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Stereospecific Suzuki−Miyaura Coupling of Chiral α-(Acylamino)benzylboronic Esters with Inversion of Configuration

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Abstract: The first invertive *B*-alkyl Suzuki−Miyaura coupling has been achieved. The coupling of enantioenriched α-(acylamino)benzylboronic esters with aryl bromides and chlorides took place efficiently in toluene at 80 °C in the presence of $Pd(dba)_2$ (5 mol %), XPhos (10 mol %), K_2CO_3 (3 equiv), and H_2O (2 equiv). The reaction proceeded with inversion of configuration to give diarylmethanamine derivatives in high yields with high conservation of enantiomeric excesses.

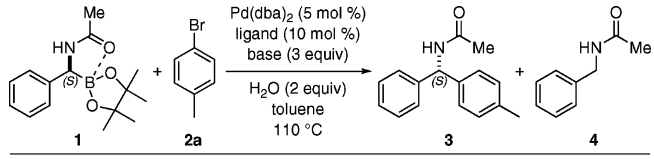
The Suzuki−Miyaura coupling utilizing alkylboron compounds has become a powerful tool in organic synthesis.[1] Cross-coupling of deuterated, configurationally defined primary alkyl-9-BBN derivatives with alkenyl and aryl iodides proceeds with complete retention of configuration.[2] Retention of configuration was also established in the coupling of diastereomerically pure cyclopropylboron compounds with organic halides and triflates.[3] Quite recently, Crudden and co-workers demonstrated the first stereospecific cross-coupling of acyclic secondary alkylboron compounds, in which enantioenriched 1-arylethylboronic esters produced the coupling product with retention of configuration.[4] There seems to be great potential in the development of the stereospecific coupling of α-branched alkylboron compounds not only for greater utilization of cross-coupling in asymmetric synthesis but also for clarifying the mechanism of the coupling reaction.[5]

We have recently developed the Suzuki−Miyaura coupling of α-(acetylamino)benzylboronic esters with aryl and alkenyl halides.[6] Because the reaction is expected to be a useful method for synthesis of enantioenriched benzylamines, our interest was then focused on the establishment of a stereospecific coupling system using enantioenriched organoboron reagents. Herein, we describe the highly stereospecific cross-coupling of enantioenriched α-(acylamino)benzylboronic esters, which proceeds with *inversion of configuration*.

Reaction of enantioenriched α-(acetylamino)benzylboronic ester **1**[7] with 4-bromotoluene (**2a**, 1.2 equiv) was carried out in toluene at 110 °C in the presence of $Pd(dba)_2$ (5 mol %), ligand (10 mol %), base (3 equiv), and H_2O (2 equiv) (Table 1).[8,9] The yield of coupling product **3** and enantiospecificity (es)[10] of the reaction strongly depended on the ligands and bases. For example, a Pd/P(*t*-Bu)$_3$ catalyst gave **3** in good yield using KF as a base, whereas a significant amount of protodeborylation product **4** was formed with K_2CO_3 (entry 1). The es values were low under both conditions (19 and 21% es, entry 1). Among several other combinations of ligands (Q-phos,[5c] SPhos,[11] RuPhos,[12] and XPhos[13]) and bases (KF and K_2CO_3) (entries 2−5), use of XPhos and K_2CO_3 gave the best yield along with the highest es (59%) (entry 5, right).

Further improvement of the es was achieved by modification of the acyl group on the nitrogen atom of the starting boron compounds (Table 2). Reactions of **2a** with propionyl (**5**) and benzoyl (**7**) derivatives gave the coupling products **6** and **8** with higher es's than the reaction of the acetyl derivatives **1** (entries 2 and 3). We finally found that a highly stereospecific coupling could be achieved using boronic ester **9a** bearing a sterically more demanding pivaloyl group (96.5% es, entry 4). The optimized conditions using XPhos

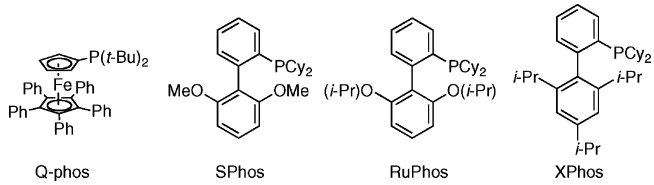
Table 1. Effects of Ligands and Bases[a]



1 2a 3 4

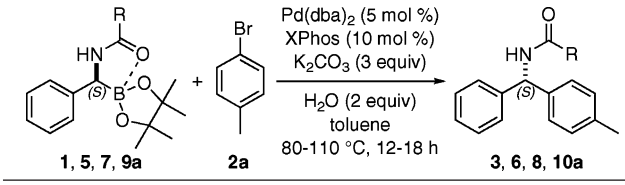
		base: KF			base: K_2CO_3		
entry	ligand	time (h)	% yield[b]	% es[c]	time (h)	% yield[b]	% es[c]
1	P(*t*-Bu)$_3$	18	78 (8)	19	3	28 (38)	21
2	Q-phos	60	85 (8)	19	3	83 (4)	47
3	SPhos	18	34 (44)	35	3	75 (17)	35
4	RuPhos	18	88 (9)	6	3	46 (45)	8
5	XPhos	48	73 (27)	28	18	95 (<1)	59

[a] **1** (0.10 mmol), **2a** (0.12 mmol), $Pd(dba)_2$ (5.0 μmol), ligand (10 μmol), base (0.30 mmol), and H_2O (0.20 mmol) were stirred in toluene (0.2 mL) at 110 °C. [b] Isolated yield of **3**. GC yield of **4** in parentheses. [c] See ref 10.



Q-phos SPhos RuPhos XPhos

Table 2. Effects of Acyl Groups[a]



1, 5, 7, 9a 2a 3, 6, 8, 10a

entry	substrate	temp (°C)	% yield[b]	% ee[c]	% es[d]	config
1	**1** (R = Me, 87% ee)	110	95 (**3**)	51	59	*inv*
2	**5** (R = Et, 95% ee)	110	85 (**6**)	65	68	*inv*
3	**7** (R = Ph, 87% ee)	110	65 (**8**)	77	89	*inv*
4	**9a** (R = *t*-Bu, 96% ee)	110	80 (**10a**)	92.7	96.5	*inv*
5[e]	**9a** (R = *t*-Bu, 96% ee)	80	84 (**10a**)	93.4	97.3	*inv*

[a] Organoboronic ester (0.10 mmol), **2a** (0.12 mmol), $Pd(dba)_2$ (5.0 μmol), XPhos (10 μmol), K_2CO_3 (0.30 mmol), and H_2O (0.20 mmol) were stirred in toluene (0.2 mL) at 80−110 °C for 12−18 h. [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase column. [d] See ref 10. [e] 0.20 mmol scale reaction.

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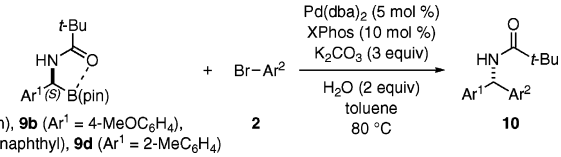
Table 3. Suzuki−Miyaura Coupling of Enantioenriched **9** with **2**[a]



9a (Ar^1 = Ph), **9b** (Ar^1 = 4-$MeOC_6H_4$), **9c** (Ar^1 = 2-naphthyl), **9d** (Ar^1 = 2-MeC_6H_4) | **2** | **10**

entry	(*S*)-**9** (% ee)	Ar^2Br	time (h)	% yield[b]	% ee[c]	% es[d]
1	**9a** (96)	**2b** (Ar^2 = 4-$MeOC_6H_4$)	12	76 [(*S*)-**10b**]	93	97
2	**9a** (96)	**2c** (Ar^2 = 4-$EtO_2CC_6H_4$)	12	87 [(*S*)-**10c**]	93	97
3	**9a** (96)	**2d** (Ar^2 = 4-$CF_3C_6H_4$)	12	85 [(*S*)-**10d**]	92	96
4	**9a** (96)	**2e** (Ar^2 = 4-AcC_6H_4)	12	71 [(*S*)-**10e**]	92	96
5	**9a** (96)	**2f** (Ar^2 = 4-$CHOC_6H_4$)	12	84 [(*S*)-**10f**]	94	98
6	**9a** (96)	**2g** (Ar^2 = 3-MeC_6H_4)	12	89 [(*S*)-**10g**]	93	97
7	**9a** (96)	**2h** (Ar^2 = 2-naphthyl)	12	76 [(*S*)-**10h**]	92	96
8	**9a** (96)	**2i** (Ar^2 = 2-MeC_6H_4)	18	79 [(*S*)-**10i**]	91	95
9	**9a** (96)	**2j** (Ar^2 = 3-thienyl)	12	80 [(*S*)-**10j**]	92	96
10[e]	**9a** (96)	**2k** (Ar^2 = 3-pyridyl)	72	83 [(*S*)-**10k**]	88	92
11	**9b** (>99)	**2l** (Ar^2 = Ph)	12	79 [(*R*)-**10b**]	98	98
12	**9c** (>99)	**2l**	12	68 [(*R*)-**10h**]	95	95
13	**9d** (90)	**2l**	18	55 [(*R*)-**10i**]	74	82

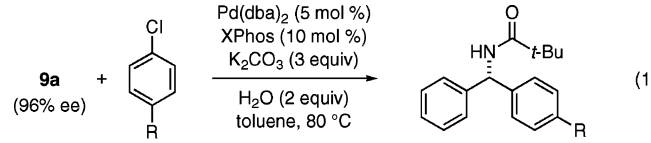
[a] **9** (0.20 mmol), **2** (0.24 mmol), $Pd(dba)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.60 mmol), and H_2O (0.40 mmol) were stirred in toluene (0.4 mL) at 80 °C. [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase column. [d] See ref 10. [e] **9a** (0.30 mmol) and **2k** (0.20 mmol) were used.

and K_2CO_3 were effective for the reaction of **9a** even at 80 °C to give **10a** in 84% yield with 97.3% es (entry 5).[14,15]

Absolute configurations of the major enantiomers of **3**, **6**, **8**, and **10a** were determined to be *S* by comparison with the specific rotation of the authentic samples, which were prepared by *N*-acylation of (*S*)-phenyl(*p*-tolyl)methanamine.[16] The stereochemical assignment clearly indicated that the C−C bond formation took place with inversion of configuration. The stereochemical course was also confirmed by our independent determination of the absolute configurations of the starting material and the product by X-ray crystallographic analysis.[16]

Various aryl bromides were subjected to Suzuki−Miyaura coupling with **9a** under the optimized conditions (entries 1−10, Table 3). The reactions of electron-rich **2b** and electron-deficient **2c**−**f** took place efficiently to give the corresponding amides **10b**−**f** in high yields (entries 1−5). The es's of the reactions were 98−96%, indicating that the electronic nature of the aryl bromides does not affect the stereospecificity. Sterically more demanding **2g**−**i** also reacted with high es's (entries 6−8). 3-Bromothiophene (**2j**) reacted efficiently with a high es (entry 9), whereas a slow reaction with a slightly lower es was observed in the reaction of 3-bromopyridine (**2k**) (entry 10). Enantioenriched **9b** and **9c** also reacted with bromobenzene (**2l**) with high es's to give **10b** and **10h** in good yields, respectively (entries 11 and 12). However, inefficient coupling was observed in the reaction of sterically demanding **9d**, which gave **10i** in moderate yield with a lower es (entry 13). It should be noted that **10i** could be obtained from the coupling of **9a** with **2i** with a better es (entry 8).

Aryl chlorides could also be used for the invertive Suzuki−Miyaura coupling under the optimized conditions (eq 1). 4-Chlorotoluene (**11a**) and 4-chlorobenzaldehyde (**11b**) reacted smoothly with **9a** at 80 °C to give amides **10a** and **10f**, respectively, in high yields with remarkably high es's. The 1:1 coupling of **9a** with 1,4-dichlorobenzene (**11c**, 1.2 equiv) was also successfully achieved. The absolute configuration of **10l** was assigned to be *S*,[17] indicating again that the coupling proceeded with inversion of configuration.

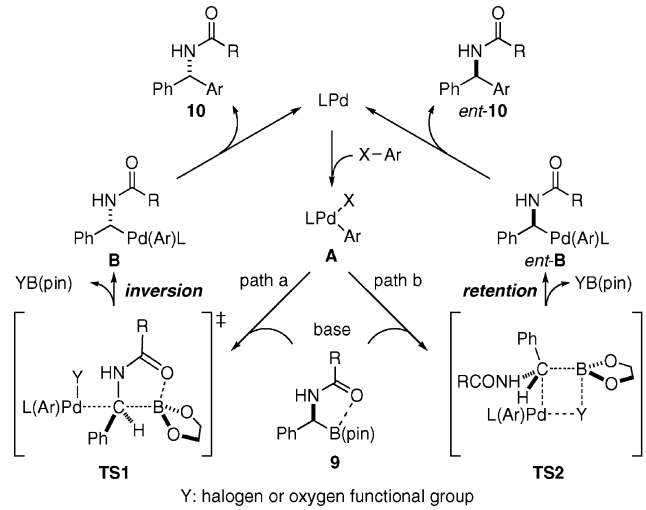


11a (R = Me)
11b (R = CHO)
11c (R = Cl)

10a (80% yield, 92% ee, 96% es)
10f (85% yield, 94% ee, 98% es)
10l (85% yield, 93% ee, 97% es)

A mechanism involving transmetalation via transition state **TS1** is proposed as the rationale for the stereochemical outcome (path a, Scheme 1).[18,19] We assume that backside attack of the palladium complex on the benzylic carbon atom of α-(acylamino)benzylboronic ester is preferred because of strong intramolecular coordination of the carbonyl group to boron,[20] which prevents an approach from the boron side by occupation of the vacant p-orbital of boron. Competitive transmetalation via conventional transition state **TS2**, which would lead to a stereoretentive transformation (path b), may lower the es as observed in some of the reactions.[21]

Scheme 1. Possible Mechanism



In conclusion, we reported the first highly stereospecific Suzuki−Miyaura coupling of acyclic α-heteroatom substituted benzylboron compounds. The stereochemical course of the reaction, inversion of configuration, is particularly notable.[22] Mechanistic details are now under investigation in our laboratory.

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Supporting Information Available: Experimental details and characterization data of the products. This material is available free of charge via Internet at http://pubs.acs.org.

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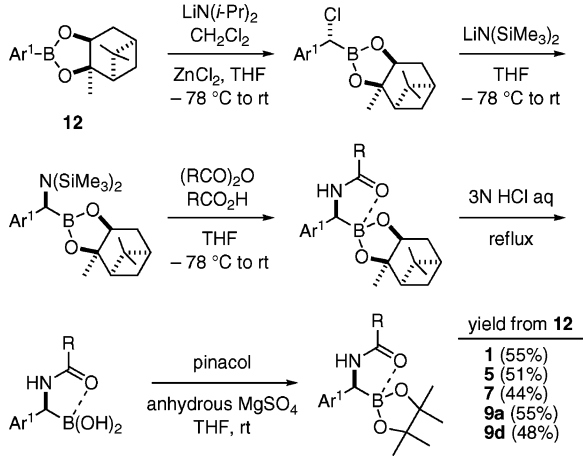
(7) Enantioenriched **1**, **5**, **7**, **9a**, and **9d** were prepared in 10 mmol scale via Matteson's asymmetric homologation starting from (−)-pinanediol derivative **12** as shown in the scheme below. (a) Matteson, D. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; p 305. (b) Caselli, E.; Danieli, C.; Morandi, S.; Bonfiglio, B.; Forni, A.; Prati, F. *Org. Lett.* **2003**, *5*, 4863. (c) Morandi, S.; Caselli, E.; Forni, A.; Bucciarelli, M.; Torre, G.; Prati, F. *Tetrahedron: Asymmetry* **2005**, *16*, 2918. Enantioenriched **9b**−**c** were obtained by optical resolution of the corresponding racemates.



(8) Initial attempts applying the conditions established previously (in 1,4-dioxane at 110 °C in the presence of Pd/P(*t*-Bu)$_3$ catalyst, H_2O, and KF) gave poor results: reaction of **1** with **2a** gave **3** in 55% yield with only 6% es.

(9) Preliminary screening indicated that protodeborylation of **1** was slower in toluene than in 1,4-dioxane.

(10) The term enantiospecificity [% es = (product ee/starting material ee) × 100] has been used to describe the conservation of optical purity over the course of stereospecific reactions: (a) Denmark, S. E.; Vogler, T. *Chem.—Eur. J.* **2009**, *15*, 11737. (b) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232. (c) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917.

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(14) Larger scale reaction of **9a** (317 mg, 1.0 mmol) with **2a** (205 mg, 1.2 mmol) was also successfully achieved under the optimized conditions to give **10a** in 80% yield (225 mg) with 97% es.

(15) Water (2 equiv) was used in all reactions according to our previous study (ref 6), in which addition of water was crucial in gaining coupling product in high yields. We eventually found that water had no critical effect on the yield or es in the present coupling system.

(16) For details, see Supporting Information.

(17) Absolute configuration of **10l** was determined by comparison of specific rotation of the authentic sample that was prepared by *N*-acylation of (*S*)-(Ph)(4-ClC_6H_4)CHNH_2. For details, see Supporting Information.

(18) The mechanism has been proposed for coupling of chiral benzylic stannanes and silanes, which proceed with full or partial inversion of configuration. (a) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (b) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. (c) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666. For related reviews, see: (d) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (e) Malinakova, H. C. *Chem.—Eur. J.* **2004**, *10*, 2636. (f) Wendt, O. F. *Curr. Org. Chem.* **2007**, *11*, 1417.

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(21) Racemization of α-(acylamino)benzylboronic esters under the coupling conditions is another possible factor in the lowering of the es. The racemization took place slowly with base even in the absence of the palladium catalyst, and the rate was decreased in the order **1** > **5** > **9a**. Es values after treatment with K_2CO_3 (1 equiv) in toluene at 110 °C for 6 h were as follows: **1** (86% es), **5** (94% es), and **9a** (96% es). On the other hand, we confirmed that no racemization of the coupling products, diarylmethanamines, took place under the coupling conditions reported.

(22) Inversion of configuration at the oxidative addition step has been reported in the Suzuki−Miyaura coupling of chiral alkyl triflates with aryl boronic acids. He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524.

JA106632J