Dipeptide-Derived Chiral Tri- or Diammonium Salt-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition Reaction of Nitrones with α-(Acyloxy)acroleins

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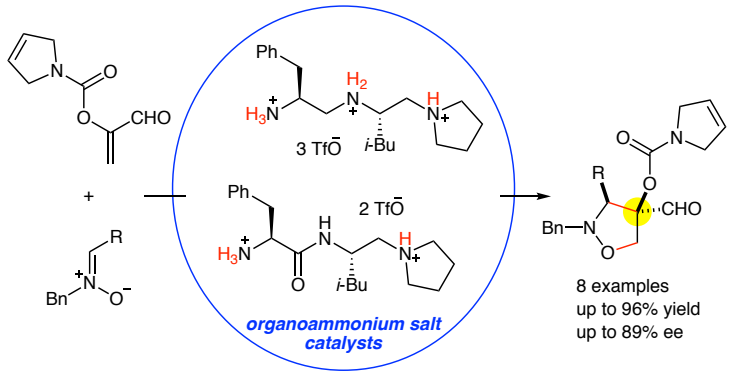


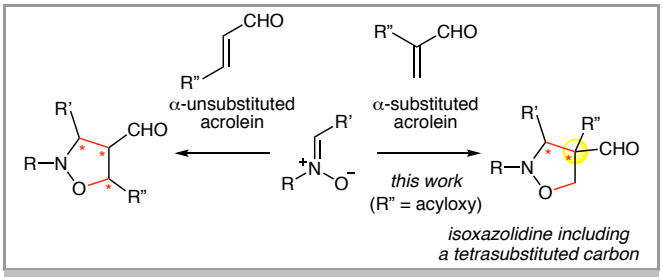
Received:
Accepted:
Published online:
DOI:

Abstract Organoammonium salts of dipeptide-derived chiral triamine or diamine with TfOH catalyze the enantioselective 1,3-dipolar cycloaddition reaction of α-acyloxyacroleins with nitrones to give the corresponding adducts in good yields (up to 96%) with high diastereo- and enantioselectivity (up to 89% ee). Although α-(*p*-methoxybenzoyloxy)acrolein is rather unstable under the reaction conditions, α-(3-pyrroline-1-carbonyloxy)acrolein is stable enough to be smoothly converted to the corresponding adducts with the aid of chiral organoammonium salt catalysts.

Key words α-(acyloxy)acrolein, 1,3-dipolar cycloaddition, enantioselective, isoxazolidine, nitrone, organoammonium salt, tetrasubstituted carbon center

Isoxazolidine, a five-membered ring containing adjacent nitrogen and oxygen atoms, is an important structure in medicinal chemistry.[1] It is also a useful building block since it can be easily converted to β-amino acids, β-lactams, or β-amino alcohols.[2] Isoxazolidines are generally synthesized through the 1,3-dipolar cycloaddition reaction of nitrones. Thus, for the stereoselective synthesis of isoxazolidines, many methods have been developed for the catalytic asymmetric 1,3-dipolar cycloaddition of nitrones.[3] In many of these methods, α-unsubstituted α,β-unsaturated carbonyl compounds are used as 1,3-dipolarophiles (Scheme 1). On the other hand, when α-substituted α,β-unsaturated carbonyl compounds are used as 1,3-dipolarophiles, isoxazolidines with a tetrasubstituted carbon center are obtained. Thus, several methods have been developed for the asymmetric 1,3-dipolar cycloaddition of nitrones with α-substituted α,β-unsaturated carbonyl compounds.[4] However, in most of these reports, 1,3-dipolarophiles are limited to methacrolein or methacrylonitrile.

α-(Acyloxy)acrolein,[5] an α-substituted acrolein, is highly useful as a dienophile for asymmetric cycloaddition reactions. For example, Ishihara's group reported an enantioselective Diels–Alder reaction and [2+2] cycloaddition reaction with α-(acyloxy)acroleins.[6–8] Chiral primary ammonium salt catalysts stereoselectively promote these reactions to give carbocyclic quaternary α-hydroxycarbonyl compound derivatives. Based on this study, we envisioned that chiral primary ammonium salts would stereoselectively promote the 1,3-dipolar cycloaddition of nitrones with α-(acyloxy)acroleins and give isoxazolidines with an oxygen-containing tetrasubstituted carbon center. These isoxazolidines could be new chiral building blocks with synthetic utility, since they could be easily converted to acyclic aminoalcohols via N–O bond cleavage under mild reducing conditions.[9] We report here our study on the development of an enantioselective 1,3-dipolar cycloaddition reaction of nitrones with α-(acyloxy)acroleins.



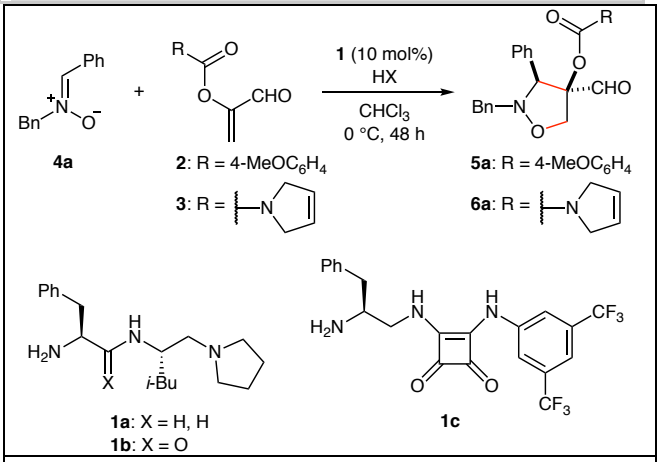
Scheme 1 1,3-Dipolar cycloaddition reactions of nitrones with α-substituted or α-unsubstituted acroleins

Our study commenced with examination of the 1,3-dipolar cycloaddition reaction of nitrone **4a** with α-(*p*-methoxybenzoyloxy)acrolein (**2**). According to the procedure for the Diels–Alder reaction with **2**,[7] the reaction of **4a** (2 equiv) with **2** was conducted in the presence of a chiral triammonium salt **1a**·2.8$C_6F_5SO_3H$ (10 mol%) in THF or $EtNO_2$. However, the

corresponding adduct **5a** was not obtained, and almost all of **2** decomposed.[10] By the screening of solvents, we found that the reaction proceeded slowly in $CHCl_3$ to give *endo*-**5a** as a major diastereomer (5.9:1 dr) with 75% ee, although the yield was poor (Table 1, entry 1). This low yield was attributed to the lower reactivity of **4a** compared to dienes, and to the instability of **2** under the reaction conditions. Thus, the use of two equivalents of **2** relative to **4a** improved the yield of **5a** (52%) without decreasing the enantioselectivity (entry 2).

The ester group of **2** was gradually hydrolyzed during the reaction. We assumed that the decomposition of **2** could be attributed to the high acidity of triammonium salt catalyst **1a**·2.8$C_6F_5SO_3H$. Therefore, we next examined the catalytic activities of various di- and monoammonium salts,[10] the acidities of which should be lower than those of the corresponding triammonium salts. We found that the use of diammonium salt **1b**·2$C_6F_5SO_3H$ or monoammonium salt **1c**·$C_6F_5SO_3H$ significantly suppressed the decomposition of **2** during the reaction course, and *endo*-**5a** was obtained with good enantiomeric excess (65 and 74% ees) (entries 3 and 4). However, the yield of **5a** was not improved, and a significant amount of unreacted **2a** was recovered. These results showed that the catalytic activities of **1b**·2$C_6F_5SO_3H$ and **1c**·$C_6F_5SO_3H$ were similar to that of **1a**·2.8$C_6F_5SO_3H$.

Table 1 Examination of **1**·nHX-Catalyzed [3+2] Cycloaddition of **2** with **3a**[a]



Entry	**2**, **3**	**1**	HX (mol%)[b]	yield (%)[b]	*endo*/*exo*[c]	ee (%)[d]
1[e]	**2**	**1a**	$C_6F_5SO_3H$ (28)	**5a**, 24	5.9:1	75
2	**2**	**1a**	$C_6F_5SO_3H$ (28)	**5a**, 52	4.5:1	74
3	**2**	**1b**	$C_6F_5SO_3H$ (20)	**5a**, 32	7.8:1	65
4	**2**	**1c**	$C_6F_5SO_3H$ (10)	**5a**, 51	5.0:1	74
5	**3**	**1a**	$C_6F_5SO_3H$ (28)	**6a**, 50	9.0:1	70
6	**3**	**1b**	$C_6F_5SO_3H$ (20)	**6a**, 43	10:1	63
7	**3**	**1c**	$C_6F_5SO_3H$ (10)	**6a**, 3	3.3:1	ND
8	**3**	**1a**	TfOH (28)	**6a**, 58	14:1	86
9	**3**	**1b**	TfOH (20)	**6a**, 55	20:1	80
10	**3**	**1b**	Tf_2NH (20)	**6a**, 20	2.5:1	54

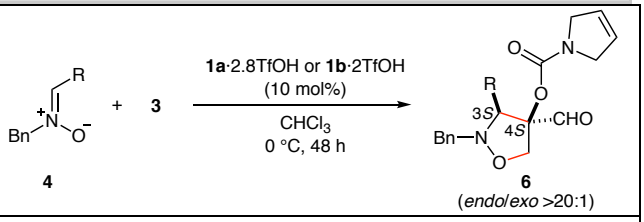
[a]The reaction of **4a** (0.1 mmol) with **2** or **3** (2 equiv) was conducted in the presence of **1**·nHX (10 mol%) in $CHCl_3$ (0.5 mL) at 0 °C for 48 h. [b]Isolated yield. [c]Evaluated by ^1H NMR analysis. [d]Enantiomeric excess of *endo*-isomer. Evaluated by chiral HPLC analysis after reduction of the formyl group ($NaBH_4$, MeOH). [e]The reaction of **2** (0.1 mmol) was conducted with **4a** (2 equiv) for 24 h.

To suppress the decomposition of 1,3-dipolarophiles, we next examined the cycloaddition with **3**, the carbamoyl group[11] of which should be more stable than a *p*-methoxybenzoyl group. As we expected, in the presence of triammonium salt **1a**·2.8$C_6F_5SO_3H$ or diammonium salt **1b**·2$C_6F_5SO_3H$, the reaction of **3** proceeded without significant decomposition of **3**, and gave the corresponding *endo*-**6a** in moderate yields (entries 5 and 6).[12] In contrast, acrolein **3** was almost inert in the **1c**·$C_6F_5SO_3H$-catalyzed reaction (entry 7). It was conceivable that the electron-donating 3-pyrroline group decreased the reactivity of **3**, and that monoammonium salt **1c**·$C_6F_5SO_3H$ did not have enough catalytic activity to promote the reaction with less-active **3**.

Since acrolein **3** was found to be more stable than **2**, we envisioned that ammonium salts of **1** with TfOH, a stronger acid than $C_6F_5SO_3H$,[13] could be used as catalysts to show high activities without the decomposition of **3**. As expected, the use of **1a**·2.8TfOH or **1b**·2TfOH successfully improved the yield of **6a** (58 and 55%) (entries 8 and 9).[14] In addition, the diastereo- and enantioselectivity of **6a** were also unexpectedly improved (14:1 dr, 86% ee and 20:1 dr, 80% ee). However, the use of **1b**·2Tf_2NH as a catalyst resulted in the significant decomposition of **3** to decrease the yield of **6a** (entry 10).

With the optimal reaction conditions in hand, we next examined the substrate scope and limitations of the present enantioselective 1,3-dipolar cycloaddition reaction of nitrone **4** with α-(carbamoyloxy)acrolein **3** (Table 2).[15] The electronic properties of the substituent on nitrone **4** significantly affected the reactivity. For example, in the presence of **1a**·2.8TfOH as a catalyst, the reaction of nitrones **4b** and **4c** bearing an electron-rich aromatic substituent gave the corresponding adducts **6b** and **6c** in high yields (83 and 96%) with good enantioselectivities (86 and 76% ee) (entries 1 and 3). Although **1b**·2TfOH showed catalytic activity similar to that of **1a**·2.8TfOH in the reaction of **4a**, the use of **1b**·2TfOH gave **6b** and **6c** in moderate yields (66 and 50%) (entries 2 and 4). The absolute configuration of *endo*-**6c** was determined to be (3*S*,4*S*) based on an analysis of CD spectra.[10] This stereochemistry could be explained by the transition state assemblies shown in Figure 1. As in the Diels–Alder reaction and [2+2] cycloaddition reaction with α-(acyloxy)acroleins,[7] (*Z*)-iminium ion intermediate would be generated from **1a**·3TfOH[16] and **3** as an active species. This (*Z*)-iminium ion intermediate would be stabilized by intramolecular hydrogen bonding of the pyrrolidinium group with the carbamoyl group. In this active species, *re*-face of the iminium group is shielded by the benzyl group. Thus, nitrones **4** should approach the *si*-face of the iminium group to give (4*S*)-adducts preferentially. The result that the use of **3** improved the diastereo- and enantioselectivity might be attributed to the stronger intramolecular hydrogen bonding with the carbamoyl group than with the *p*-methoxybenzoyl group to make the asymmetric environment more rigid.

Table 2 Substrate Scope and Limitations[a]



Entry	**4**, R	catalyst	yield (%)[b]	ee (%)[c]
1	**4b**, 4-$MeOC_6H_4$	**1a**·2.8TfOH	**6b**, 83	86
2		**1b**·2TfOH	**6b**, 66	80

3	**4c**, 2-naphthyl	**1a**·2.8TfOH	**6c**, 96	76 (3*S*,4*S*)
4		**1b**·2TfOH	**6c**, 50	71 (3*S*,4*S*)
5	**4d** 2-furyl	**1a**·2.8TfOH	**6d**, 16	85
6		**1b**·2TfOH	**6d**, 19	89
7	**4e**, 4-BrC_6H_4	**1a**·2.8TfOH	**6e**, 55	82
8		**1b**·2TfOH	**6e**, 59	83
9	**4f**, 4-$NO_2C_6H_4$	**1a**·2.8TfOH	**6f**, 12	82
10		**1b**·2TfOH	**6f**, 15	85
11	**4g**, (*E*)-PhCH=CH	**1a**·2.8TfOH	**6g**, 28	79
12		**1b**·2TfOH	**6g**, 35	81
13	**4h**, cyclopropyl	**1a**·2.8TfOH	**6h**, 45	48
14		**1b**·2TfOH	**6h**, 44	46

[a]The reaction of **4** (0.1 mmol) with **3** (2 equiv) was conducted in the presence of **1a**·2.8TfOH or **1b**·2TfOH (10 mol%) in $CHCl_3$ (0.5 mL) at 0 °C for 48 h. [b]Isolated yield. [c]Enantiomeric excess of *endo*-isomer. Evaluated by chiral HPLC analysis after reduction of the formyl group ($NaBH_4$, MeOH).

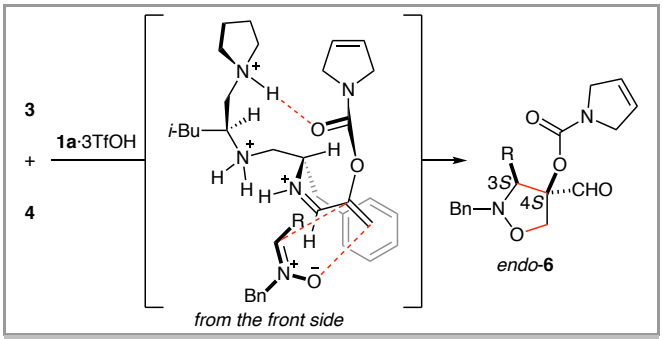
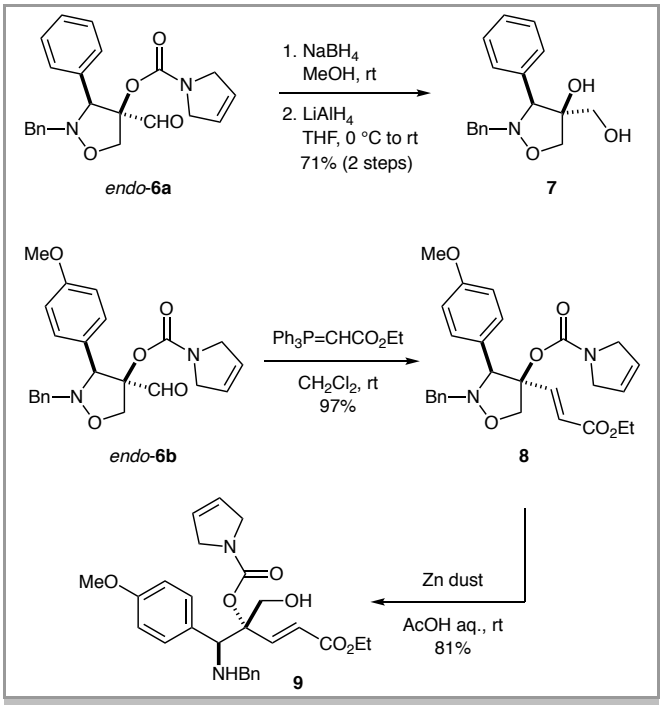


Figure 1 Proposed transition state assemblies

2-Furyl-substituted **4d** showed unexpectedly poor reactivity despite the electron-rich furyl group, albeit the enantioselectivity was high (entries 5 and 6). In contrast to electron-rich nitrones, **4e** and **4f** bearing an electron-deficient aromatic substituent showed moderate to poor reactivities (entries 7–10).

In addition to aromatic substituents, a 2-phenylethenyl group could be successfully incorporated into adduct **6g** with ca. 80% ee, although the yield was moderate (entries 11 and 12). Cyclopropyl-substituted adduct **6h** was also obtained in moderate yield (44–45%) with moderate enantioselectivity (46–48% ee) (entries 13 and 14). Notably, **1b**·2TfOH gave slightly better results than **1a**·2.8TfOH in the reaction of less-reactive nitrones **4d**–**4g**.

The 1,3-dipolar cycloadducts **6** are useful compounds for the synthesis of various chiral aminoalcohols with an oxygen-containing tetrasubstituted carbon center (Scheme 2). For example, reduction of the formyl group of *endo*-**6a** with $NaBH_4$ gave the corresponding carbamoyl-protected diol. The subsequent reductive removal of the 3-pyrroline-1-carbonyl group with $LiAlH_4$ gave diol **7** in 71% yield (two steps). In addition, Wittig reaction of *endo*-**6b** with $Ph_3P{=}CHCO_2Et$ gave unsaturated ester **8** in 97% yield. Reductive N–O bond cleavage of **8** with Zn dust[17] gave the corresponding acyclic aminoalcohol **9** in 81% yield.



Scheme 2 Transformation of cycloadduct **6b**

In conclusion, we have developed a dipeptide-derived tri- or diammonium salt-catalyzed enantioselective 1,3-dipolar cycloaddition of α-(acyloxy)acroleins with nitrones to provide chiral isoxazolidines with an oxygen-containing tetrasubstituted carbon center. The ammonium salts of chiral triamine **1a** and diamine **1b** with TfOH successfully promoted the reaction with high diastereo- and enantioselectivity.

Acknowledgment

The authors gratefully thank the Division of Instrumental Analysis, Department of Instrumental Analysis & Cryogenics, Advanced Science Research Center, Okayama University, for the NMR and HRMS measurements.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-xxxxxxx.

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(10) See the Supporting Information for details.

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(12) Compound **3** was more stable and less reactive than **2**. Thus, 30–50% of **3** was recovered during the reaction, while **2** was completely consumed under the same conditions. This would be the reason why the yield of **6a** was moderate.

(13) pK_a (CD_3CO_2D) of TfOH: –0.74, pK_a (CD_3CO_2D) of $C_6F_5SO_3H$: 9.2. See: (a) Rode, B. M.; Engelbrecht, A.; Schantl, J. *Z. Phys. Chem. (Leipzig)* **1973**, *253*, 17–24. (b) Sakakura, A.; Koshikari, Y.; Akakura, M.; Ishihara, K. *Org. Lett.* **2012**, *14*, 30–33.

(14) When **1a**·2.8TfOH or **1b**·2TfOH was used as a catalyst in the reaction of **2**, a more-labile acrolein than **3**, a significant amount of **2** was decomposed.

(15) **Typical Procedure for the 1a·2.8TfOH-Catalyzed 1,3-Dipolar Cycloaddition Reaction with 3:** To a solution of triamine **1a** (3.2 mg, 0.0105 mmol) and TfOH (2.6 μL, 0.0295 mmol) in $CHCl_3$ (0.15 mL) was added a solution of nitrone **4a** (21.5 mg, 0.10 mmol) and acrolein **3** (34.5 mg, 0.206 mmol) in $CHCl_3$ (0.30 mL) at 0 °C. The resulting solution was stirred at 0 °C for 48 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with brine. The organic layer was dried over Na_2SO_4. After filtration, the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane–EtOAc as eluent to give **6a** (21.9 mg, 0.0579 mmol, 58% yield).

(16) Although the triammonium salt catalyst was prepared *in situ* by mixing **1a** and 2.8 equivalents of TfOH, active catalytic species should be **1a**·3TfOH.[7b] To suppress undesired catalysis by TfOH, a slightly less than 3 equivalents of TfOH was used for the preparation of the triammonium salt catalyst.

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