ORGANIC LETTERS

2001
Vol. 3, No. 1
139−142

The Copper-Mediated Cross-Coupling of Phenylboronic Acids and *N*-Hydroxyphthalimide at Room Temperature: Synthesis of Aryloxyamines

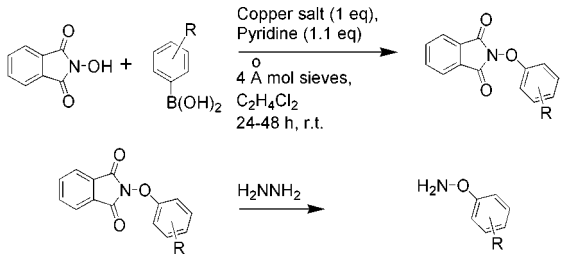
H. Michael Petrassi, K. Barry Sharpless, and Jeffery W. Kelly*

Department of Chemistry and The Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, MB12, La Jolla California 92037

jkelly@scripps.edu

Received November 16, 2000

ABSTRACT



A novel route to aryloxyamines via the copper-mediated cross-coupling of *N*-hydroxyphthalimide and phenylboronic acids is reported. The reaction is mediated by selected copper(I) and (II) salts in the presence of pyridine and is tolerant of several functional groups on the phenylboronic acid. The phthalimide group is removed using hydrazine to afford the corresponding aryloxyamine.

The rapid identification of interesting protein, RNA, and DNA pharmaceutical targets is driving the need for easily prepared, chemically diverse, target specific small molecules. Oxime ethers appear to be privileged in this regard, as this functionality is incorporated into over 20 FDA-approved drugs and numerous others currently under evaluation.[1] Oxime ethers form spontaneously upon mixing a ketone or aldehyde with an alkoxy- or aryloxyamine.[2] Their ease of synthesis and biocompatibility explains why they are used to stitch together a variety of chemically diverse libraries.[3] Oxime ether formation tolerates a wide range of functional groups; however, the relative scarcity of commercially available alkoxy- and aryloxyamines limits the diversity of products one is able to prepare. Ellman and coworkers have provided access to a wider range of alkyloxyamines using 3,3′-di-*tert*-butyloxyaziridine to readily convert 1°, 2°, and to a lesser extent, 3° alcohols to their corresponding alkyloxyamines.[4] The scope of this chemistry was further expanded with the recent report of a Boc-trichloromethyloxaziridine,[5] which also transforms 4-methoxyphenol to the respective Boc-protected aryloxyamine in high yield.

Approaches for preparing aryloxyamines currently in use are narrow in scope, with the possible exception of the Boc-trichloromethyloxazaridine method.[5] Historically,

(1) MDL Drug Data Report, MDL Information Systems, Inc., San Leandro, CA.

(2) Abele, E.; Lukevics, E. *Org. Prep. Proced. Int.* **2000**, *32*, 235.

(3) (a) Maly, J. M.; Choong, I. C.; Ellman, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2419. (b) Nazarpack-Kandlousy, N., Chernushevich, I. V.; Meng, L.; Yang, Y.; Eliseev, A. V. *J. Am. Chem. Soc.* **2000**, *122*, 3358.

(4) Choong, I. C.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 6528.

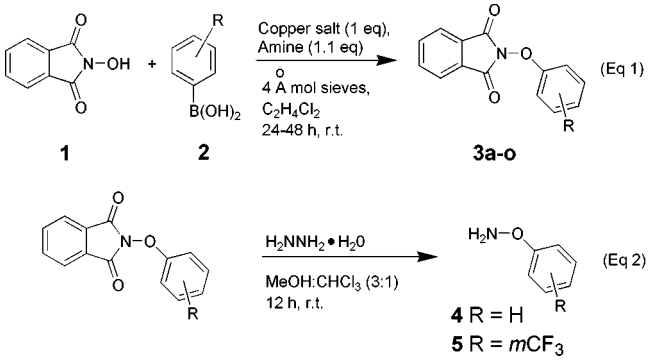
(5) Foot, O. F.; Knight, D. W. *Chem. Comm*. **2000**, 975. For a synthesis of this oxaziridine, see: Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett*. **1998**, *39*, 8845.

10.1021/ol0003533 CCC: $20.00
Published on Web 12/19/2000

aryloxyamines have been prepared using halobenzenes substituted with several electron-withdrawing groups facilitating a nucleophilic aromatic substitution by the conjugate base of *N*-hydroxyphthalimide (**1**).[6] Activated arene complexes, especially diphenyl iodonium chloride and the tricarbonyl (chloroarene) complexes, facilitate nucleophilic attack by PhthN-O$^-$, which upon hydrazinolysis affords the aryloxyamine.[7] Another route involves nitrogen transfer to a phenoxide. However, some of the best N-transfer reagents (e.g., (2,4,-dinitrophenoxy)amine) are themselves aryloxyamines which are difficult to prepare and unstable to long term storage. Furthermore, the N-transfer reaction is not general for all phenoxides, especially electron rich phenoxides.[8]

Several groups have reported the use of $Cu^{II}(OAc)_2$ in the presence of an amine base to cross-couple a phenylboronic acid with a variety of coupling partners including phenols,[9] amines,[10] alkanethiols,[11] or the like.[12] As shown in Scheme 1, *N*-hydroxyimides (e.g., **1**) can now be added to the long

Scheme 1



list of partners that participate in these arylboronic acid coupling processes. Examples of this new method for the synthesis of aryloxyamines are reported below.

The initial conditions explored were those reported simultaneously by Chan[12a] and Evans et al.[9] for the $Cu^{II}(OAc)_2$-mediated cross-couplings of arylboronic acids. *N*-Hydroxyphthalimide (**1**) was chosen as the hydroxyamine donor, although a few others were evaluated.[13] Three equivalents of phenylboronic acid, 1 equiv of **1**, and 1 equiv of $Cu^{II}(OAc)_2$ were allowed to react at room temperature in methylene chloride, while varying the amine. This revealed that pyridine was by far the best amine evaluated and similar yields were observed irrespective of the excess utilized between 1 and 10 equiv (Table 1, entries 1−4). Both Et_3N and DMAP are inferior and inhibit the reaction at higher concentrations (Table 1, entries 5−10). Interestingly, under an atmosphere of argon the reaction gave slightly depressed yields in comparison to an ambient atmosphere, a phenomenon also observed in other copper-mediated cross-couplings.[9,10d,12b]

Table 1. Optimization of the Amine for the Cross Coupling[a]

			yield (%)	
entry	amine	equiv	$Cu^{II}(OAc)_2$	$Cu^{I}Cl$
1[b]	pyridine	1	58	NA
2	pyridine	1	92	93
3	pyridine	5	84	70
4	pyridine	10	88	64
5	Et_3N	1	33	37
6	Et_3N	5	13	13
7	Et_3N	10	6	0
8	DMAP	1	40	75
9	DMAP	5	0	0
10	DMAP	10	0	0
11	Cs_2CO_3	5	0	0
12	DABCO	5	0	0

[a] Reaction conditions: 1 mmol $Cu^{II}(OAc)_2$, 3 mmol phenylboronic acid, 1 mmol **1**, ~250 mg of 4 Å molecular sieves (freshly activated), and the amine base in CH_2Cl_2, at room temperature for 24 h under an ambient atmosphere. Yields refer to those determined via the integrated area of the **3a** RP-HPLC peak compared to a **3a** calibration curve. Each yield is an average of two experiments. [b] 1 mmol phenylboronic acid, everything else as in footnote *a*. NA: not available.

A rationale for the enhancement of the reaction by O_2 has been offered by Lam et al. for the *N*-arylation of saturated heterocycles.[10d] The copper complex coordinates **1** and presumably transmetalates the arylboronic acid releasing boric acid. Molecular oxygen could then oxidize the pyridine-coordinated copper complex to Cu(III), facilitating the reductive elimination of the *N*-aryloxyphthalimide.[10d,12b] The oxidizing reaction conditions likely promote peroxide formation. The resultant peroxide would decompose the arylboronic acid. This would explain the lower yields when 1 equiv of phenylboronic acid (Table 1, entry 1), is employed.

Several common copper(I) and (II) salts were evaluated for the desired reactivity (Table 2). While selected copper-(I) and (II) sources effect the cross-coupling reaction, there is not a direct correlation between the effectiveness of a specific salt and its oxidation state. For example, $Cu^{I}Cl$ very

(6) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Org. Prep. Proced. Int.* **1977**, *29*, 594.
(7) (a) Cadogan, J. I. G.; Rowley, A. G. *Synth. Comm.* **1977**, *7*, 365. (b) Baldoli, C.; Del Bettero, P.; Licandro, E.; Maiorana, S. *Synthesis* **1988**, 344.
(8) (a) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1348. (b) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *Synthesis* **1977**, 1.
(9) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
(10) (a) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623. (b) Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett.* **1998**, *39*, 7979. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (d) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674.
(11) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Organic Lett.* **2000**, *2*, 2019.
(12) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (b) Collman, J. P.; Zhong, M. *Organic Lett.* **2000**, *2*, 1233.
(13) Several other *N*-hydroxylamine sources were also evaluated. *N*-Hydroxynaphthalimide and *endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximide were viable *N*-hydroxylamine sources but afforded inferior yields relative to **1**. Cross-couplings with *N*-hydroxy succinimide and *N*-hydroxy carbamate were unsuccessful.

Table 2. Evaluation of Copper Salts

entry	copper salt	yield (%)
1	$Cu^{I}Cl$	91
2	$Cu^{I}Br{\cdot}SMe_2$	90
3	Cu^{II}	0
4	$Cu^{I}(OAc)$	5
5	$Cu^{II}Cl_2$	0
6	$Cu^{II}(OAc)_2$	90
7	$Cu^{II}(OTf)_2$	50
8	$Cu^{II}(CF_3COCHCOCH_3)_2$	0

[a] Reaction conditions: 1 mmol copper salt, 2 mmol phenylboronic acid, 1 mmol **1**, 1.1 mmol pyridine, ~250 mg of 4 Å molecular sieves (freshly activated), in CH_2Cl_2, at room temperature for 24 h under an ambient atmosphere. Yields refer to isolated **3a**.

efficiently effects the cross-coupling but the analogous Cu(II) salt is completely ineffective. This trend is reversed in the case of the acetate salt. A limited examination of solvents revealed that 1,2-dichloroethane is optimal. Therefore, 2 equiv of arylboronic acid and 1 equiv of **1**, combined with 1 equiv of $Cu^{I}Cl$ (Table 2) and 1.1 equiv of pyridine (Table 1) in 1,2 dichloroethane (0.1 M), gave the most efficient cross-coupling rates while minimizing the amount of unidentified aryl side products.[14]

The functional group tolerance is good (Table 3). The reaction proceeds with both electron-rich and electron-deficient arylboronic acids and works in the presence of additional functional groups including halides, esters, ethers, nitriles, and aldehydes, (Table 3, entries 4−9). However a second boronic acid functionality appears to interfere with the reaction (Table 3, entry 10). While an *ortho* methyl substituent was tolerated, an *ortho* fluorine group was not (Table 3, entries 15 and 16). Representative hydrazinolyses[15] of *N*-aryloxyphthalimides **3a** and **3j** gave excellent yields (77−90% after Kueglrohr distillation or precipitation of the HCl salt) of aryloxyamines **4** and **5**, respectively (Scheme 1, eq 2).

The conditions used in Table 3 were those optimized for the unsubstituted phenylboronic acid, and it is likely that optimization of copper salt, amine, and solvent used in addition to the stoichiometry could result in higher yields for specific phenylboronic acids. The requirement of 2 equiv of phenylboronic acid and the incompatibility of an *ortho* heteroatom substituent or a second boronic acid functionality on the phenylboronic acid represent the known limitations of this methodology.

Table 3. O-Arylation of **1** with Arylboronic Acids[14,a]

Entry	Boronic Acid	*N*-Phenoxy Phthalimide	Yield (%)
1	R = H	**3a**	90
2	CF_3	**3b**	65
3	OMe	**3c**	37
4	I	**3d**	57
5	Br	**3e**	73
6	CO_2Me	**3f**	64
7	$HC{=}CH_2$	**3g**	87
8	CHO	**3h**	52
9	CN	**3i**	66[b]
10	$B(OH)_2$		0
11	R = CF_3	**3j**	87
12	OMe	**3k**	57
13	F	**3l**	65
14	iPr	**3m**	68
15	R = Me	**3n**	60
16	F		0
17	R = 3,5 diF	**3o**	72

[a] Yields refer to the average isolated yield of two experiments. [b] Single experiment.

In conclusion, a route to aryloxyamines from commercially available starting materials via a copper-mediated cross-coupling reaction is described. To our knowledge these conditions represent the first metal-mediated *O*-arylation of

(14) **Procedure for 3a.** A 20 mL scintillation vial equipped with a magnetic stir bar was charged with **1** (163 mg, 1 mmol, 1 equiv), CuCl (99 mg, 1 mmol, 1 equiv), freshly activated 4 Å molecular sieves (~250 mg), and phenylboronic acid (244 mg, 2 mmol, 2 equiv). The 1,2-dichloroethane solvent (5 mL) was added followed by pyridine (90 μL, 1.1 mmol, 1.1 equiv), resulting in a light brown suspension. The cap was loosely applied such that the reaction was open to the atmosphere. Reaction progress was followed by analytical RP-HPLC and was complete in 48 h. The reaction mixture became green as the reaction proceeded. The reaction products were adsorbed to SiO_2 by removing the solvent under reduced pressure in the presence of silica gel (5 g). Chromatography of the reaction mixture (50 g of SiO_2, 25% EtOAc in hexanes) afforded **3a** as a white solid (216 mg, 90%). See Supporting Information for characterization of **3a**. Notes: Reactions that did not work (e.g., Table 3, entry 16) did not exhibit the brown to green color change. The use of a discolored amine resulted in drastically reduced yields, and therefore all amines were freshly distilled. The use of 4 Å molecular sieves that were not freshly activated gave inferior yields.

(15) A 50 mL round-bottom flask, equipped with a magnetic stirbar, was charged the *N*-aryloxyphthalimide **3a** (652 mg, 2.73 mmol, 1 equiv), 10% MeOH in $CHCl_3$ (25 mL), and hydrazine monohydrate (0.401 mL, 8.2 mmol, 3 equiv), resulting in a colorless solution. The reaction was allowed to stir at room temperature. Upon completion (TLC monitoring, 12 h) a white precipitate appeared (the phthalizine) in a colorless reaction solution. The reaction mixture was adsorbed to 6 g of silica gel and passed through a plug of silica gel (50 g) washing with 30% EtOAc in hexane (300 mL). Removal of the hexane/EtOAc produced a slightly pale yellow oil, which upon Kugelrohr distillation (10 mmHg, 80 °C) from K_2CO_3 (<10 mg) provided pure aryloxyamine **4** as a clear colorless oil (238 mg, 80%). Alternatively the amine could be isolated as the HCl salt. After removal of the hexane/EtOAc solvent, the yellow oil was taken up in Et_2O (10 mL) and cooled to 0 °C for 10 min, at which point 4 N HCl in dioxane was added dropwise until pH 3 was reached (prehydrated pH paper). The resulting white solid was filtered and washed with Et_2O (2 × 10 mL) to afford the pure HCl salt of **4** (306 mg, 77%). See Supporting Information for characterization of **4**.

a protected hydroxylamine donor for the preparation of aryloxyamines. The mild reaction conditions and functional group tolerance make this approach potentially useful for the rapid preparation of a wide spectrum of aryloxyamines that were difficult to prepare previously.

Acknowledgment. We thank the National Institutes of General Medical Sciences, National Institutes of Health (GM-28384 [K.B.S.], DK46335 [J.W.K.]), the National Science Foundation (CHE-9531152 [K.B.S.]), the Skaggs Institute of Chemical Biology, W. M. Keck Foundation (K.B.S.), the Lita Annenberg Hazen (J.W.K.), Donald and Delia Baxter Foundation (J.W.K.), and the ACS Organic Division (predoctoral fellowship, H.M.P.) for financial support. We also thank H. Razavi and V. Fokin for helpful discussions.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for compounds **3a**−**o**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0003533