α-Amidobenzylation of Aryl and Alkenyl Halides via Palladium-catalyzed Suzuki–Miyaura Coupling with α-(Acylamino)benzylboronic Esters

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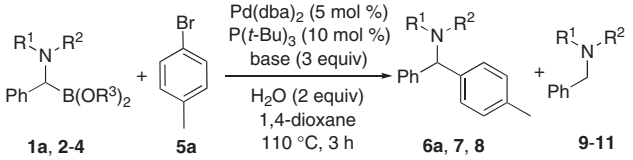
The Suzuki–Miyaura coupling of α-(acetylamino)benzylboronic esters with aryl and alkenyl halides has been achieved using a Pd/P(*t*-Bu)$_3$ catalyst with KF and H_2O in 1,4-dioxane, giving α-substituted benzylamines in high yields.

Increasing attention has been paid to α-amino organoboronic acids and their derivatives, because of their potential bioactivities as analogues of amino acids.[1] Much effort has therefore been devoted to development of their efficient synthetic methods including Matteson's asymmetric route, which involves homologation of chiral organoboronic esters.[2,3] In contrast, less attention has been paid to the use of α-amino-substituted organoboron compounds as intermediates in organic synthesis,[4,5] despite recent great advances in organoboron transformations, which include the Suzuki–Miyaura coupling, the Miyaura conjugate addition, and the Petasis reaction.[6] Exploration of the methodology utilizing α-amino organoboron compounds would provide powerful tools for synthesis of nitrogen-containing organic molecules.

The Suzuki–Miyaura coupling of α-amino-substituted organoboron compounds with organic halides is an attractive strategy that enables efficient access to functionalized amine derivatives. Molander and co-workers have developed the coupling reaction of potassium (dialkylaminomethyl)trifluoroborates for aminomethylation of organic halides.[5] While the reaction is applicable to various organic halides such as aryl and alkenyl bromides, the scope of the organoboron reagents is limited to unbranched, aminomethylboron compounds.[7] As far as we are aware, no success has been achieved in the coupling of branched α-amino alkylboranes. Herein, we describe the first application of branched, α-amino-substituted organoboron compounds to the Suzuki–Miyaura coupling, in which the protective group on the amino nitrogen has a critical effect on the reaction efficiency.

Alkylboranes with an α-NH_2 substituent are thermally unstable and tend to decompose via 1,2-boryl-rearrangement, whereas their N-acylated derivatives are stable to handle.[8] Thus, we focused on a benzylboronic acid and its pinacol esters bearing an acylamino group at the α-position of the boryl group as a coupling reagent.[9,10] Initial attempts at reaction of α-(acetylamino)benzylboronic ester **1a** with 4-bromotoluene (**5a**) encountered fast protodeborylation under the standard coupling conditions such as those using Pd/PPh_3 or Pd/DPPF catalysts (see Supporting Information).[11] After screening of Pd precursors, ligands, bases, and solvents, we found the best conditions for the coupling reaction, in which $Pd(dba)_2$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), KF (3 equiv), and H_2O (2 equiv) were employed in 1,4-dioxane at 110 °C.[7b] Under these conditions, the reaction of **1a** with **5a** (1.2 equiv) gave diarylmethanamine derivative **6a** in 56% yield, although a small amount of benzylacetamide (**9**, 6%) was also formed (Entry 1, Table 1). Reaction using other bases such as CsF, K_2CO_3, K_3PO_4, and NaOH gave poor results because of preferential formation of **9** (Entries 2–5).[12]

Table 1. The Suzuki–Miyaura coupling of α-(acylamino)benzylboronic acid and their esters with **5a**[a]



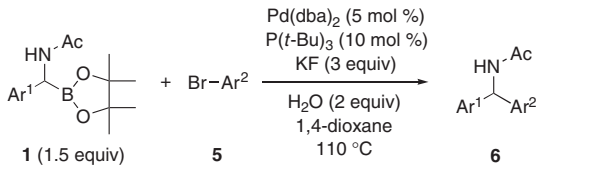
Entry	Boron compound [NR^1R^2, $B(OR^3)_2$]	Base	Yield/%[b]	
			Coupling	Protodeborylation
1	**1a** [NHAc, B(pin)]	KF	56 (**6a**)	6 (**9**)
2	**1a**	CsF	23 (**6a**)	67 (**9**)
3	**1a**	K_2CO_3	39 (**6a**)	38 (**9**)
4	**1a**	K_3PO_4	<1 (**6a**)	88 (**9**)
5	**1a**	NaOH	0 (**6a**)	88 (**9**)
6	**2** [NHBz, B(pin)]	KF	23[c] (**7**)	62[c] (**10**)
7	**3** [NMeAc, B(pin)]	KF	0 (**8**)	0 (**11**)
8	**4** [NHAc, $B(OH)_2$]	KF	9 (**6a**)	53 (**9**)

[a]$Pd(dba)_2$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), organoboron compound (0.10 mmol), **5a** (0.12 mmol), KF (3 equiv), and H_2O (2 equiv) in 1,4-dioxane (0.2 mL) were stirred at 110 °C for 3 h. [b]GC yield based on organoboron compound. [c]Isolated yield.

Other α-aminobenzylboron compounds, bearing various substituents on the nitrogen atom, were used in the reaction with **5a** (Entries 6–8, Table 1). Reaction of α-(benzoylamino)benzylboronic ester **2** gave coupling product **7** in low yield with major formation of protodeborylation product **10** (Entry 6). In contrast, no reaction took place with **3**, which has an α-acetyl(methyl)amino group (Entry 7). Formation of **9** was found to be the major reaction pathway in the reaction of boronic acid **4** (Entry 8). Attempts at using α-H_2N- and α-Me_2N-substituted benzylboronic esters failed because of the instability of these organoboron compounds.[8] These results indicate that acetylamino-substituted benzylboronic ester is the reagent of choice for the α-amidobenzylation of aryl halides.

α-Amidobenzylation of aryl bromides **5** via the Suzuki–Miyaura coupling of (α-acetylamino)benzylboronic esters **1** was carried out using an excess amount of **1** under the optimized conditions (Table 2). The yield of **6a** was improved to 70% when the reaction was carried out with 1.5 equiv of **1a** (Entry 1). Reaction of **1a** with electron-deficient aryl bromides **5d** and **5e** was complete within 3 h to give **6d** and **6e** in high yields (Entries 4 and 5). In contrast, a longer reaction time was required for the reaction with aryl bromides bearing an electron-donating methoxy group (Entry 2). Sterically demanding **5f** and **5g** reacted slowly to give the corresponding products in 78 and 70% yields, respectively (Entries 6 and 7). Reaction of 3-pyridyl and 3-thien-

Table 2. α-Amidobenzylation of aryl bromides **5** via the Suzuki–Miyaura coupling of α-(acetylamino)benzylboronic esters **1**[a]



1 (1.5 equiv) **5** **6**

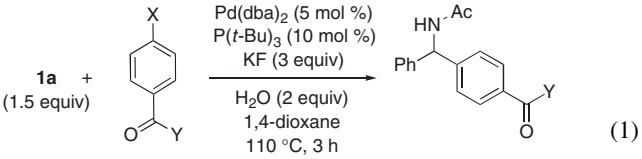
Entry	Boron compound	Aryl bromide	Time /h	Yield /%[b]
1	**1a** (Ar^1 = Ph)	**5a** (Ar^2 = 4-MeC_6H_4)	3	70 (**6a**)
2	**1a**	**5b** (Ar^2 = 4-$MeOC_6H_4$)	6	61 (**6b**)
3	**1a**	**5c** (Ar^2 = Ph)	3	85 (**6c**)
4	**1a**	**5d** (Ar^2 = 4-$EtO_2CC_6H_4$)	3	88 (**6d**)
5	**1a**	**5e** (Ar^2 = 4-$CF_3C_6H_4$)	3	96 (**6e**)
6	**1a**	**5f** (Ar^2 = 3-MeC_6H_4)	6	78 (**6f**)
7	**1a**	**5g** (Ar^2 = 2-MeC_6H_4)	18	70 (**6g**)
8	**1a**	**5h** (Ar^2 = 3-pyridyl)	3	79 (**6h**)
9	**1a**	**5i** (Ar^2 = 3-thienyl)	3	60 (**6i**)
10	**1b** (Ar^1 = 4-$MeOC_6H_4$)	**5c**	3	72 (**6b**)
11	**1c** (Ar^1 = 4-$CF_3C_6H_4$)	**5c**	3	9 (**6e**)
12[c]	**1d** (Ar^1 = 2-MeC_6H_4)	**5c**	3	58 (**6g**)

[a]$Pd(dba)_2$ (5 mol %), P(*t*-Bu)$_3$ (10 mol %), **1** (0.30 mmol), **5** (0.20 mmol), KF (3 equiv), and H_2O (2 equiv) in 1,4-dioxane (0.4 mL) were stirred at 110 °C. [b]Isolated yield based on **5**. [c]3.0 equivs of **1d** was used.

yl bromide **5h** and **5i** also gave the corresponding coupling product **6h** and **6i** in good yields (Entries 8 and 9).

Boronate **1b** bearing a 4-methoxyphenyl group showed comparable reactivity to **1a** in the reaction with **5c** (Entry 10). In sharp contrast, the reaction of 4-trifluoromethyl-substituted **1c** with **5c** gave **6e** only in 9% yield because of fast protodeborylation (Entry 11). Protodeborylation also proceeded in the reaction of 2-methylphenyl-substituted **1d** with **5c**, resulting in a moderate yield of **6g** (Entry 12).

Functional-group-tolerability of the present α-amidobenzylation was demonstrated by the reaction of carbonyl-substituted aryl halides (eq 1). Cross-coupling of **1a** with 4-acetyl- and 4-formyl-substituted bromobenzenes **5j** and **5k** proceeded with high chemoselectivity under the optimized conditions, leading to the selective formation of **6j** and **6k**. It should also be noted that the reaction was applicable to aryl chlorides **12a** and **12b**, giving the corresponding products in good yields.



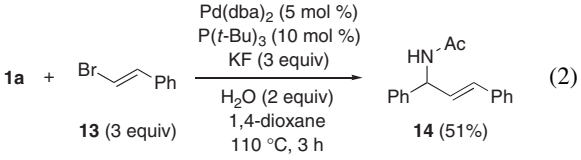
(1)

5j (X = Br, Y = Me)
5k (X = Br, Y = H)
12a (X = Cl, Y = Me)
12b (X = Cl, Y = H)

6j (Y = Me)
85% from **5j**, 80% from **12a**

6k (Y = H)
77% from **5k**, 79% from **12b**

Alkenyl bromide **13** also underwent α-amidobenzylation with **1a**, giving allylic amine **14** in 51% yield (eq 2).



(2)

13 (3 equiv) **14** (51%)

In conclusion, we have demonstrated the synthetic utility of α-(acetylamino)benzylic boronates as reagents for α-amidobenzylation of aryl and alkenyl halides via the Suzuki–Miyaura coupling. Further synthetic applications of α-(acylamino)organoboron compounds are being undertaken in this laboratory.

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11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

12 For details of optimization of the reaction conditions including screening of ligands, see Supporting Information.

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