

# Electrochemical generation of silver acetylides from terminal alkynes with a Ag anode and integration into sequential Pd-catalysed coupling with arylboronic acids

Koichi Mitsudo,\* Takuya Shiraga, Jun-ichi Mizukawa, Seiji Suga and Hideo Tanaka\*

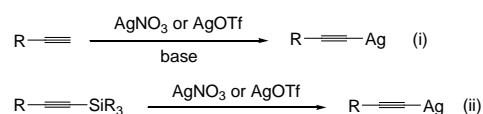
5 Received (in XXX, XXX) Xth XXXXXXXXXX 200X, Accepted Xth XXXXXXXXXX 200X

First published on the web Xth XXXXXXXXXX 200X

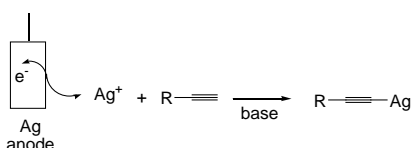
DOI: 10.1039/b000000x

An electro-oxidative method for generating silver acetylides from acetylenes with a Ag anode was developed. The reaction could be integrated into a Pd-catalysed electrochemical Sonogashira-type reaction. In the presence of the catalytic amount of Pd(OAc)<sub>2</sub> and 4-BzO-TEMPO, electro-generated silver acetylides reacted immediately with arylboronic acids to afford the corresponding coupling adducts in high yields.

15 Silver acetylides are among the oldest organometallics and several applications to organic syntheses have been reported.<sup>1,2</sup> The most common methods for preparing silver acetylides are (i) the reaction of terminal alkynes with silver salts such as silver nitrate and silver triflate, and (ii) the  
20 reaction of alkynylsilanes with silver salts.



We have been interested in the electrochemical transformation of organometallics and in reactions which involve thus-generated organometallic species.<sup>3</sup> During the course of our study, we found that terminal alkynes were transformed easily to silver acetylides under the electro-oxidative conditions with a Ag anode (Scheme 1). This electrochemical system for the generation of silver acetylides could be readily integrated into an electro-oxidative reaction. The advantage of the reaction is that the synthesis and reaction of silver acetylide proceeded simultaneously in one reactor. We report here a facile electrochemical method for the synthesis of silver acetylides and integration of this method to the Pd-catalysed electro-oxidative coupling of arylboronic acids and terminal alkynes.<sup>4</sup>



40 **Scheme 1.** Strategy for the electro-oxidative synthesis of silver acetylides

We first chose silver phenylacetylide (**2a**) as a target compound (Table 1). Electro-oxidation was performed in a two-compartment cell divided by a glass filter. To the anodic chamber was added a solution of terminal alkyne **1a** (0.2

45 mmol) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 2.0 equiv) in 0.05 M Et<sub>4</sub>NOTs/CH<sub>3</sub>CN (10 mL), and to the cathodic chamber was added a solution of 0.05 M Et<sub>4</sub>NOTs/CH<sub>3</sub>CN (10 mL). Constant-current electrolysis of the solution afforded silver acetylide **2a** in 88% yield (entry 1).  
50 Similarly, silver acetylides **2b** and **2c** could be obtained in respective yields of 65% and 70% (entries 2 and 3).

We next investigated the integration of this electrochemical synthesis of silver acetylides to Pd-catalysed coupling with arylboronic acids. First, the electro-oxidative coupling of phenylacetylene (**1a**) and phenylboronic acid (**3a**) was carried out in the presence of several bases (Table 2). In the presence of Pd(OAc)<sub>2</sub> (10 mol %), TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 30 mol %), and Et<sub>3</sub>N (2 equiv), the electrooxidative coupling reaction proceeded smoothly to afford product **4aa** in 51% yield (entry 1). Further screening revealed that the addition of DBU was highly advantageous for the reaction, and the yield of **4aa** increased drastically up to 81% (entry 2). The addition of DABCO (1,4-diazabicyclo[2.2.2]octane) or potassium carbonate did not promote the reaction efficiently (entries 3 and 4). The addition of base was indispensable for the reaction. Without base, the yield of **4aa** decreased to 5% (entry 5).

**Table 1** Electro-oxidative synthesis of several silver acetylides<sup>a</sup>

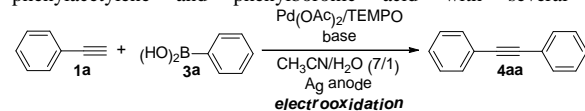
| Entry          | <b>1</b> | <b>2</b> | Yield (%) <sup>b</sup> |
|----------------|----------|----------|------------------------|
| 1              |          |          | 88                     |
| 2              |          |          | 65                     |
| 3 <sup>c</sup> |          |          | 70                     |

<sup>a</sup> Reaction conditions: **1** (0.2 mmol), DBU (2 equiv), CH<sub>3</sub>CN (10 mL), 5 mA, 1 F/mol. <sup>b</sup> Isolated yield. <sup>c</sup> 1.5 F/mol

To evaluate the utility of the obtained silver acetylide, several different anodes were used in the reaction (Table 3). With a Cu anode, the reaction also proceeded to afford internal alkyne **4aa** in 56% yield (entry 2). In contrast, only a trace amount of **4aa** was obtained with a Pt anode, which could not act as a sacrificial anode (entry 3). These results suggest that the generation of a metal acetylide, such as silver

acetylide or copper acetylide, might be essential for the reaction. We next examined the reaction with a Pt anode in the presence of Ag wire in the reaction mixture. The reaction proceeded, and **4aa** was obtained in 36% yield (entry 4). The lower yield compared to that of entry 1 might be due to the lower efficiency of the generation of silver acetylide.

**Table 2** Pd/TEMPO-Catalysed electro-oxidative coupling of phenylacetylene and phenylboronic acid with several bases<sup>a</sup>



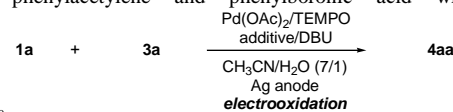
| Entry | Base                           | Yield (%) <sup>b</sup> |
|-------|--------------------------------|------------------------|
| 1     | Et <sub>3</sub> N              | 51                     |
| 2     | DBU                            | 81                     |
| 3     | DABCO                          | 42                     |
| 4     | K <sub>2</sub> CO <sub>3</sub> | 24                     |
| 5     | none                           | 5                      |

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **3a** (0.5 mmol), Pd(OAc)<sub>2</sub> (10 mol %), TEMPO (30 mol %), base (2 equiv), NaClO<sub>4</sub> (0.2 M), CH<sub>3</sub>CN/H<sub>2</sub>O (7/1), 50 mA, 4 F/mol. <sup>b</sup> Isolated yield.

To exploit the utility of this reaction, the scope of the reaction was investigated (Table 4). During the course of the optimization of the conditions, we found that the amount of Pd(OAc)<sub>2</sub> could be reduced to 5 mol %, and 4-BzO-TEMPO was better mediator than TEMPO. The electro-oxidative coupling of **1a** and **3a** afforded **4aa** in 93% yield under the optimized conditions (entry 1). Unexpectedly, the reaction also proceeded without mediator to afford **4aa** in a similar yield. For arylboronic acids bearing an electron-donating

group, the addition of mediator was essential. In the reaction of **1a** with **3b** or **3c**, the reactions proceeded smoothly to afford **4ab** and **4ac** in respective yields of 91% and 99% (entries 2 and 3). In contrast, in the reaction of electron-deficient arylboronic acids, the electro-oxidative reaction was not affected by the mediator (entries 4 and 5). *p*-Tolylacetylene (**1b**) exhibited high reactivity in the reaction, and the corresponding alkynes **4** were obtained in excellent yields (entries 6–8). In contrast, when *p*-nitrophenylacetylene (**1c**) was used, the yields of **4** were slightly lower than those of **1a** and **1b** (entries 9 and 10). We assumed that this difference is due to the efficiency of the generation of silver acetylide. Electron-rich alkynes would interact efficiently with Ag<sup>+</sup>, and silver acetylide would be generated faster than electron-deficient alkynes.

**Table 3** Pd/TEMPO-Catalysed electro-oxidative coupling of phenylacetylene and phenylboronic acid with several anodes<sup>a</sup>

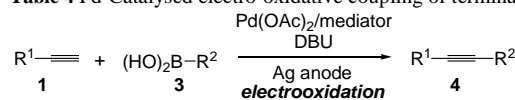


| Entry | Anode | Additive | Yield (%) <sup>b</sup> |
|-------|-------|----------|------------------------|
| 1     | Ag    | none     | 81                     |
| 2     | Cu    | none     | 56                     |
| 3     | Pt    | none     | 5                      |
| 4     | Pt    | Ag wire  | 36                     |
| 5     | Pt    | Cu wire  | 2                      |

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **3a** (0.5 mmol), Pd(OAc)<sub>2</sub> (10 mol %), TEMPO (30 mol %), base (2 equiv), NaClO<sub>4</sub> (0.2 M), CH<sub>3</sub>CN/H<sub>2</sub>O (7/1), 50 mA, 4 F/mol. <sup>b</sup> Isolated yield.

A plausible mechanism for the coupling reaction is illustrated in Figure 1. First, R<sup>1</sup>Pd(II)L<sub>n</sub> (L = ligand) would be

**Table 4** Pd-Catalysed electro-oxidative coupling of terminal alkynes and arylboronic acids<sup>a</sup>

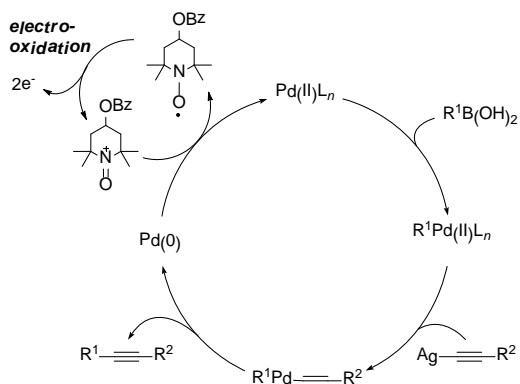


| Entry           | 1 | 3 | 4 | Yield (%) <sup>b</sup> |
|-----------------|---|---|---|------------------------|
| 1               |   |   |   | 93 (91) <sup>c</sup>   |
| 2 <sup>d</sup>  |   |   |   | 91                     |
| 3 <sup>d</sup>  |   |   |   | 99 (42) <sup>c</sup>   |
| 4               |   |   |   | 91 (84) <sup>c</sup>   |
| 5 <sup>d</sup>  |   |   |   | 76 (77) <sup>c</sup>   |
| 6               |   |   |   | 99                     |
| 7               |   |   |   | 95 <sup>c</sup>        |
| 8               |   |   |   | 96 <sup>c</sup>        |
| 9 <sup>d</sup>  |   |   |   | 80 <sup>c</sup>        |
| 10 <sup>d</sup> |   |   |   | 76                     |

<sup>a</sup> Reaction conditions: **1** (0.5 mmol), **3** (0.5 mmol), Pd(OAc)<sub>2</sub> (5 mol %), 4-BzO-TEMPO (15 mol %), DBU (2 equiv), NaClO<sub>4</sub> (0.2 M), CH<sub>3</sub>CN/H<sub>2</sub>O (7/1), 50 mA, 4 F/mol. <sup>b</sup> Isolated yield. <sup>c</sup> Without mediator. <sup>d</sup> 10 mA of electricity was passed.

generated from Pd(II) and arylboronic acid. Following transmetalation with silver acetylide would give an alkynylpalladium intermediate, and subsequent reductive elimination would afford the coupling product and Pd<sup>0</sup> species.<sup>5</sup> Pd(II) complex would be regenerated through the oxidation by *N*-oxoammonium cation, which would be generated by the electro-oxidation of 4-BzO-TEMPO. In the absence of 4-BzO-TEMPO, silver species would act as a mediator.

(5) Another plausible mechanism is that transmetalation with a silver acetylide would be the first step, and following transmetalation with arylboronic acid and reductive elimination would afford the coupling product. The detail of the mechanism is currently under investigation.



**Figure 1.** A plausible mechanism for the electro-oxidative coupling of terminal alkynes and arylboronic acids

In summary, we have developed an electro-oxidative method for preparing silver acetylides. The in situ integration of the synthetic procedure of silver acetylides and the Pd-mediatory electro-oxidative cross-coupling with arylboronic acids was also successful. The further application of this strategy is being studied in our laboratory.

## Notes and references

<sup>a</sup> Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan. Fax: +81-86-251-8079; Tel: +81-86-251-8079; E-mail: tanaka95@cc.okayama-u.ac.jp

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

- (1) For a review, see: U. Halbes-Letinois, J.-M. Weibel, P. Pale, *Chem. Soc. Rev.*, 2007, **36**, 759.
- (2) Recent examples, see: (a) S. Kim, B. Kim, J. In, *Synthesis*, 2009, 1963; (b) B. J. Albert, K. Koide, *J. Org. Chem.*, 2008, **73**, 1093; (c) R. H. Pouwer, J. B. Harper, K. Vyakaranam, J. Michl, C. M. Williams, C. H. Jessen, P. V. Bernhardt, *Eur. J. Org. Chem.*, 2007, 241; (d) R. H. Pouwer, C. M. Williams, A. L. Raine, J. B. Harper, *Org. Lett.*, 2005, **7**, 1323; (e) S. P. Shahi, K. Koide, *Angew. Chem., Int. Ed.*, 2004, **43**, 2525; (f) D. Bruyere, D. Bouyssi, G. Balme, *Tetrahedron*, 2004, **60**, 4007.
- (3) (a) K. Mitsudo, T. Shiraga, D. Kagen, D. Shi, J. Y. Becker, H. Tanaka, *Tetrahedron*, 2009, **65**, 8384; (b) K. Mitsudo, T. Ishii, H. Tanaka, *Electrochemistry*, 2008, **76**, 859; (c) K. Mitsudo, T. Imura, T. Yamaguchi, H. Tanaka, *Tetrahedron Lett.*, 2008, **49**, 7287; (d) K. Mitsudo, T. Shiraga, H. Tanaka, *Tetrahedron Lett.*, 2008, **49**, 6593; (e) K. Mitsudo, T. Kaide, E. Nakamoto, K. Yoshida, H. Tanaka, *J. Am. Chem. Soc.*, 2007, **129**, 2246.
- (4) Pd or Cu-Catalysed coupling of terminal alkynes and arylboronic acids, see: (a) G. Zou, J. Zhu, J. Tang, *Tetrahedron Lett.*, 2003, **44**, 8709; (b) F. Yang, Y. Wu, *Eur. J. Org. Chem.*, 2007, 3476; (c) C. Pan, F. Luo, W. Wang, Z. Ye, J. Cheng, *Tetrahedron Lett.*, 2009, **50**, 5044; (d) J. Mao, J. Guo, S. J. Ji, *J. Mol. Catal. A: Chem.*, 2008, 85.