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Inversion or Retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki–Miyaura Coupling of α-(Acetylamino)benzylboronic Esters

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Supporting Information

ABSTRACT: The stereochemical course of the stereospecific Suzuki–Miyaura coupling of enantioenriched α-(acetylamino)benzylboronic esters with aryl bromides can be switched by the choice of acidic additives in the presence of a Pd/XPhos catalyst system. Highly enantiospecific, invertive C–C bond formation takes place with the use of phenol as an additive. In contrast, high enantiospecificity for retention of configuration is attained in the presence of Zr(O*i*-Pr)$_4$·*i*-PrOH as an additive.

Increasing attention has been paid to asymmetric synthesis through transition-metal-catalyzed cross-coupling reactions at stereogenic sp^3 carbon centers.[1] Recent remarkable progress involves asymmetric cross-couplings of chiral secondary alkyl halides using chiral transition metal catalysts, which proceed through a dynamic kinetic resolution (DKR) pathway.[2] Cross-couplings using stereochemically labile chiral alkylmetal reagents such as Grignard reagents have also been studied with remarkable success.[3] The asymmetric reactions also proceed through facile racemization at the metal-bound stereogenic carbon centers, being classified as DKR processes. While DKR-based asymmetric cross-couplings have been achieved with highly effective chiral ligands on transition metal catalysts, interest has also focused on the cross-couplings of stereochemically defined, stable α-chiral alkylmetals such as alkylsilanes,[4] alkylstannanes,[5] and alkylboron compounds[6] with achiral ligands.[7,8] In particular, much effort is currently being devoted to the development of cross-coupling of sterochemically defined, chiral alkylboronates.[9] Although stereochemical retention had been accepted generally in the Suzuki–Miyaura coupling of α-chiral alkylboron compounds,[6] our recent report[10] in conjunction with reports from other groups[11,12] has established that the coupling can proceed with highly enantiospecific inversion of stereochemistry at the boron-bound stereogenic carbon centers. In the invertive cross-coupling system, intramolecular coordination of a carbonyl group of an amide[10a,11] or ester[12] functionality to boron is commonly involved and regarded as the key for the inversion of stereochemistry in the transmetalation step. It would be highly attractive if the change of the intramolecular coordination mode leads to a switch of stereochemical course from inversion to retention. Although there is no example for selective production of both enantiomers from a single enantiopure α-chiral alkylboron compounds in Suzuki–Miyaura coupling reactions, such a switch of stereospecificity would be highly interesting not only from the viewpoint of synthetic applications, but also from the mechanistic point of view. It should be noted that a switch of stereospecificity was achieved in Hiyama coupling of enantioenriched chiral benzylic silanes with aryl triflates, although the enantiospecificity (es)[13] was not very high.[4] In this paper, we disclose remarkable effects of acidic additives on the stereochemical course of the Suzuki–Miyaura coupling of enantiopure α-(acylamino)benzylboronic esters. We have found that some acidic additives can make the reaction highly "retentive", while some other acids enhance the "invertive" nature of the Suzuki–Miyaura coupling of α-(acetylamino)benzylboronic esters.

In our previous report on the invertive Suzuki–Miyaura coupling of α-(acylamino)benzylboronic esters,[10a] introduction of a bulky acyl group, for example, a pivaloyl group, was found to be essential to gain high es. Reaction of enantioenriched α-(acetylamino)benzylboronic ester **1a**, which showed moderate es under the previously reported coupling conditions,[10a] with 4-bromotoluene (**2a**, 1.2 equiv) was carried out in toluene at 80 °C in the presence of Pd(dba)$_2$ (5 mol %), XPhos[14] (10 mol %), K_2CO_3 (3.0 equiv), and various protic additives (2.0 equiv) (Table 1). Although the coupling took place smoothly even in the absence of the additives, low es was observed (entry 1). The es's were improved to 53–61% when the reaction was carried out in the presence of protic additives such as water, benzoic acid, and acetic acid (entries 2–4). We found that phenol was the most effective additive for the enantiospecific Suzuki–Miyaura coupling, in which **3a** was formed in 85% yield with 96% es (entry 5). The absolute configuration of the major enantiomer of **3a** was determined to be *S*,[15] indicating that the reaction proceeded with inversion of configuration. Use of a larger amount of phenol induced higher es's with a decrease in the chemical yields (entries 10 and 11). It is interesting to note that the reaction in the presence of *i*-PrOH and *t*-BuOH proceeded with retention of configuration, although the es's were low (entries 8 and 9).

Suzuki–Miyaura coupling of **1a** and **1b** with aryl bromides **2a–2d** was examined in the presence of phenol (2.5 equiv) (Table 2). High enantiospecificities for inversion of stereochemistry were generally achieved by the addition of phenol.

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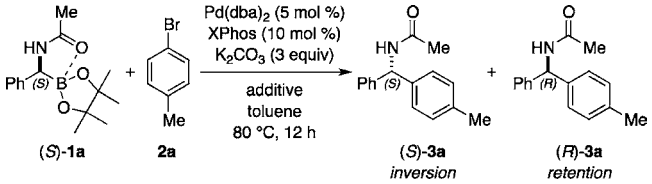
Table 1. Reaction in the Presence of Protic Additives[a]



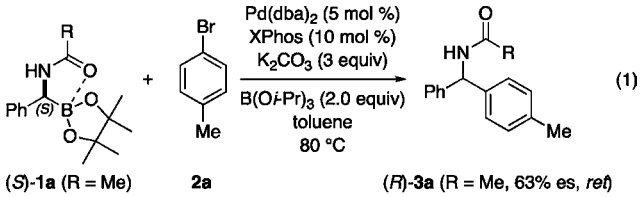
(*S*)-**1a** **2a** (*S*)-**3a** *inversion* (*R*)-**3a** *retention*

entry	additive	equiv	% yield[b]	% es[c]	configration[d] inversion / retention
1	-	-	87	29	
2	H_2O	2.0	85	53	
3	$PhCO_2H$	2.0	85	56	
4	AcOH	2.0	87	61	
5	PhOH	2.0	85	96	
6	MeOH	2.0	91	12	
7	EtOH	2.0	87	4	
8	*i*-PrOH	2.0	90	15	
9	*t*-BuOH	2.0	89	32	
10	PhOH	1.0	89	69	
11	PhOH	3.0	51	99	

[a]**1** (0.10 mmol), **2a** (0.12 mmol), $Pd(dba)_2$ (5.0 μmol), ligand (10 μmol), base (0.30 mmol), and additive (0–0.30 mmol) were stirred in toluene (0.2 mL) at 80 °C for 12 h. The ee of **3a** and absolute configuration of major enantiomer were determined by HPLC analysis with a chiral stationary phase column. [b]Isolated yield. [c]See ref 13. [d]Bar color indicates a major configuration of **3a** (red: *S*, inversion; blue: *R*, retention) and bar size is corresponding to the % es value.

The reaction of electron-rich **2b** showed higher es than that of electron-deficient **2c** (entries 2 and 3). Sterically demanding **2d** reacted with **1a** with slightly low es (entry 4). Enantioenriched **1b** also reacted with **2a** in high es with inversion of configuration (entry 5).

We then focused our attention on metal alkoxides as additives. A preliminary investigation was carried out for the reaction of **2a** with α-(acylamino)benzylboronic esters **1a** and **4**–**6** using $B(Oi\text{-}Pr)_3$ as an additive (eq 1). We found a remarkable change in the stereochemical course in the reaction of **1a** with **2a** in the presence of $B(Oi\text{-}Pr)_3$ (2.0 equiv). The reaction gave the *R*-isomer as the major product,[15] indicating that the stereochemical course was inverted to "retention" of configuration (63% es). Although the reaction of propionyl (**4**) and benzoyl (**5**) derivatives also gave the corresponding products **7** and **8** with retention of configuration, the es's



(1)

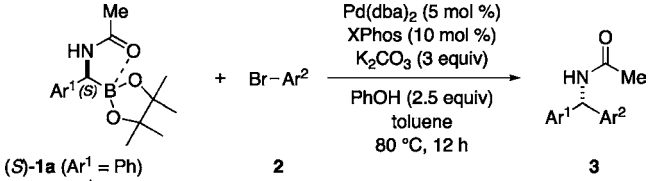
(*S*)-**1a** (R = Me) **2a** (*R*)-**3a** (R = Me, 63% es, *ret*)
(*S*)-**4** (R = Et) (*R*)-**7** (R = Et, 36% es, *ret*)
(*S*)-**5** (R = Ph) (*R*)-**8** (R = Ph, 11% es, *ret*)
(*S*)-**6** (R = *t*-Bu) (*S*)-**9** (R = *t*-Bu, 83% es, *inv*)

were much lower than for the reaction of **1a**. In contrast, the pivaloyl-substituted **6** reacted with **2a** with high es with inversion of configuration. These results indicate that metal alkoxides can switch the stereochemical course of the reaction, and that less bulky acyl group makes retentive coupling more favorable.

To achieve further improvement of the stereoretentive cross-coupling, we screened metal alkoxides (Table 3).[16] Reaction of **1a** with **2a** in the presence of metal alkoxides is generally found to be slower than that in the absence of them. Trialkoxyboranes gave **3a** in 60–85% yields with retention of configuration with es's in the range of 24–63% (entries 1–4). Because $B(Oi\text{-}Pr)_3$ showed the best es among the four (63% es, entry 3), isopropoxides of Group 4 and 13 elements were then screened (entries 5–9). The reactions using $Al(Oi\text{-}Pr)_3$, $Ga(Oi\text{-}Pr)_3$, $In(Oi\text{-}Pr)_3$, and $Ti(Oi\text{-}Pr)_4$ proceeded in good yields (55–74%) with retention of configuration (36–75% es's, entries 5–8). Use of $Zr(Oi\text{-}Pr)_4$ resulted in an unexpectedly low yield of **3a** with low es (entry 9). However, we fortuitously found that $Zr(Oi\text{-}Pr)_4{\cdot}i\text{-}PrOH$[17] induced high es with retention of configuration (entry 10). Decreasing the molar equivalents of the zirconium complex to 1–0.5 equiv improved both the yields of **3a** and the es's (entries 11 and 12). However, the es dropped when the reaction was carried out in the presence of 0.1 equiv of the zirconium complex (entry 13). The es improved to 83% in the reaction at 60 °C, although the reaction was rather slow (entry 14).

Stereospecific Suzuki–Miyaura coupling in the presence of $Zr(Oi\text{-}Pr)_4{\cdot}i\text{-}PrOH$ (0.5 equiv) was conducted with several combinations of **1** with **2** (Table 4). Electron-rich **2b** reacted with **1a** to give **3b** with retention of configuration (78% es, entry 1). The reaction of **1a** with electron-deficient **2c** took place smoothly to afford **3c** with higher es (entry 2). The es of this reaction improved to 87% when the reaction was carried

Table 2. Suzuki–Miyaura Coupling with Inversion of Configuration[a]



(*S*)-**1a** (Ar^1 = Ph) **2** **3**
(*S*)-**1b** (Ar^1 = 4-$MeOC_6H_4$) *inversion*

entry	**1**	ArBr	% yield[b]	% es[c]	config
1	(*S*)-**1a**	**2a** (Ar^2 = 4-MeC_6H_4)	67 [(*S*)-**3a**]	98	*inv*
2	(*S*)-**1a**	**2b** (Ar^2 = 4-$MeOC_6H_4$)	60 [(*S*)-**3b**]	99	*inv*
3	(*S*)-**1a**	**2c** (Ar^2 = 4-$CF_3C_6H_4$)	83 [(*S*)-**3c**]	94	*inv*
4	(*S*)-**1a**	**2d** (Ar^2 = 2-MeC_6H_4)	69 [(*S*)-**3d**]	91	*inv*
5	(*S*)-**1b**	**2a**	75 [(*R*)-**3e**]	98	*inv*

[a]**1a** (0.10 mmol), **2** (0.12 mmol), $Pd(dba)_2$ (5.0 μmol), XPhos (10 μmol), K_2CO_3 (0.30 mmol), and PhOH (0.25 mmol) were stirred in toluene (0.2 mL) at 80 °C for 12 h. The ee of **3** was determined by HPLC with a chiral stationary phase column. [b]Isolated yield. [c]See ref 13.

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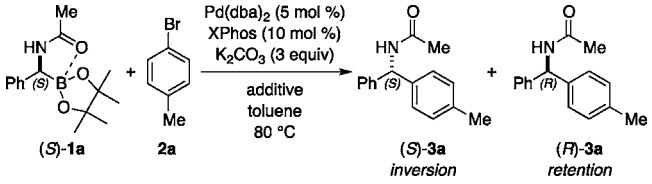
Table 3. Reaction in the Presence of Metal Alkoxides[a]



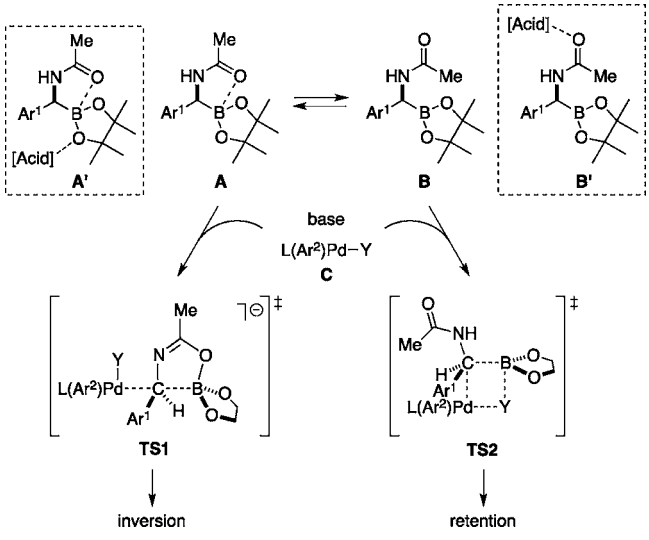
entry	additive	equiv	time (h)[b]	% yield[c]	% es[d]	Configration[e] inversion / retention
1	$B(OMe)_3$	2.0	36	60	24	
2	$B(OEt)_3$	2.0	48	85	57	
3	$B(Oi\text{-}Pr)_3$	2.0	48	74	63	
4	$B(Ot\text{-}Bu)_3$	2.0	18	80	28	
5	$Al(Oi\text{-}Pr)_3$	2.0	36	68	61	
6	$Ga(Oi\text{-}Pr)_3$	2.0	18	74	75	
7	$In(Oi\text{-}Pr)_3$	2.0	18	55	74	
8	$Ti(Oi\text{-}Pr)_4$	2.0	18	74	36	
9	$Zr(Oi\text{-}Pr)_4$	2.0	36	14	3	
10	$Zr(Oi\text{-}Pr)_4$•*i*-PrOH	2.0	18	10	76	
11	$Zr(Oi\text{-}Pr)_4$•*i*-PrOH	1.0	36	50	78	
12	$Zr(Oi\text{-}Pr)_4$•*i*-PrOH	0.5	18	86	78	
13	$Zr(Oi\text{-}Pr)_4$•*i*-PrOH	0.1	18	85	53	
14[f]	$Zr(Oi\text{-}Pr)_4$•*i*-PrOH	0.5	96	63	83	

[a] **1a** (0.10 mmol), **2a** (0.12 mmol), $Pd(dba)_2$ (5.0 μmol), XPhos (10 μmol), base (0.30 mmol), and additive (0.01−0.20 mmol) were stirred in toluene (0.2 mL) at 80 °C. The ee of **3a** and absolute configuration of major enantiomer were determined by HPLC analysis with a chiral stationary phase column. [b] A period that required for full conversion of **1a**. [c] Isolated yield of **3**. [d] See ref 13. [e] See footnote *d* in Table 1. [f] At 60 °C.

out at 60 °C (entry 3). Highly enantiospecific coupling took place in the reaction of **1a** with sterically demanding **2d**, giving **3d** in up to 93% es (entries 4 and 5). Enantioenriched **1b** was also reacted with **2a** in high yield with retention of configuration (entry 6). The es in the reaction of **1b** (85%, entry 6) was higher than that in the reaction of **1a** (78%, entry 12 in Table 3).

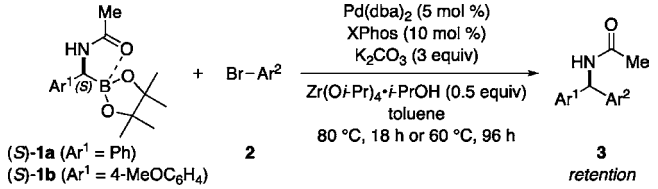
The roles of the acidic additives in the stereospecific Suzuki−Miyaura coupling of **1** can be assumed on the basis of the mechanism that we proposed for the original invertive cross-coupling (Scheme 1).[10a] In the invertive cross-coupling system,

Scheme 1. Possible Effects of the Acidic Additives on the Stereochemical Course of the Transmetallation



we proposed that the intramolecular coordination of the amide oxygen atom to the boron center (in **A**) allowed electrophilic attack of the palladium species (**C**) on the boron-bound carbon atom only from the opposite side of the boron atom, leading to the formation of the open-chain transition state **TS1** for invertive transmetalation. One of the roles of the acidic additives in the present coupling system should be cleavage of the intramolecular coordination by competitive coordination of the acid to the amide oxygen atom (**B′**). Cleavage of the intramolecular coordination results in the formation of tricoordinated boron species **B**, which is suitable for the formation of a four-membered-ring transition state **TS2**, in which the oxygen or halogen atom serves as a bridging group (Y). Transmetalation via this cyclic transition state should proceed with retention of configuration at the boron-bound carbon atom through electrophilic attack of the palladium atom from the same side as the boron atom. Another contrasting role of acidic additives would be to *enhance* the intramolecular coordination by the coordination of the acid to the oxygen atom of the pinacol ligand (**A′**). Thus, the oxygen atom of the pinacol ligand may be protonated in the presence of phenol,

Table 4. Suzuki−Miyaura Coupling with Retention of Configuration[a]



entry	1	Ar^2Br	temp (°C)	% yield[b]	% es[c]	config
1	(*S*)-**1a**	**2b** (Ar^2 = 4-$MeOC_6H_4$)	80	67 [(*R*)-**3b**]	78	*ret*
2	(*S*)-**1a**	**2c** (Ar^2 = 4-$CF_3C_6H_4$)	80	96 [(*R*)-**3c**]	83	*ret*
3	(*S*)-**1a**	**2c**	60	54 [(*R*)-**3c**]	87	*ret*
4	(*S*)-**1a**	**2d** (Ar^2 = 2-MeC_6H_4)	80	73 [(*R*)-**3d**]	86	*ret*
5	(*S*)-**1a**	**2d**	60	56 [(*R*)-**3d**]	93	*ret*
6	(*S*)-**1b**	**2a** (Ar^2 = 4-MeC_6H_4)	80	71 [(*S*)-**3e**]	85	*ret*

[a] **1** (0.10 mmol), **2** (0.12 mmol), $Pd(dba)_2$ (5.0 μmol), XPhos (10 μmol), K_2CO_3 (0.30 mmol), and additive (0.050 mmol) were stirred in toluene (0.2 mL) at 80 °C for 18 h or at 60 °C for 96 h. The ee of **3** was determined by HPLC with a chiral stationary phase column. [b] Isolated yield. [c] See ref 13.

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making the boron atom more electropositive to strengthen the intramolecular O−B coordination.[18] This may be the major reason for the enhanced enantiospecificity in the invertive coupling reaction.

In conclusion, we have achieved a switch of stereochemical course in enantiospecific cross-coupling at the boron-bound stereogenic carbon center with high efficiency. The stereospecificity largely depends on the acidic additives: $Zr(O\textit{i}\text{-}Pr)_4\cdot\textit{i}$-PrOH made the reaction retentive, while PhOH resulted in the invertive coupling with higher enantiospecificity than the original reaction system in which no acidic additive was used. Mechanistic details, as well as synthetic applications, of this reaction are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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

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(15) Absolute configuration was determined by comparison with the specific rotation of the authentic samples. For details, see Supporting Information.

(16) Use of $BF_3\cdot OEt_2$, $AlCl_3$, and $TiCl_4$ resulted in decomposition of **1a** and no formation of **3a**.

(17) Vaartstra, B. A.; Huffman, J. C.; Gradeff, P. S.; Hubert-Pfalzgraf, L. G.; Daran, J.-C.; Parraud, S.; Yunlu, K.; Caulton, K. G. *Inorg. Chem.* **1990**, *29*, 3126.

(18) Activation of the boron center of allylic boronates by coordination of Lewis and Brønsted acids to the boronate oxygen has been proposed in allylboration of carbonyl compounds. See: (a) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (c) Elford, T. G.; Arimura, Y.; Yu, S. H.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276. For theoretical study, see (d) Sakata, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12519.