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Cross Coupling Reactions of Chiral Secondary Organoboronic Esters With Retention of Configuration

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Transition metal catalyzed cross coupling reactions are arguably among the most important and versatile reactions for the formation of C−C bonds.[1] With Pd as the most commonly employed catalyst, a wide range of main-group organometallic species, ranging from very reactive organomagnesium species to air and moisture tolerant boronic acids, can be coupled with halide- and triflate-based electrophiles. However, this reaction is generally only applicable to the preparation of bonds between sp^2-hybridized carbons, which is a significant limitation.

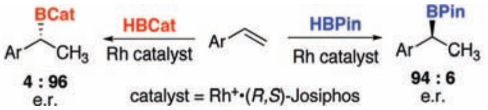
This limitation has begun to be addressed in recent years. For example Fu[2] has shown that a variety of racemic secondary alkyl halides can be employed as coupling partners in Ni-catalyzed processes that lead to single enantiomers. Gagné,[3a] Vicic,[3b] and others[3c,d] have also examined Ni-catalyzed processes employing alkyl electrophiles. With respect to the organometallic partner, primary alkyl organometallics are effective in many cases,[4] but the use of secondary organometallics is still an unsolved problem.[5,6] Since chiral organometallic species such as organoboranes and silanes can be readily prepared by enantioselective additions of organoelement species across alkenes,[7] developing a successful coupling reaction using these nucleophiles would provide ready access to a unique class of chiral compounds.

Cyclopropyl boronic esters/acids and their derivatives are by far the most well studied examples of coupling reactions of secondary boron-based organometallics.[6,8] Being immune to the β-hydride elimination reaction that plagues many other secondary boronic esters, these specialized nucleophiles participate in Suzuki−Miyaura coupling reactions in high yield, without loss of stereochemistry.[8]

In 2000, Fu reported another rare example of the coupling of secondary organoboron species, cyclopentyl boronic acid, which underwent coupling with aryl chlorides in high yields.[9a] Recently and independently, Dreher and Molander[9b] and van den Hoogenband[9c] demonstrated that cyclopentyl fluoroborate-type nucleophiles are also effective when bulky electron-rich phosphines are employed.

However, β-hydride elimination/addition remains an important side reaction for these substrates, leading to the production of linear products when starting with branched boronate esters.[9b,d] Although the β-hydride elimination can be minimized,[9b,c,10] the application of these conditions to enantiomerically enriched substrates would lead to racemization.

As part of our program directed at understanding and applying the metal catalyzed hydroboration reaction,[11] we were intrigued by the possibility of carrying out coupling reactions on the product of the hydroboration of styrene (eq 1). Pioneered by Hayashi and Ito, this reaction can be carried out with high levels of regio- and enantiocontrol.[7]

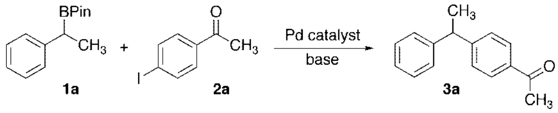


(1)

We sought to develop a method for the cross coupling of the benzylic boronic ester products of this reaction, since the resulting unsymmetrically substituted 1,1-diarylethanes are unique structures which are difficult to prepare by other methods.[12]

Initial studies employing Pd catalysts modified by phosphine ligands led to none of the desired coupling product (Table 1, entries 1, 2). Based on the detailed study of Matos and Soderquist,[5a] we postulated that the slow transmetalation step might be impeding the desired coupling reaction. Thus silver oxide was examined as the base, because of its potential ability to accelerate this step.[13] As shown in Table 1, this resulted in a dramatic increase to 65% yield (entry 3).

Table 1. Optimization of Coupling of **1** and **2** with Pd Catalyst[a]



(2)

entry	catalyst (%)	ligand (equiv)	base	yield (%)[b]
1	$Pd_2(dba)_3$ (4)	PPh_3 (8)	K_3PO_4	0
2	$Pd_2(dba)_3$ (4)	PPh_3 (8)	Cs_2CO_3	0
3	$Pd_2(dba)_3$ (8)	PPh_3 (8)	Ag_2O	65
4	$Pd(PPh_3)_4$ (4)	−−	Ag_2O	30
5	$Pd_2(dba)_3$ (4)	PPh_3 (4)	Ag_2O	25
6	$Pd_2(dba)_3$ (8)	PPh_3 (12)	Ag_2O	64
7	$Pd_2(dba)_3$ (4)	PCy_3 (4)	Ag_2O	5
8	$Pd_2(dba)_3$ (4)	Binap (4)	Ag_2O	2
9	$Pd_2(dba)_3$ (4)	P(*p*-MeOPh)$_3$ (4)	Ag_2O	31
10	$Pd_2(dba)_3$ (8)	PPh_3 (12)	Ag_2CO_3	38
11	$Pd_2(dba)_3$ (8)	PPh_3 (12)	AgOTf[c]	0
12	$Pd_2(dba)_3$ (8)	PPh_3 (12)	$AgBF_4$[c]	3

[a] Reaction conditions: 1−1.5 equiv of base employed, 1−1.5 equiv of **1** employed, THF, 70 °C, N_2 atmosphere. [b] Yields obtained by GC vs calibrated internal standard. [c] 3 equiv employed.

Substituting the $Pd_2(dba)_3/PPh_3$ combination with the commonly employed catalyst $Pd(PPh_3)_4$ resulted in a surprising drop in yield to 30% (entry 4). To confirm this was due to the change in the phosphine/Pd ratio, we repeated the reaction employing $Pd_2(dba)_3$ and PPh_3 in a 1:4 ratio and found that indeed the reaction proceeds to lower yield without excess of PPh_3 (compare entries 5 and 3). Increasing the amount of PPh_3 to 12 equiv per Pd did not increase the yield further (entry 6).[14] Substituting other ligands for PPh_3 was largely unsuccessful,[15] with the exception of P(*p*-MeOPh)$_3$, entry 9. Since this ligand gave a similar yield to that for PPh_3 and is significantly more expensive, we employed PPh_3 as our standard ligand. Interestingly, silver carbonate was effective but gave the product in approximately half the yield as silver oxide, and silver triflate and tetrafluoroborate were completely ineffective.

Employing these optimized conditions, we then proceeded to examine the reaction of enantiomerically enriched boronate ester **1**. Since it is stable and more easily handled, pinacol boronate **1** was prepared by hydroboration of styrene with HBCat followed by a pinacol quench.[16] Under standard conditions, this substrate underwent coupling in the expected yield, and analysis of the optical

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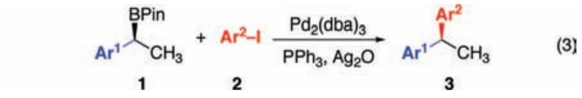
purity indicated that >90% of the configuration of the starting material was retained during the coupling reaction.

As shown in Table 2, the reaction is fairly general, and most importantly, *all substrates examined reacted with virtually complete retention of configuration*.[17] Absolute configuration of compound **3a** was assigned by correlation of optical rotation with the same compound prepared by Hiyama, confirming retention of configuration.[10] Lower yields are obtained when steric hindrance is introduced near the reaction site (compare entries 3 and 6).[18] Isolated yields are somewhat decreased relative to NMR yields because of the difficulty of removing trace amounts (ca. 5%) of homocoupled products, which elute closely with the desired product. In addition to these byproducts, trace amounts (2−3%) of Heck products from reaction between the aryl iodide and the styrene derived from **1** are observed, indicating that trace amounts of the boronic acid are converted into styrene derivatives; however this appears to be a very minor pathway.

Table 2. Scope and Limitation of Coupling Reaction of Secondary Boronic Esters[a]



(3)

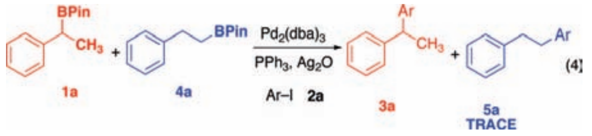
entry	Ar^1	Ar^2-I	3	yield (%)[b]	stereo-retention
1	Ph	*p*-CH_3COPhI	**3a**	65% (63)	92%
2	Ph	*p*-ClPhI	**3b**	81% (62)	91%
3	Ph	*p*-CH_3PhI	**3c**	86% (60)[c]	92%
4	Ph	3,5-diMePhI	**3d**	86% (64)[c]	93%
5	Ph	*p*-MeOPhI	**3e**	48%	93%
6	Ph	*o*-CH_3PhI	**3f**	48%	93%
7	*p*-ClPh	PhI	*ent*-**3b**	84% (64)	84%
8	*p*-CH_3Ph	PhI	*ent*-**3c**	54% (38)	94%

[a] Reaction conditions: 0.15 mmol of Ag_2O, 0.15 mmol of **1**, 0.1 mmol of **2**, 8% $Pd_2(dba)_3$, 8−12 equiv of PPh_3 per Pd, THF, 70 °C, 16−24 h. See Supporting Information for full details. [b] Determined by ^{1}H NMR vs an internal standard; average of two runs. Isolated yields by column chromatography are shown in parentheses. [c] Trace homocoupled product (ca. 5%) still remained after chromatography.

Interestingly, functionalized aryl groups can be introduced via either the boronic ester or the aryl iodide. For example, **3b** can be prepared by coupling 1-iodo-4-chlorobenzene with the boronic ester generated by hydroboration of styrene as shown in entry 2. Alternatively, hydroboration of *p*-Cl-styrene followed by coupling with PhI generates the same structure (entry 7). If the same enantiomer of Binap is employed in the hydroboration, this generates the opposite enantiomer of **3b**. This was the only case in which <90% stereochemical retention was observed (entry 7), indicating that the coupling reaction may be sensitive to the electronics of the aryl substituent on the boronic ester component.

Finally, we examined the reaction of primary alkyl boronates under the same reactions conditions. Thus a mixture of **1a** and the linear product **4a** (65:35) was subjected to the reaction conditions (eq 4). Remarkably, under these conditions, we observed complete selectivity for coupling of the secondary boronic ester yielding **3a** with only traces of **5a**. Independently subjecting **4a** to the reaction conditions confirmed that, even in a noncompetitive situation, this compound is unreactive. This unique selectivity for coupling of these difficult and important substrates provides a valuable counterpart to the expanding literature on the coupling of primary boronic esters and their derivatives.

In conclusion, we have described the first example of the cross-coupling of chiral secondary boronic esters that proceeds without any loss of regiochemistry and with high retention of enantioselectivity. In addition, we have shown that, under optimized conditions, coupling of the secondary boronic ester proceeds to the virtual exclusion of primary derivatives. The mechanism and applicability of this novel reaction to more complex targets are currently under study in our laboratories.



(4)

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Supporting Information Available: Detailed experimental procedures for the preparation and characterization of **3a**−**3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (d) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.

(2) (a) Zhou, J. R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727. (b) Zhou, J. R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. (d) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.

(3) (a) Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908–1909. (b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183. (c) Phapale, V. B.; Bunuel, E.; Garcia-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795. (d) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805–3807.

(4) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321. (b) Mu, Y. Q.; Gibbs, R. A. *Tetrahedron Lett.* **1995**, *36*, 5669–5672. (c) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405–1408. (d) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396. (e) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

(5) (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470. (b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

(6) Doucet, H. *Eur. J. Org. Chem.* **2008**, *201*, 2013–2030.

(7) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426–3428. (b) Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *125*, 9200–9201. (c) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887–9888.

(8) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198–7199.

(9) (a) Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028. (b) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257–9259. (c) van den Hoogenband, A.; Lange, J. H. M.; Terpstra, J. W.; Koch, M.; Visser, G. M.; Visser, M.; Korstanje, T. J.; Jastrzebski, J. T. B. H. *Tetrahedron Lett.* **2008**, *49*, 4122–4124. (d) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2000**, *67*, 5553–5566.

(10) Note that a similar coupling was observed using organosilca compounds, with coupling yields of 31−51% with retention of chirality. No comment was made on the presence or absence of styrene: Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793–7794.

(11) (a) Edwards, D. R.; Hleba, Y. B.; Lata, C. J.; Calhoun, L. A.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7799–7802. (b) Edwards, D. R.; Crudden, C. M.; Yam, K. *Adv. Synth. Catal.* **2005**, *347*, 50–54.

(12) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331–9334.

(13) (a) Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758. (b) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299–301.

(14) $OPPh_3$ was observed as a byproduct which may explain the requirement for excess PPh_3. When added to the reaction, $OPPh_3$ did not accelerate the reaction. The oxidation of the phosphine may explain the ineffectiveness of more electron-rich phosphines. No reaction was observed in the absence of Pd.

(15) See Supporting Information.

(16) Chen, A. C.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704–9710.

(17) With the exception of entry 7. The reason for this is currently under investigation.

(18) Aryl bromides do undergo reaction, but with reduced yields.

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