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Pd-Catalyzed Regioselective and Stereospecific Suzuki–Miyaura Coupling of Allylic Carbonates with Arylboronic Acids

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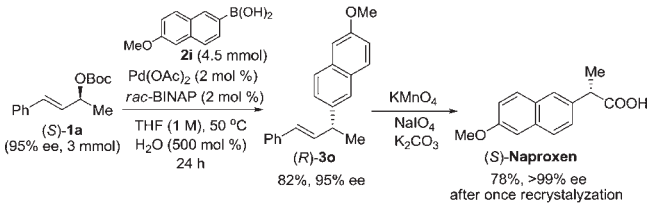
ABSTRACT



The Pd-catalyzed Suzuki–Miyaura coupling reaction of unsymmetric 1,3-disubstituted secondary allylic carbonates with arylboronic acids has been developed in a wet solvent under a base-free system to afford allyl–aryl coupling products in a high level of isolated yields with complete regio- and *E*/*Z*-selectivities with good to excellent chemoselectivities. The coupling reaction of optically active allyl carbonates gave allyl–aryl coupling products with excellent enantioselectivities with inversion of the stereochemistry. This coupling method was successfully applied to the synthesis of (*S*)-naproxen.

The Pd-catalyzed Suzuki–Miyaura coupling reaction is one of the most powerful methods for C–C bond formation because of the broad functional group tolerance, the availability of organoboronic acids, and the lack of toxic byproducts.[1] A broad range of electrophiles undergo cross-couplings with organoboronic acids, including alkyl, aryl, akenyl, and alkynyl groups. However, the coupling reaction with allylic derivatives has been rarely reported,[2] and in most of the reports, the allylic partners have been confined to primary allylic halides or alcohol derivatives. The allyl–aryl coupling reaction of unsymmetric 1,3-disubstituted secondary allylic alcohol derivatives with arylboronic acids remains a significant challenge.[3] Generally, the reaction starts with oxidative addition of palladium(0) to an allylic partner **1a** to produce a π-allylpalladium intermediate, which subsequently undergoes transmetalation with arylboronic acid

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(1) (a) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(2) For a review, see: (a) Pigge, F. C. *Synthesis* **2010**, 1745. For selected recent examples, see:(b) Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 12103. (c) Yamada, Y. M. A.; Watanabe, T.; Torii, K.; Uozumi, Y. *Chem. Commun.* **2009**, 5594. (d) Mino, T.; Kajiwara, K.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 2711. (e) Tsukamoto, H.; Uchiyama, T.; Suzuki, T.; Kondo, Y. *Org. Biomol. Chem.* **2008**, *6*, 3005. (f) Nájera, C.; Gil-Moltó, J.; Karlström, S. *Adv. Synth. Catal* **2004**, *346*, 1798. (g) Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200.

(3) There is only one effective example for allyl–aryl coupling reaction of secondary allylic acetates with arylboronic acids using heterogeneous palladium catalyst in the presence of excess base; see: Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384.

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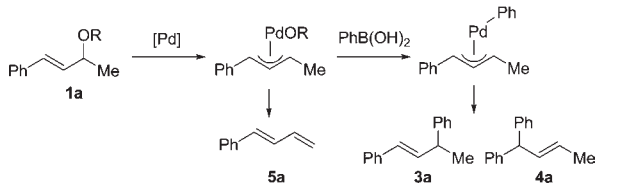
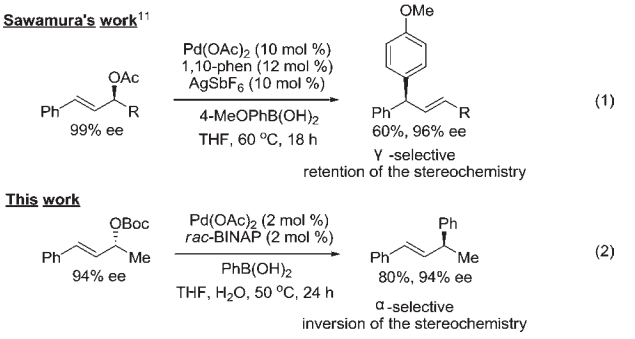
Scheme 1. Allyl–Aryl Coupling vs β-H Elimination



to give a π-allyl(aryl)palladium intermediate, followed by reductive elimination to afford allyl–aryl products (Scheme 1).[2a,4] However, the reaction generally gave conjugated diene **5a** instead of the desired coupling products because the π-allylpalladium intermediate underwent the β-H elimination more quickly than the transmetalation with arylboronic acid.[2a,5] This phenomenon might be one explanation for the limited development of Suzuki–Miyaura coupling with secondary allylic fragments.

Although transition-metal-catalyzed allylic arylation with arylmetallic reagents is another powerful approach for allyl–aryl coupling, the reactions have not been well exploited, and the arylmetallic reagents have mostly been limited to highly reactive ones, such as aryl Grignard,[6] zinc,[7] and aluminum[8] reagents. The allylic arylation with arylboronic acid derivatives has been much less explored because of their poor nucleophilicity.[9,10] Most recently, Sawamura and co-workers reported a Pd(II)-catalyzed γ-selective allyl–aryl coupling reaction using nitrogen-based ligands (eq 1).[11] The reaction was catalyzed by cationic acetoxopalladium(II) to afford allyl–aryl coupling products with α to γ chirality transfer with retention of the stereochemistry.



Herein, we disclose an effective method for the Pd-catalyzed Suzuki–Miyaura coupling reaction of unsymmetric 1,3-disubstituted secondary allylic carbonates[12] with arylboronic acids (eq 2). The reaction afforded the allyl–aryl coupling products in a high level of isolated yields with excellent chemo- and regioselectivity. The reaction of optically active allylic carbonates furnished allyl–aryl coupling products with excellent enantioselectivities with inversion of the absolute configuration. The methodology provides a simple and practical protocol that allows rapid access to allyl–aryl coupling products using in-situ-generated palladium–phosphine complex as a catalyst and a wet solvent under a base-free system.

Preliminary studies demonstrated that the in-situ-generated palladium complex from $Pd(OAc)_2$[13,14] (2 mol %) and triphenylphosphine (4 mol %) was found to catalyze the coupling of allylic carbonate **1a** with phenylboronic acid (**2a**) in THF in the presence of water (500 mol %) at 50 °C, affording allyl–aryl coupling product **3a** in 87% isolated yield with complete regio- and E/Z-selectivities with a trace amount of β-H elimination product **5a** (Table 1, entry 1). Notably, water played a significant role in the coupling reaction.[15] The coupling reaction can tolerate different allylic carbonate to give allyl–aryl coupling product with the same efficiency (Table 1, entry 2). Under identical reaction conditions, however, the reactions of allylic acetate and benzoylate gave comparatively poor results (Table 1, entries 3 and 4). The reaction efficiency was also sensitive to the nature of the phosphine

(4) For Pd-catalyzed regioselective allylic alkylation, see: (a) Norsikian, S.; Chang, C.-W. *Curr. Org. Synth.* **2009**, *6*, 264. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(5) (a) ref 2e. (b) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445. (c) Chen, H.; Deng, M.-Z. *J. Organomet. Chem.* **2000**, *603*, 189. (d) Kobayashi, Y.; Mizojiri, R.; Ikeda, E. *J. Org. Chem.* **1996**, *61*, 5391. (e) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *24*, 2075.

(6) (a) Lauer, A. M.; Mahmud, F.; Wu, J. *J. Am. Chem. Soc.* **2011**, *133*, 9119. (b) Selim, K. B.; Nakanishi, H.; Matsumoto, Y.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2011**, *76*, 1398. (c) Thalén, L. K.; Sumic, A.; Bogár, K.; Norinder, J.; Persson, A. K. A.; Bäckvall J.-E. *J. Org. Chem.* **2010**, *75*, 6842. (d) Lölsberg, W.; Ye, S.; Schmalz H.-G. *Adv. Synth. Catal.* **2010**, *352*, 2023. (e) Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733. (f) Selim, K. B.; Yamada, K.; Tomioka, K. *Chem. Commun.* **2008**, 5140.

(7) (a) Polet, D.; Rathgeb, X.; Falciola, C. A.; Langlois, J.-B.; Hajjaji, S. E.; Alexakis, A. *Chem.—Eur. J.* **2009**, *15*, 1205. (b) Alexakis, A.; Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett.* **2007**, *9*, 3393. (c) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554. (d) Evans, P. A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158. (e) Kobayashi, Y.; Tokoro, Y.; Watatani, K. *Eur. J. Org. Chem.* **2000**, 3825.

(8) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370.

(9) For Rh-catalyzed allylic arylation with aryboronic acids, see: (a) Menard, F.; Perez, D.; Roman, D. S.; Chapman, T. M.; Lautens, M. *J. Org. Chem.* **2010**, *75*, 4056. (b) Yu, B.; Menard, F.; Isono, N.; Lautens, M. *Synthesis* **2009**, 853. (c) Miura, T.; Takahashi, Y.; Murakami, M. M. *Chem. Commun.* **2007**, 595. (d) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569. (e) Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2005**, *7*, 4285. (f) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.

(10) For Cu-catalyzed γ-selective allylic arylation with arylboronic acids, see: (a) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656. (b) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438. (c) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216.

(11) (a) Makida, Y.; Ohmiya, H.; Sawamura, M. *Chem.—Asian J.* **2011**, *6*, 410. (b) Li, D.; Tanaka, T.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3344. (c) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879. (d) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276.

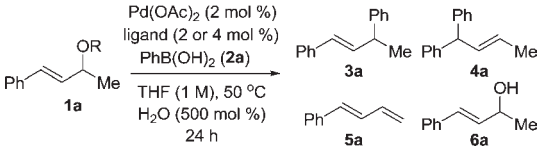
(12) For Suzuki–Miyaura coupling of propargylic carbonates, see: Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149.

(13) Other Pd(0) or Pd(II) precursors, for example, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $PdCl_2$, and $Pd(CF_3CO_2)_2$, were attempted in the coupling reaction, but they were less effective under otherwise identical conditions.

(14) The reaction between $Pd(OAc)_2$ and arylboronic acid gave reactive Pd(0) species, which works as a catalyst in the allyl–aryl coupling as shown in Scheme 1; see: Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.

(15) The reaction was remarkably inhibited in the absence of water. Water likely accelerates the transmetalation step as outlined in Scheme 1 to lead to allyl–aryl coupling product effectively. See ref 1e.

Table 1. Pd-Catalyzed Suzuki–Miyaura Coupling of **1a** with **2a** under Various Conditions[a]



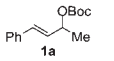
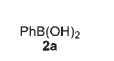
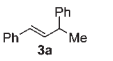
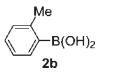
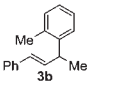
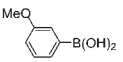
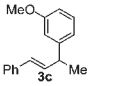
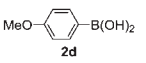
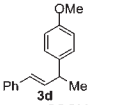
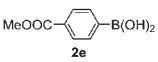
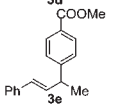
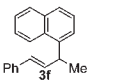
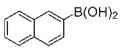
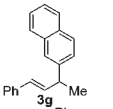
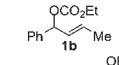
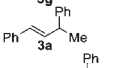
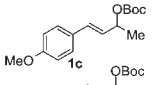
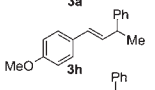
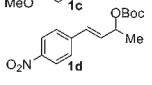
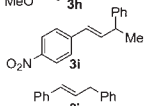
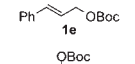
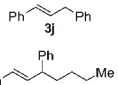
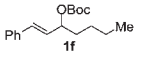
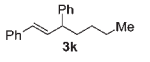
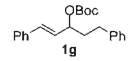
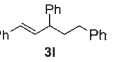
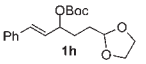
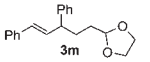
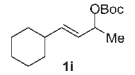
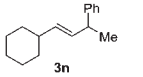
entry	R	ligand	conversion[b] (%) (**3a**:**4a**:**5a**:**6a**)	yield of **3a**[c] (%)
1	Boc	PPh_3	>99 (97:0:3:0)	87
2	CO_2Et	PPh_3	>99 (97:0:0:3)	86
3	Ac	PPh_3	24 (25:0:0:75)	[d]
4	Bz	PPh_3	14 (12:0:0:88)	[d]
5	Boc	$P(C_6F_5)_3$	68 (97:0:0:3)	59
6	Boc	PCy_3	>99 (26:0:74:0)	20
7	Boc	*rac*-BINAP	>99 (90:0:0:10)	81
8	Boc	DPPF	>99 (63:0:12:25)	54
9	Boc	Xantphos	>99 (45:0:12:43)	40

[a] Conditions: $Pd(OAc)_2$ (2 mol %), ligand (4 mol % for monophosphines; 2 mol % for bisphosphines), **1a** (0.50 mmol), **2a** (0.75 mmol), water (500 mol %), THF (0.5 mL), 50 °C, 24 h. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Yields are of isolated material. [d] Not determined. Cy: cyclohexyl.

ligand. When replacement of PPh_3 with electronic deficient phosphine ligand, $P(C_6F_5)_3$, the reaction still performed well to afford coupling product **3a** as a single product, but the reaction did not complete within 24 h (68% conversion, Table 1, entry 5). However, the reaction with σ-donating tricyclohexylphosphine gave elimination product **5a** as a major product (**3a**:**5a** = 26:74, Table 1, entry 6). Bisphosphine ligand, *rac*-BINAP, promoted the reaction with good selectivity in 81% yield (Table 1, entry 7), but the reactions with DPPF and xantphos resulted in a loss of selectivity (Table 1, entries 8 and 9).

To evaluate the scope of this process, the reaction conditions were applied to various combinations of allylic carbonates **1** and arylboronic acids **2**. As illustrated in Table 2, a wide range of unsymmetric 1,3-disubstituted secondary allylic carbonates **1** and arylboronic acids **2** were tolerated in this coupling reaction to give allyl–aryl coupling products **3** in a high level of isolated yields with good to excellent selectivities. The coupling reactions of **1a** with various substituted arylboronic acids **2** with different electronic or steric natures proceeded to the corresponding allyl–aryl products **3** in a high level of yields with excellent selectivities (Table 2, entries 1–7). When 1-phenyl-2-butenyl carbonate **1b** as a regioisomer of **1a** was used, the coupling reaction occurred to furnish single regioisomeric product **3a** in 82% yield (Table 2, entry 8). This result supports the possible mechanism outlined in Scheme 1, in which the reductive elimination takes place at the less hindered site of the π-allylpalladium complex, yielding the coupling product regioselectively. The allylic carbonates **1c**–**1i** were employed successfully

Table 2. Scope of Pd-Catalyzed Suzuki–Miyaura Coupling of Allyl Carbonates **1** with Arylboronic Acids **2**[a]

entry	allylic carbonate	boronic acid	product	yield (%)[b] (**3**:**5+6**)[c]
1	 **1a**	 **2a**	 **3a**	87 (>20:1)
2	**1a**	 **2b**	 **3b**	89 (>20:1)
3	**1a**	 **2c**	 **3c**	89 (>20:1)
4	**1a**	 **2d**	 **3d**	91 (>20:1)
5	**1a**	 **2e**	 **3e**	84 (16:1)
6	**1a**	 **2g**	 **3f**	86 (>20:1)
7	**1a**	 **2h**	 **3g**	85 (14:1)
8	 **1b**	**2a**	 **3a**	82 (9:1)
9	 **1c**	**2a**	 **3h**	81 (6:1)
10	 **1d**	**2a**	 **3i**	82 (9:1)
11	 **1e**	**2a**	 **3j**	86 (>20:1)
12	 **1f**	**2a**	 **3k**	89 (>20:1)
13	 **1g**	**2a**	 **3l**	94 (>20:1)
14	 **1h**	**2a**	 **3m**	95 (>20:1)
15	 **1i**	**2a**	 **3n**	76 (5:1)

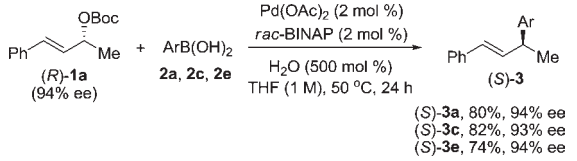
[a] Conditions: $Pd(OAc)_2$ (2 mol %), PPh_3 (4 mol %), **1** (0.50 mmol), **2** (0.75 mmol), water (500 mol %), THF (0.5 mL), 50 °C, 24 h. [b] Yields are of isolated material. [c] Determined by ^1H NMR of the crude reaction mixture. All of the reactions gave coupling products with complete regio- and *E*/*Z*-selectivities.

in the coupling reaction to afford corresponding allyl–aryl coupling products in a high level of isolated yields with complete rigio- and *E*/*Z*-selectivities and good to excellent chemoselectivies (Table 2, entries 9–15).

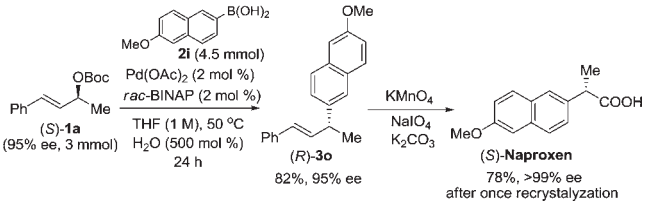
The ability to obtain excellent chemo- and regioselectivity prompted the examination of the coupling reaction of enantiomerically enriched allylic carbonate (*R*)-**1a**[16] with aryl boronic acids to determine the stereochemical

(16) Enantioenriched allylic alcohol precursor was synthesized using Sharpless kinetic resolution; see: Carlier, P. R.; Mungall, W. S.; Sohröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978.

Scheme 2. Stereospecific Allyl–Aryl Coupling



Scheme 3. Synthesis of (*S*)-Naproxen



course of this coupling reaction. The reaction of (*R*)-**1a** (94% ee) with arylboronic acids, **2a**, **2c**, and **2e** with the palladium complex in-situ-generated from $Pd(OAc)_2$ and racemic BINAP[17] furnished allyl–aryl coupling products (*S*)-**3a** (94% ee), (*S*)-**3c** (93% ee), and (*S*)-**3e** (94% ee) in high yields with inversion of absolute configurations[18] (Scheme 2). These results demonstrate that the reaction proceeds with inversion of stereochemistry in the step of oxidative addition to form π-allylpalladium complex stereospecifically, after which subsequently takes place transmetalation and reductive elimination as illustrated in Scheme 1 to afford inversed allyl–aryl coupling products. This Suzuki–Miyaura coupling method was successfully applied to the synthesis of (*S*)- naproxen[19] as an antiinflammatory drug. The coupling reaction of (*S*)-**1a**[16] (95% ee, 3 mmol scale) with arylboronic acid **1i** gave allyl–aryl coupling product (*R*)-**3o**[18] in 82% yield with 95% ee (Scheme 3). Oxidation[20] of (*R*)-**3o** furnished (*S*)-naproxen in 78% yield with >99% ee after one recrystallization.

In conclusion, we have described an effective method for Pd-catalyzed Suzuki–Miyaura coupling reaction of unsymmetric 1,3-disubstituted secondary allylic carbonates with arylboronic acids under mild conditions. The reaction has been developed in a wet solvent under a base-free system to afford allyl–aryl coupling products in a high level of isolated yields with complete regio- and *E*/*Z*-selectivities and with good to excellent chemoselectivities. In the stereochemical course of the coupling reaction, it has been demonstrated that the reaction of optically active allylic carbonates gave allyl–aryl coupling products with excellent enantioselectivities with inversion of the stereochemistry. This coupling method was successfully applied to the synthesis of (*S*)-naproxen. Further studies will focus on the development of an asymmetric version of this important coupling reaction.

Acknowledgment. This work was supported by Shanghai Pujiang Program and Shanghai Jiao Tong University. We thank the Instrumental Analysis Center of Shanghai Jiao Tong University for HRMS analysis.

Supporting Information Available. Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) When using PPh_3 as a ligand for the reaction of (*R*)-**1a** with **2a**, the reaction partially racemized to afford product (*S*)-**3a** with 50% ee.

(18) The absolute configurations were determined by comparing the sign of the optical rotation with that reported in ref 6c.

(19) For a review, see: Harrington, P. J.; Lodewijk, E. *Org. Process Res. Dev.* **1997**, *1*, 72.

(20) (a) Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 3066. (b) Hirama, T.; Inoue, M. *Synthesis* **1986**, 689.