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Enantiospecific Suzuki-Miyaura Coupling of Nonbenzylic α-(Acylamino)alkylboronic Acid Derivatives

Toshimichi Ohmura,*^[a] Kyoko Miwa,^[a] Tomotsugu Awano,^[a] and Michinori Suginome*^[a]

Abstract: Suzuki-Miyaura coupling of nonbenzylic α -(acylamino)alkylboron compounds with aryl halides is established. A Pd/PCy₂Ph catalyst promotes the reaction efficiently at 145 °C. The reaction of enantioenriched α -(acylamino)alkylboron compounds affords chiral 1-arylalkylamides in high enantiospecificity and inversion of configuration.

From both synthetic and mechanistic points of view, interest in the stereochemical course of the cross-coupling of chiral alkylboron compounds that contain boron-bound stereogenic centers has been increasing.[1] Over the past decade, much effort has been devoted to improving catalysts and reaction conditions to enable the enantiospecific Suzuki-Miyaura coupling of various α -branched acyclic alkylboron compounds,^{[2][3]} which had been considered much less reactive than n-alkylboron and cycloalkylboron compounds. In addition to the concern about the reaction efficiency, the stereochemical course of the reaction, in conjunction with the enantiospecificity (es), has been of great concern in the enantiospecific Suzuki-Miyaura coupling. The stereochemical course has been determined to depend on the structure of the alkylboron compounds. In addition to stereoretentive cross-coupling reactions, it has been reported that cross-coupling of α -(acylamino)benzylboronates A, [2a,2b,3g] β -borylbutanamides B, [3b] β,β -diborylpropanoate and amide **C**,^[3c,3n] 2-borylbutanes **D**,^[3] and 1,1-diborylhexane **E**^[3h,3k] proceeds with stereochemical inversion at the boron-bound stereogenic carbon centers (Scheme 1). Taking advantage of enantiospecific Suzuki-Miyaura coupling in asymmetric synthesis, it is highly desirable to broaden the scope of alkylboron compounds through improvement of the catalyst. A study of the stereochemical course of the reaction would also lead to clarification of the mechanism of the transmetalation process. To date, the mechanism remains unclear, although it is involved in other reactions of various transition metal catalysts.



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Scheme 1. Enantioenriched α -Branched Alkylboron Compounds that Induce Enantiospecific Suzuki-Miyaura Coupling with Inversion of Configuration

Enantioenriched α -(acylamino)alkylboronic acids and their derivatives have received much attention due to their potential bioactivities as analogues of α -amino acids.^[4] More than 6,500 enantioenriched α -(acylamino)alkylboronic acids have already been reported in the literature.^[5] Such structural diversity of α -(acylamino)alkylboronic acids makes their utilization as feedstock for asymmetric synthesis highly attractive. We have reported previously on the palladium-catalyzed enantiospecific Suzuki-Miyaura coupling of aryl halides with α -(acylamino)benzylboronic esters A (Scheme 1) to afford diarylmethaneamine derivatives.^[2] However, the reaction conditions are not applicable to nonbenzylic α -(acylamino)alkylboronates.

Herein, we describe an efficient new catalytic system for the reaction of nonbenzylic α -(acylamino)alkylboron compounds in Suzuki-Miyaura coupling with aryl halides (Scheme 2). The coupling proceeds with inversion of stereochemistry at the boron-bound stereogenic carbon center with high es.



Scheme 2. This Work: Enantiospecific Suzuki-Miyaura Coupling o Nonbenzylic α-(Acylamino)alkylboron Compounds with Inversion o Configuration

Racemic 1-(acetylamino)-3-phenylpropylboronic ester 1a was reacted with bromobenzene (2a) (Table 1). No coupling reaction took place when the reaction was carried out in toluene at 80 °C in the presence of Pd(dba)₂ (5 mol %), XPhos (10 mol %), and K₂CO₃ (3 equiv) under reaction conditions identical to those used for the coupling of benzylic boronates (entry 1).^[2a] We found that the reaction proceeded at elevated temperature (135-145 °C) using m-xylene as a solvent, although yields of the coupling product 3a were still low (11-15%, entries 3 and 4). Among the bases examined, K₂CO₃ and CsF gave better yields (entries 4-9). Phosphine ligands were then screened at 145 °C using CsF as a base (entries 10-14). The product yield was improved to 22% and 48% by CyJohnPhos and PCy2Ph, respectively (entries 10 and 11), indicating that the aryldicyclohexylphosphine with a less sterically hindered aryl group is more effective. PCyPh₂, PPh₃, and PCy₃ gave lower yields than did PCy₂Ph (entries 12-14). We finally established reaction conditions using a small excess of 1a (1.2 equiv) to obtain 3a in 81% isolated yield (entry 15).

Table 1. Screening of Reaction Conditions^[a]

Table 2. Suzuki-Miyaura Coupling of α-(Acetylamino)alkylboronic Esters 1^[a]

			Pd(dba) ₂ (5 mol %) ligand (10 mol %)	NHAc
Ph 🤨	BO O	Br-Pn	base (3 equiv) <i>m</i> -xylene	Ph
	rac-1a	2a (1.2 equiv)	80-145 °C, 12 h	3a
entry	ligand	base	temp/°C	% yield ^[b]
1 ^[c]	XPhos	K ₂ CO ₃	80	0
2 ^[c]	XPhos	K ₂ CO ₃	110	0
3	XPhos	K ₂ CO ₃	135	11
4	XPhos	K ₂ CO ₃	145	15
5	XPhos	KF	145	0
6	XPhos	K ₃ PO ₄	145	4
7	XPhos	КОН	145	4
8	XPhos	Cs_2CO_3	145	5
9	XPhos	CsF	145	17
10	CyJohnPhos	CsF	145	22
11	PCy₂Ph	CsF	145	48
12	PCyPh ₂	CsF	145	46
13	PPh₃	CsF	145	29
14	PCy ₃	CsF	145	40
15 ^[d]	PCy₂Ph	CsF	145	83 ^[e] (81) ^[f]

[a] Pd(dba)₂ (0.0050 mmol), a ligand (0.010 mmol), a base (0.30 mmol), **1a** (0.10 mmol), and **2a** (0.12 mmol) were reacted in *m*-xylene (0.4 mL) for 12 h at the temperature indicated. [b] GC yield based on 1a. [c] In toluene instead of *m*-xylene. [d] **1a** (0.12 mmol) and **2a** 0.10 mmol) were reacted. [e] GC yield based on **2a**. [f] Isolated yield based on **2a**. XPhos: 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl. CyJohnPhos: 2-(dicyclohexylphosphino)biphenyl.

The optimized reaction conditions were applied to the coupling of α -(acetylamino)alkylboronic esters **1** with aryl bromides **2** or aryl chlorides **4** (Table 2). The reaction of **1a** with electron-rich 4-bromoanisole (**2b**) and electron-deficient 1-bromo-4-(trifluoromethyl)benzene (**2c**) afforded **3b** and **3c** in 74% and 89% yields, respectively (entries 1 and 2). Sterically demanding 2-bromotoluene (**2d**) also afforded **3d** in 83% yield (entry 3). These results indicated that the electronic and steric differences of aryl bromides have little effect on the coupling. Aryl chlorides **4a**, **4b**, and **4c** afforded the coupling products **3a**, **3e**, and **3f** in 65-78% yields under the identical conditions (entries 4-6). 1-Aminoalkylboronic esters **1b** and **1c** reacted with **2a** to afford the coupling products **3g** and **3h** in 84% and 80% yields, respectively (entries 7 and 8).



	HN O + X $B O + X$ $O + X$	-Ar $\frac{Pd(dba)_2 (5 \text{ mol }\%)}{PCy_2Ph (10 \text{ mol }\%)}$ $\frac{PCy_2Ph (10 \text{ mol }\%)}{CsF (3 \text{ equiv})}$ $\frac{m-xylene}{145 °C, 12 h}$ $\frac{145 °C, 12 h}{CsF}$	NHAC R Ar
entry	R	X, Ar	% yield ^[b]
1	Ph(CH ₂) ₂ (1a)	Br, 4-MeOC ₆ H ₄ (2b)	74 (3b)
2	Ph(CH ₂) ₂ (1a)	Br, 4-CF ₃ C ₆ H ₄ (2c)	89 (3c)
3	Ph(CH ₂) ₂ (1a)	Br, 2-MeC ₆ H ₄ (2d)	83 (3d)
4	Ph(CH ₂) ₂ (1a)	Cl, Ph (4a)	78 (3a)
5	Ph(CH ₂) ₂ (1a)	CI, 4-MeO ₂ CC ₆ H ₄ (4b)	71 (3e)
6	Ph(CH ₂) ₂ (1a)	Cl, 1-naphthyl (4c)	65 (3f)
7	<i>n</i> -C ₈ H ₁₇ (1b)	Br, Ph (2a)	84 (3g)
8	(CH ₃) ₂ CHCH ₂ (1c)	Br, Ph (2a)	80 (3h)
4			

[a] $Pd(dba)_2$ (0.0050 mmol), PCy_2Ph (0.010 mmol), CsF (0.30 mmol), **1** (0.12 mmol), and **2** or **4** (0.10 mmol) were reacted in *m*-xylene (0.4 mL) at 145 °C for 12 h. [b] Isolated yield based on **2** or **4**.

We then focused on the stereochemical course of the reaction (Table 3). Under the conditions established above, a reaction of enantioenriched (S)-1a (90% ee) with 2a afforded 3a in 82% yield with 24% ee (27% es, entry 1). The absolute configuration of the major enantiomer was assigned as S^[6] indicating that the C-C bond formation proceeded with inversion of configuration at the boron-bound carbon atom. This stereochemical course is in accord with that observed for α aminobenzylboronate in our previous work. The es of the reaction of (S)-1a was improved to 71% when the reaction was carried out with phenol (2.5 equiv) as an additive, [2b] although the chemical yield decreased (42%, entry 2).^[7] Boron reagents (S)-5, (S)-7, and (S)-9a bearing propionyl, benzoyl, and pivaloyl groups on the nitrogen atoms, respectively, reacted with 2a efficiently to afford 6, 8, and 10a in 70-76% yields with es values of 42-95% (entries 3-5).^[6] These results indicate that es is strongly dependent on the structure of the acyl group. Here, the highest es was realized with the sterically demanding pivaloyl group (95% es, entry 5).

Table 3. Effect of Acyl Groups on Stereochemical Course of the Coupling^[a]

		Pd(dba) ₂ (5 mol %) PCy ₂ Ph (10 mol %) CsF (3 equiv) <i>m</i> -xylene 145 °C, 12 h		O HN R Ph Ph (S)-3a, 6, 8, 10a	
Ph	(S)-1a, 5, 7, 9a 2a (1.2 equiv)				
entry	boronic ester	% yield ^[b]	% ee ^[c]	% es ^[d]	config
1	1a (R = Me, 90% ee)	82 (3a)	24	27	inv
2 ^[e]	1a (R = Me, 90% ee)	42 (3a)	64	71	inv

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3	5 (R = Et, 97% ee)	75 (6)	41	42	inv
4	7 (R = Ph, 96% ee)	76 (8)	66	69	inv
5	9a (R = <i>t</i> -Bu, 91% ee)	70 (10a)	86	95	inv

[a] Pd(dba)₂ (0.0050 mmol), PCy₂Ph (0.010 mmol), CsF (0.30 mmol), an organoboron compound (0.12 mmol), and **2a** (0.10 mmol) were reacted in *m*-xylene (0.4 mL) for 12 h at 145 °C. [b] Isolated yield based on **2a**. [c] Determined by HPLC or SFC with a chiral stationary phase column. [d] % es = (product ee/starting material ee) x 100. [e] PhOH (2.5 equiv) was added.

Stereospecific coupling of enantioenriched α -(pivalovlamino)alkylboronic esters **9** was carried out (Table 4). The reaction of (S)-9a (98% ee) with electron-rich 2b and electron-deficient 2c afforded 10b and 10c with 98% and 95% es, respectively. This indicated that the electronic effect of aryl bromides does not play a key role in control of the stereochemical course of the reaction (entries 1 and 2). High es was also achieved in the coupling with sterically demanding 2d (94% es, entry 3). Chlorobenzene (4a) gave a similar es to that of 2a in the coupling (95% es, entry 4). 1-Aminononan-1vlboronic acid derivative (R)-9b (92% ee) and 1-amino-3methylbutan-1-ylboronic acid derivative (R)-9c (90% ee) reacted with 2a to afford products with 99% and 97% es, respectively (entries 5 and 6). In contrast, the es dropped to 73% in the reaction of (amino)cyclohexylmethylboronic acid derivative (R)-9d.

Table 4. Enantiospecific Suzuki-Miyaura Coupling of // (Pivaloylamino)alkylboronates $\mathbf{9}^{[a]}$

	t-Bu	+ V A=	Pd(dba) ₂ (5 m PCy ₂ Ph (10 m	iol %) iol %)	NHPiv	
	R BO	+ X-Ar	CsF (3 equiv) <i>m</i> -xylene	R´	Ar	
	(<i>S</i>)-9 (1.2 equi	v) 2 (X = Br) 4 (X = Cl)	110 0, 0121	(,	<i>S</i>)-10	
entry	R	X, Ar	time/h	% yield ^[b]	% ee ^{lo}	^{:]} % es ^{[0}
1	Ph(CH ₂) ₂ (9a , 98% ee)	Br, 4-MeOC ₆ H	4 (2b) 12	65 (10b)	96	98
2	Ph(CH ₂) ₂ (9a , 98% ee)	$Br, \operatorname{4-CF_3C_6H_4}$	(2c) 8	73 (10c)	93	95
3	Ph(CH ₂) ₂ (9a , 98% ee)	Br, 2-MeC ₆ H ₄ ((2d) 6	70 (10d)	92	94
4	Ph(CH ₂) ₂ (9a , 91% ee)	Cl, Ph (4a)	12	58 (10a)	87	96
5 ^[e]	<i>n</i> -C ₈ H ₁₇ (9b , 92% ee)	Br, Ph (2a)	12	83 (10e) ^[f]	91	99
6 ^[e]	(CH ₃) ₂ CHCH ₂ (9c , 90% ee)	Br, Ph (2a)	12	85 (10f) ^[f]	88	97
7 ^[e]	<i>cyclo</i> -C ₆ H ₁₁ (9d , 90% ee)	Br, Ph (2a)	12	35 (10g) ^[f]	65	73

[a] Pd(dba)₂ (0.0050 mmol), PCy₂Ph (0.010 mmol), CsF (0.30 mmol), (S)-9 (0.12 mmol), and **2** or **4** (0.10 mmol) were reacted in *m*-xylene (0.4 mL) at 145 °C. [b] Isolated yield based on **2** or **4**. [c] Determined by SFC with a chiral stationary phase column. [d] % es = (product ee/starting material ee) x

100. [e] (R)-9 was used. [f] (R)-10 was formed.

As demonstrated in Table 3, the acyl groups on the nitrogen atom play an important role in chirality transfer through the cross-coupling reaction. We then turned our attention to controlling the stereospecificity through the structure of the boryl group. A trifluoroborate salt (R)-11 (95% ee), prepared from (R)-1a with KHF₂ in MeOH, was subjected to coupling with 2a (Table 5). Although the coupling did not proceed at all under the conditions identical to those used for the coupling of 1a (entry 1), the desired reaction took place when using water as an additive; i.e., the coupling product 3a was obtained in moderate yield (entry 2). It is noteworthy that a significant improvement in es (85%) was achieved compared with the corresponding acetylprotected boronic ester 1a (27% es, entry 1, Table 3). Further improvements in the chemical yield and es were achieved by using K₂CO₃ as a base; i.e., 3a was obtained in 78% yield with 90% es (entry 4). Stereochemical inversion was confirmed. Electronically and sterically different aryl bromides 2b-d were then subjected to coupling with (R)-11 under the modified conditions (entries 5-7). As observed in the coupling of enantioenriched 9a (entries 1-3, Table 4), no significant electronic and steric effects of aryl bromides were observed in the es of the coupling, and 3b-d were obtained in 67-90% yields with 83-89% es.

Table	5.	Enantiospecific	Suzuki-Miyaura	Coupling	of	α
Acetyla	mino)	alkyltrifluoroborate 1	1 ^[a]			

	Ph HN Me BF ₃ K (<i>R</i>)-11 95% ee (1.2 equiv)	Br–Ar 2	Pd(dba) ₂ (5 m PCy ₂ Ph (10 m base (3 equiv) H ₂ O (0 or 39 e m-xylene 145 °C, 12 h	ol %) ol %) Ph equiv) (R	NHAd Ar	:
entry	Ar	base	additive	% yield ^[b]	% ee ^l	ɛ]% es[
1	Ph (2a)	CsF	-	0 (3a)	-	-
2	Ph (2a)	CsF	H₂O	44 (3a)	80	85
3	Ph (2a)	K ₂ CO ₃	-	30 (3a)	78	82
4	Ph (2a)	K ₂ CO ₃	H ₂ O	78 (3a)	85	90
5	4-MeOC ₆ H ₄ (2b)	K ₂ CO ₃	H ₂ O	67 (3b)	84	89
6	$4\text{-}CF_{3}C_{6}H_{4}$ (2c)	K ₂ CO ₃	H ₂ O	89 (3c)	83	88
7	2-MeC ₆ H ₄ (2d)	K ₂ CO ₃	H₂O	72 (3d)	79	83

[a] Pd(dba)₂ (0.0050 mmol), PCy₂Ph (0.010 mmol), a base (0.30 mmol), H₂O (0 or 70 μ L), (*R*)-**11** (0.12 mmol), and **2** (0.10 mmol) were reacted in *m*-xylene (0.5 mL) at 145 °C. [b] Isolated yield based on **2**. [c] Determined by SFC with a chiral stationary phase column. [d] % es = (product ee/starting material ee) x 100.

The observed configuration inversion is assumed to be the consequence of stereoinvertive transmetallation (Scheme 3A), as we proposed previously for the coupling of α -(acylamino)benzylboronates.^[2] Transmetallation to form alkylpalladium intermediates takes place through an open transition state **TS1** because intramolecular coordination of the

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carbonyl group to the boron atom blocks the approach of the palladium to the boron-bound carbon atom, which should be involved in stereoretentive transmetallation (**TS2**). The *N*-Pivaloyl derivative resulted in higher es than the *N*-acetyl, *N*-propionyl, and *N*-benzoyl analogues (Table 3), because the steric bulkiness of the pivaloyl group makes the coordinated conformation I more favorable than the open conformation II. In the reaction of trifluoroborate **11**, carbonyl-coordinated **I'** is formed through partial hydrolysis of the borate, which promotes the coupling with inversion of configuration (Scheme 3B). Even the sterically less bulky acetyl derivative gave high es, because the coordination of the carbonyl group to the more acidic boron atom in **I'** is stronger than that in **I** (*Z* = OR).



Scheme 3. Mechanistic Considerations

In conclusion, we have established suitable reaction conditions for the Suzuki-Miyaura coupling of nonbenzylic α -(acylamino)alkylboronic esters. Use of Pd/PCy₂Ph catalyst at 145 °C was found to be essential for the efficient coupling. The coupling proceeded with stereochemical inversion at the boronbound carbon center with high stereospecificity. Further investigations into applicable organoboron reagents in the stereospecific Suzuki-Miyaura coupling are currently underway in our laboratory.

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Keywords: Asymmetric synthesis • Cross-coupling • Organoboron compounds • Stereospecific reaction • Synthetic methods

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- [5] A result of searching SciFinder with "R–CH(NHCOR')–B(OH)₂ having R configuration".
- [6] Absolute configuration of the major enantiomer of 3a, 6, 8, and 10a were assigned to be S by comparison with specific rotation of authentic samples.
- [7] To check the possibility of stereoretentive coupling,^[2b] the reaction of 1a with 2a was carried out in the presence of Zr(Oi-Pr)₄•*i*-PrOH (0.5 equiv) under the conditions demonstrated in Table 3. However, the additive completely suppressed the coupling reaction and no 3a was formed at all.

Entry for the Table of Contents

COMMUNICATION



Inside-out: Suzuki-Miyaura coupling of nonbenzylic α -(acylamino)alkylboron compounds with aryl halides is established. A Pd/PCy₂Ph catalyst promotes the reaction efficiently at 145 °C. The reaction of enantioenriched α -(acylamino)alkylboron compounds gives chiral 1-arylalkylamides in high enantiosepecificity with inversion of configuration.

T. Ohmura,* K. Miwa, T. Awano, M. Suginome*

Page No. – Page No.

Enantiospecific Suzuki-Miyaura Coupling of Nonbenzylic α-(Acylamino)alkylboronic Acid Derivatives

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