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Stereoselective Preparation of β-Aryl-β-Boronyl Enoates and Their Copper-Catalyzed Enantioselective Conjugate Reduction

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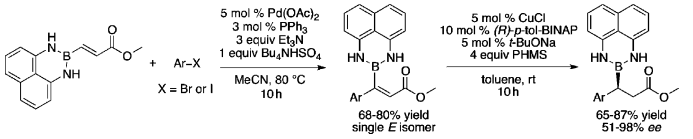
ABSTRACT



A new methodology has been developed for the stereoselective preparation of β-aryl-β-boronyl α,β-unsaturated esters via Heck coupling, and their subsequent copper(I)-catalyzed enantioselective conjugate reduction. Various chiral secondary boronate derivatives can be accessed in excellent yields and good to high levels of enantioselectivity through the efficient copper-catalyzed process using polymethylhydrosiloxane (PMHS) as the hydride source.

Optically enriched chiral organoboronate derivatives are important synthetic intermediates,[1,2] which may be employed in cross-coupling chemistry or as precursors of alcohols and amines following a C−B bond oxidation. Borylative conjugate addition[3] provides an attractive methodology to access chiral boronates, as recently demonstrated by the groups of Yun,[4a] Fernandéz,[4b] Hoveyda,[4c] Shibasaki,[4d] Nishiyama,[4e] and McQuade[4f] (**a**, Figure 1). Our group has developed a complementary conceptual approach where the boronate group is preinstalled on a universal α,β-unsaturated ester substrate, which is then subjected to a catalytic asymmetric conjugate addition with unstabilized carbanions[5a] or to an asymmetric conjugate borylation[5b] that provides optically enriched boronates (**b**, Figure 1). As part of our ongoing search for new ways to access chiral secondary boronates, we reasoned that the corresponding copper-catalyzed enantioselective conjugate reduction of β-alkyl-β-boronyl α,β-unsaturated esters would provide a useful alternative. Various chiral secondary boronate derivatives were accessed in excellent yields and good to high levels of enantioselectivities through this efficient copper catalyzed process using polymethylhydrosiloxane (PMHS) as a hydride source (**c**, Figure 1).[6a] However, with this

(1) Hall, D. G. *Boronic Acids*, 2nd ed.; Wiley-VCH: Weinheim, 2011.

(2) (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555–10607. (b) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308–9309. (c) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200–9201. (d) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628–1629. (e) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem.—Eur. J.* **2006**, *13*, 3132–3142. (f) Carosi, L.; Hall, D. G. *Can. J. Chem.* **2009**, *87*, 650–661. (g) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612–9613. (h) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24–39. (i) Thomas, S. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1896–1898. (j) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740–1741. (k) Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. *Chem.—Asian J.* **2011**, *6*, 1967–1969. (l) Schuster, C. H.; Li, B.; Morken, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7906–7909. (m) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16794–16797. (n) Pulis, A. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2012**, *134*, 7570–7574. (o) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277–8285. (p) Hall, D. G.; Lee, J. C. H.; Ding, J. *Pure Appl. Chem.* **2012**, *ASAP*. DOI: 10.1351/PAC-CON-12-02-04.

(3) (a) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194–1196. (b) Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, *47*, 7917–7932.

(4) (a) Chea, H.; Sim, H.-S; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855–858. (b) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130–5134. (c) Lee, K.-S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255. (d) Chen, I.-H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098–4101. (e) Shiomi, T.; Adachi, T.; Toribatake, K.; Zhou, L.; Nishiyama, H. *Chem. Commun.* **2009**, *44*, 5987–5989. (f) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008–5011.

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method, the R group on the enoate substrate was limited to alkyl substituents because established methodologies for the preparation of the substrates did not permit the use of aryl groups (**i**, **ii** in Scheme 1). Herein, we have developed a new method for the preparation of β-aryl-β-boronyl α,β-unsaturated esters via Heck coupling (**iii**, Figure 1), and their subsequent copper-catalyzed enantioselective conjugate reduction with polymethylhydrosiloxane (PMHS) as a hydride source.

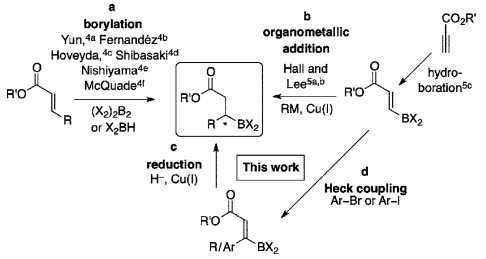
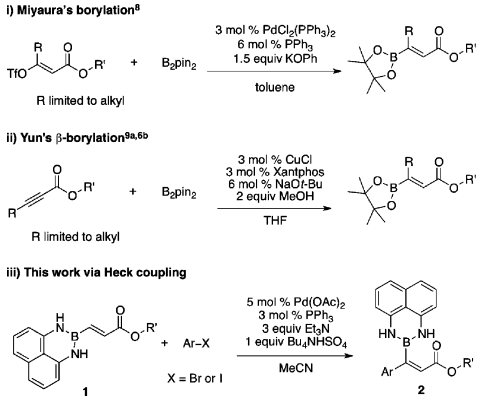


Figure 1. Possible conjugate addition approaches to chiral secondary boronates.

β-Boronyl α,β-unsaturated esters are important synthetic intermediates.[1,7] To date, Miyaura's borylation of alkenyl triflates[8] and Yun's β-borylation of ynoates[9a,6b] are the two main ways of preparing these compounds (Scheme 1, **i** and **ii**). However, both methods are limited to the preparation of β-alkyl-β-boronyl enoates, while the preparation of β-aryl derivatives has not yet been reported. A new method for the preparation of β-aryl-β-boronyl α,β-unsaturated esters would be valuable due to the synthetic applications associated with these boron compounds. We surmised that this class of compounds could be accessed through Heck coupling of previously reported β-boronyl enoate **1** (Scheme 1, **iii**).[5]

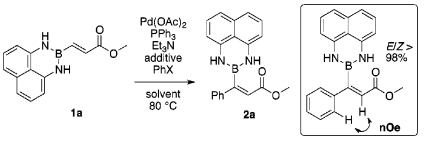
Scheme 1. Methods for Preparation of β-Boronyl α,β-Unsaturated Esters



With this idea in mind, optimal conditions were first sought for the Heck coupling reaction, and 1,8-diaminonaphthalene (dan) adduct **1a**[5a] was utilized as a test substrate (Table 1). When 5 mol % $Pd(OAc)_2$ was applied as the catalyst with 10 mol % PPh_3 as the ligand, the desired coupling product **2a** was obtained in a decent yield as a single *E* stereoisomer, which was verified by NOE experiments (Table 1).[10] Further optimization revealed that the Bu_4NHSO_4 additive was highly beneficial,[11] allowing better conversions and yields of the desired products to be afforded (entry 4). When bromobenzene instead of iodobenzene was employed as the aryl halide substrate, an improved yield was observed (entry 7). In terms of the reaction solvent, DMF and acetonitrile were found to be optimal, while other solvents such as toluene afforded lower yields (entries 9−11). Overall, the reaction conditions shown in entry 11 were found to be optimal for the syntheses of various β-aryl-β-boronyl enoates.

The scope of aryl halides toward the preparation of β-aryl-β-boronyl α,β-unsaturated esters was examined under the optimal reaction conditions. As shown in Table 2, while bromobenzene and 4-bromotoluene can be used as coupling partners to afford the desired coupling product **2a** and **2b** with good yields, coupling of 2-bromotoluene failed to occur (entries 1−3, Table 2). Presumably, steric hindrance from the ortho-substituent inhibits the desired coupling. In terms of electronic effects, both electron-rich and -deficient aryl halides afforded the desired β-aryl-β-boronyl α,β-unsaturated esters as single stereoisomers with good yields (entries 4−6). Oligoaryl halides such as 2-bromonaphthalene were also tolerated, providing the desired enoate **2g** with good efficiency (entry 7).

Table 1. Optimization of Reaction Conditions for the Preparation of β-Aryl-β-boronyl α,β-Unsaturated Esters via Heck Coupling[a]

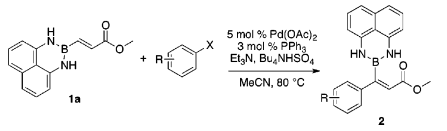


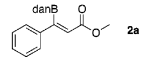
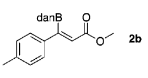
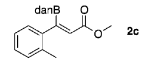
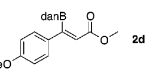
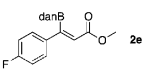
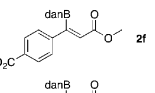
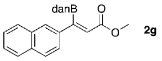
entry	X	catalyst (mol %)	additive	solvent	yield (%)[b]
1	I	5% $Pd(OAc)_2$, 10% PPh_3	–	DMF	52
2	I	5% $Pd(OAc)_2$, 10% PPh_3	–	DMF	24
3	I	10% $Pd(OAc)_2$, 6% PPh_3	–	DMF	58
4	I	10% $Pd(OAc)_2$, 6% PPh_3	Bu_4NHSO_4	DMF	63
5	I	10% $Pd(PPh_3)_4$	–	DMF	20
6	Br	10% $Pd(OAc)_2$, 6% PPh_3	–	DMF	55
7	Br	10% $Pd(OAc)_2$, 6% PPh_3	Bu_4NHSO_4	DMF	75
8	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	DMF	76
9[c]	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	DMF	75
10	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	toluene	61
11	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	MeCN	74

[a] Reaction conditions: **1a** (1.0 mmol), PhX (2.0 mmol), Et_3N (3.0 mmol), additive (1.0 mmol), solvent (5 mL), 80 °C for 10 h. [b] Isolated yield, E/Z > 98% by ^1H NMR. [c] DMF 1.0 mL.

The Buchwald[12] and Lipshutz[13] groups have independently developed efficient copper-catalyzed enantioselective methods for conjugate reduction of α,β-unsaturated compounds with polymethylhydrosiloxane (PMHS) as a mild hydride source. Recently, for the first time, our group applied these methodologies to the reduction of β-alkyl-β-boronyl α,β-unsaturated esters to access various corresponding chiral secondary boronates in excellent yields and good to high levels of enantioselectivity.[6a] To further expand this methodology, we decided to explore the scope of asymmetric conjugate reduction on β-aryl-β-boronyl enoate substrates. With β-aryl-β-boronyl enoates **2** now in hand (Table 2), their subsequent copper-catalyzed asymmetric reductions were then tested. With Josiphos as the chiral ligand,[14] both $(Ph_3P)CuH$[13] and $Cu(OAc)_2$[15] can be used as the copper salts to give the desired product **3a** with decent yields and enantioselectivities (entries 1, 2). When CuCl was used as the copper source, a slightly higher reactivity and enantioselectivity were obtained (entry 3). In terms of chiral ligands, (*R*)-Tol-BINAP was found to be optimal, while Josiphos and Walphos ligands provided relatively lower enantiomeric excesses (entries 3−5). The asymmetric conjugate reduction was equally efficient at rt (entry 6). As the reaction solvent, both dichloromethane and toluene proved to be effective, but no product was obtained when tetrahydrofuran was employed as the solvent (entries 6−8). Interestingly, even though β-Bdan-β-phenyl enoate **2a** can be reduced to the chiral β-Bdan carboxyester **3a** with good yield and enantiomeric excess, the corresponding β-Bpin-β-phenyl enoate showed no reactivity under the same reaction conditions (entry 9). Thus, the reaction conditions of entry 8 were found to be optimal to explore the substrate scope.

Table 2. Scope of Preparation of β-Aryl-β-boronyl α, β-Unsaturated Esters[a]



entry	Ar–X	product (**2**)		yield (%)[b]
1			**2a**	76
2			**2b**	72
3			**2c**	0
4			**2d**	76
5			**2e**	77
6			**2f**	80
7			**2g**	68

[a] Reaction conditions: **1a** (1.0 mmol) and ArX (2.0 mmol) in MeCN (0.2 M) with 5 mol % $Pd(OAc)_2$, 3 mol % PPh_3, 3 equiv of Et_3N (3.0 mmol), and 1 equiv of Bu_4NHSO_4 (1.0 mmol) at 80 °C for 10 h. [b] Isolated yield, E/Z > 98% by ^1H NMR.

As shown in Table 4, both electron-rich and -poor substrates afforded the desired products with moderate to high yields. However, substrates bearing β-aryl groups other than phenyl were reduced with lower enantiomeric excesses (entries 2−4). Carbomethoxy-substituted **2f** (entry 5) afforded the corresponding protodeboronation product. On the other hand, naphthyl substituted substrate **2g** showed excellent enantioselectivity (entry 6), possibly due to its highly conjugate planar structure, which can lead to enhanced interactions with the catalyst. To study the influence of boron protecting groups on enantioselectivity, the 1,8-diaminonaphthalene (dan) protecting group was compared with the pinacol (pin) protecting group, which was previously reported for the enantioselective reduction of alkyl-substituted substrates[6,10] (entries 7−10). Similar to the results observed for the β-Bdan-β-phenyl enoate **2a** (Table 3, compare entries 8 and 9), an improvement for the Bdan substrates was also observed for β-Bdan-β-cyclohexyl enoate **2i**[16] (Table 4, entries 7, 8). The key for the improved reactivity and enantioselectivity in the reduction of these substrates is the utilization of 1,8-diaminonaphthalene as a planar masking group over the bulky pinacol protecting group. The same levels of reactivity and enantioselectivity were obtained for β-Bdan-β-(*n*-hexyl) enoate **2k**[16] (entries 9, 10).

(5) (a) Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544–5545. (b) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894–899. (c) Gravel, M.; Touré, B. B.; Hall, D. G. *Org. Prep. Proc. Intl.* **2004**, *36*, 573–579.

(6) (a) Ding, J.; Hall, D. G. *Tetrahedron* **2012**, *68*, 3428–3434. (b) Jung, H.-Y.; Feng, X.; Kim, H.; Yun, J. *Tetrahedron* **2012**, *68*, 3444–3449.

(7) For reviews, see: (a) Suzuki, A. In *Organoboranes in Syntheses*; ACS symposium series 783; Ramachandran, P. V., Brown, H. C., Eds.; American Chemical Society: Washington, DC, 2001; Chapter 6, pp 80−93. (b) Miyaura, N. In *Organoboranes in Syntheses*, ACS symposium series 783; Ramachandran, P. V., Brown, H. C., Eds.; American Chemical Society: Washington, DC, 2001; Chapter 7, pp 94−107. (c) Tusiji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, U.K., pp 218−227.

(8) Ishiyama, T.; Takagi, J.; Kamon, A.; Miyaura, N. *J. Organomet. Chem.* **2003**, *687*, 284–290.

(9) (a) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, *43*, 733–734. (b) Mannathan, S.; Jeganmohan, M.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2192–2195.

(10) See Supporting Information for details.

(11) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254–278.

(12) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474.

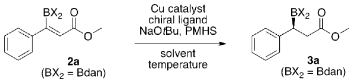
(13) (a) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353. (b) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273–1275.

(14) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927.

(15) (a) Lee, D.; Kim, D.; Yun, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2785–2787. (b) Lee, D.; Yang, Y.; Yun, J. *Org. Lett.* **2007**, *9*, 2749–2751.

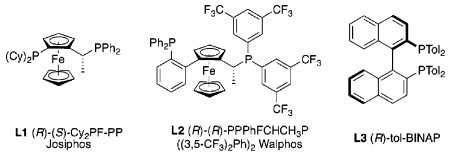
(16) See Supporting Information for the syntheses of **2i** and **2k**.

Table 3. Possible Conjugate Addition Approaches to Chiral Secondary Boronates[a]



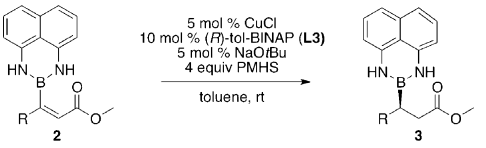
entry	X_2	Cu catalyst	ligand	temp (°C)	solvent	yield (%)[b]	ee (%)[c]
1	dan	$(Ph_3P)CuH$	**L1**	0	toluene	67	71
2	dan	$Cu(OAc)_2$	**L1**	0	toluene	71	70
3	dan	CuCl	**L1**	0	DCM	83	75
4	dan	CuCl	**L2**	0	DCM	83	72
5	dan	CuCl	**L3**	0	DCM	87	85
6	dan	CuCl	**L3**	rt	DCM	88	84
7	dan	CuCl	**L3**	rt	THF	0	–
8	dan	CuCl	**L3**	rt	toluene	88	85
9	pin	CuCl	**L3**	rt	toluene	0	–

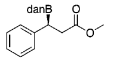
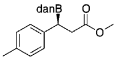
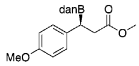
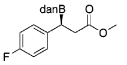
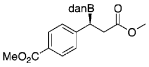
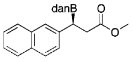
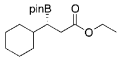
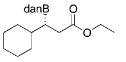
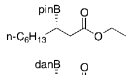
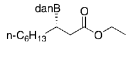
[a] Reaction conditions: 0.25 M **2a** (1.0 mmol) in solvent with 4 equiv of PMHS, 5 mol % catalyst, 10 mol % ligand, and 5 mol % NaO*t*Bu. [b] Isolated yields. [c] Measured by chiral HPLC; see Supporting Information for details.



In summary, we have successfully developed a new and efficient approach to access synthetically valuable β-aryl-β-boronyl enoates through Heck coupling, and the subsequent copper(I)-catalyzed enantioselective conjugate reduction of these enoates to produce various chiral secondary boronate derivatives. This method constitutes the first general approach for synthesizing β-aryl-β-boronyl enoates in very high E/Z selectivity. In addition, these Bdan derivatives were asymmetrically reduced with good to excellent enantiomeric excesses, affording the desired optically enriched secondary boronates with substantially improved reactivity and selectivity compared to our previously reported conditions. These improvements are attributed to the utilization of the planar 1,8-diaminonaphthalene as a superior boron masking group over the bulky pinacol group. Accordingly, with chiral boronic acid derivatives emerging as an important and versatile functional group in organic synthesis, we believe that the synthetic methods reported herein are valuable tools to access a variety of important organic intermediates.

Table 4. Scope for the Copper-Catalyzed Enantioselective Conjugate Reduction[a]



entry	2	product (3)		yield (%)[b]	ee (%)[c]
1	**2a**		**3a**	88	85
2	**2b**		**3b**	72	51[d]
3	**2d**		**3d**	77	65
4	**2e**		**3e**	85	66
5	**2f**		**3f**	0[e]	–
6	**2g**		**3g**	65	98
7	**2h**		**3h**	79	81
8	**2i**		**3i**	87	97
9	**2j**		**3j**	82	91
10	**2k**		**3k**	80	94

[a] Reaction conditions: 0.25 M of **2** (1.0 mmol) in toluene with 4 equiv of PMHS, 5 mol % CuCl, 5 mol % NaO*t*-Bu, and 10 mol % **L3** at rt. [b] Isolated yield. [c] Measured by chiral HPLC; see Supporting Information for details. Absolute configuration assigned by comparison with optical rotation of known compound. [d] The Bdan derivative **3b** could not be well resolved by chiral HPLC, so further derivatization was applied for the measurement of enantiomeric excess; see Supporting Information for details. [e] The protodeboronation product was obtained exclusively.

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Supporting Information Available. Experimental procedures, NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.