DOI: 10.1002/adsc.200800730

Copper-Catalyzed *N*-Arylation of Hindered Substrates Under Mild Conditions

Michael T. Wentzel,[a] J. Brian Hewgley,[a] Rajesh M. Kamble,[a] Philip D. Wall,[a] and Marisa C. Kozlowski[a,*]

[a] Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA
Fax: (+1)-215-573-7156; phone: (+1)-215-898-3048; e-mail: marisa@sas.upenn.edu

Received: November 24, 2008; Revised: March 4, 2009; Published online: April 6, 2009

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A mild, efficient method utilizing a copper-diamine catalyst at room temperature is reported for the coupling of hindered imidazoles with unsubstituted, *ortho*-substituted, and bis-*ortho*-substituted boronic acids in good to excellent yields. Aryl halides do not reaction under these conditions permitting sequential *N*-arylation reactions.

Keywords: *N*-arylation; boronic acids; copper catalysis; nitrogen heterocycles

Introduction

N-Arylation has received much attention due to the use of arylated heterocycles in agricultural and pharmaceutical chemistry. Successful C–N coupling methods[1] have employed palladium, nickel[2] and copper[3] catalysts in the coupling of amines with aryl halides; however, mild methods are scarce. These reactions typically require stoichiometric quantities of base and elevated reaction temperatures. Alternative approaches have been developed using aryllead,[4] -tins,[5] -bismuths,[6] -silanes,[7] and -boronic acids[8] as transmetallating reagents. A reactivity pattern for heterocycles in *N*-arylation reactions has begun to be seen based on nucleophilicity, complexing ability of catalyst, and acidity. Heterocycles with fewer nitrogens are more reactive: carbazole > imidazole > indole ~ pyrrole > triazole ≫ tetrazole.[9]

In general, these methods are limited to sterically unhindered *N*-arylation when nitrogen heterocycles are employed.[10] However, a few reports for hindered cases have surfaced. Buchwald and co-workers have successfully coupled 2-substituted indoles, pyrroles, imidazoles, and benzimidazoles with aryl halides using using copper-diamine catalysts at elevated temperatures (110–150 °C)[11] Related reports have appeared recently for futher *N*-aryl heterocycles, but high temperatures (110–170 °C) were required.[12] The same catalyst system was also effective in coupling *ortho*-substituted aryl halides with unsubstituted indole[11] and 2-substituted pyrroles.[13] With imidazoles and benzimidazoles, C–N biaryls with substitution at up to two *ortho*-positions could be achieved using Cu_2O, Cs_2CO_3, polyethylene glycol, and a phenanthroline ligand at 110–150 °C.[14] Related reports have appeared recently for *N*-aryl heterocycles, but high temperatures (125–170 °C) were requried and there were no cases leading to C–N bonds with more than two *ortho*-substituents.[15] In all of these reports, there were no cases leading to C–N bonds with more than two *ortho*-substituents.

While the more reactive boronic acid precursors permit *N*-arylations of heterocycles to proceed at lower temperatures, the formation of the hindered C–N biaryls remains a challenge.[16] For example, Yu and co-workers developed a method to couple *ortho*-substituted boronic acids with imidazole using catalytic CuCl in MeOH at reflux. However, this method was only effective for mono-*ortho*-substituted boronic acids and imidazole.[17] Furthermore, Alcade and co-workers reported that benzimidazole underwent poor coupling with arylboronic acids using catalytic copper conditions.[12c]

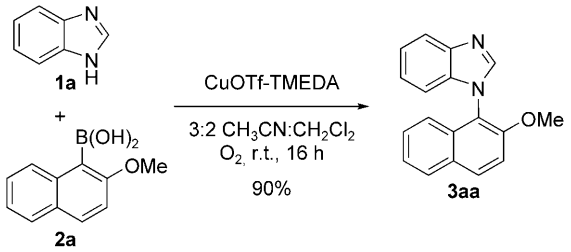
Results and Discussion

Together, these results highlight the limits of current methods, namely, the synthesis of a biaryl C–N bond with more than two *ortho*-substituents. Therefore, we were motivated to develop a method aimed at this product category. Herein, we report our efforts result-

ing in the coupling of benzimidazoles and 2-substituted imidazoles with mono- and bis-*ortho*-substituted boronic acids under mild conditions (catalytic copper at room temperature).

Boronic acids were selected as the *N*-arylation coupling partners since they are more reactive than the corresponding halides but remain stable and easy to handle. While most copper-based *N*-arylation methods with arylboronic acids require stoichiometric quantities of the metal, Lam and Buchwald have reported a catalytic arylation of amines using 10 mol% $Cu(OAc)_2$.[18] Collman was also able to render the arylation of imidazoles catalytic when CuClOH-(TMEDA) was used (TMEDA = tetramethylethylenediamine).[19]

Our studies commenced with hindered substrates **1a** and **2a**, *a combination which does not react under the conditions reported by Lam[18a] or Collman.[19a]* We discovered that 20 mol% of the CuOTf-TMEDA complex under the conditions outlined in Scheme 1 furnished the product **3aa** in 90% isolated yield.



Scheme 1. Mild copper-catalyzed *N*-arylation.

With this result in hand, a variety of copper salt complexes with TMEDA were surveyed (Table 1). Copper(I) and copper(II) triflate gave yields similar to $Cu(NO_3)_2$ 2.5 H_2O. The latter was utilized for further studies (Table 2) as it is inexpensive, readily obtained, and stable [copper(I) species oxidize and anhydrous copper(II) salts hydrate upon storage].

Under identical conditions, a 1:1 mixture of MeOH:CH_3CN gave 81% conversion (Table 1 entry 5) whereas MeOH alone provided a slightly lower 72% conversion. All other solvent combinations were less optimal.

The amount of TMEDA relative to the copper species was studied in two solvent systems. In a mixture of 3:2 CH_3CN:CH_2Cl_2, the TMEDA:Cu ratio has a large effect on the conversion. Using an excess of TMEDA with respect to the copper salt proved to be the most beneficial beneficial (Table 3, entry 5). On the other hand, the TMEDA:Cu ratio does not effect the conversion strongly when MeOH was used as the solvent (Table 3). These results point to a coordination role for the MeOH which solubilizes and activates the copper species to a large extent. In the ab-

Table 1. Survey of copper salts with TMEDA in the reaction from Scheme 1.[a]

Entry	Copper source	Cu oxidation state	Conversion [%][b]
1	$Cu(OTf)_2$	II	100
2	$Cu(NO_3)_2 \cdot 2.5\,H_2O$	II	99
3	$CuBr_2$	II	37
4	$Cu(OAc)_2$	II	2
5	$CuSO_4$	II	2
6	$CuCl_2$	II	1
7	Cu(OTf)·toluene	I	99
8	CuCl	I	76
9	CuI	I	67
10	CuBr	I	30

[a] *Conditions:* 20 mol% ligand and Cu salt, 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of 3:2 CH_3CN:CH_2Cl_2 under O_2 atmosphere at room temperature for 16 h.

[b] Determined by GC using 4-phenoxylbiphenyl as a standard.

Table 2. Survey of solvent with $Cu(NO_3)_2 \cdot 2.5\,H_2O$ and TMEDA in the reaction from Scheme 1.[a]

Entry	Solvent	Conversion [%][b]
1	1:1 CH_3CN: MeOH	81
2	MeOH	72
3	CH_3CN	61
4	3:2 CH_3CN:CH_2Cl_2	60
5	EtOAc	5
6	CH_2Cl_2	1

[a] *Conditions:* 20 mol% ligand and Cu salt, 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of solvent under O_2 atmosphere at room temperature for 1.5 h.

[b] Determined by GC using 4-phenoxylbiphenyl as a standard.

Table 3. Effect of the TMEDA ratio with 20 mol% $Cu(NO_3)_2 \cdot 2.5\,H_2O$ in MeOH on the reaction from Scheme 1.[a]

Entry	TMEDA (mol%)	Conversion [%][b]	
		3:2 CH_3CN:CH_2Cl_2	MeOH
1	0	21	72
2	5	14	80
3	10	10	99
4	20	76	88
5	50	92	94

[a] *Conditions:* 20 mol% Cu salt, 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of CH_3CN:CH_2Cl_2 or MeOH under O_2 atmosphere at room temperature for 16 h.

[b] Determined by GC using 4-phenoxylbiphenyl as a standard.

sence of MeOH, a much larger amount of diamine (TMEDA) is needed for the same effect; there may also be competition between TMEDA coordination and substrate coordination. A screen of other diamines showed that 1,2-dimethylethylenediamine and 1,3-dimethylpropylenediamine were just as effective. However, 1,2-ethylenediamine provided no reaction and more hindered diamines compromised reactivity. For simplicity, MeOH alone was used as the solvent in the next series of studies to maxmize the solubility of the polar imidazoles that would be employed. In addition, a 1:1 TMEDA:$Cu(NO_3)_2$ stoichiometry could be employed, minimizing the amount of diamine required.

The catalyst loading was examined in MeOH by GC monitoring (Figure 1). Using 1 mol% of the catalyst, 74% conversion was observed after 23 h and progressed to 90% after 48 h. With 1.5 mol% catalyst, very good conversion (90%) was observed after 23 h and little further progress was observed afterward. With 2 mol% of the catalyst, very good conversions occurred rapidly (91% after 12 h) that increased to 98% after 48 h.

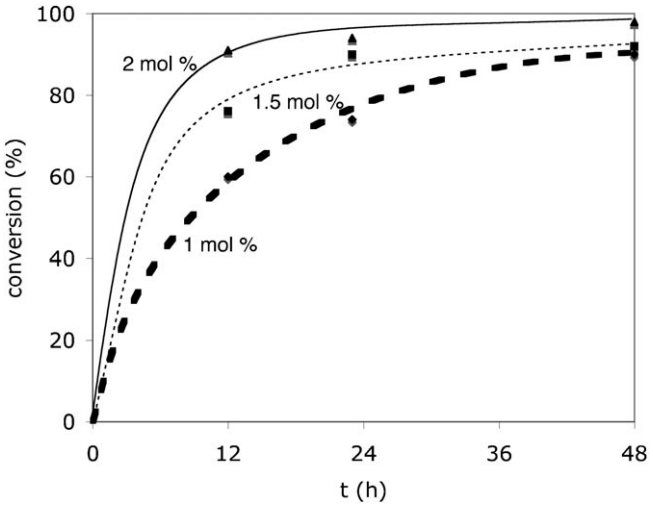
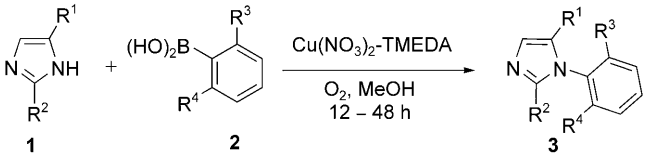


Figure 1. Effect of the $Cu(NO_3)_2$-TMEDA catalyst loading on the reaction from Scheme 1. *Conditions:* 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of MeOH under O_2 atmosphere at room temperature. Conversion determined by GC using 4-phenoxylbiphenyl as a standard.

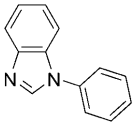
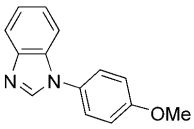
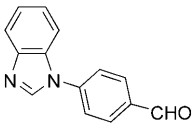
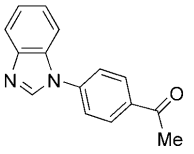
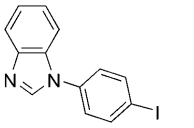
With optimal conditions [1:1 $Cu(NO_3)_2$:TMEDA) in MeOH under O_2 at ambient temperature] established, a series of substrates were screened (Scheme 2). With other hindered substrates (2-tolylboronic acid), the standard conditions using a 2 mol% catalyst loading gave variable results. Apparently, the substrates also contribute to the equilibrium phenomena observed in Table 3. As such, 10 mol% catalyst, which allowed consistent results without reoptimization, was used for the remaining substrates.



Scheme 2. *Conditions:* 10–50 mol% $Cu(NO_3)_2 \cdot 2.5\,H_2O$, 10–50 mol% TMEDA, under O_2 in MeOH.

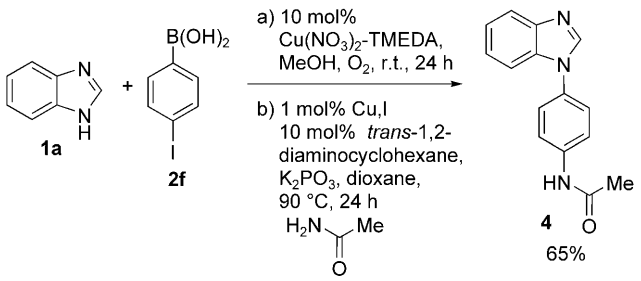
With benzimidazole, couplings to unhindered boronic acid substrates by far and large proceeded very well (Table 4). From the series of *para*-substituted phenylboronic acids, no electronic effect was readily apparent. Pleasingly, sensitive substrates could be employed including those containing aldehyde (entry 3) and iodide (entry 5) groups. The latter (product **3af**) is especially noteworthy as it would not be accessible *via* a benzimidazole/aryl halide coupling. The iodo group also provides a means for further cross-coupling chemistries.

Table 4. Unhindered couplings (Scheme 2) using 10 mol% $Cu(NO_3)_2$-TMEDA catalyst.[a]

Entry	**1**	**2**	Product **3**	Yield [%][b]
1	**1a**	**2b**	 **3ab**	99
2	**1a**	**2c**	 **3ac**	83
3	**1a**	**2d**	 **3ad**	99
4	**1a**	**2e**	 **3ae**	59
5	**1a**	**2f**	 **3af**	84

[a] *Conditions:* 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of MeOH under O_2 atmosphere at room temperature for 24 h.
[b] Isolated yield after chromatography.

To illustrate the utility of the idodide species, a sequential bis-*N*-arylation was undertaken (Scheme 3). In this three-component coupling, the iodoarylboronic



Scheme 3. Sequential bis-*N*-arylation.

acid first undergoes chemoselective *N*-arylation with benzimidazole at the boronic acid position using the catalyst system described herein. Next, the conditions of Buchwald and co-workers[20] were applied to generate a second C–N bond from the iodide and acetamide.

Next, more hindered boronic acids and imidazoles were examined leading to a variety of products with two *ortho*-groups (Table 5). With benzimidazole (entries 1–4), a selection of *ortho*-substituted boronic acids could be coupled quite well. The reactions of 2-phenylimidazole (entries 5–7) proved particularly difficult requiring higher catalyst loadings (30–50 mol%). On the other hand, 2-methylimidazole (entries 8 and 9) was quite tractable providing the products in high yield at 10 mol% loading. Finally, the very challenging 2-methylbenzimidazole (two *ortho* substituents on the imidazole portion) was also coupled effectively to phenylboronic acid (entry 10).

Finally, substrates were examined leading to even more hindered products (Table 6). The results leading to products with three *ortho*-groups (entries 1–4) highlight the utility of this method. During this study, one substrate (2,3-dimethoxyphenylboronic acid, **2m**) produced unexpected product **5** upon attempted coupling with benzimidazole (Scheme 4). Either the product of initial *N*-arylation undergoes a rapid hydration and subsequent *O*-arylation (*path a*) or 2,6-dimethoxyphenol is somehow formed and undergoes imine addition (*path b*) to the *N*-arylation product. Finally, a survey of the less reactive 2-methylimidazole with *ortho*-phenylboronic acids (entries 5–7) showed that high yields can be obtained simply and rapidly.

Conclusions

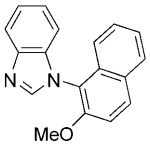
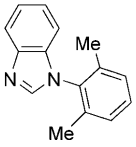
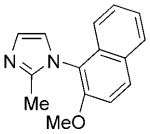
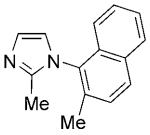
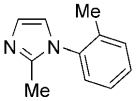
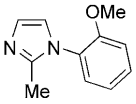
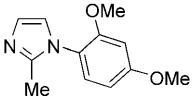
In conclusion, an effective catalyst system has been developed to form hindered C–N biaryls. The method has been illustrated in the cross-coupling of imidazoles and arylboronic acids. For most cases, the reaction conditions are very mild proceeding at ambient temperature with a simple catalyst system: $Cu(NO_3)_2$-TMEDA catalyst in MeOH under O_2. Further studies to examine the utility with other *N*-coupling partners are underway.

Table 5. Hindered couplings (Scheme 2) using $Cu(NO_3)_2$-TMEDA catalyst.[a]

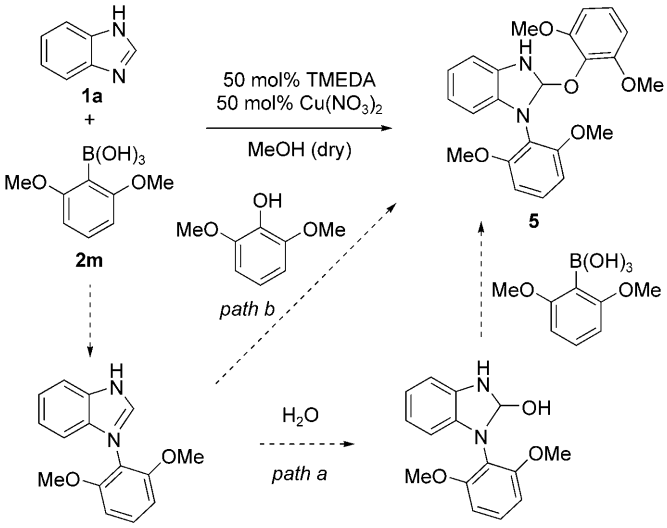
Entry	1	2	Product 3	Catalyst [mol%]	Yield [%][b]
1	**1a**	**2g**	**3ag**	10	97
2	**1a**	**2h**	**3ah**	10	95
3	**1a**	**2i**	**3ai**	10	82
4	**1a**	**2j**	**3aj**	30	99[c]
5	**1b**	**2b**	**3bb**	30	71[f]
6	**1b**	**2h**	**3bh**	30	71[f]
7	**1b**	**2g**	**3bg**	50	70[d,e]
8	**1c**	**2b**	**3cb**	10	99
9	**1c**	**2c**	**3cc**	10	86[c]
10	**1d**	**2b**	**3db**	10	82

[a] *Conditions:* 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of MeOH under O_2 atmosphere at room temperature for 24 h.
[b] Isolated yield after chromatography.
[c] Further 0.16 mmol of $ArB(OH)_2$ added after 24 h and quenched after 48 h total.
[d] $ArB(OH)_2$ added in two 0.24 mmol portions, the second after 3 h.
[e] Heated to 65 °C.
[f] $ArB(OH)_2$ added in two 0.24 mmol portions, the second after 24 h, reaction quenched after 48 h total.

Table 6. Very hindered couplings (Scheme 2) using $Cu(NO_3)_2$-TMEDA catalyst.[a]

Entry	1	2	Product 3		Catalyst [mol%]	Yield [%][b]
1	**1a**	**2a**		**3aa**	10	98
2	**1a**	**2k**		**3ak**	50	48[c,e]
3	**1c**	**2a**		**3ca**	10	65
4	**1c**	**2l**		**3cl**	30	90[c,e]
5	**1c**	**2g**		**3cg**	30	99
6	**1c**	**2h**		**3ch**	30	99[f]
7	**1c**	**2j**		**3cj**	30	99[f]

[a] *Conditions:* 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of MeOH under O_2 atmosphere at room temperature for 24 h.
[b] Isolated yield after chromatography.
[c] Further 0.16 mmol of $ArB(OH)_2$ added after 24 h and reaction quenched after 48 h total.
[d] $ArB(OH)_2$ added in two 0.24 mmol portions, the second after 3 h.
[e] Heated to 65 °C.
[f] $ArB(OH)_2$ added in two 0.24 mmol portions, the second after 24 h, quenched after 48 h total.



Scheme 4. Unusual coupling. *Conditions:* 0.16 mmol of imidazole, 0.32 mmol of $ArB(OH)_2$ in 2 mL of MeOH under O_2 atmosphere at room temperature. Further 0.16 mmol of $ArB(OH)_2$ added after 24 h and reaction quenched after 48 h total.

Experimental Section

General Considerations

Unless stated all reactions were carried out in oven-dried glassware. TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) was distilled from CaH_2. $Cu(NO_3)_2 \cdot 2.5\,H_2O$ was purchased from Fisher and was used as received. All imidazoles are commercially available, as were the boronic acids except for 2-methoxy-1-napthylboronic acid which was synthesized according to a literature[21] procedure. Distilled HPLC grade methanol was used for all reactions. All reactions were performed under a positive flow of oxygen. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light or $KMnO_4$ stain. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh).[22]

^1H NMR spectra were recorded on Bruker AM-500 (500 MHz), AM-360 (360 MHz), AM-250 (250 MHz), or AM-200 (200 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance ($CDCl_3$ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Decoupled ^{13}C NMR spectra were recorded on a Bruker AM-500 (125 MHz) spectrometer. IR spectra were taken on a ASI ReactIR 1000 equipped with an Si-Comp probe. High resolution mass spectra were performed by Dr. Kohli at the Mass Spectrometry Laboratory at the University of Pennsylvania.

Typical Procedure A: 1-(4-Iodophenyl)-1*H*-benzo[*d*]-imidazole (3af)

Here, the individual catalyst components were added directly to the reagents. The imidazole (0.16 mmol) and the boronic acid (0.32 mmol) were added to a 2 dram vial with a septum. Distilled MeOH (to achieve a final volume of 2 mL), a stock solution of $Cu(NO_3)_2$ in MeOH (0.16 M, volume used based on mol% required), and a stock solution of TMEDA in MeOH (0.16 M, volume used based on mol% required) were added to the vial while under 1 atm of O_2. The solution was stirred for 24 h at ambient temperature. After addition of H_2O (1 mL), the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. Chromatography (1% $MeOH/CH_2Cl_2$) afforded the *N*-arylation product as a yellow film; yield: 84%; $R_f = 0.68$ (10% $MeOH/CH_2Cl_2$);

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.07$ (s, 1H), 7.88 (m, 2H), 7.49 (m, 1H), 7.33 (m, 2H), 7.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.2$, 142.0, 139.3 (2C), 136.2, 125.8 (2C), 124.1, 123.2, 120.9, 110.4 (2C), 92.8; IR (film): $\nu =$ 3084, 3057, 1613, 1586, 1498, 1455, 1289, 1231 cm^{-1}; HR-MS (ES): $m/z = 320.9878$, calcd. for $C_{13}H_9IN_2$ (M^+): 319.9808.

Typical Procedure B: 1-*o*-Tolyl-1*H*-benzo[*d*]imidazole (3ag)

Here, the catalyst solution was generated shortly before addition of the reagents. No practical difference was observed between this protocol and that described above in Typical Procedure A. A 0.16 M TMEDA (3.38 μmol, volume used based on mol% required) methanolic stock solution was added to a 0.053 M cupric nitrate (3.38 μmol, volume used based on mol% required) methanolic stock solution in a 5 mL vial. After stirring at ambient temperature for 15 min, the mixture was diluted with MeOH to a final volume of 2 mL. The imidazole (0.16 mmol) and boronic acid (0.32 mmol) were added as solids and the mixture placed under a positive flow of oxygen at room temperature. After 24 h, H_2O (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3×2 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. Chromatography (EtOAc/hexanes) afforded the *N*-arylation product as a yellow film; yield: 97%; $R_f = 0.68$ (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.96$ (s, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.42 (m, 2H), 7.43–7.26 (m, 4H), 7.13 (d, $J = 7.9$ Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 143.3$, 142.9, 135.3, 134.7, 131.5, 129.3, 127.6, 127.1, 123.5, 122.4 (2C), 120.4, 110.4, 17.5; IR (film): $\nu =$ 3057, 2922, 1613, 1502, 1459, 1231 cm^{-1}; HR-MS (ES): $m/z =$ 208.1003, calcd. for $C_{14}H_{12}N_2$ (M^+): 208.1001.

GC Reaction Monitoring

4-Phenoxybiphenyl was used as an internal standard for GC analysis of reactions. At regular intervals, aliquots (~100 μL) were removed. To the respective aliquot were added H_2O and CH_2Cl_2. The solution was then shaken and the organic phase was filtered through SiO_2 (10% MeOH/CH_2Cl_2). Gas chromatography (GC) analyses of reaction progress were conducted with an Agilent 6850 gas chromatograph with a flame ionization detector equipped with an HP-1 column (Agilent): length = 30 m, ID = 0.32 mm, film = 0.25 mm, flow = 2 mL min^{-1}, 165 °C to 180 °C, pressure 27.29 psi; carrier gas: N_2; injector = 185 °C; detector 250 °C. Retention times; product: 4.41 min, 4-phenoxybiphenyl (internal standard): 12.4 min.

Acknowledgements

We are grateful to the NSF (CHE-0616885) for financial support.

References

[1] For a general review: M. Kienle, S. R. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem.* **2007**, 4166–4176.

[2] Selected reviews (Pd and Ni): a) J. P. Wolfe, S Wagaw, J. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818; b) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; c) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852–860; d) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146; e) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131–209; f) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361.

[3] Selected reviews (Cu): a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; b) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, *15*, 2428–2439; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.

[4] P. López-Alvarado, C. Avendaño, J. C. Menéndez, *J. Chem. Soc. Perkin Trans. 1* **1997**, 229–233.

[5] a) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, M. T. Chan, A. Combs, *Synlett* **2000**, *5*, 674–676; b) Y. S. L. Lam, G. Vincent, D. Bonne, C. G. Clark, *Tetrahedron Lett.* **2002**, *43*, 3091–3094; c) V. D. Davydov, I. B. Beletskaya, B. B. Semenov, Y. I. Smushkevich, *Tetrahedron Lett.* **2002**, *43*, 6217–6219.

[6] D. M. T. Chan, *Tetrahedron Lett.* **1996**, *37*, 9013–9016.

[7] P. Y. S. Lam, S. Deudon, K. M. Averill, L. Ming, M. Y. He, P. DeShong, C. G. Clark, *J. Am. Chem. Soc.* **2000**, *122*, 7600–7601.

[8] a) D. J. Cundy, S. A. Forsyth, *Tetrahedron Lett.* **1998**, *39*, 7979–7982; b) D. M. C. Chan, K. L. Monaco, R. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933–2936; c) W. W. K. R. Mederski, M. Lefort, M. Germann, D. Kux, *Tetrahedron* **1999**, *55*, 12757–12770; d) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, K. M. Averill, M. T. Chan, A. Combs, *Synlett* **2000**, *5*, 674–676; e) V. Collot, P. R. Bovy Rault, S. , *Tetrahedron Lett.* **2000**, *41*, 9053–9057 f) S. Yu, J. Saenez, J. K. Srirangam, *J. Org. Chem.* **2002**, *67*, 1699–1702.

[9] G. Evano, N. Blanchard, M. Toumi *Chem. Rev.* **2008**, *108*, 3054–3131.

[10] For other entries into hindered C–N biaryls, see: oxidative dimerization: a) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth, W. Lobin, *J. Am. Chem. Soc.* **2001**, *123*, 2703–2711; S_NAr: b) K. Kamikawa, S. Kinoshita, H. Matsuzaka, M. Uemura, *Org. Lett.* **2006**, *8*, 1097–1100; c) K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka, M. Uemura, *J. Org. Chem.* **2007**, *72*, 3394–3402; for entries into hindered *N*-aryl lactams, see: [2+2+2] cycloaddition: d) J. Oppenheimer, R. P. Hsung, R. Figueroa, W. L. Johnson, *Org. Lett.* **2007**, *9*, 3969–3972; lactam cyclization *via N*-arylation: e) O. Kitagawa, M. Takahashi, M. Yoshikawa, T. Taguchi, *J. Am. Chem. Soc.* **2005**, *127*, 3676–3677; f) O. Kitagawa, M. Yoshikawa, H. Tanabe, T. Morita, M. Takahashi, Y. Dobashi, T. Taguchi, *J. Am. Chem. Soc.* **2006**, *128*, 12923–12931; g) O. Kitaga-

wa, D. Kurihara, H. Tanabe, T. Shibuya T. Taguchi, *Tetrahedron Lett.* **2008**, *49*, 471–474.
[11] a) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688; b) J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578–5587; c) R. A. Altman, E. D. Koval, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 6190–6199.
[12] a) E. Alcalde, I. Dinares, S. Rodriguez, C. G. de Miguel, *Eur. J. Org. Chem.* **2005**, 1637–1643; b) R. Hosseinzadeh, M. Tajbakhsh, M. Alikarami, *Tetrahedron Lett.* **2006**, *47*, 5203–5205; c) Z. Zhang, J. Mao, D. Zhu, F. Wu, H. Chen, B. Wan, *Tetrahedron* **2006**, *62*, 4435–4443; d) A. K. Verma, J. Singh, V. K. Sankar, R. Chaudhary, R. Chandra, *Tetrahedron Lett.* **2007**, *48*, 4207–4210; e) M. Periasamy, P. Vairaprakash, M. Dalai, *Organometallics* **2008**, *27*, 1963–1966; f) H. Maheswaran, G. Gopi Krishna, K. Leon Prasanth, V. Srinivas, G. Krishna Chaitanya, K. Bhanuprakash, *Tetrahedron* **2008**, *64*, 2471–2479.
[13] J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578–5587.
[14] R. A. Altman, E. D. Koval, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 6190–6199.
[15] a) M. Periasamy, P. Vairaprakash, M. Dalai, *Organometallics* **2008**, *27*, 1963–1966; b) H. Maheswaran, G. Gopi Krishna, K. Leon Prasanth, V. Srinivas, G. Krishna Chaitanya, K. Bhanuprakash, *Tetrahedron* **2008**, *64*, 2471–2479; c) E. Alcalde, I. Dinares, S. Rodriguez, C. G. de Miguel, *Eur. J. Org. Chem.* **2005**, 1637–1643.
[16] Selected examples (no more than two *ortho*-substituents are present about the biaryl C–N bond in the product): a) K. Nishiura, Y. Urawa, S. Soda, *Adv. Synth. Catal.* **2004**, *346*, 1679–1684; b) Y. Yue, Z. G. Zheng, B. Wu, C. Q. Xia, X. Q. Yu, *Eur. J. Org. Chem.* **2005**, 5154–5157; c) M. L. Kantam, B. Neelima, C. V. Reddy, V. Neeraja, *J. Mol. Catal. A* **2006**, *249*, 201–206; d) R. R. Likhar, S. Roy, M. Roy, M. L. Kantama, R. L. De, *J. Mol. Catal. A* **2007**, *271*, 57–62; e) H. Bekolo, *Can. J. Chem.* **2007**, *85*, 42–46.
[17] J. Lan, L. Chen, X. Yu, J. You, R. Xie, *Chem. Commun.* **2004**, 188–189.
[18] a) P. Y. S. Lam, V. Guillaume, C. G. Clark, S. Deudon, P. K. Jadhav, *Tetrahedron Lett.* **2001**, *42*, 3415–3418; b) J. C. Antilla, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 2077–2079.
[19] a) J. P. Collman, M. Zhong, *Org. Lett.* **2000**, *2*, 1233–1236; b) J. P. Collman, M. Zhong, L. Zeng, S. Costanzo, *J. Org. Chem.* **2001**, *66*, 1528–1531; c) J. P. Collman, M. Zhong, C. Zhang, S. Costanzo, *J. Org. Chem.* **2001**, *66*, 7892–7897.
[20] A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
[21] S. Chowdhury, P. E. Georghiou, *J. Org. Chem.* **2002**, *67*, 6808.
[22] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

