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Palladium-catalyzed synthesis of arylacetamides from arylboronic acids

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Abstract—Aryl amides were synthesized by the palladium catalyzed cross-coupling reaction of α-bromoacetamides with arylboronic acids in good yields. Both electron-donating and electron-withdrawing substituents on the aromatic ring are found to be compatible. The addition of Cu_2O and PPh_3 was found to be essential for good reaction yields.

Among the various methodologies of palladium-catalyzed coupling of organic electrophiles with organometallic compounds to form carbon–carbon bonds, the Suzuki-type reaction has attracted much interest due to its attractive features (high yields, mild conditions, tolerance for many functional groups and solvent moisture, etc.).[1] The electrophilic sites in these cross-coupling reactions are usually sp^2-carbons attached to a good leaving group (e.g. aryl and vinyl halides or triflates). In contrast, general methods to cross-couple electrophiles having C(sp^3)–X bonds with organoboronic acids are scarce, presumably because of their slow oxidative addition to palladium catalysts.[2] Suzuki and co-workers have reported only one such example—the cross-coupling of ethyl bromoacetate with phenylboronate using (the highly toxic) Tl_2CO_3 as a base.[3] Recently, Gooßen reported that the palladium-catalyzed cross-coupling of bromoacetic acid derivatives with arylboronic acids was accomplished using a special ligand, P(α-Nap)$_3$.[4] We have been also interested in this kind of reaction and earlier found that Cu_2O could promote the Suzuki-type cross-coupling of ethyl bromoacetate with arylboronic acids without recourse to any special ligand.[5] To expand the scope of electrophiles we investigated the cross-coupling of bromoacetamides with arylboronic acids.

Amides are useful building blocks both for laboratory synthesis as well as industrial manufacturing.[6] A number of elegant routes to amides have been developed.[7] Some of which utilize carbon monoxide as the carbonyl source, and the reaction were carried out under a CO atmosphere.[8] Herein, we report an alternative route to arylacetamides via the Suzuki-type coupling of arylboronic acids with bromoacetamides.

The cross-coupling reactions were initially carried out using 3-methylphenylboronic acid and *N*,*N*-dibutyl bromoacetamide as the starting materials to optimize the conditions (Table 1). Under traditional Suzuki conditions, only 29% yield of coupling product was obtained (entry 1). We then turned our attention to the use of Cu_2O as an additive because its beneficial effect on the cross-coupling of ethyl bromoacetate with arylboronic acids was noted by us earlier.[5] However, in the present case the use of catalytic amount of Cu_2O alone still did not give satisfactory results though the yield of the cross-coupled acetamide product increased somewhat (entry 2). In view that PPh_3 is expected to react with α-bromoacetamides to give the corresponding phosphonium salts,[9] the elec-

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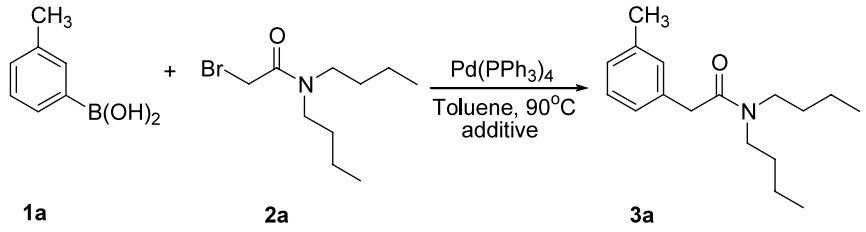
Table 1. Effects of the reaction conditions on the cross-coupling reaction[a]



1a 2a 3a

Entry	Additive	Yield[b] (%)
1	$K_3PO_4 \cdot 3H_2O$	29
2	$K_3PO_4 \cdot 3H_2O$, Cu_2O (6 mol%)	41
3	$K_3PO_4 \cdot 3H_2O$, PPh_3 (6 mol%)	73
4	$K_3PO_4 \cdot 3H_2O$, Cu_2O (6 mol%), PPh_3 (6 mol%)	79
5	K_2CO_3, Cu_2O (6 mol%), PPh_3 (6 mol%)	62
6	$K_3PO_4 \cdot 3H_2O$, Cu_2O (6 mol%), $AsPh_3$ (6 mol%)	79

[a] Reactions were carried out at 90°C for 24 h using a mixture of 3-methylphenylboronic acid (0.6 mmol), *N*,*N*-dibutyl bromoacetamide (0.5 mmol), 3 mol% $Pd(PPh_3)_4$, and base (3.3 equiv.) in 4 mL of toluene.
[b] Isolated yields.

trophilicity of which would be considerably stronger than that of α-bromoacetamides themselves, the effect of PPh_3 as an additive was also examined. To our delight, a much improved reaction was indeed observed (entry 3). The combined effect of Cu_2O and PPh_3 was noticeable, though not substantial, and after considerable experimentation, the best result (entry 4) was obtained for our model reaction with 6 mol% each of Cu_2O and PPh_3 added to a reaction mixture containing $K_3PO_4 \cdot 3H_2O$ (3.3 equiv.), 3-methylphenylboronic acid (1.2 equiv.), *N*,*N*-dibutylacetamide (1.0 equiv,) and $Pd(PPh_3)_4$ (3 mol%). Although $AsPh_3$ was as effective as PPh_3 (entry 6), the latter is preferred for obvious reasons.

The coupling reactions of various arylboronic acids with bromoacetamides were carried out under optimized conditions[10] and the results are collected in Table 2.

As can be seen in Table 2, the cross-coupling reactions of arylboronic acids with various *N*,*N*-dialkylbromoacetamides proceed readily to give the corresponding arylacetamides in good yields (entries 1–9). In the case of *N*-alkylacetamides, the yields of cross-coupling are somewhat lower than that of *N*,*N*-dialkyl bromoacetamides (entries 10–12 versus entries 1–9). When bromoacetamide was used for coupling with 3-methylboronic acid, no cross-coupling product was obtained (entry 13). This process tolerates a number of functional groups on the aromatic ring (entries 4–7). While an electron-donating substituent on the arylboronic acid decreases the cross-coupling yield (entry 5), electron-withdrawing substituents increase the yield (entries 6 and 7).

In summary, it was found for the first time that Cu_2O and PPh_3 can efficiently promote the Suzuki-type coupling reaction of arylboronic acids with bromoacetamides to afford arylacetamides in good yields. The conditions are mild that many functional groups may be tolerated. The procedure is suitable for preparing various arylacetamides and may be useful for a wide range of applications in medicinal chemistry in particular because amides are a common class of organic compounds. A detailed mechanistic study as well as an examination of the scope of the reaction are currently underway in our laboratory.

Acknowledgements

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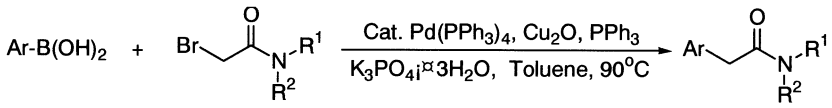
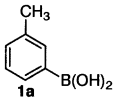
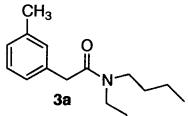
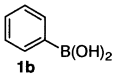
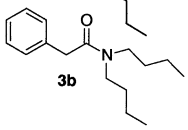
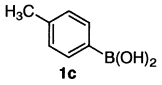
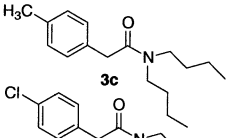
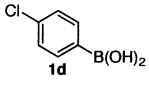
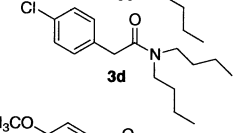
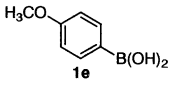
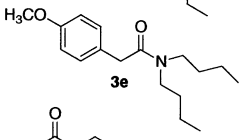
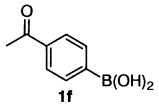
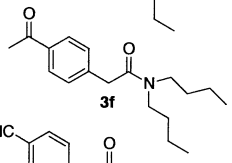
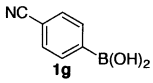
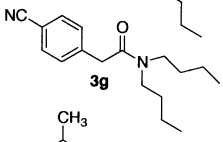
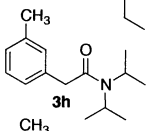
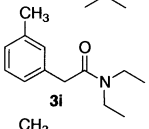
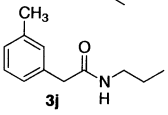
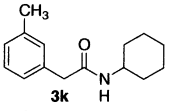
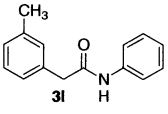
References

1. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
2. (a) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187; (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018.
3. Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405.
4. Gooßen, L. J. *Chem. Commun.* **2001**, 669.

Table 2. Palladium-catalyzed cross-coupling reactions of arylboronic acids with various bromoacetamides[a]



1 2 3

Entry	Arylboronic acid **1**	2-Bromoacetamide **2**	Product **3**	Yield[b][%]
1	 **1a**	R_1=*n*-Bu R_2=*n*-Bu **2a**	 **3a**	79
2	 **1b**	**2a**	 **3b**	69
3	 **1c**	**2a**	 **3c**	76
4	 **1d**	**2a**	 **3d**	75
5	 **1e**	**2a**	 **3e**	61
6	 **1f**	**2a**	 **3f**	84
7	 **1g**	**2a**	 **3g**	83
8	**1a**	R_1=*i*-Pr R_2=*i*-Pr **2b**	 **3h**	80
9	**1a**	R_1=Et R_2=Et **2c**	 **3i**	69
10	**1a**	R_1=*n*-Pr R_2=H **2d**	 **3j**	61
11	**1a**	R_1=Cy R_2=H **2e**	 **3k**	66
12	**1a**	R_1=Ph R_2=H **2f**	 **3l**	57
13	**1a**	R_1=R_2=H **2g**	--	0

[a]Reactions were carried out at 90 °C for 24 h using a mixture of arylboronic acids (0.6 mmol), bromoacetamides (0.5 mmol), 3.3 equiv of $K_3PO_4 \cdot 3H_2O$, 6 mol% Cu_2O, 6 mol% PPh_3, and 3 mol%$Pd(PPh_3)_4$ in 4 mL toluene under a nitrogen atmosphere. All products were characterized by ^1H NMR, IR, mass spectral and elemental analysis.

[b]Isolated yields.

5. Liu, X.-X.; Deng, M.-Z. *Chem. Commun.* **2002**, *6*, 622.
6. (a) Lewis, J. R. *Nat. Prod. Rep.* **2002**, *19*, 223; (b) Jin, Z.; Li, Z.; Huang, R. *Nat. Prod. Rep.* **2002**, *19*, 454.
7. Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p. 381.
8. (a) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327; (b) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 2931; (c) Lee, S. L.; Son, S. U.; Chung, Y. K. *Chem. Commun.* **2002**, 1310.
9. Bordwell, F. G.; Zhang, S.-Z.; Zhang, X.-M.; Liu, W.-Z. *J. Am. Chem. Soc.* **1995**, *27*, 7092.
10. **Typical experimental procedure for the synthesis of *N,N*-dibutyl-2-(3-methylphenyl)acetamide (3a)**: Arylboronic acid **1a** (82 mg, 0.55 mmol), $Pd(PPh_3)_4$ (18 mg, 0.016 mmol), Cu_2O (4 mg, 0.028 mmol), PPh_3 (8 mg, 0.030 mmol), $K_3PO_4{\cdot}3H_2O$ (439 mg, 1.65 mmol, 3.3 equiv.) were placed in a flask under Ar atmosphere. Toluene (4 mL) and bromoacetamide **2a** (125 mg, 0.5 mmol) were added and the reaction mixture was stirred at 90°C for 24 h. The reaction mixture was allowed to cool to rt, and H_2O (5 mL) was added. The mixture was then extracted with diethyl ether (10 mL×3). The combined organic layer was washed with brine (10 mL×3), dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (elution with hexanes/ethyl acetate = 5:1) to afford the corresponding arylacetamide **3a**. ^{1}H NMR (300 MHz, $CDCl_3$–TMS) δ 7.20 (d, J = 7.7 Hz, 1H), 7.03–7.07 (m, 3H), 3.65 (s, 2H), 3.32(t, J = 7.7 Hz, 2H), 3.19 (t, J = 7.7 Hz, 2H), 2.32 (s, 3H), 1.41–1.54 (m, 4H), 1.23–1.33 (m, 4H), 0.88–0.95 (m, 6H) ppm; EIMS m/z 261 (M^+, 36), 57 (100), 105 (74), 86 (74), 156 (70), 100 (44), 261 (36), 41 (26), 106 (17); IR (neat) 2960, 2932, 2874, 1643, 1608, 1458, 1425, 766 cm^{-1}; Anal. cald for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.78; H, 10.07; N, 5.17.