TS-Si ***TS-Re***

Figure S7. 3D structures of the transition states for the C-C bond forming step.

Cartesian coordinates of calculation results.

TS-Si

Thermal Free Energies = -3620.205898 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-1.720045	0.343494	0.023893
2	6	0	-1.762828	-0.955341	0.734540
3	6	0	-2.918775	0.673857	-0.771863
4	6	0	-2.259812	-2.047920	-0.205066
5	6	0	-4.182510	0.334396	0.001469
6	6	0	-3.619018	-2.036893	-0.514847
7	6	0	-4.155708	-2.950315	-1.486004
8	6	0	-3.283962	-3.938645	-2.035405
9	6	0	-1.918516	-3.953589	-1.652088

10	6	0	-1.379395	-3.023216	-0.792368
11	6	0	-5.007830	1.346704	0.600577
12	6	0	-6.132037	0.954306	1.293644
13	6	0	-6.456738	-0.409811	1.503448
14	6	0	-5.617977	-1.422350	0.946270
15	6	0	-4.500936	-1.015569	0.138708
16	6	0	-7.580393	-0.782656	2.288919
17	6	0	-7.851004	-2.106587	2.546908
18	6	0	-6.998030	-3.111689	2.033126
19	6	0	-5.911448	-2.780229	1.253935
20	6	0	-5.496453	-2.899554	-1.959542
21	6	0	-5.954125	-3.804341	-2.892335
22	6	0	-5.097866	-4.807982	-3.403042
23	6	0	-3.788625	-4.867886	-2.984193
24	6	0	-0.560336	1.019788	-0.146034
25	6	0	-0.351928	1.934196	-1.219325
26	6	0	0.893280	2.455344	-1.453329
27	6	0	1.762537	1.408683	0.456858
28	6	0	0.543309	0.860847	0.741510
29	7	0	1.955890	2.165065	-0.659320
30	6	0	3.314162	2.639603	-1.124288
31	8	0	3.329371	3.463748	-2.026598
32	8	0	4.121341	2.684357	0.011533
33	6	0	4.859289	3.837286	0.287697
34	6	0	5.725709	4.421463	-0.635805
35	6	0	4.746366	4.336108	1.585850
36	6	0	6.472228	5.533430	-0.242822
37	6	0	5.508453	5.440586	1.967381
38	6	0	6.370498	6.046411	1.051967
39	1	0	-0.770246	-1.186045	1.094583
40	1	0	-2.431170	-0.868982	1.596617
41	1	0	-2.889822	1.732144	-0.997288
42	1	0	-2.901067	0.116525	-1.717229
43	1	0	-1.281907	-4.713554	-2.090963
44	1	0	-6.788450	1.699287	1.729213

45	1	0	-8.213795	0.002004	2.695807
46	1	0	-8.708264	-2.382728	3.154705
47	1	0	-7.199785	-4.155244	2.258956
48	1	0	-5.263736	-3.561699	0.874345
49	1	0	-6.163153	-2.131502	-1.584613
50	1	0	-6.981167	-3.743900	-3.242335
51	1	0	-5.472763	-5.519244	-4.133942
52	1	0	-3.112796	-5.619684	-3.384597
53	1	0	-1.140634	2.178699	-1.917588
54	1	0	1.124187	3.106334	-2.286015
55	1	0	2.625404	1.268956	1.089190
56	1	0	0.456293	0.267219	1.640908
57	1	0	5.812636	4.010720	-1.632939
58	1	0	4.067119	3.853303	2.282003
59	1	0	7.148038	5.994398	-0.958290
60	1	0	5.423366	5.826961	2.979701
61	1	0	6.962813	6.908298	1.346808
62	6	0	-4.681925	2.850745	0.443288
63	6	0	0.137154	-3.035051	-0.470391
64	8	0	0.552649	-1.698475	-0.762849
65	1	0	1.527952	-1.595486	-0.701515
66	6	0	0.377411	-3.388870	1.018083
67	6	0	1.523617	-2.918866	1.678430
68	6	0	-0.507806	-4.216239	1.723759
69	6	0	1.764021	-3.259583	3.011034
70	1	0	2.241266	-2.289515	1.160912
71	6	0	-0.264447	-4.558803	3.055965
72	1	0	-1.397444	-4.596465	1.231007
73	6	0	0.871521	-4.078233	3.705912
74	1	0	2.656431	-2.884726	3.504130
75	1	0	-0.967794	-5.199260	3.582396
76	1	0	1.062561	-4.340273	4.743332
77	6	0	0.917475	-4.009789	-1.382912
78	6	0	1.291582	-3.579895	-2.664957
79	6	0	1.258925	-5.310206	-0.990762

80	6	0	1.991234	-4.423194	-3.526994
81	1	0	1.033582	-2.574111	-2.978058
82	6	0	1.957247	-6.156991	-1.855154
83	1	0	0.989703	-5.666903	-0.002120
84	6	0	2.328171	-5.717407	-3.125484
85	1	0	2.276827	-4.065917	-4.513118
86	1	0	2.217540	-7.160026	-1.526718
87	1	0	2.877686	-6.374119	-3.794835
88	8	0	-3.297283	2.984057	0.836658
89	1	0	-3.162785	3.906182	1.107999
90	6	0	-5.513903	3.733685	1.399067
91	6	0	-6.591767	4.520180	0.976062
92	6	0	-5.163214	3.755068	2.760290
93	6	0	-7.299264	5.308934	1.887287
94	1	0	-6.881234	4.526303	-0.068855
95	6	0	-5.867277	4.543907	3.668242
96	1	0	-4.335999	3.141379	3.103069
97	6	0	-6.939787	5.326351	3.234147
98	1	0	-8.129894	5.915510	1.536367
99	1	0	-5.578447	4.545512	4.715969
100	1	0	-7.488808	5.943490	3.940157
101	6	0	-4.862266	3.298379	-1.025182
102	6	0	-4.013415	4.265644	-1.579519
103	6	0	-5.894211	2.783492	-1.821819
104	6	0	-4.188670	4.706224	-2.892054
105	1	0	-3.195477	4.667567	-0.990127
106	6	0	-6.074144	3.225968	-3.133912
107	1	0	-6.558716	2.026877	-1.415963
108	6	0	-5.221579	4.188772	-3.675042
109	1	0	-3.514675	5.453886	-3.301833
110	1	0	-6.878848	2.809934	-3.734304
111	1	0	-5.357386	4.529152	-4.697845
112	6	0	6.231573	0.671518	-1.354183
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TS-Re

Thermal Free Energies = -3620.200904 A.U.

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73	6	0	8.405179	-0.520392	0.781140
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142	1	0	-4.800795	-3.149684	4.345822
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Chapter 4. Enantioselective Steglich Rearrangement of Furanyl Carbonates with Binaphthyl-Based DMAP Derivatives

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4-1. Abstract

We developed an efficient enantioselective acyl migration reaction of benzofuranyl carbonates to construct all-carbon quaternary stereogenic centers. The reaction required only 0.05–3 mol % (minimum 500 ppm order) of catalyst and showed high TOF value (3,640 h^{-1}). Wide range of functional group tolerance was confirmed (16 examples, >98% yield, up to >99:1 er), and provides optically active 3,3′-disubstituted benzofuranone derivatives, which are useful for synthesis of natural product or pharmaceutical molecules. Multigram scale reaction (10 grams) also proceeded with high enantioselectivity (>99:1 er) in quantitative yield. The catalyst was robust and easily recovered in 98% yield and recyclable in the same reaction without loss of any catalytic activity and enantioselectivity. Computational calculations and control experiments found out that catalytic activity and enantioselectivity were controlled by hydrogen bonding between catalyst and substrate. Moreover, this system was applied to challenging γ-selective acyl migration reaction of furanyl carbonates with high γ-selectivity and high enantioselectivity (α:γ = 10:90, 95:5 er).

4-2.Introduction

Enantioselective construction of all-carbon quaternary stereogenic centers is one of the important transformations in organic synthesis.[1-3] Among them, the enantioselective Steglich type[4-6] (Black[7]) rearrangements (to give azlactones,[8-15] oxindoles,[9,10,16-18] furanones,[9,10,19] benzofuranones,[9,10,15,16,20] pyrazole[21]) are well established methods for an enantioselective construction of all carbon quaternary stereogenic center at its 3-position (Figure 1a). Particularly, 3,3′-disubstituted 2-benzofuranone skeleton was frequently found in numerous natural product (Figure1b).[22-25]

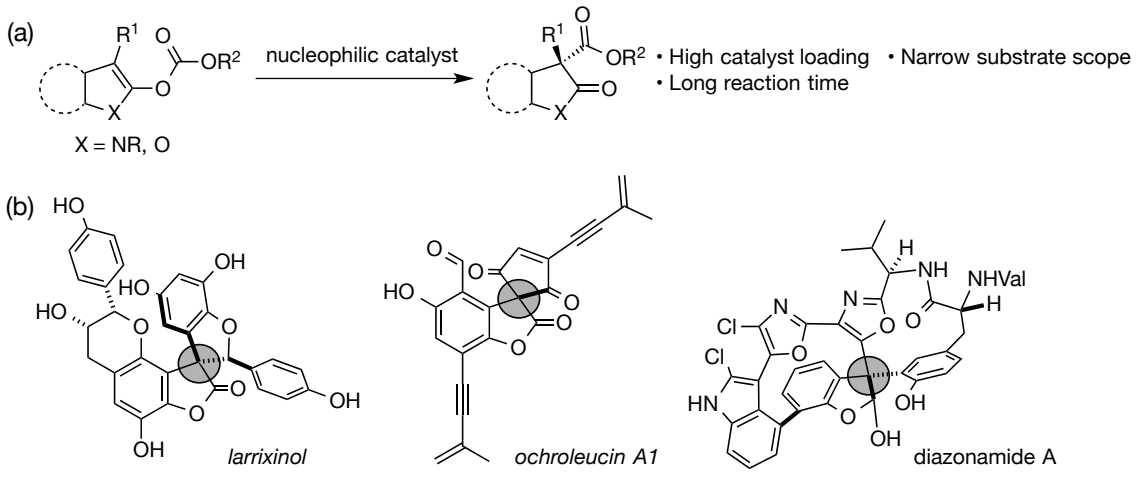


Figure 1. (a) Steglich type rearrangements (b) Natural products consist of benzofuranone skeleton

In 2003, Fu and co-worker reported the first enantioselective Steglich type (Black) rearrangement of furanyl carbonates by ferrocene based nucleophilic catalyst.[16] Triggered by their beautiful study, various methods using nucleophilic catalyst were reported.[9,10,15,20] These methods, particularly rearrangements of benzofuranyl carbonates, show high enantioselectivity, but required high catalyst loading (typically 10–20 mol %), long reaction time (>24 h), and functional group tolerance of reaction were not fully studied (only simple alkyl and aryl groups were tested). Accordingly, development of enantioselective Steglich type rearrangement of benzofuranyl carbonates by extremely low catalyst loading within short reaction time is still challenging transformation. On the other hand, we developed binaphthyl-based chiral *N*,*N*-dimethyl-4-aminopyridine (DMAP) derivatives and found that the catalyst showed the drastic rate enhancement and high enantioselectivity in Steglich type rearrangement of *O*-acylated oxindoles (chapter 3). According to various control experiments and DFT calculation, two *tert*-alcohol units of catalyst were responsible for achieving high catalytic activity and high enantioselectivity (contribution of attractive interaction between *tert*-alcohol of catalyst and enolate delivered substrate).[26] This chapter, I described on the rapid and highly enantioselective construction of all-carbon quaternary stereogenic centers through Steglich type rearrangement of *O*-acylated benzofuranones with highly active nucleophilic catalysts by hydrogen bonding strategy.[26-29] Furthermore, challenging γ-selective acyl migration reaction of furanyl carbonate was also accomplished with a binaphthyl-based DMAP catalyst.

2-3. Optimization of Reaction Conditions

We initially screened the catalyst **1d**–**o** under the conditions in the presence of 3 mol % of catalyst, carbonate **2a** in THF (0.1 M) at 0 ºC for 5 h (Figure 2). All catalysts have almost same reactivity (>98% conv), among them, the catalyst **1o** showed somewhat higher enantioselectivity. Thus, we selected the catalyst **1o** as optimal catalyst.

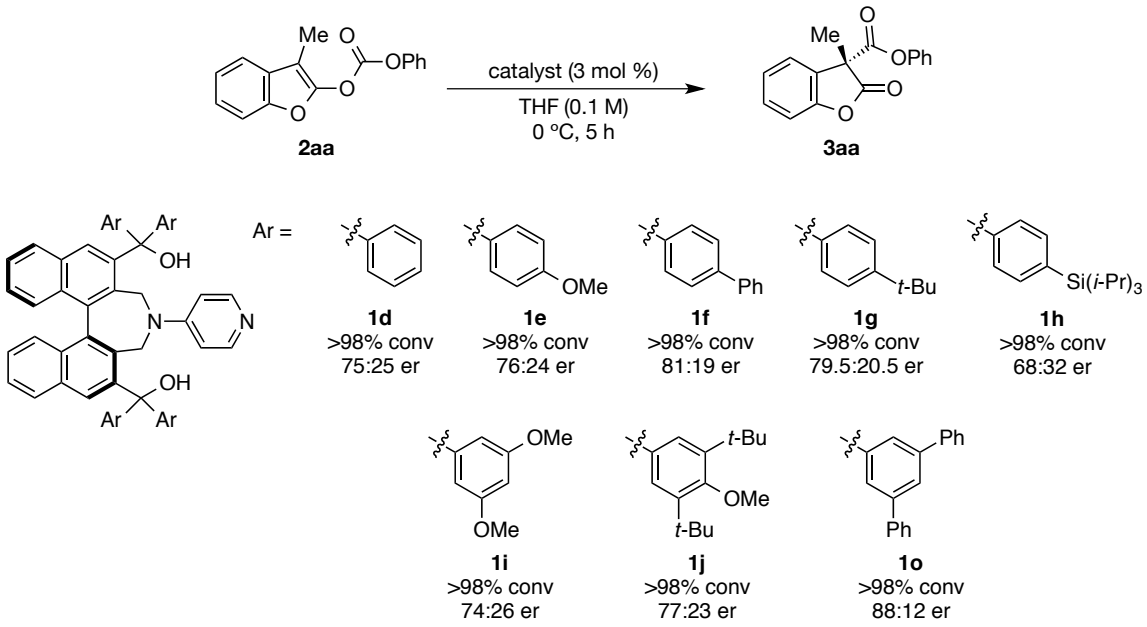


Figure 2. Catalyst screening

Next, we explored suitable migrating group with catalyst **1o** (Figure 3) for this catalysis under same reaction conditions as shown in Figure 1. When the phenyl carbonate **2aa** was used, enantioselectivity was lower than that of using alkyl carbonates **2ab**, **2ac**, and **2a**. Especially, 1,1,1-trichloro-*tert*-butyloxycarbonyl group offers high enantioselectivity (**3a**: 98.5:1.5 er).

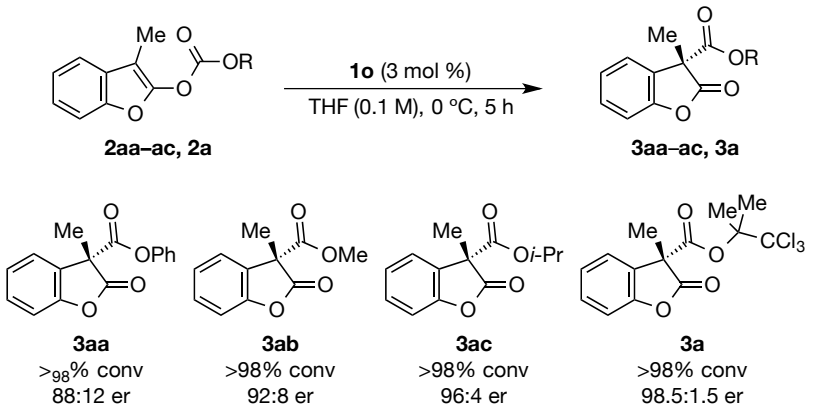
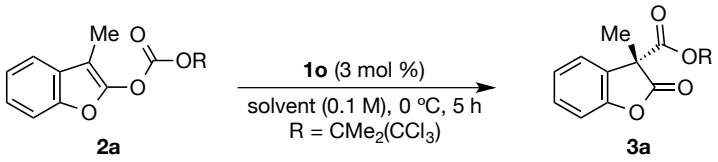


Figure 3. Screening of migrating group

Next we conducted solvent screening (Table 1). Any solvent could be used in this reaction (entries 1–12). When protic solvent (*t*-amyl alcohol, entry 11) was used in this reaction, enantioselectivity was decreased than that of in aprotic solvent. We considered that this observation caused by that the protic solvent inhibited the hydrogen bonding networks between catalyst and substrate in transition state (same results observed in rearrangement of indolyl carbonates, chapter 3). In consideration of solubility and operable temperature, further optimizations of reaction conditions were carried out using toluene as an optimal solvent.

Table 1. Solvent screening

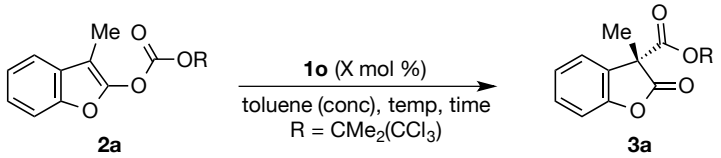


Entry	Solvent	Conv (%)[b]	Er of **3a**[c]
1	THF	>98	98.5:1.5
2	*t*-BuOMe	>98	99:1
3	CPME	>98	99:1
4	Et_2O	>98	99:1
5	*i*-Pr_2O	>98	99:1
6	hexane	>98	91:9
7	acetone	>98	98:2
8	EtOAc	>98	99:1
9	DMF	>98	89:11
10	CH_2Cl_2	>98	98:2
11	*t*-amyl alcohol	>98	93:7
12	toluene	>98	99:1

[a]Performed on a 0.1 mmol scale under an argon atmosphere. [b]Conversions (± 2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures.

We also carried out the reaction at low temperature (Table 2). The reaction at –20 °C proceeded with almost perfect enantioselectivity in full conversion (>98% conv; >99:4 er; entries 2). The reaction with at least 0.05 mol % of catalyst **1o** also proceeded, and the desired product **3a** was obtained in 84% conversion with >99:1 er (entries 3–6). After tuning of substrate concentration and reaction time (entries 7–11), we decided the 0.05 mol % catalyst in toluene (0.5 M) at –20 ºC within 1 h as an optimal reaction conditions (entry 10).

Table 2. Screening of reaction conditions



Entry	Temp (ºC)	X (mol %)	Conc (M)	Time	Conv (%)[b]	Er of **3a**[c]
1	0	3	0.1	5	>98	99:1
2	–20	3	0.1	5	>98	>99:1
3	–20	0.5	0.1	5	>98	>99:1
4	–20	0.1	0.1	5	>98	99:1
5	–20	0.05	0.1	5	84	>99:1
6	–20	0.01	0.1	5	<2	–
7	–20	0.05	0.3	5	>98	99.5:0.5
8	–20	0.05	0.5	5	>98	99.5:0.5
9	–20	0.05	0.5	2	>98	99:1
10	–20	0.05	0.5	1	>98	>99:1
11	–20	0.05	0.5	0.5	91	99:1

[a]Performed on a 50.0 μmol scale under an argon atmosphere. [b]Conversions (± 2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures. [d]*S*-factors were calculated by Kagan's equation.[30]

4-4. Substrate Scope

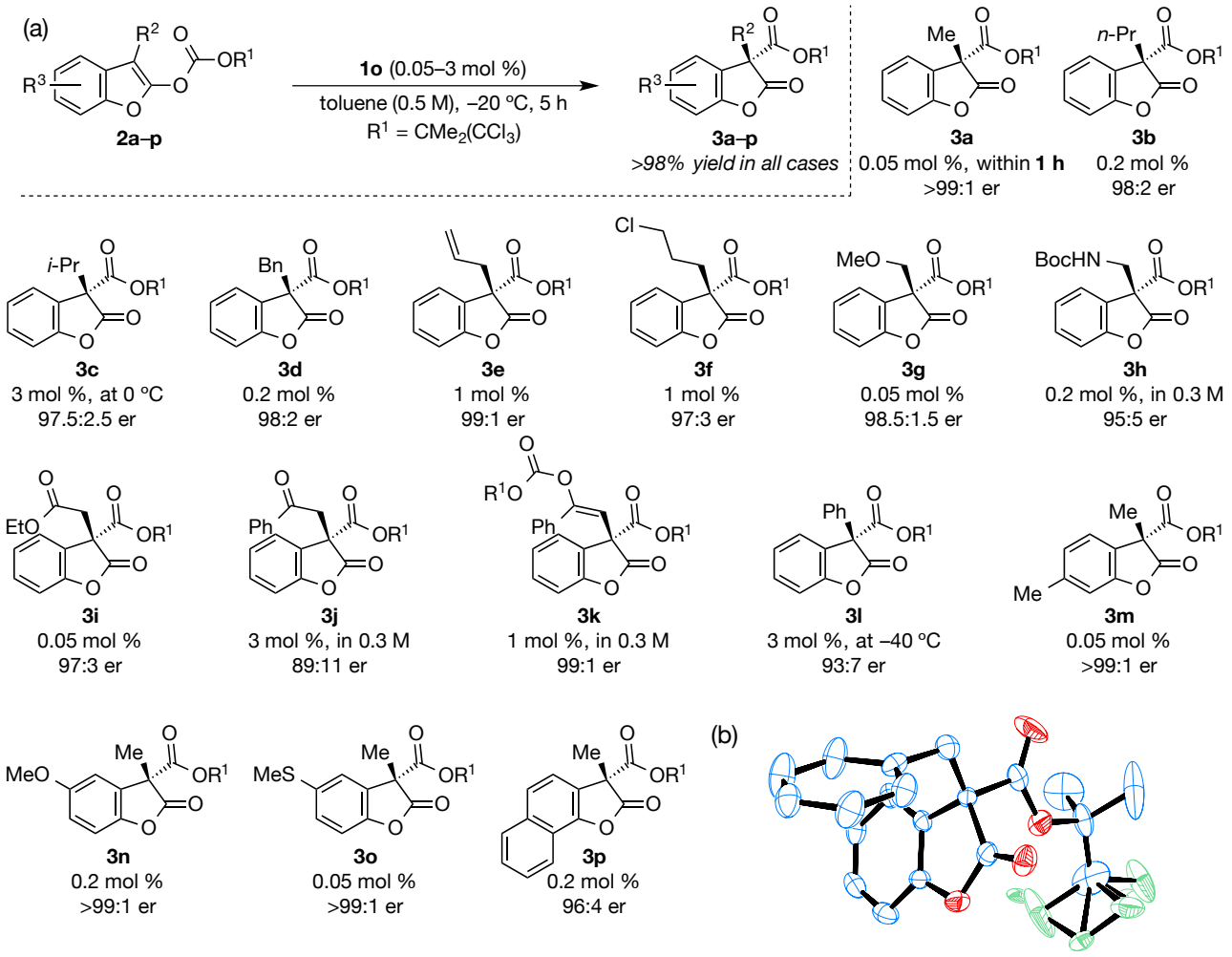
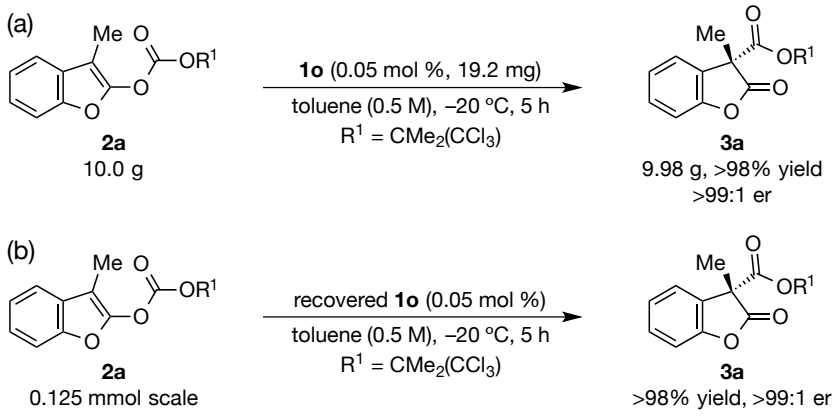


Figure 4. (a) Substrate scope (b) ORTEP drawings of **3d** (50% probability ellipsoids; Hydrogen atoms were omitted for clarity. Chloro groups disordered).

Functional group tolerance in this reaction was investigated (Figure 4a, **3a**–**p**). In most cases using less reactive substrates than model substrate **2a**, reaction did not fully proceed under the optimal conditions for **2a** (0.05 mol % of **1o**, 1 h for the reaction time). Therefore, modified reaction conditions was applied to less reactive substrates (0.2–3 mol % of catalyst, prolonged the reaction time (5 h), and/or higher reaction temperature). Any alkyl and allyl group substituted substrate were not seriously influence in enantioselectivity (**3a**–**e**: >97.5:2.5 er) with low catalyst loading (<1 mol %, except for **3c**). Considerably bulky substrate **2c** (R^2 = *i*-Pr) was compelled the use of high catalyst loading (3 mol %) and temperature rising (0 ºC). The product **3c** was obtained in quantitative yield with high enantioselectivity under the modified reaction conditions (>98% yield, 97.5:2.5 er). The reaction with nucleophilic catalyst often became a problem that the catalyst occurs nucleophilic addition to leaving groups (Cl) of substrate as a consequence of shut down a

reaction. Fortunately, enol carbonate **2f** (R^2 = $CH_2CH_2CH_2Cl$) was uneventfully converted to desired product **3f** in high enantioselectivity (97:3 er) without occurring any side reactions. Functionalized enol carbonates **2g-k** were easily converted to the products **3g–k** in moderate to high enantioselectivity at low catalyst loading (<3 mol % of **1o**). It is notable that **3h** with hydrogen bonding donating groups (amide group) and **3g, 3i, 3j** with hydrogen bonding accepting groups (methoxy and carbonyl group) did not have much influence on enantioselectivity (at least 89:11 er). Moreover, α-proton of ester (**3i**) or ketone (**3j**) was prevented from side reactions. Enol carbonate **3k** has another enol carbonate moiety, but the Steglich type rearrangement only proceeded, namely this result shows perfect chemoselectivity of this reaction. Finally, we screened the diversity of benzene ring, enantioselectivities and yields shows also high (**3n**–**p**, >96:4 er). Absolute configuration of the product **3d** was determined by X-ray analysis (Figure 4b).

Scheme 1. (a) Multigram-scale reaction of **2a** (b) Small scale reaction with recovered **1o**



Next, we conducted multigram scale reaction with **2a** to test the scalability of this reaction. With an only 19.2 mg (0.05 mol %) of catalyst **1o**, 10.0 grams of carbonate **2a** smoothly converted to desired product **3a** in quantitative yield (9.98 g, >98% yield) with excellent enantioselectivity (>99:1 er) within only 1 h (Scheme 1a, product **3a**). Furthermore, catalyst **1o** was recovered in 98% yield by simple silica gel plug filtration and recyclability was confirmed by same reaction[31] (0.125 mmol scale, Scheme 1b).

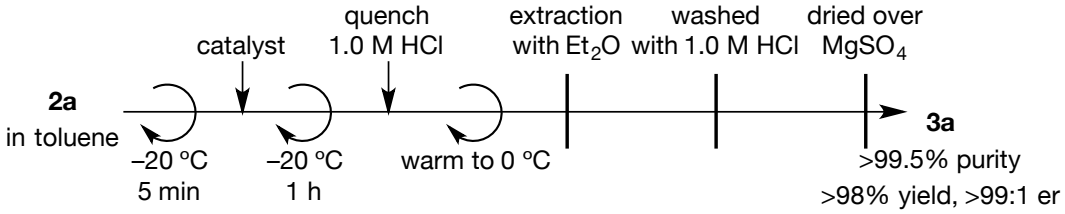


Figure 5. The reaction of **2a** without silica gel column chromatography.

We already found out that the catalyst was decomposed and converted to water-soluble compound in acidic conditions. We believe that the pure product could be obtained by only separating operation from acidic aqueous solution. Accordingly, We tried the experiment without column chromatography purification (Figure 5). After quenching the reaction and washing the organic layer with aqueous HCl solution (1 M), the product was obtained in quantitative yield er [>99.5% purity (area % in HPLC analysis)] with >99:1 er.[32]

4-5. Control Experiments

As shown in Figure 6, the normal DMAP should be sterically advantageous compared with **1o**, but showed poor reactivity and the reaction proceeded very slowly (only 8% conv). It was proven that catalyst **1o** have much higher catalytic activity (>98% conv) than normal DMAP. We previously discussed the mechanistic rationale of rate acceleration effect of **1o** (or its analogues) in this type of reaction and proved that this rate acceleration effect caused by hydrogen bondings stabilization (consist between *tert*-alcohol unit (–C(OH)Ar_2) of catalyst and O^- of substrate) in transition state.[26] In this reaction, same stabilization effect was observed by the experiment with catalyst analogues **1o´** and **1o´´**. Analogue **1o´** having one hydrogen bonding unit showed moderate conversion and high enantioselectivity (34 % conv, 99.3:0.7 er). In comparison, with the use of **1o´´** which have no hydrogen bonding unit, the reaction resulted in no conversion. These results manifested that one of the hydrogen bonding unit stabilized the energy level of transition state and realized high catalytic activity and enantioselectivity.

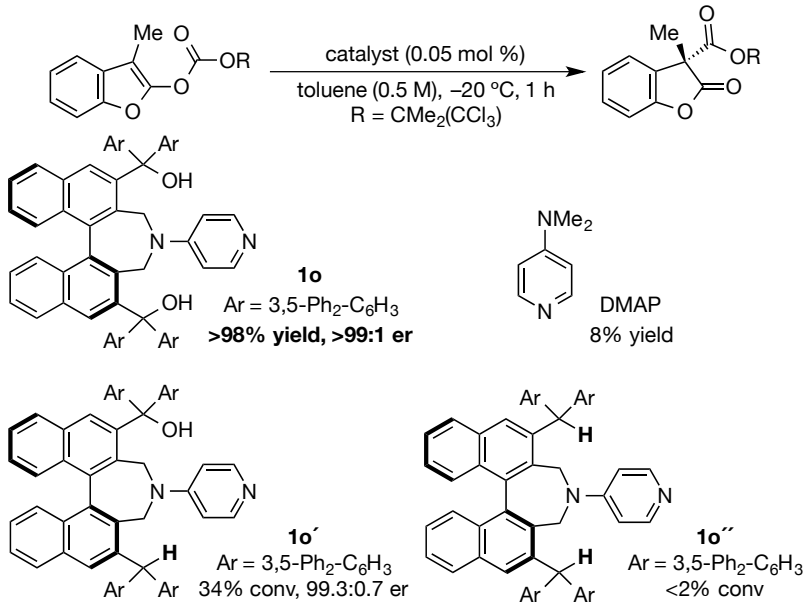


Figure 6. Comparative experiment

We performed density functional theory (DFT) calculations at the B97D/6-31G(g) level after upon due consideration of comparative experiments (Figure 7). To simplify the calculations, the 1,1,1-trichlorobutoxy carbonyl group of the substrate was changed to methyl carbonate (substrate **3ab**, Figure 3). The calculation results appeared the two critical hydrogen bonding interactions between the catalyst and enolate generated from substrate **3ab**. In the lowest energy transition state for providing major enantiomer **TS-I**, the hydroxy unit of catalyst and *ortho*-CH of aryl group (Ar-H) captured the enolate. The two bulky aryl groups of catalyst on a same carbon (*tert*-alcohol unit) led to control preferred hydroxy group position to interact oxygen atom of enolate. The lowest energy transition state for providing opposite enantiomer (**TS-II**, +5.01 kcal/mol) has same stabilization effect by hydroxyl group, however, there was a little chance of Re-face attack of enolate because of steric repulsion between sterically hindered aryl group and α-substituent (Me) of enolate. In addition, the second attractive interaction, which is Ar-H/enolate interaction, was not observed in **TS-II**. According to these results, catalyst **1o** preferred to give *S*-product via **TS-I**.

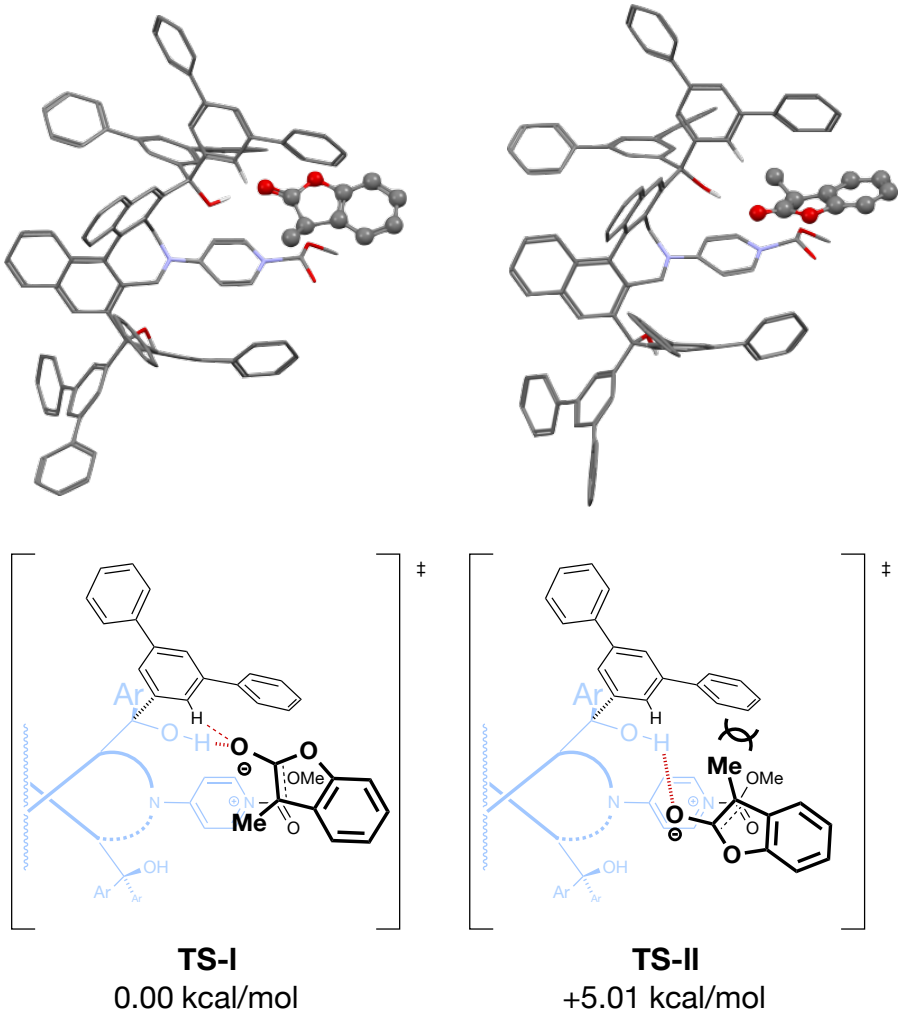


Figure 7. DFT calculation of transition states consist of catalyst **1o** and **3ab**

4-6. Regio- and enantioselective acyl migration of furanyl carbonates

We tried more challenging regioselective carbonyl migration reaction of furanyl carbonates, which provide a quaternary carbon center at γ-position of butenolide. Butenolide, especially γ-butenolide, is often found in natural products and medicinal molecules (Figure 8).[33]

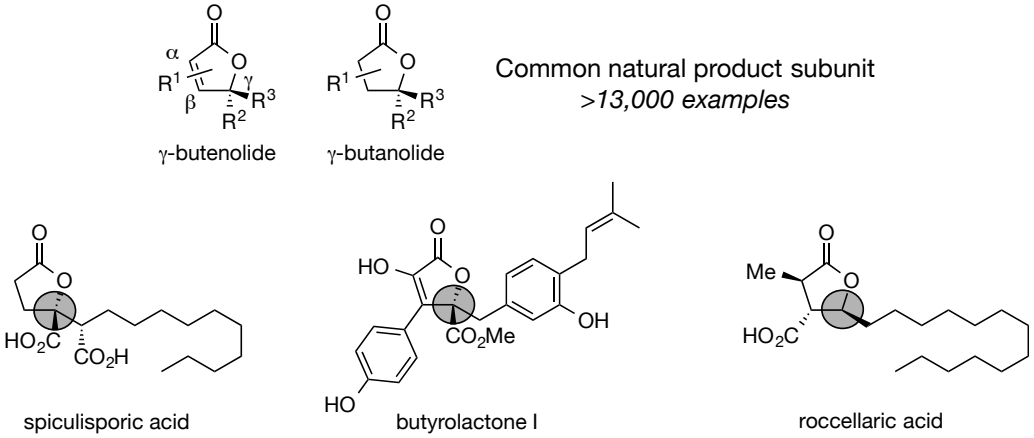
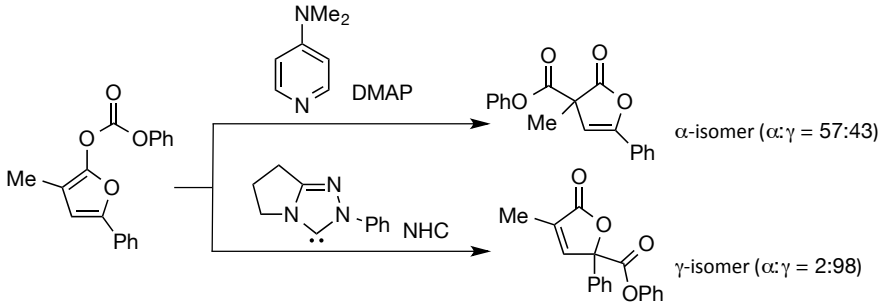


Figure 8. DFT calculation of transition states consist of catalyst **1o** and **3ab**

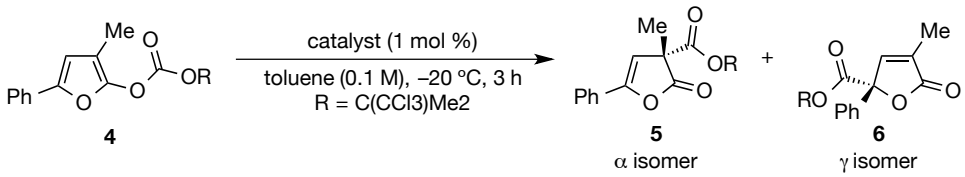
It is difficult to control regioselectivity in the DMAP catalyzed Steglich type rearrangement of furanyl carbonate. In 2015, although Smith and co-workers reported that non-enantioselective and highly regioselective this type of reaction to obtain γ-butenolide by achiral *N*-heterocyclic carbene,[34] the use of DMAP preferred to form α-butenolide (Scheme 2). Thus, regio- and enantioselective synthesis of γ-butenolide has not been accomplished to date.[35]

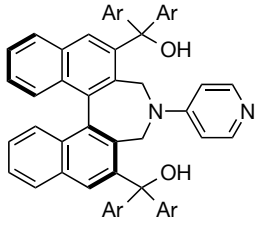


Scheme 2. Regiodivergent acyl migrations of furanyl carbonates

We anticipated that binaphthyl-based DMAP derivatives with two polar functional groups (*tert*-alcohol units) might influence on regioselectivity and enantioselectivity. We initially screened the catalyst **1d**–**p** under the conditions in the presence of 1 mol % of catalyst, carbonate **4** in THF (0.1 M) at –20 ºC for 3 h (Table 3). The catalysts **1d** and **1h** obtained γ-butenolide **6** as major products under this reaction conditions but other catalysts **1e**–**g**, **1i-o** obtained γ-butenolide **6** in low ratio. The catalyst **1p** showed the highest γ-selectivity. Thus, we selected the catalyst **1p** as optimal catalyst.

Table 3. The screening of catalyst in acyl migration of **4**[a]





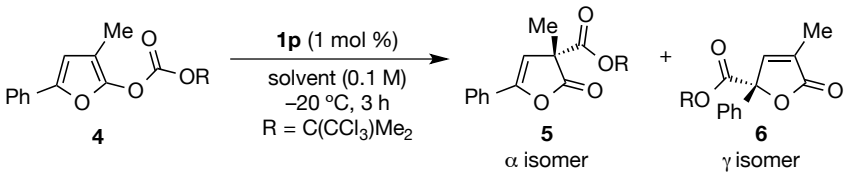
catalyst
1d: R = Ph
1e: R = 4-$MeOC_6H_4$
1f: R = 4-PhC_6H_4
1g: R = 4-*t*-BuC_6H_4
1h: R = 4-Si(*i*-Pr)$_3C_6H_4$
1i: R = 3,5-$(MeO)_2C_6H_3$
1j: R = 3,5-$(MeO)_2$-4-*t*-BuC_6H_2
1o: R = 3,5-$Ph_2C_6H_3$
1p: R = 4-$SiPh_3C_6H_4$

Entry	Catalyst	Yield of **5** (%)[b]	Yield of **6** (%)[b]	α:γ[b]	Er of **5**[c]	Er of **6**[c]
1	**1d**	17	41	30:70	83:17	91:9
2	**1e**	20	33	38:62	83:17	74:26
3	**1f**	16	16	50.5:49.5	88:12	85:15
4	**1g**	41	40	51:49	79:21	91:9
5	**1h**	13	43	23:77	76:24	95:5
6	**1i**	40	41	49:51	57:43	93:7
7	**1j**	56	43	57:43	64:36	92:8
8	**1o**	40	30	57:43	79:21	93:7
9	**1p**	15	42	26.5:73.5	76:24	95:5

[a]Performed on a 0.1 mmol scale under an argon atmosphere. [b]Yields (± 2%) and α/γ ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures using 2-methoxynaphtalene as internal standard. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures.

The solvent screening was conducted (Table 4). Any solvent could be used, which showed moderate γ-selectivity. Among them, in the case of using THF showed the highest γ-selectivity (entry 9, α:γ = 12:88) but showed low yield (31% yield of **6**). The higher yield of **6** was obtained by increasing substrate concentration (0.1 M to 0.5 M, 81% yield of **6**). These reaction conditions were selected as optimal reaction conditions and used further examinations.

Table 4. The screening of solvent in acyl migration of **4**[a]



Entry	Solvent	Yield of **5** (%)[b]	Yield of **6** (%)[b]	α:γ [b]	Er of **5**[c]	Er of **6**[c]
1	toluene	15	42	26.5:73.5	76:24	95:5
2	*t*-BuOMe	14	42	25:75	79:21	96:4
3	CPME	31	57	35.5:64.5	87:13	92.5:7.5
4	Et_2O	17	50	26:74	84:16	97:3
5	CH_2Cl_2	3	17	14:86	77:23	92:8
7	HFIP	17	79	18:82	75:25	95:5
8	DME	7	45	13:87	67:33	97:3
9	THF	4	31	12:88	62:38	94:6
10[e]	THF	9[f]	81[f]	10:90	60:40	95:5

[a]Performed on a 0.1 mmol scale under an argon atmosphere. [b]Yields (± 2%) and α/γ ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures using 2-methoxynaphtalene as internal standard. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures. [e]The reaction conducted in 0.5 M THF. [f]The yields were isolated materials.

We finally found out that reaction of **4** with catalyst **1p** (Figure 9) offered desired **6** in high γ-selectivity and enantioselectivity (γ-isomer = 81% yield, 95:5 er). For comparison, binaphthyl-based catalyst analogue **1k** showed no conversion. We considered that two-hydroxyl group of catalyst contribute largely to γ-selectivity and rate enhancement. The same reaction with 5 mol % of DMAP gave α-isomer **5** as a major product in 4% yield along with γ-isomer **6** in 2% yield (α:γ = 66:34). To the best of our knowledge, this unprecedented enantio- and regioselectivity are the first example with a DMAP-based chiral nucleophilic catalyst, which can be applied to γ-butenolide synthesis.

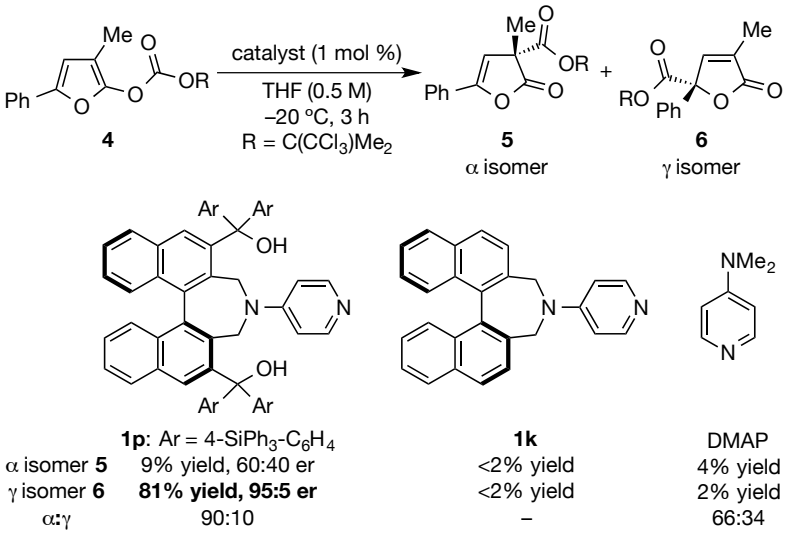


Figure 9. Competitive experiment with catalyst **1p**, **1k**, and DMAP

4-7. Conclusion

We demonstrated that low catalyst loading of **1o** allowed to construct all-carbon quaternary stereogenic center with high enantioselectivity through Steglich type rearrangement. Multigram scale reaction could be easily conducted and only 0.05 mol % (500 ppm) of **1o** was sufficient to promote the reaction within 1 h. An array of substrate having various functional groups can be applied to this reaction, and it required only 0.05-3 mol % of catalyst to give the desired products with excellent enantioselectivity (>95:5 er; 14 out of 16 examples) in quantitative yields (all cases). This reaction system could be applied to column chromatographic free purification, which delivered high purity product **3a** in quantitative yield with up to >99:1 er. Several comparative experiments and DFT calculation elucidated that at least one hydroxy group was responsible for achieving high enantioselectivity and acceleration of the reaction rate. Finally, we also demonstrated that catalyst **1p** show the high regio- and enantioselectivity in the carbonyl migration reaction to give γ-butenolide **6** (81% yield, 95:5 er) for the first time.

4-8. Experimental Section and Material Data

General

Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian 600 MR (^{1}H 600 MHz, ^{13}C 150 MHz), Varian 400 MR (^{13}C 100 MHz) or JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometers. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin =quintet, sext = sextet, sep = septet, b = broad, m = multiplet), coupling constants, and integration. Chemical shifts for ^{13}C NMR were reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) with complete proton decoupling. Infrared (IR) spectra were recorded on JASCO FT/IR-4100 spectrophotometer, Vmax in cm^{-1}. High-resolution mass spectrometry was performed on JEOL JMS-700 MStation (FAB-MS and EI-MS), Agilent 6520 Accurate Mass Q−TOF LC/MS (ESI-MS) or Thermo Fisher Scientific EXACTIVE Plus (ESI-MS). Optical rotations were measured on a JASCO DIP-1000. Melting points were recorded on a SANSYO SMP-300. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC) Shimadzu chromatograph (DAICEL CHIRALPAK® IA-3 (4.6 × 150 mm), DAICEL CHIRALPAK® AS-3 (4.6 × 150 mm), DICEL CHIRALCEL OJ-H (4.6 × 250 mm), and DICEL CHIRALCEL® OD-H (4.6 × 250 mm)) in comparison with authentic racemic samples. Column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm) purchased from KANTO CHEMICAL CO.,INC. Celitre®503RV [Celite] was purchased from NAKARAI TESQUE, INC. Unless otherwise noted all reactions were carried out under argon atmosphere in oven-dried screw-top test tube or flame-dried glassware.

Materials

All reagents were obtained commercial sources and used as received unless otherwise noted. Dry tetrahydrofuran [THF], diethyl ether [Et_2O], *t*-amyl alcohol, triethylamine [Et_3N], dibromobis(triphenylphosphine)nickel (II) [$NiBr_2(PPh_3)_2$], ammonia solution [aq. NH_3], and *N,N*-dimethyl-4-aminopyridine [DMAP] were purchased from Wako Pure Chemical Industries, Ltd. Dry diisopropyl ether [*i*-Pr_2O], 2,2,2-trichloro-1,1dimethylethyl chloroformate [TcBocCl], 2-methoxyphenylacetonitorile, allyl bromide, and potassium bis(trimethylsilyl)amide [KHMDS] were purchased from Sigma-ALDRICH Japan. Dichloromethane [CH_2Cl_2], toluene, hydrochloric acid aqueous solution [HCl], magnesium sulfate [$MgSO_4$], ammonium chloride [NH_4Cl], isopropyl iodide [*i*-PrI], hydrobromic acid [HBr], diethylamine [Et_2NH], and diisopropylamine [*i*-Pr_2NH] were purchased from NAKARAI TESQUE, INC. Hexane, dimethylformamide [DMF], *n*-butyl lithium [*n*-BuLi], triethylaluminium [Et_3Al], and di-*tert*-butyl dicarbonate [Boc_2O] were purchased from KANTO CHEMICAL CO.,INC. Cyclopentyl methyl ether [CPME], *t*-butyl methyl ether

[*t*-BuOMe], sodium hydride [NaH], 5′-bromo-*m*-terphenyl, triethyl silane [Et_3SiH], trifluoroacetic acid [TFA], 2-coumaranone, *tert*-butylmethyl chloride [TBSCl], 1-Bromo-3-chloropropane, and palladium Hydroxide (20% on carbon) [$Pd(OH)_2/C$] were purchased from Tokyo Chemical Industry Co.,Ltd. Acetone was purchased from Japan Alcohol Trading CO.,LTD. Hexane, DMF, CPME, *t*-BuOMe, DMF, and *t*-amyl alcohol were used after dehydration process with MS4A. CH_2Cl_2, $(i\text{-PrCO})_2O$, Et_3N, *i*-Pr_2NEt, and TMEDA were distilled over CaH_2. Toluene was distilled over CaH_2 and stored in the presence of MS4A. MS4A was used after drying process with heat gun under reduced pressure.

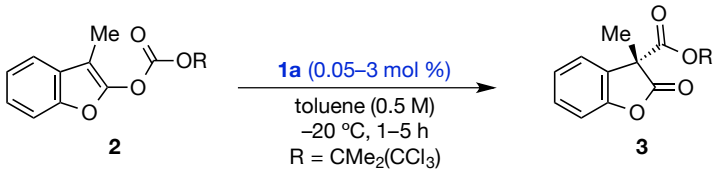
Synthetic methods for all catalysts and analytical data were recorded on according literature[26] except for catalyst **1a**, **1a′**, **1a′′**, and **1b**.

Substrate **2aa**,[9,15] **2ab**,[15] **2ac**,[15] **2a**,[15] **2d**,[15,16] **2l**,[9,16] and **2m**,[16] were synthesized by reported method.

Experimental procedures for synthesis of substrates **2b–j**, **2l**, **2n–o**, **2q–w**, **7**, and **8** were recorded on the section of "synthesis of substrate".

Racemic samples were synthesized with 5 mol % of DMAP in THF at room temperature.

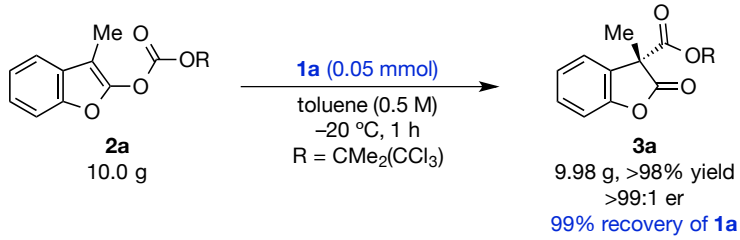
General procedure of acyl migration reaction



When the catalytic amounts were less than 0.5 mol %, a solution of the catalyst in toluene (10.0–20.0 mM) was prepared in advance and this stock solution was used the following reaction.

In a dry screw-top test tube, to a solution benzofuranyl carbonate **2** (1.0 equiv) in toluene (0.5 M) was added a solution of catalyst **1a** (0.05–3 mol %) at –20 ºC. The reaction mixture was stirred for 1–5 h at –20 ºC, and then 1.00 M aqueous HCl (2.0 mL) was added to reaction vessel at –20 ºC. After warming up to room temperature, the resulted solution was extracted by a solution of hexane and ether (10:1, v/v). The organic layer was passed through a short pad of $MgSO_4/SiO_2$ column (eluent: hexane/Et_2O = 1:1, v/v) to give the pure corresponding product (>98% yield in all cases). The enantiomeric ratio was determined by chiral HPLC analysis. ^1H NMR spectra of product clearly indicated that simple plug filtration was enough for obtaining analytically pure product. Analytical data were shown in the following section of "**Analytical data of 3a-p, 5, and 6**".

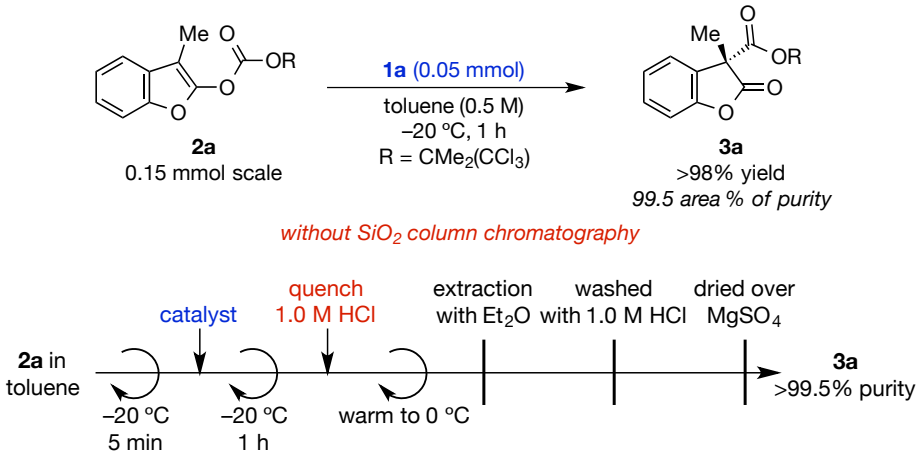
The procedure of multigram synthesis of benzofuran 3a



A stock solution of the catalyst (20.0 mg, 14.9 μmol) in toluene (1.49 mL) was prepared in advance.

In a dry two-necked flask, to a solution benzofuranyl carbonate **2a** (10.0 g, 28.5 mmol) in toluene (55.6 mL) was added a solution of catalyst **1a** in toluene (10.0 mM, 1.43 mL, 14.3 μmol) at –20 ºC. The reaction mixture was stirred for 1 h at –20 ºC, then monitored by TLC. After checking of disappearance of **2a**, the reaction solution was warmed up to room temperature, and diluted by a solution of hexane and ether (10:1, v/v). The resulting solution was directly passed through a short pad of $MgSO_4/SiO_2$ column (eluent: hexane/Et_2O = 10:1, v/v) to give the product **3a** (9.98 g, 28.4 mmol, >98% yield) as colorless solid. The second elution of polar solvent (EtOAc/MeOH = 10/1, v/v) gave recovered catalyst **1a** (18.9 mg, 14.0 μmol, 99% recovery) as pale yellow solid. The enantiomeric ratio was determined by chiral HPLC analysis. Analytical data were shown in the following section of "**Analytical data of 3a-p, 5, and 6**".

The experiment without chromatography purification

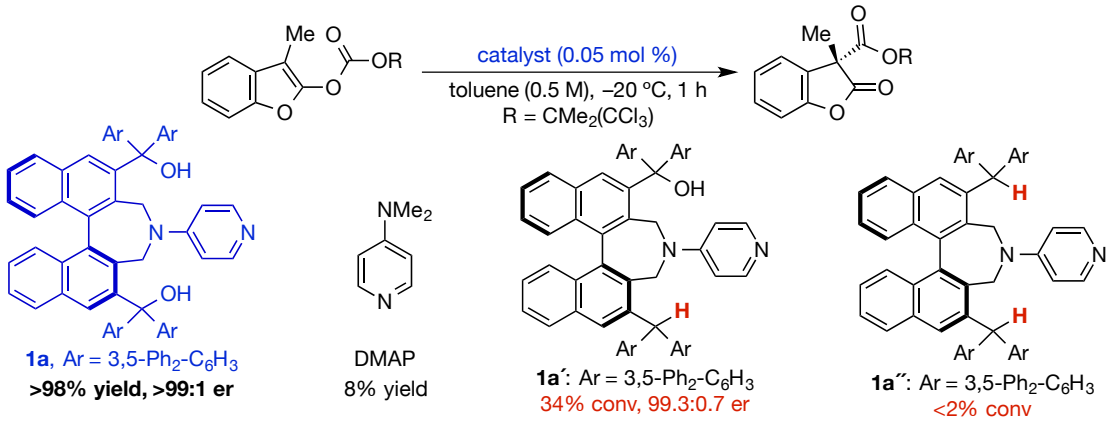


A stock solution of the catalyst (1.00 mg, 0.750 μmol) in toluene (150 μL) was prepared in advance.

In a dry two-necked flask, to a solution benzofuranyl carbonate **2a** (52.4 mg, 0.149 mmol) in toluene (285 μL) was added a solution of catalyst **1a** in toluene (5.00 mM, 15.0 μL, 0.0750 μmol) at –20 ºC. The reaction mixture was stirred for 1 h at –20 ºC, and then 1.00 N aqueous HCl (2.0 mL) was added to reaction vessel at –20 ºC. After warming up to room temperature, the quenched

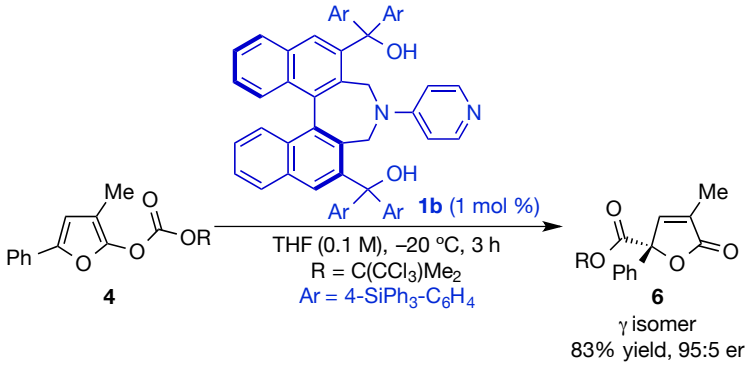
reaction solution was extracted by a solution of hexane and ether (10:1, v/v). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the product **3a** (52.0 mg, 0.148 μmol, >98% yield). The enantiomeric ratio and purity were determined by chiral HPLC analysis. Analytical data were shown in the following section of "**Analytical data of 3a-p, 5, and 6**".

General procedure of comparative experiment and HPLC charts



These experiment were conducted under similar manner for "general procedure of acyl migration reaction (Scheme 2)". The HPLC charts for each catalyst were shown below.

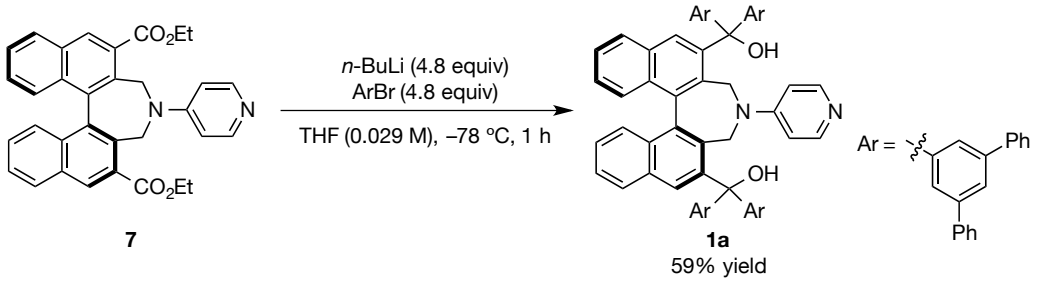
Typical procedure of acyl migration of furanyl carbonate 4



In a dry two-necked flask, to a solution furanyl carbonate **4** (200 mg, 0.530 mmol) in THF (1.06 mL) was catalyst **1b** (9.4 mg, 5.3 μmol) at –20 ºC. The reaction mixture was stirred for 3 h at –20 ºC, and then 1.00 N aqueous HCl (2.0 mL) was added to reaction vessel at –20 ºC. After warming up to room temperature, the resulting solution was extracted by a solution of hexane and ether (1:1, v/v), dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/toluene = 5:1 to 1:1 to 0:1) gave α-isomer **5** (19.2 mg, 50.8 μmol, 9% yield) as colorless solid and γ-isomer **6** (163 mg, 0.432 mmol, 82% yield) as colorless solid. Analytical data were shown in the following section of "**Analytical data of 3a-p, 5, and 6**".

Synthesis of catalyst

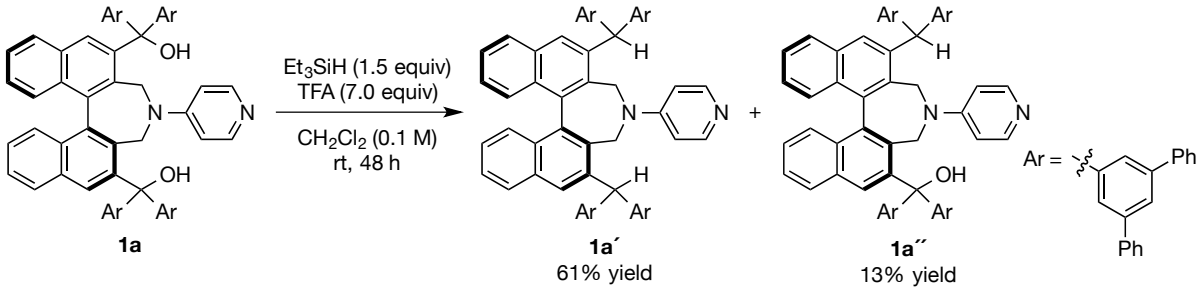
Synthesis of **1a**



To a solution of 5′-bromo-*m*-terphenyl (296 mg, 0.957 mmol) in THF (4.00 mL) was added a solution of *n*-BuLi (1.63 M in hexane, 589 μL, 0.960 mmol) at –78 ºC. The solution was stirred for 20 min at –78 ºC, then a solution of **7** (104 mg, 0.201 mmol) in THF (3.00 mL) was added dropwise to reaction vessel. The reaction mixture was stirred for 1 h at –78 ºC, and then water was added to quench the reaction. The resulting solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: Et_2O/MeOH = 100:1 to 75:1 to 50:1 to 10:1 to 5:1) gave the impure **1a**. Impure **1a** was further purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 2:1 to EtOAc only to Et_2O/MeOH = 20:1) gave the pure **1a** (159 mg, 0.118 mmol, 59% yield) as pale yellow solid.

データ未記入

Synthesis of **1a′** and **1a′′**



To a solution of **1a** (673 mg, 0.500 mmol) in CH_2Cl_2 (5.00 mL) was added EtSiH (120 μL, 0.751 mmol) and TFA (268 μL, 3.5 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature, and then excess K_2CO_3 powder was added to reaction vessel to

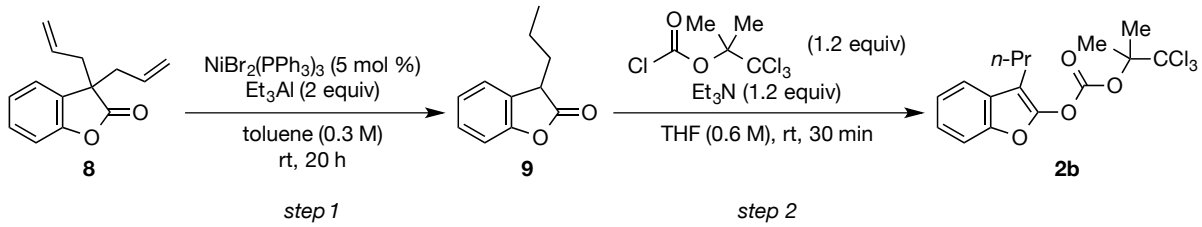
neutralize. After neutralization, the water was added to the resulting solution. The resulting solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: toluene/EtOAc = 5:1) gave the **1a´** (391 mg, 0.304 mmol, 61% yield) as colorless solid and **1a´´** (88.0 mg, mmol, 18% yield) as colorless solid.

Data of **1a´**

Data of **1a´´**

Synthesis of substrate

Synthesis of Synthesis of **2b**



We tried synthesis of mono-deallylated compound according to the literature,[36] but the reaction obtained over-reductive mono-deallylated compound **9**.

Step 1

To a solution of **8**[36] (5.57g, 26.0 mmol) and $NiBr_2(PPh_3)_3$ (969 mg, 1.30 mmol) in toluene (87 mL) was slowly added dropwise solution of Et_3Al (1.8 M in toluene, 28.9 mL, 52.0 mmol) at room temperature. The reaction mixture was stirred for 20 h at room temperature, then the reaction solution was cooled down to 0 ºC and water was slowly added to reaction vessel using dropping funnel at 0 ºC. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 30:1) gave **9** (2.09 g, 11.9 mmol, 46% yield) as colorless liquid.

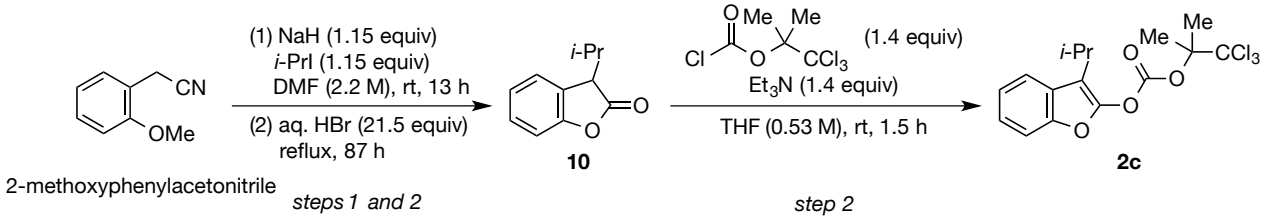
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 2H), 7.14 (td, *J* = 7.6, 0.9 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 3.73 (t, *J* = 6.4 Hz, 1H), 2.05–1.89 (m, 2H), 1.54–1.36 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 153.6, 128.5, 127.5, 124.1, 123.9, 110.4, 43.1, 33.0, 19.1, 13.7; IR (KBr) 2962, 1807, 1464, 1231, 1045, 754 cm^{-1}; HRMS (EI^+) $[M]^+$ calculated for $C_{11}H_{12}O_2$ 176.0831, found 176.0801.

Step 2

To a solution of **9** (552 mg, 3.13 mmol) and TcBocCl (911 mg, 3.80 mmol) in THF (5.00 mL) was added Et_3N (550 μL, 3.95 mmol) at room temperature. The reaction mixture was stirred for 30 min at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 20:1) gave **2b** (1.13 g, 2.98 mmol, 95% yield) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.46 (m, 1H), 7.39 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.27 (td, *J* = 7.2, 1.8 Hz, 1H), 7.24 (td, *J* = 7.2, 1.6 Hz, 1H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.02 (s, 6H), 1.71 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 149.2, 149.0, 128.9, 124.1, 122.9, 119.8, 111.1, 104.7, 103.0, 92.0, 24.3, 21.9, 21.1, 14.1; IR (KBr) 2968, 1788, 1659, 1452, 1238, 1130, 804 cm^{-1}; HRMS (ESI^+) $[M+Na]^+$ calculated for $C_{16}H_{17}O_4Cl_3Na$ 401.0085, found 401.0092.

Synthesis of **2c**



Step 1

Slightly modified procedure of reported method of synthesis of **10**.[37]

To a suspension of sodium hydride (60% purity, 956 mg, 23.9 mmol) in DMF (9.0 mL) was added portionwise 2-methoxyphenylacetoniteile (2.93 g, 19.9 mmol) at room temperature. The reaction mixture was stirred for 5 min at room temperature, then isopropyl iodide (2.3 mL, 23.0 mmol) was added to reaction vessel at room temperature. The reaction mixture was stirred for 13 h, then water was added to reaction vessel. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The crude product was directly used for next step without further purification.

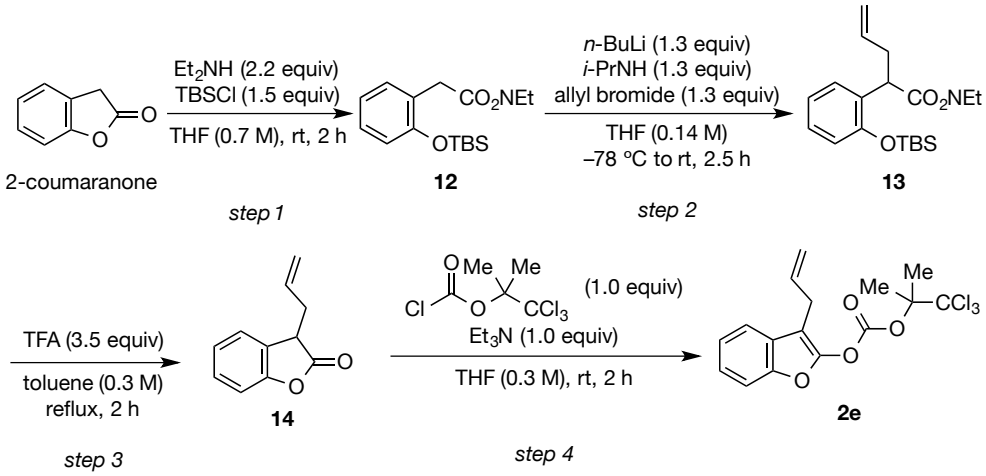
Step 2

To the crude was added aqueous HBr (ca. 8.6 M, 50 mL, 430 mmol) at room temperature. The reaction mixture was warmed up to refluxed temperature and stirred for 87 h at this temperature, then the reaction mixture was cooled down to 0 ºC and quenched by powder $NaHCO_3$ (added until CO_2 gas was not generated). After adding water, the resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **10** (3.23 g). The crude product was directly used for next step without further purification. Analytical data of **10** was identical to the according literature.[37]

Step 3

To a solution of the crude **10** (481 mg, ca. 2.73 mmol) and TcBocCl (944 mg, 3.93 mmol) in THF (5.20 mL) was added Et_3N (548 μL, 3.93 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 50:1) gave **2c** (574 mg, 1.51 mmol, 53% yield in 3 steps) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.2, 2.3 Hz, 1H), 7.39 (dd, J = 7.2, 1.8 Hz, 1H), 7.29–7.19 (m, 2H), 3.07 (sep, J = 7.0 Hz, 1H), 2.02 (s, 6H), 1.37 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 149.2, 147.8, 128.0, 124.0, 122.9, 120.4, 111.3, 108.5, 104.8, 92.1, 24.2, 21.7, 21.2; IR (KBr) 2970, 1786, 1655, 1456, 1236, 1148, 860 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{16}H_{17}O_4Cl_3Na$ 401.0085, found 401.0098; mp 51.8–52.5 ºC.

Synthesis of **2e**



Slightly modified procedure of reported method of synthesis of **13** and **14**. [38]

Step 1

To a solution of 2-coumaranone (3.01 g, 22.4 mmol) in THF (22.4 mL) was added Et_2NH (5.10 mL, 49.3 mmol) at room temperature. The reaction mixture was stirred for 30 min at room temperature, then a solution of TBSCl (3.37 M in THF, 10 mL, 33.7 mmol) was added to reaction vessel at room temoetarure. The reaction mixture was stirred for 1.5 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 5:1 to 3:1 to 1:1) gave **12** (6.22 g, 19.3 mmol, 86% yield) as yellow liquid. Analytical data of **12** was reported and identical to the according literature.[38].

Step 2

To a solution of *i*-Pr_2NH (1.70 mL, 12.1 mmol) in THF (43.0 mL) was added a solution of *n*-BuLi (1.64 M in hexane, 7.40 mL, 12.1 mmol) at 0 ºC. After stirring for 10 min at 0 ºC, the reaction mixture was cooled down to –78 ºC and a solution of **12** (0.42 M in THF, 22.2 mL, 9.32 mmol) was added. The reaction mixture was stirred for 1 h, then allyl bromide (1.05 mL, 12.1 mmol) was added dropwise to reaction vessel at –78 ºC. The reaction mixture was warmed up to room temperature and stirred for 2.5 h, then aqueous NH_4Cl was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **13**. The crude product was directly used for next step without further purification. Analytical data of **13** was reported and identical to the according literature.[38].

Step 3

To a solution of crude **13** in toluene (30 mL) was added TFA (2.48 mL, 32.4 mmol) at room temperature. The reaction mixture was warmed up to refluxed temperature and stirred for 2 h. After stirring 2 h, the reaction mixture was cooled down to room temperature, then water was added to

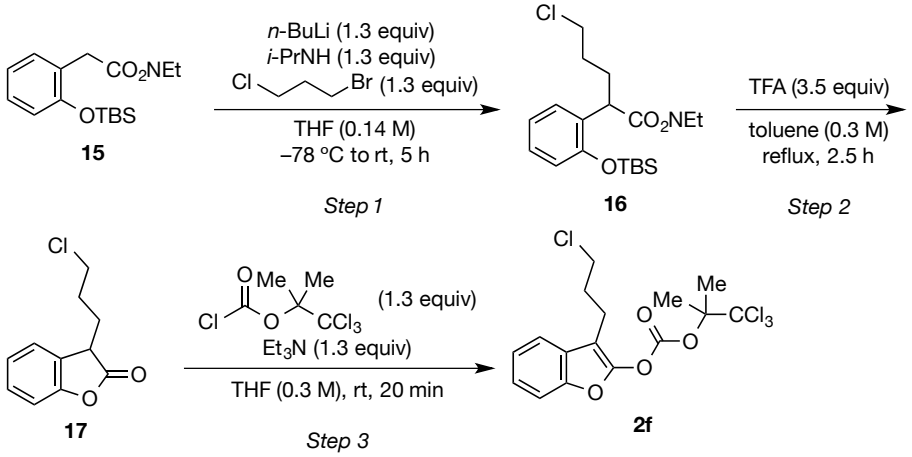
reaction vessel. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **14**. The crude product was directly used for next step without further purification. Analytical data of **14** was reported and identical to the according literature.[38]

Step 4

To a solution of the crude **14**[38] (1.62 g, ca. 9.30 mmol) and TcBocCl (2.75 g, 11.5 mmol) in THF (30.0 mL) was added Et_3N (2.10 mL, 15.1 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: toluene/Et_2O = 5:1 to 3:1) gave **2e** (1.83 g, 4.85 mmol, 52% yield in 3 steps) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.40 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.31–7.20 (m, 2H), 5.97 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H), 5.20 (ddd, *J* = 16.9, 1.6, 1.5 Hz, 1H), 5.11 (ddd, *J* = 10.1, 1.6, 1.5 Hz, 1H), 3.36 (dt, *J* = 6.5, 1.6 Hz, 2H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 149.3, 148.8, 134.3, 128.6, 124.2, 123.1, 119.9, 116.7, 111.1, 104.7, 100.8, 92.1, 26.8, 21.1; IR (KBr) 3073, 1786, 1655, 1456, 1211, 1140, 908, 793 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{16}H_{15}Cl_3O_4Na$ 377.0109, found 398.9927; mp 45.7–46.3 ºC.

Synthesis of **2f**



Step 1

To a solution of *i*-Pr_2NH (570 μL, 4.07 mmol) in THF (6.20 mL) was added a solution of *n*-BuLi (1.64 M in hexane, 2.46 mL, 4.03 mmol) at 0 ºC. After stirring for 10 min at 0 ºC, the reaction mixture was cooled down to –78 ºC and a solution of **15** (0.42 M in THF, 7.40 mL, 3.11 mmol) was added. The reaction mixture was stirred for 1 h, then a solution of 1-bromo-3-chloropropane (0.529 M in THF, 8.00 mL, 4.74 mmol) was added dropwise to reaction vessel at –78 ºC. The reaction

mixture was warmed up to room temperature and stirred for 4 h, then aqueous NH_4Cl was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **16**. The crude product was directly used for next step without further purification. Analytical data of **16** was reported and identical to the according literature.[38]

Step 2

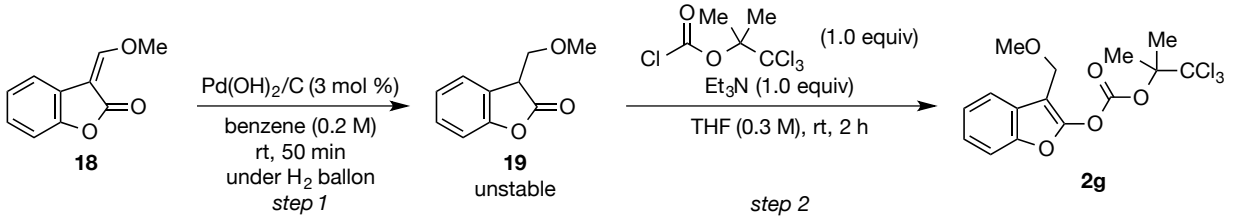
To a solution of crude **16** in toluene (10.4 mL) was added TFA (840 μL, 11.0 mmol) at room temperature. The reaction mixture was warmed up to refluxed temperature and stirred for 2.5 h. After stirring 2.5 h, the reaction mixture was cooled down to room temperature, then water was added to reaction vessel. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **17**. The crude product was directly used for next step without further purification. Analytical data of **17** was reported and identical to the according literature.[38]

Step 3

To a solution of the crude **16**[38] (ca. 3.11 mmol) and TcBocCl (1.02 g, 4.25 mmol) in THF (10.0 mL) was added Et_3N (570 μL, 4.10 mmol) at room temperature. The reaction mixture was stirred for 20 min at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 70:1) gave **2f** (612 mg, 1.48 mmol, 48% yield in 3 steps) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (m, 1H), 7.39 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.31–7.20 (m, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H), 2.13 (quin, *J* = 6.6 Hz, 2H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 149.5, 148.9, 128.4, 124.3, 123.2, 119.5, 111.2, 104.7, 101.4, 92.2, 44.1, 31.1, 21.1, 19.0; IR (KBr) 2947, 1790, 1659, 1456, 1217, 1136, 827 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{16}H_{16}Cl_4O_4Na$ 434.9695, found 434.9706; mp 44.7–45.1 ºC.

Synthesis of **2g**



Step 1

To a solution of **18**[39-42] (578 mg, 2.49 mmol) in benzene (12.5 mL) was added Pd/C (114 mg, 81.2 μmol) at room temperature. After hydrogen gas purging, the reaction mixture was stirred for

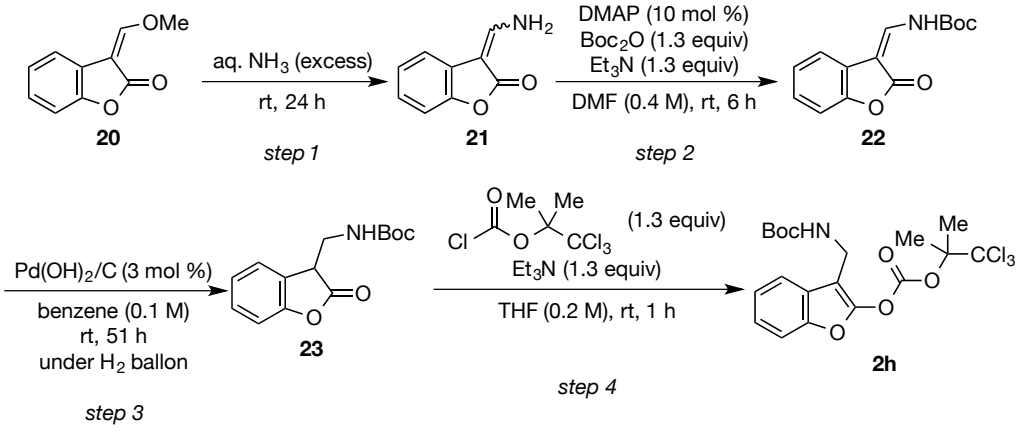
50 min at room temperature. After stirring for 50 min, the reaction mixture was passed through a short pad of Cerite® with washing Et_2O. The resulting solution was concentrated *in vacuo* to give crude **19**. The compound **19** was unstable and easily converted to eliminated product (3-methylenebenzofuranone) over time. The crude product **19** was immediately used for next step without further purification.

Step 2

To a solution of the crude **19**[38] (ca. 2.49 mmol) and TcBocCl (603 mg, 2.51 mmol) in THF (12.5 mL) was added Et_3N (349 μL, 2.50 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 20:1 to 5:1) and GPC purification (eluent: $CHCl_3$) gave **2g** (620 mg, 1.62 mmol, 65% yield in 2 steps) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 1H), 7.41 (dd, J = 7.1, 1.6 Hz, 1H), 7.33–7.23 (m, 2H), 4.55 (s, 2H), 3.36 (s, 3H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 149.7, 148.5, 127.7, 124.5, 123.5, 120.2, 111.1, 104.6, 100.2, 92.2, 63.3, 57.9, 21.0; IR (KBr) 2934, 1786, 1655, 1452, 1238, 1144, 910, 826 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{15}H_{15}Cl_3O_5Na$ 402.9877, found 402.9897; mp 42.4–42.9 ºC.

Synthesis of **2h**



Step 1

A mixture of **20** (1.98 g, 8.53 mmol) and aqueous ammonia (ca. 30% v/v, 100 mL) was stirred for 24 h at room temperature. The precipitate was separated by filtration and washed with Et_2O and dried over *in vacuo* to give crude product (1.08 g). The crude product was directly used for next step without further purification.

Step 2

To a suspension of crude **21** (322 mg, ca. 2.0 mmol), Boc_2O (597 μL, 2.60 mmol), and Et_3N (362 μL, 2.60 mmol) in DMF (5.00 mL) was added DMAP (23.4 mg, 0.192 mmol) at room temperature. The reaction mixture was stirred for 6 h at room temperature, and then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 5:1 to 1:1) gave major diastereomer **22** (365 mg, 1.40 mmol, 55% yield in 2 steps, single diastereomer) as colorless solid. Trace amount minor diastereomer of **22** was also detected by ^{1}H NMR analysis of crude product, but it was not isolated in high purity and analytical data was not collected.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 11.9 Hz, 1H), 7.99 (d, *J* = 11.9 Hz, 1H), 7.36 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.23 (td, *J* = 8.0, 1.5 Hz, 1H), 7.17–7.08 (m, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 151.4, 136.0, 127.3, 123.9, 123.3, 118.1, 110.7, 100.2, 83.5, 28.0; IR (neat or KBr) 3343, 1734, 1497, 1321, 1144, 1082, 880 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{14}H_{16}NO_4$ 262.1074, found 262.1070; mp 154.0–154.9 ºC.

To a solution of **22** (352 mg, 1.35 mmol) in benzene (13.5 mL) was added Pd/C (65.0 mg, 46.3 μmol) at room temperature. After hydrogen gas purging, the reaction mixture was stirred for 51 h at room temperature. After stirring for 51 h, the reaction mixture was passed through a short pad of Cerite® with washing Et_2O. The resulting solution was concentrated *in vacuo* to give **23** (345 mg, 1.31 mmol, 97% yield) as colorless solid.

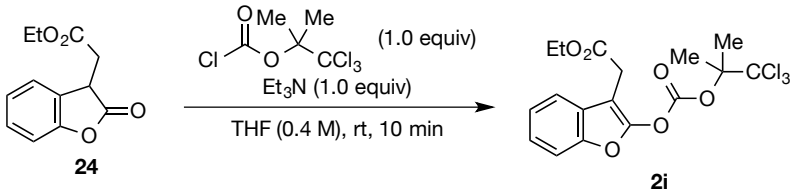
^{1}H NMR (400 MHz, $CDCl_3$, 0.03% TMS) δ 7.39–7.29 (m, 2H), 7.17 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 5.08 (bs, 1H), 3.95–3.79 (m, 2H), 3.61–3.43 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 0.03% TMS) δ 176.3, 155.8, 154.1, 129.5, 124.9, 124.8, 124.5, 110.9, 80.1, 44.4, 41.1, 28.4; IR (KBr) 3362, 2988, 2932, 1796, 1682, 1526, 1071, 759 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{14}H_{18}NO_4$ 264.1230, found 264.1212; mp 84.1–84.9 ºC.

To a solution of **23** (318 mg, 1.21 mmol) and TcBocCl (384 mg, 1.60 mmol) in THF (6.10 mL) was added Et_3N (219 μL, 1.57 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by recrystallization from Et_2O/hexane gave **2h** (479 mg, 1.03 mmol, 85% yield) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.2 Hz, 1H), 7.40 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.31 (td, *J* = 7.2, 1.8 Hz, 1H), 7.27 (td, *J* = 7.2, 1.6 Hz, 1H), 4.77 (bs, 1H), 4.36 (d, *J* = 6.0 Hz, 2H), 2.03 (s, 6H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 149.8, 149.6, 148.6, 127.5, 124.6, 123.5, 120.2,

111.1, 104.6, 101.1, 92.4, 79.6, 33.0, 28.4, 21.1; IR (KBr) 3347, 1786, 1684, 1533, 1234, 1142, 752 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{19}H_{23}Cl_3NO_6$ 466.0585, found 466.0557; mp 131.8–132.2.

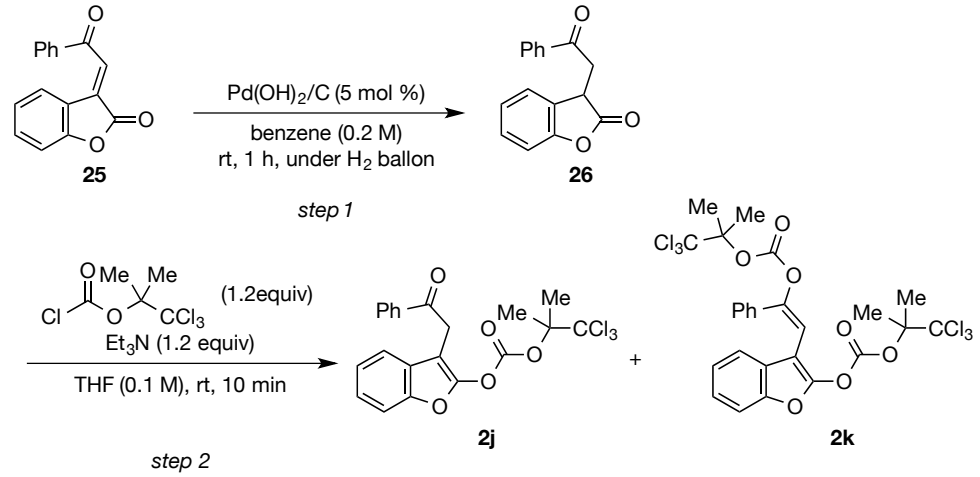
Synthesis of **2i**



To a solution of **24**[43] (2.08 g, 9.45 mmol) and TcBocCl (2.25 g, 9.38 mmol) in THF (23.0 mL) was added Et_3N (1.32 mL, 9.47 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature, and then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/toluene = 3:2 to 2:3) and GPC (eluent: $CHCl_3$) gave **2i** (905 mg, 2.14 mmol, 23% yield) as colorless liquid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.50 (m, 1H), 7.41 (dd, J = 6.9 Hz, 1.8 Hz, 1H), 7.33–7.23 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.61 (s, 2H), 2.02, (s, 6H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 149.9, 149.5, 148.3, 128.1, 124.4, 123.3, 119.8, 111.1, 104.6, 96.5, 92.2, 61.1, 28.5, 20.9, 14.1; IR (KBr) 2984, 1732, 1454, 1028, 743 cm^{-1}; HRMS (ESI^+) $[M+Na]^+$ calculated for $C_{17}H_{17}Cl_3O_6Na$ 444.9983, found 445.0006;

Synthesis of **2j** and **2k**



Step 1

To a solution of **25**[44] (1.01 g, 4.04 mmol) in benzene (20 mL) was added Pd/C (78.4 mg, 55.8 μmol) at room temperature. After hydrogen gas purging, the reaction mixture was stirred for 1 h at

room temperature. After stirring for 1 h, the reaction mixture was passed through a short pad of Cerite® with washing Et_2O. The resulting solution was concentrated *in vacuo* to give **26** (890 mg, 3.53 mmol, 87% yield) as pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$, 0.03% TMS) δ 8.01–7.94 (m, 2H), 7.61 (tt, *J* = 7.9, 1.4 Hz, 1H), 7.49 (tt, *J* = 7.4, 1.4 Hz, 2H), 7.31 (tt, *J* = 7.9, 1.1 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.10 (td, *J* = 7.4, 1.0 Hz, 1H), 4.29 (dd, *J* = 8.2, 3.3 Hz, 1H), 3.90 (dd, *J* = 18.3, 3.2 Hz, 1H), 3.63 (dd, *J* = 18.3, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 0.03% TMS) δ 195.7, 177.5, 154.1, 135.8, 133.9, 129.0, 128.9, 128.3, 127.3, 124.4, 124.2, 110.8, 40.2, 39.2; IR (KBr) 3082, 2945, 1790, 1682, 1464, 1231, 1065, 768 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{16}H_{12}O_3Na$ 275.0679, found 275.0698; mp 137.5–137.9 ºC.

Step 2

To a solution of **26** (443 mg, 1.76 mmol) and TcBocCl (516 mg, 2.15 mmol) in THF (18 mL) was added Et_3N (296 μL, 2.12 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature, and then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/toluene = 1:1 to 1:2) gave **2j** (471 mg, 1.03 mmol, 59% yield) as colorless solid and **2k** (253 mg, 0.383 mmol, 22% yield) as colorless solid.

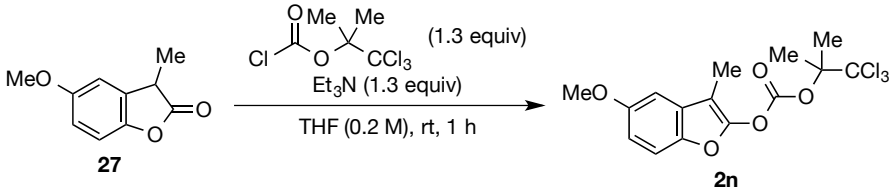
Analytical data of **2j**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.01 (m, 2H), 7.58 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.48 (m, 3H), 7.41 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.32–7.22 (m, 2H), 4.25 (s, 2H), 2.0 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 150.0, 149.6, 148.2, 136.1, 133.4, 128.7, 128.6, 128.3 (2), 124.4, 123.3, 119.8, 111.1, 104.6, 96.8, 92.2, 32.5, 20.9; IR (KBr) 3057, 1792, 1692, 1454, 1242, 1211, 1146, 760 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{21}H_{17}Cl_3O_5Na$ 477.0034, found 477.0052; mp 107.0–107.8 ºC.

Analytical data of **2k**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.83 (m, 1H), 7.62–7.57 (m, 2H), 7.46–7.34 (m, 4H), 7.33–7.23 (m, 2H), 6.64 (s, 1H), 2.03 (s, 6H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.9, 149.2, 147.8, 147.1, 134.5, 129.2, 128.9, 126.3, 124.8, 124.7, 123.8, 122.1, 111.1, 105.2, 104.6, 104.5, 99.1, 92.6, 90.9, 77.4, 21.2, 20.9; IR (KBr) 2930, 1819, 1778, 1755, 1464, 1236, 1209, 1150, 797 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{26}H_{23}Cl_6O_7$ 656.9569, found 656.9578; mp 136.3–137.1 ºC.

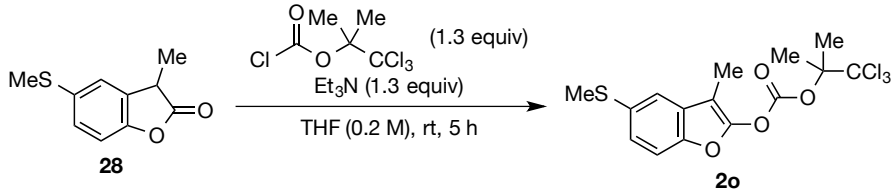
Synthesis of **2n**



To a solution of **27**[45] (403 mg, 2.26 mmol) and TcBocCl (707 mg, 2.95 mmol) in THF (11.3 mL) was added Et_3N (410 μL, 2.94 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by recrystallization from Et_2O/hexane gave **2n** (843 mg, 2.21 mmol, 98% yield) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 3.85 (s, 3H), 2.12 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 149.5, 148.7, 144.2, 129.8, 112.3, 111.5, 104.7, 102.4, 98.8, 91.9, 55.7, 20.9, 6.6; IR (KBr) 2990, 2835, 1782, 1668, 1456, 1240, 1150, 802 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{15}H_{16}Cl_3O_5$ 381.0058, found 381.0036; mp 81.3–81.5 ºC.

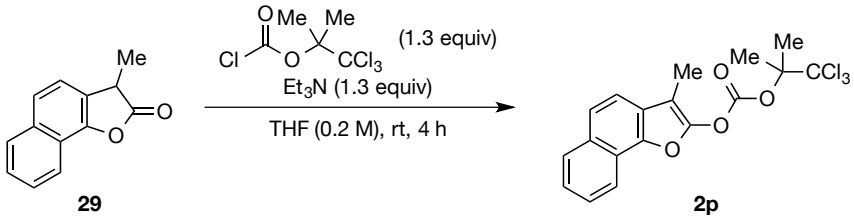
Synthesis of **2o**



To a solution of **28**[45] (241 mg, 1.24 mmol) and TcBocCl (405 mg, 1.69 mmol) in THF (6.00 mL) was added Et_3N (224 μL, 1.61 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 30:1) gave **2o** (455 mg, 1.14 mmol, 92% yield) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.24 (dd, J = 8.7, 1.8 Hz, 1H), 2.52 (s, 3H), 2.12 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 148.5, 148.0, 132.3, 130.1, 124.7, 118.9, 111.4, 104.6, 98.4, 92.1, 21.0, 17.9, 6.6; IR (KBr) 2922, 1786, 1665, 1458, 1240, 1146, 799 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{15}H_{15}Cl_3O_4SNa$ 418.9649, found 418.9637; mp 94.8–95.1 ºC.

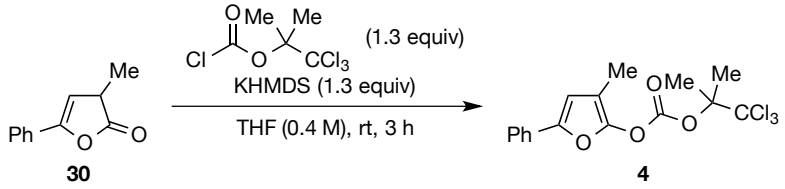
Synthesis of **2p**



To a solution of **29**[45] (589 mg, 2.97 mmol) and TcBocCl (959 mg, 4.00 mmol) in THF (15.0 mL) was added Et_3N (544 μL, 3.90 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature, then water was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 30:1) gave **2p** (946 mg, 2.36 mmol, 79% yield) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 8.2, 0.9 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.59–7.53 (m, 2H), 7.46 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 2.23 (s, 3H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 148.4, 144.4, 131.3, 128.4, 126.4, 124.9, 124.7, 123.5, 120.8, 119.6, 117.8, 104.7, 99.8, 91.9, 21.0, 6.8; IR (KBr) 3013, 2930, 1786, 1234, 1213, 1136, 808 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{18}H_{16}Cl_3O_4$ 401.0109, found 401.0081; mp 112.0–112.9 ºC.

Synthesis of **4**



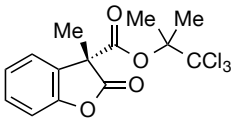
To a solution of **30** (5.23 g, 30.0 mmol) and TcBocCl (9.32 g, 38.8 mmol) in THF (75.0 mL) was added KHMDS (0.500 M in toluene, 78.0 mL, 39.0 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature, then 1 N aqueous HCl was added to reaction vessel at room temperature. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/toluene = 3:1) and recrystallization from cold hexane gave **4** (2.72 g, 7.20 mmol, 24% yield) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.54 (m, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.23 (tt, J = 7.6, 1.4 Hz, 1H), 6.49 (s, 1H), 2.02 (s, 6H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 146.9, 146.3, 130.2, 128.7, 127.3, 123.3, 108.6, 104.8, 104.6, 91.8, 21.0, 8.5; IR (KBr) 2926, 1786, 1234, 1207, 1142, 795, 758 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{16}H_{16}Cl_3O_4$ 377.0109, found 377.0085; mp 103.1–103.6 ºC.

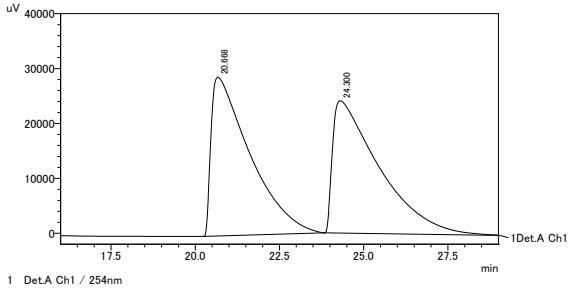
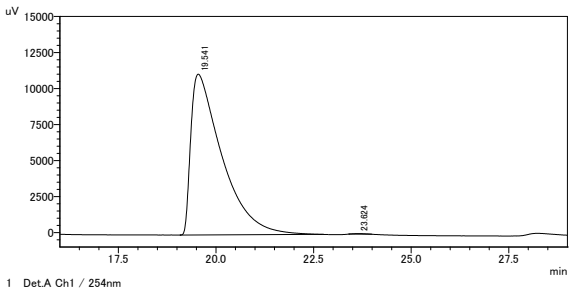
Analytical data of 3a-p, 5, and 6

1,1,1-Trichloro-2-methylpropan-2-yl

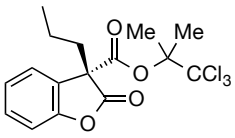
(*S*)-3-methyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3a)



According to general procedure, substrate **2a** (10.0 g, 28.5 mmol) with 0.05 mol % of catalyst **1a** (0.01 M in toluene, 1.43 mL, 14.3 μmol) in toluene (55.6 mL) at –20 ºC for 1 h gave a colorless solid (9.98 g, 28.4 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99.8/0.2, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 19.5 min (major) and T_R = 23.6 min (minor), >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (td, *J* = 7.6, 1.4 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 1.88 (s, 3H), 1.78 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 165.9, 153.6, 130.2, 128.4, 124.7, 123.2, 111.3, 105.2, 90.6, 55.0, 21.3, 21.0, 19.8; IR (KBr) 3007, 2940, 1813, 1746, 1616, 1599, 1464, 1252, 1159, 1042, 891 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{14}H_{14}Cl_3O_4$ 350.9952, found 350.9944; mp 44.9–45.4 ºC; $[\alpha]^{21}_D$ = +79.3 (*c* = 1.0, CH_2Cl_2, >99:1 er) [lit.[15] $[\alpha]^{23}_D$ = +77 (c 1.0, $CHCl_3$, *S* configuration)].

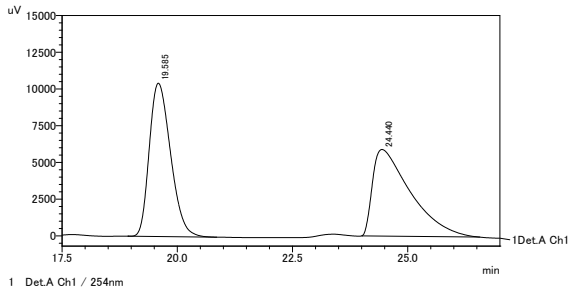
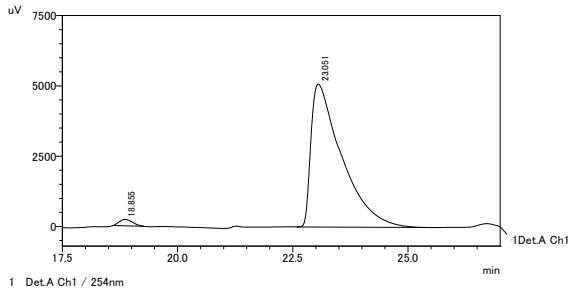
Racemic sample of **3a**				(*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	20.668	2321744	49.934	1	19.541	619663	99.874
2	24.300	2327837	50.066	2	23.624	782	0.126

1,1,1-Trichloro-2-methylpropan-2-yl (*S*)-2-oxo-3-propyl-2,3-dihydrobenzofuran-3-carboxylate (3b)



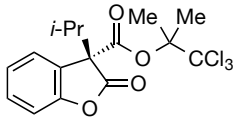
According to general procedure, substrate **2b** (75.2 mg, 0.198 mmol) with 0.2 mol % of catalyst **1a** (0.01 M in toluene, 40.0 μL, 0.400 μmol) in toluene (360 μL) at –20 ºC for 5 h gave a colorless solid (74.4 mg, 0.196 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® OD-H (hexane/*i*-PrOH = 99.6/0.4, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 18.9 min (minor) and T_R = 23.1 min (major), 98:2 er; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.29 (m, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 2.29 (td, *J* = 12.9, 4.8 Hz, 1H), 2.20 (td, *J* = 12.9, 4.7 Hz, 1H), 1.87 (s, 3H), 1.79 (s,

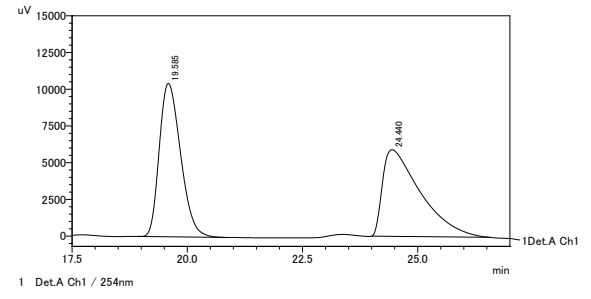
3H), 1.27–1.08 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 165.6, 153.9, 130.1, 126.6, 124.6, 123.7, 111.2, 105.3, 90.6, 59.8, 36.0, 21.3, 21.0, 17.6, 14.0; IR (KBr) 2972, 1813, 1751, 1477, 1462, 1242, 995, 883, 793 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{16}H_{17}O_4Cl_3Na$ 401.0085, found 401.0080; mp 78.1–78.8 ºC; $[\alpha]^{20}_D$ + 57.6 (*c* 1.03, CH_2Cl_2, 98:2 er).

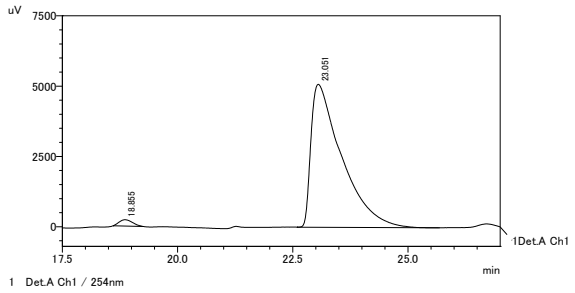
Racemic sample of **3b**				(*S*)-**3b**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	19.585	335802	49.875	1	18.855	4579	1.904
2	24.440	337492	50.125	2	23.051	235930	98.096

1,1,1-Trichloro-2-methylpropan-2-yl

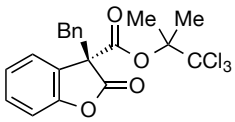
(*S*)-3-isopropyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3c)



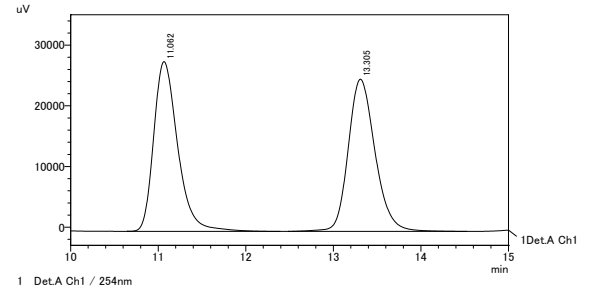
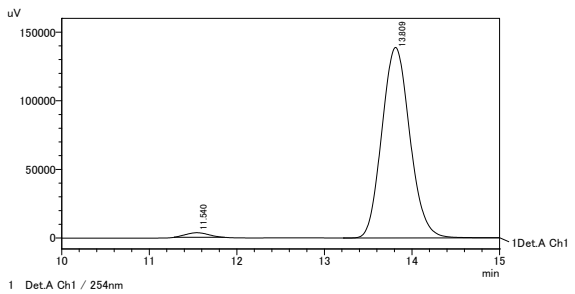




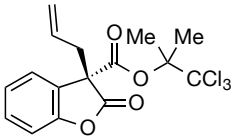
1,1,1-Trichloro-2-methylpropan-2-yl (*S*)-3-benzyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3d)



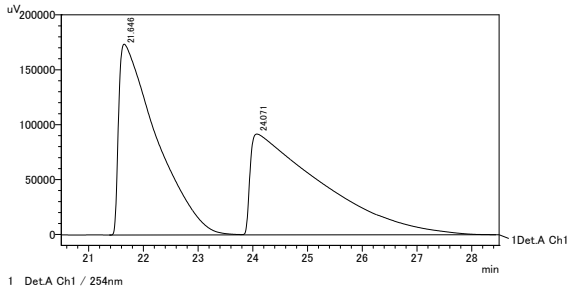
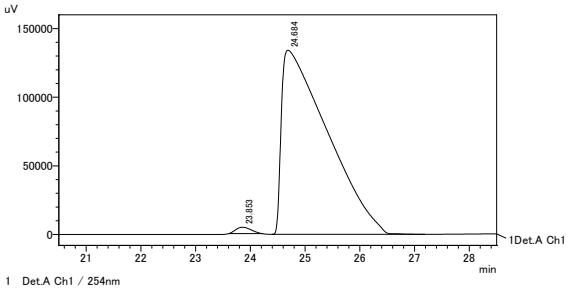
According to general procedure, substrate **2d** (53.1 mg, 0.124 mmol) with 0.2 mol % of catalyst **1a** (0.02 M in toluene, 12.5 μL, 0.250 μmol) in toluene (237 μL) at –20 ºC for 5 h gave a colorless solid (52.2 mg, 0.122 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 11.5 min (minor) and T_R = 13.8 min (major), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.30–7.23 (m, 1H), 7.17 (td, *J* = 7.6, 0.9 Hz, 1H), 7.13–7.05 (m, 3H), 6.95–6.89 (m, 3H), 3.60 (s, 2H), 1,92 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 165.4, 153.8, 133.5, 130.3, 130.1, 128.4, 127.5, 125.8, 124.4, 124.2, 111.2, 105.2, 90.9, 61.3, 39.6, 21.4, 21.1; IR (KBr) 3030, 2938, 1800, 1751, 1462, 1240, 1157, 797 cm^{-1}; $[\alpha]^{24}_D$ +119.7 (*c* 0.90, CH_2Cl_2, 98:2 er) [lit[16] $[\alpha]^{20}_D$ = –7.6 (c = 0.90, CH_2Cl_2, 88% ee, *R* configuration) lit[15] $[\alpha]^{23}_D$ = +99 (c 0.9, CH_2Cl_2, 89% ee, *S* configuration)].

Racemic sample of **3d**				(*S*)-**3d**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	11.062	533857	49.957	1	11.540	60165	1.911
2	13.305	534776	50.043	2	13.809	3088689	98.089

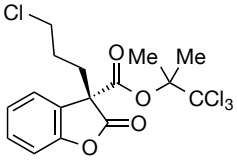
1,1,1-Trichloro-2-methylpropan-2-yl (*S*)-3-allyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3e)



According to general procedure, substrate **2e** (37.6 mg, 99.6 μmol) with 1.0 mol % of catalyst **1a** (1.3 mg, 0.966 μmol) in toluene (200 μL) at –20 ºC for 5 h gave a colorless solid (37.1 mg, 98.2 μmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® OD-H (hexane/*i*-PrOH = 99.6/0.4, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 23.9 min (minor) and T_R = 24.7 min (major), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (td, *J* = 7.8, 1.0 Hz, 2H), 7.18 (td, *J* = 7.8, 1.0 Hz, 1H), 7.13 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.47 (ddt, *J* = 17.0, 10.0, 7.3 Hz, 1H), 5.13 (ddd, *J* = 17.0, 2.6, 1.6 Hz, 1H), 5.06 (dt, *J* = 10.0, 1.6 Hz, 1H), 3.07–2.95 (m, 2H), 1.88 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 165.1, 153.7, 130.2, 129.9, 125.9, 124.6, 123.8, 121.3, 111.1, 105.2, 90.7, 59.4, 38.0, 21.3, 21.0; IR (KBr) 3009, 2955, 1813, 1751, 1462, 1242, 1018, 791 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{16}H_{15}Cl_3O_4$ 398.9928, found 398.9934; mp 92.1–92.3 ºC; $[\alpha]^{23}_D$ +84.9 (*c* 1.03, CH_2Cl_2, 99:1 er).

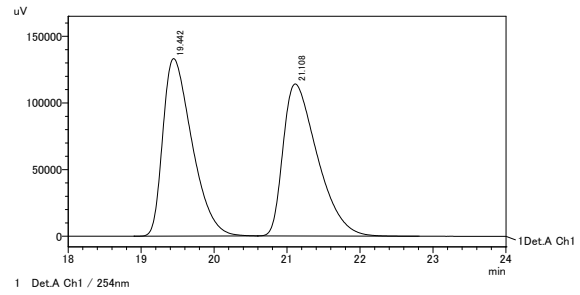
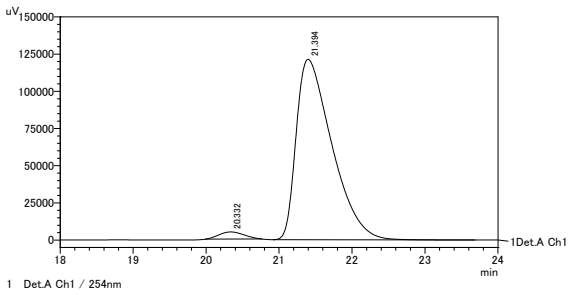
Racemic sample of **3e**				(*S*)-**3e**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	21.646	8326258	49.957	1	23.853	88673	1.118
2	24.071	8340434	50.043	2	24.684	7845021	98.882

1,1,1-Trichloro-2-methylpropan-2-yl (*S*)-3-(3-chloropropyl)-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3f)

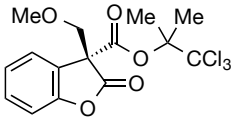


According to general procedure, substrate **2f** (41.2 mg, 99.5 μmol) with 1.0 mol % of catalyst **1a** (1.50 mg, 1.11 mmol) in toluene (200 μL) at –20 ºC for 5 h gave a colorless liquid (40.5 mg, 97.8 μmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® OD-H (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 20.3 min (minor) and T_R = 21.4 min (major), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (td, *J* = 7.4, 1.4 Hz, 1H), 7.23 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 3.49 (t, *J* = 6.4 Hz,

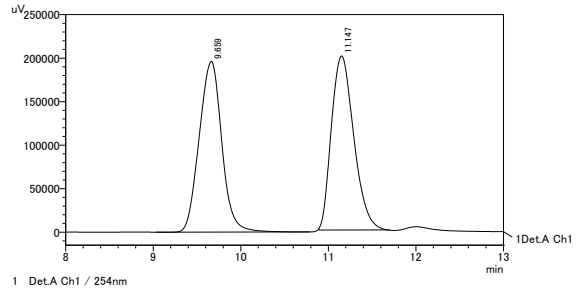
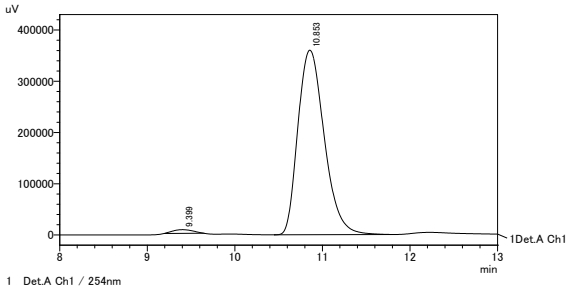
2H), 2.51–2.33 (m, 2H), 1.88 (s, 3H), 1.78 (s, 3H), 1.75–1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 165.2, 153.8, 130.5, 126.1, 124.9, 123.6, 111.4, 105.2, 90.8, 59.0, 44.2, 31.3, 27.2, 21.4, 21.0; IR (KBr) 3005, 2957, 1807, 1732, 1599, 1447, 1236, 1045, 795 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{16}H_{17}Cl_4O_4$ 412.9875, found 412.9879; $[\alpha]^{20}_D$ +56.2 (*c* 1.03, CH_2Cl_2, 97:3 er).

Racemic sample of **3f**				(*S*)-**3f**			
						
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	19.442	3694446	49.799	1	20.332	114834	2.712
2	21.108	3724245	50.201	2	21.394	4119162	97.288

1,1,1-Trichloro-2-methylpropan-2-yl
(*R*)-3-(methoxymethyl)-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3g)



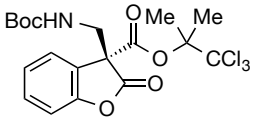
According to general procedure, substrate **2f** (47.2 mg, 0.124 mmol) with 0.05 mol % of catalyst **1a** (0.01 M in toluene, 6.25 μL, 0.0625 μmol) in toluene (244 μL) at –20 ºC for 5 h gave a colorless solid (46.9 mg, 0.123 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 9.4 min (minor) and T_R = 10.9 min (major), 98.5:1.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 2H), 7.19 (td, *J* = 7.9, 0.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 4.10 (d, *J* = 11.8 Hz, 1H), 4.08 (d, *J* = 11.8 Hz, 1H), 3.30 (s, 3H), 1.88 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 163.8, 154.3, 130.5, 125.2, 124.7, 123.8, 111.2, 105.2, 90.9, 73.0, 60.5, 59.9, 21.4, 21.1; IR (KBr) 2951, 1809, 1750, 1462, 1254, 1099, 1041, 787 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{15}H_{15}Cl_3O_5Na$ 402.9877, found 402.9862; mp 122.5–122.8 ºC; $[\alpha]^{24}_D$ +53.7 (*c* 1.00, CH_2Cl_2, 98.5:1.5 er).

Racemic sample of **3g**	(*R*)-**3g**
	

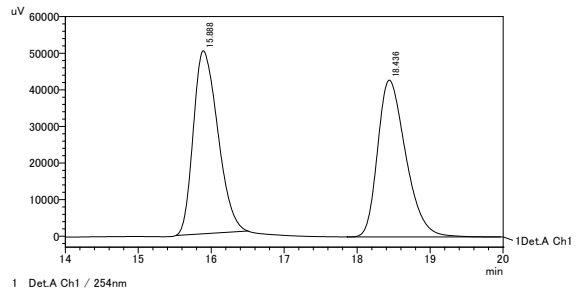
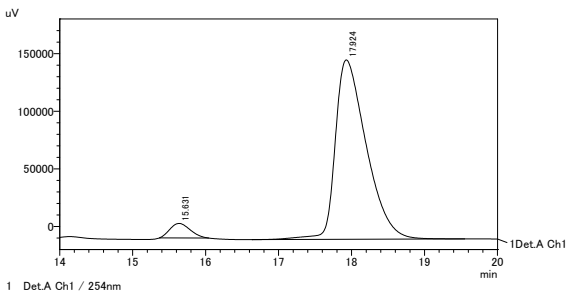
Peak	T_R	Area	Area %
1	9.659	3513448	49.695
2	11.147	3556516	50.305

Peak	T_R	Area	Area %
1	9.399	116182	1.519
2	10.853	7534686	98.481

1,1,1-Trichloro-2-methylpropan-2-yl (*R*)-3-(((*tert*-butoxycarbonyl)amino)methyl)-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3h)



According to general procedure, substrate **2h** (58.3 mg, 0.125 mmol) with 0.2 mol % of catalyst **1a** (0.01 M in toluene, 25.0 μL, 0.250 μmol) in toluene (225 μL) at –20 ºC for 5 h gave a colorless solid (57.5 mg, 0.123 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 97/3, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 15.6 min (minor) and T_R = 17.9 min (major), 95:5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 2 H), 7.23–7.10 (m, 2H), 5.08 (bs, 1H), 4.01 (dd, *J* = 14.2, 6.6 Hz, 1H), 3.92 (dd, *J* = 14.2, 6.6 Hz, 1H), 1.89 (s, 3H), 1.80 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 164.6, 155.5, 154.0, 130.7, 124.7, 124.6, 124.5, 111.2, 105.1, 91.2, 80.2, 59.8, 43.4, 28.3, 21.4, 21.1; IR (KBr) 3402, 2976, 1800, 1753, 1722, 1516, 1244, 1157, 795 cm^{-1}; HRMS (FAB$^+$) $[M+Na]^+$ calculated for $C_{19}H_{23}Cl_3NO_6$ 466.0585, found 466.0563; mp 119.2–119.6 ºC; $[\alpha]^{20}_D$ +55.3 (*c* 1.01, CH_2Cl_2, 95:5 er).

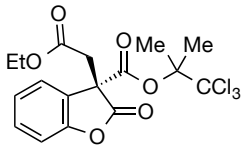
Racemic sample of **3h**	(*R*)-**3h**
	

Peak	T_R	Area	Area %
1	15.888	1167195	50.418
2	18.436	1147864	49.582

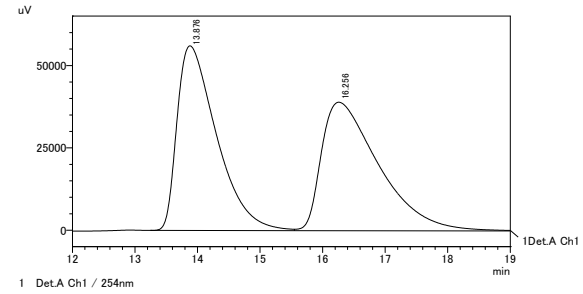
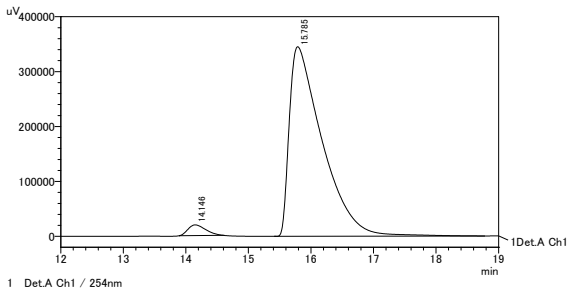
Peak	T_R	Area	Area %
1	15.631	242295	5.014
2	17.924	4590262	94.986

1,1,1-Trichloro-2-methylpropan-2-yl

(*S*)-3-(2-ethoxy-2-oxoethyl)-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3i)

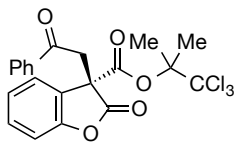


According to general procedure, substrate **2i** (53.0 mg, 0.125 mmol) with 0.05 mol % of catalyst **1a** (0.01 M in toluene, 6.25 μL, 0.0625 μmol) in toluene (225 μL) at –20 ºC for 5 h gave a colorless solid (52.9 mg, 0.125 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98.6/1.4, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 14.1 min (minor) and T_R = 15.8 min (major), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (td, *J* = 7.7, 1.2 Hz, 1H), 7.31 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.19–7.12 (m, 2H), 4.09–3.93 (m, 2H), 3.39 (s, 2H), 1.86 (s, 3H), 1.77 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 168.6, 164.4, 154.5, 130.6, 126.1, 124.6, 123.3, 111.3, 105.1, 91.0, 61.6, 56.6, 38.0, 21.3, 21.0, 13.1; IR (KBr) 2994, 1807, 1759, 1734, 1462, 1231, 1028, 797 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{17}H_{17}Cl_3O_6Na$ 423.0163, found 423.0145; mp 84.4–85.1 ºC; $[\alpha]^{24}_D$ +50.2 (*c* 1.02, CH_2Cl_2, 97:3 er).

Racemic sample of **3i**				(*S*)-**3i**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	13.876	2462201	49.705	1	14.146	384332	2.953
2	16.256	2491425	50.295	2	15.785	12630254	97.047

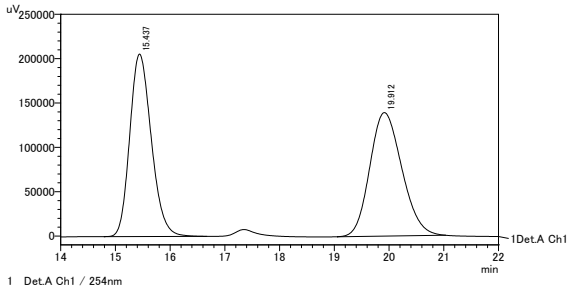
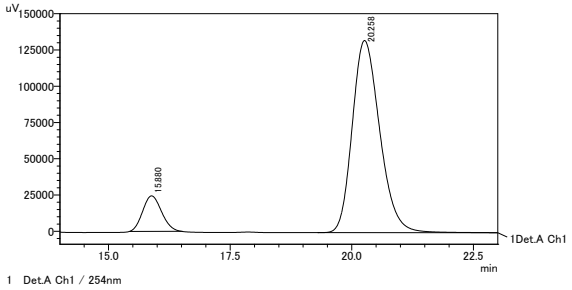
1,1,1-Trichloro-2-methylpropan-2-yl-1,1,1-trichloro-2-methylpropan-2-yl

(*S*)-2-oxo-3-(2-oxo-2-phenylethyl)-2,3-dihydrobenzofuran-3-carboxylate (3j)

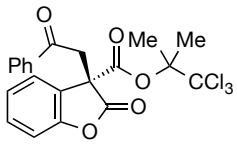


According to general procedure, substrate **2i** (31.1 mg, 68.2 μmol) with 3.0 mol % of catalyst **1a** (2.8 mg, 2.08 μmol) in toluene (233 μL) at –20 ºC for 5 h gave a colorless solid (31.0 mg, 68.0 μmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 93/7, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 15.9 min (minor) and T_R = 20.3 min (major), 89:11 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.35 (td, *J* = 7.9, 1.2 Hz, 1H), 7.28 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.10 (td, *J* = 7.9, 0.9) 4.28 (d, *J* = 18.6 Hz, 1H), 3.99 (d, *J* = 18.6 Hz, 1H), 1.89

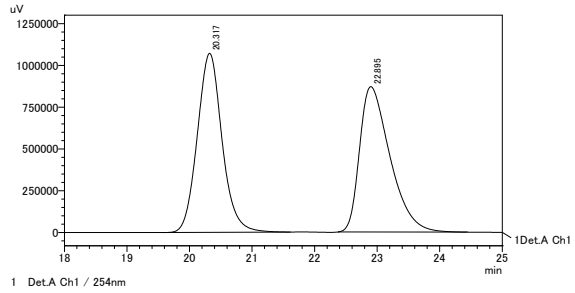
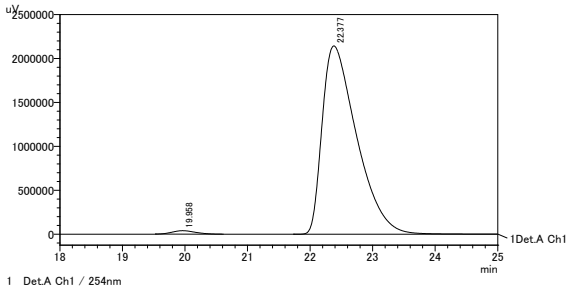
(s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 172.8, 165.0, 154.8, 135.5, 134.1, 130.3, 128.9, 128.3, 126.7, 124.4, 123.3, 111.3, 105.1, 91.0, 56.4, 43.3, 21.3, 21.0; IR (KBr) 2928, 1821, 1748, 1688, 1464, 1231, 1211, 1155, 1069, 750 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{21}H_{18}Cl_3O_5$ 455.0214, found 455.0192; mp 121.0–122.0 ºC; $[\alpha]^{23}_D$ –7.20 (*c* 1.00, CH_2Cl_2, 89:11 er).

Racemic sample of **3j**				(*S*)-**3j**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.437	5631184	49.833	1	15.880	660777	11.242
2	19.912	5668814	50.167	2	20.258	5217066	88.758

1,1,1-Trichloro-2-methylpropan-2-yl (*S*)-2-oxo-3-(2-phenyl-2-((((1,1,1-trichloro-2-methylpropan-2-yl)oxy)carbonyl)oxy)vinyl)-2,3-dihydrobenzofuran-3-carboxylate (3k)



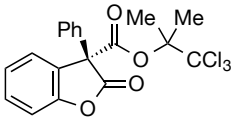
According to general procedure, substrate **2k** (32.1 mg, 48.7 μmol) with 1.0 mol % of catalyst **1a** (0.700 mg, 0.520 μmol) in toluene (162 μL) at –20 ºC for 5 h gave a colorless solid (31.9 mg, 48.4 μmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 20.0 min (minor) and T_R = 22.4 min (major), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 2H), 7.39–7.29 (m, 5H), 7.19–7.11 (m, 2H), 6.40 (s, 1H), 1.89 (s, 3H), 1.82 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.4, 154.1, 151.3, 148.1, 133.7, 130.5, 129.8, 128.9, 127.6, 125.1, 124.9, 123.8, 111.4, 111.4, 105.1, 105.0, 91.2, 58.5, 21.4, 20.9 (2); IR (KBr) 3011, 1792, 1761, 1456, 1233, 1213, 1142, 799 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{26}H_{23}Cl_6O_7$ 656.9569, found 656.9592; mp 64.1–65.0 ºC; $[\alpha]^{21}_D$ +30.9 (*c* 1.03, CH_2Cl_2, 99:1 er).

Racemic sample of **3k**	(*S*)-**3k**
	

Peak	T_R	Area	Area %
1	20.317	29471035	50.044
2	22.895	29418918	49.956

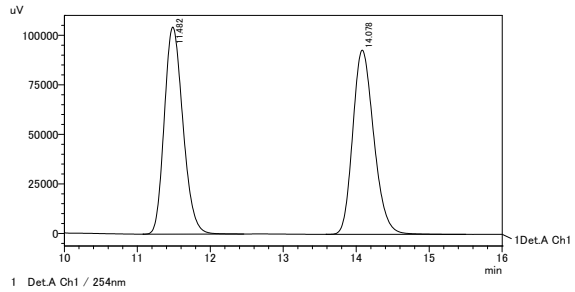
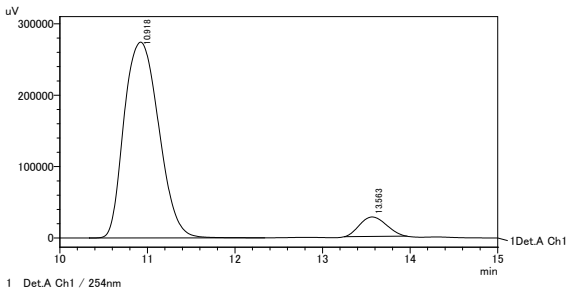
Peak	T_R	Area	Area %
1	19.958	1027435	1.233
2	22.377	82299397	98.767

1,1,1-Trichloro-2-methylpropan-2-yl



(*S*)-2-oxo-3-phenyl-2,3-dihydrobenzofuran-3-carboxylate (3l)

According to general procedure, substrate **2l** (41.1 mg, 99.4 μmol) with 3.0 mol % of catalyst **1a** (4.20 mg, 3.12 μmol) in toluene (200 μL) at –40 ºC for 5 h gave a colorless solid (40.5 mg, 97.9 μmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 10.9 min (major) and T_R = 13.6 min (minor), 93:7 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.50–7.33 (m, 5H), 7.32–7.19 (m, 3H), 1.91 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.4, 154.1, 133.8, 130.9, 129.1, 129.0, 127.9, 126.4, 125.2, 124.8, 111.6, 105.1, 91.1, 63.5, 21.5, 20.9; IR (KBr) 2957, 1821, 1755, 1460, 1207, 1059, 800, 754 cm^{-1}; $[\alpha]^{21}_D$ +136.8 (*c* 1.00, CH_2Cl_2, 93:7 er).

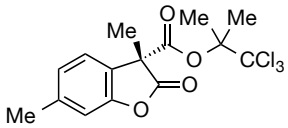
Racemic sample of **3l**	(*S*)-**3l**
	

Peak	T_R	Area	Area %
1	11.482	1854212	49.877
2	14.078	1863357	50.123

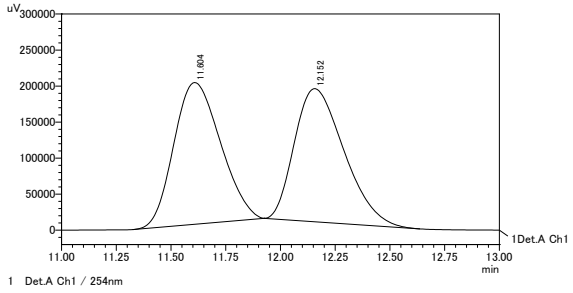
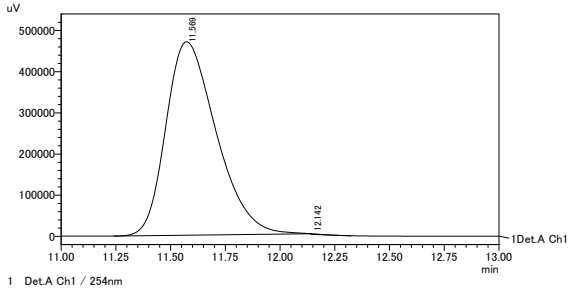
Peak	T_R	Area	Area %
1	10.918	7546369	92.854
2	13.563	580727	7.146

1,1,1-Trichloro-2-methylpropan-2-yl

(*S*)-2-oxo-3-phenyl-2,3-dihydrobenzofuran-3-carboxylate (3m)

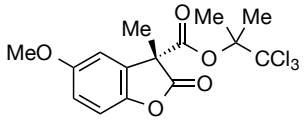


According to general procedure, substrate **2m** (45.5 mg, 0.124 mmol) with 0.05 mol % of catalyst **1a** (0.01 M in toluene, 6.25 μL, 0.0625 μmol) in toluene (244 μL) at –20 ºC for 5 h gave a colorless solid (45.0 mg, 0.123 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 11.6 min (major) and T_R = 12.1 min (minor), >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.2 Hz, 1H), 7.00–6.94 (m, 2H), 2.38 (s, 3H), 1.87 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 166.1, 153.6, 140.9, 125.3, 122.9, 111.9, 105.3, 90.5, 54.9, 21.9, 21.3, 21.0, 19.9; IR (KBr) 2941, 1820, 1738, 1261, 1032, 789 cm^{-1}; $[\alpha]^{21}_D$ +79.3 (*c* 1.02, CH_2Cl_2, >99:1 er).

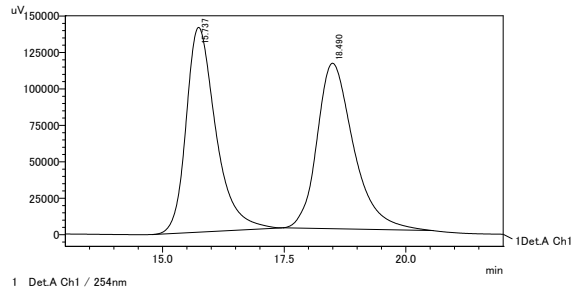
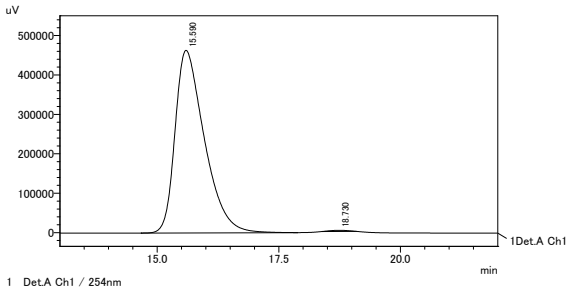
Racemic sample of **3m**				(*S*)-**3m**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	11.604	2917341	50.033	1	11.569	7520936	99.963
2	12.152	2913482	49.967	2	12.142	2802	0.037

1,1,1-Trichloro-2-methylpropan-2-yl

(*S*)-2-oxo-3-phenyl-2,3-dihydrobenzofuran-3-carboxylate (3n)



According to general procedure, substrate **2n** (47.6 mg, 0.125 mmol) with 0.2 mol % of catalyst **1a** (0.01 M in toluene, 25.0 μL, 0.250 μmol) in toluene (225 μL) at –20 ºC for 5 h gave a colorless liquid (47.3 mg, 0.124 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® OJ-H (hexane/*i*-PrOH = 97/3, v/v, flow rate = 0.5 mL/min, 30 °C, UV = 254 nm), T_R = 15.6 min (major) and T_R = 18.7 min (minor), >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 6.6, 2.5 Hz, 1H), 6.86 (s, 1H), 6.85 (dd, *J* = 6.6, 2.5 Hz, 1H), 3.78 (s, 3H), 1.88 (s, 3H), 1.79 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 165.9, 157.0, 147.3, 129.1, 115.2, 111.9, 109.1, 105.3, 90.6, 56.1, 55.6, 21.3, 21.1, 19.9; IR (KBr) 2940, 1798, 1748, 1487, 1279, 1026, 802 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{15}H_{16}Cl_3O_5$ 381.0058, found 381.0050; $[\alpha]^{24}_D$ +44.0 (*c* 1.09, CH_2Cl_2, >99:1 er).

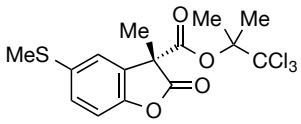
Racemic sample of **3n**	(*S*)-**3n**
	

Peak	T_R	Area	Area %
1	15.737	5957407	50.019
2	18.490	5952849	49.981

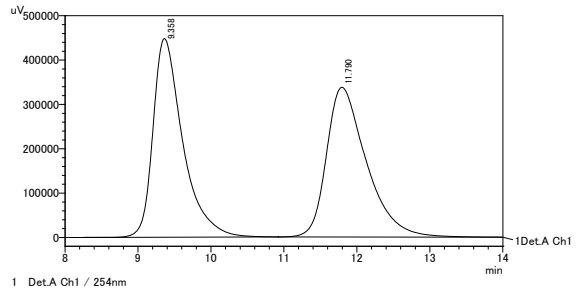
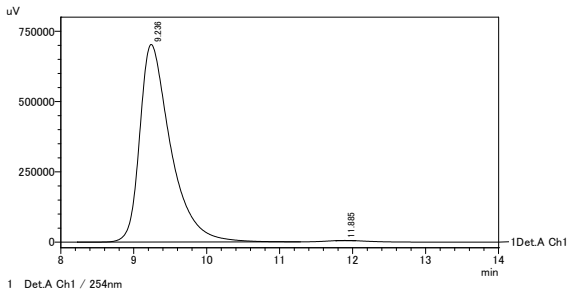
Peak	T_R	Area	Area %
1	15.590	19420040	99.627
2	18.730	72645	0.373

1,1,1-Trichloro-2-methylpropan-2-yl

(*S*)-3-methyl-5-(methylthio)-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (3o)



According to general procedure, substrate **2o** (49.0 mg, 0.123 μmol) with 0.05 mol % of catalyst **1a** (0.01 M in toluene, 6.25 μL, 0.0625 μmol) in toluene (244 μL) at –20 ºC for 5 h gave a colorless solid (48.8 mg, 0.123 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® OJ-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 9.2 min (major) and T_R = 11.9 min (minor), >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.29 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 1H), 2.47 (s, 3H), 1.88 (s, 3H), 1.80 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 165.6, 151.5, 134.7, 129.4, 129.1, 122.6, 111.8, 105.2, 90.7, 55.1, 21.3, 21.1, 19.9, 17.4; IR (KBr) 2928, 1805, 1751, 1476, 1229, 1155, 1040, 495 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{15}H_{15}Cl_3O_4SNa$ 418.9649, found 418.9642; $[\alpha]^{23}_D$ –1.23 (*c* 1.1, CH_2Cl_2, >99:1 er).

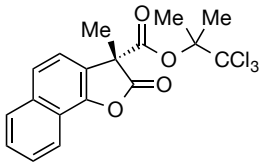
Racemic sample of **3o**	(*S*)-**3o**
	

Peak	T_R	Area	Area %
1	9.358	12684020	49.679
2	11.790	12848158	50.321

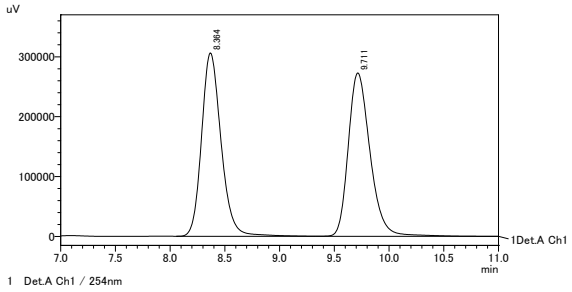
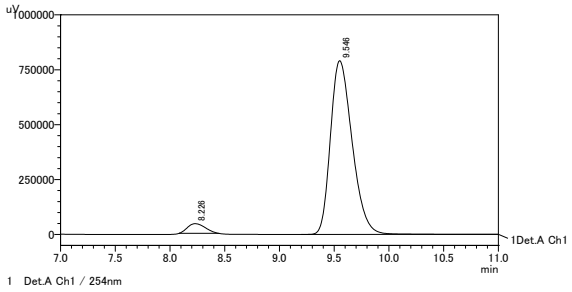
Peak	T_R	Area	Area %
1	9.236	20685969	99.961
2	11.885	8081	0.039

1,1,1-Trichloro-2-methylpropan-2-yl

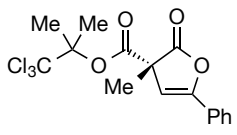
(*S*)-3-methyl-2-oxo-2,3-dihydronaphtho[1,2-*b*]furan-3-carboxylate (3q)



According to general procedure, substrate **2q** (50.1 mg, 0.125 mmol) with 0.2 mol % of catalyst **1a** (0.01 M in toluene, 25.0 μL, 0.250 μmol) in toluene (225 μL) at –20 ºC for 5 h gave a colorless solid (49.7 mg, 0.124 mmol, >98% yield): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 8.2 min (minor) and T_R = 9.5 min (major), 96:4 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.88 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.60 (td, *J* = 7.9, 1.6 Hz, 1H), 7.56 (td, *J* = 7.9, 1.6 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 1.88 (s, 3H), 1.86 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 166.0, 149.5, 134.5, 128.4, 127.4, 127.3, 124.8, 122.4, 121.4, 119.9, 119.4, 105.2, 90.7, 56.1, 21.3, 21.0, 19.8; IR (KBr) 2947, 1817, 1728, 1377, 1252, 1042, 821, 789 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{18}H_{15}Cl_3O_4$ 401.0109, found 401.0113; mp 145.4–145.9 ºC; $[\alpha]^{20}_D$ +169.6 (*c* 0.600, CH_2Cl_2, 96:4 er).

Racemic sample of **3q**				(*S*)-**3q**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.364	3800524	50.157	1	8.226	493421	4.325
2	9.711	3776787	49.843	2	9.546	10913955	95.675

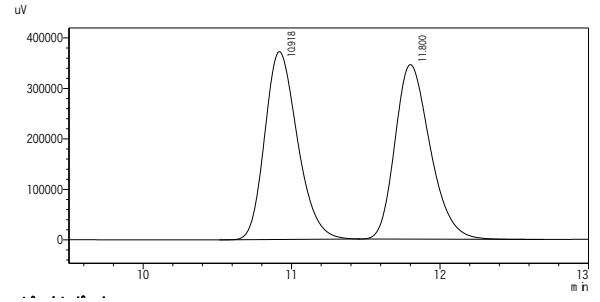
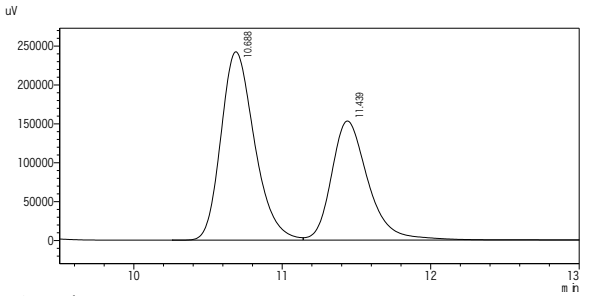
1,1,1-Trichloro-2-methylpropan-2-yl



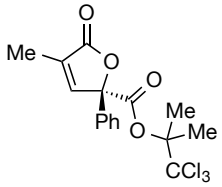
(*S*)-3-methyl-2-oxo-5-phenyl-2,3-dihydrofuran-3-carboxylate (5)

According to general procedure, substrate **4** (200 mg, 0.530 mmol) with 1.0 mol % of catalyst **1b** (9.4 mg, 5.31 μmol) in THF (1.1 mL) at –20 ºC for 3 h gave a colorless solid (19.2 mg, 50.8 μmol, >98% yield) after flash column chromatography on silica gel (eluent: hexane/toluene = 5:1 to 1:1 to 0/1): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99:1, v/v, flow rate = 0.5 mL/min, 25 °C, UV = 254 nm), T_R = 10.7 min (major) and T_R = 11.4 min (minor), 60:40 er; ^{1}H NMR (400 MHz, $CDCl_3$, 0.03% TMS) δ 7.65–7.58 (m, 2H), 7.46–7.39 (m, 3H), 5.85 (s, 1H), 1.92 (s, 3H), 1.90 (s,

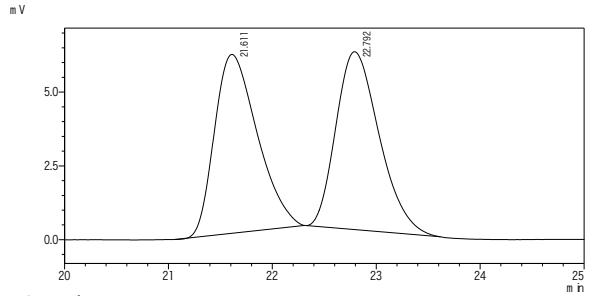
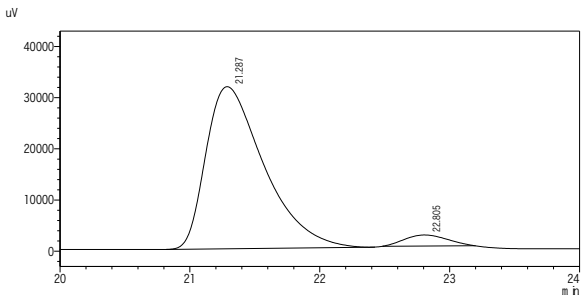
3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 0.03% TMS) δ 174.4, 166.1, 154.8, 130.4, 128.9, 127.7, 125.3, 105.4, 103.8, 90.5, 56.9, 21.3 (2), 19.7; IR (KBr) 3119, 2940, 1798, 1728, 1449, 1254, 1088, 1013, 797 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{16}H_{16}Cl_3O_4$ 377.0109, found 377.0087; mp 108.3–108.3 ºC; $[\alpha]^{24}_D$ –39.3 (*c* 1.02, $CHCl_3$, 60:40 er).

Racemic sample of **5**				(*S*)-**5**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	10.918	5700780	50.002	1	10.688	3796815	59.198
2	11.800	5700336	49.998	2	11.439	2616950	40.802

1,1,1-Trichloro-2-methylpropan-2-yl
(*R*)-4-methyl-5-oxo-2-phenyl-2,5-dihydrofuran-2-carboxylate (6)



According to general procedure, substrate **4** (200 mg, 0.530 mmol) with 1.0 mol % of catalyst **1b** (9.4 mg, 5.31 μmol) in THF (1.1 mL) at –20 ºC for 3 h gave a colorless solid (163 mg, 0.432 μmol, 82% yield) after flash column chromatography on silica gel (eluent: hexane/toluene = 5:1 to 1:1 to 0/1): enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99:1, v/v, flow rate = 0.5 mL/min, 25 °C, UV = 254 nm), T_R = 21.3 min (major) and T_R = 22.8 min (minor), 95:5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.50 (m, 2H), 7.49–7.45 (m, 1H), 7.43–7.33 (m, 3H), 1.99 (s, 3H), 1.99 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 165.0, 146.1, 135.3, 131.1, 129.4, 128.9, 126.2, 105.4, 91.1, 87.8, 21.4, 21.1, 10.9; IR (KBr) 3102, 2928, 1771, 1757, 1234, 1152, 1042, 806, 752 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{16}H_{16}Cl_3O_4$ 377.0109, found 377.0088; mp 109.1–109.3 ºC; $[\alpha]^{22}_D$ –29.0 (*c* 1.12, $CHCl_3$, 95:5 er).

Racemic sample of **6**				(*S*)-**6**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	21.611	173447	49.818	1	21.287	985448	95.218
2	22.792	174718	50.182	2	22.805	49486	4.782

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Chapter 5. Kinetic Resolution of Carbinols with Binaphthyl-Based DMAP Derivatives

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5-1. Abstract

We developed an acylative kinetic resolution of secondary carbinols with a binaphthyl-based DMAP derivative **1g** with *tert*-alcohol substituents. The reaction applied to a wide range of carbinols with moderate to high selectivity (up to s = 79.5). Kinetic studies revealed that catalyst **1g** was more catalytically active than the corresponding bis-methyl ether **1g′** or DMAP. Hydrogen bonding between *tert*-alcohols of the catalyst and secondary carbinols was responsible for the rate enhancement and high enantioselectivity.

5-2. Introduction

Nucleophilic catalysts (i.e. chiral phosphines,[1] diamines,[2] imidazole,[3,4] isothioureas,[5] *N*-heterocyclic carbenes,[6,7] and combination of chiral thiourea and DMAP[8]) for enantioselective acyl transfer reaction have been actively studied for two decades. Among them, DMAP and PPY have been recognized as very powerful and useful acyl-transfer catalysts.[9,10] Detailed studies have been also performed on the reaction mechanism[11] and the reactivity of DMAP derivatives.[12-16] The development of chiral variants has been extensively studied in response to pioneering studies by Vedejs[17] and Fu,[18] and these have been used in various enantioselective transformations, such as the kinetic resolution of racemic alcohols[5,19-36] or amines,[37,38] desymmetrization of *meso*-compounds,[39,40] Steglich type rearrangement[41-44] and many other examples.[45] However, most DMAP- or PPY-based chiral catalysts showed high enantioselectivity for only a limited range of substrates or reactions. Thus, the development of a chiral nucleophilic catalyst, which can be used in various transformations with high enantioselectivity, is great interest in synthetic organic chemistry.

We developed acyl-transfer reactions promoted by chiral DMAP derivatives (chapters 2–4). Binaphthyl-based DMAP derivatives **1g** with hydrogen-bonding substituents at the 3,3′-positions were shown to remarkably rate enhancement and high enantioselectivity in the Steglich rearrangement (*intramolecular* acyl transfer) of indolyl carbonates and furanyl carbonates (chapters 3 and 4). This reaction only required 0.5 mol % of catalyst to give the desired products in >98% yield with high enantioselectivity (up to >99:1 er). Several verification experiments and computational studies have clearly indicated that hydrogen bonding between the catalyst and the counteranion of *N*-acylpyridinium ion (= nucleophile) stabilizes the transition state of the reaction (oxyanion stabilization)[46] to enhance the catalytic activity and enantioselectivity. These catalysts were applicable to kinetic resolutions of secondary carbinols (*intermolecular* acyl transfer), however, the origin of the rate acceleration and the enantioselectivity have not been systematically investigated.

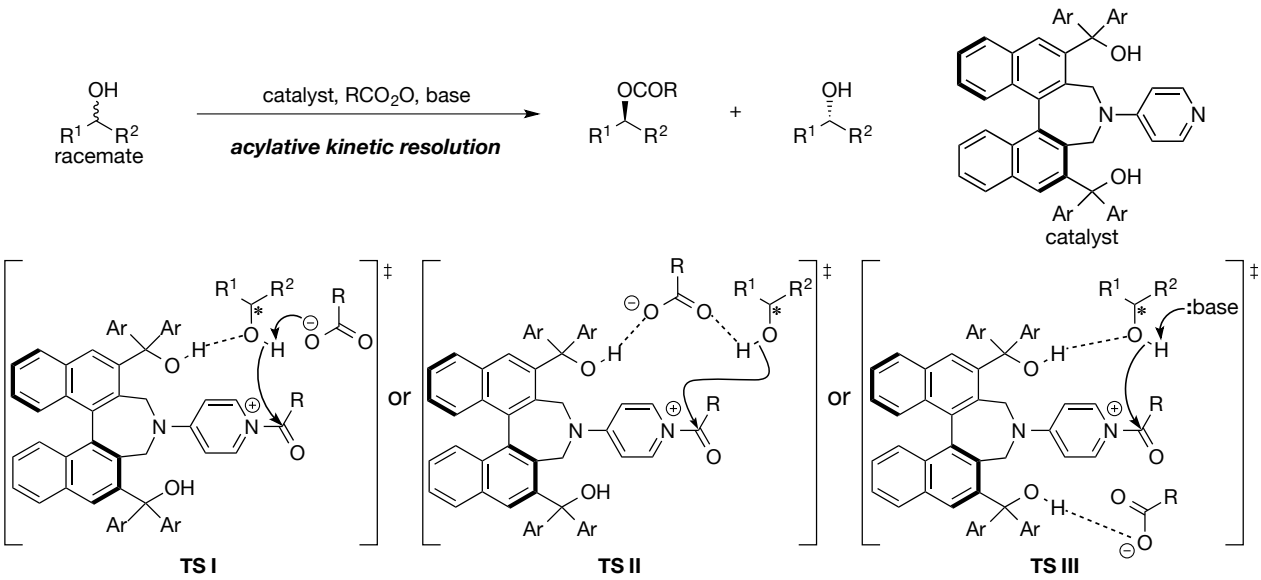


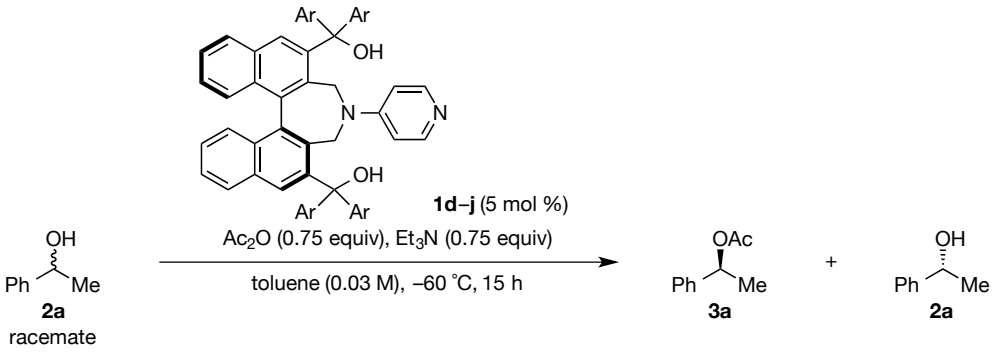
Figure 1. Our working hypotheses regarding the transition state

Based on considerations for Steglich rearrangement (chapters 3 and 4), we also expected that such an attractive electrostatic interaction would enhance the catalytic activity and enantioselectivity in the acylation of alcohols through hydrogen bonding between the catalyst and substrate. We hypothesized that a *tert*-alcohol moiety of the catalyst would pull in either a carbinol (Figure 1, **TS I**) or a counteranion of *N*-acylpyridinium ion ($^{-}$OCOR, Figure 1, **TS II**). Another model that includes the simultaneous interaction between two *tert*-alcohol moieties and both a carbinol and a counteranion, and an outer base to deprotonate the carbinol, would be possible (Figure 1, **TS III**). We expected that such transition states **TS-I-III** should lead to high enantioselectivity and accelerate the rate of the reaction. In this paper, we describe the acylative kinetic resolution of secondary benzylic alcohols, and the results of several experimental studies to elucidate the reaction mechanism.

5-3. Optimization of Reaction Conditions

Initially, to identify a suitable catalyst, kinetic resolution of the secondary alcohol **2a** was carried out in the presence of 5 mol % of catalysts **1d–j**, 0.75 equiv of acetic anhydride and 0.75 equiv of triethylamine in toluene (0.03 M) at –60 °C for 15 h (Table 1). Catalysts **1d** and **1e** showed low selectivity factors (s = 1.2–1.6, entries 1 and 2). Therefore, the catalyst structure was studied further (entries 3–7). As a result, catalyst **1g** (Ar = 4-*t*-Bu-C_6H_4) showed the highest selectivity factor (s = 3.8) among the catalysts examined. Surprisingly, catalyst **1i** (Ar = 3,5-$(MeO)_2$-C_6H_3) gave an opposite enantioselectivity even though it had the same chiral scaffold (s = 1.7). According to these results, we selected catalyst **1g** as the optimal catalyst for further optimization of the reaction conditions.

Table 1. Initial screening of catalysts[a]



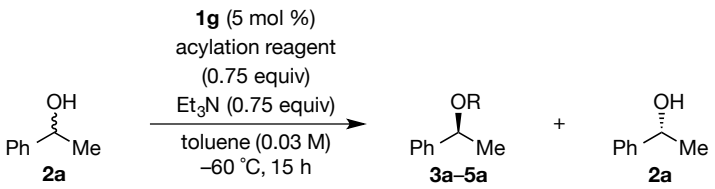
1d: Ar = Ph
1e: Ar = 4-MeO-C_6H_4
1f: Ar = 4-Ph-C_6H_4
1g: Ar = 4-*t*-Bu-C_6H_4
1h: Ar = 4-$(i\text{-Pr})_3$Si-C_6H_4
1i : Ar = 3,5-$(MeO)_2$-C_6H_3
1j: Ar = 3,5-$(t\text{-Bu})_2$-4-MeO-C_6H_2

Entry	Catalyst	Conv (%)[b]	Er of **3a**[c]	Er of **2a**[c]	S[d]
1	**1d**	65	52:48	54:46	1.2
2	**1e**	32	60:40	45.5:54.5	1.6
3	**1f**	42	60:40	57.5:42.5	1.7
4	**1g**	58	70:30	77:23	3.8
5	**1h**	51	65.6:33.5	67:33	2.7
6[e]	**1i**	49	41:59	42:58	1.7
7	**1j**	68	59:41	70:30	2.1

[a]Reactions were performed on a 0.10 mmol scale under an argon atmosphere. [b]Conversions were calculated from the enantioselectivity of the substrate and product. [c]Enantioselectivities were determined by HPLC analysis. [d]S-factors were calculated by Kagan's equation.[47]

Next, the effects of the acylation reagent were examined with the optimal catalyst **1g** (Table 2). While acetic anhydride gave a moderate *s*-factor (*s* = 3.8, entry 1), acetyl chloride showed an astonishingly low conversion, and gave racemates of **3a** and **2a** (*s* = 1.0, entry 2). These results showed that the leaving group of the acylation reagent ($^{-}$OAc vs $^{-}$Cl), which serves as a counteranion of *N*-acylpyridinium ion in the transition state (Figure 1), profoundly affected the reactivity[48] and enantioselectivity. Further examination showed that isobutyric anhydride gave the highest *s*-factor (*s* = 8.0, entry 3). Consequently, isobutyric anhydride was used as the optimal acylation reagent in this reaction.

Table 2. Examination of acylation reagents[a]



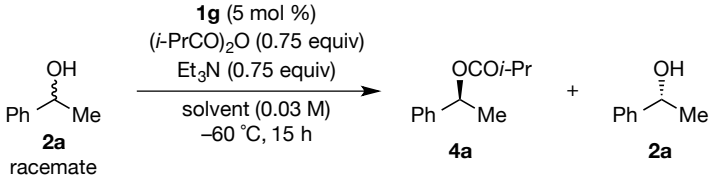
3a: R = Ac, **4a**: R = CO*i*-Pr, **5a**: R = Bz

Entry	Acylation reagent	Conv (%)[b]	Er of **3a**–**5a**[c]	Er of **2a**[c]	*S*[d]
1	Ac_2O	58	70:30	77:23	3.8
2	AcCl	6	51:49	50:50	1.0
3	$(i\text{-PrCO})_2O$	72	70:30	98:2	8.0
4	Bz_2O	70	55:45	61:39	1.3

[a]Reactions were performed on a 0.10 mmol scale under an argon atmosphere. [b]Conversions were calculated from the enantioselectivity of the substrate and product. [c]Enantioselectivities were determined by HPLC analysis. [d]*S*-factors were calculated by Kagan's equation.[47]

We next investigated various solvents with optimal catalyst **1g** to explore the optimal conditions (Table 3). Toluene, diethyl ether and *tert*-butyl methyl ether could be used for this reaction and showed good conversions with moderate *s*-factors (entries 1–3; s = 8.1–10.7; 44–60% conv), however the use of polar or protic solvents such as tetrahydrofuran, acetone, dimethylformamide and *tert*-amyl alcohol gave low *s*-factors, probably because of the weak hydrogen bond networks between the catalyst and substrate (entries 4–7). Thus, we selected toluene, which showed the highest *s*-factor, as the optimal solvent.

Table 3. Solvent screening[a]

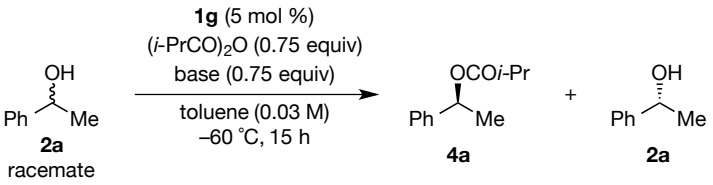


Entry	Solvent	Conv (%)[b]	Er of **4a**[c]	Er of **2a**[c]	*S*[d]
1	toluene	60	78:22	92:8	10.7
2	Et_2O	44	86:14	78:22	9.2
3	*t*-BuOMe	58	78:22	89:11	8.1
4	THF	38	72.5:27.5	64:36	3.4
5	acetone	23	67.5:32.5	55:45	2.3
6[e]	DMF	43	64:36	64:36	2.3
7[f]	*t*-amyl alcohol	42	72:28	66:34	3.4

[a]Reactions were performed on a 0.10 mmol scale under an argon atmosphere. [b]Conversions were calculated from the enantioselectivity of the substrate and product. [c]Enantioselectivities were determined by HPLC analysis. [d]*S*-factors were calculated by Kagan's equation.[47]

Finally, to improve the *s*-factor, we screened several bases (Table 4). The reaction proceeded while retaining a moderate *s*-factor in the absence of base (entry 1). These results suggest that **TS III** would have little impact. While we continued to screen various organic and inorganic bases, the *s*-factors and conversions were not dramatically improved (entries 2–8). Thus, we selected cesium carbonate as the optimal base, which showed the highest *s*-factor and conversion among the bases tested (entry 8). Further studies of the catalyst loading, substrate concentration, reaction temperature, and reaction time did not provide additional insights. Accordingly, the optimal conditions were considered to be 5 mol % of catalyst **1g**, 0.75 equiv of isobutyric anhydride, and 0.75 equiv of cesium carbonate in diethylether (0.03 M) at –60 ºC for 15 h (entry 8).

Table 4. Screening of bases[a]



Entry	Base	Conv (%)[b]	Er of **4a**[c]	Er of **2a**[c]	*S*[d]
1	none	29	88:12	65.5:34.5	10.3
2	Et_3N	44	86:14	78:22	10.7
3	*i*-PrEtN	36	88:12	71:29	11.0
4	pyridine	37	84:16	70:30	7.9
5	KOAc	30	88:12	66.5:33.5	10.5
6	K_3PO_4	37	88:12	72:28	11.4
7	K_2CO_3	31	88:12	67:33	10.6
8	Cs_2CO_3	53	84:16	88:12	11.4

[a]Reactions were performed on a 0.10 mmol scale under an argon atmosphere. [b]Conversions were calculated from the enantioselectivity of the substrate and product. [c]Enantioselectivities were determined by HPLC analysis. [d]*S*-factors were calculated by Kagan's equation.[47]

5-4. Substrate Scope

We next investigated the substrate scope of the reaction system using various secondary carbinols (secondary alcohol) under the optimal reaction conditions (Figure 2). The reactions of carbinols **2a**–**d** with aryl alkyl substituents showed moderate to high *s*-factors (*s* = 11.4–20.1), and steric hindrance of the substituent strongly affected the reaction efficiency [R^2 = Me (53% conv) vs *t*-Bu (14% conv)]. The effects of the substituents on the benzene ring were also investigated. While **2e** and **2f** with *ortho*- and *meta*- methoxy groups, respectively, gave moderate *s*-factors (*s* = 7.1–14.8), **2g** with a *para*-methoxy group showed a high *s*-factor (*s* = 29.8). In addition, an electron-withdrawing group on the aryl ring of alcohols did not significantly decrease the *s*-factors (**2g**, *s* = 29.8 vs **2h**, *s* = 22.8). Carbinol **2i** with a *para*-formyl group can be used without a loss of functionality under these conditions with a moderate *s*-factor (*s* = 7.1). Substrates **2j**–**l** with sterically demanding substituents, i.e., mesityl, 2-naphtyl, and 1-naphtyl group, gave moderate to excellent *s*-factors (*s* = 10.7–79.5), while 9-anthryl alcohol derivative **2m** showed a somewhat low *s*-factor (*s* = 2.6). To our great surprise, this reaction system could resolve alcohols with different two aryl substituents **2n–q** in moderate selectivity (*s* =2.2–5.5, respectively) (for selected examples of the synthesis of these compounds by enantioselective addition to aldehyde, see Refs. [49-53]; for selected examples of the synthesis of these compounds by enantioselective reduction, see Refs. [54-56]). To the best of our knowledge, these alcohols have never been subjected to acylative kinetic resolution with chiral DMAP or PPY derivatives, probably due to the electrostatic recognition ability of the catalyst. Unfortunately, the current reaction system did not give good results except benzylic alcohols. For example, propargylic alcohol **2r**, cyclic alcohols **2s**, and **2t** resulted in decreased level of conversion with poor *s*-factor. In order to solve these issues, a new class of catalysts suitable for such substrates would be required.

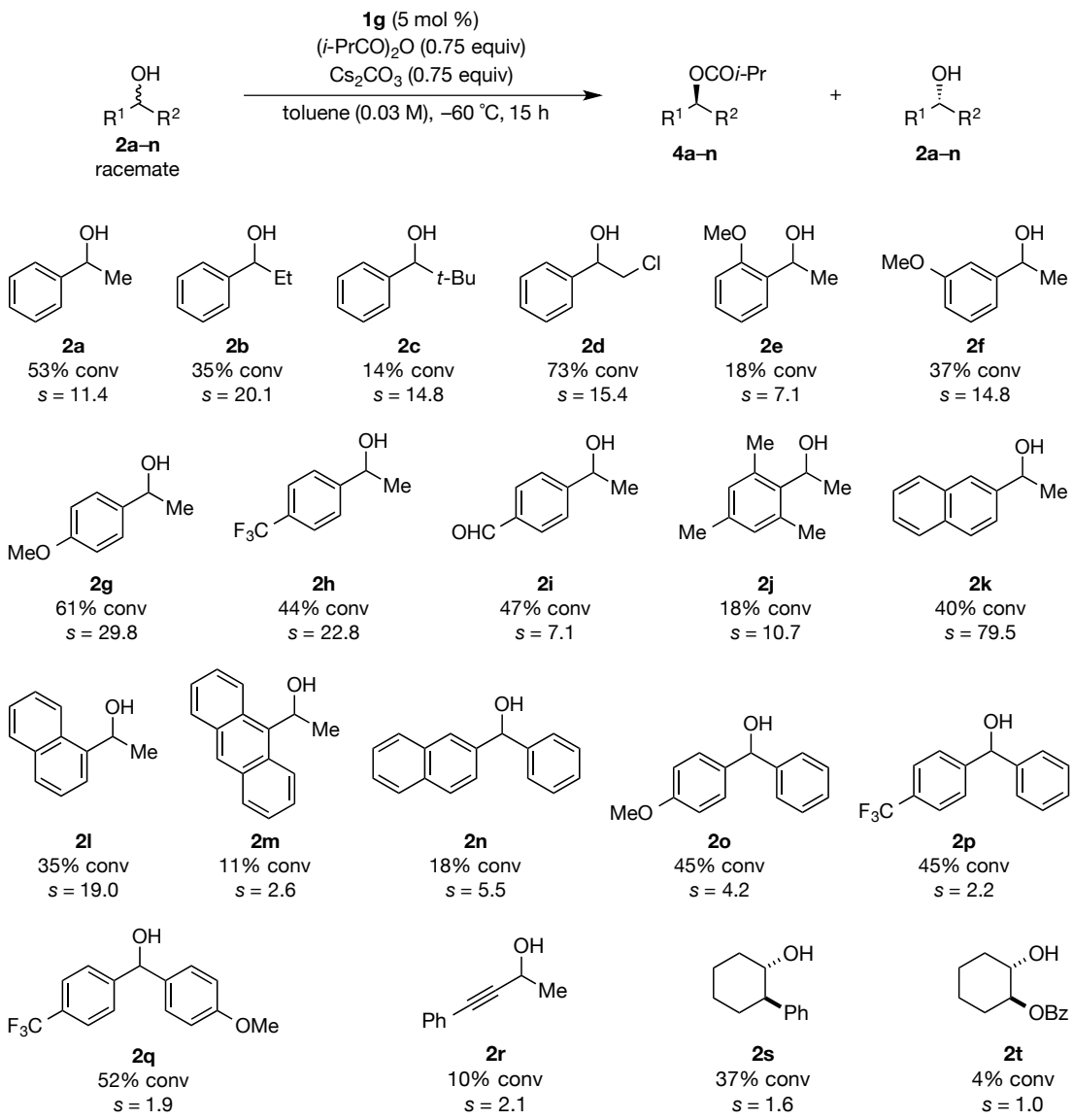
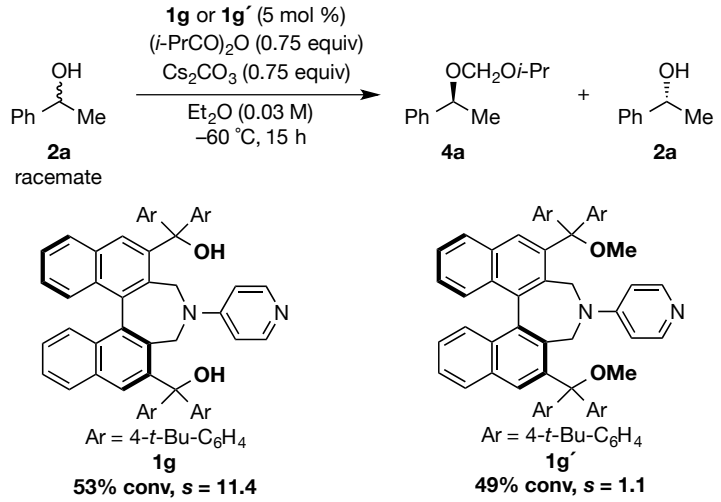


Figure 2. Substrate scope

5-5. Control Experiments

We assumed that hydrogen bonding between the catalyst and substrate was important for achieving high enantioselectivity and catalytic activity in this reaction. Thus, we carried out several key control experiments. The reaction with catalyst **1g** or bis-methyl ether **1g´** (where we could neglect the effect of hydrogen bonding) at –60 ºC for 15 h (optimal conditions) proceeded smoothly to give **4a** along with unreacted **2a** (Scheme 1). Catalyst **1g** gave much a higher *s*-factor than **1g´** despite their nearly identical catalyst structures (*s* = 11.4 with **1g**, *s* = 1.1 with **1g´**). These results strongly suggested that one enantiotopic face of carbinol was recognized due to not only the steric factors of the 3,3´-substituents of the catalyst but also to the electrostatic interaction between the substrate and a catalyst stemming from the hydrogen bonding network.



Scheme 1. Enantioselectivities with **1g** vs **1g´**

5-6. Kinetic Experiments

Kinetic experiments were also carried out using (*S*)-1-phenylethanol, which is a fast-reacting enantiomer in this reaction, as a substrate. The reactions were carried out under pseudo-first-order conditions with 5 mol % of catalyst **1g**, **1g´** or DMAP, 10 equiv of isobutyric anhydride, and 3 equiv of cesium carbonate in diethylether (0.03 M) at –60 °C (Figure 3). Catalyst **1g** showed higher activity than **1g´** ($k_{\mathbf{1g}}$ = 1.5 x10^2 min^{-1}, $k_{\mathbf{1g'}}$ = 9.1 x 10^3 min^{-1} and $k_{\mathbf{1g}}/k_{\mathbf{1g'}}$ = 1.6). We surmised that the rate acceleration was caused by the appropriate arrangement of carboxylate anion in the transition state[57] through hydrogen bonding, to stabilize the transition state. According to the kinetic experiments and studies of the leaving groups of the acylation reagent (Table 2; entry 1 vs 2; $^-$OAc vs $^-$Cl), hydrogen bonding between a *tert*-alcohol unit and a carboxylate anion brought about high enantioselectivity and accelerated the rate of the reaction. Interestingly, **1g** bearing a relatively sterically hindered moiety accelerated the reaction more than DMAP (k_{DMAP} = 6.3 x 10^3 min^{-1} and

$k_{\mathbf{1g}}/k_{\mathrm{DMAP}}$ = 2.4). The catalytic activity of **1g´** was also higher than that of DMAP, although the substituents of **1g´** are hindered much more than those of DMAP. The reasons for this observation are not yet clear, and more detailed experiments will be needed to elucidate these acceleration effects.

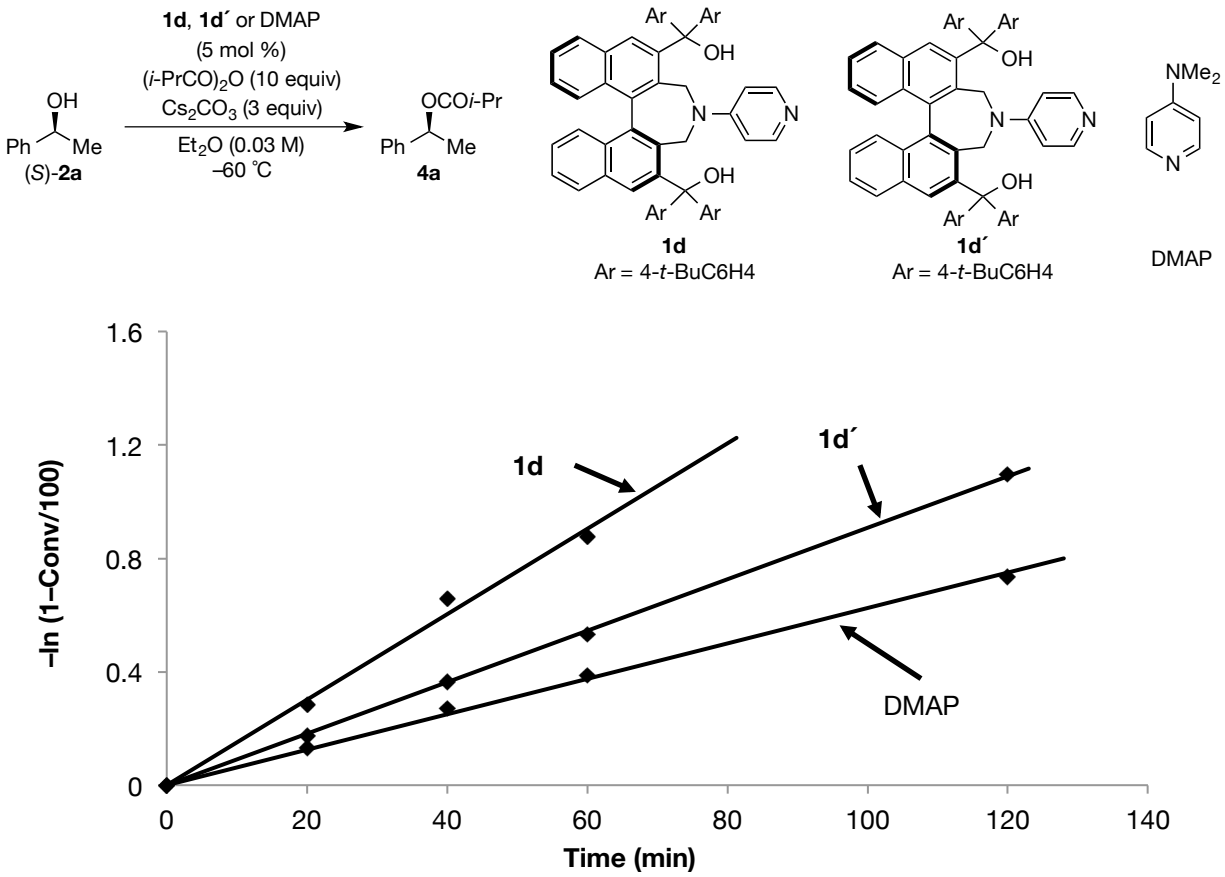


Figure 3. Kinetic profiles with **1g**, **1g´** and DMAP pseudo-first-order conditions

5-7. Conclusion

In summary, we have developed a kinetic resolution of secondary carbinols with chiral DMAP derivatives having hydrogen bonding substituents. Catalyst **1g** offers moderate to excellent *s*-factors (up to *s* = 79.5) with broad substrate generality. In addition, this catalyst system could resolve alcohols with two different aryl groups **2n**–**q** in moderate enantioselectivities (*s* = 2.2–5.5), which has never been reported in acylative kinetic resolution. According to our working hypothesis (Figure 1), we proposed that *tert*-alcohols of the catalyst would acquire either a carbinol (**TS I**) or counteranion of *N*-acylpyridinium ion (**TS II**), or simultaneously interact with a carbinol and counteranion in the transition state (**TS III**). The results of kinetic studies strongly support the notion that hydroxy groups of **1g** play an important role in acceleration of the reaction rate and the

high enantioselectivity. Although the mechanism of acceleration is not yet clear, we speculate that several experimental results, such as the effect of the leaving group of the acylation reagent ($^{-}$OAc vs $^{-}$Cl), the effect of hydrogen bonding in enantioselectivity (solvent screening), the effect of base (base screening) and kinetic studies are more likely to support **TS II** (Figure 1). In addition, considering the high enantioselectivity with isobutyric anhydride, **TS II´** (two hydrogen bondings between the carboxylate anion and both the *ortho*-position hydrogen of the pyridine moiety and the hydroxy group of the catalyst) might be more presumable according to Spivey,[58] Zipse,[11] and Kawabata's explanation[59,60] (Figure 4).

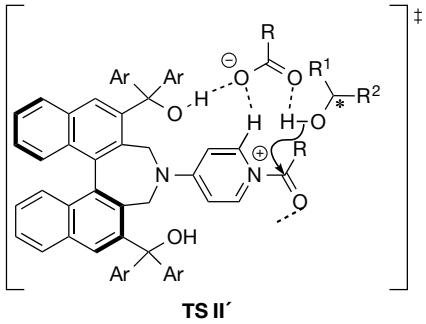


Figure 4. Possible transition state **II´**

We expect that catalyst **1g** may be useful in other important enantioselective transformations, and further investigations in our laboratory are now underway.

5-8. Experimental Section and Analytical Data

General

Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian 600 MR (^{1}H 600 MHz, ^{13}C 150 MHz), Varian 400 MR (^{1}H 400 MHz, ^{13}C 100 MHz) and JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometers. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin =quintet, sext = sextet, sep = septet, b = broad, m = multiplet), coupling constants, and integration. Chemical shifts for ^{13}C NMR were reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) with complete proton decoupling. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer and Vmax is given in cm^{-1}. High-resolution mass spectrometry was performed on a JEOL JMS-700 MStation (FAB-MS and EI-MS), or Agilent 6520 Accurate Mass Q-TOF LC/MS (ESI-MS). Optical rotations were measured on a JASCO DIP-1000. Melting points were recorded on a SANSYO SMP-300. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC) on a Shimadzu chromatograph (DICEL CHIRALPAK® AS-3 (4.6 × 150 mm), DICEL

CHIRALPAK® AD-H (4.6 × 250 mm), DICEL CHIRALCEL OJ-H (4.6 × 250 mm) and DICEL CHIRALCEL® OD-H (4.6 × 250 mm)) with comparison to authentic racemic materials. Column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm) purchased from Kanto Chemical. All experiments were carried out under an argon atmosphere unless otherwise noted.

Materials

All reagents were obtained commerically available and used as received unless otherwise noted. CH_2Cl_2, toluene, and Et_3N were distilled over CaH_2. Dry tetrahydrofuran [THF] and dry Et_2O were purchased from Wako Pure Chemical Industries and used without further purification. Dry dimethylformamide [DMF], (±)-2,2-dimethyl-1-phenyl-1-propanol (**2c**), and (±)-4-phenyl-3-butyn-2-ol (**2r**) were purchased from Sigma-ALDRICH Japan and used without further purification. (±)-1-Phenylethanol (**2a**) was purchased from KANTO CHEMICAL CO.,INC. and used without further purification. (±)-1-(2-Naphthyl)ethanol (**2k**) and (±)-2-phenylcyclohexan-1-ol (**2s**) were purchased from Tokyo Chemical Industry Co., Ltd. and used without further purification. Other alcohols were synthesized by $NaBH_4$ reduction of the corresponding ketones and the nucleophilic addition of organolithium reagents or Grignard reagents to the corresponding aldehydes. *trans*-2-Hydroxycyclohexyl benzoate (**2t**) was synthesized by general benzoylation of *trans*-1,2-cyclohexanediol purchased from Sigma-ALDRICH Japan.

General procedure for the acylative kinetic resolution of carbinols

To a solution of substrate **2a**−**q** (0.100 mmol), Cs_2CO_3 (24.4 mg, 75.0 μmol) and catalyst **1g** (4.8 mg , 5.00 μmol) in Et_2O (3.00 mL) was added isobutyric anhydride (12.4 μL, 75.0 μmol) at −60 ºC. The reaction mixture was stirred for 15 h at −60 ºC. MeOH (2 mL) was then added to destroy unreacted isobutyric anhydride and the mixture was stirred for 30 min as it warmed to room temperature. The resulting solution was concentrated *in vacuo*. The resulting mixture was passed through a short pad of silica gel (eluent: hexane/Et_2O = 1/1, v/v) to give the ester product and the unreacted alcohol, which were directly analyzed by chiral HPLC. The enantiomeric ratio (er) and enantiomeric excess (ee) values of the ester and the unreacted alcohol were obtained by HPLC analysis. The conversion (*C*) and *s*-factor (*s*) of kinetic resolution were calculated as follows:[47]

$$s = \frac{\ln[1-C(1+ee')]}{\ln[1-C(1-ee')]} = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} = \frac{k_{fast}}{k_{slow}} \quad (1)$$

ee = *enantiomeric excess measured for the starting material* (2)

ee' = *enantiomeric excess measured for the product* (3)

$$C = \frac{ee}{ee + ee'}100 = \textit{conversion} \quad (4)$$

General procedure for kinetic experiment

To a solution of (*S*)-**2a** (24.1 μL, 0.200 mmol), Cs_2CO_3 (195.5 mg, 0.6 mmol) and **1g**, **1g´**, or DMAP (10.0 μmol) in Et_2O (6.00 mL) was added isobutyric anhydride (333.2 μL, 2.01 mmol) at −60 ºC. After stirring the indicated periods in Tables S1, the reaction mixture was sucked 300 μL by syringe, poured into MeOH (3 mL), stirred for 30 min during warming up to room temperature, and concentrated *in vacuo*. The resulting mixture was passed through a short pad of silica gel (eluent: hexane/Et_2O = 1/1, v/v). The conversion was calculated by ^{1}H NMR analysis. The kinetic profile of acylation of (*S*)-**2a** with **1g**, **1g´** or DMAP was shown bellow.

Table S1. The time course analysis of acylation of **2a** with **1g**, **1g´** or DMAP

Catalyst **1g**

Time (min)	20	40	60	120	180	240	300	360
Conversion (%)	24.8	48.1	58.3	76.9	93.2	>98	>98	>98
ln (1-Conv/100)	0.285	0.656	0.875	1.465	2.688	–	–	
Kinetic constant (k_{1g})	1.5 x10^2 min^{-1}							

Catalyst **1g´**

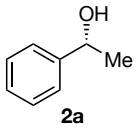
Time (min)	20	40	60	120	180	240	300	360
Conversion (%)	15.9	30.6	41.3	66.6	82.0	92.1	>98	>98
ln (1-Conv/100)	0.173	0.365	0.533	1.097	1.715	2.538	–	
Kinetic constant (k_{1g})	9.1 x 10^3 min^{-1}							

DMAP

Time (min)	20	40	60	120	180	240	300	360
Conversion (%)	12.4	23.7	32.1	52.1	72.5	87.7	>98	>98
ln (1-Conv/100)	0.132	0.270	0.387	0.736	1.29	2.10	–	–
Kinetic constant (k_{DMAP})	6.3 x 10^3 min^{-1}							

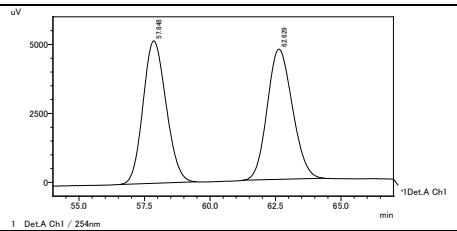
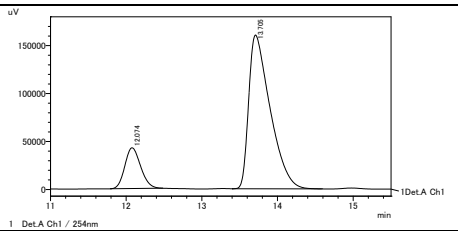
Analytical data and HPLC Chart

(*R*)-1-Phenylethanol (2a)

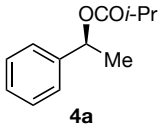


2a

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 57.6 min (minor) and T_R = 61.4 min (major), 88:12 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.30 (m, 4H), 7.30–7.21 (m, 1H), 4.91 (q, *J* = 6.5 Hz, 1H), 1.51 (d, *J* = 6.5Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 128.5, 127.5, 125.5, 70.4, 25.2; IR (KBr) 3354, 2974, 1454, 1282, 899, 760, 698 cm^{-1}; $[\alpha]^{20}_D$ +12.4 (*c* 0.49, $CHCl_3$, 68:32 er) [lit.[61] $[\alpha]^{20}_D$ +27.0 (*c* 0.270, $CHCl_3$, 38% ee, (*R*) form)].

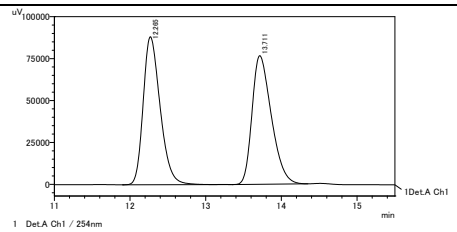
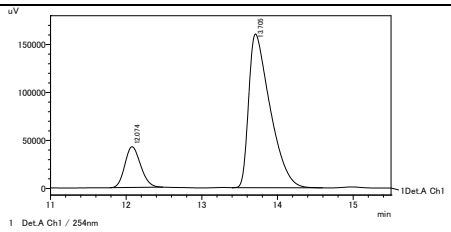
Racemic sample of **2a**				(*R*)-**2a**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	57.848	316410	50.055	1	57.555	369292	12.022
2	62.629	315721	49.945	2	61.422	2702792	87.974

(*S*)-1-Phenylethyl isobutyrate (4a)[62]



4a

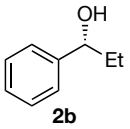
Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 12.1 min (minor) and T_R = 13.7 min (major), 84:16 er; ^{1}H NMR (400 MHz, $CDCl_3$) 7.40–7.21 (m, 5H), 5.87 (q, *J* = 6.7 Hz, 1H), 2.57 (sep, *J* = 6.9 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 142.1, 128.6, 127.8, 126.0, 72.0, 34.2, 22.4, 19.0; IR (KBr) 3034, 2978, 2934, 2876, 1732, 1454, 1192, 1157, 1065, 760, 698 cm^{-1}; $[\alpha]^{22}_D$ −29.7 (*c* 1.09, $CHCl_3$, 81:19 er).

Racemic sample of **4a**	(*S*)-**4a**
	

Peak #	Ret. Time	Area	Area %
1	12.265	1376503	50.322
2	13.711	1358904	49.678

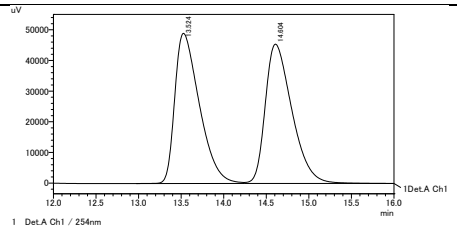
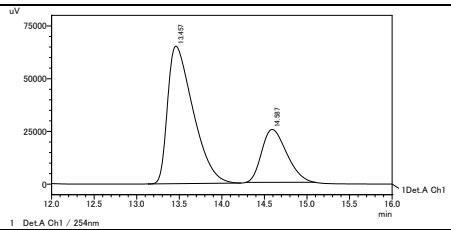
Peak #	Ret. Time	Area	Area %
1	12.074	616839	16.386
2	13.705	3147745	83.614

(*R*)-1-Phenyl-1-propanol (2b)[63]



2b

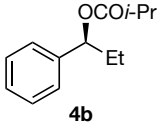
Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 13.5 min (major) and T_R = 14.6 min (minor), 72.5:27.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 4.61 (t, *J* = 6.6 Hz, 1H), 1.90–1.54 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 128.5, 127.6, 126.1, 76.1, 31.9, 10.2; IR (KBr) 3389, 3063, 3028, 2965, 2932, 2876, 1493, 1454, 1202, 974, 764, 700 cm^{-1}; $[\alpha]^{24}_D$ +4.54 (*c* 1.03, $CHCl_3$, 72.5:27.5 er) [lit.[64] $[\alpha]^{20}_D$ +45.9 (*c* 2.0, $CHCl_3$, 94% ee, (*R*) form)].

Racemic sample of **2b**	(*R*)-**2b**
	

Peak #	Ret. Time	Area	Area %
1	13.524	983775	49.867
2	14.604	989029	50.133

Peak #	Ret. Time	Area	Area %
1	13.457	1356549	72.539
2	14.587	513559	27.461

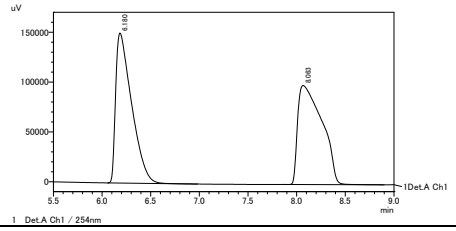
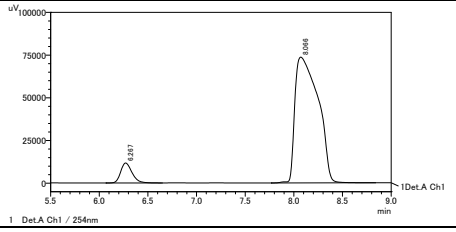
(*S*)-1-Phenylpropyl isobutyrate (4b)



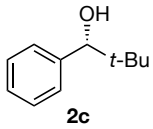
4b

Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 99.9/0.1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.3 min (minor) and T_R = 8.1 min (major), 93:7 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H), 5.65 (t, *J* = 7.0, 1H), 2.57 (m, 1H), 1.99–1.72 (m, 2H), 1.18 (d, *J* = 7.6, 3H), 1.14 (d, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 141.0, 128.5, 127.8, 126.5, 77.0, 34.3, 29.6, 19.1, 19.0, 10.0; IR (KBr) 2972, 2936,

2878, 1734, 1470, 1456, 1192, 1155, 754, 700 cm^{-1}; HRMS (FAB^+) calculated for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1379, found 207.1365; $[\alpha]^{21}_D$ −17.4 (*c* 0.22, $CHCl_3$, 93:7 er).

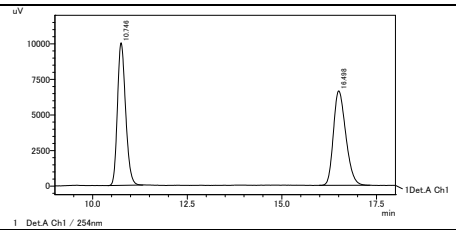
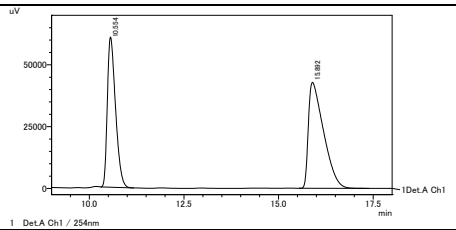
Racemic sample of **4b**				(*S*)-**4b**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	6.180	1717051	49.835	1	6.267	94619	7.184
2	8.063	1728389	50.165	2	8.066	1222423	92.816

(*R*)-2,2-Dimethyl-1-phenyl-1-propanol (2c)

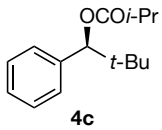


2c

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 0.900 mL/min, 30 °C, UV = 254 nm), T_R = 10.6 min (minor) and T_R = 15.9 min (major), 57:43 er; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 4.40 (s, 1H), 1.80 (bs, 0.7H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 127.7, 127.4, 82.6, 35.7, 26.1; IR (KBr) 3420, 3032, 2995, 2955, 2868, 1452, 1005, 899, 735, 702, 648 cm^{-1}; $[\alpha]^{22}_D$ +6.3 (*c* 0.19, $CHCl_3$, 57:43 er) [lit.[65] $[\alpha]^{20}_D$ +19.2 (*c* 0.48, $CHCl_3$, 99% ee, (*R*) form)].

Racemic sample of **2c**				(*R*)-**2c**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	10.746	150256	49.869	1	10.554	911235	43.293
2	16.498	151043	50.131	2	15.892	1193559	56.707

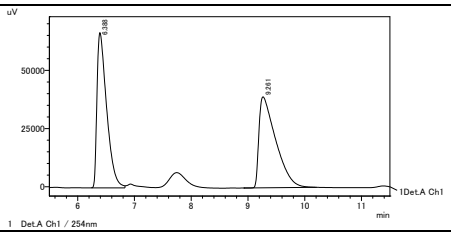
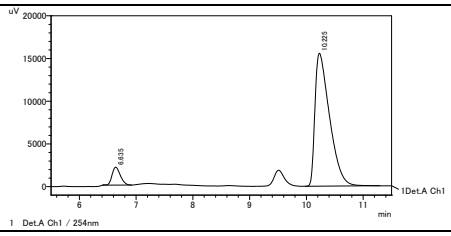
(*S*)-2,2-Dimethyl-1-phenylpropyl isobutyrate (4c)



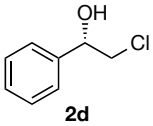
4c

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 99.9/0.1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.6 min (minor) and T_R = 10.2 min (major), 93:7 er; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5H), 5.47 (s, 1H), 2.61 (sep., *J* = 7.1 Hz, 1H), 1.20 (d, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 138.7,

127.8, 127.7, 127.5, 82.5, 35.3, 34.5, 26.2, 19.1, 19.0; IR (KBr) 2972, 2909, 2874, 1736, 1470, 1192, 1155, 735, 702 cm^{-1}; HRMS (FAB^+) calculated for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1692, found 235.1699; $[\alpha]^{22}_D$ –5.8 (*c* 0.13, $CHCl_3$, 93:7 er).

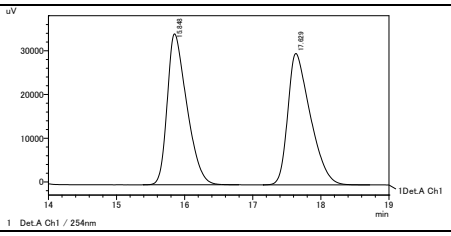
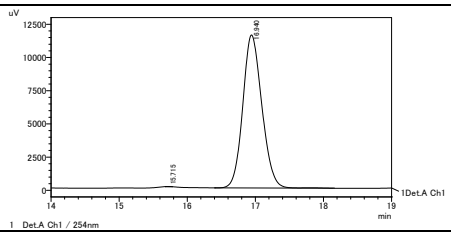
Racemic sample of **4c**				(*S*)-**4c**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	6.388	790098	49.633	1	6.635	21390	7.143
2	9.261	801786	50.367	2	10.225	278081	92.857

(*S*)-2-Chloro-1-phenylethanol (2d)[66]

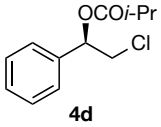


2d

Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 93/7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 15.7 min (minor) and T_R = 16.9 min (major), >99.9:<0.1 er; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.29 (m, 5H), 4.91 (d, *J* = 8.9 Hz, 1H), 3.76 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.66 (dd, *J* = 11.2, 8.9 Hz, 1H), 2.62 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 128.8, 128.6, 126.2, 74.2, 51.0; IR (KBr) 3395, 3032, 2955, 2893, 1454, 1065, 770, 723, 698, 615 cm^{-1}; $[\alpha]^{23}_D$ +18.1 (*c* 0.05, $CHCl_3$, >99.9:<0.1 er) [lit.[67] $[\alpha]^{27}_D$ +38.5 (*c* 0.90, $CHCl_3$, 81% ee, (*S*) form)].

Racemic sample of **2d**				(*S*)-**2d**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	15.848	690229	50.003	1	15.715	27	0.012
2	17.629	690154	49.997	2	16.940	224244	99.988

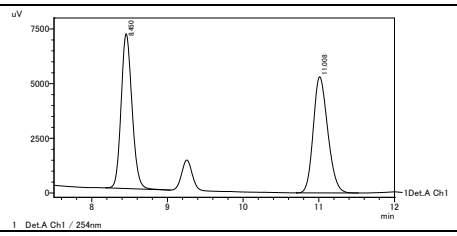
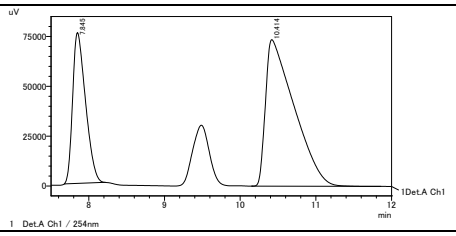
(*R*)-2-Chloro-1-phenylethyl isobutyrate (4d)



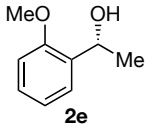
4d

Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 99.3/0.7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 7.8 min (minor) and T_R = 10.4 min (major), 68:32 er; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5H), 5.96 (dd, *J* = 8.2, 4.6 Hz, 1H), 3.85–3.67 (m, 2H),

2.65 (sep., J = 7.1 Hz, 1H), 1.23 (d, J = 7.1 Hz, 3H), 1.19 (d, J =7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 137.5, 128.9, 128.8, 126.7, 74.8, 46.9, 34.2, 19.1, 19.0; IR (KBr) 2976, 2936, 2878, 1742, 1470, 1456, 1188, 1150, 729, 698 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{12}H_{16}ClO_2$ $[M+H]^+$ 227.0833, found 227.0816; $[\alpha]^{24}_D$ –6.0 (*c* 0.38, $CHCl_3$, 68:32 er).

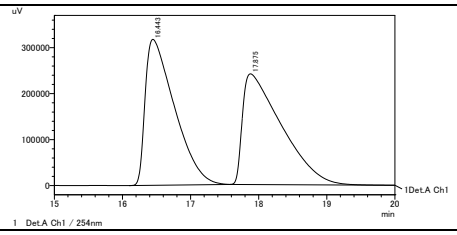
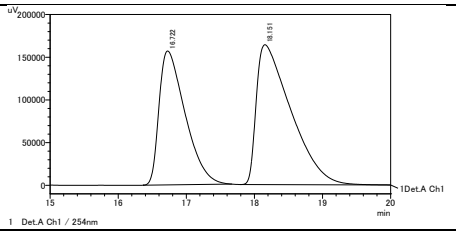
Racemic sample of **4d**				(*R*)-**4d**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	8.450	70881	50.022	1	7.845	897227	31.745
2	11.008	70818	49.978	2	10.414	1929098	68.255

(*R*)-1-(2-Methoxyphenyl)ethanol (2e)[68]

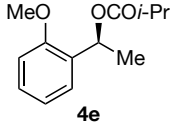


2e

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 16.7 min (minor) and T_R = 18.2 min (major), 58:42 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 7.7, 1.4 Hz, 1H), 7.29–7.22 (m, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 5.10 (q, J = 6.5 Hz, 1H), 3.87 (s, 3H), 1.94 (bs, 1H), 1.51 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 133.6, 128.2, 126.0, 120.7, 110.3, 66.1, 55.2, 23.0; IR (KBr) 3312, 3007, 2967, 2913, 2835, 1601, 1587, 1281, 1234, 1074, 1026, 1007, 897, 748, 733 cm^{-1}; $[\alpha]^{22}_D$ +6.6 (*c* 0.29, $CHCl_3$, 58:42 er) [lit.[69] $[\alpha]^{25}_D$ +18.5 (*c* 1.0, $CHCl_3$, 50% ee, (*R*) form)].

Racemic sample of **2e**				(*R*)-**2e**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	16.443	9485419	49.742	1	16.722	4171986	41.887
2	17.875	9583682	50.258	2	18.151	5788107	58.113

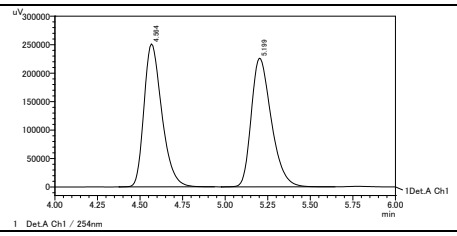
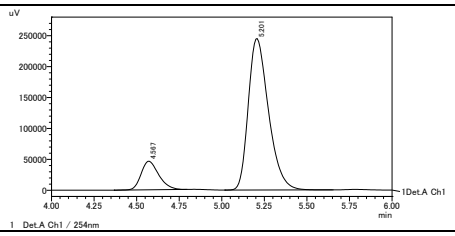
(*S*)-1-(2-Methoxyphenyl)ethyl isobutyrate (4e)



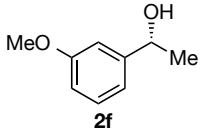
4e

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C,

UV = 254 nm), T_R = 4.6 min (minor) and T_R = 5.2 min (major), 86:14 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* =7.6 Hz, 1H), 7.30–7.19 (m, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.22 (q, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 2.59 (qd, *J* = 6.9, 1.5 Hz, 1H), 1.47 (dd, *J* = 6.8, 1.6 Hz, 3H), 2.42 (dd, *J* = 6.9, 1.5 Hz, 3H), 1.18 (dd, *J* = 6.9, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 156.1, 130.8, 128.6, 125.8, 120.7, 110.6, 66.9, 55.5, 34.3, 21.3, 19.1, 19.1; IR (KBr) 2976, 2936, 1734, 1495, 1466, 12346, 1192, 1157, 1065, 754 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{13}H_{19}O_3$ $[M+H]^+$ 222.1250, found 222.1250; $[\alpha]^{21}_D$ +13.3 (*c* 0.12, $CHCl_3$, 86:14 er).

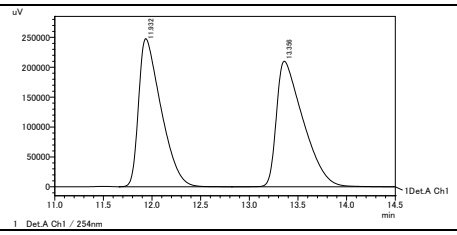
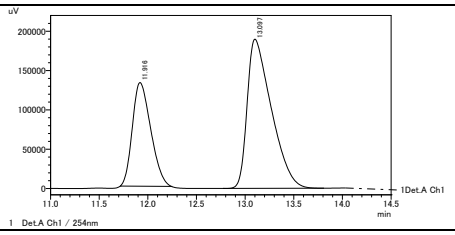
Racemic sample of **4e**				(*S*)-**4e**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	4.564	1832390	49.753	1	4.567	333024	14.133
2	5.199	1850566	50.247	2	5.201	2023297	85.867

(*R*)-1-(3-Methoxyphenyl)ethanol (2f)[70]

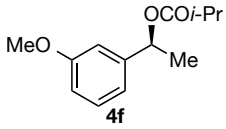


2f

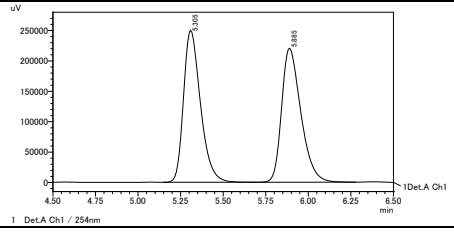
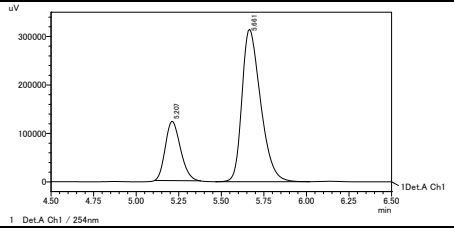
Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 93/7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 11.9 min (minor) and T_R = 13.1 min (major), 65:35 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 1H), 6.98–6.91 (m, 2H), 6.82 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.88 (q, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 1.69 (bs, 1H), 1.50 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 147.7, 129.6, 117.8, 112.9, 111.0, 70.3, 55.3, 25.2; IR (KBr) 3395, 2972, 2930, 2835, 1603, 1585, 1258, 1157, 1045, 856, 785, 700 cm^{-1}; $[\alpha]^{21}_D$ +9.5 (*c* 0.44, $CHCl_3$, 65:35 er) [lit.[71] $[\alpha]^{25}_D$ +51.2 (*c* 1.0, $CHCl_3$, 96% ee, (*R*) form)].

Racemic sample of **2f**				(*R*)-**2f**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	11.932	3971800	49.713	1	11.916	1730715	34.563
2	13.356	4017603	50.287	2	13.097	3276755	65.437

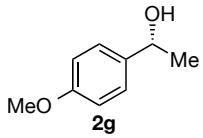
(*S*)-1-(3-Methoxyphenyl)ethyl isobutyrate (4f)



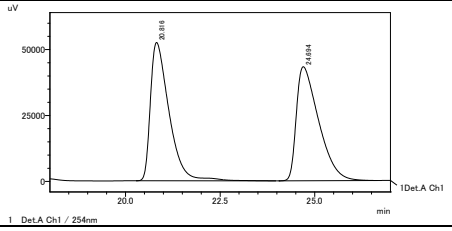
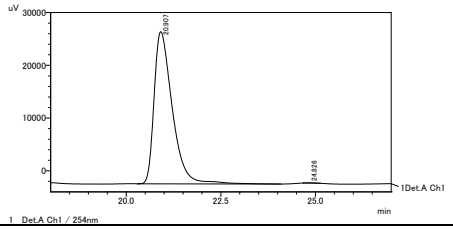
Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 93/7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 5.2 min (minor) and T_R = 5.7 min (major), 76:24 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 6.82 (dd, *J* = 8.2, 2.8 Hz, 1H), 5.84 (q, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 2.58 (sep., *J* = 7.1 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.22–1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 159.8, 143.8, 129.7, 118.3, 113.1, 111.8, 71.9, 55.3, 34.3, 22.6, 19.1; IR (KBr) 2978, 2936, 1732, 1470, 1157, 1063, 1049, 781, 698 cm^{-1}; HRMS (ESI$^+$) calculated for $C_{13}H_{18}O_3$ $[M+H]^+$ 223.1329, found 223.1322; $[\alpha]^{21}_D$ –17.9 (*c* 0.36, $CHCl_3$, 76:24 er).

Racemic sample of **4f**				(*S*)-**4f**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	5.305	1731717	50.004	1	5.207	759653	24.094
2	5.885	1731444	49.996	2	5.661	2393221	75.906

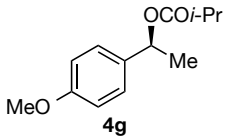
(*R*)-1-(4-Methoxyphenyl)ethanol (2g)[63]



Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 20.9 min (major) and T_R = 24.8 min (minor), >99.9:<0.1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.87 (q, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 1.48 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 138.1, 126.7, 113.9, 70.0, 55.4, 25.1; IR (KBr) 3441, 2972, 2930, 2835, 1612, 1514, 1246, 1175, 1036, 831, 810 cm^{-1}; $[\alpha]^{22}_D$ +7.56 (*c* 0.09, $CHCl_3$, 99.9:0.1 er) [lit.[71] $[\alpha]^{25}_D$ +53.5 (*c* 1.7, $CHCl_3$, 94% ee, (*R*) form)].

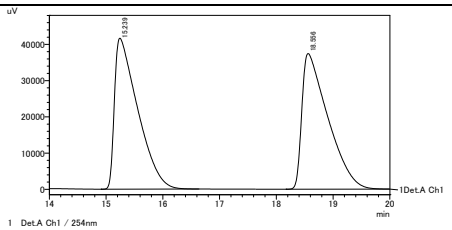
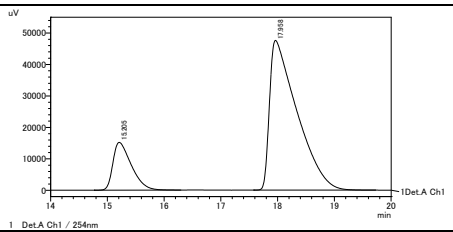
Racemic sample of **2g**				(*R*)-**2g**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	20.816	1796675	50.374	1	20.907	964002	99.903
2	24.694	1770031	49.626	2	24.826	936	0.097

(*S*)-1-(4-Methoxyphenyl)ethyl isobutyrate (4g)

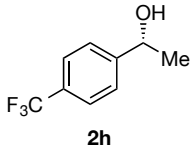


4g

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 99.9/0.1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 15.2 min (minor) and T_R = 18.0 min (major), 82:18 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 6.6, 1.8 Hz, 2H), 6.87 (dd, *J* = 6.6, 1.8 Hz, 2H), 5.84 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 2.54 (sep., *J* = 7.1 Hz, 1H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 159.3, 134.2, 127.5, 113.9, 71.7, 55.4, 34.3, 22.2, 19.1, 19.0; IR (KBr) 2972, 2936, 2837, 1732, 1514, 1470, 1034, 970, 833, 698 cm^{-1}; HRMS (FAB^+) calculated for $C_{13}H_{19}O_3$ $[M+H]^+$ 222.1250, found 222.1275; $[\alpha]^{21}_D$ −10.6 (*c* 0.52, $CHCl_3$, 82:18 er).

Racemic sample of **4g**				(*S*)-**4g**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	15.239	1186907	49.878	1	15.205	341451	17.624
2	18.556	1192715	50.122	2	17.958	1595974	82.376

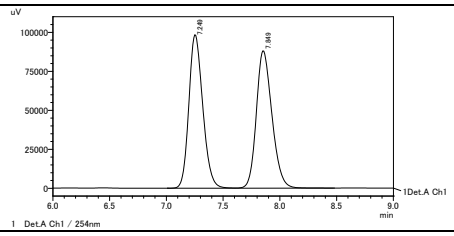
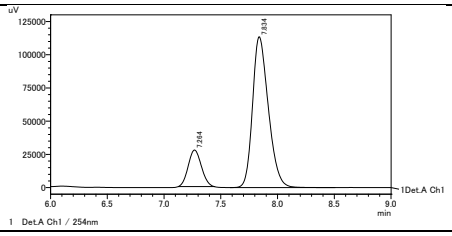
(*R*)-1-(4-(Trifluoromethyl)phenyl)ethanol (2h)[72]



2h

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 7.3 min (minor) and T_R = 7.8 min (major), 83:17 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 4.98 (q, *J* = 6,4 Hz, 1H), 1.85 (bs, 0.8H), 1.51 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 129.7 (q, *J* = 32.1

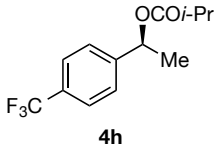
Hz), 125.8, 125.6, 124.2 (q, J = 271.1 Hz), 69.2, 25.5; IR (KBr) 3352, 2978, 1622, 1415, 1327, 1165, 1126, 1090, 1069, 843 cm^{-1}; $[\alpha]^{21}_D$ +33.0 (*c* 0.075, $CHCl_3$, 83:17 er) [lit.[73] $[\alpha]^{20}_D$ +34.9 (*c* 1.0, $CHCl_3$, 94% ee, (*R*) form)].

Racemic sample of **2h**	(*R*)-**2h**
	

Peak #	Ret. Time	Area	Area %
1	7.249	839789	49.909
2	7.849	842837	50.091

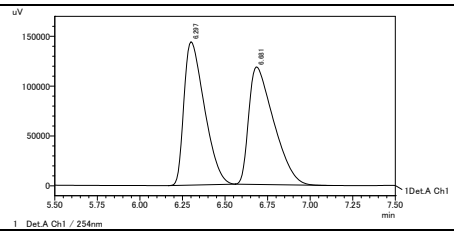
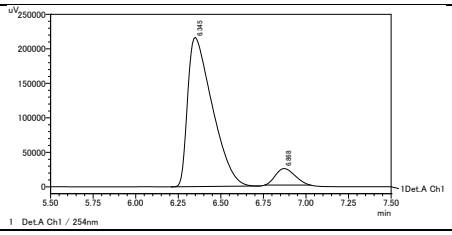
Peak #	Ret. Time	Area	Area %
1	7.264	221945	16.800
2	7.834	1099139	83.200

(*S*)-1-(4-(Trifluoromethyl)phenyl)ethyl isobutyrate (4h)



4h

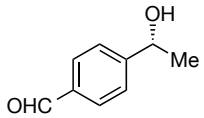
Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 99.9/0.1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.3 min (major) and T_R = 6.9 min (minor), 92:8 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 5.89 (q, J = 6.5 Hz, 1H), 2.59 (sep., J = 6.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 3H), 1.23–1.12 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.0, 176.3, 146.1, 130.1 (q, J = 32.6 Hz), 126.9, 125.7 (q, J = 3.6 Hz), 124.2 (q, J = 270.6 Hz), 71.4, 34.2, 33.9, 22.5, 19.0, 19.0; IR (KBr) 2980, 2938, 2879, 1738, 1327, 1159, 1126, 1070, 841 cm^{-1}; HRMS (FAB^+) calculated for $C_{13}H_{16}F_3O_2$ $[M+H]^+$ 261.1096, found 261.1125; $[\alpha]^{21}_D$ −32.6 (*c* 0.185, $CHCl_3$, 92:8 er).

Racemic sample of **4h**	(*S*)-**4h**
	

Peak #	Ret. Time	Area	Area %
1	6.297	1202305	50.013
2	6.681	1201673	49.987

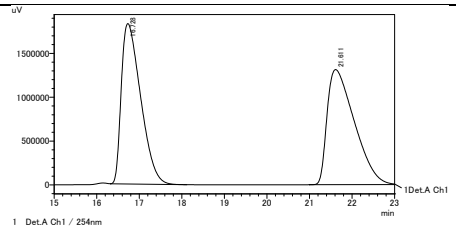
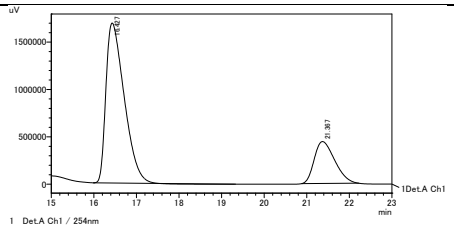
Peak #	Ret. Time	Area	Area %
1	6.345	2175733	91.971
2	6.868	189944	8.029

(*R*)-4-(1-Hydroxyethyl)benzaldehyde (2i)[74]

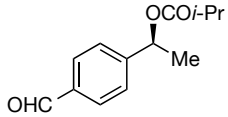


2i

Pale yellow green liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.000 mL/min, 30 °C, UV = 254 nm), T_R = 16.4 min (major) and T_R = 21.4 min (minor), 77:23 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 5.00 (q, *J* = 6.6 Hz, 1H), 1.86 (bs, 1H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 153.1, 135.3, 130.0, 125.9, 69.6, 25.2; IR (KBr) 3458, 1694, 1607, 1090, 899, 831, 748 cm^{-1}; $[\alpha]^{22}_D$ −13.6 (*c* 0.480, $CHCl_3$, 77:23 er) [lit.[74] $[\alpha]^{26}_D$ +34.8 (*c* 0.979, $CHCl_3$, 90% ee, (*R*) form)].

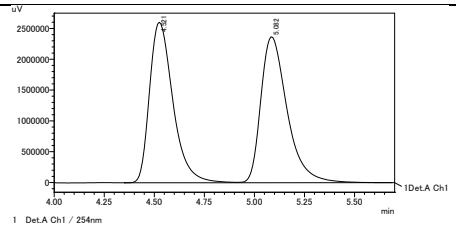
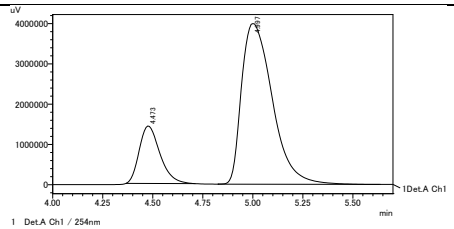
Racemic sample of **2i**				(*R*)-**2i**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	16.728	57736554	49.705	1	16.427	50091778	77.230
2	21.611	58421116	50.295	2	21.367	14769137	22.770

(*S*)-1-(4-Formylphenyl)ethyl isobutyrate (4i)

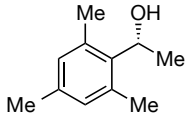


4i

Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.000 mL/min, 30 °C, UV = 254 nm), T_R = 4.5 min (minor) and T_R = 5.0 min (major), 81:19 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 5.90 (q, *J* = 7.0 Hz, 1H), 2.60 (sep., *J* = 7.1 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.71 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 176.3, 149.0, 136.0, 130.2, 126.5, 71.5, 34.2, 22.4, 19.0 (2); IR (KBr) 2976, 2936, 2876, 1732, 1697, 1611, 1470, 1209, 1192, 1157, 1066, 1007, 829 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{13}H_{17}O_3$ $[M+H]^+$ 221.1172, found 221.1161; $[\alpha]^{24}_D$ −13.5 (*c* 1.04, $CHCl_3$, 81:19 er).

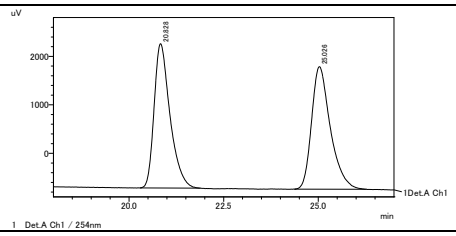
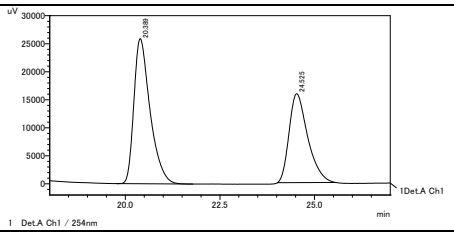
Racemic sample of **4i**				(*S*)-**4i**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	4.521	21206989	49.493	1	4.473	10281057	19.426
2	5.082	21641498	50.507	2	4.997	42642649	80.574

(*R*)-1-Mesitylethanol (2j)[75]

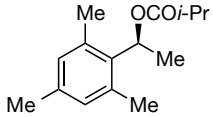


2j

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AD-H (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.800 mL/min, 30 °C, UV = 254 nm), T_R = 20.4 min (major) and T_R = 24.5 min (minor), 59:41 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 5.37 (q, *J* = 7.0 Hz, 1H), 2.42 (s, 6H), 2.25 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.3, 135.6, 130.1, 67.3, 21.5, 20.7, 20.5; IR (KBr) 3232, 2986, 2920, 1611, 1447, 1364, 1211, 895, 851 cm^{-1}; $[\alpha]^{23}_D$ +27.5 (*c* 0.090, CH_2Cl_2, 59:41 er) [lit.[76] $[\alpha]^{25}_D$ +52.5 (*c* 1.1, $CHCl_3$, 50% ee, (*R*) form)].

Racemic sample of **2j**				(*R*)-**2j**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	20.828	86674	49.850	1	20.389	769774	58.592
2	25.026	87196	50.150	2	24.525	544006	41.408

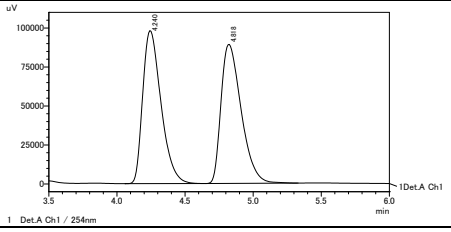
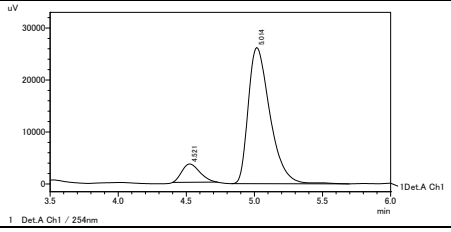
(*S*)-1-Mesitylethyl isobutyrate (4j)



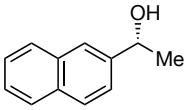
4j

Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AD-H (hexane/*i*-PrOH = 99.9/0.1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 4.5 min (minor) and T_R = 5.0 min (major), 90:10 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 6.26 (q, *J* = 6.9 Hz, 1H), 2.55 (sep., *J* = 7.0 Hz, 1H), 2.51 (s, 6H), 2.24 (s, 3H), 1.54 (d, *J* = 5.6 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 137.0, 136.1, 134.6, 130.1, 69.4, 34.3, 20.9, 20.6, 19.7, 19.2, 18.9; IR (KBr) 2974, 2934, 2874, 1732, 1470, 1371, 1194, 1155, 1061, 851 cm^{-1}; HRMS

(FAB$^+$) calculated for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1692, found 235.1702; $[\alpha]^{22}_D$ +11.1 (*c* 0.095, $CHCl_3$, 90:10 er).

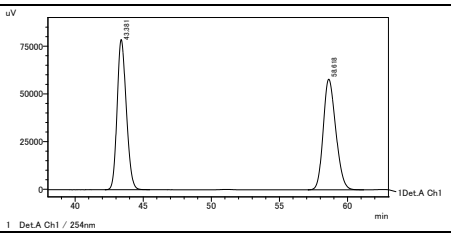
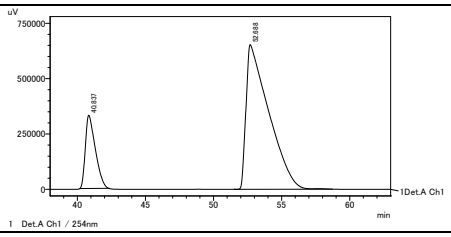
Racemic sample of **4j**				(*S*)-**4j**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	4.240	917780	50.031	1	4.521	32248	9.996
2	4.818	916629	49.969	2	5.014	290355	90.004

(*R*)-1-(2-Naphthyl)ethanol (2k)

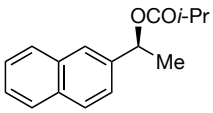


2k

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 95/5, v/v, flow rate = 0.600 mL/min, 30 °C, UV = 254 nm), T_R = 40.8 min (minor) and T_R = 52.7 min (major), 84:16 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.77 (m, 4H), 7.56–7.41 (m, 3H), 5.09 (q, *J* = 6.4 Hz, 1H), 1.80–1.53 (m, over rap with water); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 133.5, 133.1, 128.5, 128.1, 127.8, 126.3, 125.9, 123.9, 70.7, 25.3; IR (KBr) 3323, 3053, 2970, 2880, 1599, 1364, 1275, 826, 743 cm^{-1}; $[\alpha]^{22}_D$ +14.7 (*c* 0.35, $CHCl_3$, 84:16 er) [lit.[73] $[\alpha]^{20}_D$ +60.4 (*c* 1.0, $CHCl_3$, 97% ee, (*R*) form)].

Racemic sample of **2k**				(*R*)-**2k**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	43.381	3696692	49.858	1	40.837	14398617	16.004
2	58.618	3717701	50.142	2	52.688	75567194	83.996

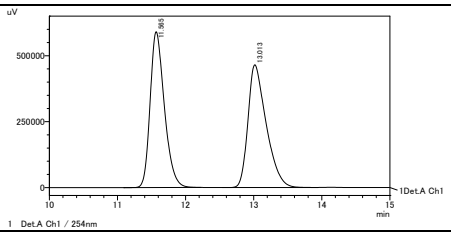
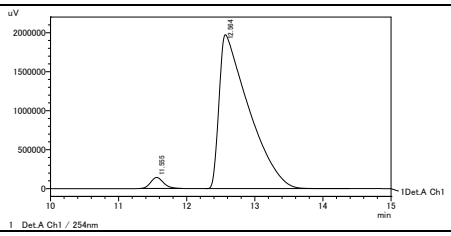
(*S*)-1-(2-Naphthyl)ethyl isobutyrate (4k)



4k

Pale yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 95/5, v/v, flow rate = 0.600 mL/min, 30 °C, UV = 254 nm), T_R = 11.6 min (minor) and T_R = 12.6 min (major), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.78 (m, 4H), 7.52–7,45 (m, 3H), 6.04 (q, *J* = 6.5 Hz, 1H), 2.60

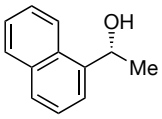
(sep., J = 6.9 Hz, 1H), 1.61 (d, J = 6.5 Hz, 3H), 1.24–1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 139.4, 133.3, 133.1, 128.5, 128.1, 127.8, 126.3, 126.1, 125.0, 124.2, 72.2, 34.3, 22.4, 19.1; IR (KBr) 2976, 1934, 1732, 1470, 1387, 1155, 1063, 818, 748 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{16}H_{19}O_2$ $[M+H]^+$ 243.1379, found 243.1349 ; $[\alpha]^{24}_D$ −31.7 (*c* 0.33, $CHCl_3$, 98:2 er).

Racemic sample of **4k**	(*S*)-**4k**
	

Peak #	Ret. Time	Area	Area %
1	11.565	8575939	49.796
2	13.013	8646323	50.204

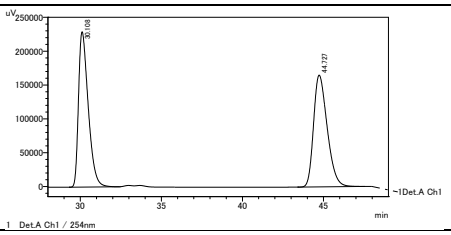
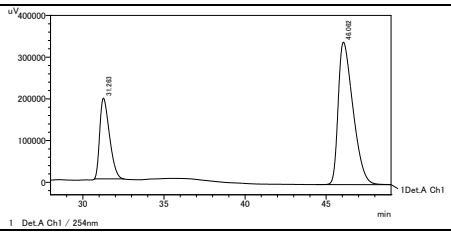
Peak #	Ret. Time	Area	Area %
1	11.555	1457039	2.381
2	12.564	59757734	97.619

(*R*)-1-(1-Naphthyl)ethanol (2l)[58]



2l

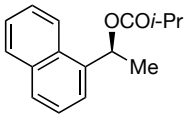
Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 90/10, v/v, flow rate = 0.300 mL/min, 30 °C, UV = 254 nm), T_R = 31.3 min (minor) and T_R = 46.1 min (major), 73:27 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.60–7.46 (m, 3H), 5.70 (q, J = 6.4 Hz, 1H), 1.89 (bs, 0.6H), 1.69 (d, J = 6.4 z, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 133.9, 130.4, 129.0, 128.0, 126.1, 125.6, 123.3, 122.1, 67.2, 24.5; IR (KBr) 3200, 2976, 2903, 1595, 1229, 899, 802, 775 cm^{-1}; $[\alpha]^{20}_D$ +32.5 (*c* 0.47, $CHCl_3$, 73:27 er) [lit.[71] $[\alpha]^{25}_D$ +43.6 (*c* 1.0, $CHCl_3$, 60% ee, (*R*) form)].

Racemic sample of **2l**	(*R*)-**2l**
	

Peak #	Ret. Time	Area	Area %
1	30.108	9562084	49.788
2	44.727	9643577	50.212

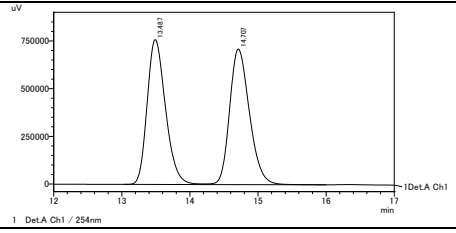
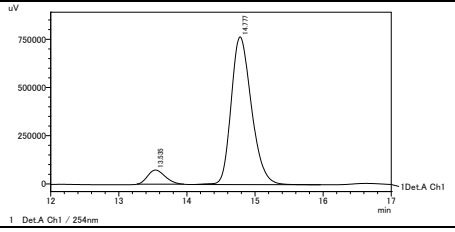
Peak #	Ret. Time	Area	Area %
1	31.263	8084088	27.149
2	46.062	21692652	72.851

(*S*)-1-(1-Naphthyl)ethyl isobutyrate (4l)[58]

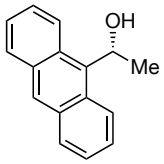


4l

Yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 90/10, v/v, flow rate = 0.300 mL/min, 30 °C, UV = 254 nm), T_R = 13.5 min (minor) and T_R = 14.8 min (major), 92:8 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.08 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.57–7.45 (m, 3H), 6.64 (q, *J* = 6.4 Hz, 1H), 2.62 (sep., *J* = 7.3 Hz, 1H), 1.70 (d, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 7.3 Hz, 3H), 1.18 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 40 ºC) δ 176.4, 137.9, 134.1, 130.5, 129.0, 128.5, 126.3, 125.8, 125.5, 123.4, 123.3, 69.4, 34.4, 21.8, 19.1, 18.9; IR (KBr) 2976, 2934, 1732, 1470, 1387, 1157, 1069, 800, 777 cm^{-1}; $[\alpha]^{21}_D$ −17.2 (*c* 0.41, $CHCl_3$, 92:7 er).

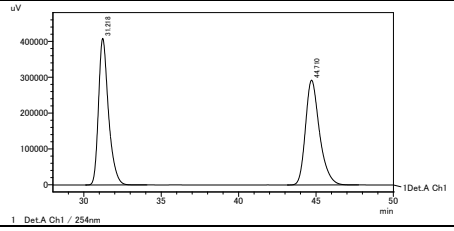
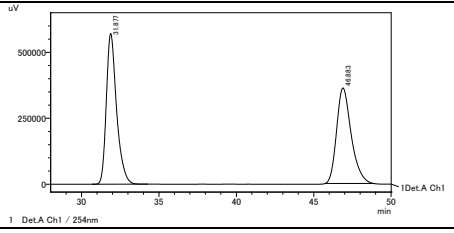
Racemic sample of **4l**				(*S*)-**4l**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	13.487	14232227	49.724	1	13.535	1309921	7.626
2	14.707	14390029	50.276	2	14.777	15868336	92.374

(*R*)-1-(9-Anthryl)ethanol (2m)[68]

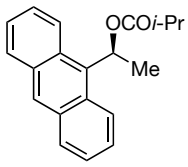


2m

Yellow solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AD-H (hexane/*i*-PrOH = 96/4, v/v, flow rate = 0.800 mL/min, 30 °C, UV = 254 nm), T_R = 31.9 min (major) and T_R = 46.9 min (minor), 52.5:47.5 er; ^{1}H NMR (400 MHz, $CDCl_3$, 50 ºC) δ 8.67 (d, *J* = 8.4 Hz, 2H), 8.39 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.56–7.40 (m, 4H), 6.46 (q, *J* = 6.8 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 ºC) δ 135.8, 131.7, 129.4, 128.8, 127.9, 125.5, 124.8, 67.2, 23.4; IR (KBr) 3290, 2968, 1622, 1115, 889, 791, 729 cm^{-1}; $[\alpha]^{24}_D$ +1.76 (*c* 0.825, $CHCl_3$, 52.5:47.5 er) [lit.[77] $[\alpha]_D$ +18.5 (*c* 1, $CHCl_3$, >99% ee, (*R*) form)].

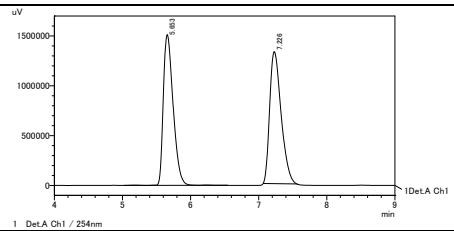
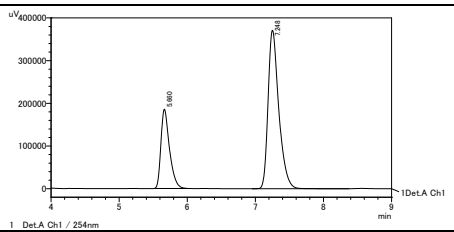
Racemic sample of **2m**				(*R*)-**2m**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	31.218	18280269	49.804	1	31.877	26300336	52.495
2	44.710	18424135	50.196	2	46.883	23800219	47.505

(*S*)-1-(9-Anthryl)ethyl isobutyrate (4m)[68]

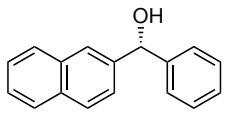


4m

Orange solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AD-H (hexane/*i*-PrOH = 96/4, v/v, flow rate = 0.800 mL/min, 30 °C, UV = 254 nm), T_R = 5.7 min (minor) and T_R = 7.2 min (major), 71:29 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (bd, *J* = 8.0 Hz, 2H), 8.42 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.57–7.37 (m, 5H), 2.69–2.55 (m, 1H), 1.94 (dd, *J* = 6.0, 1.6 Hz, 3H), 1.18 (dd, *J* = 7.1, 1.9 Hz, 3H), 1.08 (dd, *J* = 7.1, 2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 132.5, 131.8, 129.5, 129.1, 128.5, 125.9, 124.9, 68.8, 34.3, 21.7, 19.0; IR (KBr) 2974, 2934, 1732, 1450, 1157, 1086, 1040, 731 cm^{-1}; $[\alpha]^{21}_D$ +6.49 (*c* 0.55, $CHCl_3$, 71:29 er).

Racemic sample of **4m**				(*S*)-**4m**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	5.653	15172197	49.556	1	5.660	1623903	28.633
2	7.226	15444082	50.444	2	7.248	4047758	71.367

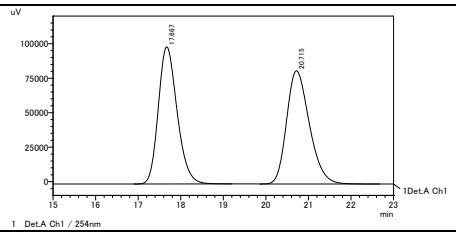
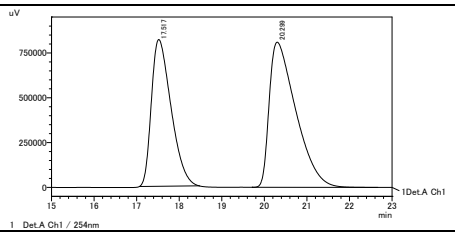
(*R*)-(2-Naphthyl)phenylmethanol (2n)[78]



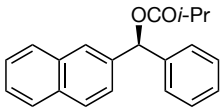
2n

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 92/8, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 17.5 min (minor) and T_R = 20.3 min (major), 57:43 er; ^{1}H NMR (400 MHz, $CDCl_3$, 50 ºC) δ 7.93–7.70 (m, 5H), 7.52–7.10 (m, 7H), 6.02 (s, 1H), 2.23 (bs, 0.8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 141.2, 133.4, 133.0, 128.7, 128.5, 128.2, 127.8, 126.8, 126.3, 126.1, 125.1, 124.9, 76.5; IR (KBr) 3227, 3057, 1454, 1034, 1024, 816, 739, 700 cm^{-}

[1]; $[\alpha]^{23}_D$ –2.9 (*c* 0.62, $CHCl_3$, 76.5:23.5 er) [lit.[79] $[\alpha]^{24}_D$ +8.6 (*c* 0.50, $CHCl_3$, 92% ee, (*S*) form)].

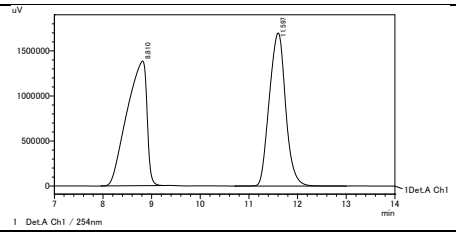
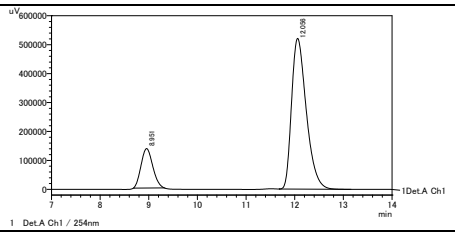
Racemic sample of **2n**				(*R*)-**2n**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	17.667	3052458	50.002	1	17.517	26205836	42.765
2	20.715	3052182	49.998	2	20.299	35072846	57.235

(*S*)-(2-Naphthyl)phenylmethyl isobutyrate (4n)

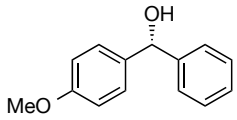


4n

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 99.5/0.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 9.0 min (minor) and T_R = 12.1 min (major), 83:17 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.78 (m, 4H), 7.55–7.22 (m, 8H), 7.03 (s, 1H), 2.71 (sep., *J* = 7.2 Hz, 1H), 1.30–1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 140.4, 137.9, 133.2, 133.0, 128.6, 128.5, 128.3, 128.0, 127.8, 127.2, 126.4, 126.2, 125.0, 76.8, 34.4, 19.1; IR (KBr) 176.1, 140.4, 137.9, 133.2, 133.0, 128.6, 128.5, 128.3, 128.0, 127.8, 127.2, 126.4, 126.2, 125.0, 76.8, 34.4, 19.1 cm^{-1}; HRMS (ESI^+) calculated for $C_{21}H_{20}O_2$ $[M+H]^+$ 305.1536, found 305.1560; mp 63.0–63.7 ºC; $[\alpha]^{23}_D$ –5.9 (*c* 0.79, $CHCl_3$, 76:24 er).

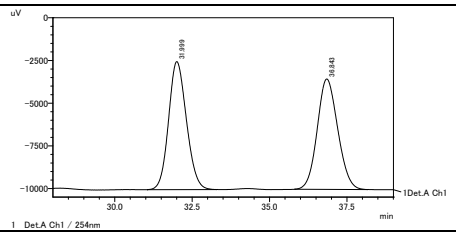
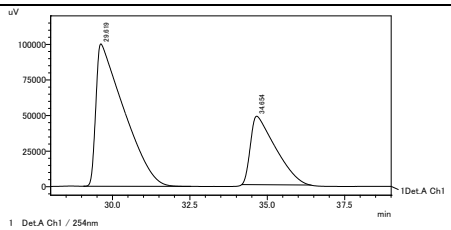
Racemic sample of **4n**				(*S*)-**4n**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	8.810	39389847	49.975	1	8.951	2279454	17.200
2	11.597	39428494	50.025	2	12.056	10973446	82.800

(*R*)-(4-Methoxyphenyl)phenylmethanol (2o)[78]

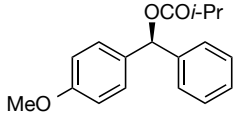


2o

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 29.6 min (major) and T_R = 34.7 min (minor), 70:30 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.21 (m, 7H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.82 (d, *J* = 2.8 Hz, 1H), 3.79 (s, 3H), 2.14 (d, *J* = 2.8 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 144.1, 136.3, 128.5, 128.0, 127.5, 126.5, 114.0, 75.9, 55.4; IR (KBr) 3395, 2951, 2837, 1611, 1518, 1252, 1034, 810, 717, 696 cm^{-1}; $[\alpha]^{21}_D$ +1.2 (*c* 0.98, $CHCl_3$, 61:39 er) [lit.[79] $[\alpha]^{24}_D$ +12.7 (*c* 0.50, $CHCl_3$, 93% ee, (*R*) form)].

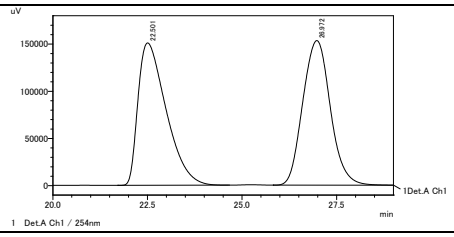
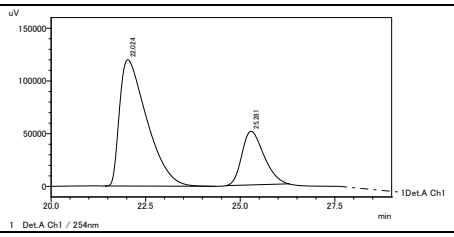
Racemic sample of **2o**				(*R*)-**2o**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	31.999	300841	50.242	1	29.619	6296157	69.931
2	36.843	297946	49.758	2	34.654	2707247	30.069

(*S*)-(4-Methoxyphenyl)phenylmethyl isobutyrate (4o)



4o

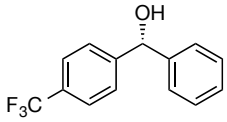
Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AD-H (hexane/*i*-PrOH = 99.5/0.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 22.0 min (major) and T_R = 25.3 min (minor), 74:26 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (m, 7H), 6.90–6.81 (m, 3H), 3.79 (s, 3H), 2.65 (sep., *J* = 7.2 Hz, 1H), 1.26–1.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 159.3, 140.8, 132.8, 128.7, 128.6, 127.8, 126.9, 114.0, 76.3, 55.4, 34.3, 19.1; IR (KBr) 2974, 2936, 1732, 1514, 1250, 1150, 833, 698 cm^{-1}; HRMS (FAB^+) calculated for $C_{18}H_{21}O_3$ $[M+H]^+$ 285.1485, found 285.1457; $[\alpha]^{21}_D$ –11.4 (*c* 0.64, $CHCl_3$, 74:26 er).

Racemic sample of **4o**	(*S*)-**4o**
	

Peak #	Ret. Time	Area	Area %
1	22.501	7787607	50.061
2	26.972	7768687	49.939

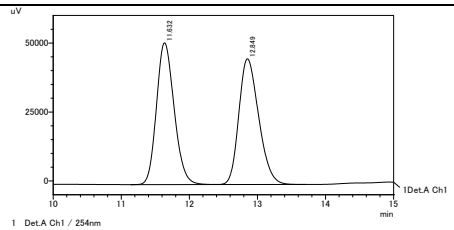
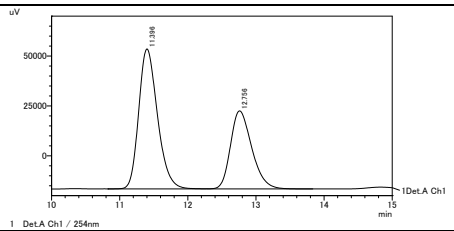
Peak #	Ret. Time	Area	Area %
1	22.024	6016757	74.375
2	25.281	2073053	25.625

(*R*)-Phenyl(4-(trifluoromethyl)phenyl)methanol (2p)[80]



2p

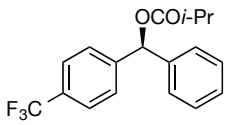
Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 93/7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 11.4 min (major) and T_R = 12.8 min (minor), 61:39 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.41–7.27 (m, 5H), 5.87 (s, 1H), 2.36 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 143.0, 129.6 (q, *J* = 32.6 Hz), 128.8, 128.1, 126.7, 125.4 (m), 124.3 (q, *J* = 271.9 Hz), 75.7; IR (KBr) 3329, 1497, 1327, 1171, 1111, 731 cm^{-1}; $[\alpha]^{17}_D$ –9.9 (*c* 0.42, $CHCl_3$, 61:39 er) [lit.[80] $[\alpha]^{20}_D$ = –19.4 (*c* 1.05, $CHCl_3$, 51% ee, (*R*) form)].

Racemic sample of **2p**	(*R*)-**2p**
	

Peak #	Ret. Time	Area	Area %
1	11.632	929142	50.146
2	12.849	923747	49.854

Peak #	Ret. Time	Area	Area %
1	11.396	1345424	61.283
2	12.756	850000	38.717

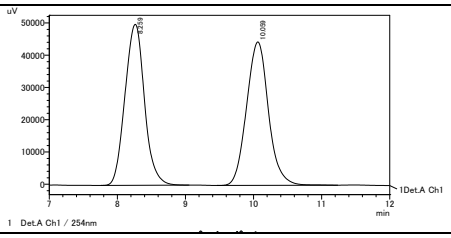
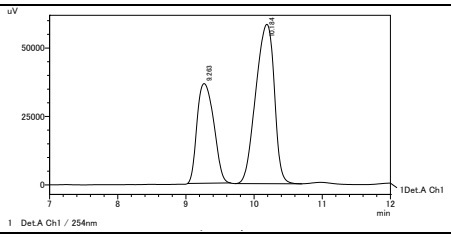
(*S*)-Phenyl(4-(trifluoromethyl)phenyl)methyl isobutyrate (4p)



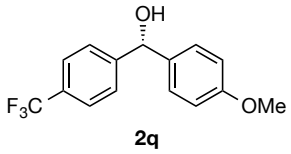
4p

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AD-H (hexane/*i*-PrOH = 99.5/0.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 9.3 min (minor) and T_R = 10.2 min (major), 64:36 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40–7.24 (m, 5H), 6.88 (s, 1H), 2.69 (sep., *J* = 7.0 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 144.6, 139.7, 130.1 (q, *J* = 32.6 Hz), 128.8, 128.3, 127.3, 127.1,

125.6 (q, J = 3.8 Hz), 124.1 (q, J = 272.2 Hz), 76.0, 34.3, 19.0, 18.9; IR (KBr) 2976, 1738, 1470, 1327, 1150, 1126, 1113, 1067, 839, 698 cm^{-1}; HRMS (FAB^+) calculated for $C_{18}H_{17}F_3O_2Na$ $[M+Na]^+$ 345.1072, found 345.1054; $[\alpha]^{23}_D$ +9.44 (*c* 0.54, $CHCl_3$, 64:36 er)

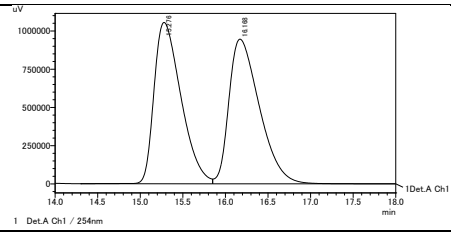
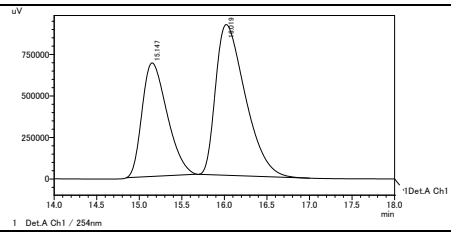
Racemic sample of **4p**				(*S*)-**4p**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	8.259	993337	49.960	1	9.263	621403	36.071
2	10.059	994909	50.040	2	10.184	1101313	63.929

(4-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methanol (2q)[81]

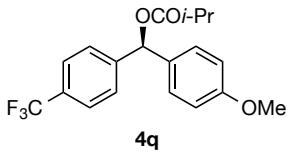


2q

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 93/7, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 15.1 min (minor) and T_R = 16.0 min (major), 61:39 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4, 2H), 7.31–7.22 (m, 2H), 6.95–6.85 (m, 2H), 5.85 (s, 1H), 3.80 (s, 3H), 2.18 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.0, 135.4, 129.3 (q, J = 32.3 Hz), 128.1, 126.6, 125.2 (q, J = 3.8 Hz), 124.3 (q, J = 271.9 Hz), 114.0, 75.1, 55.0; IR (KBr) 3300, 2959, 2897, 2845, 1614, 1585, 1514, 1325, 1067, 812, 779 cm^{-1}; $[\alpha]^{23}_D$ +10.0 (*c* 1.03, $CHCl_3$, 61:39 er, unknown absolute configuration).

Racemic sample of **2q**				(*R*) or (*S*)-**2q**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	15.276	23198628	49.615	1	15.147	14014441	38.883
2	16.168	23558478	50.385	2	16.019	22028295	61.117

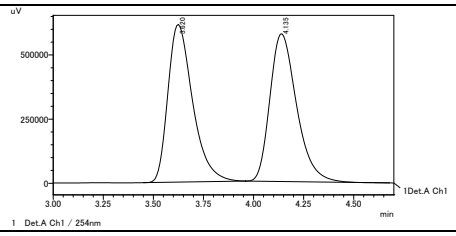
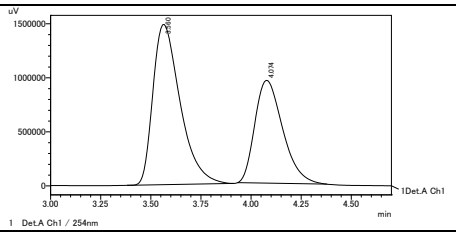
(4-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methyl isobutyrate (4q)



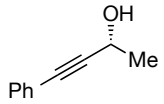
4q

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 3.6 min (major) and T_R = 4.1 min (minor), 60:40 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.27–7.17 (m, 2H), 6.90–6.80 (m, 3H), 3.79 (s, 3H), 2.67 (sep., J = 7.0 Hz,

1H), 1.22 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ175.8, 159.8, 144.9, 132.0, 130.0 (q, J = 32.6 Hz), 128.8, 127.2, 125.5 (q, J = 3.8 Hz), 124.2 (q, J = 272.2 Hz, overap several pearks), 114.2, 75.8, 55.3, 34.3, 18.9 (2); IR (KBr) 2976, 2938, 2839, 1736, 1585, 1329, 1252, 1125, 1067, 1018, 829, 766, 603 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{19}H_{20}F_3O_3$ $[M+H]^+$ 353.1359, found 353.1374; $[\alpha]^{23}_D$ +10.0 (*c* 1.03, $CHCl_3$, 60:40 er, unknown absolute configuration)

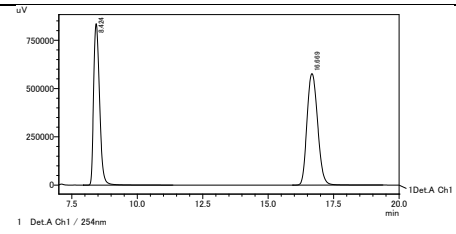
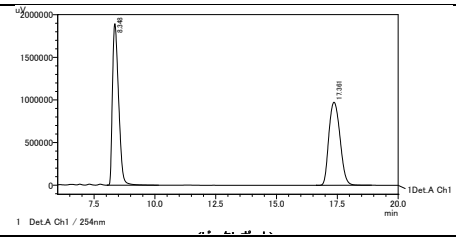
Racemic sample of **4q**				(*S*) or (*R*)-**4q**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	3.620	5278741	49.738	1	3.560	14001893	60.374
2	4.135	5334345	50.262	2	4.074	9190213	39.626

(*R*)-4-Phenyl-3-butyn-2-ol (2r)

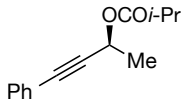


2r

Yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 80/20, v/v, flow rate = 0.800 mL/min, 30 °C, UV = 254 nm), T_R = 8.3 min (major) and T_R = 17.4 min (minor), 52:48 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.39 (m, 2H), 7.32–7.26 (m, 3H), 4.76 (q, J = 7.0 Hz, 1H), 1.74 (bs, 1H), 1.56 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.4, 128.3, 122.7, 91.1, 84.0, 58.8, 24.4; IR (KBr) 3354, 2982, 2232, 1489, 1107, 934, 751; $[\alpha]^{21}_D$ = +2.78 (*c* 0.55, Et_2O, 52:48 er) [lit.[82] $[\alpha]^{25}_D$ –50.6 (*c* 1.475, Et_2O, >95% ee, (*S*) form)].

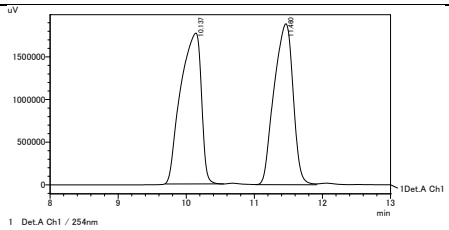
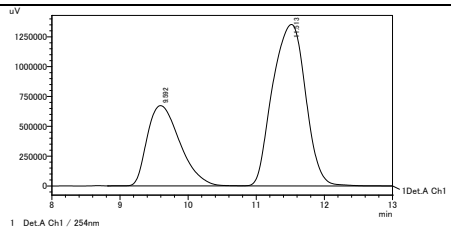
Racemic sample of **2r**				(*R*)-**2r**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	8.424	13210336	49.767	1	8.348	33377340	51.702
2	16.669	13298812	50.233	2	17.361	31179480	48.298

(*S*)-4-Phenylbut-3-yn-2-yl isobutyrate (4r)



4r

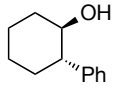
Yellow liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 9.6 min (minor) and T_R = 11.5 min (major), 67:33 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.32–7.26 (m, 3H), 5.69 (q, *J* = 6.5 Hz, 1H), 2.59 (sep., *J* = 7.1 Hz, 1H), 1.57 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 132.0, 128.7, 128.4, 122.5, 87.7, 84.5, 60.7, 34.1, 21.6, 19.1, 18.9; IR (KBr) 3051, 2976, 2936, 1732, 1470, 1069, 800, 777; HRMS (FAB$^+$) calculated for $C_{14}H_{16}O_2$ $[M+H]^+$ 216.1144, found 216.1154; $[\alpha]^{24}_D$ = –1.91 (*c* 0.338, Et_2O, 67:33 er).

Racemic sample of **4r**	(*S*)-**4r**
	

Peak #	Ret. Time	Area	Area %
1	10.137	37188744	50.436
2	11.460	36545252	49.564

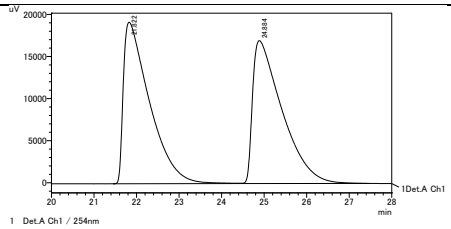
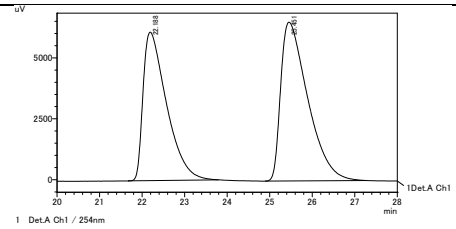
Peak #	Ret. Time	Area	Area %
1	9.592	22495587	33.018
2	11.513	45635512	66.982

(1*R*,2*S*)-2-Phenylcyclohexan-1-ol (2s)

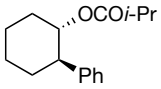


2s

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 99.5/0.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 22.2 min (minor) and T_R = 22.5 min (major), 55:45 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H), 7.29–7.20 (m, 3H), 3,67 (td, *J* = 11.5, 4.4 Hz, 1H), 2.43 (ddd, *J* = 11.5, 9.7, 3.3 Hz, 1H), 2.17 (s, 0.13H), 2.15–2.06 (m, 1H), 1.92–1.80 (m, 2H), 1.80–1.61 (m, 1H), 1.61–1.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 128.9, 128.0, 126.9, 74.5, 53.3, 34.5, 33.4, 26.2, 25.2; IR (KBr) 3298, 2932, 2855, 1447, 1051, 746, 696; $[\alpha]^{23}_D$ = –3.20 (*c* 0.23, EtOH, 55:45 er) [lit.[83] $[\alpha]^{23}_D$ +69.65 (*c* 1565, EtOH, 85% ee, (1*S*, 2*R*) form)].

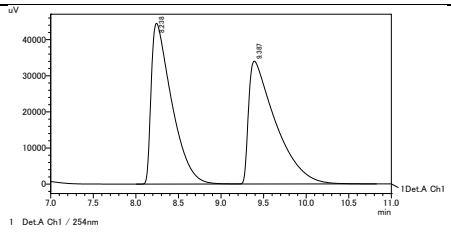
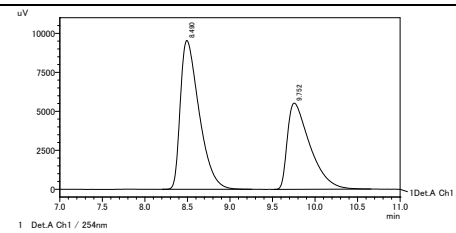
Racemic sample of **2s**				(1*R*, 2*S*)-**2s**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	21.822	819410	50.113	1	22.188	233311	44.830
2	24.884	815726	49.887	2	25.451	287122	55.170

(1*S*,2*R*)-2-Phenylcyclohexyl isobutyrate (4s)

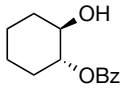


4s

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 99.9/0.1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.5 min (major) and T_R = 9.8 min (minor), 59:41 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.10 (m, 5H), 4.96 (td, *J* = 11.5, 4.4 Hz, 1H), 2.66 (td, *J* = 11.5, 3.8 Hz, 1H), 2.24 (sep., *J* = 7.1 Hz, 1H), 2.13–2.03 (m, 1H), 1.97–1.71 (m, 3H), 1.63–1.28 (m, 4H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.74 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 143.3, 128.3, 127.7, 126.5, 75.6, 50.2, 34.2, 34.1, 32.5, 26.0, 24.9, 18.9, 18.7; IR (KBr) 2974, 2936, 1732, 1470, 1155, 1061, 851; HRMS (FAB$^+$) calculated for $C_{14}H_{23}O_2$ $[M+H]^+$ 247.1692, found 247.1677; $[\alpha]^{21}_D$ = 0.46 (*c* 0.19, EtOH, 59:41 er).

Racemic sample of **4s**				(1*S*, 2*R*)-**4s**			
							
Peak #	**Ret. Time**	**Area**	**Area %**	**Peak #**	**Ret. Time**	**Area**	**Area %**
1	8.238	745568	49.788	1	8.490	146830	59.002
2	9.387	751903	50.212	2	9.752	102028	40.998

***trans*-2-Hydroxycyclohexyl benzoate (2t)**

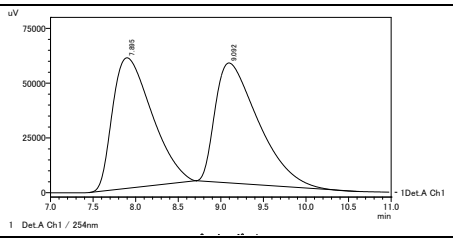


2t

Colorless solid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99.5/0.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.7 min and T_R = 10.2 min, 50:50 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 5.24 (ddd, *J* = 11.1, 8.2, 4.4 Hz, 1H), 2.31–2.19 (m, 1H), 2.17 (s, 0.1H), 1.91–1.73 (m, 1H), 1.70–1.40 (m, 5H); ^{13}C NMR

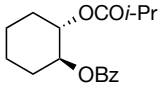
(100 MHz, $CDCl_3$) δ 166.2, 133.0, 130.3, 129.7, 128.4, 74.4, 30.4, 23.6; IR (KBr) 3526, 3065, 3032, 1699, 1450, 1277, 1111, 714.

Racemic sample of **2t**



Peak #	Ret. Time	Area	Area %
1	7.895	1923366	49.788
2	9.092	1939753	50.212

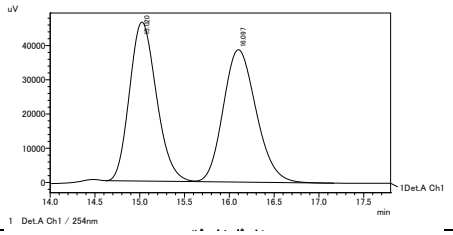
***trans*-2-(Isobutyryloxy)cyclohexyl benzoate (4t)**



4t

Colorless liquid. Enantiomeric ratio was determined by HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 81.7/18.3, v/v, flow rate = 0.300 mL/min, 30 °C, UV = 254 nm), T_R = 17.9 min and T_R = 20.7 min, 50:50 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 5.10–4.99 (m, 2H), 2.44 (sep., *J* = 7.0 Hz, 1H), 2.23–2.15 (m, 1H), 2.10–2.01 (m, 1H), 1.85–1.71 (m, 2H), 1.61–1.31 (m, 4H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 165.9, 133.0, 130.2, 129.7, 128.4, 77.4, 74.7, 73.1, 34.1, 30.3, 23.6, 19.0, 18.8; IR (KBr) 2972, 2864, 2349, 1732, 1714, 1454, 845, 711; HRMS (FAB$^+$) calculated for $C_{17}H_{23}O_4$ $[M+H]^+$ 291.1590, found 291.1600.

Racemic sample of **4t**



Peak #	Ret. Time	Area	Area %
1	15.020	970737	49.535
2	16.097	988978	50.465

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Chapter 6. Kinetic Resolution of *d,l*-1,2-Diols with Binaphthyl-Based DMAP Derivatives

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6-1. Abstract

An extremely efficient acylative kinetic resolution of *d,l*-1,2-diols in the presence of only 0.5 mol % of binaphthyl-based chiral *N*,*N*-4-dimethylaminopyridine was developed (selectivity factor up to 180). Several key experiments revealed that hydrogen bonding between the *tert*-alcohol unit(s) of the catalyst and the 1,2-diol unit of the substrate is critical for accelerating the rate of monoacylation and achieving high enantioselectivity. This catalytic system can be applied to a wide range of substrates involving racemic acyclic and cyclic 1,2-diols with high selectivity factors. The kinetic resolution of *d,l*-hydrobenzoin and *trans*-1,2-cyclohexanediol on a multigram scale (10 g) also proceeded with high selectivity and under moderate conditions: (i) Very low catalyst loading (0.1 mol %); (ii) an easily achievable low reaction temperature (0 ºC); (iii) high substrate concentration (1.0 M); and (iv) short reaction time (30 min).

6-2. Introduction

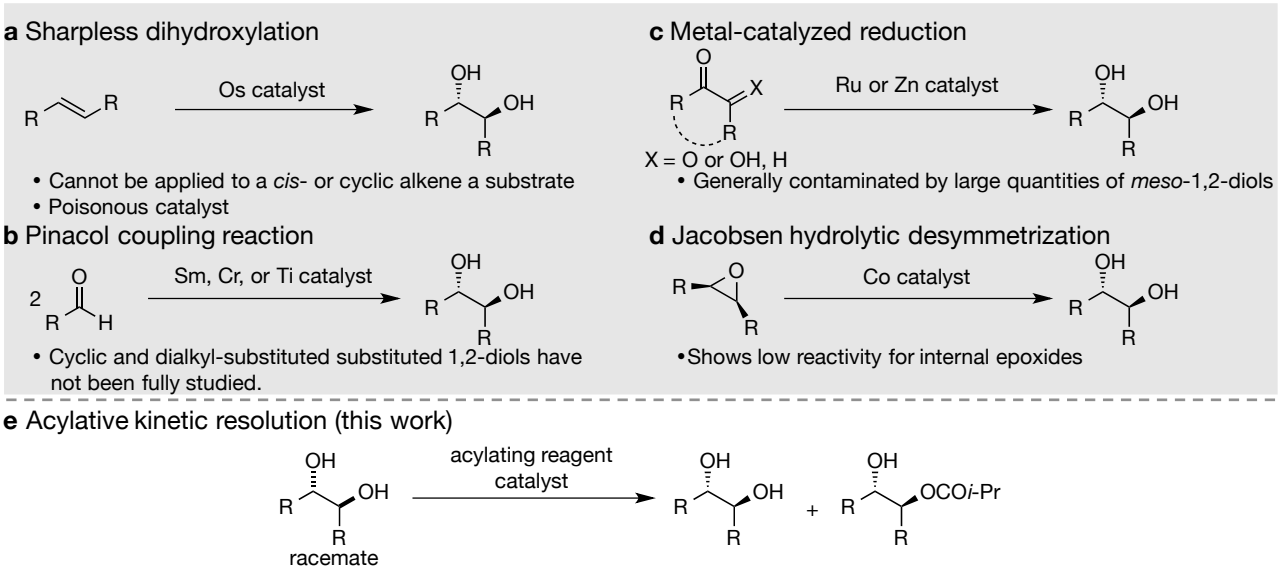


Figure 1. Various enantioselective syntheses for 1,2-diols

The establishment of a general method for obtaining a pure enantiomer with two or more adjacent chiral carbons is a challenging topic in organic synthesis.[1-12] An enantiomerically pure 1,2-diol moiety which has two contiguous chiral carbon centers is often found in biologically important molecules,[13,14] chiral ligands for metal catalysis,[15-23] auxiliaries,[24-27] and organocatalysts.[28-30] A variety of enantioselective methods have been developed to obtain such enantiomerically pure 1,2-diols, including enantioselective Sharpless dihydroxylation,[31-34] pinacol coupling,[35-38] reduction of α-hydroxy ketones or 1,2-diketones,[39-42] and Jacobsen hydrolysis of epoxide[43-49] (Figure 1). The enantioselective Sharpless dihydroxylation (Figure 1a) is a splendid synthetic method that has been frequently used to synthesize chiral building blocks and natural products. However, it has several drawbacks: (1) It requires the use of poisonous osmium (VIII)

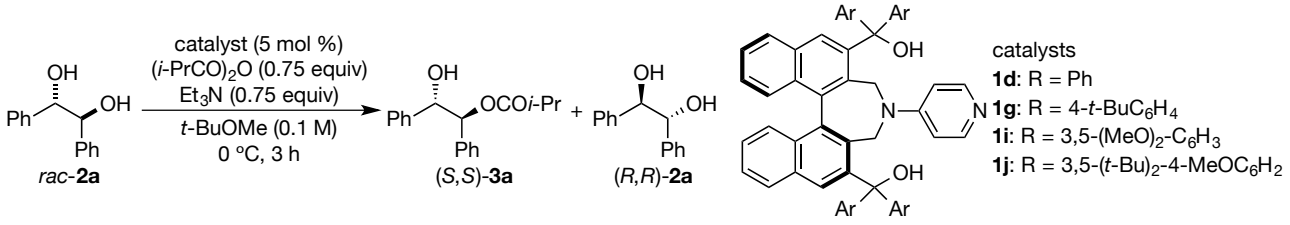
oxide; (2) *trans*-alkenes are prepared because the reaction proceeds via *syn*-addition (when *cis*-alkene is used as a substrate, the reaction gives only *meso*-diol); and (3) *trans*-1,2-cyclic diols cannot be obtained (*trans*-cycloalkenes have extraordinary ring strain, except for an eight-membered ring). The most satisfactory results with enantioselective pinacol coupling (Figure 1b) were reported by Yamamoto,[38] which also showed high diastereoselectivity and enantioselectivity for a variety of hydrobenzoin-type 1,2-diols, while cyclic and dialkyl substituted 1,2-diols have not been fully studied (except for 1,2-diol derivatives obtained from cyclohexyl aldehyde). There have been only a few reports on the enantioselective reduction of α-hydroxy ketones or 1,2-diketones to deliver enantiopure 1,2-diols (Figure 1c), since most metal-catalyzed reductions give the *meso*-isomer as a major product by substrate control.[50] An alternative method for obtaining enantiopure 1,2-diol is the enantioselective hydrolysis of *meso*-epoxide (Figure 1d).[43-48] This reaction is a nearly ideal catalytic enantioselective reaction for obtaining 1,2-diols and offers several advantages (diastereospecific and highly enantioselective, low cost, air- and water-stable, and recyclable catalyst). However, the reaction has mainly been shown to be effective when terminal epoxides are used as substrates (there has been no report of an enantioselective hydrolysis for *cis*-stilbene oxide).[48] Thus, it can not be cover all of various structure of 1,2-diols. On the other hand, racemic acyclic or cyclic 1,2-diols were much easier to access than in the enantioselective variant.[51-62] Against this background, we were interested in the enantioselective separation of *d,l*-1,2-diol using a chiral catalyst (i.e., kinetic resolution, Figure 1e), but substrate limitations and over-reactions (e.g., diacylation) sometimes became problematic. Lewis acid catalyzed acylative kinetic resolutions of diols often proceed with good enantioselectivity, but these reactions needed high catalyst loading (1–5 mol %) and showed unsatisfactory substrate scope (high selectivities were only observed with the use of *d,l*-hydrobenzoin series).[63-65] Fujimoto,[66] Schreiner,[67-69] and Yamada[70] have previously reported the efficient kinetic resolution of *d,l*-1,2-diols with organocatalysts. These catalytic systems showed excellent selectivity factors (*s*-factors)[71] for a limited number of substrates. For example, Fujimoto's method could be applied to acyclic *d,l*-1,2-diols (*d,l*-hydrobenzoin series), but the use of cyclic and acyclic *d,l*-1,2-diols resulted in moderate *s*-factors (s = 11–20). In contrast, Schreiner's and Yamada's methods were particularly effective with cyclic *trans*-1,2-diols, but the efficacy of their application to acyclic *d,l*-1,2-diols is unclear. Oriyama reported organocatalyzed enantioselective acylation of diols with a proline-derived diamine catalyst. It was applicable to desymmetrization of *meso*-diols with high enantioselectivity, and suppressed undesired over-acylation (required very low reaction temperature); however, this system was not applied to kinetic resolution of *d,l*-diols.[72] Accordingly, the development of a general and reliable synthetic method for accessing an array of enantiopure 1,2-diols would be extremely valuable.

Our developed binaphthyl-based DMAP derivatives with hydrogen-bonding substituents at the 3,3′-positions remarkably accelerated the rate of the reaction and showed high enantioselectivity in the Steglich rearrangement of *O*-acylated oxindole derivatives (chapter 3). According to extensive mechanistic studies on Steglich rearrangement, the reaction system effectively used hydrogen bonding between the catalyst and the counteranion of *N*-acylpyridinium ion to stabilize the transition state (oxyanion stabilization)[73] to in turn enhance the catalytic activity and enantioselectivity. In this chapter, I report the details of the acylative kinetic resolution of acyclic and cyclic *d,l*-1,2-diols using chiral DMAP derivative **1d**, and reveal that hydrogen bonding between **1d** and *d,l*-1,2-diols plays a key role due to enhancement of the reaction rate, enantioselectivity, and mono/di selectivity.

6-3. Optimization of Reaction Conditions

We began by exploring an optimal catalyst for acyclic *d*,*l*-1,2-diol **2a** (hydrobenzoin) as a model substrate. The reaction was carried out in the presence of 5 mol % of catalysts, 0.75 equiv of isobutyric anhydride, and 0.75 equiv triethylamine in *tert*-butyl methyl ether at 0 ºC for 3 h (Table 1). Catalyst **1d** (Ar = Ph) showed excellent selectivity of monoacylation and good *s*-factor (entry 1, mono:di = 99:1, *s* = 33.4). Although catalyst **1g** was effective in the enantioselective Steglich rearrangement of oxindoles and the kinetic resolution of secondary carbinols, **1g** showed low *s*-factor (entry 2, *s* = 7.4). The use of catalyst **1i** or **1j** containing 3,5- or 3,4,5-substituted aryl group showed extremely low selectivity of monoacylation and *s*-factors (entries 3 and 4; mono:di = 92:8 and 64.5:35.5; *s* = 3.7 and 1.5, respectively). At this point, we selected **1d** as the optimal catalyst for further optimization of reaction conditions.

Table 1. Screening of catalysts[a-d]

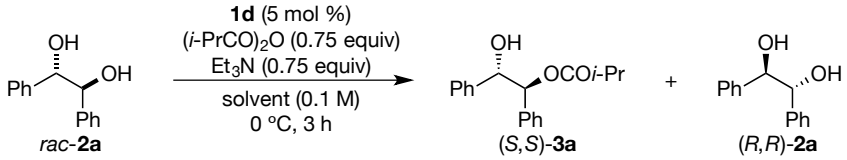


Entry	Catalyst	Conv (%)	Mono:di	Er of **3a**	Er of **2a**	*s*
1	**1d**	53	99:1	88:12	95:5	21.2
2	**1g**	52	97.5:2.5	79.5:20.5	82:18	7.4
3	**1i**	55	92:8	71:29	71:29	3.7
4	**1j**	39	64.5:35.5	58:42	58:42	1.5

[a]Performed on a 50.0 μmol scale under an argon atmosphere. [b]Conversions (± 2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures. [d]*S*-factors were calculated by Kagan's equation.[71]

We next screened the solvent (Table 2). The use of ether, toluene, hexane, CH_2Cl_2, EtOAc, and acetone as solvent showed high selectivity factors in good conversion (s = 9.4–21.2, entries 1–7). Contrarily, the use of aprotic or protic high polar solvent gave low selectivity factors, probably because of the weak hydrogen bond networks between the catalyst and substrate (s = 1.6–4.2, entries 11 and 12). Thus, we selected THF, which showed the highest s-factor, as the optimal solvent.

Table 2. Screening of solvent[a-d]

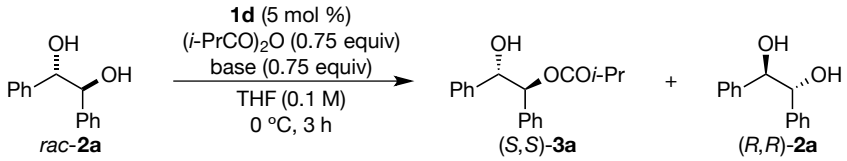


Entry	Solvent	Conv (%)	Mono:di	Er of **3a**	Er of **2a**	s
1	*t*-BuOMe	53	99:1	88:12	95:5	21.2
2	CPME	51	99:1	88.5:11.5	91:9	19.2
3	Et_2O	48	>99:1	87:13	85:15	13.5
4	*i*-Pr_2O	54	99:1	82:18	86.5:13.5	9.5
5	THF	46	>99:1	92:8	87.5:12.5	27.0
6	toluene	55	99:1	86.5:13.5	98:2	25.5
7	hexane	43	90:10	86:14	73:27	9.4
8	CH_2Cl_2	56	>99:1	85:15	96:4	18.5
9	EtOAc	55	99:1	87:13	95:5	19.5
10	acetone	54	99:1	86:14	91:9	14.9
11	DMF	50	97:3	73:27	74:26	4.2
12	*t*-amyl alcohol	51	97:3	59:41	58:42	1.6

[a]Performed on a 50.0 μmol scale under an argon atmosphere. [b]Conversions (± 2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures. [d]S-factors were calculated by Kagan's equation.[71]

Next, to improve the selectivity factor, we screened several bases (Table 3). The reaction proceeded while retaining a high selectivity factor in the absence of base (entry 1). While we continued to screen various organic and inorganic bases, the selectivity factors and conversions were not dramatically improved (entries 2–10). Thus, we selected TMEDA as the optimal base, which showed the highest selectivity factor and conversion among the bases tested (entry 7).

Table 3. Screening of base[a-d]

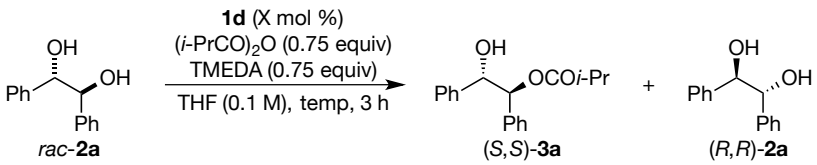


Entry	Base	Conv (%)	Mono:di	Er of **3a**	Er of **2a**	*s*
1	None	54	99:1	89:11	92:8	22.0
2	Et_3N	51	>99:1	91:9	94:6	29.3
3	*i*-Pr_2Net	56	99:1	89:11	98:2	29.3
4	pyridine	54	99:1	88:12	98:2	29.6
5	DBU	28	98:2	87:13	64.5:35.5	9.5
6	NMI	52	98.5:1.5	87:13	93:7	18.7
7	TMEDA	59	98:2	84:16	>99:1	33.4
8	proton-sponge	59	98:2	85:15	>99:1	29.7
9	K_3PO_4	37	99:1	90:10	73.5:26.5	14.5
10	KOAc	58	98:2	86:14	99:1	28.2

[a]Performed on a 75.0 μmol scale under an argon atmosphere. [b]Conversions (± 2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Er values (± 1%) were determined by chiral HPLC analysis of unpurified mixtures. [d]*S*-factors were calculated by Kagan's equation.

After screening of base and solvent the effect of reaction temperature, catalyst loading, and substrate concentration were examined with the optimal catalyst **1d** and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as optimal base in tetrahydrofurane (THF) (Table 4). The mono acylation smoothly preceded with good to excellent *s*-factors at various reaction temperature even if the reaction run at 25 ºC (entries 1–4, *s* = 16–113). Since the maximum *s*-factor was reached at –78 ºC, we next examined reducing the catalyst loading (entries 5–7). The reaction with no less than 0.5 mol % of catalyst **1d** also proceeded with excellent *s*-factors (*s* >100) but conversions were slightly decreased (33 and 37% conv; *s* = 122 and 125; entries 5 and 6). The presence of 0.1 mol % of **1d** in the reaction gave low conversion but still maintaining excellent *s*-factor (10% conv; *s* = 125; entry 7). After further tuning of substrate concentration and reaction time, the optimal reaction conditions (0.5 mol % of **1d**, 0.75 equiv of isobutyric anhydride, and TMEDA in THF (0.2 M) at –78 ºC for 9 h) were determined (entry 8, 52% conv, *s* = 125.1).

Table 4. Optimization of reaction conditions[a,b]



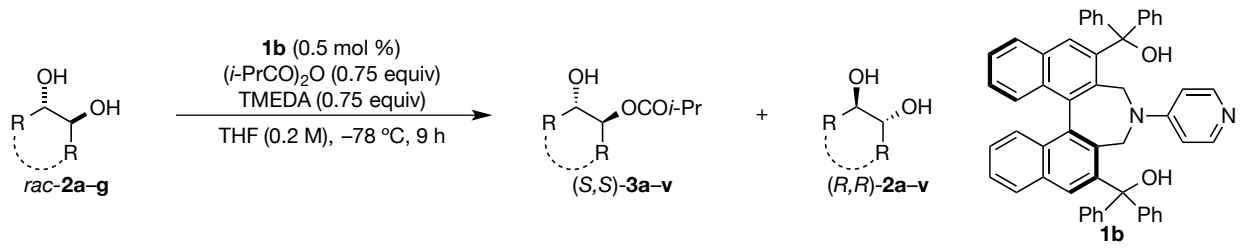
Entry	X (mol %)	Temp (ºC)	Conv (%)[c]	Er of **3a**[c]	Er of **2a**[c]	*S*[d]
1	5	25	52	87:13	90:10	16.1
2	5	0	59	84:16	>99:1	33.4
3	5	–40	57	87:13	>99:1	45.9
4	5	–78	54	93:7	>99:1	113.2
5	1	–78	37	99:1	72:28	144.6
6	0.5	–78	33	99:1	74:26	122.3
7	0.1	–78	10	99:1	57:43	125.3
8[e]	0.5	–78	52	97:3	99:1	125.1
9[e, f]	0.5	–78	<2	72:28	50:50	2.6

[a]Preformed on a 0.050–1.5 mmol scale under an argon atmosphere. [b]Mono/di ratios were gave >97:3 in all cases. [c]Conversions (± 2%) and mono/di ratio were determined by analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Er values (± 1%) was determined by chiral HPLC analysis of unpurified mixtures. [d]*S*-factors were calculated by Kagan's equation. [e]Stirred in THF (0.2 M) for 9 h [f]Used isobutyric chloride instead of isobutyric anhydride.

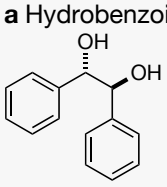
6-4. Substrate Scope

The kinetic resolution of various 1,2–diols including acyclic and cyclic variants was examined under the optimal conditions (Figure 2). We initially focused on hydrobenzoin derivatives **2a**–**j** as a substrate (Figure 2a). The reactions of **2a**–**j** proceeded with good conversions and excellent *s*-factors (32–55% conv, *s* = 54.0–180.3, except for **2b**). In all cases, monoacylated product was obtained with high selectivity (mono:di = >96:4, except for **2b**). Diol **2b**, which contained 2-naphthyl groups, showed somewhat a low selectivity of monoacylation and a low *s*-factor (mono:di = 82:12, *s* = 6.7). In contrast, structurally similar diol **2c**, which contains 1-naphthyl groups, showed an excellent ratio of monoacylation and an excellent *s*-factor (mono:di = 99:1, *s* = 180.3). This catalytic system could also achieve the separation of enantiomers from *para*-substituted hydrobenzoin derivatives **2d**–**g** with excellent *s*-factors even though these molecules have diverse substituents such as electron-donating groups, electron-withdrawing groups, or hydrogen bond-accepting groups (*s* = 74.9–139.3). *Ortho*- or *meta*- substituted hydrobenzoin derivatives **2h**–**j** could also be resolved with high *s*-factors (*s* = 54.0–146.0).

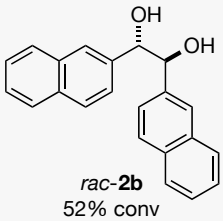
Additionally, this kinetic resolution could be applied to cyclic 1,2-diols in good conversions and with high *s*-factors (Figure 2b). Remarkably, *trans*-cyclohexane-1,2-diol **2k** and its structurally similar variants **2l** and **2m** showed high to excellent *s*-factors under the optimal conditions (*s* = 146.1, 48.7, and 20.1, respectively). Diols containing seven-membered **2n** and eight-membered rings **2o** could also be resolved with high *s*-factors (*s* = 27.7 and 74.7, respectively). Unfortunately, this catalytic system could not be applied to a five-membered ring system (**2p**: *s* = 3.0, **2q**: *s* = 6.4). Notably, acyclic diols with alkyl, vinyl, or allyl substituents **2r**–**t** could be resolved under these catalytic systems with moderate to excellent *s*-factors (*s* = 9.7–36.3, Figure 2c). It was difficult to resolve these substrates under the kinetic resolution conditions, perhaps because the conformationally flexible nature of acyclic *d*,*l*-1,2-diol would result in undesirable conformations in the transition state. Thus, there have been only a few reports on the acylative kinetic resolution of acyclic *d,l*-1,2-diols with alkyl substituents with moderate *s*-factors.[66,69] On the other hand, the reactions of acyclic diols **2u** and **2v** with neighboring functional groups resulted in low *s*-factors and poor selectivity of monoacylation. While there are no clear explanations for these results, we considered that neighboring functional groups might inhibit the hydrogen bonding between the catalyst and the substrate. To the best of our knowledge, this is the first example of a case where a very small amount of DMAP-based chiral nucleophilic catalyst (0.5 mol % of **1d**) can be applied to various *d*,*l*-1,2-diols involving acyclic and cyclic substrates with good to excellent *s*-factors.



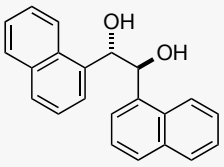
a Hydrobenzoin derivatives



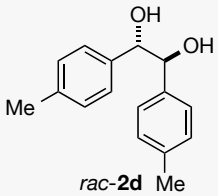
rac-**2a**
52% conv
mono:di = 99:1
s = 125.1



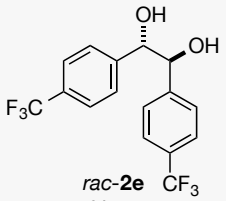
rac-**2b**
52% conv
mono:di = 82:18
s = 6.7



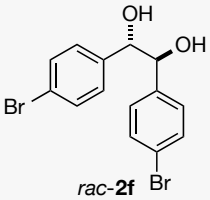
rac-**2c**
44% conv
mono:di = 99:1
s = 180.3



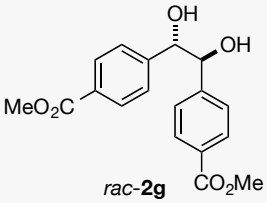
rac-**2d**
47% conv
mono:di = >99:1
s = 139.3



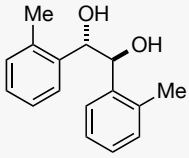
rac-**2e**
55% conv
mono:di = 98:2
s = 105.9



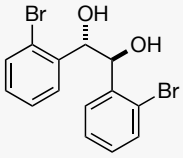
rac-**2f**
51% conv
mono:di = 98:2
s = 76.0



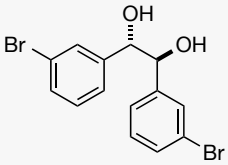
rac-**2g**
32% conv
mono:di = 96:4
s = 74.9



rac-**2h**
51% conv
mono:di = >99:1
s = 114.4

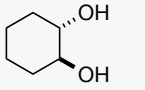


rac-**2i**
42% conv
mono:di = >99:1
s = 146.0

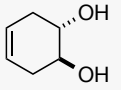


rac-**2j**
52% conv
mono:di = 96:4
s = 54.0

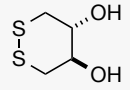
b Cyclic diols



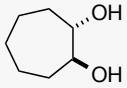
rac-**2k**
53% conv
mono:di = >99:1
s = 146.1



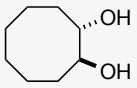
rac-**2l**
55% conv
mono:di = 99:1
s = 48.7



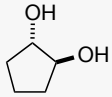
rac-**2m**
56% conv
mono:di = >99:1
s = 20.1



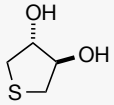
rac-**2n**
52% conv
mono:di = >99:1
s = 27.7



rac-**2o**
58% conv
mono:di = >99:1
s = 74.7

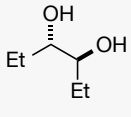


rac-**2p**
33% conv
mono:di = 80:20
***s* = 3.0**

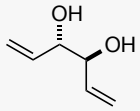


rac-**2q**
43% conv
mono:di = >99:1
***s* = 6.4**

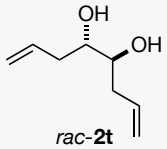
c Acyclic diols



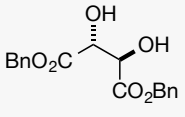
rac-**2r**
46% conv
mono:di = 98:2
s = 23.1



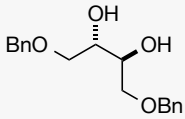
rac-**2s**
40% conv
mono:di = 99:1
s = 9.7



rac-**2t**
52% conv
mono:di = 99:1
s = 36.3



rac-**2u**
40% conv
mono:di = 83.5:16.5
s = 2.0



rac-**2v**
39% conv
mono:di = 84:16
s = 2.3

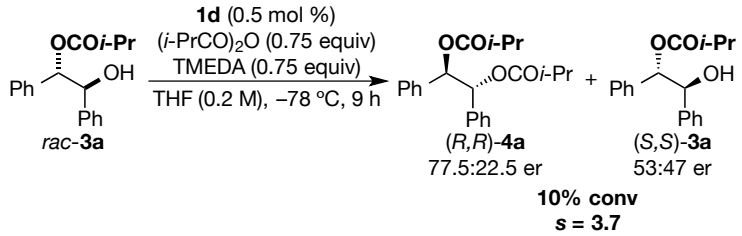
Figure 2. Substrate scope

6-5. Control Experiments

・Investigation of the subsequent kinetic resolution

We also investigated the subsequent kinetic resolution step[74] (Scheme 1). Under the optimized reaction conditions for the kinetic resolution of *d,l*-1,2-diols (see the supporting information, Table S1–5), racemic monoacylate **3a** was barely converted to (*R,R*)-**4a** with very low *s*-factors (10% conv, s = 3.7). As a result, the minor enantiomer in the first acylative kinetic resolution step ((*R,R*)-**3a**) was consumed in the second acylation step. This result showed that the enantiomeric ratio of monoacylate **3a** was slightly amplified by the second acylation step, but this subsequent reaction proceeded very slowly. This control experiment clearly showed that the enantiomeric ratio of monoacylate **3a** was determined by the first acylation step, and catalyst **1d** accelerated the rate of the first acylation (i.e., monoacylation of diol **2a** vs acylation of monool **3a**, Figure 2a vs Scheme 1). This observation supports the notion that catalyst **1d** only gives a monoacylate with high selectivity.

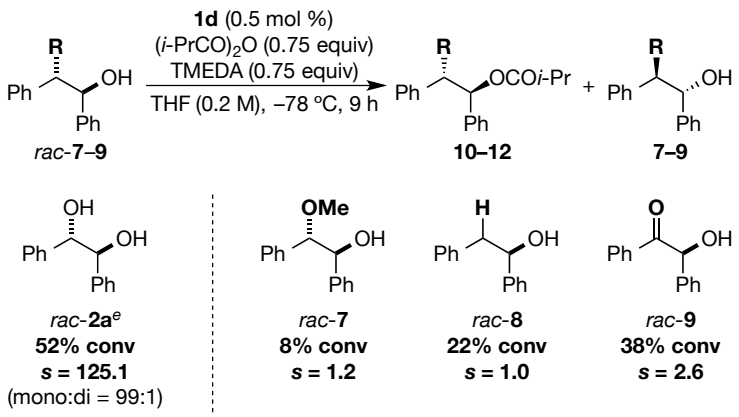
Scheme 1. Investigation of the subsequent kinetic resolution step[a–d]



・Effects of hydrogen bondings

We investigated in more detail the effect of hydrogen bonding between the hydroxy groups of the catalyst and two hydroxy groups of the substrate by several control experiments. We focused on the structure of the substrate, and performed kinetic resolution for various control substrates (Scheme 2). These experiments clearly indicated that racemic substrates require two adjacent free hydroxy groups to achieve a high *s*-factor and conversion. For example, the use of racemic monomethyl-capped 1,2-diol **7**, benzyl phenyl carbinol **8**, and benzoin **9** as substrates gave quite low *s*-factors (s =1.0–2.6) and conversions (8–38% conv) under the optimal conditions. We presumed that the catalyst **1d** recognizes two adjacent hydroxy groups on the substrate to accelerate the reaction and discriminate between the two enantiomers of the substrate.

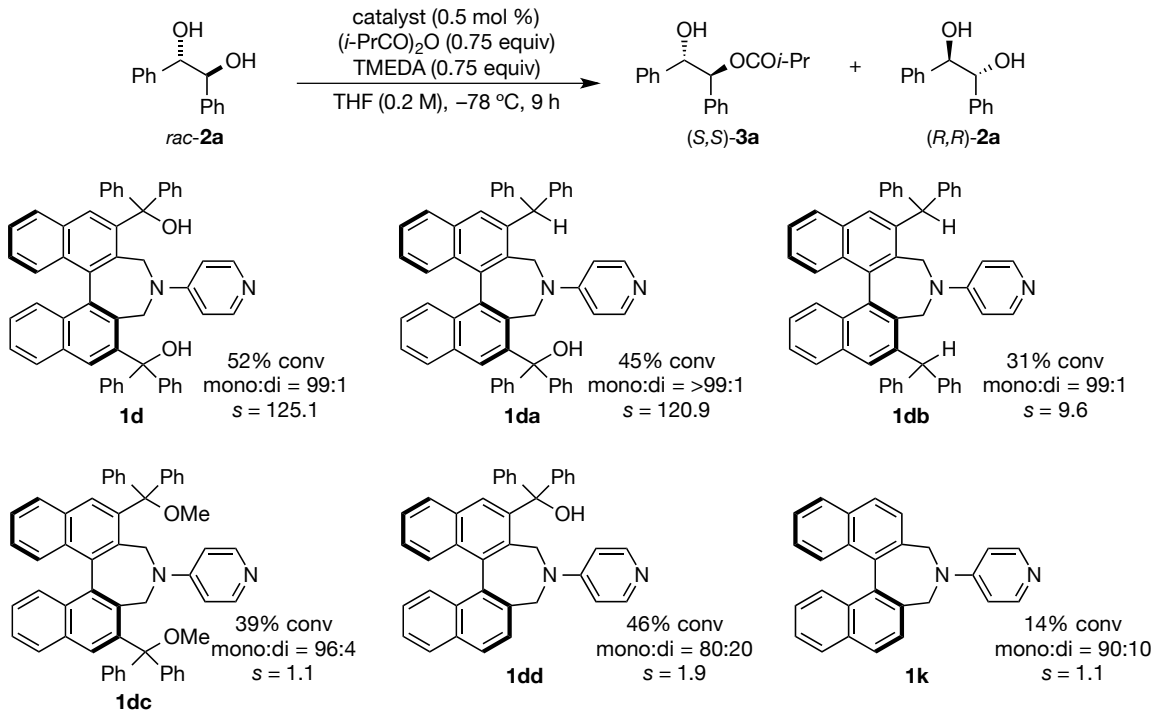
Scheme 2. Control experiments with various substrates[a–d]



[a] Performed on a 0.3 mmol scale under an argon atmosphere. [b] Conversions (±2%) were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c] The er values (±1%) were determined by the chiral HPLC analysis of unpurified mixtures. [d] The *s*-factors were calculated by Kagan's equation. [e] The same data as in Scheme 2b.

Next, we considered the catalyst structure (Scheme 3). The acylative kinetic resolution of **2a** was carried out using four catalyst analogues, including the optimal catalyst **1d**, monohydroxy analogue **1da**, dehydroxy analogue **1db**, methyl ether analogue **1dc**, C_1-symmetric analogue **1dd**, and analogue **1k** without *tert*-alcohol units. The use of catalyst **1d** and **1da** gave an excellent *s*-factor and selectivity of monoacylation, whereas catalyst **1db** and **1dc** gave quite a low *s*-factor (*s* = 125.1 with **1d** vs *s* = 9.6 with **1db** and *s* = 1.1 with **1dc**). Similarly, the use of catalyst **1dd** resulted in a low *s*-factor and a significant amount of diacylate was obtained (*s* = 1.9 and mono:di = 80:20). To our great surprise, catalyst **1k** gave the lowest catalytic activity and almost no enantioselectivity (*s* = 1.1). These results indicate that the catalyst have at least of one hydroxyl units, and is effective in the enantioselective monoacylation of the *d,l*-1,2-diol series.

Scheme 3. Control experiments focused on hydroxy groups on the catalyst[a–d]



[a] Performed on a 0.3 or 0.6 mmol scale under an argon atmosphere. [b] Conversions (±2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c] The er values (±1%) were determined by the chiral HPLC analysis of unpurified mixtures. [d] The *s*-factors were calculated by Kagan's equation. [e] The same data as in Figure 2a

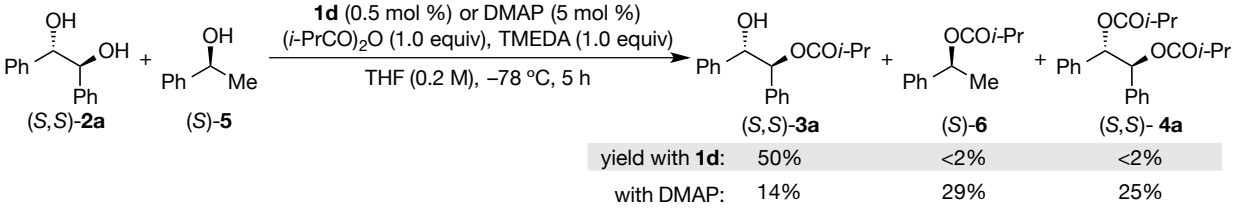
・Selective acylation

When a diol is subjected to monoacylation, suppression of the diacylated product (over-acylation) becomes a significant issue. In the ideal kinetic resolution of diols, the monoacylated product should show high selectivity regardless of the *d*,*l*-1,2-diol structure. In other words, the reaction rate of the first acylation step should be much faster than that of the second acylation step. Our catalyst can evidently recognize the 1,2-diol moiety and accelerate the first monoacylation step. We performed a competitive experiment with (*S*,*S*)-**2a** and (*S*)-**5** (the fast-reacting enantiomer in the kinetic resolution of racemic alcohol **2a** or **5** with **1d**)[75] in the presence of 0.5 mol % catalyst **1d**, 1.0 equiv of isobutyric anhydride, and 1.0 equiv of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) in THF (0.2 M) at –78 ºC for 5 h (Scheme 4a). Although a hydroxy group of (*S*,*S*)-**2a** was thought to be more sterically hindered than that of (*S*)-**5**, only the selective monoacylation of (*S*,*S*)-**2a** proceeded to afford (*S*,*S*)-**3a**, and (*S*)-**6** was not detected. For comparison, we performed the same reaction with 5 mol % of DMAP.[76] Acylation of (*S,S*)-**2a** and (*S*)-**5** proceeded to give a mixture of (*S,S*)-**3a** (14% yield) and (*S*)-**6** (29% yield). Furthermore, significant amount of diacylate (*S,S*)-**4a** was obtained (25% yield). This control experiment strongly suggested that monoacylation of 1,2-diol using **1d** proceeded much faster than that of a monool.

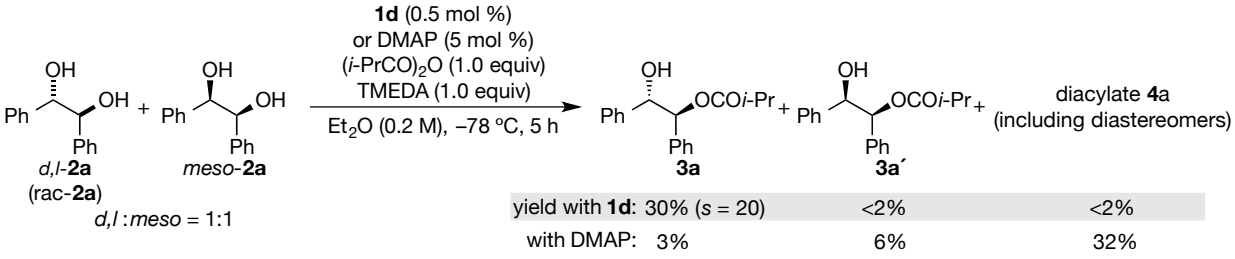
Surprisingly, catalyst **1d** can adequately recognize not only a diol unit but also its diastereomers (Scheme 4b). Although the acylation of two diastereomers, *d,l*-**2a** and *meso*-**2a** (*d,l*:*meso* = 1:1), with 5 mol % of DMAP under slightly modified reaction conditions (1.0 equiv of isobutyric anhydride, 1.0 equiv of TMEDA in Et_2O (0.2 M)[77] for 5 h) gave almost the same ratio of two diastereomers of monoacylate (**3a** and **3a´**) in quite low yields and considerable amount of diacylates **4a**, the use of **1d** only gave **3a** (30% yield) with high enantioselectivity (*s* = 20) as a sole product. It is quite difficult to separate a 1:1 mixture of *d,l*- and *meso*-1,2-diols. Nevertheless, this catalytic process with **1d** allows the reaction with *d*,*l*-diol selectively in the presence of structurally similar *meso*-1,2-diol.

Scheme 4. Catalytic accelerating effect of *d,l*-1,2-diol over monool and *meso*-diol[a–e]

a Selective acylation of 1,2-diol in the presence of a secondary carbinol



b Competitive and enantioelective acylation of the 1,2-diol



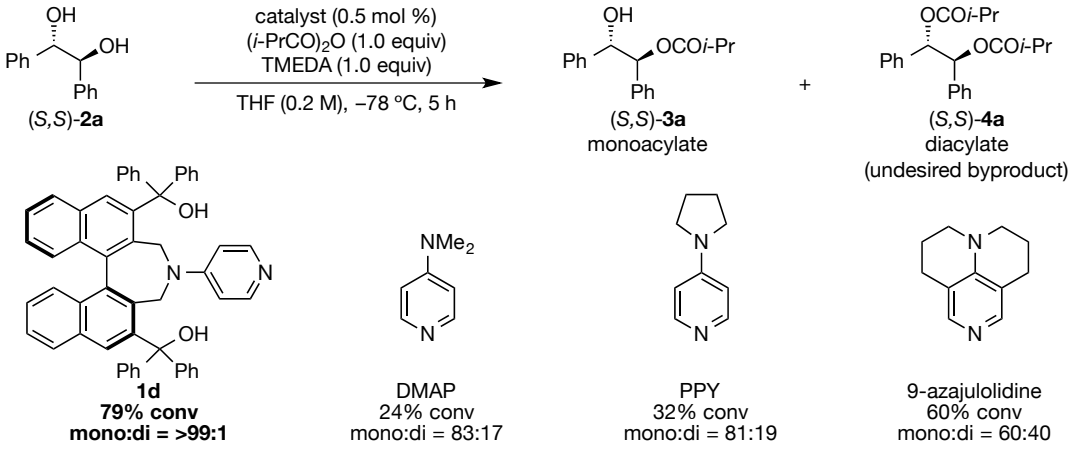
[a] Performed on a 0.15 mmol scale under an argon atmosphere. [b] Conversions (±2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c] Product yields were determined by ^{1}H NMR spectra using 2-methoxynaphthalene as an internal standard. [d] The er values (±1%) were determined by the chiral HPLC analysis of unpurified mixtures. [e] The *s*-factors were calculated by Kagan's equation.

・Comparison of catalytic activity

To examine the enhancement of the reaction rate by catalyst **1d**, we next examined the catalytic activity of this reaction system by comparison with commercially available pyridine-based nucleophilic catalysts (Scheme 5). With the use of 0.5 mol % of catalyst **1d**, the monoacylation of (*S*,*S*)-**2a**, which is the fast-reacting enantiomer (if we exclude the process of kinetic resolution), proceeded in 79% conversion after 5 h and perfectly suppressed over-acylation. The use of 0.5 mol % of DMAP and PPY gave low conversions (24% and 32%, respectively) with a considerable

amount of diacylate (*S,S*)-**4a** under the identical reaction conditions. Despite the stoichiometric reaction conditions (1.0 equiv of $(i\text{-PrCO})_2O$), a large amount of undesirable diacylate was obtained by the use of 9-azajulolidine, which is known to be a highly active pyridine-based nucleophilic catalyst[78-81] (60% conv, mono:di = 60:40). These results clearly showed that catalyst **1d** selectively accelerated the monoacylation step.

Scheme 5. Comparison of various nucleophilic catalysts in monoacylation of (*S*,*S*)-2a[a], [b]

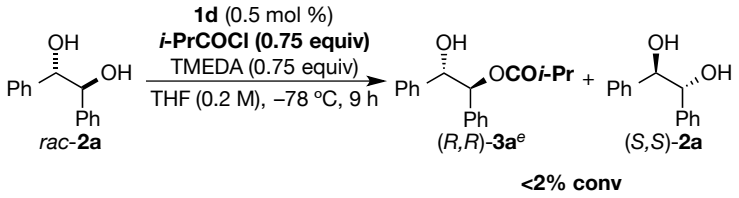


[a] Performed on a 0.30 mmol scale under an argon atmosphere. [b] Conversions (±2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures.

・Effect of leaving group of acylating group

The results of several control experiments regarding the effect of hydrogen bonding (Scheme 2, 3, and 4) strongly support the notion that hydroxy groups on **1d** and two hydroxy groups on the substrate play an important role in the rate acceleration and high enantioselectivity. Furthermore, in the kinetic resolution of previous chapter, we stated that the leaving group of an acylating reagent strongly affected the enantioselectivity in the acylative kinetic resolution of secondary carbinol. We also investigated the benefits of this acylating reagent in this reaction (Scheme 6). The use of 0.75 equiv of isobutyric chloride instead of isobutyric anhydride under otherwise optimal conditions resulted in almost no conversion with a very low enantioselectivity[82] (<2% conv). This implies that the leaving group of acylating reagents ($^-$OCO*i*-Pr vs $^-$Cl), which consist of the counteranion of *N*-acylpyridinium ion in the transition state, strongly affects the reactivity and enantioselectivity in this kinetic resolution process.[75,83]

Scheme 6. Investigation of the effect of an acylating reagent[a–d]



[a] Performed on a 0.300 mmol scale under an argon atmosphere. [b] Conversions (±2%) were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [c] The er values (±1%) were determined by the chiral HPLC analysis of unpurified mixtures. [d] The er value of **3a** was undetectable.

・Consideration of the transition state

To summarize these observations, and after considering the explanations offered by Spivey,[84] Zipse,[85] and Kawabata,[86,87] we speculated that the transition state involves several hydrogen bonding networks among the *tert*-alcohol unit of the catalyst, the *ortho*-hydrogen of the pyridine moiety, the carboxylate anion, and a hydroxy group of the substrate (Figure 3). After the formation of appropriate hydrogen bonding networks in the favored transition state, the more acidic proton of the hydroxy group (activated by a neighboring hydroxy group through *intermolecular* hydrogen bonding) of the substrate is deprotonated by the closest carboxylate anion fixed by the catalyst, and thus another hydroxy group is acylated to give (*S*,*S*)-**3a**. In the disfavored transition state, steric repulsion between the phenyl group (drawn Ph as blue in Figure 3) and the isopropyl group of acylating agent would be dominant. These transition states may explain all of the observations obtained in the control experiments at present stage. Although computational calculations to elucidate the reaction mechanism and the high selectivity in the transformations are currently conducted, the enormous numbers of possibilities of the alignments prevent us from drawing a conclusion. These results will be reported elsewhere. The hydrogen bonding interactions in acylative kinetic resolution were already studied in detail by Miller (H-bonds between a peptide-based imidazole catalyst and a vicinal aminoalcohol[88,89] or carbinol[90]) and Seidel (H-bonds between a chiral thiourea-DMAP combination catalyst and a vicinal amine)[91]. The present study also clearly demonstrated the utility of the hydrogen bonding network in designing enantioselective acyl-transfer reactions.

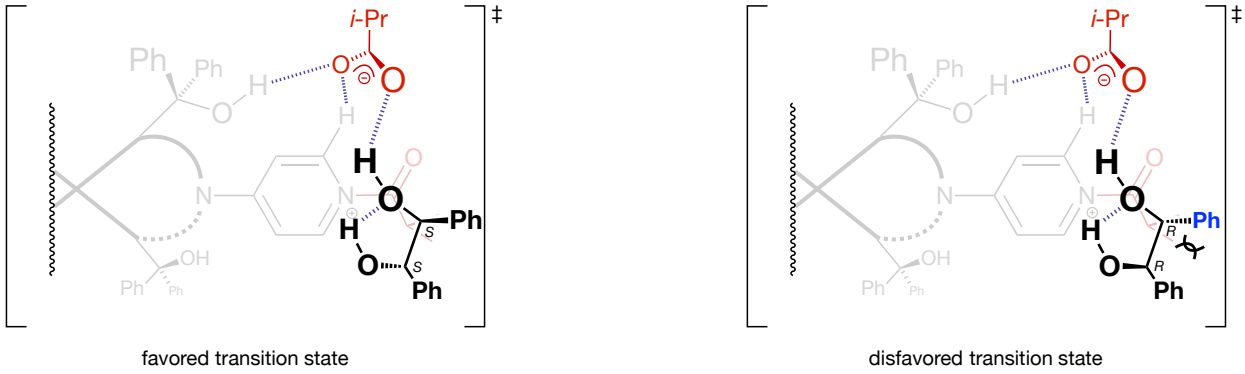
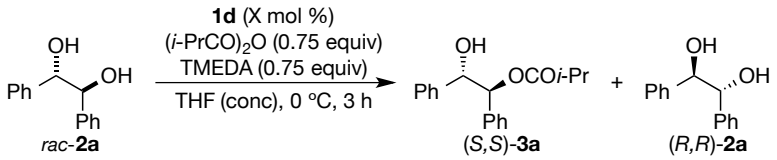


Figure 3. Postulated transition states

6-6. Multigram Scale Experiment

In principle, a practical-scale reaction should offer a very low catalyst loading, a higher substrate concentration (to reduce the amount of solvent needed), a high *s*-factor (*s* >20),[92] and an easily achievable low reaction temperature. As previously mentioned, catalyst **1d** combined high catalytic activity and excellent chiral recognition for *d,l*-1,2-diols (0.5 mol % of **1d**, THF (0.2 M), –78 ºC, 9 h, Figure 2). Hence, we reexamined the reaction conditions for a practical-scale reaction with maintaining synthetically useful *s*-factor (s > 20).[92] We began by reducing the catalyst loading in THF (0.1 M) at 0 °C for 3 h (Table 5, entries 1–3). The results with 0.1 mol % of catalyst **1d** showed good conversion and a good *s*-factor (47% conv; *s* = 26.3; entry 2), and the reaction with 0.05 mol % of catalyst **1d** also proceeded smoothly while maintaining a satisfactory *s*-factor (41% conv; *s* = 21.6; entry 3). Since the use of 0.1 mol % of **1d** was thought to be optimal with respect to both conversion and *s*-factor, we next performed screening reactions regarding the substrate concentration and reaction time (entries 4–6). A higher substrate concentration (0.5 and 1.0 M) did not significantly affect the *s*-factor (entries 4 and 5). Finally, the reaction within a shorter time (0.5 h) under otherwise identical conditions gave monoacylate **3a** and unreacted enantio-enriched **2a** in 52% conversion with a high *s*-factor (*s* = 21.0, entry 6). For a practical-scale reaction, the optimized conditions were determined to be 0.1 mol % of catalyst **1d**, 0.75 equiv of isobutyric anhydride, 0.75 equiv of TMEDA in THF (1.0 M) at 0 ºC for 0.5 h.

Table 5. Exploration of the conditions for a practical-scale reaction[a, b]

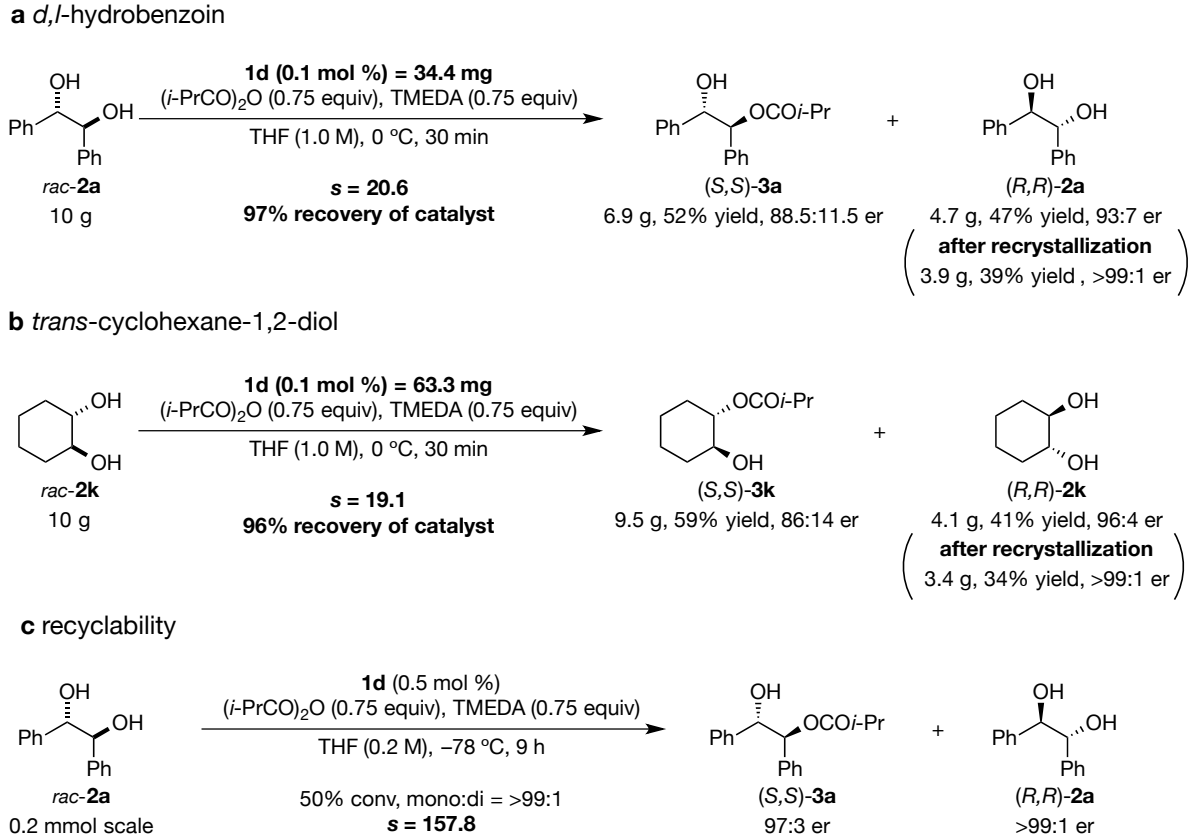


Entry	X (mol %)	Conc. (M)	Conv (%)[c]	er of **3a**[d]	er of **2a**[d]	*s*[e]
1	0.5	0.1	56	88:12	99:1	31.9
2	0.1	0.1	47	91:9	91:9	26.3
3	0.05	0.1	41	91.5:8.5	84:16	21.6
4	0.1	0.5	58	85:15	99:1	25.9
5	0.1	1.0	56	86:14	97:3	21.6
6[f]	0.1	1.0	52	88:12	93:7	21.0

[a] Performed on a 0.1–0.4 mmol scale under an argon atmosphere. [b] Mono/di ratios were >98:2 in all cases. [c] Conversions (±2%) and mono/di ratios were determined by the analysis of ^{1}H NMR spectra of unpurified mixtures. [d] The er values (±1%) were determined by the chiral HPLC analysis of unpurified mixtures. [e] The *s*-factors were calculated by Kagan's equation. [f] Stirred for 0.5 h.

With the optimized conditions for a practical-scale reaction in hand, we carried out the kinetic resolution of two different substrates on a multigram scale (Scheme 7a and b). The use of 10 grams of racemic hydrobenzoin **2a** under the practical-scale conditions (only 0.1 mol % of **1d** = 34.4 mg was used) gave the monoacylate **3a** in 52% yield with 88.5:11.5 er along with the recovery of **2a** in 47% yield with 93:7 er (purified by column chromatography on silica gel). Recrystallization of recovered **2a** improved the enantiomeric ratio (>99:1 er) in 39% yield. Furthermore, catalyst **1d** was recovered in 97% yield. We also conducted a 10 gram-scale reaction with *trans*-cyclohexane-1,2-diol **2k** to give monoacylate **3k** in 59% yield with 86:14 er along with the recovery of **2k** in 34% yield with >99:1 er (after chromatographic separation and recrystallization), and recovered catalyst **1d** in 96% yield. Both reactions clearly demonstrated the near-perfect selectivity of monoacylation (mono:di = >99:1) and synthetically acceptable *s*-factors[92] (*s* = 20.6 and 19.1, respectively) even when the reaction was carried out on a multigram scale reaction. Furthermore, the recyclability of **1d** was confirmed by performing the kinetic resolution of racemic hydrobenzoin **2a** (0.3 mmol scale) under the optimal reaction conditions, which showed almost the same *s*-factor (*s* = 157.8), selectivity of the monoacylate, and conversion (Scheme 7c vs Figure 2).

Scheme 7. Kinetic resolution on a multigram scale and recyclability



6-7. Application to acylative desymmetrization of *meso*-1,2-diols

Our catalyst system could be applied to acylative desymmetrization of *meso*-1,2-diols (Figure 4). After tuning of the reaction conditions, we explored scope and limitation of this reaction under optimal reaction conditions (in the presence of 0.1 mol % of **1d**, 1.3 equiv of isobutyric anhydride, and 1.3 equiv of triethylamine in 0.1 M *t*-BuOMe at –20 ºC for 3 h). The reactions with *meso*-hydrobenzoin derivatives **13a**−**d** gave the products in good yields with excellent enantioselectivities (64−79% isolated yields of **14a**−**d** with 95:5 to 97:3 er), and the chemoselectivities of these monoacylates were synthetically useful (**14**/**15** = 5.3−14.6). Acyclic diols with alkyl-, allyl-, and heteroatom functionalized alkyl substituents **13e**−**j** could be subjected to this catalytic system to afford monoacylates **14e**−**j** in moderate to good yields with high enantioselectivities (46−85% isolated yields of **14e**−**j** with 86:14 to 97:3 er). Among them, substrates **13i** and **13j** with electron-withdrawing groups gave significant amounts of diacylates **15i** and **15j**; the reason for this formation of undesirable diacylates is not yet clear. Next, we tested cyclic substrates **13k**−**p**. The enantioselective desymmetrization only proceeded with six-membered-ring 1,2-diols **13m** and **13n** (79% isolated yield of 3m with 97:3 er, and 86% isolated yield of 3n with 94:6 er), and the reactions of other cyclic substrates **13k**, **13l**, **13o**, and **13p** under

the optimal conditions only afforded racemate of monoacylates, albeit with high chemoselectivity (**14**/**15** = 7.3−14.7). A possible explanation for this result may be intramolecular acyl migration (racemization) during the reaction (3 h).

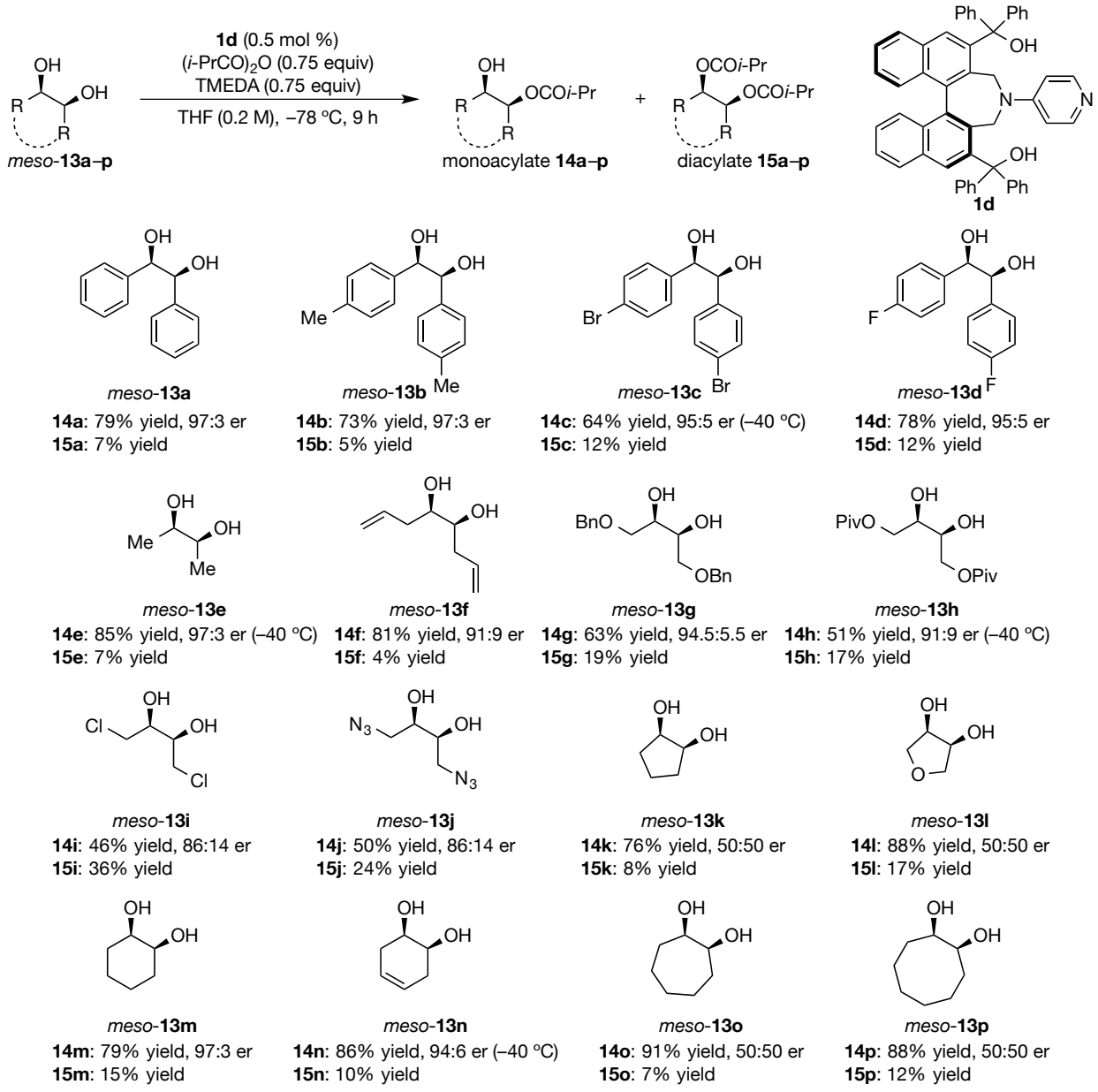


Figure 4. Acylative desymmetrization of *meso*-1,2-diols with **1d**

6-8. Conclusion

We have developed a highly accelerated kinetic resolution of diverse *d*,*l*-1,2-diols with a small amount of high-performance chiral DMAP derivatives (0.1–0.5 mol %). Several key experiments revealed that such transformations were due to a hydrogen bonding network among *tert*-alcohol units and the *ortho*-hydrogen of a pyridine moiety of the catalyst, the carboxylate anion generated

by the acylating reagent, and the 1,2-diol moiety of the substrate. The current catalytic system allows the use of hydrobenzoin derivatives with various functional groups, *trans*-1,2-cyclic diols, and acyclic dialkyl-substituted 1,2-diols with an excellent selectivity of monoacylation and high *s*-factors (up to s = 180.3, 22 examples). The multigram scale reaction using less than 0.1 mol % of the catalyst in the milder conditions also proceeded smoothly with an excellent selectivity of monoacylation and synthetically acceptable *s*-factors (**2a**: s = 20.6 and **2k**: 19.1, respectively) under reoptimized conditions for a practical-scale. Furthermore, the catalyst could be easily recovered in >96% yield and recycled without a loss of catalytic activity or enantioselectivity. We believe that the present method to access highly enantio-enriched 1,2-diols with catalyst **1d** is extremely valuable from a viewpoint of process chemistry for the pharmaceutical productions.

6-9. Experimental Section and Analytical Data

General

Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian 600 MR (^{1}H 600 MHz, ^{13}C 150 MHz), Varian 400 MR (^{13}C 100 MHz) or JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometers. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin =quintet, sext = sextet, sep = septet, b = broad, m = multiplet), coupling constants, and integration. Chemical shifts for ^{13}C NMR were reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.16 ppm) with complete proton decoupling. Infrared (IR) spectra were recorded on JASCO FT/IR-4100 spectrophotometer, Vmax in cm^{-1}. High-resolution mass spectrometry was performed on JEOL JMS-700 MStation (FAB-MS and EI-MS), Agilent 6520 Accurate Mass Q-TOF LC/MS (ESI-MS) or Thermo Fisher Scientific EXACTIVE Plus (ESI-MS). Optical rotations were measured on a JASCO DIP-1000. Melting points were recorded on a SANSYO SMP-300. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC) Shimadzu chromatograph (DAICEL CHIRALPAK® IA-3 (4.6 × 150 mm), DAICEL CHIRALPAK® AS-3 (4.6 × 150 mm), DICEL CHIRALCEL OJ-H (4.6 × 250 mm), and DICEL CHIRALCEL® OD-H (4.6 × 250 mm)) in comparison with authentic racemic samples. Column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm) purchased from KANTO CHEMICAL CO.,INC. Celitre®503RV [Celite] was purchased from NAKARAI TESQUE, INC. Unless otherwise noted all reactions were carried out under argon atmosphere in oven-dried screw-top test tube or flame-dried glassware.

Materials

All reagents were obtained commercial sources and used as received unless otherwise noted. Dry tetrahydrofuran [THF], dry diethyl ether [Et_2O], diethyl ether [Et_2O], *t*-amyl alcohol, 1,4-dioxane, dimethyl sulfoxide [DMSO], ethanol [EtOH], 4-pyrrolidinopyridine [PPY], triethylamine [Et_3N], *N*-ethyldiisopropylamine [*i*-Pr_2NEt], pyridine, 1-methylimidazole [NMI], *N*,*N*,*N*′,*N*′-tetramethylethylenediamine [TMEDA], tripotassium phosphate [K_3PO_4], potassium acetate [KOAc], 4-bromobenzaldehyde, cycloheptene, 1,2-dibromoethane, *p*-toluenesulfonic acid monohydrate [TsOH•H_2O], sodium sulfide nonahydrate [Na_2S•$9H_2O$], L-(+)-dimethyl tartrate, *d,l*-tartaric acid, 2,2-dimethoxypropane, benzyl alcohol [BnOH], silver oxide [Ag_2O], and 1,2-diphenylethane-1,2-diol were purchased from Wako Pure Chemical Industries, Ltd. Dry diisopropyl ether [*i*-Pr_2O], 1,8-bis(dimethylamino)naphthalene [proton-sponge], sodium hydroxide [NaOH], tetrabutylammonium iodide [*n*-Bu_4NI], *trans*-cyclohexane-1,2-diol *rac*-**2k**, *trans*-cyclopentane-1,2-diol *rac*-**2p**, cyclohexa-1,4-diene, and *cis*-1,2-epoxycyclooctane were purchased from Sigma-ALDRICH Japan. Ethyl acetate [EtOAc], methanol [MeOH], dichloromethane [CH_2Cl_2], toluene, benzene, cesium carbonate [Cs_2CO_3], potassium carbonate [K_2CO_3], hydrochloric acid aqueous solution [HCl], magnesium sulfate [$MgSO_4$], ammonium chloride [NH_4Cl], sodium thiosulfate [$Na_2S_2O_3$], copper (I) bromide [CuBr], benzyl bromide [BnBr], sodium bicarbonate [$NaHCO_3$] and molecular sieve 4A [MS4A] were purchased from NAKARAI TESQUE, INC. Hexane, dimethylformamide [DMF], chloroform [$CHCl_3$], 2-naphthtaldehyde, methyl 4-formylbenzoate, 3-bromobenzaldehyde, *n*-butyl lithium [*n*-BuLi], and copper(I) iodide [CuI] were purchased from KANTO CHEMICAL CO.,INC. Isobutyric anhydride [(*i*-$PrCO)_2O$], [*i*-PrCOCl], 9-azajulolidine, cyclopentyl methyl ether [CPME], *t*-butyl methyl ether [*t*-BuOMe], 1,8-diazabicyclo[5,4,0]-7-undecene [DBU], Phenyllithium [PhLi], trifluoromethanesulfonic acid [TfOH], *d,l*-hydrobenzoin *rac*-**2a**, DL-1,4-dichloro-2,3-butanediol, titanium(IV) chloride [$TiCl_4$], 1-naphthtaldehyde, racemic benzoin **9**, 4-methylbenzaldehyde, 4-(trifluoromethyl)benzaldehyde, methyl iodide [MeI], *m*-chloroperoxybenzoic acid [*m*CPBA], *d,l*-dithiothreitol, D-(–)-dimethyl tartrate, sodium borohydride [$NaBH_4$], sodium hydride [NaH], methylmagnesium bromide [MeMgBr], vinylmagnesium bromide, and trimethylsulfonium iodide [$Me_3S^+I^-$] were purchased from Tokyo Chemical Industry Co.,Ltd. *p*-Toluenesulfonyl chloride [TsCl] was purchased from Alfa Aesar. Acetone was purchased from Japan Alcohol Trading CO.,LTD. Hexane, DMF, EtOAc, CPME, *t*-BuOMe, DMF, and *t*-amyl alcohol were used after dehydration process with MS4A. CH_2Cl_2, (*i*-$PrCO)_2O$, Et_3N, *i*-Pr_2NEt, and TMEDA were distilled over CaH_2. Toluene was distilled over CaH_2 and stored in the presence of MS4A. MS4A was used after drying process with heat gun under reduced pressure. *d,l*-Dimethyl tartarate was prepared by mixing same amount of L-(+)-dimethyl tartrate and D-(–)-dimethyl tartrate.

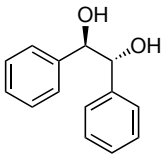
Experimental procedures for synthesis of substrates **2b**–**j**, **2l**, **2n**–**o**, **2q**–**w**, **7**, and **8** were recorded on the section of "synthesis of substrate".

Racemic sample of monoacylate and diacylate were synthesized by general acylation method with 5 mol % of DMAP, 1.5 equiv of $(i\text{-PrCO})_2O$, and 1.5 equiv of Et_3N) in CH_2Cl_2. To determine enantiomeric ratio, benzoate was synthesized by general benzoylation method with 1.5 equiv of TMEDA and 1.5 equiv of benzoyl chloride [BzCl] in CH_2Cl_2.

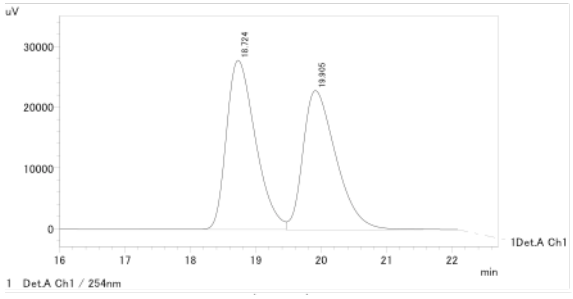
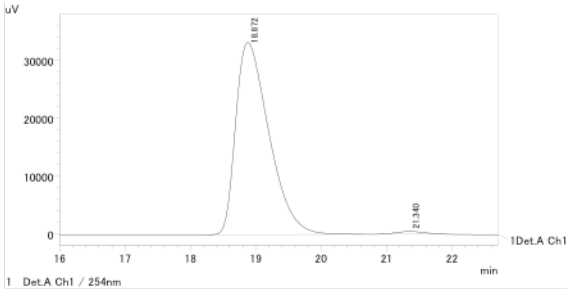
General procedure for acylative kinetic resolution with 1d: In a dry screw-top test tube, to a solution of substrate (1.0 equiv), TMEDA (0.75 equiv), and stock solution of **1d** (0.5 mol %) in THF (0.200 M) was added $(i\text{-PrCO})_2O$ (0.75 equiv) at –78 ºC. The reaction mixture was stirred for 9 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexan/EtOAc or hexane/Et_2O adjusted $R_f = 0.5$ (unreacted substrate)) to give the crude mixture. The conversion and ratio of mono/diacylate were determined by ^{1}H NMR analysis of the crude mixture. The enantiomeric ratios of monoacylate and recovered substrate were determined by chiral HPLC analysis of the crude mixture. In the case of using a substrate without chromophores, benzoylation of isolated monoacylate and recovered substrate were conducted. The monobenzoate and dibenzoate was used to determine of the enantiomeric ratios by chiral HPLC analysis.

Analytical data of for 2a–v, 3a–v, and 4a–v (Figure 2)

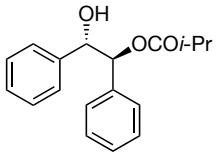
(1*R*,2*R*)-1,2-diphenylethane-1,2-diol (2a)[38]



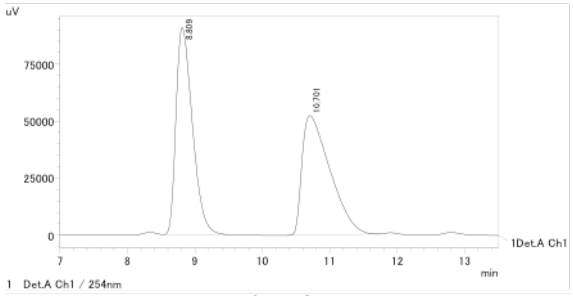
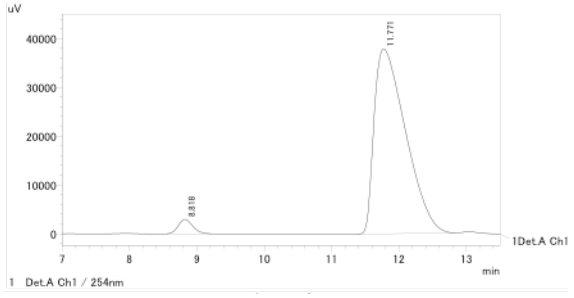
48% recovery from kinetic resolution of *rac*-**2a** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 18.9 min (major) and T_R = 21.3 min (minor), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$+0.01% TMS) δ 7.29–7.19 (m, 6H), 7.17–7.09 (m, 4H), 4.72 (s, 2H), 2.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 128.2, 128.0, 127.1, 79.2; IR (KBr) 3499, 3395, 2895, 1452, 1198, 1045, 777, 706, 694 cm^{-1}. Optical rotation was shown in the following section of "Kinetic resolution of *d,l*-hydrobenzoin on multigram scale (Scheme 7a)".

Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	18.872	1172564	98.787
2	19.905	632317	50.202	2	21.340	14395	1.213

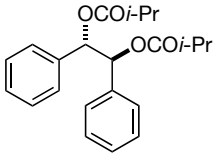
(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl isobutyrate (3a)[63]



52% conversion from kinetic resolution of *rac*-**2a** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.8 min (minor) and T_R = 11.8 min (major), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$+0.01% TMS) δ 7.25–7.20 (m, 6H), 7.19–7.09 (m, 4H), 5.85 (d, *J* = 7.4 Hz, 1H), 4.94 (dd, *J* = 7.4, 3.6 Hz, 1H), 2.64 (sep., *J* = 7.1 Hz, 1H), 2.49 (d, *J* =3.6 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 139.2, 137.2, 128.2, 127.1, 79.8, 34.2, 19.1, 19.0; Optical rotation was shown in the following section of "Kinetic resolution of *d,l*-hydrobenzoin on multigram scale (Scheme 7a)".

Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.818	43462	3.406
2	10.701	1505824	49.635	2	11.771	1232480	96.594

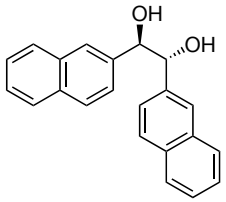
1,2-Diphenylethane-1,2-diyl bis(2-methylpropanoate) (4a)



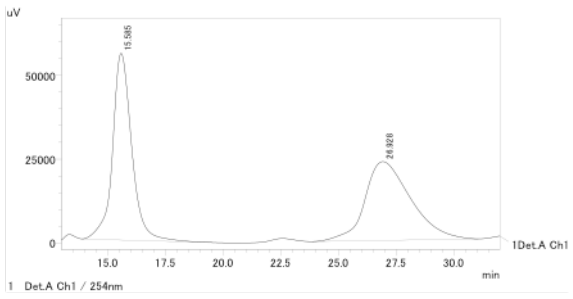
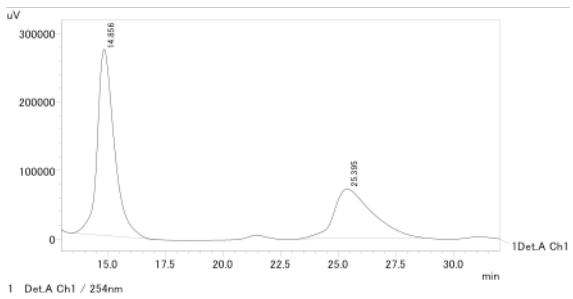
<2% conversion from kinetic resolution of *rac*-**2a** under the optimal conditions. Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.16 (m, 6H), 7.15–7.07 (m, 4H), 6.05 (s, 2H), 2.59 (sep., J = 6.9 Hz, 2H), 1.15 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 136.6, 128.4, 128.3, 127.5, 77.1, 34.2, 19.0 (2); IR (KBr) 2976, 2938, 1736, 1456, 1198, 1151, 773, 770 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{22}H_{27}O_4$ 355.1904, found 355.1886; mp 73.1–74.0 ºC;

Enantiomeric ratio and optical rotation was not analyzed in this reaction.

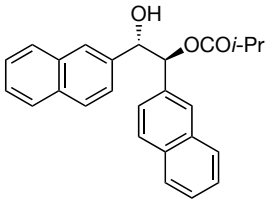
(1*R*,2*R*)-1,2-Di(naphthalen-2-yl)ethane-1,2-diol (2b)



52% recovery from kinetic resolution of *rac*-**2b** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 50/50, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 14.9 min (major) and T_R = 25.4 min (minor), 62.5:37.5 er; ^{1}H NMR (400 MHz, DMSO-D6) δ 7.83–7.77 (m, 2H), 7.77–7.71 (m, 2H), 7.71–7.65 (m, 4H), 7.45–7.38 (m, 4H), 7.32 (dd, J = 8.5, 1.6 Hz, 2H), 5.54 (bs, 2H), 4.49 (s, 2H); ^{13}C NMR (100 MHz, DMSO-D6) δ 140.2, 132.5, 132.2, 127.7, 127.4, 126.6, 125.8, 125.8, 125.7, 125.4, 77.5; IR (KBr) 3197, 1599, 1361, 1120, 1074, 1032, 829, 781, 741 cm^{-1}; HRMS (FAB$^+$) $[M+Na]^+$ calculated for $C_{22}H_{18}O_2Na$ 337.1998, found 337.1221; mp 210.9–211.3 ºC; $[\alpha]^{24}_D$ +20.0 (*c* 1.01, THF, 62.5:37.5 er, (1*R*, 2*R*)-configuration) [lit[38] $[\alpha]^{29}_D$ +201.4 [*c* 1.0, THF, (1*R*, 2*R*)-configuration, 95% ee]].

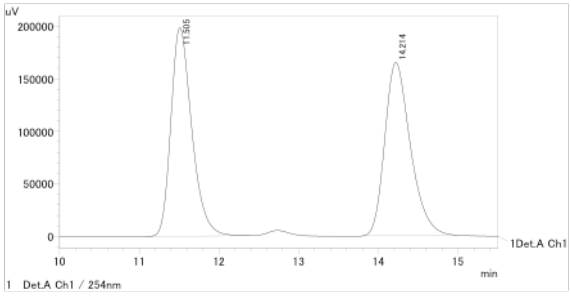
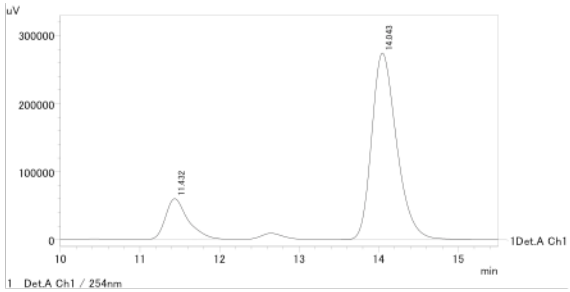
Racemic sample of **2b**				(1*R*,2*R*)-**2b**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.585	3232530	49.897	1	14.856	13994455	62.478
2	26.928	3245863	50.103	2	25.395	8404612	37.522

(1*S*,2*S*)-2-Hydroxy-1,2-di(naphthalen-2-yl)ethyl isobutyrate (3b)[38]

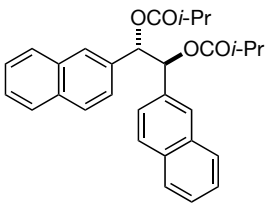


39% conversion from kinetic resolution of *rac*-**2b** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 90/10, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 11.4 min (minor) and T_R = 14.0 min (major), 84:16 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.65 (m, 8H), 7.47–7.39 (m, 4H), 7.29–7.23 (m, 2H), 6.15 (d, *J* = 6.9 Hz, 1H), 5.23 (dd, *J* = 6.9, 3.2 Hz, 1H), 2.73–2.61 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 136.7, 134.6, 133.3, 133.2, 133.1, 128.2 (2), 128.0, 127.8, 126.7, 126.4, 126.3, 126.3, 126.2 (2), 125.0, 124.9, 79.7, 77.2, 34.3, 19.1, 19.0; IR (KBr) 3493, 3048, 2980, 1705, 1398, 1261, 1078, 829 cm^{-1}; HRMS (FAB$^+$) $[M+Na]^+$ calculated for $C_{26}H_{24}O_3Na$ 407.1617, found 407.1605; $[\alpha]^{23}_D$ +0.68 (*c* 1.01, THF, 84:16 er, (1*S*, 2*S*)-configuration).

Racemic sample of **3b**				(1*S*,2*S*)-**3b**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	11.505	3619962	49.536	1	11.432	1132119	15.965
2	14.214	3687781	50.464	2	14.043	5959032	84.035

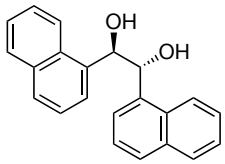
1,2-Di(naphthalen-2-yl)ethane-1,2-diyl bis(2-methylpropanoate) (4b)



9% conversion from kinetic resolution of *rac*-**2b** under the optimal conditions.

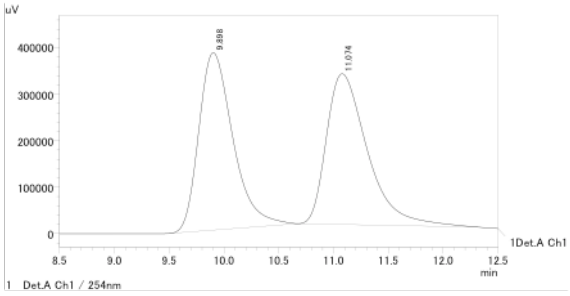
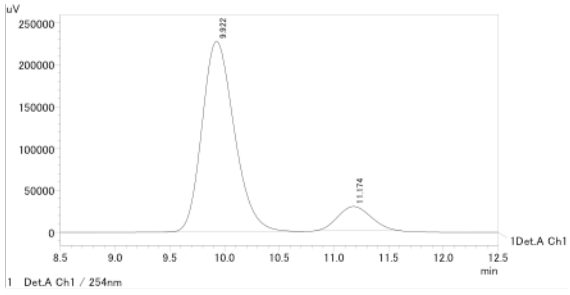
Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.64 (m, 8H), 7.46–7.38 (m, 4H), 7.27 (dd, *J* = 8.5, 1.6 Hz, 2H), 6.35 (s, 2H), 2.62 (sep., *J* = 7.2 Hz, 2H), 1.17 (d, *J* = 7.2 Hz, 6H), 1.15 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 134.0, 133.3, 133.0, 128.2, 128.1, 127.7, 127.2, 126.4, 126.3, 125.1, 77.1, 34.3, 19.0; IR (KBr) 3049, 2978, 2876, 1734, 1466, 1192, 1148, 1113, 999, 856, 752 cm^{-1}; HRMS (EI$^+$) $[M]^+$ calculated for $C_{30}H_{30}O_4$ 454.2171, found 454.2168; mp 112.5–113.1 ºC.

(1*R*,2*R*)-1,2-Di(naphthalen-1-yl)ethane-1,2-diol (2c)[38]

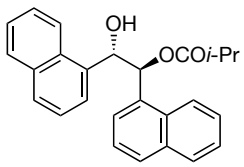


56% recovery from kinetic resolution of *rac*-**2c** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 85/15, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 9.9 min (major) and T_R = 11.2 min (minor), 88:12 er; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.78 (s, 2H), 2.97 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.2, 133.8, 131.0, 128.8, 128.8, 125.9, 125.5, 125.3, 125.0, 123.1, 74.5; IR (KBr) 3356, 3049, 1597, 1514, 1414, 1352, 1171, 1063, 976, 800, 773 cm^{-1}; $[\alpha]^{24}_D$ +40.7 (*c* 0.99, THF, 88:12 er, (1*R*, 2*R*)-configuration) [lit[38] $[\alpha]^{29}_D$ +64.5 [*c* 0.86, THF, (1*R*, 2*R*)-configuration, 97% ee]].

Racemic sample of **2c**				(1*R*,2*R*)-**2c**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	9.898	8273858	49.471	1	9.922	4670921	88.273
2	11.074	8450897	50.529	2	11.174	620517	11.727

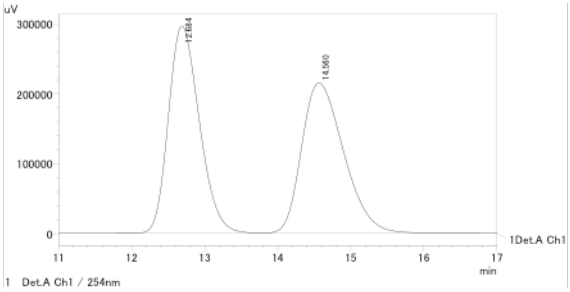
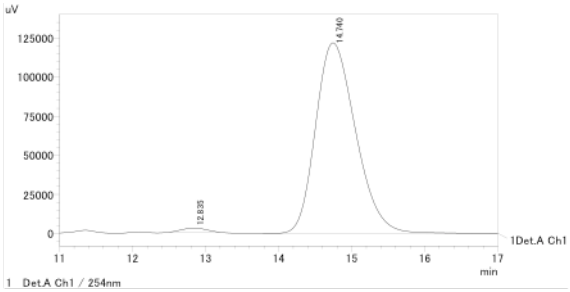
(1*S*,2*S*)-2-Hydroxy-1,2-di(naphthalen-1-yl)ethyl isobutyrate (3c)



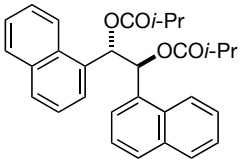
44% conversion from kinetic resolution of *rac*-**2c** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 12.8 min (minor) and T_R = 14.7 min (major), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.03 (m, 2H), 7.77–7.71 (m, 2H), 7.68 (t, *J* = 7.1 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.43–7.28 (m, 6H), 6.91 (d, *J* = 6.5 Hz, 1H), 5.93 (d, *J* = 6.5 Hz, 1H), 2.67 (sep., *J* = 7.2 Hz, 1H), 2.62 (bs, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 ºC) δ 176.1, 135.7, 134.0, 133.8, 131.2 (2), 129.0, 128.9, 126.2, 126.0, 125.8, 125.7, 125.6, 125.5, 125.0, 123.5, 123.5, 76.3, 74.2, 34.5, 19.1; IR (KBr) 3466, 3049, 2968, 1705, 1514, 1468, 1207, 1157, 773 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{26}H_{25}O_3$ 385.1798, found 385.1806; mp 110.2–111.0 ºC; $[\alpha]^{21}_D$ –35.5 (*c* 1.02, THF, 99:1 er, (1*S*,

2*S*)-configuration).

Racemic sample of **3c**				(1*S*,2*S*)-**3c**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	12.684	8758834	50.342	1	12.835	59767	1.273
2	14.560	8639906	49.658	2	14.740	4636241	98.727

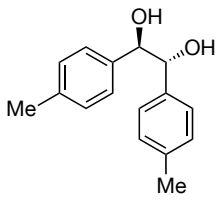
1,2-Di(naphthalen-1-yl)ethane-1,2-diyl bis(2-methylpropanoate) (4c)



<2% conversion from kinetic resolution of *rac*-**2c** under the optimal conditions.

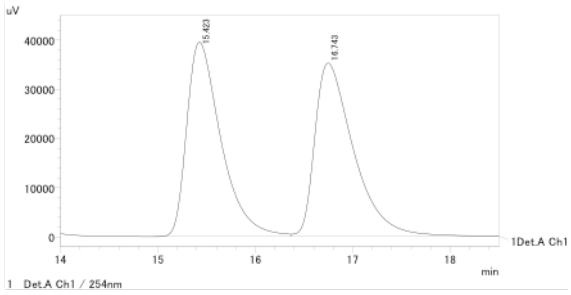
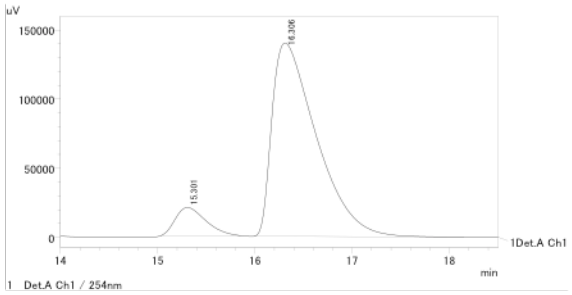
Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (bs, 2H), 7.72–7.65 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.41–7.32 (m, 6H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.07 (s, 2H), 2.62 (sep., *J* = 7.1 Hz, 2H), 1.18 (d, *J* = 7.1 Hz, 6H), 1.14 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 ºC) δ 176.0, 133.7, 132.6, 130.9, 129.2, 128.8, 126.5, 126.2, 125.6, 124.8, 123.6, 74.6, 34.3, 19.0 (2); R (KBr) 3051, 2970, 2933, 1732, 1470, 1389, 1256, 962, 799, 775 cm^{-1}; HRMS (EI$^+$) $[M]^+$ calculated for $C_{30}H_{30}O_4$ 454.2138, found 454.2141; mp 113.6–114.0 ºC.

(1*R*,2*R*)-1,2-Di-*p*-tolylethane-1,2-diol (2d)[38,93]

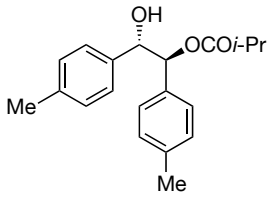


53% recovery from kinetic resolution of *rac*-**2d** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 15.3 min (minor) and T_R = 16.3 min (major), 91:9 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 8H), 4.67 (s, 2H), 2.72 (bs, 2H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.1, 129.0, 127.0, 78.9, 21.3; IR (KBr) 3337, 3030, 2914, 1518, 1422, 1204, 1059, 1013, 818 cm^{-1}; $[\alpha]^{23}_D$ +33.8 (*c* 0.99, EtOH, 91:9 er, (1*R*, 2*R*)-configuration) [lit[38] $[\alpha]^{28}_D$ +101.0 [*c* 1, EtOH, (1*R*, 2*R*)-configuration, 97% ee]]

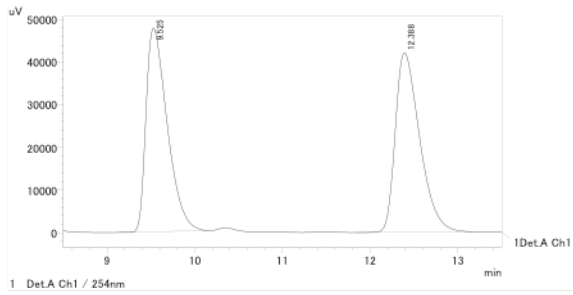
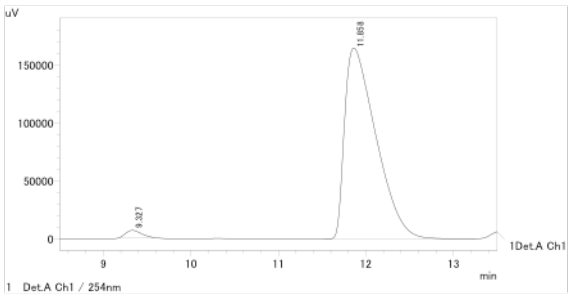
Racemic sample of **2d**				(1*R*,2*R*)-**2d**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.423	964410	49.608	1	15.301	439068	8.989
2	16.743	979665	50.392	2	16.306	4445665	91.011

(1*S*,2*S*)-2-Hydroxy-1,2-di-*p*-tolylethyl isobutyrate (3d)

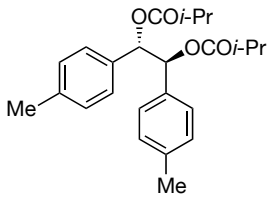


47% conversion from kinetic resolution of *rac*-**2d** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 9.3 min (minor) and T_R = 11.9 min (major), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–6.98 (m, 8H), 5.81 (d, *J* = 7.3 Hz, 1H), 4.89 (d, *J* = 7.3 Hz, 1H), 2.62 (sep., *J* = 7.0 Hz, 1H), 2.43 (bs, 1H), 2.29 (s, 3H), 2.29 (s, 3H), 1.16 (d, *J* = 7.6 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 137.9, 137.7, 136.3, 134.3, 129.0, 128.9, 127.2, 127.1, 79.7, 77.1, 34.3, 21.3 (2), 19.1, 19.0; IR (KBr) 3507, 2972, 2918, 1713, 1518, 1385, 1271, 1198, 1086, 995, 820, 733 cm^{-1}; HRMS (ESI) $[M+H]^+$ calculated for $C_{20}H_{25}O_3$ 313.1798, found 313.1802; mp 76.1–76.9 ºC; $[\alpha]^{21}_D$ +4.4 (*c* 1.00, EtOH, 98:2 er, (1*S*, 2*S*)-configuration).

Racemic sample of **3d**				(1*S*,2*S*)-**3d**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	9.525	800234	49.648	1	9.327	75224	1.806
2	12.388	811590	50.352	2	11.858	4090986	98.194

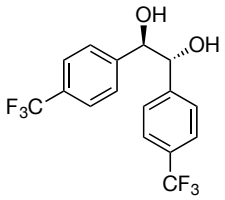
1,2-Di-*p*-tolylethane-1,2-diyl bis(2-methylpropanoate) (4d)



<2% conversion from kinetic resolution of *rac*-**2d** under the optimal conditions.

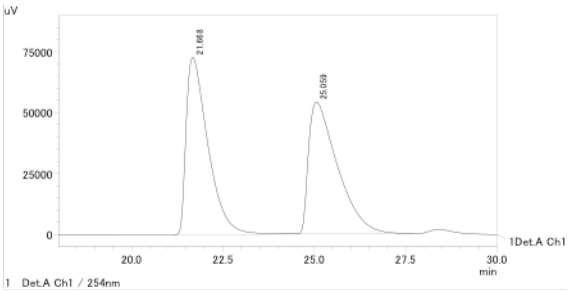
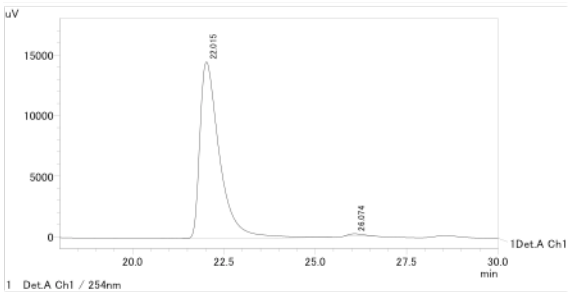
Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04–6.97 (m, 8H), 6.00 (s, 2H), 2.55 (sep., J = 6.8 Hz, 2H), 2.26 (s, 6H), 1.14 (d, J = 6.8 Hz, 6H), 1.12 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.0, 133.7, 129.0, 127.5, 77.0, 34.3, 21.3, 19.0 (2); IR (KBr) 2974, 2924, 1736, 1516, 1470, 1157, 821 cm^{-1}; HRMS (ESI^{+}) $[M+Na]^{+}$ calculated for $C_{24}H_{30}O_4Na$ 405.2036, found 405.2064; mp 58.5–58.8 ºC.

(1*R*,2*R*)-1,2-Bis(4-(trifluoromethyl)phenyl)ethane-1,2-diol (2e)[38,94,95]

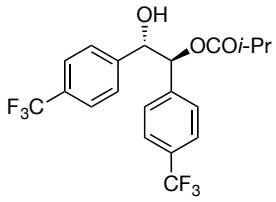


45% recovery from kinetic resolution of *rac*-**2e** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 97/3, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 22.0 min (major) and T_R = 26.1 min (minor), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.2 Hz, 4H), 7.25 (d, J = 8.2 Hz, 4H), 4.77 (s, 2H), 2.94–2.89 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.7, 130.8 (q, J = 32.4 Hz), 127.5, 125.4 (q, J = 3.9 Hz), 124.2 (q, J = 272.0 Hz), 78.6; IR (KBr) 3343, 1624, 1420, 1333, 1163, 1121, 1072, 839 cm^{-1}; $[\alpha]^{21}_{D}$ +43.6 (*c* 1.01, $CHCl_3$, 99:1 er, (1*R*, 2*R*)-configuration) [lit[38] $[\alpha]^{29}_{D}$ +67.8 [*c* 0.95, $CHCl_3$, (1*R*, 2*R*)-configuration, 95% ee]].

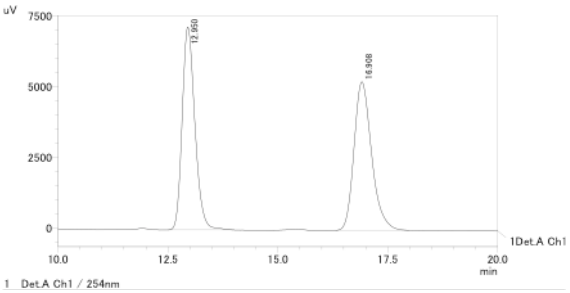
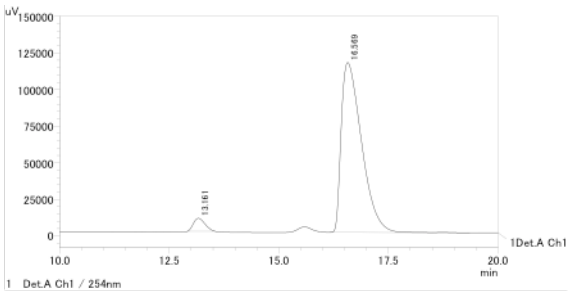
Racemic sample of **2e**				(1*R*,2*R*)-**2e**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	21.668	3023462	50.245	1	22.015	541672	99.008
2	25.059	2993995	49.755	2	26.074	5429	0.992

(1*S*,2*S*)-2-Hydroxy-1,2-bis(4-(trifluoromethyl)phenyl)ethyl isobutyrate (3e)

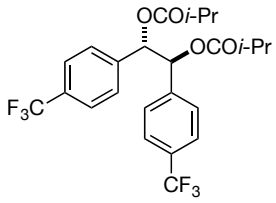


54% conversion from kinetic resolution of *rac*-**2e** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 97/3, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 13.2 min (minor) and T_R =16.6 min (major), 96:4 er; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.27 (*J* = 8.7 Hz, 2H), 7.25 (*J* = 8.7 Hz, 2H), 5.88 (d, *J* = 6.5 Hz, 1H), 5.03 (dd, *J* = 6.5, 3.5 Hz, 1H), 2.64 (sep., *J* = 7.0 Hz, 1H), 2.56 (d, *J* = 3.5 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.0, 142.7, 140.6, 130.7 (q, *J* = 32.4 Hz), 130.6 (q, *J* = 32.7 Hz) 127.6, 127.4, 125.5 (q, *J* = 4.6 Hz), 125.3 (q, *J* = 4.6 Hz), 124.0 (q, *J* = 272.4 Hz) (2), 78.6, 76.2, 34.2, 19.0, 18.9; IR (KBr) 3464, 2982, 1717, 1620, 1420, 1333, 1130, 1070, 847 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{20}H_{19}F_6O_3$ 421.1232, found 421.1215; mp 148.2–148.3 ºC; $[\alpha]^{23}_D$ –1.06 (*c* 1.01, $CHCl_3$, 96:4 er, (1*S*, 2*S*)-configuration).

Racemic sample of **3e**				(1*R*,2*R*)-**3e**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	12.950	144573	49.777	1	13.161	162461	4.156
2	16.908	145869	50.223	2	16.569	3746904	95.844

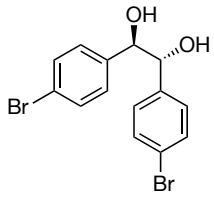
2-Hydroxy-1,2-bis(4-(trifluoromethyl)phenyl)ethyl isobutyrate (3e)



<2% conversion from kinetic resolution of *rac*-**2e** under the optimal conditions.

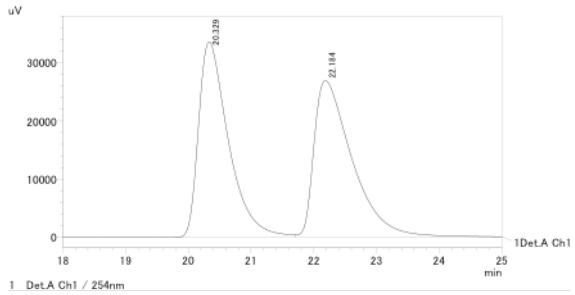
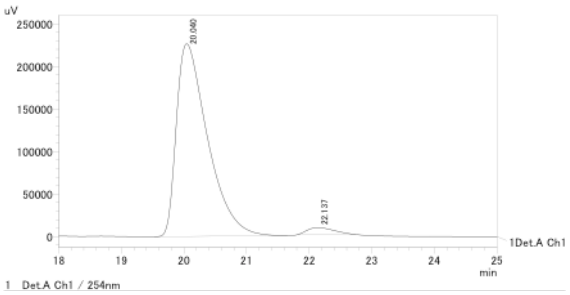
Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 4H), 7.25 (d, *J* = 8.8 Hz, 4H), 6.10 (s, 2H), 2.59 (sep., *J* = 7.0 Hz, 2H), 1.14 (d, *J* = 7.0 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 140.1, 130.9 (q, *J* = 32.4 Hz), 127.7, 125.5 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 272.0 Hz), 75.9, 34.1, 18.9 (2); IR (KBr) 2984, 1744, 1622, 1325, 1167, 1067, 1018, 855 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{24}H_{25}F_6O_4$ 491.1651, found 491.1652; mp 108.2–108.6 ºC.

(1*R*,2*R*)-1,2-Bis(4-bromophenyl)ethane-1,2-diol (2f)[38,93]

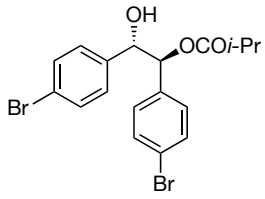


49% recovery from kinetic resolution of *rac*-**2f** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 20.0 min (major) and T_R = 22.1 min (minor), 97:3 er; ^{1}H NMR (400 MHz, Acetone-D6) δ 7.41–7.35 (m, 4H), 7.16–7.08 (m, 4H), 4.70 (s, 4H); ^{13}C NMR (100 MHz, Acetone-D6) δ 141.8, 131.4, 130.1, 121.3, 78.5; IR (KBr) 3318, 1591, 1489, 1204, 1069, 1009, 847, 820 cm^{-1}; $[\alpha]^{22}_D$ +68.1 (*c* 1.01, EtOH, 97:3 er, (1*R*, 2*R*)-configuration) [lit[38] $[\alpha]^{29}_D$ +80.9 [*c* 1.0, EtOH, (1*R*, 2*R*)-configuration, 98% ee]].

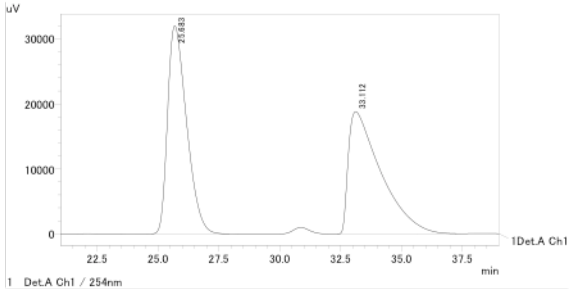
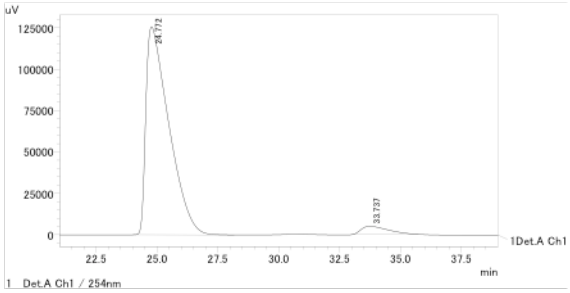
Racemic sample of **2f**				(1*R*,2*R*)-**2f**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	20.329	1111599	49.549	1	20.040	7845466	97.006
2	22.184	1131845	50.451	2	22.137	242122	2.994

(1*S*,2*S*)-1,2-Bis(4-bromophenyl)-2-hydroxyethyl isobutyrate (3f)

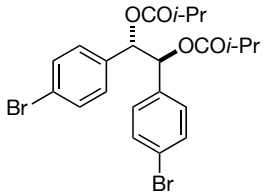


50% conversion from kinetic resolution of *rac*-**2f** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 24.8 min (major) and T_R = 33.7 min (minor), 95.5:4.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 4H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.72 (d, *J* = 7.3 Hz 1H), 4.86 (d, *J* = 7.3 Hz 1H), 2.63 (sep., *J* = 6.6 Hz, 1H), 2.54 (bs, 1H), 1.17 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 137.8, 135.8, 131.6, 131.5, 129.0, 128.8, 122.5, 122.3, 78.9, 76.3, 34.2, 19.0, 18.9; IR (KBr) 3476, 2976, 1713, 1489, 1406, 1072, 999, 831 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{18}H_{18}O_3Br_2Na$ 462.9515, found 462.9530; mp 129.9–130.3 ºC; $[\alpha]^{23}_D$ +7.8 (*c* 1.00, EtOH, 95.5:4.5 er, (1*S*, 2*S*)-configuration).

Racemic sample of **3f**				(1*S*,2*S*)-**3f**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	25.683	1741452	49.828	1	24.772	8225269	95.539
2	33.112	1753503	50.172	2	33.737	384103	4.461

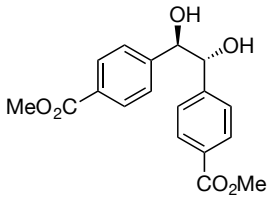
1,2-Bis(4-bromophenyl)ethane-1,2-diyl bis(2-methylpropanoate) (4f)



<2% conversion from kinetic resolution of *rac*-**2f** under the optimal conditions.

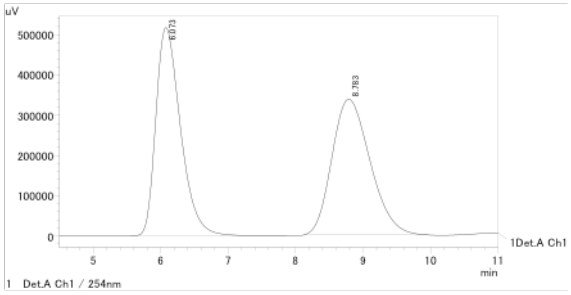
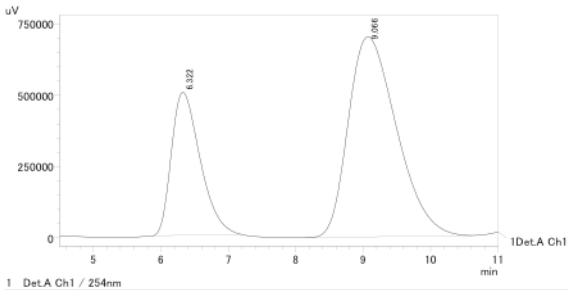
Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 4H), 7.02–6.92 (m, 4H), 5.95 (s, 2H), 2.56 (sep., J = 7.0 Hz, 2H), 1.15 (d, J = 7.0 Hz, 6H), 1.13 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 135.3, 131.6, 129.2, 122.7, 76.0, 34.2, 18.9 (2); IR (KBr) 2976, 2936, 2876, 1728, 1489, 1470, 1069, 1011, 847, 746 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{22}H_{24}O_4Br_2Na$ 532.9934, found 532.9960; mp 122.8–123.2 ºC.

Dimethyl 4,4'-((1*R*,2*R*)-1,2-dihydroxyethane-1,2-diyl)dibenzoate (2g)



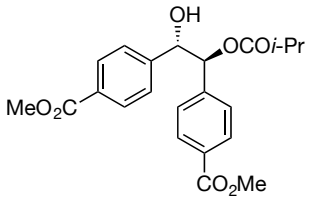
68% recovery from kinetic resolution of *rac*-**2g** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 60/40, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.3 min (minor) and T_R = 9.1 min (major), 70:30 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 4H), 7.16 (d, J = 8.2 Hz, 4H), 4.76 (s, 2H), 3.90 (s, 6H), 2.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.6, 130.1, 129.6, 127.1, 78.9, 52.3; IR (KBr) 3462, 2955, 2889, 1721, 1688, 1609, 1437, 1277, 1107, 1016, 737 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{18}H_{19}O_6$ 331.1176, found 331.1179; mp 177.8–178.6 ºC; $[\alpha]^{21}_D$ +81.9 (*c* 1.02, THF, 70:30 er, (1*R*, 2*R*)-configuration).

Racemic sample of **2g**	(1*R*,2*R*)-**2g**
	

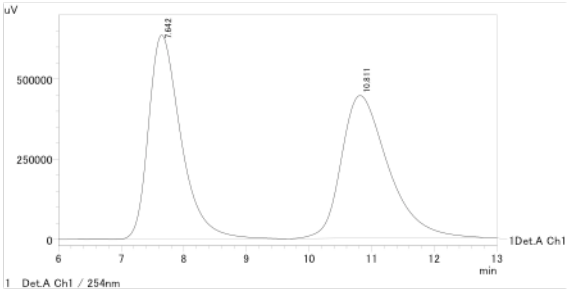
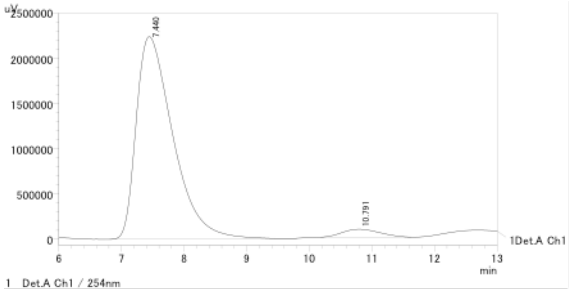
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	6.073	13151154	49.745	1	6.322	14852651	29.864
2	8.783	13286204	50.255	2	9.066	34881505	70.136

Dimethyl 4,4'-((1*S*,2*S*)-1-hydroxy-2-(isobutyryloxy)ethane-1,2-diyl)dibenzoate (3g)



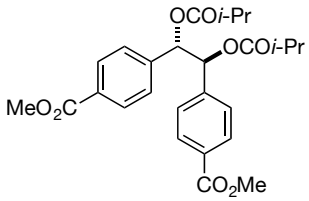
31% conversion from kinetic resolution of *rac*-**2g** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 85/15, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 7.4 min (major) and T_R = 10.8 min (minor), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.83 (m, 4H), 7.22–7.11 (m, 4H), 5.86 (d, *J* = 6.7 Hz, 1H), 4.99 (d, *J* = 6.7 Hz, 1H), 3.91–3.83 (m, 6H), 2.87 (bs, 1H), 2.69–2.52 (m, 1H), 1.18–1.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 166.9, 166.8, 143.9, 141.8, 130.1, 130.0, 129.6, 129.5, 127.2, 127.1, 79.0, 76.5, 52.3 (2), 34.2, 19.0, 18.9; IR (KBr) 3501, 2984, 2955, 2876, 1728, 1697, 1611, 1433, 1277, 1109, 1018, 729 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{22}H_{25}O_7$ 401.1595, found 401.1598; mp 109.2–110.1 ºC; $[\alpha]^{21}_D$ +22.2 (*c* 1.03, THF, 98:2 er, (1*S*, 2*S*)-configuration).

Racemic sample of **3g**	(1*S*,2*S*)-**3g**
	

Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	7.642	22885152	49.723	1	7.440	92138258	98.054
2	10.811	23140185	50.277	2	10.791	1828243	1.946

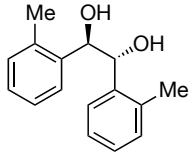
Dimethyl 4,4'-((1*S*,2*S*)-1,2-bis(isobutyryloxy)ethane-1,2-diyl)dibenzoate (4g)



<2% conversion from kinetic resolution of *rac*-**2g** under the optimal conditions.

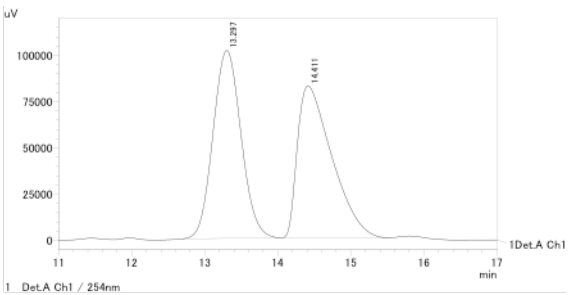
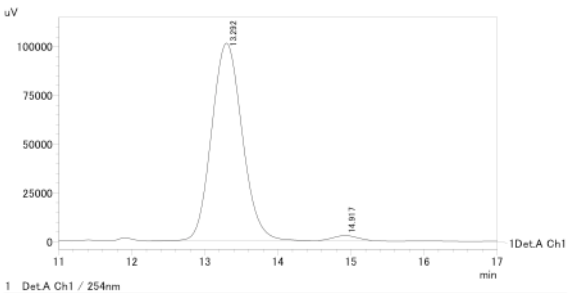
Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 4H), 6.08 (s, 2H), 3.89 (s, 6H), 2.59 (sep, *J* = 6.8 Hz, 2H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.38 (d., *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 166.6, 141.1, 130.3, 129.6, 127.4, 76.2, 52.3, 34.1, 18.9; IR (KBr) 2976, 2953, 1728, 1435, 1279, 1109 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{26}H_{31}O_8$ 427.2013, found 471.2001; mp 73.0–73.8 ºC.

(1*R*,2*R*)-1,2-Di-*o*-tolylethane-1,2-diol (2h)[61]

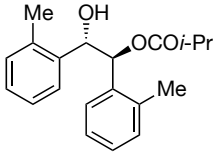


49% recovery from kinetic resolution of *rac*-**2h** under the optimal conditions.

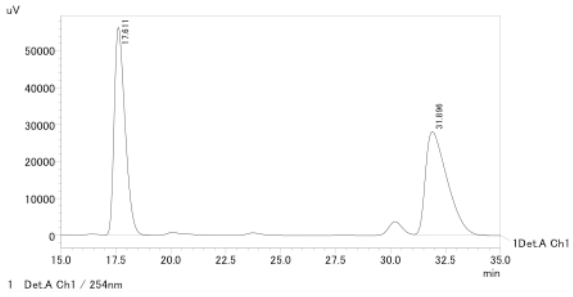
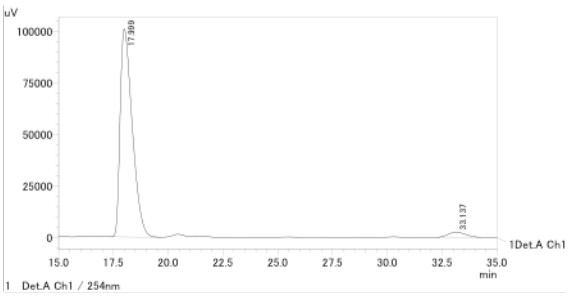
Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 13.3 min (major) and T_R = 14.9 min (minor), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.13 (td, *J* = 7.5, 1.3 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 2H), 5.00 (s, 2H), 2.87 (s, 2H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.9, 130.1, 127.6, 127.3, 125.9, 74.6, 18.7; IR (KBr) 3435, 3256, 1605, 1491, 1458, 1200, 1040, 758, 725 cm^{-1}; $[\alpha]^{22}_D$ +61.4 (*c* 0.87, EtOH, 98:2 er, (1*R*, 2*R*)-configuration) [lit[61] $[\alpha]^{25}_D$ +73.0 [*c* 0.89, EtOH, (1*R*, 2*R*)-configuration]].

Racemic sample of **2h**				(1*R*,2*R*)-**2h**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	13.297	2708539	50.220	1	13.292	2965132	98.162
2	14.411	2684757	49.780	2	14.917	55514	1.838

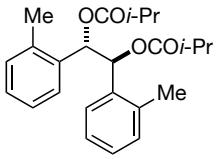
(1*S*,2*S*)-2-Hydroxy-1,2-di-*o*-tolylethyl isobutyrate (3h)



51% conversion from kinetic resolution of *rac*-**2h** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 18.0 min (major) and T_R = 33.1 min (minor), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.24–7.07 (m, 4H), 6.95 (d, *J* = 7.3 Hz, 2H), 6.04 (d, *J* = 8.2 Hz, 1H), 5.22 (dd, *J* = 8.2, 2.7 Hz, 1H), 2.70–2.56 (m, 2H), 1.90 (s, 3H), 1.82 (s, 3H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 137.1, 136.5, 135.9, 135.6, 130.4, 130.3, 128.2, 128.0, 127.7, 127.2, 126.1, 125.9, 76.0, 72.8, 34.2, 19.1, 19.0 (2), 18.9; IR (KBr) 3510, 2972, 2376, 1732, 1468, 1196, 1153, 764 cm^{-1}; HRMS (ESI$^-$) $[M–H]^-$ calculated for $C_{20}H_{23}O_3$ 311.1653, found 311.1683; $[\alpha]^{24}_D$ –9.3 (*c* 0.988, EtOH, 97:3 er, (1*S*, 2*S*)-configuration).

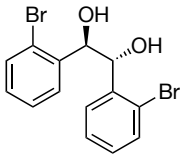
Racemic sample of **3h**				(1*S*,2*S*)-**3h**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	17.611	1928339	50.160	1	17.999	3868857	96.609
2	31.896	1916010	49.840	2	33.137	135806	3.391

1,2-Di-*o*-tolylethane-1,2-diyl bis(2-methylpropanoate) (4h)

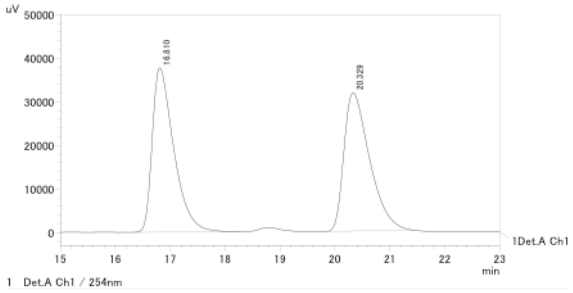
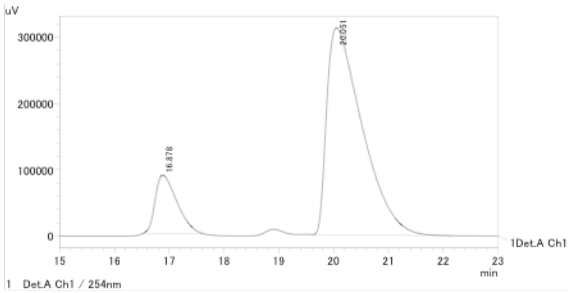


<2% conversion from kinetic resolution of *rac*-**2h** under the optimal conditions. Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.4, 1.4 Hz, 2H), 7.21–7.07 (m, 4H), 6.93 (d, *J* = 7.4 Hz, 2H), 6.31 (s, 2H), 2.56 (sep., *J* = 7.0 Hz, 2H), 6.00 (s, 6H), 1.15 (d, *J* = 7.0 Hz, 6H), 1.13 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 136.5, 135.0, 130.3, 128.3, 127.8, 125.8, 73.1, 34.2, 19.2, 19.0, 18.9; IR (KBr) 2972, 1728, 1470, 980, 727 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{24}H_{30}O_4Na$ 405.2036, found 405.2008; mp 64.5–65.4 ºC.

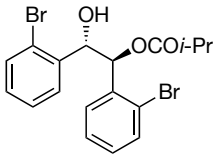
(1*R*,2*R*)-1,2-Bis(2-bromophenyl)ethane-1,2-diol (2i)[61]



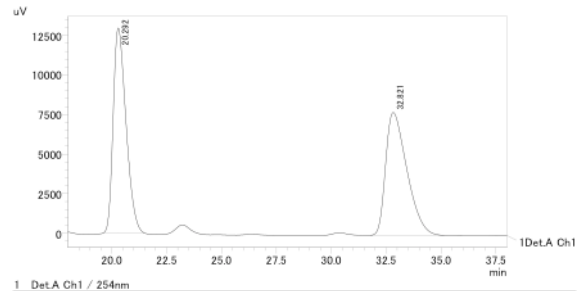
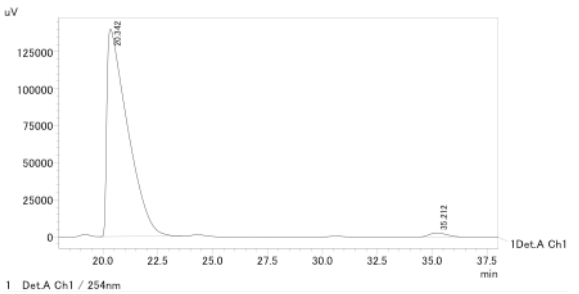
58% recovery from kinetic resolution of *rac*-**2i** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 85/15, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 16.9 min (minor) and T_R = 20.1 min (major), 85:15 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.46 (dd, *J* = 7.9, 1.1 Hz, 2H), 7.35 (td, *J* = 7.9, 1.1 Hz, 2H), 7.15 (td, *J* = 7.9, 1.5 Hz, 2H), 5.33 (dd, *J* = 2.6, 1.0 Hz, 2H), 2.78 (dd, *J* = 2.6, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 132.9, 129.9, 129.7, 127.6, 123.1, 75.3; IR (KBr) 3312, 1574, 1474, 1429, 1184, 1057, 785 cm^{-1}; $[\alpha]^{21}_D$ –15.0 (*c* 1.30, EtOH, 85:15 er, (1*R*, 2*R*)-configuration) [lit[61] $[\alpha]^{25}_D$ –33.0 [*c* 1.28, EtOH, (1*R*, 2*R*)-configuration]].

Racemic sample of **2i**				(1*R*,2*R*)-**2i**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	16.810	1026896	49.939	1	16.878	2442840	14.861
2	20.329	1029414	50.061	2	20.051	13995290	85.139

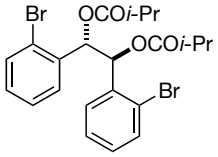
(1*S*,2*S*)-1,2-Bis(2-bromophenyl)-2-hydroxyethyl isobutyrate (3i)



42% conversion from kinetic resolution of *rac*-**2i** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 20.3 min (major) and T_R = 35.2 min (minor), 99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56–7.49 (m, 2H), 7.47 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.37–7.27 (m, 2H), 7.19–7.09 (m, 2H), 6.42 (d, *J* = 4.4 Hz, 1H), 5.51 (t, *J* = 4.4 Hz, 1H), 2.54 (sep., *J* = 7.1 Hz, 1H), 2.32 (d, *J* = 4.4 Hz, 1H), 1.10 (d, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 138.2, 136.5, 133.2, 132.8, 130.1, 129.9, 129.7 (2), 127.4, 127.2, 123.1, 122.7, 75.9, 73.7, 34.1, 19.0, 18.9; IR (KBr) 2974, 2936, 1732, 1456, 1387, 1190, 1148, 964, 737 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{18}H_{18}O_3Br_2Na$ 462.9515, found 462.9524; mp 87.1–87.6 ºC; $[\alpha]^{23}_D$ +17.5 (*c* 1.0, EtOH, 99:1 er, (1*S*, 2*S*)-configuration).

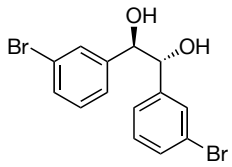
Racemic sample of **3i**				(1*S*,2*S*)-**3i**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	20.292	525526	50.149	1	20.342	9205097	98.575
2	32.821	522400	49.851	2	35.212	133096	1.425

(1*S*,2*S*)-1,2-Bis(2-bromophenyl)ethane-1,2-diyl bis(2-methylpropanoate) (4i)

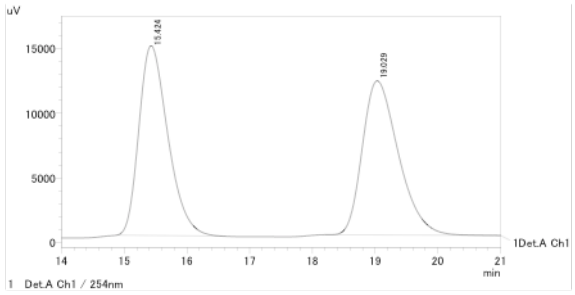
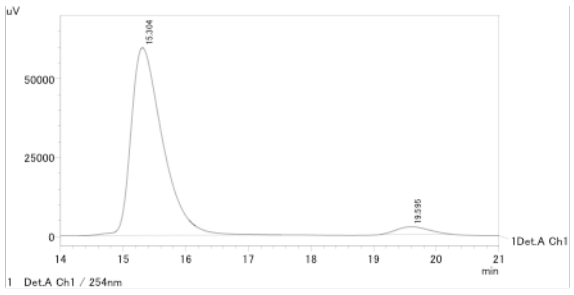


<2% conversion from kinetic resolution of *rac*-**2i** under the optimal conditions. Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.29 (td, *J* = 7.8, 1.1 Hz, 2H), 7.12 (td, *J* = 7.8, 1.8 Hz, 2H), 6.58 (s, 2H), 2.52 (sep., *J* = 6.9 Hz, 2H), 1.09 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 135.8, 133.0, 129.9, 129.8, 127.1, 123.1, 74.1, 34.0, 18.9, 18.8; IR (KBr) 2968, 2874, 1738, 1472, 1184, 1144, 1099, 1026, 766 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{22}H_{24}O_4Br_2Na$ 532.9934, found 532.9944; mp 101.8–102.5 ºC.

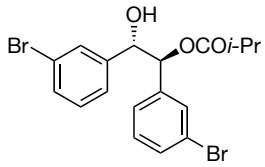
(1*R*,2*R*)-1,2-Bis(3-bromophenyl)ethane-1,2-diol (2j)



48% recovery from kinetic resolution of *rac*-**2j** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 93/7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 15.3 min (major) and T_R = 19.6 min (minor), 96:4 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.33 (m, 4H), 7.11 (t, *J* = 7.8 Hz, 2H), 6.97 (dt, *J* = 7.8, 1.4 Hz, 2H), 4.65 (s, 2H), 2.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 131.4, 130.0, 129.9, 125.8, 122.6, 78.3; IR (KBr) 3420, 1593, 1568, 1472, 1196, 1051, 1007, 845 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{14}H_{12}BrO_2Na$ 392.9096, found 392.9110; mp 103.5–104.1 ºC; $[\alpha]^{24}_D$ –17.9 (*c* 1.0, $CHCl_3$, 96:4 er, (1*R*, 2*R*)-configuration).

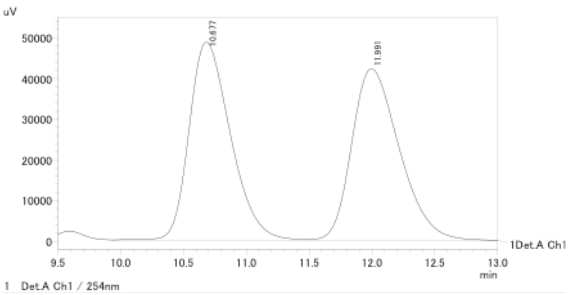
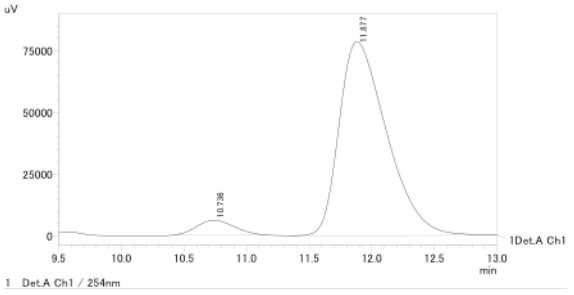
Racemic sample of **2j**				(1*R*,2*R*)-**2j**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.424	471592	49.734	1	15.304	2082736	96.006
2	19.029	476644	50.266	2	19.595	86648	3.994

(1*S*,2*S*)-1,2-Bis(3-bromophenyl)-2-hydroxyethyl isobutyrate (3j)

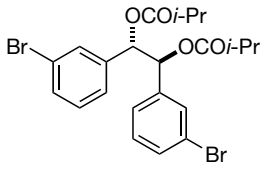


50% conversion from kinetic resolution of *rac*-**2j** under the optimal conditions.

Colorless liquid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 93/7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 10.7 min (minor) and T_R = 11.9 min (major), 94:6 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.35 (m, 3H), 7.33 (t, *J* = 1.8 Hz, 1H), 7.16–7.07 (m, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 5.76 (d, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 6.4 Hz, 1H), 2.64 (sep., *J* = 7.1 Hz, 1H), 2.46 (bs, 1H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 141.3, 139.1, 131.6, 131.4, 130.2, 130.1, 130.0, 129.8, 126.0, 125.7, 122.6, 122.5, 78.4, 76.2, 34.2, 19.0; IR (KBr) 3480, 2974, 2934, 1732, 1570, 1474, 1070, 789 cm^{-1}; HRMS (ESI^+) $[M+Na]^+$ calculated for $C_{18}H_{18}Br_2O_3$ 462.9515, found 462.9525; $[\alpha]^{21}_D$ +89.6 (*c* 1.0, $CHCl_3$, 94:6 er, (1*S*, 2*S*)-configuration).

Racemic sample of **3j**				(1*S*,2*S*)-**3j**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	10.677	1110250	50.023	1	10.736	125748	94.288
2	11.991	1109222	49.977	2	11.877	2075827	5.712

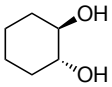
1,2-Bis(3-bromophenyl)ethane-1,2-diyl bis(2-methylpropanoate) (4j)



2% conversion from kinetic resolution of *rac*-**2j** under the optimal conditions.

Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.11 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 7.8 Hz, 2H), 5.96 (s, 2H), 2.59 (sep., J = 7.0 Hz, 2H), 1.15 (d, J = 7.0 Hz, 6H), 1.15 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 138.5, 131.7, 130.3, 129.9, 126.1, 122.5, 75.8, 34.2, 18.9; IR (KBr) 3065, 2974, 2874, 1732, 1470, 1202, 1159, 976, 785 cm^{-1}; HRMS (FAB$^+$) $[M+Na]^+$ calculated for $C_{22}H_{24}O_4Br_2Na$ 532.9933, found 532.9956; mp 98.0–98.6 ºC.

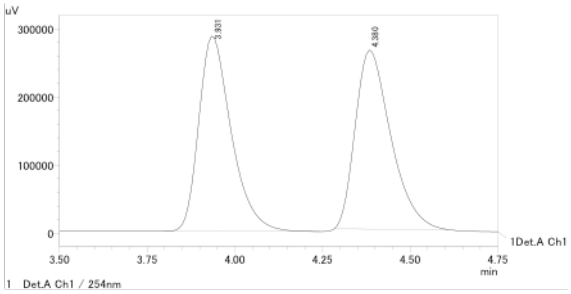
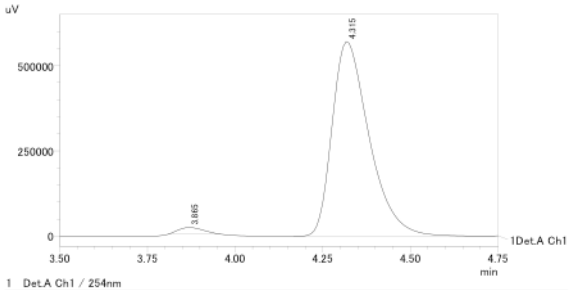
(1*R*,2*R*)-Cyclohexane-1,2-diol (2k)[96]



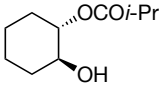
47% recovery from kinetic resolution of *rac*-**2k** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 3.9 min (minor) and T_R = 4.3 min (major), 98:2 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (bs, 2H), 2.14 (s, 2H), 2.04–1.91 (m, 2H), 1.78–1.65 (m, 2H), 1.36–1.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.7, 33.0, 24.5; IR (KBr) 3333, 2941, 2860, 1450, 1352, 1287, 1070, 853 cm^{-1}.

Optical rotation was shown in the following section of "Kinetic resolution of *d,l*-hydrobenzoin on multigram scale (Scheme 7a)".

Racemic sample of corresponding benzoate of **2k**				Corresponding benzoate of (1*R*,2*R*)-**2k**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	3.931	1847077	49.944	1	3.865	97782	2.284
2	4.380	1851197	50.056	2	4.315	4183676	97.716

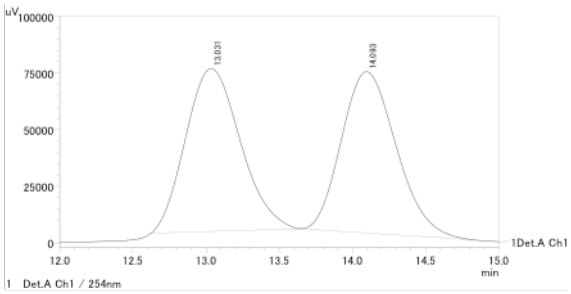
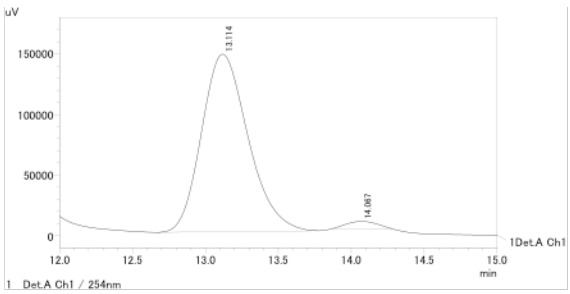
(1*S*,2*S*)-2-Hydroxycyclohexyl isobutyrate (3k)[97]



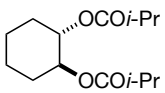
53% conversion from kinetic resolution of *rac*-**2k** under the optimal conditions.

Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00

mL/min, 30 °C, UV = 254 nm), T_R = 13.1 min (major) and T_R = 14.1 min (minor), 97.5:2.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62–4.48 (m, 1H), 3.63–3.51 (m, 1H), 2.57 (sep., *J* = 7.0 Hz, 1H), 2.18–1.94 (m, 3H), 1.77–1.64 (m, 2H), 1.43–1.20 (m, 4H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 77.6, 72.6, 34.2, 33.0, 29.8, 23.8, 23.7, 19.1, 18.9; IR (KBr) 3458, 2941, 2862, 1732, 1470, 1200, 1076, 1016, 854 cm^{-1}; $[\alpha]^{21}_D$ +18.9 (*c* 1.4, $CHCl_3$, 97.5:2.5 er, (1*S*, 2*S*)-configuration).

Racemic sample of corresponding benzoate of **3k**				Corresponding benzoate of (1*S*,2*S*)-**3k**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	13.031	1870085	50.261	1	13.114	3247515	97.451
2	14.093	1850663	49.739	2	14.067	84931	2.549

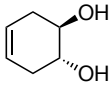
Cyclohexane-1,2-diyl bis(2-methylpropanoate) (4k)



<2% conversion from kinetic resolution of *rac*-**2k** under the optimal conditions.

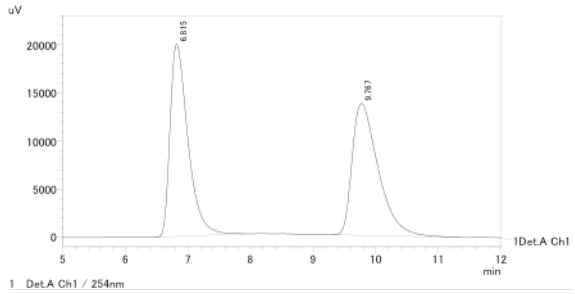
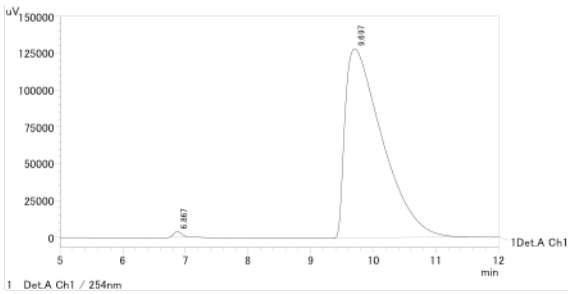
Pale yellow liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89–4.75 (m, 2H), 2.49 (sep., *J* = 7.0 Hz, 2H), 2.08–1.92 (m, 2H), 1.79–1.64 (m, 2H), 1.49–1.23 (m, 4H), 1.12 (d, *J* = 7.0 Hz, 6H), 1.12 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 73.4, 34.2, 30.2, 23.5, 19.1, 19.0; IR (KBr) 2940, 2872, 1732, 1472, 1196, 1155, 1072 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{14}H_{25}O_4$ 257.1747, found 257.1754.

(1*R*,2*R*)-Cyclohex-4-ene-1,2-diol (2l)[98,99]



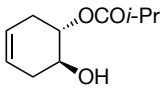
45% recovery from kinetic resolution of *rac*-**2l** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.9 min (minor) and T_R = 9.7 min (major), 99.5:0.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61–5.45 (m, 2H), 3.79–3.60 (m, 2H), 3.06–2.28 (m, 4H), 2.17–1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.7, 72.3, 33.6; IR (KBr) 3337, 2874, 1657, 1441, 1348, 1279, 1059, 976, 787 cm^{-1}; $[\alpha]^{24}_D$ –125.1 (*c* 1.0, $CHCl_3$, 99.5:0.5 er, (1*S*, 2*S*)-configuration) [lit[70] $[\alpha]^{25}_D$ –71.5 [*c* 0.658, $CHCl_3$, (1*R*, 2*R*)-configuration, 69% ee]].

Racemic sample of corresponding benzoate of **2l**	Corresponding benzoate of (1*R*,2*R*)-**2l**
	

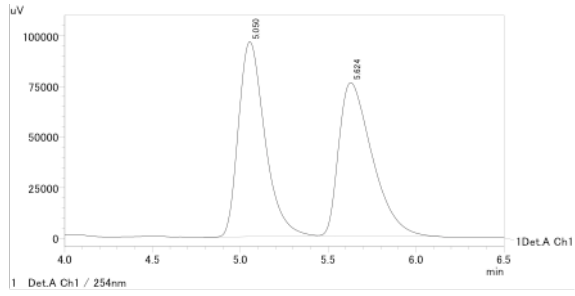
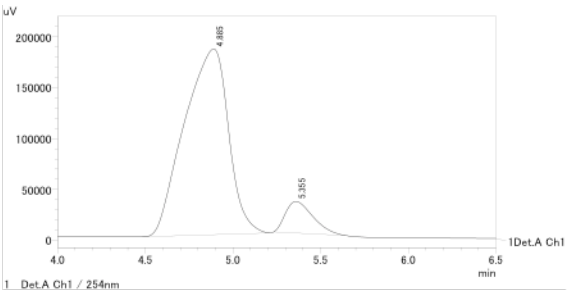
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	6.815	396197	49.915	1	6.867	27284	0.512
2	9.767	397541	50.085	2	9.697	5300709	99.488

(1*S*,6*S*)-6-Hydroxycyclohex-3-en-1-yl isobutyrate (3l)



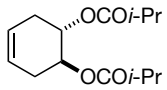
54% conversion from kinetic resolution of *rac*-**2l** under the optimal conditions.

Pale yellow liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99.3/0.7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 4.9 min (major) and T_R = 5.4 min (minor), 90.5:9.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.48 (m, 2H), 4.86 (td, *J* = 8.9, 6.0 Hz, 1H), 3.92 (td, *J* = 8.9, 6.0 Hz, 1H), 2.65–2.48 (m, 3H), 2.20–2.01 (m, 2H), 1.78 (bs, 1H), 1.91 (d, *J* = 6.9 Hz, 3H), 1.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 124.4, 123.9, 74.1, 69.1, 34.3, 33.0, 30.3, 19.2, 19.1; IR (KBr) 3458, 2974, 1732, 1470, 1074 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{10}H_{17}O_3$ 185.1172, found 185.1177; $[\alpha]^{21}_D$ +69.2 (*c* 1.0, $CHCl_3$, 90.5:9.5 er, (1*S*, 2*S*)-configuration).

Racemic sample of corresponding benzoate of **3l**	Corresponding benzoate of (1*S*,6*S*)-**3l**
	

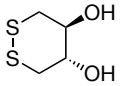
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	5.050	1003843	50.114	1	4.885	3211286	90.484
2	5.624	999262	49.886	2	5.355	337736	9.516

Cyclohex-4-ene-1,2-diyl bis(2-methylpropanoate) (4l)

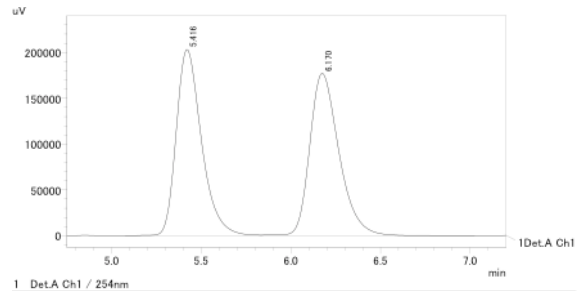
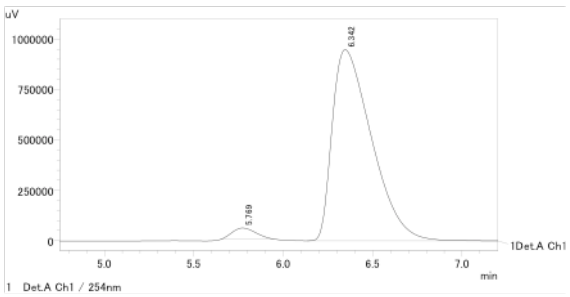


<2% conversion from kinetic resolution of *rac*-**2l** under the optimal conditions. Yellow solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.52 (m, 2H), 5.15–5.03 (m, 2H), 2.63–2.44 (m, 4H), 2.22–2.08 (m, 2H), 1.15 (d, J = 7.1 Hz, 6H), 1.14 (d, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 123.8, 69.8, 34.2, 30.3, 19.1, 19.0; IR (KBr) 2974, 1732, 1470, 1192, 1153 cm^{-1}; HRMS (ESI^{+}) $[M+H]^{+}$ calculated for $C_{14}H_{22}O_4$ 255.1591, found 255.1599.

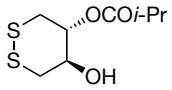
(4*S*,5*S*)-1,2-Dithiane-4,5-diol (2m)[100]



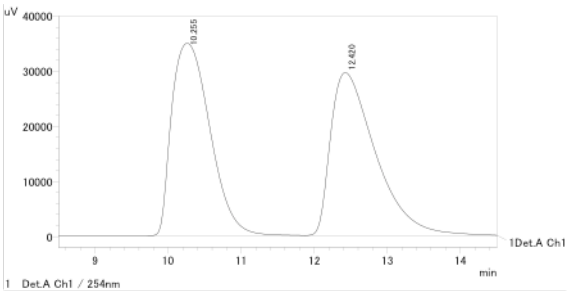
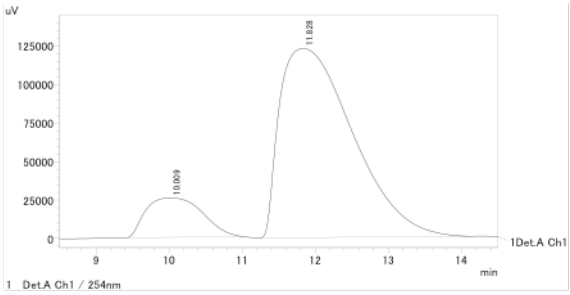
44% recovery from kinetic resolution of *rac*-**2m** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 5.8 min (minor) and T_R = 6.3 min (major), 97:3 er; ^{1}H NMR (400 MHz, Acetone-D6) δ 4.40 (bs, 2H), 3.59–3.45 (m, 2H), 3.17–2.97 (m, 2H), 2.95–2.79 (m, 2H); ^{13}C NMR (100 MHz, Acetone-D6) δ 75.3, 41.2; IR (KBr) 3425, 3310, 1456, 1036, 791 cm^{-1}; $[\alpha]^{23}_{D}$ –282.2 (*c* 2.7, MeOH, 97:3 er, (1*S*, 2*S*)-configuration) [lit[100] $[\alpha]^{22}_{D}$ +289 [*c* 2.74, MeOH, (1*R*, 2*R*)-configuration]].

Racemic sample of corresponding benzoate of **2m**				Corresponding benzoate of (4*S*,5*S*)-**2m**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	5.416	1999164	49.817	1	5.769	516370	3.427
2	6.170	2013854	50.183	2	6.342	14552238	96.573

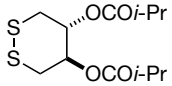
(4*R*,5*R*)-5-Hydroxy-1,2-dithian-4-yl isobutyrate (3m)



56% conversion from kinetic resolution of *rac*-**2m** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99.5/0.5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 10.0 min (minor) and T_R = 11.8 min (major), 86:14 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (ddd, *J* = 9.5, 8.6, 3.6 Hz, 1H), 3.84 (td, *J* = 9.0, 3.6 Hz, 1H), 3.27–3.11 (m, 2H), 3.01 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.95 (dd, *J* = 13.8, 9.7 Hz, 1H), 2.61 (sep., *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 ºC) δ 176.8, 74.7, 71.1, 40.4, 37.3, 34.3, 19.1, 19.0; IR (KBr) 3445, 2974, 2916, 1728, 1470, 984, 881 cm^{-1}; HRMS (ESI^+) $[M+Na]^+$ calculated for $C_8H_{14}O_3S_2Na$ 245.0277, found 245.0290; $[\alpha]^{22}_D$ +158.7 (*c* 1.0, MeOH, 86:14 er, (1*R*, 2*R*)-configuration).

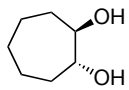
Racemic sample of corresponding benzoate of **3m**				Corresponding benzoate of (4*R*,5*R*)-**3m**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	10.255	1277067	50.060	1	10.009	1376176	13.847
2	12.420	1273991	49.940	2	11.828	8562177	86.153

1,2-Dithiane-4,5-diyl bis(2-methylpropanoate) (4m)



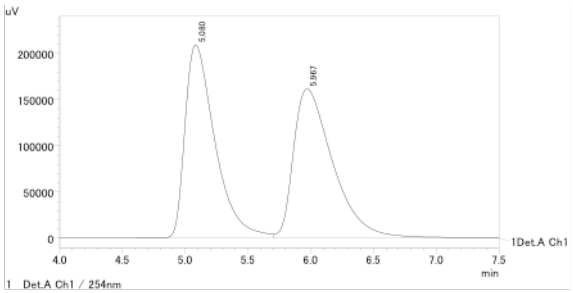
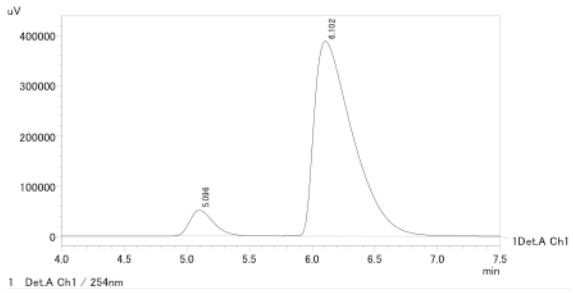
<2% conversion from kinetic resolution of *rac*-**2m** under the optimal conditions. Colorless solid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08–4.98 (m, 2H), 3.20–2.98 (m, 4H), 2.51 (sep., *J* = 7.1 Hz, 2H), 1.14 (d, *J* = 7.1 Hz, 6H), 1.13 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 71.8, 38.3, 34.0, 18.9 (2); IR (KBr) 3360, 2970, 1736, 1387, 991 cm^{-1}; HRMS (ESI^+) $[M+Na]^+$ calculated for $C_{12}H_{20}O_4S_2Na$ 315.0695, found 315.0717; mp 55.0–55.6 ºC.

(1*R*,2*R*)-Cycloheptane-1,2-diol (2n)[67,101,102]

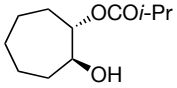


48% recovery from kinetic resolution of *rac*-**2n** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 5.1 min (minor) and T_R = 6.1 min (major), 93:7 er; ^{1}H NMR

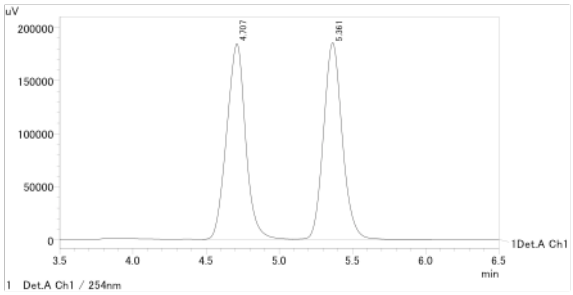
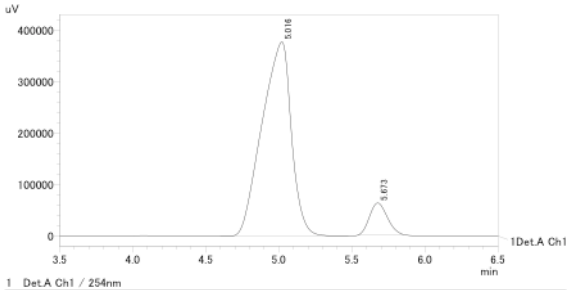
(400 MHz, $CDCl_3$) δ 3.49–3.39 (m, 2H), 2.20 (bs, 2H), 1.95–1.82 (m, 2H), 1.75–1.38 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.6, 32.2, 26.5, 22.1; IR (KBr) 3291, 2932, 1458, 1034, 760 cm^{-1}; $[\alpha]^{21}_D$ –5.8 (*c* 0.81, CHC, 93:7 er, (1*R*, 2*R*)-configuration) [lit[70] $[\alpha]^{25}_D$ –5.1 [*c* 0.700, $CHCl_3$, (1*R*, 2*R*)-configuration, >99% ee]].

Racemic sample of corresponding benzoate of **2n**				Corresponding benzoate of (1*R*,2*R*)-**2n**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	5.080	3466079	49.615	1	5.096	662718	7.366
2	5.967	3519881	50.385	2	6.102	8333692	92.634

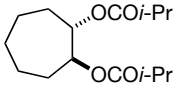
(1*S*,2*S*)-2-Hydroxycycloheptyl isobutyrate (3n)



52% conversion from kinetic resolution of *rac*-**2n** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 5.0 min (major) and T_R = 5.7 min (minor), 91:9 er; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (td, *J* = 7.8, 3.3 Hz, 1H), 3.74 (td, *J* = 8.8, 6.5, 3.3 Hz, 1H), 2.57 (sep., *J* = 6.9 Hz, 1H), 1.91–1.39 (m, 10H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 81.8, 76.1, 34.3, 32.9, 30.4, 28.3, 23.1, 23.0, 19.1, 19.0; IR (KBr) 3445, 2940, 1732, 1454, 1159, 989 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{11}H_{20}O_3Na$ 223.1305, found 223.1320; $[\alpha]^{22}_D$ +1.0 (*c* 1.0, $CHCl_3$, 91:9 er, (1*S*, 2*S*)-configuration).

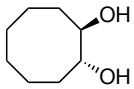
Racemic sample of corresponding benzoate of **3n**				Corresponding benzoate of (1*S*,2*S*)-**3n**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	4.707	1661051	50.183	1	5.016	5278590	91.101
2	5.361	1648964	49.817	2	5.673	515648	8.899

Cycloheptane-1,2-diyl bis(2-methylpropanoate) (4n)

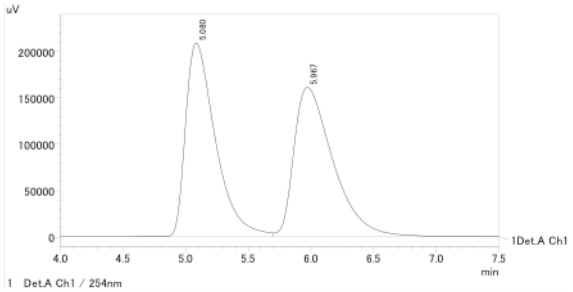
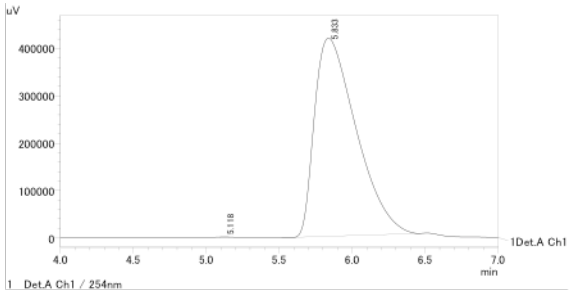


<2% conversion from kinetic resolution of *rac*-**2n** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02–4.93 (m, 2H), 2.48 (sep., J = 6.9 Hz, 2H), 1.83–1.49 (m, 10H), 1.22 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 76.5, 34.2, 30.5, 28.4, 22.8, 19.0, 18.9; IR (KBr) 2974, 2936, 2862, 1739, 1470, 1120, 989 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{15}H_{27}O_4$ 271.1903, found 271.1921.

(1*R*,2*R*)-Cyclooctane-1,2-diol (2o)[67,101]

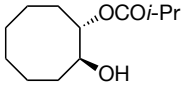


42% recovery from kinetic resolution of *rac*-**2o** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 5.1 min (minor) and T_R = 5.8 min (major), >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64–3.51 (m, 2H), 2.25–0.99 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.2, 32.0, 26.3, 23.8; IR (KBr) 3385, 2924, 1466, 1036 cm^{-1}; $[\alpha]^{24}_D$ –14.3 (*c* 1.2, $CHCl_3$, >99:1 er, (1*R*, 2*R*)-configuration) [lit[67] $[\alpha]^{25}_D$ +15.3 [*c* 1.2, $CHCl_3$, (1*S*, 2*S*)-configuration, >99% ee]].

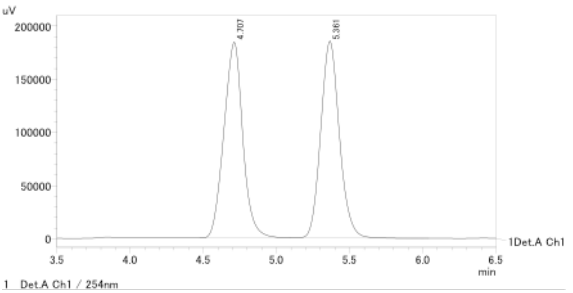
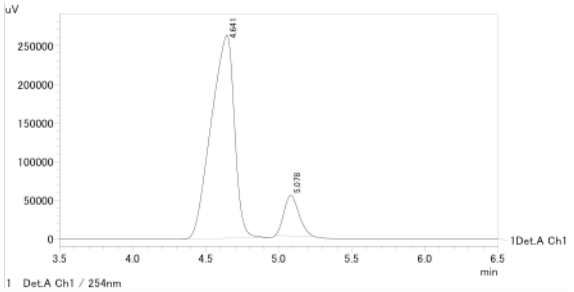
Racemic sample of corresponding benzoate of **2o**	Corresponding benzoate of (1*R*,2*R*)-**2o**
	

Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	5.080	3466079	49.615	1	5.118	370	0.004
2	5.967	3519881	50.385	2	5.833	8315340	99.996

(1*S*,2*S*)-2-Hydroxycyclooctyl isobutyrate (3o)

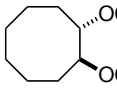


58% conversion from kinetic resolution of *rac*-**2o** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 4.6 min (major) and T_R = 5.1 min (minor), 89:11 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (ddd, *J* = 9.2, 6.0, 3.0 Hz, 1H), 3.84 (td, *J* = 8.1, 3.0 Hz, 1H), 2.57 (sep., *J* = 7.1 Hz, 1H), 2.23 (bs, 1H), 1.96–1.37 (m, 12H), 1.18 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 79.9, 74.0, 34.3, 30.8, 29.8, 26.2, 25.5, 24.8, 23.4, 19.1, 19.0; IR (KBr) 3472, 2930, 1732, 1714, 1470, 1198, 1161 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{12}H_{22}O_3$ 215.1641, found 215.1649; $[\alpha]^{21}_D$ +23.3 (*c* 1.0, $CHCl_3$, 89:11 er, (1*S*, 2*S*)-configuration).

Racemic sample of corresponding benzoate of **3o**	Corresponding benzoate of (1*S*,2*S*)-**3o**
	

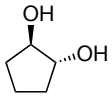
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	4.707	1661051	50.183	1	4.641	2905338	88.727
2	5.361	1648964	49.817	2	5.078	369147	11.273

Cyclooctane-1,2-diyl bis(2-methylpropanoate) (4o)

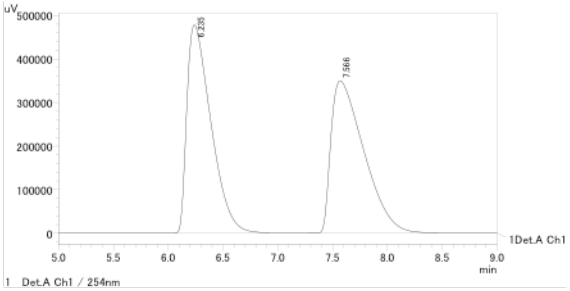
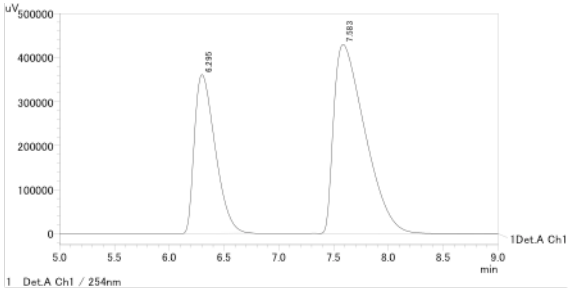


<2% conversion from kinetic resolution of *rac*-**2o** under the optimal conditions. Pale yellow liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13–5.03 (m, 2H), 2.48 (sep, *J* = 7.2 Hz, 2H), 1.87–1.35 (m,12H), 1.13 (d, *J* = 7.2 Hz, 6H), 1.11 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 75.5, 34.2, 29.1, 25.6, 24.4, 19.0; IR (KBr) 2934, 1732, 1470, 1193, 1161 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{16}H_{29}O_4$ 285.2060, found 285.2062.

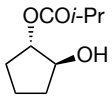
(1*R*,2*R*)-Cyclopentane-1,2-diol (2p)[103]



67% recovery from kinetic resolution of *rac*-**2p** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.3 min (minor) and T_R = 7.6 min (major), 64:35 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (bs, 2H), 2.04 (sext, *J* = 7.2 Hz, 2H), 1.75 (quin, *J* = 7.2 Hz, 2H), 1.66–1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.3, 31.3, 19.7; IR (KBr) 3327, 2941, 2862, 1452, 1043, 853 cm^{-1}; $[\alpha]^{23}_D$ –2.0 (*c* 2.0, EtOH, 64:36 er, (1*R*, 2*R*)-configuration) [lit[103] $[\alpha]^{20}_D$ –24.88 [*c* 6.0, EtOH, (1*R*, 2*R*)-configuration]].

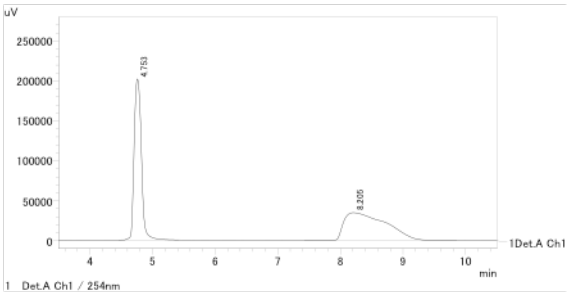
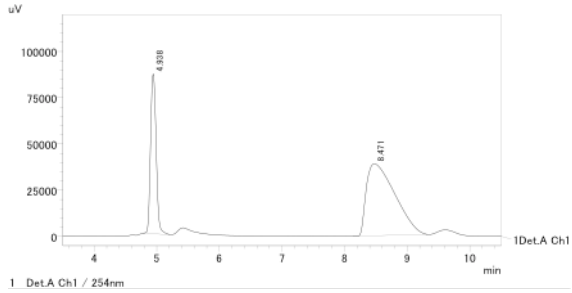
Racemic sample of corresponding benzoate of **2p**				Corresponding benzoate of (1*R*,2*R*)-**2p**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	6.235	7282884	49.993	1	6.295	4756144	35.841
2	7.566	7284932	50.007	2	7.583	8514130	64.159

(1*S*,2*S*)-2-Hydroxycyclopentyl isobutyrate (3p)

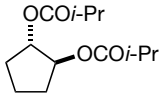


26% conversion from kinetic resolution of *rac*-**2p** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99.3/0.7, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 4.9 min (minor) and T_R = 8.5 min (major), 69:31 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (quin, *J* = 3.9 Hz, 1H), 4.08–3.99 (m, 1H), 2.89 (bs, 1H), 2.54 (sep, *J* = 7.0 Hz, 1H), 2.19–1.94 (m, 2H), 1.85–1.56 (m, 4H), 1.16 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 178.5, 83.7, 78.3, 34.1, 32.6, 30.1, 21.7, 19.0 (2); IR (KBr) 3445, 2944, 1732, 1454, 1016, 854 cm^{-1}; HRMS (ESI^+) $[M+Na]^+$ calculated for $C_9H_{16}O_3Na$ 195.0963, found 195.0992; $[\alpha]^{21}_D$ +6.79 (*c* 1.0, EtOH, 69:31 er, (1*S*, 2*S*)-configuration).

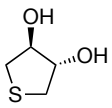
Racemic sample of corresponding benzoate of **3p**				Corresponding benzoate of (1*S*,2*S*)-**3p**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	4.753	1630987	49.793	1	4.938	539440	30.596
2	8.205	1644569	50.207	2	8.471	1223663	69.404

Cyclopentane-1,2-diyl bis(2-methylpropanoate) (4p)

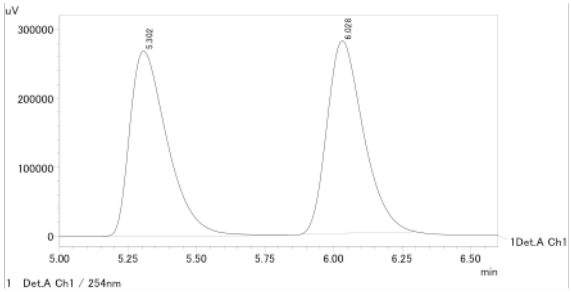
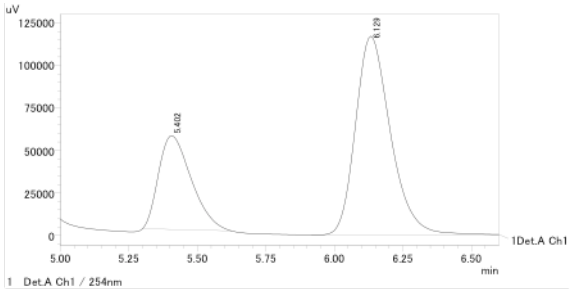


7% conversion from kinetic resolution of *rac*-**2p** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^1H NMR (400 MHz, $CDCl_3$) δ 5.09–5.02 (m, 2H), 2.51 (sep, *J* = 6.9 Hz, 2H), 2.17–2.02 (m, 2H), 1.77 (quin, *J* = 7.3 Hz, 2H), 1.67–1.57 (m, 2H), 1.15 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 78.7, 34.0, 30.4, 21.5, 18.9; IR (KBr) 2976, 1736, 1192, 1153 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{13}H_{23}O_4$ 432.1591, found 432.1573.

(3*S*,4*S*)-Tetrahydrothiophene-3,4-diol (2q)[104]

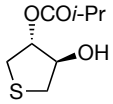


57% recovery from kinetic resolution of *rac*-**2q** under the optimal conditions. Brown solid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 5.4 min (minor) and T_R = 6.1 min (major), 69:31 er; ^1H NMR (400 MHz, CD_3OD) δ 4.24–4.17 (m, 2H), 3.08 (dd, *J* = 10.9, 3.7 Hz, 2H), 2.70 (dd, *J* = 10.9, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.0, 36.2; IR (KBr) 2943, 2359, 1734, 1217, 800 cm^{-1}; $[\alpha]^{21}_D$ –14.6 (*c* 1.2, MeOH, 69:31 er, (3*S*, 4*S*)-configuration) [lit[104] $[\alpha]_D$ +76.9 [*c* 1.22, MeOH, (3*R*, 4*R*)-configuration]].

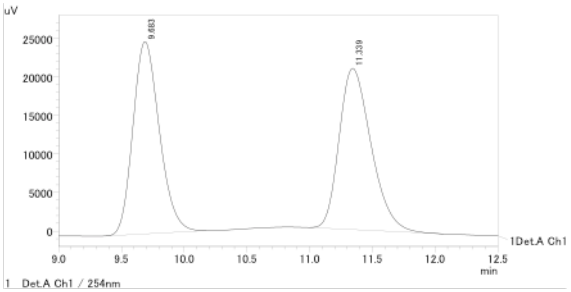
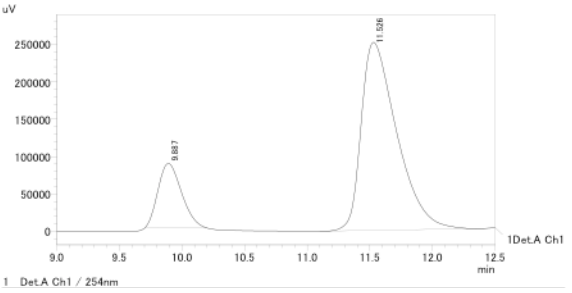
Racemic sample of corresponding benzoate of **2q**	Corresponding benzoate of (3*S*,4*S*)-**2q**
	

Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	5.302	2545169	49.686	1	5.402	458808	30.724
2	6.028	2577322	50.314	2	6.129	1034523	69.276

(3*R*,4*R*)-4-Hydroxytetrahydrothiophen-3-yl isobutyrate (3q)

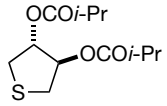


43% conversion from kinetic resolution of *rac*-**2q** under the optimal conditions. Colorless form. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 9.9 min (minor) and T_R = 11.5 min (major), 82:18 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (dt, *J* = 5.1, 2.7 Hz, 1H), 4.40 (bs, 1H), 3.26 (dd, *J* = 12.0, 5.1 Hz, 1H), 3.13 (dd, *J* = 12.0, 5.1 Hz, 1H), 2.84 (td, *J* = 11.3, 2.4 Hz, 2H), 2.55 (sep, *J* = 7.2 Hz, 1H), 2.22 (bd, *J* = 6.0 Hz, 1H), 1.16 (d, *J* = 7.2 Hz, 6H)
; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 79.9, 76.6, 36.6, 34.0, 33.4, 19.0, 18.9; IR (KBr) 3275, 2976, 2943, 2878, 1736, 1471, 1192, 1155, 1032, 995 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_8H_{15}O_3S$ 191.0736, found 191.0737; $[\alpha]^{22}_D$ +25.0 (*c* 1.0, MeOH, 82:18 er, (3*R*, 4*R*)-configuration).

Racemic sample of corresponding benzoate of **3q**	Corresponding benzoate of (3*R*,4*R*)-**3q**
	

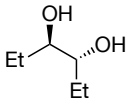
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	9.683	366301	49.696	1	9.887	1117698	18.364
2	11.339	370782	50.304	2	11.526	4968703	81.636

Tetrahydrothiophene-3,4-diyl bis(2-methylpropanoate) (4q)

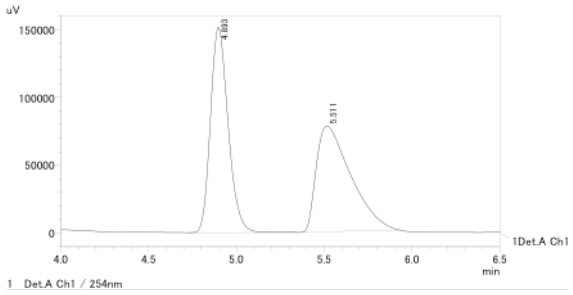
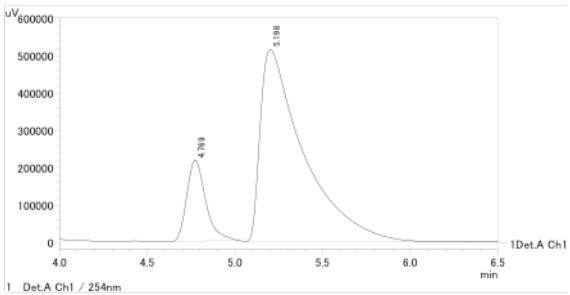


<2% conversion from kinetic resolution of *rac*-**2q** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35–5.30 (m, 2H), 3.23 (dd, *J* = 12.4, 3.7 Hz, 2H), 2.88 (dd, *J* = 12.6, 1.6 Hz, 2H), 2.63–2.49 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 77.3, 33.9, 33.7, 18.9, 18.8; IR (KBr) 2974, 2940, 1748, 1732, 1470, 1389, 1254, 997, 916 cm^{-1}; HRMS (FAB^+) $[M+H]^+$ calculated for $C_{12}H_{21}O_4S$ 261.1155, found 261.1170.

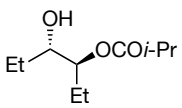
(3*R*,4*R*)-Hexane-3,4-diol (2r)[105,106]



54% recovery from kinetic resolution of *rac*-**2r** under the optimal conditions. Yellow liquid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/EtOH = 99/1, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 4.8 min (minor) and T_R = 5.2 min (major), 84:16 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41–3.31 (m, 2H), 1.94 (bs, 2H), 1.67–1.37 (m, 4H), 0.99 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.4, 26.2, 10.0; IR (KBr) 3445, 2936, 1454, 1150, 966, 891 cm^{-1}; $[\alpha]^{20}_D$ +15.3 (*c* 2.0, $CHCl_3$, 84:16 er, (3*R*, 4*R*)-configuration) [lit[105] $[\alpha]^{23}_D$ –23 [*c* 5.0, (3*S*, 4*S*)-configuration]].

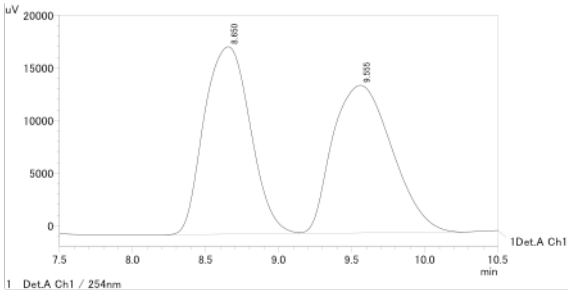
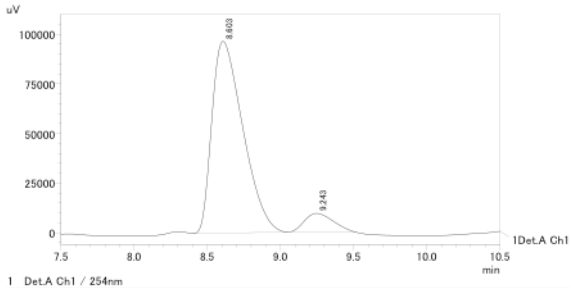
Racemic sample of corresponding benzoate of **2r**				Corresponding benzoate of (3*R*,4*R*)-**2r**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	4.893	1059635	49.856	1	4.769	1627001	15.600
2	5.511	1065771	50.144	2	5.198	8802312	84.400

(3*S*,4*S*)-4-Hydroxyhexan-3-yl isobutyrate (3r)

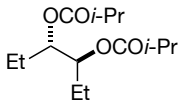


45% conversion from kinetic resolution of *rac*-**2r** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/EtOH = 99.4/0.6, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 8.6 min (major) and T_R = 9.2 min (minor), 92:8 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (ddd, *J* = 7.8, 5.8, 4.1 Hz, 1H), 3.53 (quin, *J* = 4.1 Hz, 1H), 2.60 (sep, *J* = 6.9 Hz, 1H) 1.77–1.30 (m, 6H), 1.19 (d, *J* = 6.9 Hz, 6H), 0.98 (t, *J* = 7.5 Hz, 3H),

0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 73.9, 34.4, 26.9, 23.9, 19.3, 10.2, 9.9; IR (KBr) 3472, 2972, 1732, 1714, 1470, 1161, 1072 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{10}H_{21}O_3$ 189.1485, found 189.1483; $[\alpha]^{23}_D$ –15.3 (*c* 1.0, $CHCl_3$, 92:8 er, (3*S*, 4*S*)-configuration).

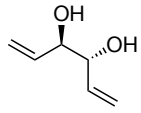
Racemic sample of corresponding benzoate of **3r**				Corresponding benzoate of (3*S*,4*S*)-**3r**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.650	391937	49.682	1	8.603	1421539	91.835
2	9.555	396950	50.318	2	9.243	126387	8.165

(3*S*,4*S*)-Hexane-3,4-diyl bis(2-methylpropanoate) (4r)

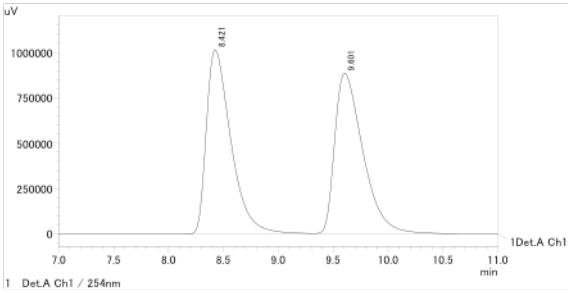
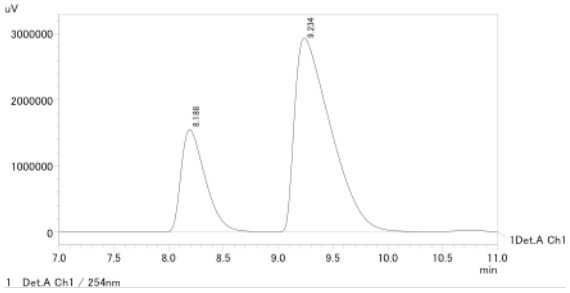


<2% conversion from kinetic resolution of *rac*-**2r** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00–4.92 (m, 2H), 2.57 (sep, *J* = 7.1 Hz, 2H), 1.64–1.46 (m, 4H), 1.17 (d, *J* = 7.1 Hz, 6H), 1.17 (d, *J* = 7.1 Hz, 6H), 0.88 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 74.5, 34.3, 23.9, 19.2, 19.1, 9.6; IR (KBr) 2974, 2880, 1732, 1470, 1196 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{14}H_{27}O_4$ 259.1923, found 259.1923.

(3*R*,4*R*)-Hexa-1,5-diene-3,4-diol (2s)[107]

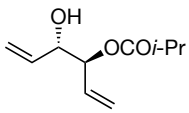


60% recovery from kinetic resolution of *rac*-**2s** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 8.2 min (minor) and T_R = 9.2 min (major), 74:26 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96–5.80 (m, 2H), 5.38 (d, *J* = 17.4 Hz, 2H), 5.26 (d, *J* = 10.5 Hz, 2H), 4.10–3.96 (m, 2H), 2.33 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 117.6, 75.8; IR (KBr) 3445, 2886, 1645, 1427, 1125, 926 cm^{-1}; $[\alpha]^{23}_D$ +17.0 (*c* 1.0, $CHCl_3$, 74:26 er, (3*R*, 4*R*)-configuration) [lit[107] $[\alpha]^{24}_D$ –31.7 [*c* 1.01, $CHCl_3$, (3*S*, 4*S*)-configuration]].

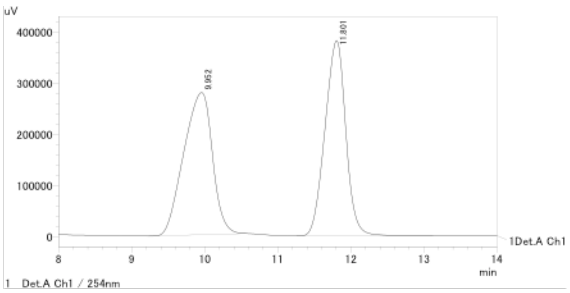
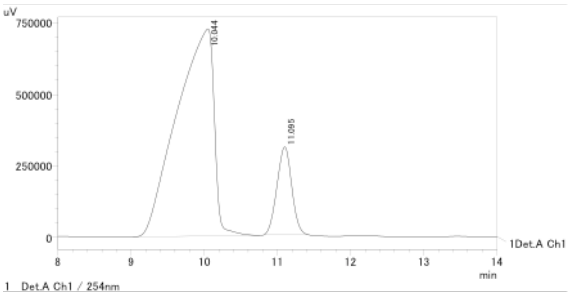
Racemic sample of corresponding benzoate of **2s**	Corresponding benzoate of (3*R*,4*R*)-**2s**
	

Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.421	15743596	50.066	1	8.188	23510852	25.943
2	9.601	15702085	49.934	2	9.234	67113056	74.057

(3*S*,4*S*)-4-Hydroxyhexa-1,5-dien-3-yl isobutyrate (3s)

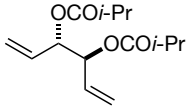


40% conversion from kinetic resolution of *rac*-**2s** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding benzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 10.0 min (major) and T_R = 11.1 min (minor), 86:14 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92–5.77 (m, 2H), 5.41–5.21 (m, 5H), 4.26–4.18 (m, 1H), 2.61 (sep, *J* = 6.9 Hz, 1H), 1.96 (bs, 1H), 1.19 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 136.2, 133.0, 119.0, 117.3, 76.5, 73.9, 34.3, 19.2, 19.1; IR (KBr) 3470, 2976, 1738, 1472, 989, 928 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{10}H_{17}O_3$ 185.1172, found 185.1165; $[\alpha]^{24}_D$ – 34.2 (*c* 1.0, $CHCl_3$, 86:14 er, (3*S*, 4*S*)-configuration).

Racemic sample of corresponding benzoate of **3s**	Corresponding benzoate of (3*S*,4*S*)-**3s**
	

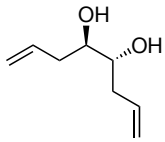
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	9.952	7572252	49.984	1	10.044	25657133	85.675
2	11.801	7576957	50.016	2	11.095	4289754	14.325

Hexa-1,5-diene-3,4-diyl bis(2-methylpropanoate) (4s)

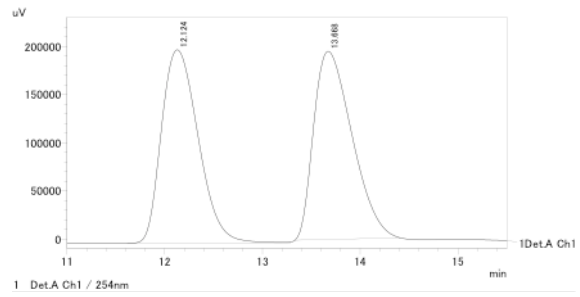
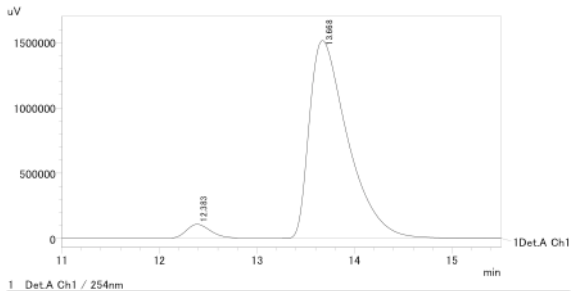


<2% conversion from kinetic resolution of *rac*-**2s** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83–5.69 (m, 2H), 5.44–5.37 (m, 2H), 5.32 (d, J = 16.9 Hz, 2H), 5.26 (d, J = 10.5 Hz, 2H), 2.57 (sep, J = 6.9 Hz, 2H), 1.17 (d, J = 6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 132.4, 119.1, 74.1, 34.2, 19.1, 19.0; IR (KBr) 2979, 1744, 1732, 1472, 1254, 1190, 1152, 988 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{14}H_{23}O_4$ 255.1591, found 255.1602.

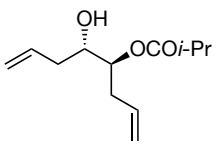
(4*R*,5*R*)-Octa-1,7-diene-4,5-diol (2t)[108]



48% recovery from kinetic resolution of *rac*-**2t** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding dibenzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 12.4 min (minor) and T_R = 13.7 min (major), 96:4 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.0, 10.0, 7.1 Hz, 2H), 5.22–5.10 (m, 4H), 3.55 (bs, 2H), 2.44–2.21 (m, 4H), 2.15 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 118.4, 72.8, 38.4; IR (KBr) 3381, 2909, 1643, 1435, 1049, 916 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_8H_{14}NaO_2$ 165.0886, found 165.0892; $[\alpha]^{22}_D$ +24.3 (*c* 0.68, EtOH, 96:4 er, (4*R*, 5*R*)-configuration) [lit[108] $[\alpha]_D$ –43.8 [*c* 0.016, EtOH, (4*S*, 5*S*)-configuration]].

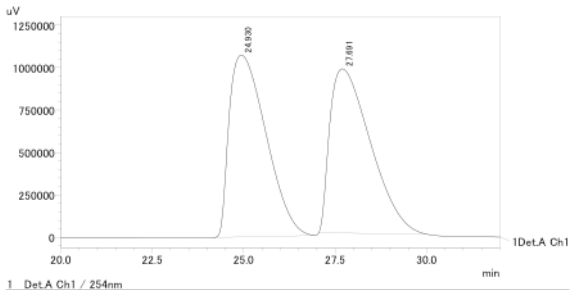
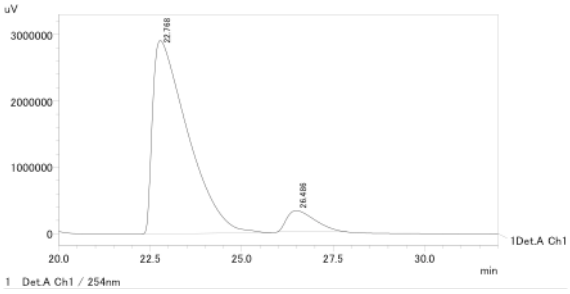
Racemic sample of corresponding benzoate of **2t**				Corresponding benzoate of (4*R*,5*R*)-**2t**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	12.124	5261944	49.732	1	12.383	1742451	4.021
2	13.668	5318622	50.268	2	13.668	41588101	95.979

(4*S*,5*S*)-5-Hydroxyocta-1,7-dien-4-yl isobutyrate (3t)

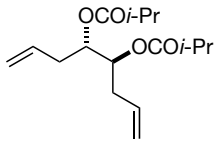


51% conversion from kinetic resolution of *rac*-**2t** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined with corresponding 4-nitorobenzoate by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99.4/0.6, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 22.8 min (major) and T_R = 26.5 min (minor), 92:8 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ

5.90–5.67 (m, 2H), 5.18–5.02 (m, 4H), 4.94–4.86 (m, 1H), 3.71 (quin, J = 4.2 Hz, 1H), 2.58 (sep, J = 7.0 Hz, 1H), 2.52–2.33 (m, 2H), 2.32–2.13 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 134.1, 133.5, 118.5, 118.2, 74.4, 71.4, 38.4, 35.5, 34.3, 19.3, 19.2, 19.0; IR (KBr) 3478, 2978, 1732, 1714, 1643, 1159, 916 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{12}H_{21}O_3$ 213.1485, found 213.1504; $[\alpha]^{24}_D$ –12.5 (*c* 1.0, EtOH, 92:8 er, (4*S*, 5*S*)-configuration).

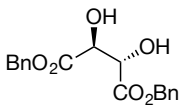
Racemic sample of corresponding nitrobenzoate of **3t**				Corresponding nitrobenzoate of (4*S*,5*S*)-**3t**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	24.930	74791991	50.003	1	22.768	194177973	91.826
2	27.691	74782394	49.997	2	26.486	17285376	8.174

Octa-1,7-diene-4,5-diyl bis(2-methylpropanoate) (4t)



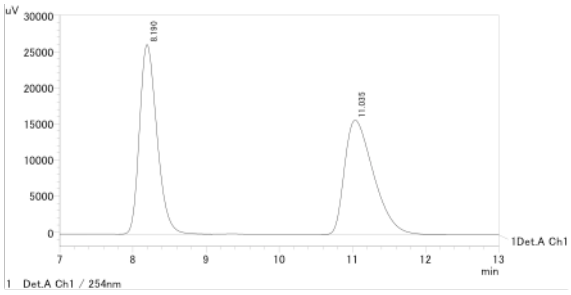
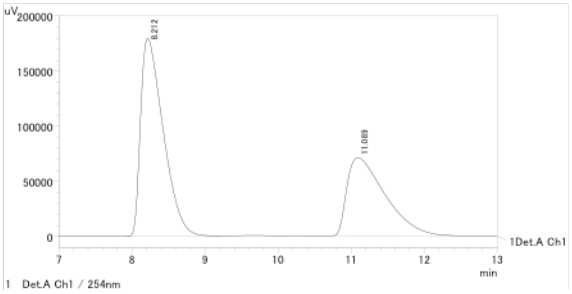
<2% conversion from kinetic resolution of *rac*-**2t** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77–5.63 (m, 2H), 5.11–5.01 (m, 6H), 2.56 (sep, J = 7.0 Hz, 2H), 2.41–2.21 (m, 4H), 1.17 (d, J = 7.0 Hz, 6H), 1.16 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 132.9, 118.5, 72.2, 35.6, 34.3, 19.2, 19.1; IR (KBr) 3460, 2976, 1732, 1472, 1159, 989, 928 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{16}H_{27}O_4$ 283.1904, found 283.1914.

Dibenzyl (2*S*,3*S*)-2,3-dihydroxysuccinate (2u)[109]

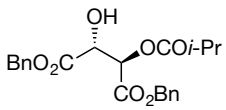


60% recovery from kinetic resolution of *rac*-**2u** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 70/30, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.2 min (major) and T_R = 11.1 min (minor), 60:40 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 10H), 5.30 (d, J = 12.1 Hz, 2H), 5.25 (d, J = 12.1 Hz, 2H), 4.61 (d, J = 7.0 Hz, 2H), 3.14 (d, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 134.9, 128.8, 128.5, 72.2, 68.2; IR (KBr) 3474, 1736, 1499, 1456, 1271, 1217, 1126, 1094, 732 cm^{-1}; $[\alpha]^{23}_D$ +1.24 (*c* 1.0, $CHCl_3$, 60:40 er, (2*S*, 3*S*)-configuration) [lit[109] $[\alpha]^{24}_D$ –10.2 [*c* 1.03, $CHCl_3$, (2*R*,

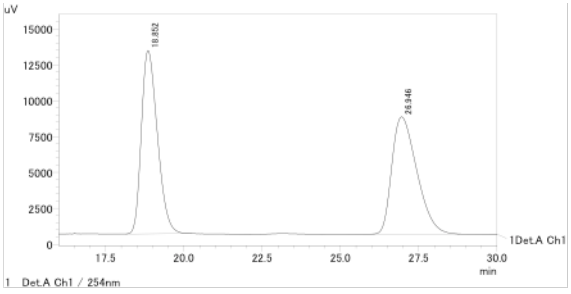
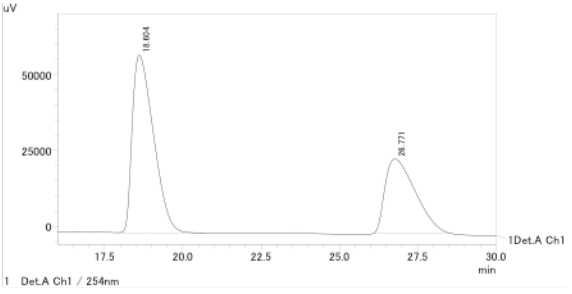
3*R*)-configuration]].

Racemic sample of **2u**				(2*R*,3*R*)-**2u**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.190	435060	49.980	1	8.212	3857258	60.234
2	11.035	435409	50.020	2	11.089	2546522	39.766

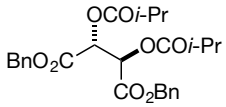
Dibenzyl (2*R*,3*R*)-2-hydroxy-3-(isobutyryloxy)succinate (3u)



33% conversion from kinetic resolution of *rac*-**2u** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined with by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 18.6 min (major) and T_R = 26.8 min (minor), 62.5:37.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10H), 5.50 (d, *J* = 2.3 Hz, 1H), 5.24 (dd, *J* = 11.6, 9.2 Hz, 2H), 5.19 (dd, *J* = 11.6, 9.2 Hz, 2H), 4.82 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.11 (d, *J* = 8.0 Hz, 1H), 2.50 (sep, *J* = 6.9 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 170.6, 166.6, 135.0, 134.6, 128.9, 128.8, 128.7, 128.6, 128.3, 72.7, 70.7, 68.2, 67.7, 33.6, 18.7, 18.7; IR (KBr) 3460, 2972, 1771, 1735, 1458, 1123, 953, 739, 696 cm^{-1}; HRMS (FAB^+) $[M+H]^+$ calculated for $C_{22}H_{25}O_7$ 401.1595, found 401.1599; mp 62.7–62.9 ºC; $[\alpha]^{21}_D$ +1.3 (*c* 1.0, $CHCl_3$, 62.5:37.5 er, (2*R*, 3*R*)-configuration).

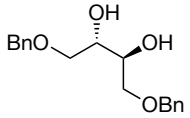
Racemic sample of **3u**				(2*R*,3*R*)-**3u**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.852	455194	50.173	1	18.604	2754711	62.552
2	26.946	452051	49.827	2	26.771	1649164	37.448

Dibenzyl 2,3-bis(isobutyryloxy)succinate (4u)

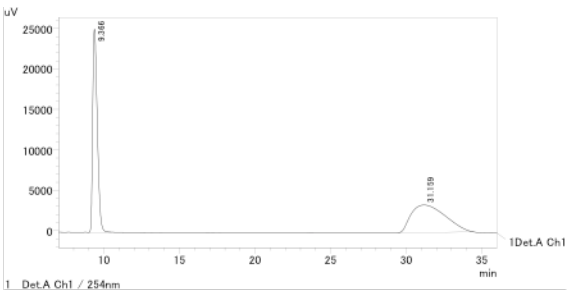
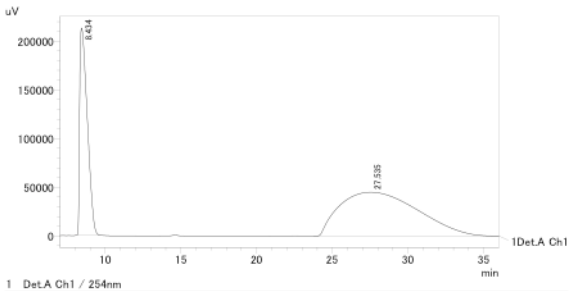


7% conversion from kinetic resolution of *rac*-**2u** under the optimal conditions. Pale yellow liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 10H), 5.74 (s, 2H), 5.19 (d, *J* = 12.4 Hz, 2H), 5.12 (d, *J* = 12.4 Hz, 2H), 2.52 (sep, *J* = 6.9 Hz, 2H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 165.9, 134.8, 128.7, 128.5, 70.6, 67.8, 33.6, 18.7; HRMS (FAB^+) $[M+H]^+$ calculated for $C_{26}H_{31}O_8$ 471.2013, found 471.2027.

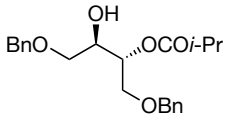
(2*S*,3*S*)-1,4-Bis(benzyloxy)butane-2,3-diol (2v)[110]



61% recovery from kinetic resolution of *rac*-**2v** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 80/20, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.4 min (minor) and T_R = 27.5 min (major), 68.5:32.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 10H), 4.57 (d, *J* = 11.9 Hz, 2H), 4.53 (d, *J* = 11.9 Hz, 2H), 3.92–3.84 (m, 2H), 3.67–3.55 (m, 4H), 2.78 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.4, 127.7, 73.4, 71.8, 70.5; IR (KBr) 3418, 3333, 2913, 2866, 1452, 1358, 1088, 700 cm^{-1}; $[\alpha]^{24}_D$ +2.3 (*c* 3.8, $CHCl_3$, 68.5:31.5 er, (2*S*, 3*S*)-configuration) [lit[110] $[\alpha]^{24}_D$ +6.16 [*c* 3.83, $CHCl_3$, (2*S*, 3*S*)-configuration]].

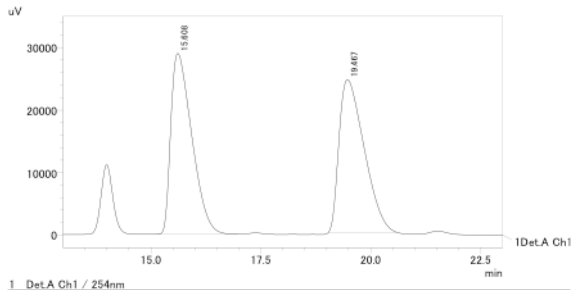
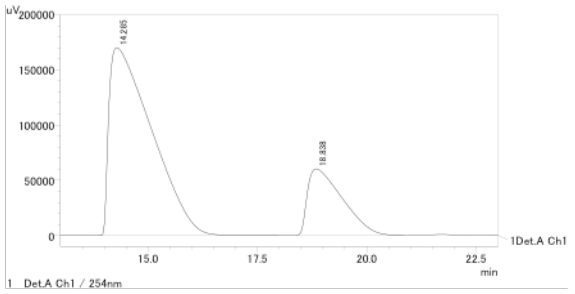
Racemic sample of corresponding benzoate of **2v**				Corresponding benzoate of (2*S*,3*S*)-**2v**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	9.366	531058	49.848	1	8.434	7442758	31.509
2	31.159	534291	50.152	2	27.535	16178426	68.491

(2*R*,3*R*)-1,4-Bis(benzyloxy)-3-hydroxybutan-2-yl isobutyrate (3v)

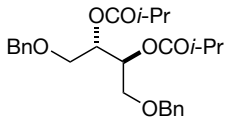


33% conversion from kinetic resolution of *rac*-**2v** under the optimal conditions. Yellow liquid. Enantiomeric ratio was determined with by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 14.3 min (major) and T_R = 18.8 min (minor), 78:22 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 10H), 5.15 (dd, *J* = 8.7, 5.0 Hz, 1H), 4.55 (d, *J* = 13.3 Hz,

1H), 4.51 (s, 2H), 4.49 (d, *J* = 13.3 Hz, 1H), 4.13–4.05 (m, 1H), 3.72 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.65 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.52 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.47 (dd, *J* = 9.6, 6.4 Hz, 1H), 2.67 (bs, 1H), 2.58 (sep, *J* = 7.0 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (MHz, $CDCl_3$) δ 176.8, 137.8, 137.8, 128.5, 127.9, 127.9, 127.7, 73.5, 73.4, 71.7, 70.9, 70.1, 69.3, 34.1, 19.1, 19.0; IR (KBr) 3458, 2872, 2359, 1732, 1454, 752 cm^{-1}; HRMS (ESI$^+$) $[M+H]^+$ calculated for $C_{22}H_{29}O_5$ 373.201, found 373.1994; $[\alpha]^{22}_D$ +4.0 (*c* 1.0, $CHCl_3$, 78:22 er, (2*R*, 3*R*)-configuration).

Racemic sample of **3v**				(2*R*,3*R*)-**3v**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.608	964121	49.795	1	14.285	11536499	77.651
2	19.467	972052	50.205	2	18.838	3320269	22.349

1,4-Bis(benzyloxy)butane-2,3-diyl bis(2-methylpropanoate) (4v)

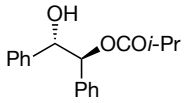


6% conversion from kinetic resolution of *rac*-**2v** under the optimal conditions. Colorless liquid. Enantiomeric ratio was not analyzed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10H), 5.37 (dt, *J* = 7.6, 4.5 Hz, 2H), 4.51 (d, *J* = 12.4 Hz, 2H), 4.42 (d, *J* = 12.4 Hz, 2H), 3.55 (d, *J* = 4.5 Hz, 4H), 2.55 (sep, *J* = 7.1 Hz, 2H), 1.14 (d, *J* = 7.1 Hz, 6H), 1.13 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 137.9, 128.5, 127.9, 73.3, 70.7, 68.4, 34.1, 19.1, 19.0; IR (KBr) 2974, 2936, 1732, 1456, 1148, 964, 737 cm^{-1}; HRMS (ESI$^+$) $[M+Na]^+$ calculated for $C_{26}H_{34}O_6Na$ 465.2248, found 465.2223.

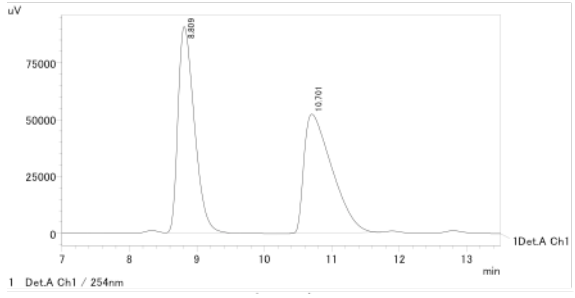
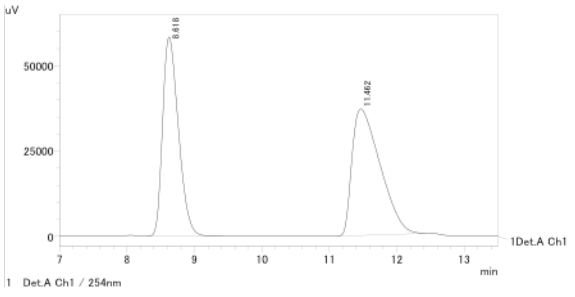
Procedure of investigation of the subsequent kinetic resolution step and HPLC chart for 3a and 4a (Scheme 1)

In a dry screw-top test tube, to a solution of *rac*-**3a** (20.0 mg, 70.3 μmol), TMEDA (7.88 μL, 52.5 μmol), and stock solution of **1d** (5.00 mM in THF, 70.0 μL, 0.350 μmol) in THF (280 μL) was added (*i*-PrCO)$_2$O (6.76 μL, 52.5 μmol) at –78 ºC. The reaction mixture was stirred for 9 h at –78 ºC, and then MeOH (1 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexan/Et_2O = 1:1, v/v) to give the crude mixture. The conversion was determined by ^{1}H NMR analysis of the crude mixture. The enantiomeric ratios of recovered monoacylate **3a** and diacylate **4a** were determined by chiral HPLC analysis of the crude mixture.

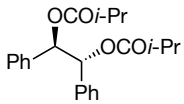
(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl isobutyrate (3a)



90% recovery from kinetic resolution of *rac*-**3a** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.6 min (minor) and T_R = 11.5 min (major), 53:47 er. Detailed analytical data of **3a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

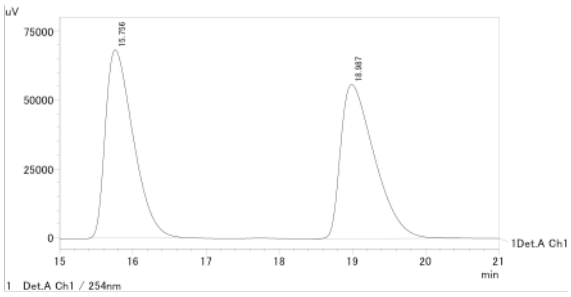
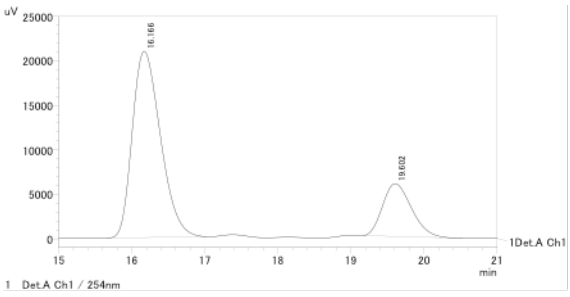
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.618	952338	46.958
2	10.701	1505824	49.635	2	11.462	1075733	53.042

(1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl bis(2-methylpropanoate) (4a)



10% conversion from kinetic resolution of *rac*-**3a** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 99/1, v/v, flow rate = 0.500 mL/min, 30 °C, UV = 254 nm), T_R = 16.1 min (major) and T_R = 19.6 min (minor), 77.5:22.5 er. Detailed analytical

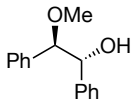
data of **4a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of **4a**				(1*R*,2*R*)-**4a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.756	1802963	50.178	1	16.166	561163	77.487
2	18.987	1790206	49.822	2	19.602	163036	22.513

General procedure for control experiments with various substrates and analytical data for 7–12 (Scheme 2)

In a dry screw-top test tube, to a solution of *rac*-**7**, **8**, or **9** (0.3 mmol), TMEDA (0.225 mmol), and **1d** (1.5 μmol) in THF (1.50 mL) was added (*i*-PrCO)$_2$O (0.75 equiv) at –78 ºC. The reaction mixture was stirred for 9 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexan/Et_2O = 1:1, v/v) to give the crude mixture. The conversion and ratio of mono/diacylate were determined by ^{1}H NMR analysis of the crude mixture. The enantiomeric ratio of monoacylate and recovered substrate were determined by chiral HPLC analysis of the crude mixture.

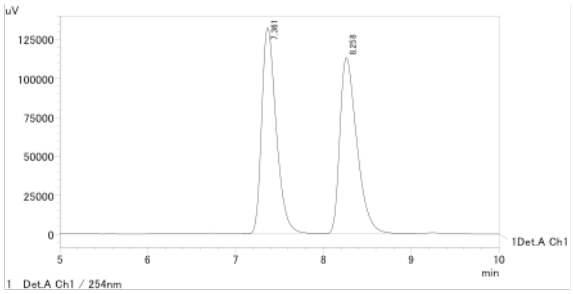
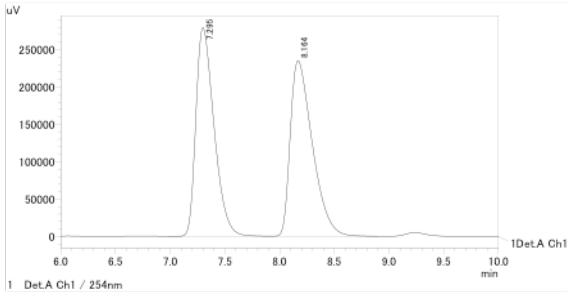
(1*R*,2*R*)-2-Methoxy-1,2-diphenylethan-1-ol (7)[15,111]



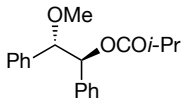
92% recovery from kinetic resolution of *rac*-**7** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 7.3 min (minor) and T_R = 8.2 min (major), 49:51 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.13 (m, 6H), 7.07–6.96 (m, 4H), 4.65 (d, *J* = 8.2 Hz, 1H), 4.12 (d, *J* = 8.2 Hz, 1H), 3.52 (s, 1H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 137.5, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 89.3, 78.7, 56.9; IR (KBr) 3462, 2872, 1452, 1204, 1099, 976, 698 cm^{-1}; $[\alpha]^{23}_D$ +0.7 (*c* 1.5, $CHCl_3$, 51:49 er, (1*R*, 2*R*)-configuration) [lit[111] $[\alpha]^{25}_D$ +53.3 [*c* 1.5, $CHCl_3$, (1*R*,

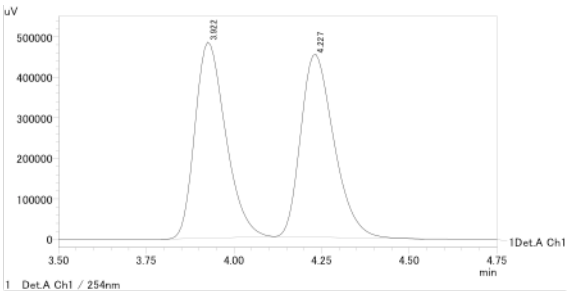
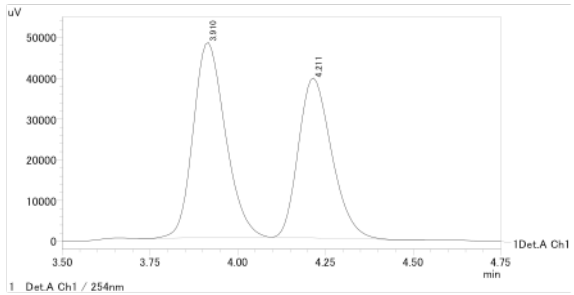
2*R*)-configuration, 92% ee]].

Racemic sample of **7**				(1*R*,2*R*)-**7**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	7.361	1528921	49.952	1	7.295	3217801	49.440
2	8.258	1531879	50.048	2	8.164	3290755	50.560

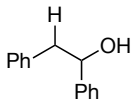
(1*S*,2*S*)-2-Methoxy-1,2-diphenylethyl isobutyrate (10)



8% conversion from kinetic resolution of *rac*-**7** under the optimal conditions. Colorless liquid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 3.9 min (major) and T_R = 4.2 min (minor), 54:46 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.14 (m, 6H), 7.11–7.03 (m, 4H), 5.94 (d, *J* = 7.1 Hz, 1H), 4.40 (d, *J* = 7.1 Hz, 1H), 3.26 (s, 3H), 2.63 (sep, *J* = 7.2 Hz, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 137.5, 137.4, 128.1, 128.0, 128.0, 127.9, 127.5, 86.4, 78.0, 57.5, 34.3, 19.1, 19.0; IR (KBr) 2976, 2938, 1736, 1456, 1153, 700 cm^{-1}; HRMS (ESI^+) $[M+H]^+$ calculated for $C_{19}H_{23}O_3$ 299.1642, found 299.1664; $[\alpha]^{24}_D$ +1.6 (*c* 0.47, $CHCl_3$, 54:46 er, (1*S*, 2*S*)-configuration).

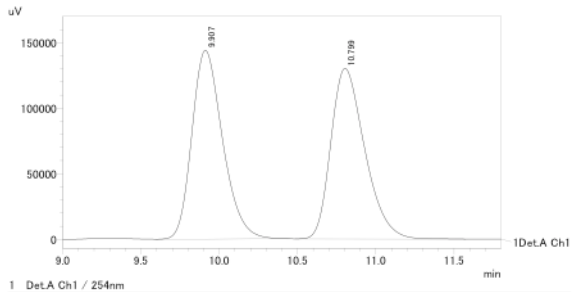
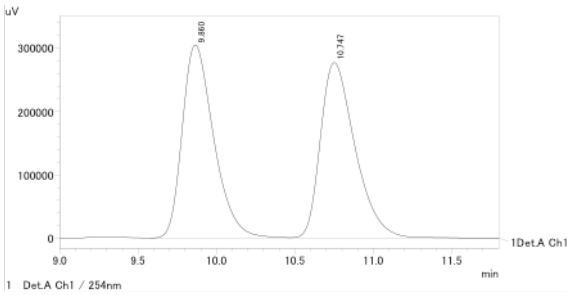
Racemic sample of **7**				(1*S*,2*S*)-**10**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	3.922	2947710	49.801	1	3.910	305540	54.134
2	4.227	2971225	50.199	2	4.211	258879	45.866

rac-1,2-Diphenylethanol (8)[112]

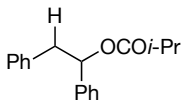


78% recovery from kinetic resolution of *rac*-**8** under the optimal conditions.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® IA-3 (hexane/*i*-PrOH = 97/3, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 9.9 min and T_R = 10.7 min, 50:50 er; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.33–7.27 (m, 3H), 7.26–7.19 (m, 3H), 4.91 (ddd, *J* = 8.7, 4.8, 3.2 Hz, 1H), 3.05 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.99 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.99 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 138.2, 129.6, 128.6, 128.5, 127.7, 126.7, 126.0, 75.5, 46.2; IR (KBr) 3318, 3026, 2862, 1491, 1456, 1026, 762, 696 cm^{-1}.

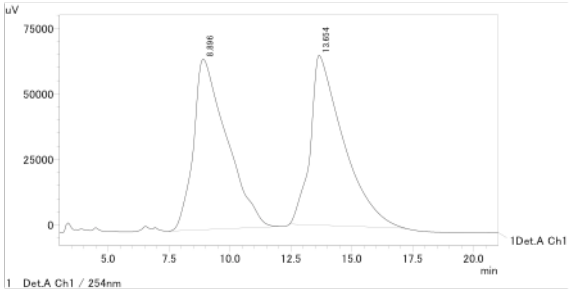
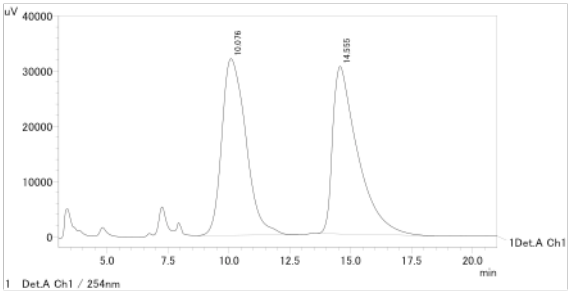
Racemic sample of **8**				Recovered **8**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	9.907	1966398	50.084	1	9.860	4259189	49.962
2	10.799	1959767	49.916	2	10.747	4265729	50.038

rac-1,2-Diphenylethyl isobutyrate (11)

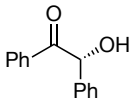


22% conversion from kinetic resolution of *rac*-**8** under the optimal conditions.

Colorless liquid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OJ-H (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 10.1 min and T_R = 14.6 min, 50:50 er; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.21 (m, 7H), 7.19 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.13–7.10 (m, 2H), 5.94 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.17 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.06 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.51 (sep, *J* = 7.0 Hz, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 140.5, 137.2, 129.7, 128.5, 128.3, 128.0, 126.6, 126.5, 76.3, 43.3, 34.2, 19.0, 18.9; IR (KBr) 2974, 1732, 1454, 1152, 758, 698 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{18}H_{20}O_2Na$ 291.1355, found 291.1327.

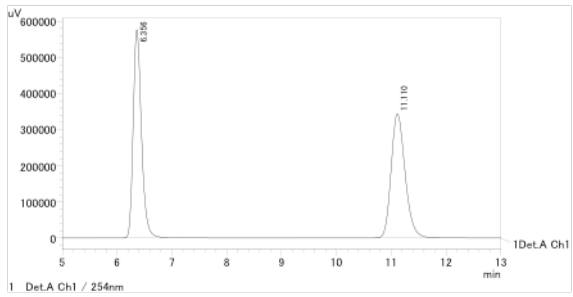
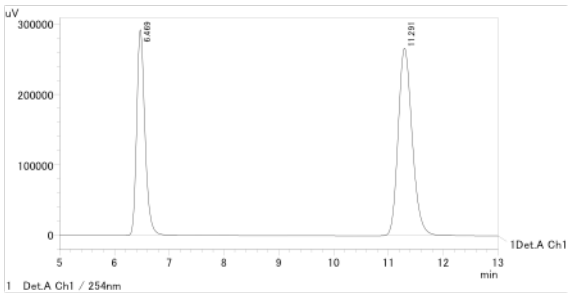
Racemic sample of **11**				Recovered **11**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.896	6192535	50.062	1	10.076	2204503	50.332
2	13.654	6177179	49.938	2	14.555	2175461	49.668

(*R*)-Benzoin (9)[113]

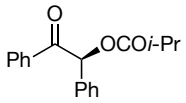


62% recovery from kinetic resolution of *rac*-**9** under the optimal conditions.

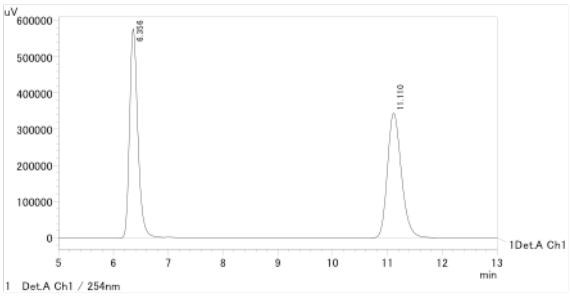
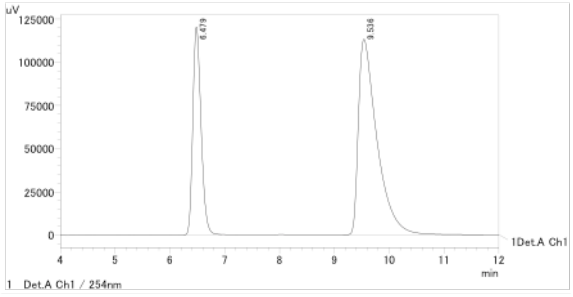
Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 85/15, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.5 min (minor) and T_R = 11.3 min (major), 61:39 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.87 (m, 2H), 7.52 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.36–7.27 (m, 5H), 5.95 (d, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 139.1, 134.0, 133.6, 129.2 (2), 128.8, 128.7, 127.9, 76.3; IR (KBr) 3474, 1734, 1454, 1125, 1093, 733 cm^{-1}; $[\alpha]^{23}_D$ –21.0 (*c* 1.0, acetone, 61:39 er, (*R*)-configuration) [lit[113] $[\alpha]^{25}_D$ –76.0 [*c* 1, acetone, (*R*)-configuration, 98% ee]].

Racemic sample of **9**				(*R*)-**9**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	6.356	6003261	49.747	1	6.469	3053545	39.176
2	11.110	6064301	50.253	2	11.291	4740888	60.824

(*S*)-2-Oxo-1,2-diphenylethyl isobutyrate (12)

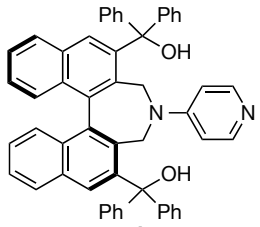


38% conversion from kinetic resolution of *rac*-**9** under the optimal conditions. Colorless solid. Enantiomeric ratio was determined by chiral HPLC with DICEL CHIRALCEL® OD-H (hexane/*i*-PrOH = 98/2, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 6.5 min (minor) and T_R = 9.5 min (major), 68:32 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.52 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.43–7.32 (m, 5H), 6.83 (s, 1H), 2.72 (sep, *J* = 7.2 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 176.7, 134.9, 133.8, 133.5, 129.3, 129.1, 128.9, 128.7, 128.6, 77.4, 33.9, 19.1, 18.8; IR (KBr) 2982, 2938, 1724, 1697, 1120, 1155, 934, 758 cm^{-1}; HRMS (FAB$^+$) $[M+H]^+$ calculated for $C_{18}H_{18}O_3Na$ 305.1148, found 305.1144; mp 79.2–80.0 ºC; $[\alpha]^{22}_D$ +53.9 (*c* 1.0, acetone, 68:32 er, (*R*)-configuration).

Racemic sample of **12**				(*S*)-**12**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	6.356	6003261	49.747	1	6.479	1250845	31.937
2	11.110	6064301	50.253	2	9.536	2665799	68.063

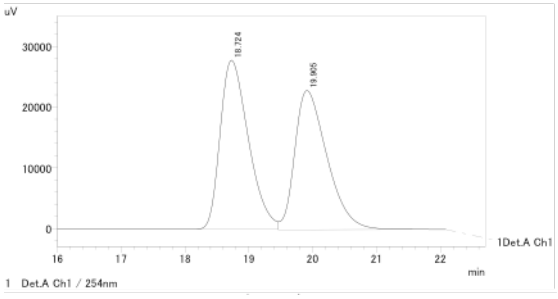
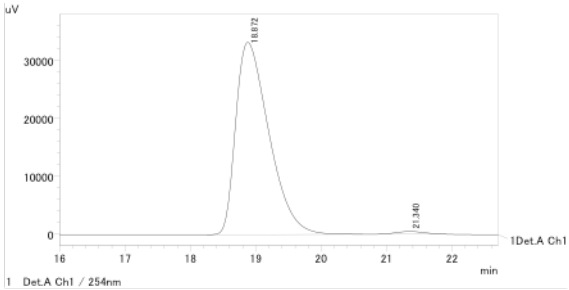
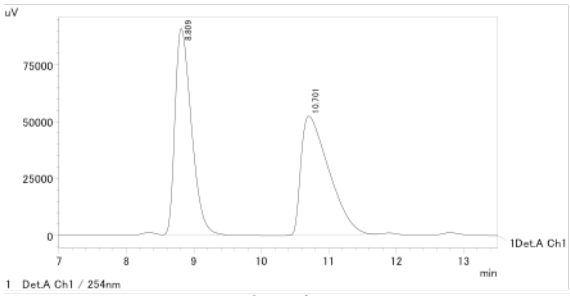
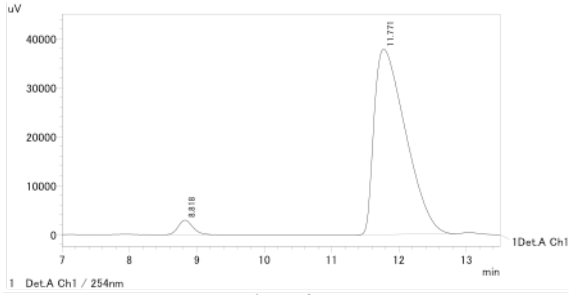
General procedure for control experiments focused on hydroxy groups on the catalyst (Scheme 3)

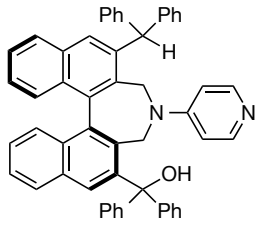
In a dry screw-top test tube, to a solution of *rac*-**2a** (0.3 mmol), TMEDA (0.225 mmol), and **1d**, **1da**, **1db, 1dc, 1dd**, or **1k** (1.5 μmol) in THF (1.50 mL) was added (*i*-PrCO)$_2$O (0.75 equiv) at –78 ºC. The reaction mixture was stirred for 9 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexan/Et_2O = 1:1, v/v) to give the crude mixture. The conversions and ratios of mono/diacylate were determined by ^{1}H NMR analysis of the crude mixture. The enantiomeric ratios of monoacylate and recovered substrate were determined by chiral HPLC analysis of the crude mixture.



1d

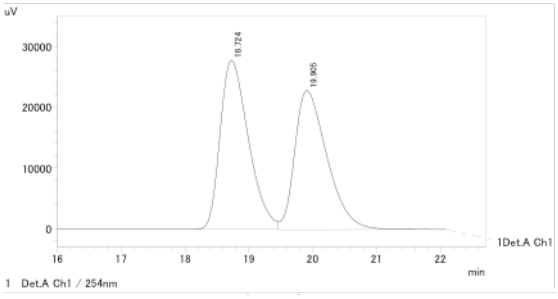
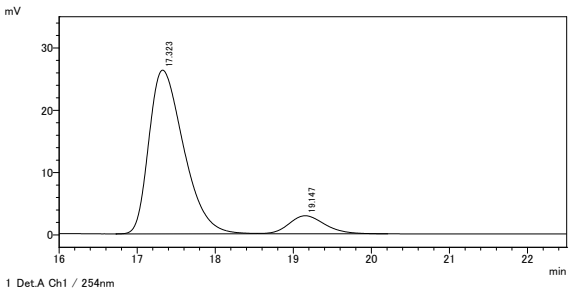
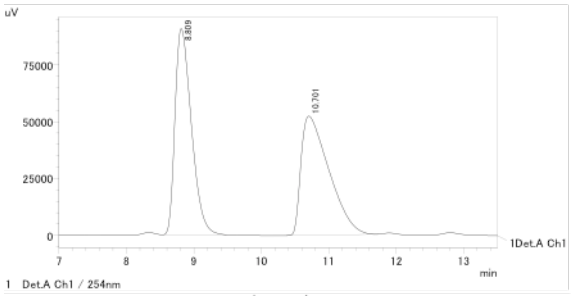
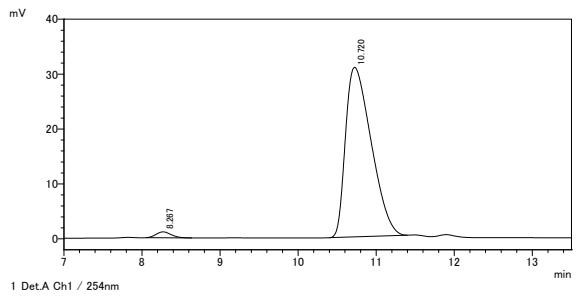
Catalyst

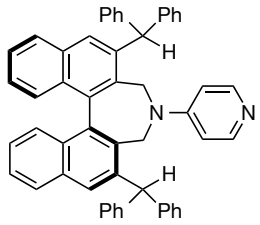
Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	18.872	1172564	98.787
2	19.905	632317	50.202	2	21.340	14395	1.213
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.818	43462	3.406
2	10.701	1505824	49.635	2	11.771	1232480	96.594



1da

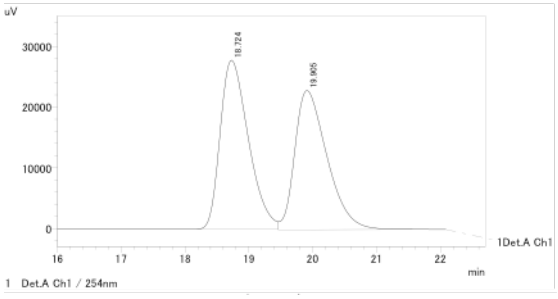
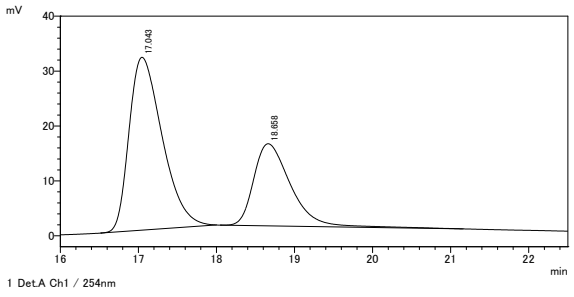
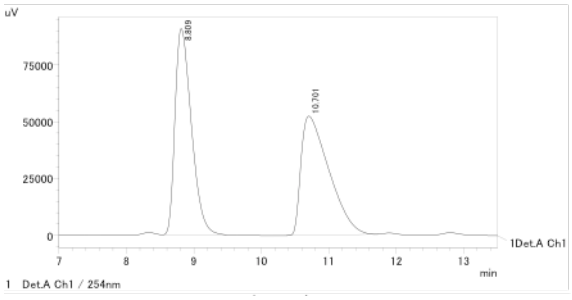
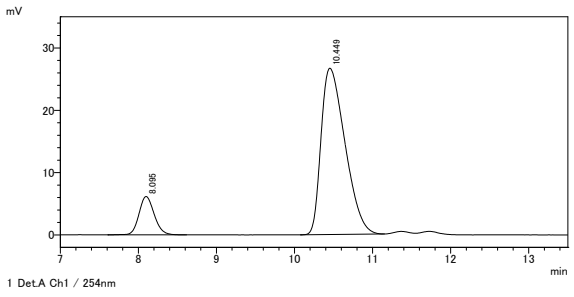
Catalyst

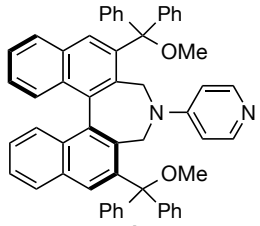
Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	17.323	811676	89.715
2	19.905	632317	50.202	2	19.147	93048	10.285
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.267	14261	1.978
2	10.701	1505824	49.635	2	10.720	706744	98.022



1db

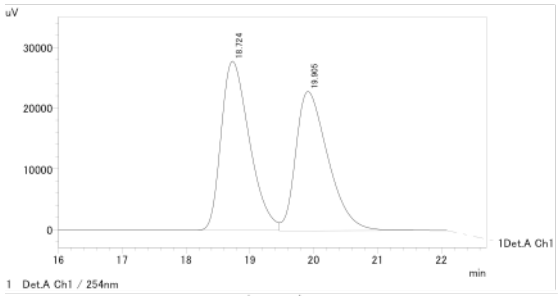
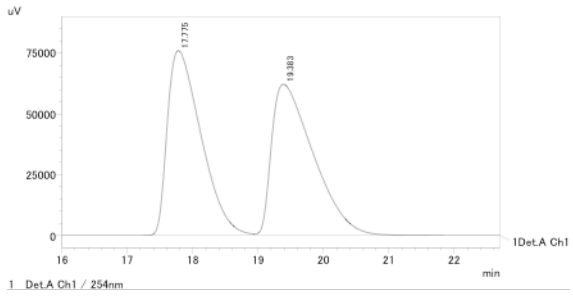
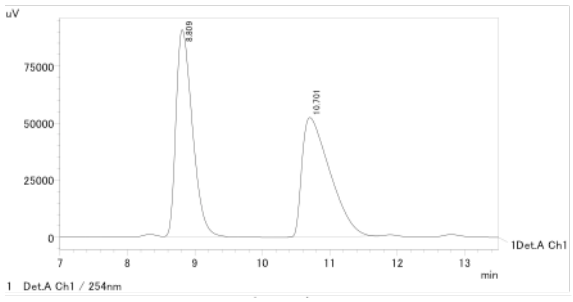
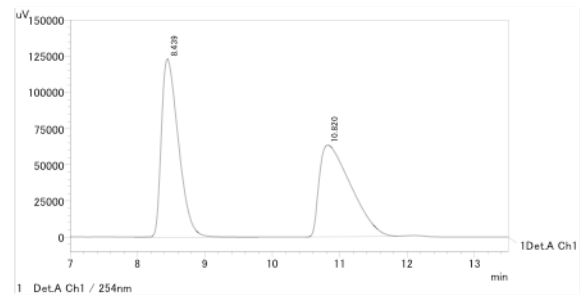
Catalyst

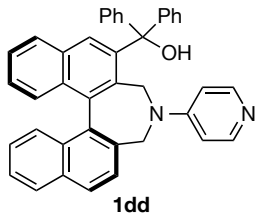
Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	17.043	928463	65.269
2	19.905	632317	50.202	2	18.658	494060	34.731
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.095	83448	12.790
2	10.701	1505824	49.635	2	10.449	569024	87.210



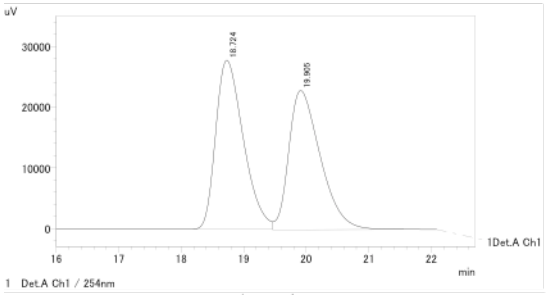
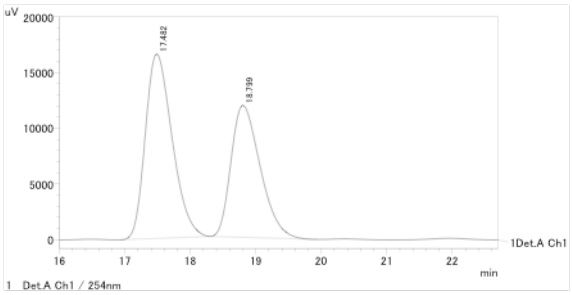
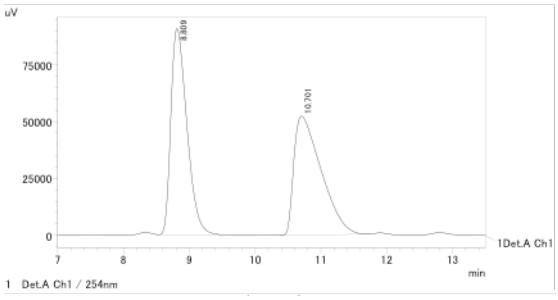
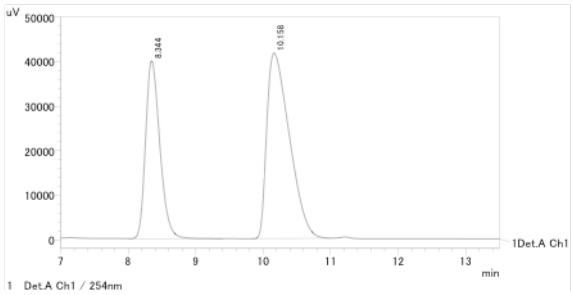
1dc

Catalyst

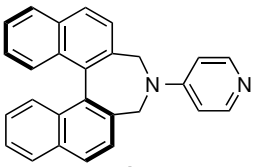
Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	17.775	2726990	49.669
2	19.905	632317	50.202	2	19.383	2763379	50.331
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.439	2160831	51.160
2	10.701	1505824	49.635	2	10.820	2062843	48.840

Catalyst 

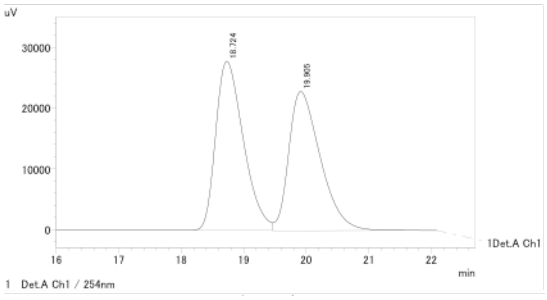
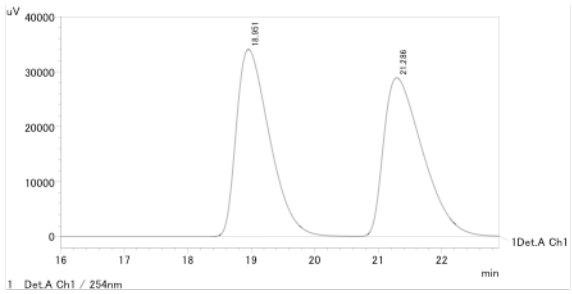
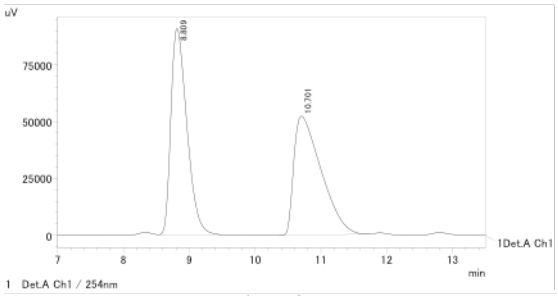
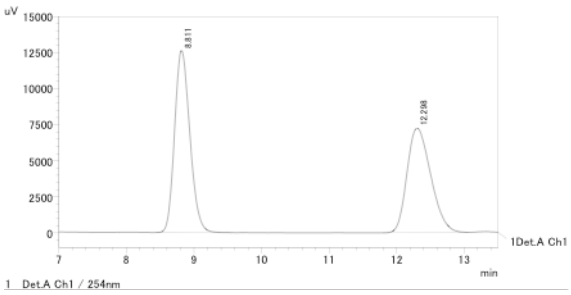
1dd

Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	17.482	471666	56.180
2	19.905	632317	50.202	2	18.799	367896	43.820
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.344	587056	37.715
2	10.701	1505824	49.635	2	10.158	969514	62.285

Catalyst



1k

Racemic sample of **2a**				(1*R*,2*R*)-**2a**			
							
Peak	T_R	Area	Area %	5	T_R	Area	Area %
1	18.724	627240	49.798	1	18.951	1238685	50.046
2	19.905	632317	50.202	2	21.286	1236415	49.954
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.811	198355	52.853
2	10.701	1505824	49.635	2	12.298	176939	47.147

Typical procedure of selective acylation of 1,2-diol in the presence of a secondary carbinol (Scheme 4a)

In a dry screw-top test tube, to a solution of (*S,S*)-**2a** (32.4 mg, 0.151 mmol), (*S*)-**5** (18.2 mg, 0.149 mmol), TMEDA (44.8 μL, 0.301 mmol), and **1d** (1.10 mg, 1.49 μmol) in THF (1.50 mL) was added (*i*-PrCO)$_2$O (49.7 μL, 0.300 mmol) at –78 ºC. The reaction mixture was stirred for 5 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et$_2$O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexane/Et2O = 1/1, v/v) to give the crude mixture. The yield was determined by ^{1}H NMR analysis of the crude mixture using 2-methoxynaphtalene (47.5 mg, 0.300 mmol) as an internal standard.

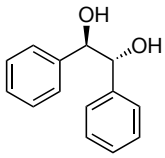
Catalyst	Yield of (*S,S*)-**3a** (%)	Yield of (*S*)-**6** (%)	Yield of (*S,S*)-**4a** (%)
1d (0.5 mol %)	50	<2	<2
DMAP (5 mol %)	14	29	25

Typical procedure of competitive and enantioselective acylation of 1,2-diol and HPLC chart for 2a and 3a (Scheme 4b)

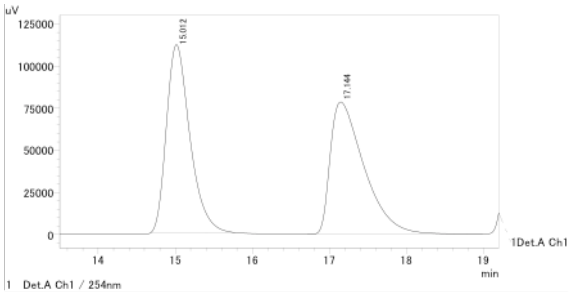
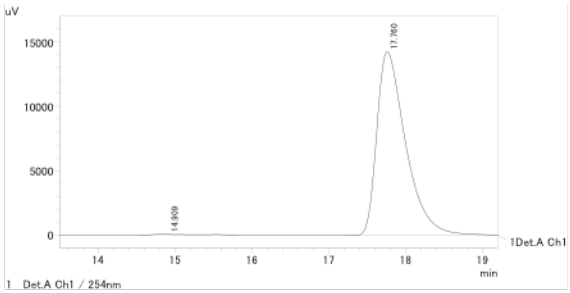
In a dry screw-top test tube, to a solution of *d,l*-**2a** (32.2 mg, 0.150 mmol), *meso*-**2a** (32.1 mg, 0.150 mmol), TMEDA (44.8 μL, 0.301 mmol), and **1d** (1.20 mg, 1.63 μmol) in Et$_2$O (1.50 mL) was added (*i*-PrCO)$_2$O (49.8 μL, 0.300 mol) at –78 ºC. The reaction mixture was stirred for 5 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et$_2$O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexane/Et2O = 1/1, v/v) to give the crude mixture. The yields of acylated products were determined by ^{1}H NMR analysis of the crude mixture using 2-methoxynaphtalene (47.9 mg, 0.303 mmol) as an internal standard. The enantiomeric ratios of **3a** (82:18 er) and recovered *d,l*-**2a** (99:1 er) were determined by chiral HPLC analysis of the crude mixture. *S*-factor (*s* = 20.1) was calculated by kagan's equation. Detailed analytical data of **2a** and **3a** were shown in the following section of "General procedure for substrate scope (Figure 2)".

Catalyst	Yield of **3a** (%)	Yield of **3a´** (%)	Diacylate-**4a** (%)
1d (0.5 mol %) in Et$_2$O	30	<2	<2
DMAP (5 mol %) in Et$_2$O	3	6	32
1d (0.5 mol %) in THF	27	29	<2

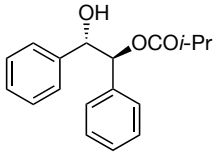
(1*R*,2*R*)-1,2-diphenylethane-1,2-diol (2a)[38]



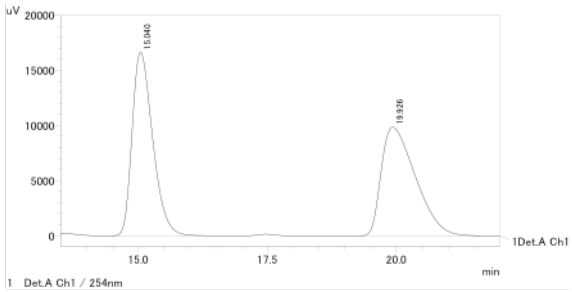
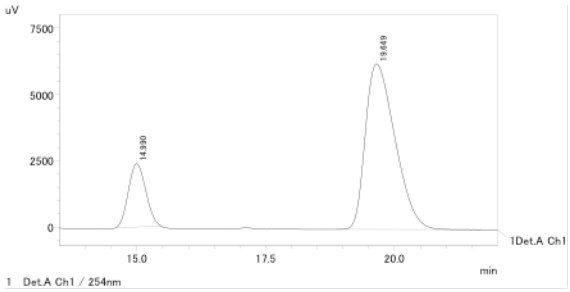
20% recovered yield (^{1}H NMR yield) from competitive and enantioselective acylation of 1,2-diol. Enantiomeric ratio of recovered *d,l*-**2a** was determined by chiral HPLC analysis using DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 14.9 min (minor) and T_R = 17.8 min (major), 99:1 er. Detailed analytical data of **2a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of **2a**				(*S*,*S*)-**2a** (with Et_2O solvent)			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.012	2373433	49.814	1	14.909	3124	0.825
2	17.144	2391191	50.186	2	17.760	375474	99.175

(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl isobutyrate (3a)[63]



30% yield (^{1}H NMR yield) from competitive and enantioselective acylation of 1,2-diol. Enantiomeric ratio of **3a** was determined by chiral HPLC analysis using DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 15.0 min (minor) and T_R = 19.6 min (major), 82:18 er.

Racemic sample of **3a**				(*S*,*S*)-**3a** (with Et_2O solvent)			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	15.040	459940	50.363	1	14.990	55720	18.256
2	19.926	453309	49.637	2	19.649	249501	81.744

General procedure of comparison of various nucleophilic catalysts in monoacylation of (*S*,*S*)-2a (Scheme 5)

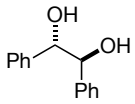
In a dry screw-top test tube, to a solution of (*S*,*S*)-**2a** (0.3 mmol), TMEDA (0.3 mmol), and nucleophilic catalyst (1.5 μmol) (in the cases of using DMAP, PPY, 9-azajulolidine, 5.00 mM (THF) of stock solution was prepared and used (300 μL, 1.5 μmol)) in THF (1.5 mL) was added (*i*-PrCO)$_2$O (0.3 mmol) at –78 ºC. The reaction mixture was stirred for 5 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexane/Et2O = 1/1, v/v) to give the crude mixture. The conversions were determined by ^{1}H NMR analysis of the crude mixture.

Procedure of investigation of the effect of an acylating reagent and HPLC chart for 2a and 3a (Scheme 6)

In a dry screw-top test tube, to a solution of *rac*-**2a** (64.6 mg, 0.302 mmol), TMEDA (33.6 μL, 0.225 mmol), and **1d** (1.10 mg, 1.50 μmol) in THF (1.50 mL) was added *i*-PrCOCl (33.6 μL, 0.225 mmol) at –78 ºC. The reaction mixture was stirred for 9 h at –78 ºC, and then MeOH (3 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexan/Et_2O = 1:1, v/v) to give the crude mixture. The conversion (1% conv) was determined by ^{1}H NMR analysis of the crude mixture. The

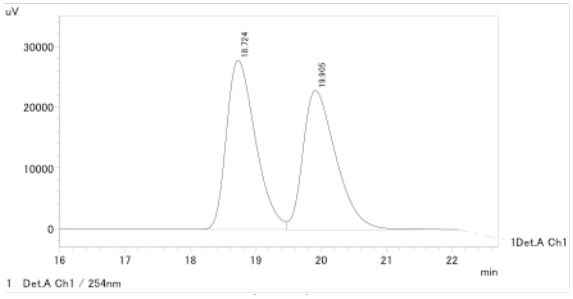
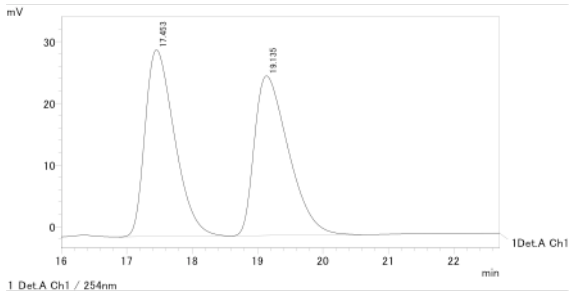
enantiomeric ratios of recovered substrate **2a** and monoacylate **3a** were determined by chiral HPLC analysis of the crude mixture.

rac-1,2-Diphenylethane-1,2-diol (2a)

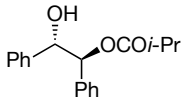


99% recovery from kinetic resolution of *rac*-**2a** under the optimal conditions with 0.75 equiv of *i*-PrCOCl instead of 0.75 equiv of $(i\text{-PrCO})_2O$.

Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 17.4 min and T_R = 20.7 min, 50:50 er. Detailed analytical data of **2a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of **2a**				Recovered **2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	17.453	949306	50.319
2	19.905	632317	50.202	2	19.135	937277	49.681

(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl isobutyrate (3a)



1% conversion from kinetic resolution of *rac*-**2a** under the optimal conditions with 0.75 equiv of *i*-PrCOCl instead of 0.75 equiv of $(i\text{-PrCO})_2O$.

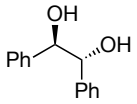
Colorless solid. Enantiomeric ratio was not determined. Detailed analytical data of **3a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Kinetic resolution of *d,l*-hydrobenzoin on multigram scale (Scheme 7a)

In a dry screw-top test tube, to a solution of *rac*-**2a** (10.0 g, 46.7 mmol), TMEDA (5.30 mL, 35.3 mmol), and **1d** (34.4 mg, 46.7 μmol) in THF (46.7 mL) was added dropwise $(i\text{-PrCO})_2O$ (4.51 mL, 35.0 mmol) for 7 min at 0 ºC. The reaction solution was stirred for 30 min at 0 ºC, and then MeOH (20 mL) was added to reaction vessel at 0 ºC in order to consume unreacted $(i\text{-PrCO})_2O$. The resulting solution was allowed to warm up to room temperature and stirred for 30 min. The resulting solution was concentrated *in vacuo*. The residue was subjected to flash column chromatography on a short pad of silica gel (eluent: hexane/Et_2O = 1:1, v/v) to give fraction I

containing mixture of products, and the use of more polar mobile phase (eluent: $CHCl_3$/MeOH = 1:1, v/v) gave fraction II containing **1d**. Fraction I was analyzed by ^1H NMR to determine the conversion (53% conv, mono:di = >99:1) and by chiral HPLC analysis to determine enantiomeric ratio with *s*-factor (**3a**: 88.5:11.5 er, **2a**: 93:7 er, *s* = 20.6). The fraction I was purified by flash column chromatography on silica gel (eluent: hexane/Et_2O = 3:1, v/v) to give (*S,S*)-**3a** (6.90 g, 24.3 mmol, 52% yield) as a colorless solid, (*R,R*)-**2a** (4.68 g, 21.8 mmol, 47% yield) as a colorless solid, and diacylate **4a** (176 mg, 0.497 mmol, 1% yield) as a colorless solid. Separated (*R,R*)-**2a** was recrystallization from THF/hexane to give pure (*R,R*)-**2a** (3.89 g, 18.2 mmol, 39% yield, >99:1 er) as a colorless solid. The fraction II was dissolved in $CHCl_3$ (10 mL) and this solution was washed with saturated aqueous $NaHCO_3$ (10 mL×3), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting solid was recrystallization from $CHCl_3$/hexane to give pure **1d** (33.4 mg, 45.3 μmol, 97% recovery) as a colorless solid.

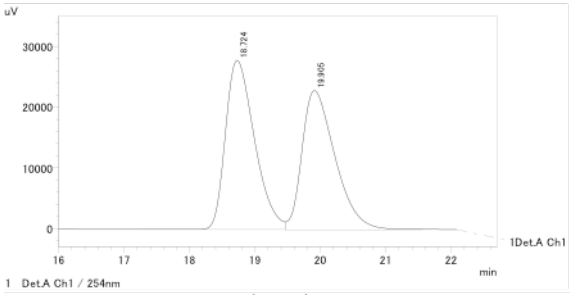
(1*R*,2*R*)-1,2-diphenylethane-1,2-diol (2a)



47% yield (39% yield after recrystallization) from kinetic resolution of *rac*-**2a** under the multigram scale conditions (Scheme 7a).

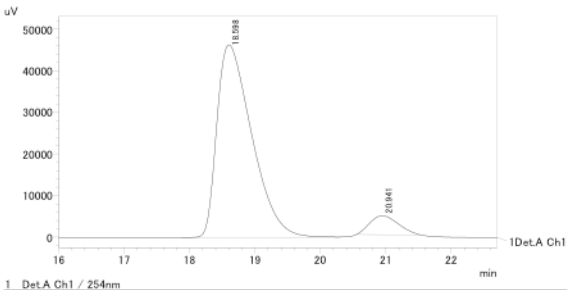
Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 18.6 min (major) and T_R = 20.9 min (minor), 93:7 er (>99:1 er after recrystallization); $[\alpha]^{21}_D$ +94.8 (*c* 1.0, EtOH, >99:1 er, (1*R*, 2*R*)-configuration) [lit[38] $[\alpha]^{28}_D$ +92.7 [*c* 1.0, EtOH, (1*R*, 2*R*)-configuration, 97% ee]]. Detailed analytical data of **2a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of **2a**



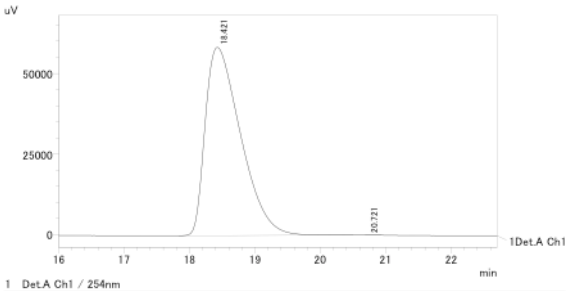
Peak	T_R	Area	Area %
1	18.724	627240	49.798
2	19.905	632317	50.202

(1*R*,2*R*)-**2a**



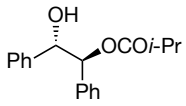
Peak	T_R	Area	Area %
1	18.598	1707616	92.602
2	20.941	136413	7.398

(1*R*,2*R*)-**2a** after recrystallization



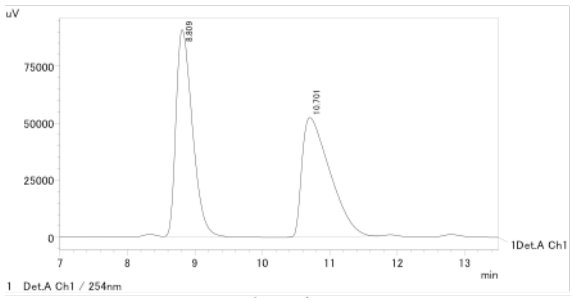
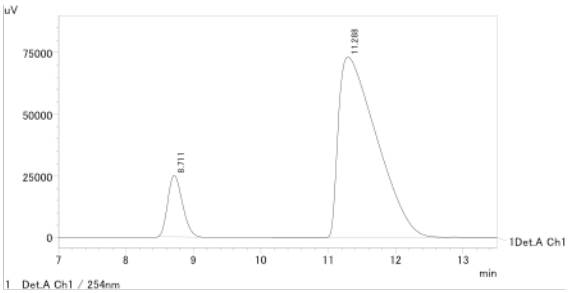
Peak	T_R	Area	Area %
1	18.421	2199468	99.996
2	20.721	85	0.004

(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl isobutyrate (3a)



52% yield from kinetic resolution of *rac*-**2a** under the multigram scale conditions (Scheme 7a).

Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.7 min (minor) and T_R = 11.3 min (major), 88.5:11.5 er; $[\alpha]^{24}_D$ +11.8 (*c* 1.0, MeOH, 88.5:111.5 er (1*S*, 2*S*)-configuration) [lit[63] $[\alpha]^{22}_D$ +1.7 [*c* 1.0, MeOH, (1*S,* 2*S*) form, 65% ee]. Detailed analytical data of **3a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

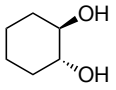
Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.711	376660	88.485
2	10.701	1505824	49.635	2	11.288	2894326	11.515

Kinetic resolution of *trans*-cyclohexane-1,2-diol on multigram scale (Scheme 7b)

In a dry screw-top test tube, to a suspension of *rac*-**2k** (10.0 g, 86.1 mmol), TMEDA (9.80 mL, 65.3 mmol), and **1d** (63.3 mg, 85.9 μmol) in THF (86.1 mL) was added dropwise $(i\text{-PrCO})_2O$ (8.32 mL, 64.6 mmol) for 2 min at 0 ºC. The reaction solution was stirred for 30 min at 0 ºC, and then MeOH (20 mL) was added to reaction vessel at 0 ºC in order to consume unreacted $(i\text{-PrCO})_2O$. The resulting solution was allowed to warm up to room temperature and stirred for 30 min. The resulting solution was concentrated *in vacuo*. The residue was subjected to flash column chromatography on a short pad of silica gel (eluent: EtOAc) to give fraction I containing mixture of products, and the use of more polar mobile phase (eluent: $CHCl_3$/MeOH = 1:1, v/v) gave fraction II containing **1d**. Fraction I was analyzed by ^{1}H NMR to determine the conversion (58% conv, mono:di = >99:1). The fraction I was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 2:1, v/v) to give (*S,S*)-**3k** (9.54 g, 51.2 mmol, 59% yield) as a pale yellow liquid and (*R,R*)-**2k** (4.15 g, 35.7 mmol, 41% yield) as a colorless solid. Analytical amount of separated (*S,S*)-**3k** and (*R,R*)-**2k** were converted to corresponding benzoyl ester (using benzoyl chloride [BzCl] (1.5 or 2.5 equiv), TMEDA (1.5 or 2.5 equiv), in CH_2Cl_2 (0.1 M) at room

temperature) to determined enantiomeric ratios by chiral HPLC analysis (**3k**: 86:14 er, **2k**: 96:4 er). Separated (*R,R*)-**2k** was recrystallization from THF/hexane to give pure (*R,R*)-**2k** (3.39 g, 29.2 mmol, 34% yield, >99:1 er corresponding dibenzoate) as a colorless solid. The fraction II was dissolved in $CHCl_3$ (10 mL) and this solution was washed saturated aqueous $NaHCO_3$ (10 mL×3), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting solid was recrystallization from $CHCl_3$/hexane to give pure **1d** (60.7 mg, 82.4 μmol, 96% recovery) as a colorless solid.

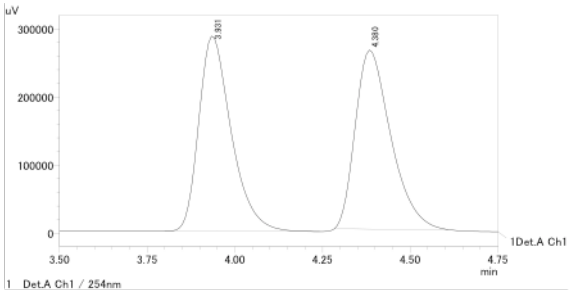
(1*R*,2*R*)-Cyclohexane-1,2-diol (2k)



41% yield (34% yield after recrystallization) from kinetic resolution of *rac*-**2k** under the multigram scale conditions (Scheme 7b).

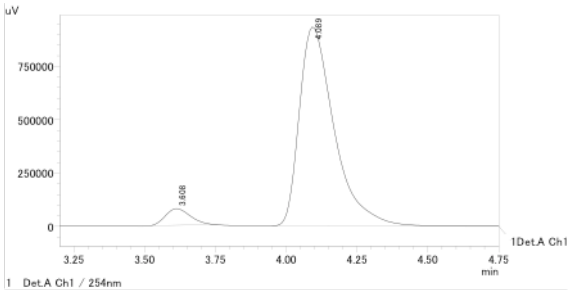
Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 3.6 min (minor) and T_R = 4.1 min (major), 96:4 er (>99:1 er after recrystallization); $[\alpha]^{24}_D$ –44.2 (*c* 0.18, H_2O, >99:1 er, (1*R*, 2*R*)-configuration) [lit[96] $[\alpha]^{20}_D$ –38.4 [*c* 0.17, H_2O, (1*R*, 2*R*)-configuration, 96% ee]]. Detailed analytical data of **2a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of corresponding benzoate of **2k**



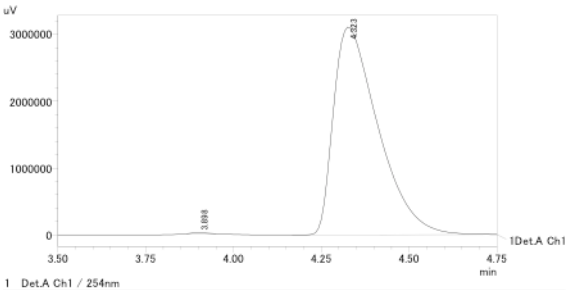
Peak	T_R	Area	Area %
1	3.931	1847077	49.944
2	4.380	1851197	50.056

Corresponding benzoate of (1*R*,2*R*)-**2k**



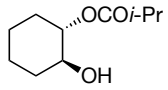
Peak	T_R	Area	Area %
1	3.608	368383	4.409
2	4.089	7987476	95.591

Corresponding benzoate of (1*R*,2*R*)-**2k** after recrystallization



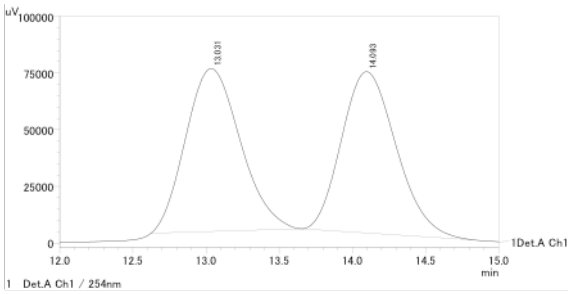
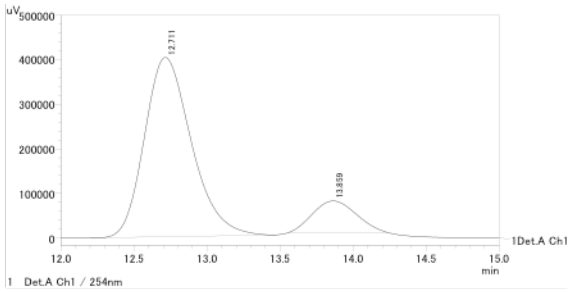
Peak	T_R	Area	Area %
1	3.898	34928	0.127
2	4.323	27479409	99.873

(1*S*,2*S*)-2-Hydroxycyclohexyl isobutyrate (3k)



59% yield from kinetic resolution of *rac*-**2k** under the multigram scale conditions (Scheme 7b).

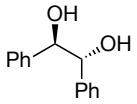
Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 12.7 min (major) and T_R = 13.9 min (minor), 86:14 er. Detailed analytical data of **2a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of corresponding benzoate of **3k**				Corresponding benzoate of (1*S*,2*S*)-**3k**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	13.031	1870085	50.261	1	12.711	8980738	86.000
2	14.093	1850663	49.739	2	13.859	1461937	14.000

Recyclability of catalyst 1d (Scheme 7c)

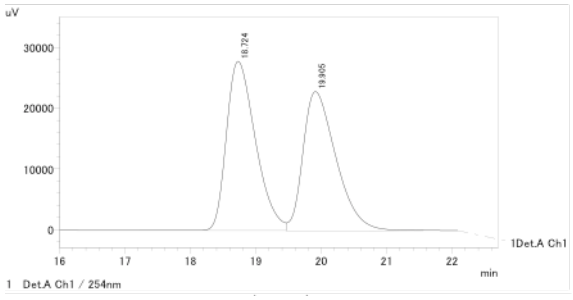
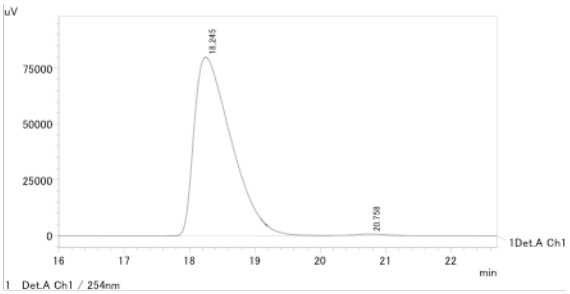
In a dry screw-top test tube, to a solution of substrate (64.1 mg, 0.299 mmol), TMEDA (33.8 µL, 0.225 mmol), and recovered **1d** (1.1 mg, 1.49 µmol) in THF (1.50 mL) was added $(i\text{-PrCO})_2O$ (29.0 µmol, 0.225 mmol) at –78 ºC. The reaction mixture was stirred for 9 h at –78 ºC, and then MeOH (5 mL) was added to reaction vessel at –78 ºC. The resulting solution was warmed up to room temperature and stirred for 15 min at room temperature. After stirring for 15 min, the resulting solution was transferred to other flask using Et_2O to wash the reaction vessel and concentrated in *vacuo*. The residue was passed through a short pad of silica gel (eluent: hexan/Et_2O = 1:1, v/v) to give the crude mixture. The conversion and ratio of mono/diacylate were determined by ^{1}H NMR analysis of the crude mixture (50% conv, mono:di = >99:1). The enantiomeric ratio of (*S,S*)-**3a** and (*R,R*)-**2a** were determined by chiral HPLC analysis of the crude mixture (**3a**: 97:3 er, **2a**: >99:1 er, *s* = 157.8).

(1*R*,2*R*)-1,2-diphenylethane-1,2-diol (2a)

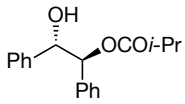


50% recovery from kinetic resolution of *rac*-**2a** under the optimal conditions (Scheme 7c).

Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 18.2 min (major) and T_R = 20.8 min (minor), 99.5:0.5 er; Detailed analytical data of **2a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

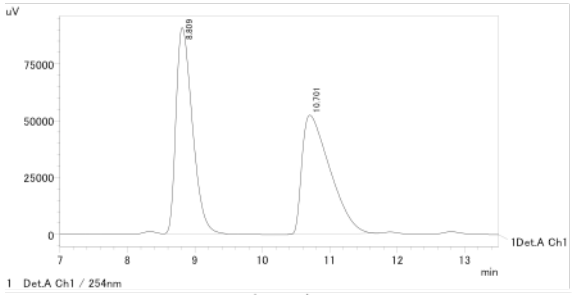
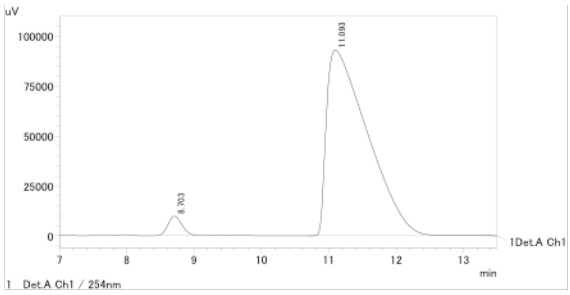
Racemic sample of **2a**				(1*R,2R*)-**2a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	18.724	627240	49.798	1	18.245	3150409	99.477
2	19.905	632317	50.202	2	20.758	16556	0.523

(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl isobutyrate (3a)



50% conversion from kinetic resolution of *rac*-**2a** under the optimal conditions (Scheme 7c).

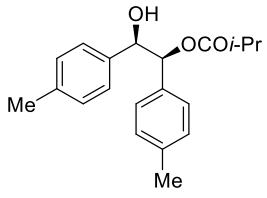
Colorless solid. Enantiomeric ratio was determined by chiral HPLC analysis with DICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.00 mL/min, 30 °C, UV = 254 nm), T_R = 8.7 min (minor) and T_R = 11.1 min (major), 97:3 er; Detailed analytical data of **3a** was shown in the following section of "General procedure for substrate scope (Figure 2)".

Racemic sample of **3a**				(1*S*,2*S*)-**3a**			
							
Peak	T_R	Area	Area %	Peak	T_R	Area	Area %
1	8.809	1527948	50.365	1	8.703	130955	3.202
2	10.701	1505824	49.635	2	11.093	3958409	96.798

General procedure for acylative desymmetrization of *meso*-1,2-diols with 1d: When 0.1 mol % of the catalyst was used in the reaction, a solution of the catalyst **1d** in chloroform (10.0 mM) was prepared in advance. This stock solution was added to a test tube, and the solvent was removed. The resulting catalyst was used for the following reaction. Catalyst **1d**, *meso*-diol **13a**−**p**, and Et_3N were stirred in *t*-BuOMe (TBME) at room temperature. The mixture was cooled to −20 °C, and then isobutyric anhydride was added. The reaction mixture was stirred for 3 h. Methanol was added to quench the reaction, and then mixture was stirred for 1 h at room temperature. After the mixture was concentrated in vacuo, the catalyst was separated from the crude product by flash column chromatography on a short pad of silica gel (eluent: Et_2O). Purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et2O = 5/1 to 3/1 to1/1 to Et_2O, v/v) gave the monoacylate **14a**−**p**, diacylate **15a**−**p**, and recovered substrate **13a**−**p**. The enantiomeric ratios of **14a**−**d** and **14f**−**p** were determined by chiral HPLC analysis, and that of **14e** was determined by chiral GC analysis.

Analytical data of for 14a–p, 15a-p (Figure 4)

(1*S*,2*R*)-2-hydroxy-1,2-di-p-tolylethyl isobutyrate (14b)

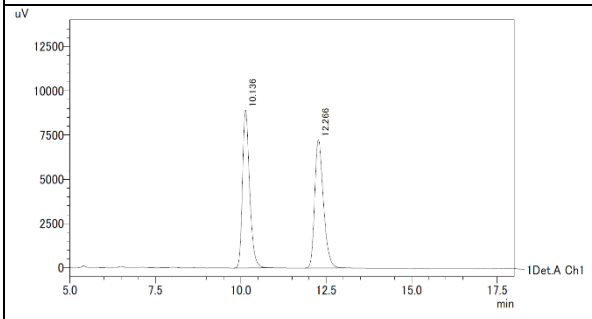


According to general procedure, substrate **13b** (72.3 mg, 0.298 mmol) with a catalyst **1d** (0.3 μmol), Et_3N (54.2 μL, 0.390 mmol), isobutyric anhydride (64.6 μL, 0.390 mmol) in TBME (3 mL) at −20 °C gave monoacylate **14b** (68.3 mg, 0.219 mmol, 73% yield, 97:3 er), diacylate **15b** (6.0 mg, 0.0157 mmol, 5% yield), and recovered **13b** (11.4 mg, 0.0470 mmol, 16% yield).

Colorless solid. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 95/5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 10.5 min (minor) and T_R = 12.7 min (major), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.08 (m, 8H), 5.84 (d, *J* =

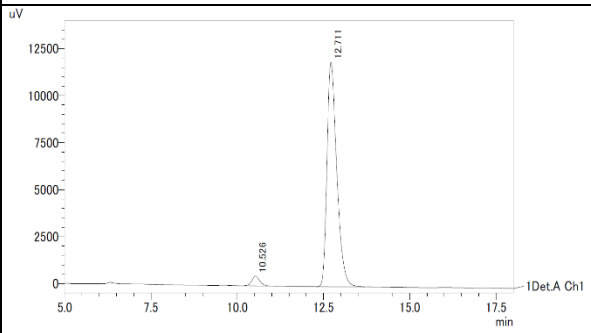
6.7 Hz 1H), 4.90 (d, *J* = 6.7 Hz, 1H), 2.45 (sep, *J* = 7.0 Hz, 1H), 2.34 (s, 3H), 2.34 (s, 3H), 2.07 (s, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 137.9, 137.5, 137.0, 134.2, 128.9, 128.7, 127.5, 127.0, 78.3, 76.3, 34.0, 21.2, 21.1, 18.7; IR (KBr) 3536, 2974, 2866, 1717, 1452, 1389, 1152, 970, 748, 706 cm^{-1}; HRMS (FAB$^+$) $[M+Na]^+$ calculated for $C_{20}H_{24}O_3Na$ 335.1617, found 335.1625; mp 83.6–84.2 °C; $[\alpha]^{24}_D$ +14.9 (*c* 1.00, $CHCl_3$, 97:3 er)

Racemic sample of **14b**



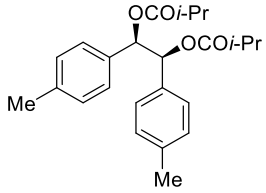
Peak	Ret. Time	Area	Area %
1	10.136	129328	50.129
2	12.266	128660	49.871

(1*S*,2*R*)-**14b**



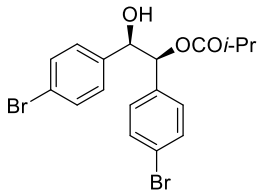
Peak #	Ret. Time	Area	Area %
1	10.526	8126	3.344
2	12.711	234887	96.656

(1*S*,2*R*)-1,2-di-p-tolylethane-1,2-diyl bis(2-methylpropanoate) (15b)



Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.05 (m, 8H), 6.02 (s, 2H), 2.47 (sep, *J* = 7.2 Hz, 2H), 2.32 (s, 6H), 1.57 (s, 1H), 1.05 (d, *J* = 7.2 Hz, 6H), 1.03 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 138.0, 133.7, 128.8, 127.7, 76.2, 34.2, 21.3, 18.9, 18.8; IR (KBr) 2974, 1736, 1516, 1354, 1182, 762 cm^{-1}; HRMS (FAB$^+$) $[M+Na]^+$ calculated for $C_{24}H_{30}O_4Na$ 405.2036, found 405.2029; mp 108.8–109.9 °C

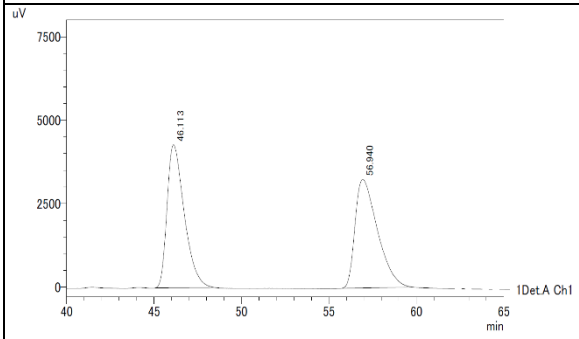
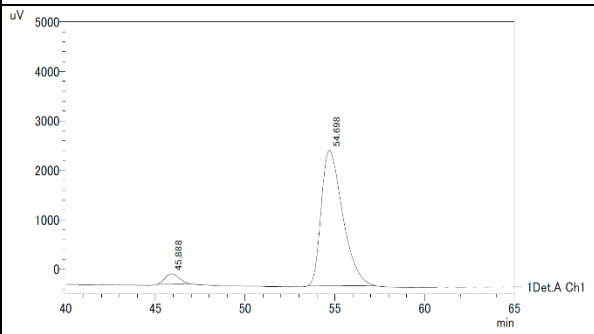
(1*S*,2*R*)-1,2-bis(4-bromophenyl)-2-hydroxyethyl isobutyrate (14c)



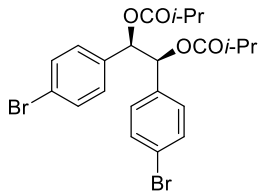
According to general procedure, substrate **13c** (111.7 mg, 0.300 mmol) with a catalyst **1d** (0.3 μmol), Et_3N (54.2 μL, 0.390 mmol), isobutyric anhydride (64.6 μL, 0.390 mmol) in TBME (3 mL) at −40 °C gave monoacylate **14c** (85.4 mg, 0.193 mmol, 64% yield, 95:5 er), diacylate **15c** (19.0 mg, 0.0371 mmol, 12% yield), and recovered **13c** (25.2 mg, 0.0677 mmol, 23% yield).

Colorless solid. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 44.9 min

(minor) and T_R = 53.5 min (major), 95:5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 4H), 7.12–7.06 (m, 4H), 5.80 (d, *J* = 5.6 Hz, 1H), 4.93 (q, *J* = 5.6, 3.1 Hz, 1H), 2.52 (sept, *J* = 6.9 Hz, 1H), 2.15 (d, *J* = 3.1 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 138.4, 135.6, 131.6, 131.4, 129.3, 128.8, 122.7, 122.3, 77.8, 75.9, 34.1, 18.9; IR (KBr) 3524, 3503, 2976, 1728, 1489, 745 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{18}H_{18}{}^{79}Br^{81}BrO_3Na$ $[M+Na]^+$ 464.9494, found 464.9470; mp 110.0–111.1 °C; $[\alpha]^{22}_D$ +7.2 (*c* 1.0, $CHCl_3$, 94:6 er).

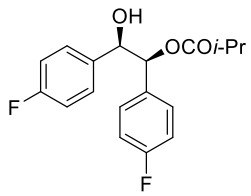
Racemic sample of **14c**				(1*S*,2*R*)-**14c**			
							
Peak	**Ret. Time**	**Area**	**Area %**	**Peak**	**Ret. Time**	**Area**	**Area %**
1	46.113	293838	50.293	1	45.888	10866	4.555
2	56.940	290418	49.707	2	54.698	227671	95.445

(1*S*,2*R*)-1,2-bis(4-bromophenyl)ethane-1,2-diyl bis(2-methylpropanoate) (15c)



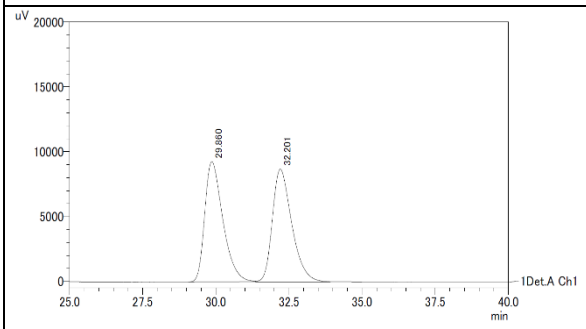
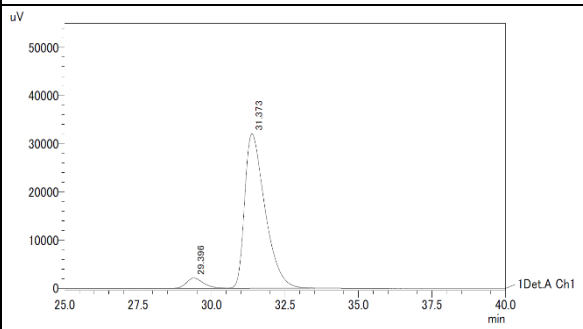
Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 4H), 7.10-7.03 (m, 4H), 5.98 (s, 2H), 2.51 (sep, *J* = 7.0 Hz, 2H), 1.08 (d, *J* = 7.0 Hz, 6H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 135.2, 131.5, 129.3, 122.7, 75.5, 34.1, 18.9, 18.8; IR (KBr) 2974, 1728, 1558, 1489, 1153, 808 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{22}H_{24}{}^{79}Br^{81}BrO_4Na$ $[M+Na]^+$ 534.9913, found 534.9938; mp 151.4–152.5 °C

(1*S*,2*R*)-1,2-bis(4-bromophenyl)-2-hydroxyethyl isobutyrate (14d)



According to general procedure, substrate **13d** (75.0 mg, 0.300 mmol) with a catalyst **1d** (0.3 μmol), Et_3N (54.2 μL, 0.390 mmol), isobutyric anhydride (64.6 μL, 0.390 mmol) in TBME (3 mL) at −20 °C gave monoacylate **14d** (74.9 mg, 0.234 mmol, 78% yield, 95:5 er), diacylate **15d** (13.5 mg, 0.0346 mmol, 12% yield), and recovered **13d** (7.4 mg, 0.0296 mmol, 10% yield).

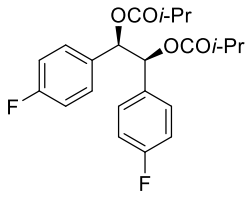
Colorless solid. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 29.4 min (minor) and T_R = 31.4 min (major), 95:5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.15 (m, 4H), 7.05–6.91 (m, 4H), 5.82 (d, *J* = 6.2 Hz, 1H), 4.91 (dd, *J* = 6.2, 2.7 Hz, 1H), 2.49 (sept, *J* = 7.0 Hz, 1H), 2.31 (bs, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 162.8 (d, *J* = 247.3 Hz), 162.6 (d, *J* = 246.3 Hz), 135.3 (d, *J* = 2.8 Hz), 132.6 (d, *J* = 2.9 Hz), 129.4 (d, *J* = 7.7 Hz), 128.8 (d, *J* = 8.6 Hz), 115.4 (d, *J* = 22.0 Hz), 115.2 (d, *J* = 22.0 Hz) 77.8, 75.9, 34.1, 18.8; IR (KBr) 3516, 2974, 1717, 1609, 1512, 1236, 797 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{18}H_{18}F_2O_3Na$ $[M+Na]^+$ 343.1116, found 343.1131; mp 104.1–104.6 °C; $[\alpha]^{22}_D$ +7.1 (*c* 1.00, $CHCl_3$, 95:5 er).

Racemic sample of **14d**	(1*S*,2*R*)-**14d**
	

Peak	Ret. Time	Area	Area %
1	29.860	400005	50.044
2	32.201	399309	49.956

Peak	Ret. Time	Area	Area %
1	29.396	83925	5.171
2	31.373	1539164	94.829

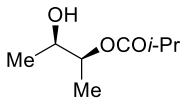
(1*S*,2*R*)-1,2-bis(4-fluorophenyl)ethane-1,2-diyl bis(2-methylpropanoate) (15d)



Colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.14 (m, 4H), 6.99 (t, *J* = 8.5 Hz, 4H), 6.02 (s, 2H), 2.49 (sep, *J* = 6.9 Hz, 2H), 1.10–0.97 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.5, 162.8 (d, *J* = 247.3 Hz), 132.3 (d, *J* = 2.9 Hz), 129.4 (d, *J* = 8.6 Hz), 115.3 (d, *J* = 22.0 Hz), 75.5, 34.2, 18.9, 18.8; IR (KBr) 2976, 1728, 1605, 1514, 123.1, 773 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{22}H_{24}F_2O_4Na$ $[M+Na]^+$ 413.1514, found 413.1518; mp 118.7–111.9 °C.

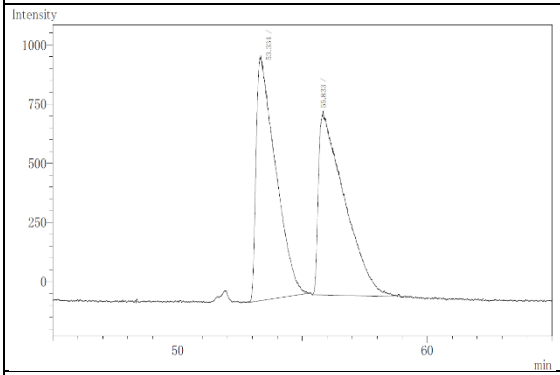
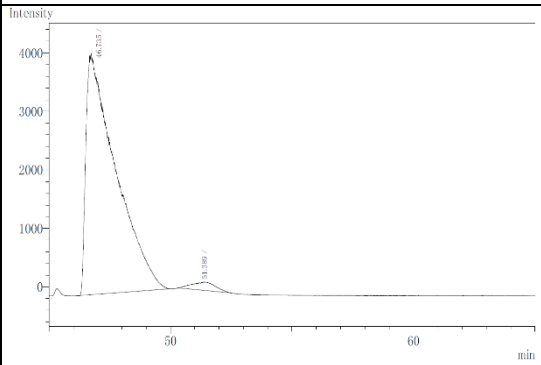
(2*S*,3*R*)-3-hydroxybutan-2-yl isobutyrate (14e)

According to general procedure, substrate **13e** (56.6 mg, 0.628 mmol) with a catalyst **1d** (0.6 μmol), Et_3N (108 μL, 0.780 mmol), isobutyric anhydride (129 μL, 0.778 mmol) in TBME (6 mL) at −40 °C gave monoacylate **14e** (85.5 mg, 0.534 mmol, 85% yield, 97:3 er), diacylate **15e** (10.5 mg,

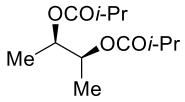


0.0456 mmol, 7% yield), and recovered **13e** (3.8 mg, 0.0422 mmol, 7% yield).

Pale yellow oil. Enantiomeric ratio was determined by chiral GC with CP-Cyclodextrin-B-2,3,6-M-19 (65 °C hold), T_R = 46.7 min (major) and T_R = 51.4 min (minor), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (dq, *J* = 6.4, 3.2 Hz, 1H), 3.87 (dq, *J* = 6.4, 3.2 Hz, 1H), 2.55 (sep, *J* = 6.9 Hz, 1H), 1.92 (s, 1H), 1.23–1.11 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 74.2, 69.8, 34.2, 19.1 (2), 18.0, 14.4; IR (neat) 3447, 2978, 1734, 1716, 1206, 1082 cm^{-1}; $[\alpha]^{21}_D$ -0.49 (*c* 1.00, $CHCl_3$, 97:3 er).

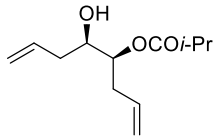
Racemic sample of **14e**				(2*S*,3*R*)-**14e**			
							
Peak	**Ret. Time**	**Area**	**Conc. %**	**Peak**	**Ret. Time**	**Area**	**Conc. %**
1	53.334	55657	49.905	1	46.735	350018	97.348
2	55.833	55868	50.095	2	51.389	9537	2.652

(2*R*,3*S*)-butane-2,3-diyl bis(2-methylpropanoate) (15e)



Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 0.03% TMS) δ 5.03–4.95 (m, 2H), 2.53 (sep, *J* = 6.9, 1H), 1.21 (d, *J* = 6.4 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 71.0, 34.2, 19.0, 18.4, 15.1; IR (neat) 2965, 2924, 1738, 1096, 1016, 800 cm^{-1}

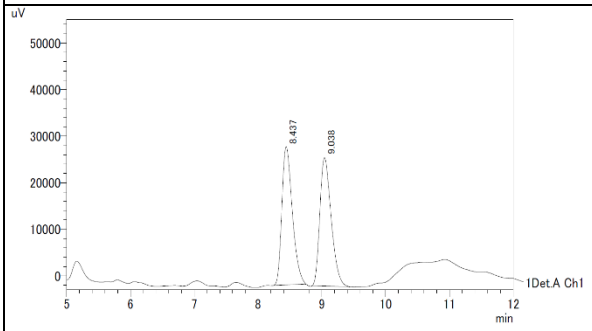
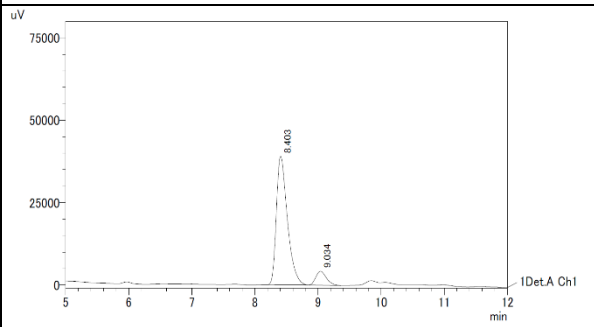
(4*S*,5*R*)-5-hydroxyocta-1,7-dien-4-yl isobutyrate (14f)



According to general procedure, substrate **13f** (40.7 mg, 0.286 mmol) with a catalyst **1d** (0.286 μmol), Et_3N (51.6 μL, 0.371 mmol), isobutyric anhydride (61.6 μL, 0.372 mmol) in TBME (2.86 mL) at −20 °C gave monoacylate **14f** (49.0 mg, 0.231 mmol, 81% yield, 91:9 er), diacylate **15f** (3.1 mg, 0.0110 mmol, 4% yield), and recovered **2f** (6.2 mg, 0.0436 mmol, 15% yield).

Colorless oil. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 205 nm), T_R = 8.4 min (major) and T_R = 9.0 min (minor), 91:9 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.66 (m, 2H), 5.15

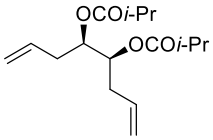
(d, J = 3.7 Hz, 1H), 5.13–5.08 (m, 3H), 4.89 (dt, J = 8.5, 4.6 Hz, 1H), 3.74 (dt, J = 8.5, 4.6 Hz, 1H), 2.54 (sep, J = 6.9 Hz, 1H), 2.48–2.24 (m, 3H), 2.23–2.05 (m, 1H), 1.15 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 134.2, 133.8, 118.6, 117.9, 75.1, 71.6, 37.3, 34.5, 34.3, 19.2, 19.0; IR (neat) 3464, 3078, 2976, 1732, 1472, 914 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{12}H_{21}O_3Na$ $[M+Na]^+$ 213.1485, found 213.1476; $[\alpha]^{23}_D$ +17.5 (*c* 1.00, $CHCl_3$, 91:9 er).

Racemic sample of **14f**	(4*S*,5*R*)-**14f**
	

Peak	**Ret. Time**	**Area**	**Area %**
1	8.437	337935	49.837
2	9.0385	340139	50.163

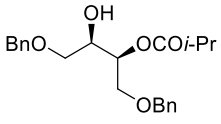
Peak	**Ret. Time**	**Area**	**Area %**
1	8.403	473272	90.562
2	9.034	49324	9.438

(4*R*,5*S*)-octa-1,7-diene-4,5-diyl bis(2-methylpropanoate) (15f)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79–5.65 (m, 2H), 5.14–5.01 (m, 6H), 2.53 (sep, J = 7.0 Hz, 2H), 2.44–2.25 (m, 4H), 1.16 (d, J = 7.0 Hz, 6H), 1.15 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 0.03% TMS) δ 176.3, 133.3, 118.2, 72.4, 34.6, 34.3, 19.1 (2); IR (neat) 2976, 1732, 1470, 1258, 918 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{16}H_{26}O_4Na$ $[M+Na]^+$ 305.1723, found 305.1710.

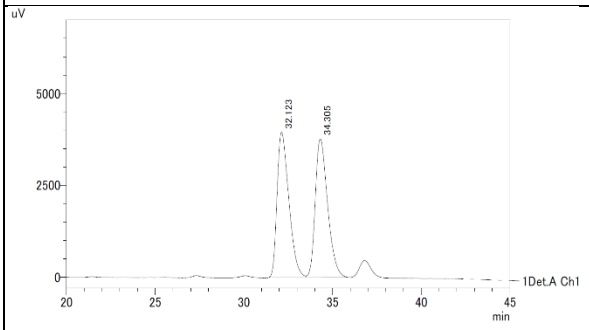
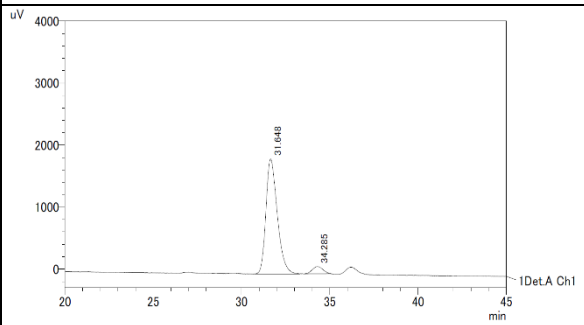
(2*S*,3*R*)-1,4-bis(benzyloxy)-3-hydroxybutan-2-yl isobutyrate (14g)



According to general procedure, substrate **13g** (90.8 mg, 0.300 mmol) with a catalyst **1d** (0.300 μmol), Et_3N (54.2 μL, 0.390 mmol), isobutyric anhydride (64.6 μL, 0.390 mmol) in TBME (3 mL) at −20 °C gave monoacylate **14g** (70.7 mg, 0.190 mmol, 63% yield, 94.5:5.5 er), diacylate **15g** (25.2 mg, 0.0569 mmol, 19% yield), and recovered **13g** (14.8 mg, 0.0489 mmol, 16% yield).

Colorless oil. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 31.6 min (minor) and T_R = 34.3 min (major), 94.5:4.5 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.23 (m, 10H),

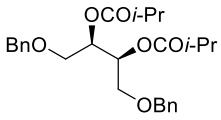
5.07 (ddd, *J* = 6.6, 4.6, 3.7 Hz, 1H), 4.54 (d, *J* = 2.7 Hz, 2H), 4.53 (d, *J* = 3.7 Hz, 2H), 4.12–4.01 (m, 1H), 3.77 (dd, *J* =11.0, 4.8 Hz, 1H), 3.71 (dd, *J* = 10.5, 3.4 Hz, 1H), 3.56 (dd, *J* = 9.6, 3.7 Hz, 1H), 3.49 (dd, *J* = 10.1, 6.2 Hz, 1H) 2.74 (bd, *J* = 5.5 Hz, 1H), 2.55 (sep, *J* = 7.0 Hz, 1H), 1.14 (d, *J* = 4.1 Hz, 3H), 1.12 (d, *J* = 3.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 137.9, 137.8, 128.5, 128.4, 127.9, 127.8, 127.7, 73.5, 73.4, 72.1, 70.7, 69.8, 68.9, 34.0, 19.0, 18.9; IR (KBr) 3468, 3446, 2974, 1732, 1454, 1194, 739 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{22}H_{28}O_5Na$ $[M+Na]^+$ 395.1828, found 395.1838; $[\alpha]^{23}_D$ +18.1 (*c* 1.0, $CHCl_3$, 94.5:5.5 er)

Racemic sample of **14g**	(1*S*,2*R*)-**14g**
	

Peak	Ret. Time	Area	Area %
1	32.123	182395	50.009
2	34.305	182326	49.991

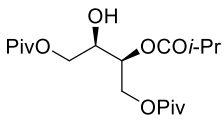
Peak	Ret. Time	Area	Area %
1	31.648	82460	94.452
2	34.285	4843	5.548

(2*R*,3*S*)-1,4-bis(benzyloxy)butane-2,3-diyl bis(2-methylpropanoate) (15g)



Colorless solid. δ 7.35–7.24 (m, 13H), 5.38–5.32 (m, 2H), 4.50 (d, *J* = 11.9 Hz, 2H), 4.45 (d, *J* = 11.9 Hz, 2H), 3.64 (dd, *J* = 10.7, 3.4 Hz 2H), 3.57 (dd, *J* = 10.7, 5.7 Hz, 2H), 2.50 (sep, *J* = 7.1 Hz, 1H), 1.11 (d, *J* = 7.1 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 138.0, 128.5, 127.8, 127.7, 73.2, 70.6, 68.2, 34.1, 19.1, 18.9; IR (KBr) 2972, 1730, 1356, 1188, 746 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{26}H_{34}O_6Na$ $[M+Na]^+$ 465.2247, found 465.2228; mp 57.4–58.2 °C

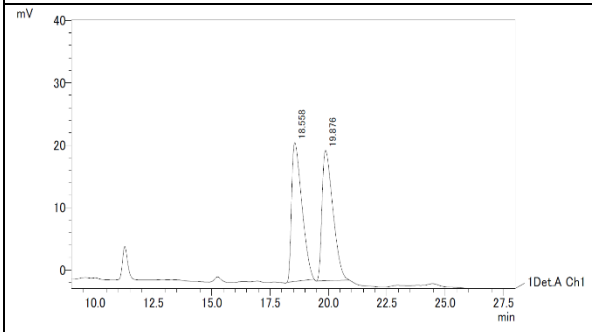
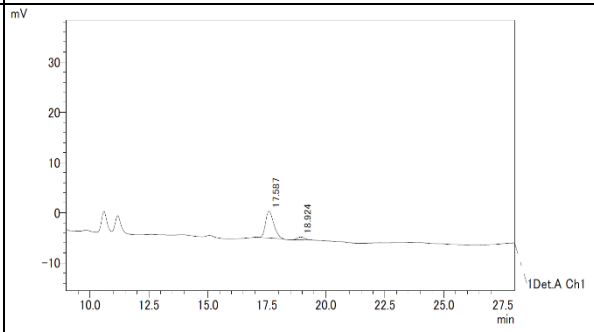
(2*R*,3*S*)-2-hydroxy-3-(isobutyryloxy)butane-1,4-diyl bis(2,2-dimethylpropanoate) (14h)



According to general procedure, substrate **13h** (87.2 mg, 0.300 mmol) with a catalyst **1d** (0.3 μmol), Et_3N (54.2 μL, 0.390 mmol), isobutyric anhydride (64.6 μL, 0.390 mmol) in TBME (3 mL) at −40 °C gave monoacylate **14h** (55.1 mg, 0.153 mmol, 51% yield, 91:9 er), diacylate **15h** (21.8 mg, 0.0506 mmol, 17% yield), and recovered

13h (27.8 mg, 0.0957 mmol, 32% yield).

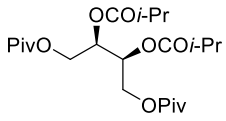
Colorless oil. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 205 nm), T_R = 17.6 min (major) and T_R = 18.9 min (minor), 91:9 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (ddd, *J* = 4.6, 5.1, 3.2 Hz, 1H), 4.44 (dd, *J* = 12.3, 2.7 Hz, 1H), 4.32 (dd, *J* = 12.3, 5.0 Hz, 1H), 4.24 (dd, *J* = 11.9, 2.7 Hz, 1H), 4.16 (dd, *J* = 11.9, 5.6 Hz, 1H), 4.02–3.91 (m, 1H), 2.80 (bs, 1H), 2.56 (sep, *J* = 7.0 Hz, 1H), 1.20 (s, 9 H), 1.18 (s, 9H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 178.6, 175.9, 70.9, 68.7, 65.1, 62.4, 39.0 (2), 34.1, 27.2, 19.0, 18.9; IR (KBr) 3501, 2978, 1732, 1157, 767 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{18}H_{32}O_7Na$ $[M+Na]^+$ 383.2045, found 383.2048; $[\alpha]^{24}_D$ +15.0 (*c* 1.030, $CHCl_3$, 91:9 er)

Racemic sample of **14h**	(1*S*,2*R*)-**14h**
	

Peak	Ret. Time	Area	Area %
1	18.558	680693	50.111
2	19.876	677688	49.889

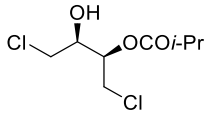
Peak	Ret. Time	Area	Area %
1	17.587	128958	90.866
2	18.924	12963	9.134

(2*R*,3*S*)-2,3-bis(isobutyryloxy)butane-1,4-diyl bis(2,2-dimethylpropanoate) (15h)



Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22–5.16 (m, 2H), 4.36 (dd, *J* = 12.1, 2.5 Hz, 2H), 4.13 (dd, *J* = 12.1, 5.7 Hz, 2H), 2.55 (sep, *J* = 6.9 Hz, 2H), 1.23–1.13 (m, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 175.7, 69.0, 61.9, 39.0, 34.1, 27.2, 19.0, 18.9; IR (KBr) 2978, 2941, 1734, 1140, 768 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{22}H_{38}O_8Na$ $[M+Na]^+$ 453.2458, found 453.2455; mp 47.1–47.9 °C

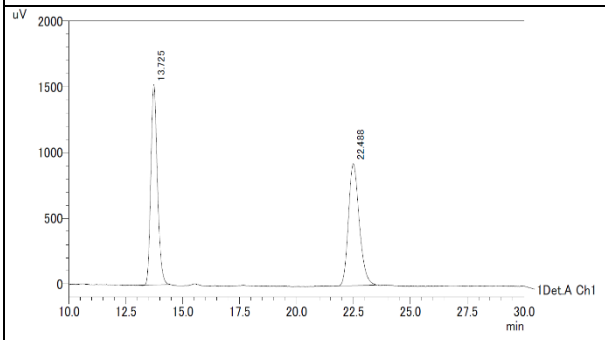
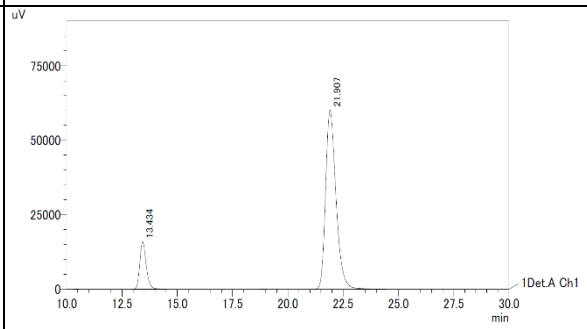
(*2R*,3*S*)-1,4-dichloro-3-hydroxybutan-2-yl isobutyrate (15i)



According to general procedure, substrate **13i** (79.2 mg, 0.498 mmol) with a catalyst **1d** (0.5 μmol), Et_3N (90.2 μL, 0.649 mmol), isobutyric anhydride (108 μL, 0.651 mmol) in TBME (5 mL) at −20 °C gave monoacylate **14i** (52.2 mg, 0.228

mmol, 46% yield, 86:14 er), diacylate **15i** (53.0 mg, 0.177 mmol, 36% yield), and recovered **13i** (14.2 mg, 0.0893 mmol, 18% yield).

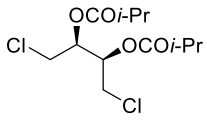
Colorless oil. Enantiomeric ratio was determined with 4-nitro benzoate by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 13.4 min (minor) and T_R = 21.9 min (major), 86:14 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dt, *J* = 8.4, 3.7 Hz, 1H), 4.16 (ddd, *J* = 8.4, 6.0, 2.7 Hz, 1H), 3.90 (d, *J* = 3.7 Hz, 2H), 3.75 (dd, *J* = 11.6, 2.7 Hz, 1H), 3.63 (dd, *J* = 11.6, 6.0 Hz, 1H), 2.68–2.55 (m, 1H), 2.52–2.32 (bs, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 70.2, 42.8, 34.1, 19.0, 18.9; IR (neat) 3335, 2974, 1740, 1153, 1070, 708 cm^{-1}; HMRS (ESI$^+$) calculated for $C_8H_{14}Cl_2O_3Na$ [M+Na]$^+$ 251.0212, found 251.0218; [α] $^{22}_D$ +5.3 (*c* 0.6, $CHCl_3$, 86:14 er).

Racemic sample of **14i**	(1*S*,2*R*)-**14i**
	

Peak	Ret. Time	Area	Area %
1	13.725	30561	49.884
2	22.488	30702	50.116

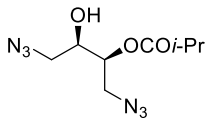
Peak	Ret. Time	Area	Area %
1	13.434	318497	13.995
2	21.907	1957297	86.005

(2*R*,3*S*)-1,4-dichlorobutane-2,3-diyl bis(2-methylpropanoate) (15i)



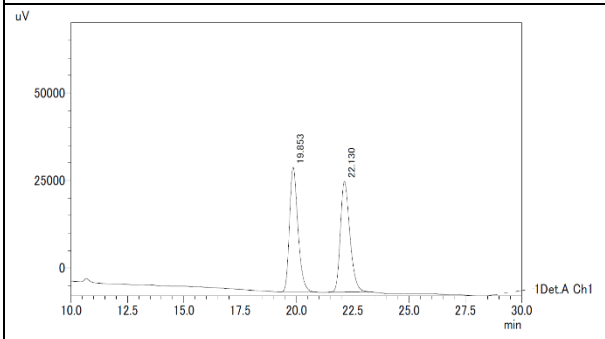
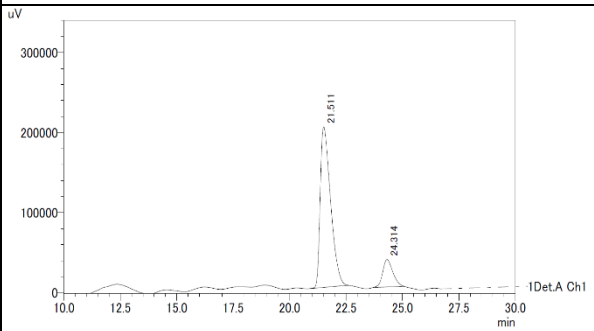
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35–5.28 (m, 2H), 3.85–3.82 (m, 1H), 3.81–3.77 (m, 1H), 3.67 (d, *J* = 2.9, 1.4 Hz, 1H), 3.64 (d, *J* = 2.9, 1.8 Hz, 1H), 2.61 (sep, *J* = 7.0 Hz, 2H), 1.20 (d, *J* = 7.0 Hz, 6H), 1.20 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 70.2, 42.8, 34.1, 19.0, 18.9; IR (neat) 2976, 2938, 1746, 1470, 1144 cm^{-1}; HMRS (ESI$^+$) calculated for $C_{12}H_{20}Cl_2O_4$ [M+Na]$^+$ 321.0632, found 321.0621

(2*S*,3*R*)-1,4-diazido-3-hydroxybutan-2-yl isobutyrate (15j)



According to general procedure, substrate **13j**[3] (68.4 mg, 0.397 mmol) with a catalyst **1d** (0.4 μmol), Et_3N (72.2 μL, 0.519 mmol), isobutyric anhydride (86.2 μL, 0.520 mmol) in TBME (4 mL) at −20 °C gave monoacylate **14j** (48.6 mg, 0.201 mmol, 50% yield, 86:14 er), diacylate **15j** (29.4 mg, 0.0941 mmol, 24% yield), and recovered **13j** (17.6 mg, 0.102 mmol, 26% yield).

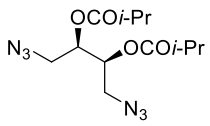
Colorless oil. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 205 nm), T_R = 21.5 min (major) and T_R = 24.3 min (minor), 86:14 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (ddd, *J* = 7.6, 4.5, 3.2 Hz, 1H), 4.04–3.95 (m, 1H), 3.62 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.58 (*J* = 13.4, 4.5 Hz, 1H), 3.48 (dd, *J* = 12.6, 3.2 Hz, 1H), 3.37 (dd, *J* = 12.6, 6.4 Hz, 1H), 2.62 (sep, *J* = 6.9 Hz, 1H), 2.45 (d, *J* = 6.0 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 72.5, 69.4, 53.7, 50.8, 34.1, 18.9, 18.8; IR (neat) 3564, 2976, 2104, 1732, 1472 cm^{-1}; HMRS (ESI^+) calculated for $C_8H_{14}N_6O_3Na$ $[M+Na]^+$ 265.102, found 265.1011; $[\alpha]^{22}_D$ +8.6 (*c* 1.0, $CHCl_3$, 86:14 er).

Racemic sample of **14j**	(1*S*,2*R*)-**14j**
	

Peak	**Ret. Time**	**Area**	**Area %**
1	19.853	929324	49.923
2	22.130	932206	50.077

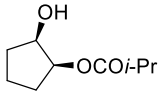
Peak	**Ret. Time**	**Area**	**Area %**
1	21.511	6407334	85.652
2	24.314	1073333	14.587

(2*R*,3*S*)-1,4-diazidobutane-2,3-diyl bis(2-methylpropanoate) (15j)



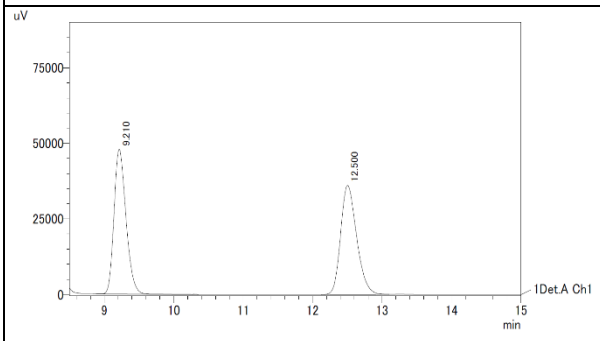
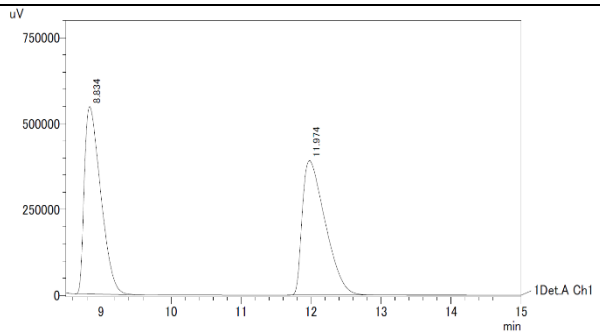
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23–5.17 (m, 2H), 3.57 (dd, *J* = 13.4, 3.2 Hz, 2H), 3.41 (dd, *J* = 13.4, 5.5 Hz, 2H), 2.16 (sep, *J* = 7.2 Hz, 2H), 1.20 (d, *J* = 7.2 Hz, 6H), 1.20 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 70.4, 50.5, 34.0, 18.8, 18.7; IR (neat) 2978, 2104, 1748, 1748, 1472, 1389 cm^{-1}; HMRS (FAB^+) calculated for $C_{12}H_{20}N_6O_4Na$ $[M+Na]^+$ 335.1438, found 335.1464.

(1*S*,2*R*)-2-hydroxycyclopentyl isobutyrate (14k)

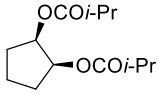


According to general procedure, substrate **13k** (62.4 mg, 0.611 mmol) with a catalyst **1d** (0.6 μmol), Et_3N (108 μL, 0.780 mmol), isobutyric anhydride (130 μL, 0.784 mmol) in TBME (6 mL) at −20 °C gave monoacylate **14k** (79.6 mg, 0.462 mmol, 76% yield, 50:50 er) and diacylate **15k** (12.5 mg, 0.0516 mmol, 8% yield).

Colorless oil. Enantiomeric ratio was determined with benzoate by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 78.4/1.6, v/v, flow rate = 0.8 mL/min, 30 °C, UV = 254 nm), T_R = 8.8 min and T_R = 11.9 min, 50:50 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (q, *J* = 5.4 Hz, 1H), 4.18 (q, *J* = 5.4 Hz 1H), 2.59 (sep, *J* = 7.0 Hz, 1H), 2.09–1.49 (m, 7H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 76.6, 73.4, 34.2, 30.9, 28.3, 19.6, 19.2; IR (neat) 3458, 2972, 1732, 1472, 1204, 1036 cm^{-1}

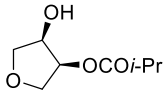
Racemic sample of **14k**				(1*S*,2*R*)-**14k**			
							
Peak	**Ret. Time**	**Area**	**Area %**	**Peak**	**Ret. Time**	**Area**	**Area %**
1	9.210	575853	49.974	1	8.834	8869599	49.802
2	12.500	576454	50.026	2	11.974	8940265	50.198

(1*R*,2*S*)-cyclopentane-1,2-diyl bis(2-methylpropanoate) (15k)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17–5.10 (m, 2H), 2.51 (sep, *J* = 6.9 Hz, 1H), 2.04–1.55 (m, 6H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 74.1, 34.2, 28.4, 19.3, 19.1, 19.0; IR (neat) 2974, 1732, 1470, 1387, 1263 cm^{-1}

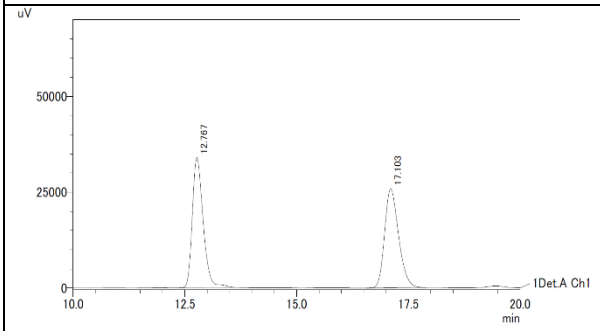
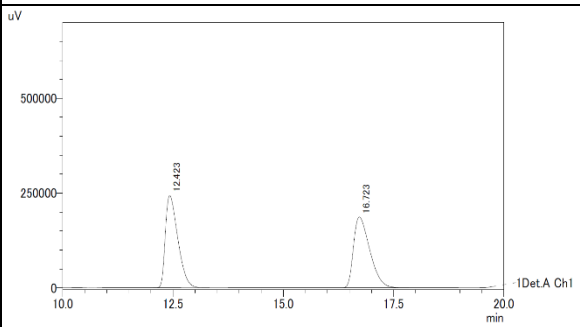
(3*S*,4*R*)-4-hydroxytetrahydrofuran-3-yl isobutyrate (14l)



According to general procedure, substrate **13l** (65.8 mg, 0.632 mmol) with a catalyst **1d** (60 μmol), Et_3N (108 μL, 0.78 mmol), isobutyric anhydride (130 μL, 0.784 mmol) in TBME (6 mL) at −20 °C gave monoacylate **14l** (97.2 mg, 0.558

mmol, 88% yield) and diacylate **15l** (9.6 mg, 0.0393 mmol, 6% yield).

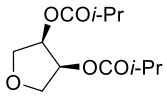
Colorless oil. Enantiomeric ratio was determined with benzoate by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 78.4/1.6, v/v, flow rate = 0.8 mL/min, 30 °C, UV = 254 nm), T_R = 12.4 min and T_R = 16.7 min, 50:50 er; ^{1}H NMR (400 MHz, $CDCl_3$, 0.03% TMS) δ 5.17–5.10 (m, 1H), 4.50–4.43 (m, 1H), 4.09 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.98 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.83 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.72 (dd, *J* = 9.3, 5.5 Hz, 1H), 2.65 (sep, *J* = 7.0 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 73.6, 72.4, 71.1, 70.9, 34.1, 19.2, 19.1; IR (neat) 3462, 2937, 1732, 1204, 988 cm^{-1}.

Racemic sample of **14l**	(1*S*,2*R*)-**14l**
	

Peak	Ret. Time	Area	Area %
1	12.767	570268	50.413
2	17.103	560919	49.587

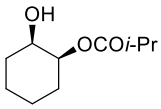
Peak	Ret. Time	Area	Area %
1	12.423	4776406	49.871
2	16.723	4801202	50.129

(3*R*,4*S*)-tetrahydrofuran-3,4-diyl bis(2-methylpropanoate) (15l)



Colorless oil.. ^{1}H NMR (400 MHz, $CDCl_3$) 5.35–5.29 (m, 2H), 4.14–4.06 (m, 2H), 3.83–3.76 (m, 2H), 2.57 (sep, *J* = 6.9 Hz, 2H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.18 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 71.4, 70.5, 33.9, 19.0, 18.9; IR (neat) 2976, 2940, 1738, 1470, 1198 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{12}H_{20}O_5Na$ $[M+Na]^+$ 267.1202, found 267.1170.

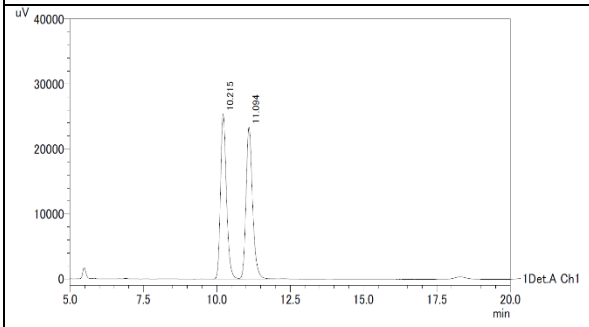
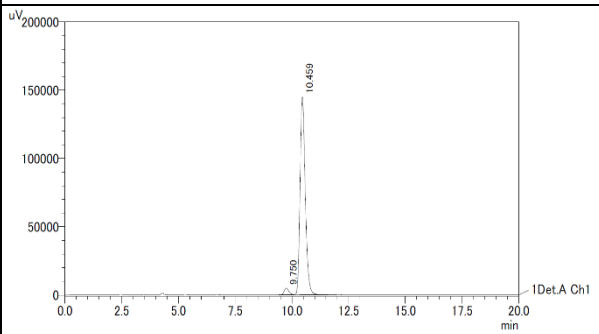
(1*S*,2*R*)-2-hydroxycyclohexyl isobutyrate (14m)



According to general procedure, substrate **13m** (69.3 mg, 0.597 mmol) with a catalyst **1d** (0.6 μmol), Et_3N (108 μL, 0.780 mmol), isobutyric anhydride (129 μL, 0.778 mmol) in TBME (6 mL) at −20 °C gave monoacylate **14m** (87.6 mg, 0.470 mmol, 79% yield, 97:3 er) and diacylate **15m** (22.4 mg, 0.0874 mmol, 15% yield).

Colorless oil. Enantiomeric ratio was determined with 4-nitro benzoate by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254

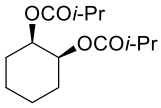
nm), T_R = 9.8 min (minor) and T_R = 10.5 min (major), 97:3 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97–4.89 (m, 1H), 3.88–3.81 (m, 1H), 2.59 (sep, *J* = 6.9 Hz, 1H), 2.11–1.52 (m, 7H), 1.44–1.31 (m, 2H), 1.19 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 73.7, 69.6, 34.3, 30.3, 27.2, 21.8, 21.5, 19.2, 19.1; IR (neat) 3462, 2937, 1732, 1204, 988 cm^{-1}; $[\alpha]^{22}_D$ +5.6 (*c* 1.4, $CHCl_3$, 97:3 er, (1*S*, 2*R*)) [lit[14]. $[\alpha]^{20}_D$ -5.6 [*c* 1.4, $CHCl_3$, 88:12 er, (1*R*, 2*S*)]

Racemic sample of **14m**	(1*S*,2*R*)-**14m**
	

Peak	Ret. Time	Area	Area %
1	10.215	356784	49.607
2	11.094	362439	50.393

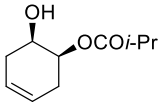
Peak	Ret. Time	Area	Area %
1	9.750	72220	3.034
2	10.459	2308280	96.966

(1*R*,2*S*)-cyclohexane-1,2-diyl bis(2-methylpropanoate) (15m)



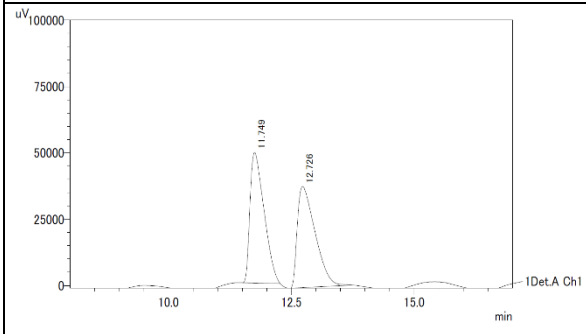
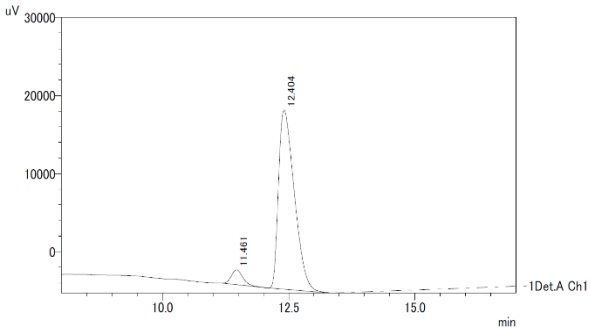
Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (d, *J* = 8.2 Hz, 2H), 2.52 (sep, *J* = 6.9, 1H), 1.90–1.73 (m, 2H), 1.71–1.55 (m, 4H), 1.52–1.35 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 70.7, 34.3, 27.8, 21.8, 19.1, 19.0; IR (neat) 2974, 2941, 1734, 1196, 984 cm^{-1}.

(1*S*,6*R*)-6-hydroxycyclohex-3-en-1-yl isobutyrate (14n)



According to general procedure, substrate **13n** (68.6 mg, 0.601 mmol) with a catalyst **1d** (0.600 μmol), Et_3N (108 μL, 0.780 mmol), isobutyric anhydride (129 μL, 0.778 mmol) in TBME (6 mL) at −40 °C gave monoacylate **14n** (95.7 mg, 0.519 mmol, 86% yield, 94:6 er) and diacylate **15n** (15.0 mg, 0.0590 mmol, 10% yield).

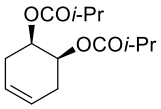
Colorless oil. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® AS-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 205 nm), T_R = 11.6 min (minor) and T_R = 12.2 min (major), 94:6 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65–5.54 (m, 2H), 5.07 (ddd, *J* = 6.1, 6.4, 2.3, 1H), 4.08–4.01 (m, 1H), 2.59 (sep, *J* = 6.9 Hz, 1H), 2.46–2.19 (m, 4H), 2.03 (bs, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 123.9, 123.3, 71.7, 67.3, 34.2, 31.3, 28.2, 19.0; IR (neat) 3478, 3032, 2974, 1732, 1202, 671 cm^{-1}

Racemic sample of **14n**	(1*S*,2*R*)-**14n**
	

Peak	Ret. Time	Area	Area %
1	11.749	976812	50.372
2	12.726	962371	49.628

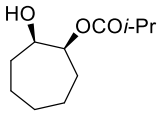
Peak	Ret. Time	Area	Area %
1	11.461	29917	5.652
2	12.404	499413	94.348

(1*S*,2*R*)-cyclohex-4-ene-1,2-diyl bis(2-methylpropanoate) (15n)



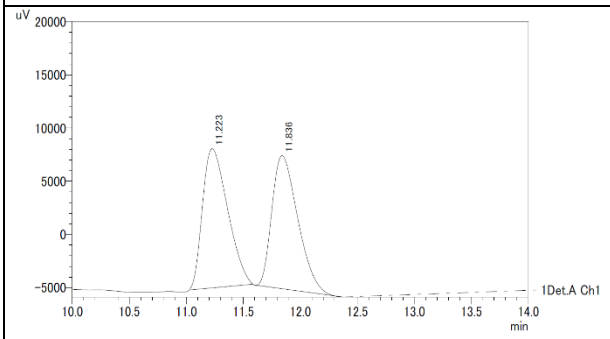
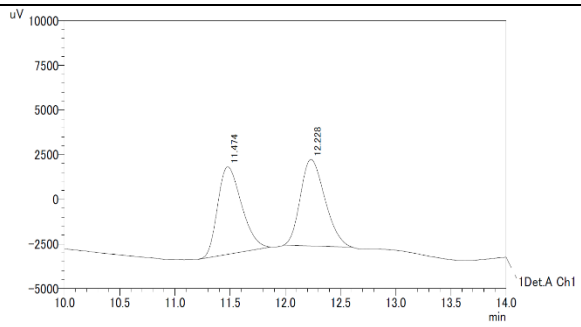
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dd, *J* = 1.8, 1.6 Hz 2H), 5.19–5.13 (m, 2H), 2.52 (sep, *J* = 7.0 Hz, 1H), 2.44–2.24 (m, 4H), 1.15 (d, *J* = 7.0 Hz, 6H), 1.13 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 123.7, 68.8, 34.2, 28.7, 19.1, 18.9; IR (neat) 3036, 2974, 1732, 1261, 671 cm^{-1}; HMRS (FAB^+) calculated for $C_{14}H_{22}O_4Na$ $[M+Na]^+$ 277.1410, found 277.1393.

(1*S*,2*R*)-2-hydroxycycloheptyl isobutyrate (14o)



According to general procedure, substrate **13o** (52.2 mg, 0.400 mmol) with a catalyst **1d** (0.4 μmol), Et_3N (72.2 μL, 0.519 mmol), isobutyric anhydride (86.2 μL, 0.520 mmol) in TBME (4 mL) at −20 °C gave monoacylate **14o** (73.3 mg, 0.366 mmol, 91% yield, 50:50 er) and diacylate **15o** (7.3 mg, 0.0270 mmol, 7% yield).

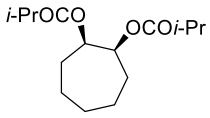
Colorless oil. Enantiomeric ratio was determined by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 205 nm), T_R = 21.5 min and T_R = 24.3 min, 50:50 er; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (dt, *J* = 8.2, 2.7 Hz, 1H), 3.96 (td, *J* = 6.0, 2.3 Hz, 1H), 2.59 (sep, *J* = 7.1 Hz, 2H), 2.39–2.11 (bs, 1H), 2.03–1.87 (m, 1H), 1.83–1.37 (m, 9H), 1.19 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 77.7, 72.7, 34.3, 31.7, 27.9, 27.1, 22.8, 22.1, 19.1 (2); IR (neat) 3480, 2934, 1732, 1456, 1159 cm^{-1}; HMRS (FAB^+) calculated for $C_{11}H_{20}O_3$ $[M+Na]^+$ 223.1304, found 223.1283

Racemic sample of **14o**	(1*S*,2*R*)-**14o**
	

Peak	Ret. Time	Area	Area %
1	11.223	200455	50.354
2	11.836	197634	49.646

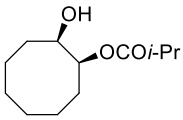
Peak	Ret. Time	Area	Area %
1	11.474	73987	49.611
2	12.228	75147	50.389

(1*R*,2*S*)-cycloheptane-1,2-diyl bis(2-methylpropanoate) (15o)



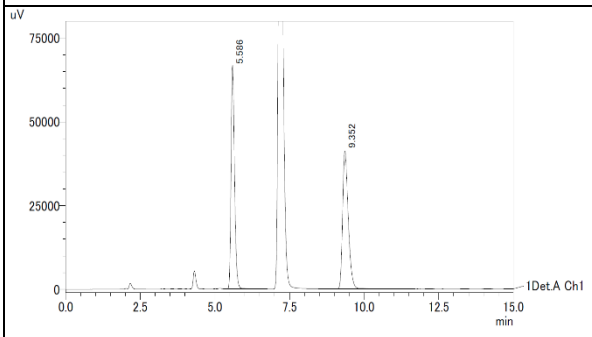
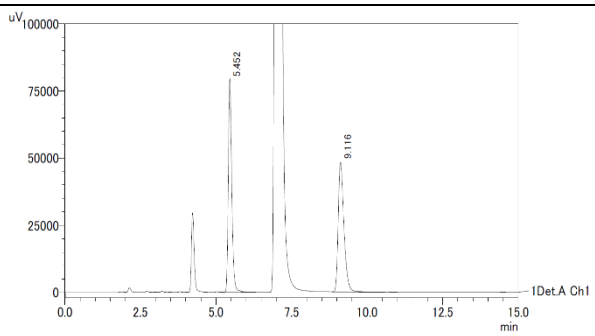
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 0.03% TMS) δ 5.08 (dd, *J* = 6.9, 2.7 Hz, 2H), 2.55 (sep, *J* = 6.9 Hz, 2H), 1.98–1.85 (m, 2H), 1.78–1.47 (m, 8H), 1.17 (d, *J* = 6.9 Hz, 6H), 1.16 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 74.3, 34.3, 28.8, 26.7, 22.6, 19.1 (2); IR (neat) 2972, 1732, 1470, 1263, 1067 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{15}H_{26}O_4$ $[M+Na]^+$ 293.1723, found 293.1739.

(1*R*,2*S*)-cyclooctane-1,2-diyl bis(2-methylpropanoate) (14p)



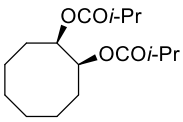
According to general procedure, substrate **13p** (86.4 mg, 0.599 mmol) with a catalyst **1d** (0.600 μmol), Et_3N (108 μL, 0.780 mmol), isobutyric anhydride (129 μL, 0.778 mmol) in TBME (6 mL) at −20 °C gave monoacylate **14p** (113.3 mg, 0.529 mmol, 88% yield, 50:50 er) and diacylate **15p** (19.8 mg, 0.0696 mmol, 12% yield).

Colorless oil. Enantiomeric ratio was determined with benzoate by HPLC with DAICEL CHIRALPAK® IA-3 (hexane/*i*-PrOH = 98.5/1.5, v/v, flow rate = 1.0 mL/min, 30 °C, UV = 254 nm), T_R = 5.5 min and T_R = 9.1 min, 50:50 er. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (dt, *J* = 9.2, 2.7 Hz, 1H), 3.99–3.90 (m, 1H), 2.57 (sep, *J* = 6.9 Hz, 1H), 2.13–1.97 (m, 1H), 1.87–1.39 (m, 11H), 1.20–1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 72.0, 34.3, 30.3, 27.9, 27.0, 25.6, 24.5, 22.0, 19.1; IR (neat) 3460, 2972, 1732, 1472, 1200 cm^{-1}; HMRS (FAB$^+$) calculated for $C_{12}H_{22}O_3$ $[M+Na]^+$ 237.1461, found 237.1436.

Racemic sample of **14p**	(1*S*,2*R*)-**14p**
	

Peak	Ret. Time	Area	Area %	Peak	Ret. Time	Area	Area %
1	5.586	539216	49.912	1	5.452	636151	49.914
2	9.352	541114	50.088	2	9.116	638344	50.086

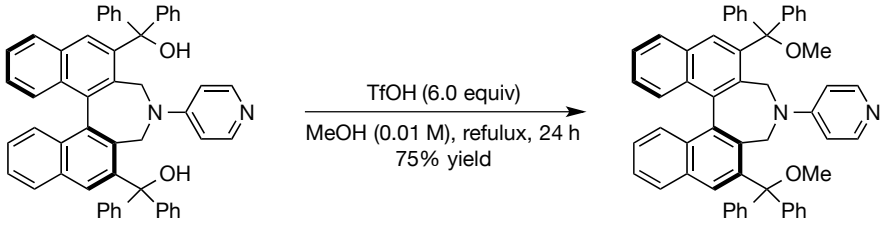
(1*S*,2*R*)-2-hydroxycyclooctyl isobutyrate (15p)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17–5.10 (m, 2H), 2.52 (sep, J = 7.0 Hz, 2H), 2.05–1.92 (m, 2H), 1.76–1.51 (m, 10H), 1.16 (d, J = 7.0 Hz, 6H), 1.15 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 73.4, 34.3, 28.5, 26.4, 23.0, 19.1, 19.0; IR (neat) 2974, 2936, 1732, 1472, 1261, 1069, 964 cm^{-1}; HMRS (FAB^{+}) calculated for $C_{16}H_{28}O_4$ $[M+Na]^+$ 307.1879, found 307.1850.

Synthesis of catalyst

Synthesis of **1dc**

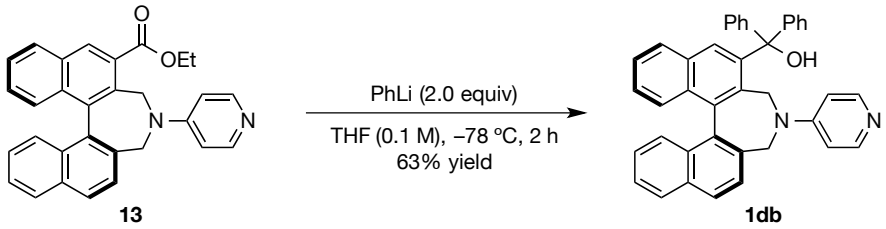


1d **1dc**

To a suspension of **1d** (34.9 mg, 47.4 μmol) in MeOH (5.00 mL) was added TfOH (26.6 μL, 0.300 mmol) at room temperature. The reaction solution was heated up to refluxed temperature and stirred for 24 h at refluxed temperature. After stirring for 24 h, the reaction mixture was cooled down to room temperature, and then aqueous NaOH (2.00 M, 2 mL, 4 mmol) was added to reaction vessel. The resulting solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The Purification of the crude product by flash column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 10/1, v/v) gave **1dc** (27.3 mg, 35.7 μmol, 75% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 8.03–7.92 (m, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.63-7.45 (m, 2H),

7.44–7.31 (m, 12H), 7.29–7.09 (m, 10H), 7.04 (t, J = 6.9 Hz, 2H), 6.03 (d, J = 4.6 Hz, 2H), 5.04 (d, J = 13.0 Hz, 2H), 3.26 (d, J = 13.0 Hz, 2H), 2.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 147.5, 146.6, 143.8, 138.3, 136.9, 132.6, 132.5, 131.6, 131.4, 128.9, 128.4, 128.1, 127.6, 127.2, 127.1, 126.8, 126.7, 126.5, 108.8, 88.0, 53.3, 45.0; IR (KBr) 2826, 1641, 1593, 1510, 1449 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{55}H_{44}N_2O_2$ $[M+H]^+$ 765.3514, found 765.3476; mp 241.1 °C dec; $[\alpha]^{24}_D$ –325.3 (*c* 0.27, $CHCl_3$, *S*-configuration).

Synthesis of **1c**

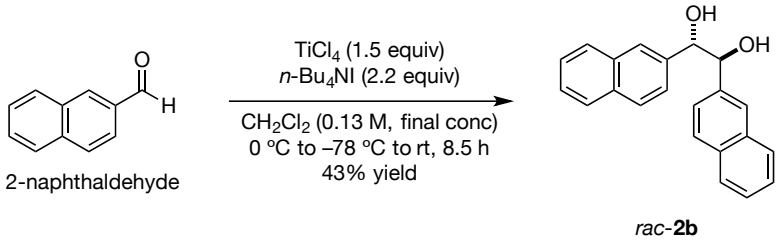


13 **1db**

To a solution of **13**[114] (88.3 mg, 0.200 mmol) in THF (2.00 mL) was added dropwise a solution of PhLi (1.60 M in dibutyl ether, 375 μL, 0.600 mmol) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, and then water (5 mL) was added to the reaction mixture. The resulting solution was extracted with $CHCl_3$ (10 mL × 3), dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 10/1 to 4/1, v/v) gave **1db** (69.8 mg, 126 μmol, 63% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 5.5 Hz, 2H), 7.91 (dd, J = 10.5, 8.7 Hz, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.52–7.10 (m, 18H), 6.37 (d, J = 5.5 Hz, 2H), 5.16 (d, J = 12.8 Hz, 1H), 4.61 (J = 12.8 Hz, 1H), 3.90 (d, J = 12.8 Hz, 1H), 3.65 (bs, 0.5H), 3.19 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.9, 147.7, 146.5, 143.7, 138.3, 134.8, 133.3, 132.7, 132.1, 131.8, 131.4, 130.9, 130.4, 129.4, 128.9, 128.4, 128.2, 127.9, 127.8, 127.7 (2), 127.3 (2), 127.1, 126.8, 126.4, 126.3, 126.2, 125.9, 108.4, 83.0, 50.3, 45.7; IR (KBr) 3055, 2349, 1595, 1508, 1246, 993, 750 cm^{-1}; HRMS (FAB$^+$) calculated for $C_{40}H_{31}N_2O$ $[M+H]^+$ 555.2431, found 555.2409; mp 198 °C dec; $[\alpha]^{26}_D$ –394.5 (*c* 0.305, $CHCl_3$, *S*-configuration).

Synthesis of substrate

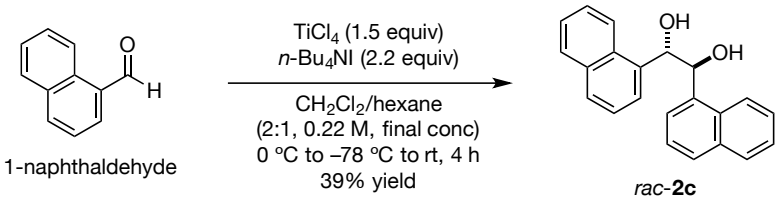
Synthesis of *rac*-**2b**



Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (8.13 g, 22.0 mmol) in CH_2Cl_2 (30.0 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 15.0 mL, 15 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of 2-naphthaldehyde (0.337 M in CH_2Cl_2, 30 mL, 10.1 mmol) was added dropwise to reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 8.5 h at room temperature. After stirring for 8.5 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with CH_2Cl_2 (100 mL × 2), washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 87:13). The purification of the crude product by flash column chromatograph on silica gel (eluent: toluene/EtOAc = 3/1 to 2/1, v/v) gave the sole diastereomer of *d,l*-**2b** (679 mg, 2.16 mmol, 43% yield) as a colorless solid. Detailed analytical data of **2b** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2c**

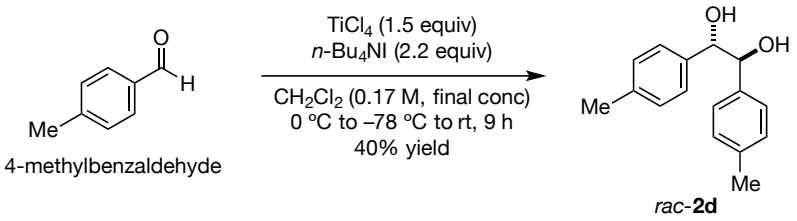


Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (12.2 g, 33.0 mmol) in CH_2Cl_2 (22.5 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 22.5 mL, 22.5 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of 1-naphthaldehyde (0.680 M in hexane, 22.5 mL, 15.3 mmol) was added dropwise to reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 4 h at room temperature. After stirring for 4 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with CH_3Cl (100 mL × 2), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 94:6). The purification of the crude product by flash column chromatograph on

silica gel (eluent: hexane/Et_2O = 1/1 to 1/3, v/v) and recrystallization from THF/hexane gave the sole diastereomer of *d,l*-**2c** (942 mg, 3.00 mmol, 39% yield) as a colorless solid. Detailed analytical data of **2c** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

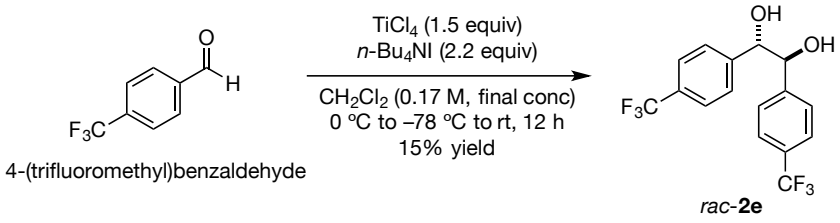
Synthesis of *rac*-**2d**



Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (16.3 g, 44.1 mmol) in CH_2Cl_2 (60 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 30.0 mL, 30.0 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of 4-methylbenzaldehyde (0.680 M in CH_2Cl_2, 30.0 mL, 20.4 mmol) was added dropwise to reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 9 h at room temperature. After stirring for 9 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with CH_2Cl_2 (100 mL × 2), washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 90:10). The purification of the crude product by flash column chromatograph on silica gel (eluent: toluene/EtOAc = 4/1 to 3/1, v/v) and recrystallization from toluene/hexane gave the sole diastereomer of *d,l*-**2d** (986 mg, 4.07 mmol, 40% yield) as a colorless solid. Detailed analytical data of **2d** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2e**

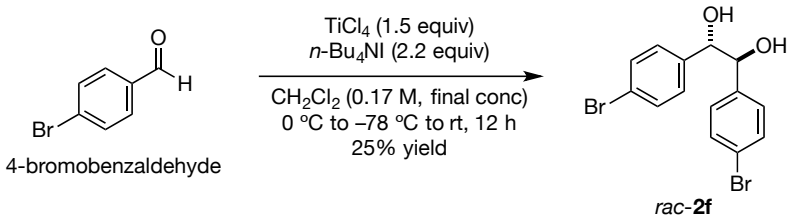


Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (16.3 g, 44.1 mmol) in CH_2Cl_2 (60 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 30.0 mL, 30.0 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of 4-(trifluoromethyl)benzaldehyde (0.700 M in CH_2Cl_2, 30.0 mL, 21.0 mmol) was added dropwise to

reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 12 h at room temperature. After stirring for 12 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with CH_2Cl_2 (100 mL × 2), washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 70:30). The purification of the crude product by flash column chromatograph on silica gel (eluent: toluene/EtOAc = 1/1, v/v) and four times recrystallizations from toluene/hexane (*d,l*:*meso* = 88:12), Et_2O/hexane (*d,l*:*meso* = 95:5), Et_2O/hexane (*d,l*:*meso* = 98:2), and CH_2Cl_2/hexane (*d,l*:*meso* = >99:1) gave the sole diastereomer of *d,l*-**2e** (533 mg, 1.52 mmol, 15% yield) as a colorless solid. Detailed analytical data of **2e** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

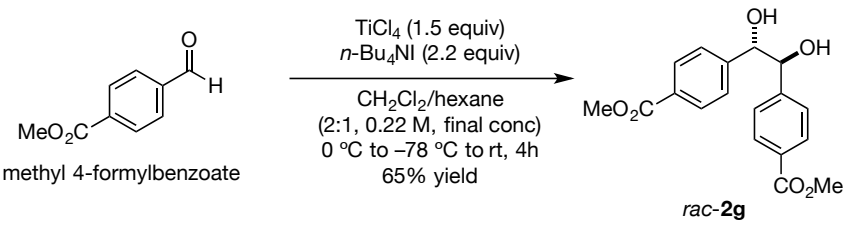
Synthesis of *rac*-**2f**



Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (8.13 g, 22.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 15.0 mL, 15.0 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of 4-bromobenzaldehyde (0.687 M in CH_2Cl_2, 15.0 mL, 10.3 mmol) was added dropwise to reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 4 h at room temperature. After stirring for 4 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with EtOAc (100 mL × 2), washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 76:24). The purification of the crude product by flash column chromatograph on silica gel (eluent: toluene/EtOAc = 3/1, v/v) and two times recrystallizations from acetone/hexane (*d,l*:*meso* = 97.5:2.5), acetone/hexane (*d,l*:*meso* = >99:1) gave the sole diastereomer of *d,l*-**2f** (482 mg, 1.30 mmol, 25% yield) as a colorless solid. Detailed analytical data of **2f** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

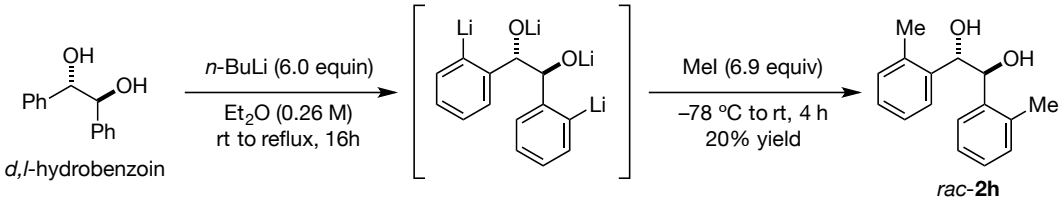
Synthesis of *rac*-**2g**



Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (12.2 g, 33.0 mmol) in CH_2Cl_2 (22.5 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 22.5 mL, 22.5 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of methyl 4-formylbenzoate (0.671 M in hexane, 22.5 mL, 15.1 mmol) was added dropwise to reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 4 h at room temperature. After stirring for 4 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with EtOAc (100 mL × 2), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 93:7). The purification of the crude product by flash column chromatograph on silica gel (eluent: toluene/Et_2O = 1/1, v/v) and two times recrystallizations from acetone/hexane (*d,l*:*meso* = 97:3), THF/hexane (*d,l*:*meso* = >99:1) gave the sole diastereomer of *d,l*-**2g** (1.61 g, 4.87 mmol, 65% yield) as a colorless solid. Detailed analytical data of **2g** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2h**

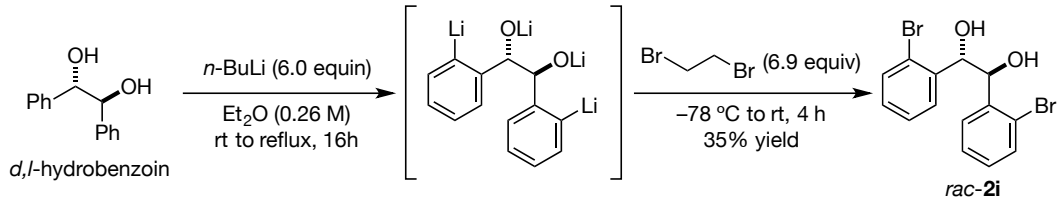


Same procedure as tetralithiation method.[61,62]

To a solution of *d,l*-hydrobenzoin (1.00 g, 4.67 mmol) in Et_2O (18.0 mL) was added *n*-BuLi (1.63 M in hexane, 17.2 mL, 28.0 mmol) at room temperature. The resulting solution was heated up to refluxed temperature and stirred for 16 h (the color of solution was changed to deep orange from yellow), and then cooled down to –78 ºC using acetone/dry ice bath. After cooling down to –78 ºC, MeI (2.0 mL, 32.1 mmol) was added dropwise to reaction vessel at –78 ºC. After addition of MeI, the reaction mixture was allowed to warm up to room temperature and stirred for 4 h at room temperature. After stirring for 4 h at room temperature, the reaction mixture was poured into water. The resulting solution was extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product containing monomethylated compound (53% conv, mono:di = 17:83). The

purification of the crude product by two times flash column chromatograph on silica gel (eluent: toluene/Et_2O = 6/1 to 4:1, and toluene/Et_2O = 8/1, v/v) gave the *d,l*-**2h** (224 mg, 0.924 mmol, 20% yield) as a colorless solid. Detailed analytical data of **2h** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

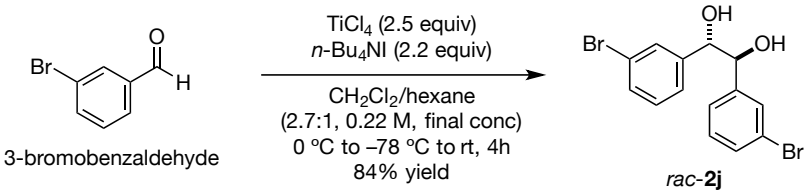
Synthesis of *rac*-**2i**



Same procedure as tetralithiation method.[61,62]

To a solution of *d,l*-hydrobenzoin (1.50 g, 7.01 mmol) in Et_2O (27.0 mL) was added *n*-BuLi (1.63 M in hexane, 25.8 mL, 42.0 mmol) at room temperature. The resulting solution was heated up to refluxed temperature and stirred for 16 h (the color of solution was changed to deep orange from yellow), and then cooled down to –78 ºC using acetone/dry ice bath. After cooling down to –78 ºC, 1,2-dibromoethane (4.12 mL, 48.2 mmol) was added dropwise to reaction vessel at –78 ºC. After addition of 1,2-dibromoethane, the reaction mixture was allowed to warm up to room temperature and stirred for 4 h at room temperature. After stirring for 4 h at room temperature, the reaction mixture was poured into water. The resulting solution was extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product containing monobrominated compound (87% conv, mono:di = 30:70). The purification of the crude product by two times flash column chromatograph on silica gel (eluent: toluene/Et_2O = 6/1) and recrystallization from toluene/Et_2O gave the *d,l*-**2i** (904 mg, 2.43 mmol, 35% yield) as a colorless solid. Detailed analytical data of **2i** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

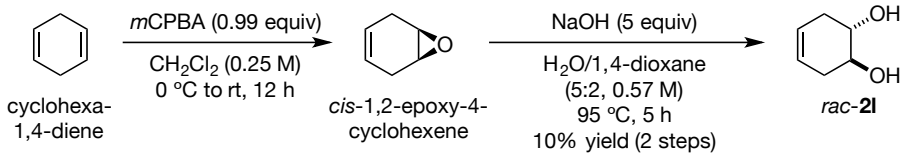
Synthesis of *rac*-**2j**



Modified procedure of *d,l*-selective pinacol coupling.[115]

To a solution of *n*-Bu_4NI (12.3 g, 33.3 mmol) in CH_2Cl_2 (15.0 mL) was added dropwise $TiCl_4$ (1.00 M in CH_2Cl_2, 37.5 mL, 37.5 mmol) at 0 ºC. The resulting mixture was stirred for 20 min, and then cooled down to –78 ºC using acetone/dry ice bath. A solution of 3-bromobenzaldehyde (0.449 M in hexane, 22.5 mL, 10.1 mmol) was added dropwise to reaction vessel at –78 ºC and the reaction mixture was allowed to warm up to room temperature and stirred for 4 h at room temperature. After stirring for 4 h, saturated aqueous NH_4Cl was added to reaction vessel. The resulting solution was extracted with EtOAc (100 mL × 2), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (*d,l*:*meso* = 98:2). The purification of the crude product by flash column chromatograph on silica gel (eluent: toluene/hexane = 2/1, v/v) recrystallization from Et_2O/hexane gave the sole diastereomer of *d,l*-**2j** (1.58 g, 4.25 mmol, 84% yield) as a colorless solid. Detailed analytical data of **2j** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2l**



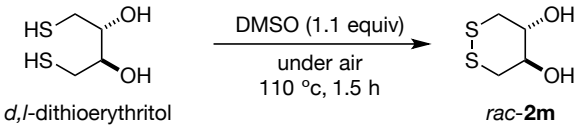
Slightly modified procedure of the literature.[98]

To a solution of cyclohexa-1,4-diene (3.22 g, 40.2 mmol) in CH_2Cl_2 (160 mL) was added portionwise *m*CPBA (contains *ca*. 30% water, 9.77 g, 39.6 mmol) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC, and then allowed to warm up to room temperature. After stirring for 12 h at room temperature, a solution of aqueous K_2CO_3 [0.724 M (100 g/L)] was added to reaction vessel at room temperature. The resulting solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The crude product was directly used next step without further purification. Detailed analytical data of *cis*-1,2-epoxy-4-cyclohexene was identical to the literature.[98]

To a solution of the crude mixture of NaOH (8.00 g, 200 mmol) in H_2O (50.0 mL) and 1,4-dioxane (20.0 mL) was added crude of *cis*-1,2-epoxy-4-cyclohexane (3.85 g) at room temperature. The reaction mixture was warmed up to 95 ºC and stirred for 5 h at 95 ºC. After

stirring for 5 h, saturated aqueous NH_4Cl (200 mL) was added to reaction vessel. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by recrystallization from EtOAc/hexane gave the *rac*-**2l** (439 mg, 3.85 mmol, 10% yield based on cyclohexa-1,4-diene) as a pale yellow solid. Detailed analytical data of **2l** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2m**

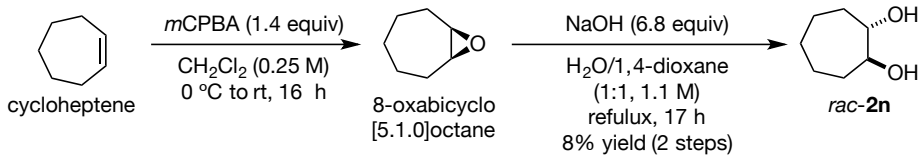


d,l-dithioerythritol *rac*-**2m**

Modified procedure of the literature.[116]

To a solid of *rac*-dithioerythritol (1.00 g, 6.48 mmol) was added DMSO (0.506 mL, 7.12 mmol) at room temperature under air atmosphere. The reaction mixture was heated up to 110 ºC and stirred for 1.5 h under air atmosphere. The resulting mixture was dissolved in EtOAc (50 mL), washed with water (25 mL×3), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by recrystallization from THF/hexane gave *rac*-**2m** (475 mg, 3.12 mmol, 48% yield) as a colorless solid. Detailed analytical data of **2m** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2n**



cycloheptene 8-oxabicyclo [5.1.0]octane *rac*-**2n**

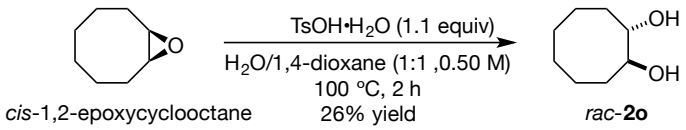
Slightly modified procedure of acceding to literature.[102]

To a solution of cycloheptene (3.85 g, 40.0 mmol) in CH_2Cl_2 (160 mL) was added portionwise *m*CPBA (contains *ca*. 30% water, 13.9 g, 56.4 mmol) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC, and then allowed to warm up to room temperature. After stirring for 15 h at room temperature, a solution of aqueous K_2CO_3 [0.724 M (100 g/L)] was added to reaction vessel at room temperature. The resulting solution was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The crude product was directly used next step without further purification.

To a solution of the crude mixture of NaOH (10.8 g, 270 mmol) in H_2O (50.0 mL) and 1,4-dioxane (20.0 mL) was added crude of 8-oxabicycl[5.1.0]octane (3.89 g) at room temperature. The reaction mixture was warmed up to refluxed temperature and stirred for 17 h at refluxed temperature. After stirring for 17 h, water (200 mL) was added to reaction vessel. The resulting

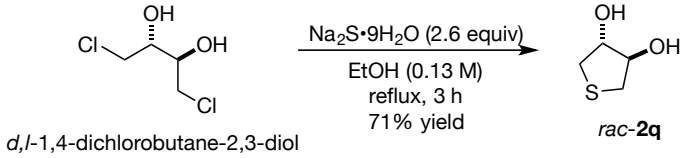
solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flash column chromatography on silica gel (eluent: Et_2O to EtOAc) gave the *rac*-**2n** (402 mg, 3.09 mmol, 8% yield based on cyclopentene) as a colorless solid. Detailed analytical data of **2n** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2o**



To a solution of *cis*-1,2-epoxycyclooctane (1.01 g, 8.00 mmol) in H_2O (8.00 mL) and 1,4-dioxane (8.00 mL) was added *p*-toluenesulfonic acid monohydrate [TsOH•H_2O] (1.69 g, 8.88 mmol) at room temperature. The reaction mixture was warmed up to 100 ºC and stirred for 2 h at 100 ºC. After stirring for 2 h, the reaction mixture was cooled down to room temperature, and then powder of $NaHCO_3$ was added to reaction vessel until bubbles did not occur. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The purification of the crude product by flush column chromatography on silica gel (eluent: EtOAc/hexane = 1:1) gave *rac*-**2o** (304 mg, 2.11 mmol, 26% yield) as a pale yellow liquid. Detailed analytical data of **2o** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

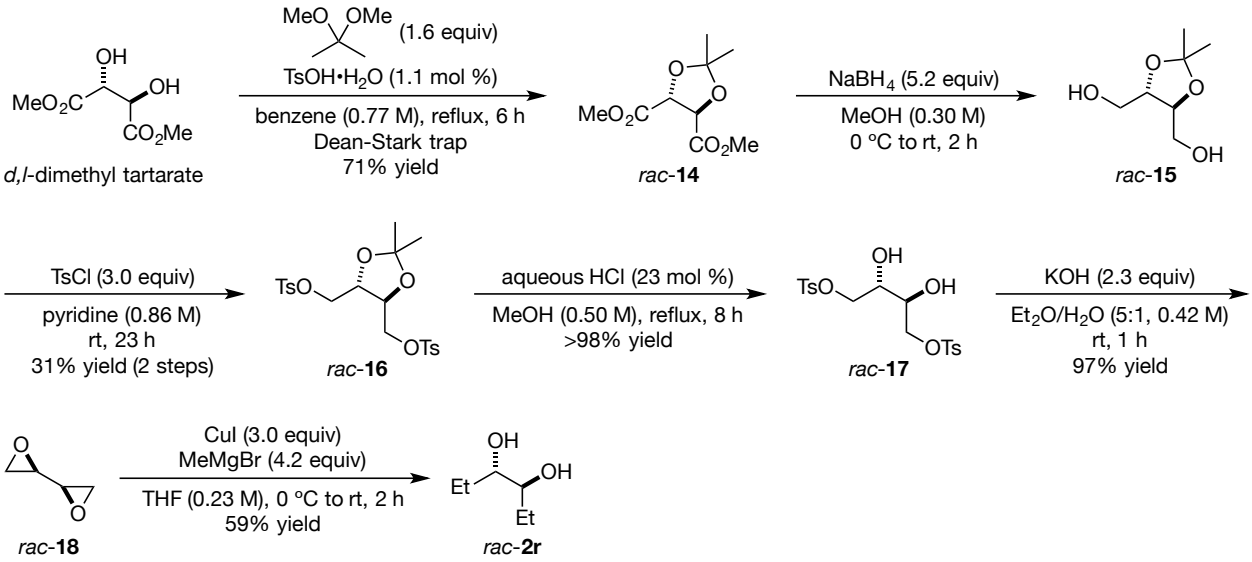
Synthesis of *rac*-**2q**



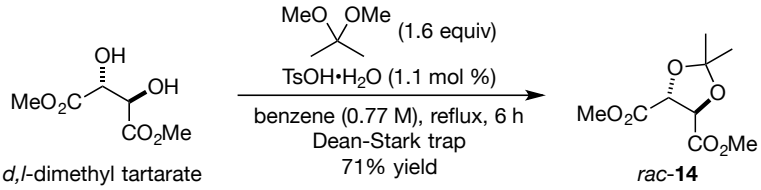
Modified procedure of the literature.[104]

To a solution of *rac*-1,4-dichlorobutane-2,3-diol (2.00 g, 12.6 mmol) in EtOH (100 mL) was added sodium sulfide nonahydrate (7.75 g, 32.3 mmol) at room temperature. The reaction mixture was heated up to refluxed temperature and stirred for 3 h at refluxed temperature. After stirring for 3 h, the reaction mixture was cooled down to room temperature and concentrated *in vacuo* to give the crude mixture. The purification of the crude product by flash column chromatography on silica gel (eluent: $CHCl_3$/MeOH = 10:1) gave *rac*-**2q** (1.08 g, 8.97 mmol, 71% yield) as a brown solid. Detailed analytical data of **2q** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

An overview for synthesis of *rac*-2r from *rac*-dimethyl tartarate



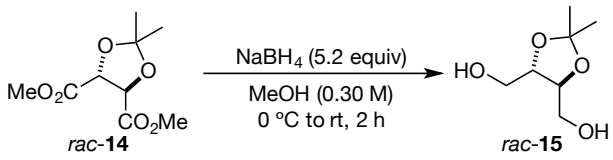
Synthesis of *rac*-**14**



Modified procedure of the literature.[117]

A two-necked round-bottomed flask was equipped with a magnetic stirrer, Dean-Stark trap, and condenser was added *rac*-dimethyl tartarate (29.0 g, 163 mmol), 2,2-dimethoxypropane (31.2 mL, 255 mmol), and benzene (212 mL). To this solution was added TsOH•H_2O (335 mg, 1.76 mmol) at room temperature. The reaction mixture was heated up to refluxed temperature and stirred for 6 h. During this period, the azeotropic solution of benzene/MeOH was collected from Dean-Stark trap. After stirring for 6 h, the resulting mixture was cooled down to room temperature and neutralized by adding powder of K_2CO_3 to reaction vessel at room temperature until bubbles did not occur. The resulting mixture was extracted with EtOAc, washed saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 5/1 to 1/1, v/v) gave *rac*-**14** (25.2 g, 115 mmol, 71% yield) as a pale yellow liquid. Detailed analytical data of *rac*-**14** was identical to the literature.[118]

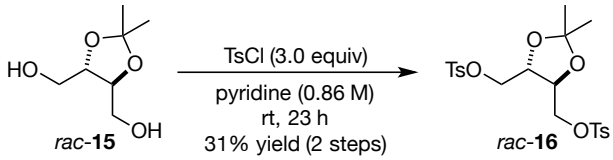
Synthesis of *rac*-**15**



Slightly modified procedure of the literature.[119]

To a solution of *rac*-**14** (19.6 g, 89.8 mmol) in MeOH (300 mL) was added portionwise $NaBH_4$ (17.8 g, 471 mmol) at 0 ºC. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h at room temperature. After stirring for 2 h, the resulting solution was concentrated *in vacuo*. The residue was dissolved in Et_2O and water was added to this solution. The two-phase solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product (8.00 g). The crude mixture was directly used for the next reaction without further purification. Detailed analytical data of *rac*-**15** was identical to the according literature.[120]

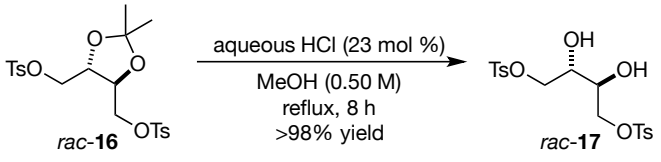
Synthesis of *rac*-**16**



Slightly modified procedure of the literature.[104]

To a solution of the crude mixture of *rac*-**15** (8.00 g) in pyridine (58.0 mL) was added *p*-toluenesulfonyl chloride [TsCl] (28.4 g, 149 mmol) at room temperature. The reaction mixture was stirred for 23 h at room temperature, and then water (200 mL) was added to reaction vessel. The resulting solution was extracted with Et_2O (150 mL×3), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 1:1 to 1:2, v/v) and reprecipitation from CH_2Cl_2/Et_2O at 0 ºC gave *rac*-**16** (13.1 g, 27.8 mmol, 31% yield based on *rac*-**14**) as a colorless solid. Detailed analytical data of *rac*-**16** was identical to the according literature.[104]

Synthesis of *rac*-**17**

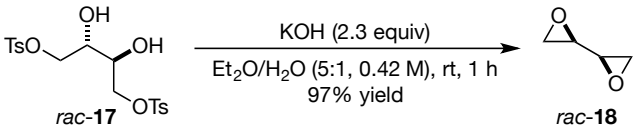


Slightly modified procedure of the literature.[104]

To a suspension of *rac*-**16** (13.1 g, 27.8 mmol) in MeOH (55.8 mL) was added HCl (0.500 M in H_2O, 2.8 mL, 1.40 mmol) at room temperature. The reaction mixture was heated up to refluxed temperature and stirred for 6 h. After cooling down to room temperature, an additional HCl (1.00 M

in H_2O, 5.00 mL, 5.00 mmol) was added to reaction vessel at room temperature. The reaction mixture was heated up to refluxed temperature and stirred for additional 2 h. After cooling down to room temperature, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) was added to this solution. The resulting solution was extracted with $CHCl_3$ (50 mL × 3), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by reprecipitation from $CHCl_3$/hexane gave *rac*-**17** (11.9 g, 27.6 mmol, >98% yield) as a colorless solid. Detailed analytical data of *rac*-**17** was identical to the according literature.[104]

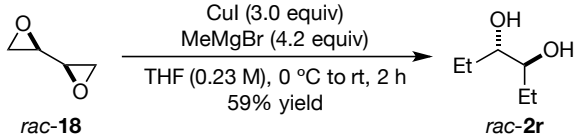
Synthesis of *rac*-**18**



Modified procedure of the literature.[121]

To a solution of *rac*-**17** (11.7 g, 27.2 mmol) in Et_2O (54.0 mL) and H_2O (11.0 mL) was added KOH (3.50 g, 62.4 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The organic layer of the resulting solution was separated with separatory funnel, and the water layer was extracted with CH_2Cl_2. The combined extracts was dried over $MgSO_4$ and concentrated *in vacuo* to give *rac*-**18** (2.26 g, 26.3 mmol, 97% yield) as a colorless liquid. Detailed analytical data of *rac*-**18** was identical to the according literature.[121]

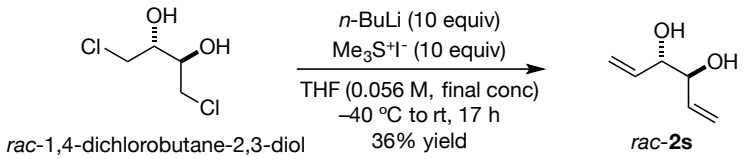
Synthesis of *rac*-**2r**



Modified procedure of the literature.[105]

To a solution of *rac*-**18** (866 mg, 10.1 mmol) and CuI (579 mg, 3.04 mmol) in THF (43.0 mL) was added dropwise MeMgBr (3.00 M in Et_2O, 14 mL, 42.0 mmol) at 0 ºC. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h at room temperature. After stirring for 2 h, the resulting mixture was poured into saturated aqueous NH_4Cl. The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: toluene/EtOAc = 2/1 to Et_2O, v/v) gave *rac*-**2r** (703 mg, 5.95 mmol, 59% yield) as a pale yellow liquid. Detailed analytical data of **2r** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

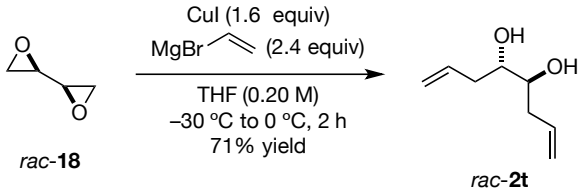
Synthesis of *rac*-**2s**



Modified procedure of the literature.[107]

To a suspension of $Me_3S^+I^-$ (16.3 g, 79.9 mmol) in THF (120 mL) was added dropwise *n*-BuLi (1.53 M in hexane, 49.5 mL, 75.7 mmol) at –40 ºC. The resulting mixture was stirred for 1 h at –40 ºC, and then *rac*-1,4-dichlorobutane-2,3-diol (0.544 M, 14.0 mL, 7.62 mmol) was added to reaction vessel at – 40 ºC. The reaction mixture was gradually warmed up to room temperature during 5 h, and stirred for additional 12 h. The reaction was quenched by saturated aqueous NH_4Cl (100 mL). The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: Et_2O/hexane = 1:1, v/v) gave *rac*-**2s** (315 mg, 2.76 mmol, 36% yield) as a colorless liquid. Detailed analytical data of **2s** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

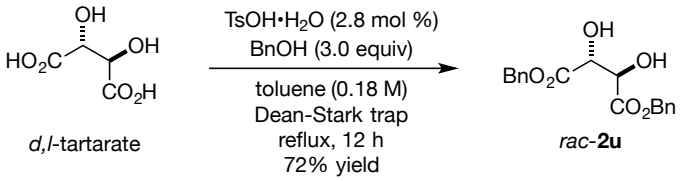
Synthesis of *rac*-**2t**



Modified procedure of the literature.[108]

To a solution of *rac*-**18** (383 mg, 4.45 mmol) CuBr (1.05 g, 7.32 mmol) in THF (23.0 mL) was added dropwise vinyl magnesium bromide (1.00 M in THF, 10.9 mL, 10.9 mmol) at –30 ºC. The reaction mixture was gradually warmed up to 0 ºC and stirred for 2 h at 0 ºC. After stirring for 2 h, saturated aqueous NH_4Cl (50 mL). The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 1:2, v/v) and gel permeation chromatography (eluent: CH_3Cl) gave *rac*-**2t** (457 mg, 3.21 mmol, 72% yield) as a colorless liquid. Detailed analytical data of **2t** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

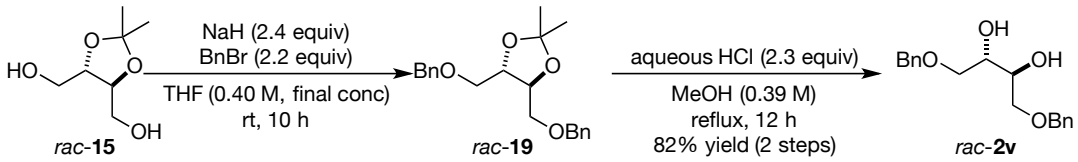
Synthesis of *rac*-**2u**



Modified procedure of the literature.[109]

A round-bottomed flask was equipped with a magnetic stirrer, Dean-Stark trap, and condenser was added *rac*-tartarate (1.51 g, 10.1 mmol), BnOH (3.10 mL, 30.0 mmol), TsOH•H_2O (52.9 mg, 0.278 mmol) and toluene (55.0 mL). To this solution was added TsOH•H_2O (335 mg, 1.76 mmol) at room temperature. The reaction mixture was heated up to refluxed temperature and stirred for 12 h. During this period, the azeotropic solution of toluene/H_2O was collected from Dean-Stark trap. After stirring for 12 h, the resulting mixture was cooled down to room temperature and neutralized by adding saturated aqueous $NaHCO_3$ to reaction vessel at room temperature until bubbles did not occur. The resulting mixture was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 1/1, v/v) gave *rac*-**2u** (2.40 g, 7.27 mmol, 72% yield) as a colorless solid. Detailed analytical data of **2u** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

Synthesis of *rac*-**2v**



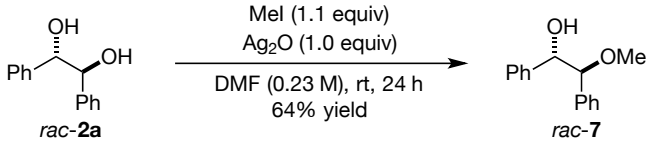
Modified procedure of the literature.[110]

To a suspension of NaH (60% dispersion in paraffin liquid, 356 mg, 8.90 mmol) in THF (4.60 mL) was added dropwise *rac*-**15** (0.807 M in THF, 4.60 mL, 3.71 mmol) at room temperature. The resulting mixture was stirred for 10 min, and then BnBr (967 μL, 8.14 mmol) was added to reaction vessel at room temperature. The reaction mixture was stirred for 10 h, and then water (50 mL) was added to reaction vessel. The resulting solution was extracted with Et_2O (50 mL×3), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product of *rac*-**19** (1.57 g). The crude product of *rac*-**19** was directly used next reaction without further purification.

To a solution of the crude product of *rac*-**19** (1.57 g) in MeOH (9.60 mL) was added aqueous HCl (1.00 M in H_2O, 8.51 mL, 8.51 mmol) at room temperature. The reaction mixture was heated up to refluxed temperature and stirred for 12 h at refluxed temperature. After stirring for 12 h and

cooling down to room temperature, a solid of $NaHCO_3$ was added to reaction vessel until bubbles did not occur. The resulting solution was concentrated *in vacuo*. The residue was dissolved in Et_2O (50 mL) and water (50 mL). The resulting solution was extracted with Et_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 1/1, v/v) gave *rac*-**2v** (926 mg, 3.06 mmol, 82% yield based on *rac*-**15**) as a colorless solid. Detailed analytical data of **2v** was shown in the previous section of "General procedure for substrate scope (Figure 2)".

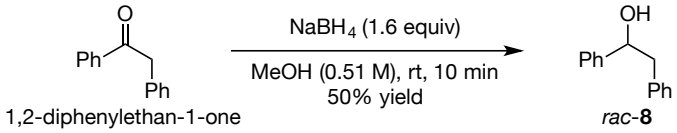
Synthesis of *rac*-**7**



Modified procedure of the literature.[15]

To a solution of *rac*-**2a** (1.00 g, 4.67 mmol) and Ag_2O (1.09 g, 4.70 mmol) in DMF (20.0 mL) was added MeI (320 μL, 5.14 mmol) at room temperature. The reaction solution was stirred for 24 h at room temperature while block the light. The resulting solution was passed through a short pad of Celite with CH_2Cl_2 as eluent. The filtrate was concentrated *in vacuo* to give the crude product. The purification of the crude product by flash column chromatography on silica gel (eluent: hexane/Et_2O = 7/1 to 3:1, v/v) gave *rac*-**7** (684 mg, 3.00 mmol, 64% yield) as a colorless solid. Detailed analytical data of **7** was shown in the previous section of "General procedure for control experiments with various substrates and analytical data for **7**–**12** (Scheme 5)".

Synthesis of *rac*-**8**



To a solution of 1,2-diphenylethan-1-one (1.50 g, 7.64 mmol) in MeOH (15.0 mL) was added portionwise $NaBH_4$ (462 mg, 12.2 mmol) at room temperature. The reaction mixture was stirred for 10 min, and then concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (eluent: Et_2O) to give *rac*-**8** as a colorless solid. Detailed analytical data of **8** was shown in the previous section of "General procedure for control experiments with various substrates and analytical data for **7**–**12** (Scheme 5)".

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List of Publications

(1) Enantioselective Acyl Transfer Catalysis by a Combination of Common Catalytic Motifs and Electrostatic Interactions
Mandai H.; Fujii K.; Yasuhara H.; Abe K.; Mitsudo K.; Korenaga T.; Suga S.
Nature Communications, Vol. 7, Article No. 11297 (2016).

(2) Kinetic Resolution of Secondary Carbinols by a Chiral *N*,*N*-4-Dimethylaminopyridine Derivative Containing a 1,1′-Binaphthyl Unit: Hydrogen Bonding Affects Catalytic Activity and Enantioselectivity
Fujii K.; Mitsudo K.; Mandai H.; Suga S.
Bulletin of the Chemical Society of Japan, Vol. 89, No. 9, pp. 1081–1092 (2016).

(3) Hydrogen Bonding-Assisted Enhancement of the Reaction Rate and Selectivity in the Kinetic Resolution of *d,l*-1,2-Diols with Chiral Nucleophilic Catalysts
Fujii K.; Mitsudo K.; Mandai H.; Suga S.
Advanced Synthesis & Catalysis, Wiley, Vol. 359, pp. 2778-2788 (2017).

(4) Desymmetrization of *meso*-1,2-Diols by a Chiral *N*,*N*-4-Dimethylaminopyridine Derivative Containing a 1,1′-Binaphthyl Unit: Importance of the Hydroxy Groups
Mandai H.; Yasuhara H.; Fujii K.; Shimomura Y.; Mitsudo K.; Korenaga T.; Suga S.
The Journal of Organic Chemistry, Vol. 82, No. 13, pp. 6846–6856 (2017).

(5) 効率的かつ劇的な反応加速効果をもたらす有機分子触媒システムの開発
萬代大樹，藤居一輝，菅　誠治
有機合成化学協会誌, Vol. 75, No. 6, pp. 632–649 (2017).