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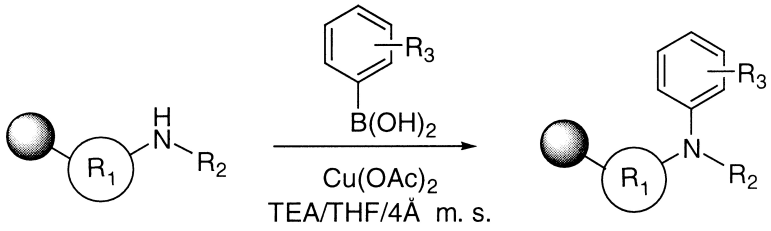

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N-Arylation of Primary and Secondary Aliphatic Amines on Solid Supports

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A general and mild method for the N-arylation of primary and secondary aliphatic amines is reported. Copper acetate, triethylamine mediated C/N cross-coupling reaction of arylboronic acids at room temperature to solid-supported primary and secondary amines gave good to excellent yields of the desired N-arylated products.

Introduction

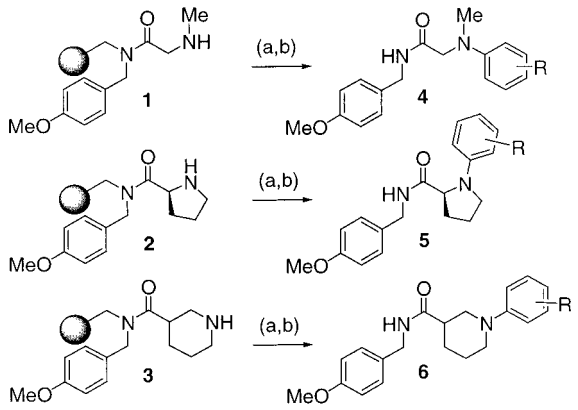
N-arylated primary and secondary aliphatic amines are important substituents in many biologically active compounds. The predominance of arylpiperidines and arylpiperazines in CNS drugs is particularly noteworthy.[1−3] A general and mild method for the solid-phase synthesis of this pharmacophore in a library format was thus desired to enable the production of diverse N-arylated libraries for general high-throughput screening (HTS) and focused libraries for generating structure−activity relationships on lead compounds. In our seminal reports on the copper acetate promoted N-arylation of various solid-supported amines, we discovered that sulfonamides and many heterocycles containing a free N−H's afford good to excellent yields and purities of the desired N-arylated products, while amides, carbamates, and ureas gave no reaction.[4,5] We report herein a detailed study of the N-arylation reaction of solid-supported aliphatic amines, further demonstrating the generality of this methodology for the solid-phase synthesis of combinatorial libraries.

Results and Discussion

Chan et al. initially reported the copper acetate promoted C/N cross-coupling reaction of a variety of compounds bearing a free N−H or O−H in solution.[6] Subsequent reports by Evans et al. and Lam et al. have further optimized these conditions and demonstrated the scope and utility of this reaction.[7−10] We were particularly impressed with the generality and mild conditions of this useful, yet previously unknown N-aryl bond-forming reaction. Solid-phase variants of reactions of this broad synthetic scope provide valuable tools for the construction of diverse compound libraries. We have thus investigated many of the solid-phase variants of this cross-coupling reaction.

The N-arylation of solid-supported cyclic and acyclic secondary aliphatic amines was initially investigated (Scheme 1). *p*-Methoxybenzylamine was reductively aminated onto Bal resin, and suitable amino acids were coupled to the secondary amine using HATU activation. Fmoc quantitation of the resins at this point provided initial resin loadings to serve as reference points for yield determinations. N-arylation substrates (**1**, **2**, **3**) were chosen to determine the steric effects due to the proximity of the linkage to the solid support with cyclic and acyclic amines. Reaction conditions previously optimized for the N-arylation of solid-supported sulfonamides ($Cu(OAc)_2$, TEA, THF) also proved to be optimal for N-arylation of these aliphatic amine substrates.[5] Noteworthy is that *powdered* 4 Å molecular sieves provide dramatically better yields of the desired products when compared to reactions run with pellet 4 Å sieves. The powdered sieves are also more convenient to use because they are much smaller than the pore size of most frits and thus are removed from the reaction vessel upon washing the resin after the reaction. A variety of boronic acids were coupled to the solid-supported amines using these conditions (Table 1). Cleavage of the products from the solid supports and HPLC analysis of the unpurified material demonstrated that conversions to the desired N-arylated products were good to excellent (68−90%) for the para-substituted boronic acids with each of the solid-supported amines. Ortho-substituted boronic acids gave consistently lower conversions (35−48%) and yields (21−31%) of the desired N-arylated products (**4d**, **5c**, **6c**). Yields determined after HPLC purification of the products were moderate to good (21−75%). While a slight erosion in yield

Scheme 1[a]



[a] Reagents and conditions: (a) $Cu(OAc)_2$ (2 equiv), R-$PhB(OH)_2$ (4 equiv), TEA (4 equiv), THF, 4 Å sieves, repeat 2×; (b) TFA/DCM (1:1).

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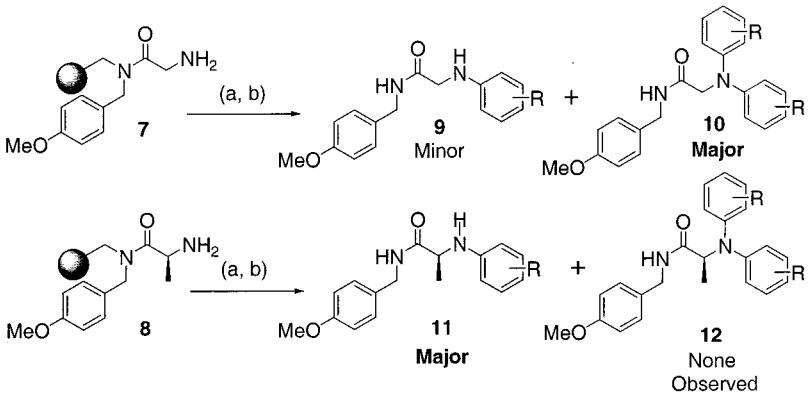
Scheme 2[a]



[a] Reagents and conditions: (a) $Cu(OAc)_2$ (2 equiv), R-$PhB(OH)_2$ (4 equiv), TEA (4 equiv), THF, 4 Å sieves, repeat 2×; (b) TFA/DCM (1:1).

Table 1. N-Arylation of Primary Amines

product	R	conversion[a] (%)	yield[b] (%)
4a	H	65	45
4b	*p*-OMe	72	65
4c	*p*-CF_3	86	65
4d	*o*-Me	35	21
5a	*p*-OMe	66	45
5b	*p*-CF_3	86	65
5c	*o*-Me	39	25
6a	H	75	52
6b	*p*-OMe	90	75
6c	*o*-Me	48	31

[a] Conversion to product based on HPLC peak area at 220 nm; starting material is the only other product present in HPLC (220 and 254 nm). [b] Purified yields of **4**−**6** based on loading determined for resins **1**−**3**, respectively.

was observed with the more sterically demanding proline derivative **2**, the cyclic and acyclic amines gave good yields of the desired N-arylated products.

The N-arylation of primary amines was expected to be problematic, since the N-arylated products could themselves serve as a substrate for the N-arylation reaction, thus affording the *N*,*N*-bisarylamine products (Scheme 2). In fact, our initial attempt at N-arylating the primary amine of the solid-supported glycine derivative **7** afforded the N,N-bisarylation product **10** as the major product (**10**/**9** ≈ 10:1). Though the N,N-bisarylated product was produced as the major product, we were encouraged to observe that the mono-N-arylated product **9** could be isolated in low yields (∼10%). This suggests that the mono-N-arylated product is less reactive than the starting primary amine under these conditions. We reasoned that the steric influence of an α-substituent to the amine would further reduce the reactivity of the product N-arylated amine, similar to the acyclic α-substituted secondary amines, and give predominantly the mono-N-arylated product. The alanine derivative **8** was thus synthesized on solid support and N-arylated under our standard coupling conditions. Gratifyingly, the N,N-bisarylated product **12** was not observed and the *only product* isolated was the mono-N-arylated species **11** in good yield and purity (Table 2).

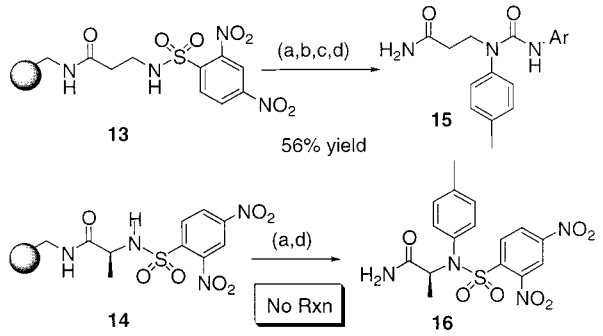
These results nicely complement our previous report,[5] in which we showed that solid-supported nitrosulfonamides **13** can be N-arylated and subsequently deprotected to afford aliphatic N-arylated products for further elaboration (Scheme 3). In these cases, substitution α to the amine of the sulfonamide **14** significantly reduces the propensity for these compounds to N-arylate, thus affording none of the desired N-arylated product **16**. We have now demonstrated in this report that the synthetic solution to N-arylation of sterically encumbered primary amines is to simply N-arylate the corresponding free primary amines.

Table 2. N-Arylation of Acyclic and Acyclic Secondary Amines

product	R	conversion[a] (%)	yield[b] (%)
10	Me	66	47
11a	H	60	40
11b	OMe	82	55
11c	Me	62	41

[a] Conversion to product based on HPLC peak area at 220 nm. [b] Purified yields of **10** and **11** based on loading determined for resins **7** and **8**, respectively.

Scheme 3[a]



[a] Reagents and conditions: (a) $Cu(OAc)_2$ (2 equiv), 4-$MePhB(OH)_2$ (4 equiv), TEA (4 equiv), THF, 4 Å sieves, repeat 2×; (b) 1 M butylamine/DCM; (c) phenyl isocyanate, DCM; (d) TFA/DCM (1:1).

Conclusions

A general synthetic method for the copper acetate promoted N-arylation of primary and secondary aliphatic amines with boronic acids has been derived for the synthesis of a variety of N-arylated products. Mild reaction conditions (room temperature with tertiary amine base) and determined chemoselectivity of these C/N cross-coupling reactions provide the combinatorial chemist with a powerful new set of tools for the N-arylation of many solid-supported molecules bearing a free NH. The use of these reactions for target-oriented synthesis, as well as diversity-oriented syn-

thesis, should provide valuable collections of molecules for biological and/or materials screening.

Experimental Section

Bal-PEG-PS (HL) resin (loading, 0.45−0.55 mmol/g) was purchased from PerSeptive Biosystem. Fmoc-protected amino acids were purchased from Advanced ChemTech. Boronic acids, amines, and molecular sieves were purchased from Aldrich. Reactions were performed in bottom-and-top-capped polypropylene-fritted tubes manufactured by Mitchell's Plastics. Reactions in the polypropylene tubes were mixed using Labquake Tube Rotor/Rocker manufactured by Thermolyne. Proton NMR spectra were obtained using a Varian Inova 400 MHz NMR spectrometer equipped with a 60 μL active volume flow probe and a Gilson 215 liquids handler. The chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or 75% DMSO-d_6/25% $CDCl_3$ or 100% DMSO-d_6 . High-resolution mass spectra were recorded using electrospray ionization. HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system using a photodiode array detector and ODS-A 5 μm (C18, 4.5 mm × 50 mm) YMC slim-bore column with a gradient of 0% acetonitrile/water containing 0.1% TFA to 100% acetonitrile over 8 min at 3 mL/min flow rate. Peak areas were integrated at 220 and 254 nm.

Reductive Amination of Bal Resin. *p*-Methoxybenzylamine (5 equiv) was dissolved in 1% AcOH in DMF, and then $NaBH(OAc)_3$ (5 equiv) was added. To this mixture was immediately added 1.0 g (0.55 mmol) of Bal-PEG-PS resin, and this was mixed overnight. The resin was washed with MeOH (1×), 10% DIEA in DMF (2×), DMF (7×), DCM (7×), and finally MeOH (3×), DCM (3×) and dried in vacuo. The completion of the reaction was monitored by solid-phase ^{13}C NMR of the resulting resin.

Typical Procedure for the Preparation of Solid-Supported Amines (1−3, 7, 8). Commercially available Fmoc-alanine-OH, Fmoc-*N*-methylglycine, Fmoc-glycine, Fmoc-proline, or Fmoc-nipecotic acid (4.5 equiv) was coupled to the amine resin using HATU (4.5 equiv), DIEA (9 equiv) in DMF at room temperature. After 4 h the resin was washed with DMF (5×), MeOH (5×), and DCM (7×). Resin loading of the Fmoc-amino acid was measured by spectroscopic analysis of the Fmoc chromophore. Typical loading of the resin was 0.43 mmol/g. Fmoc deprotection of the resin was accomplished with 20% piperidine in DMF (30 min), followed by washing with DMF (3×), MeOH (3×), and DCM (5×) and drying in vacuo.

General Procedure for N-Arylation of Resin-Bound Amines (4a−d, 5a−c, 6a−c, 9, 10, 11a−c). Resin **1** (0.200 g; loading, 0.43 mmol/g) was swelled in dry THF (0.5 mL), and the following reagents were added in a sequential fashion: phenylboronic acid (4 equiv) anhydrous copper acetate (2 equiv), 4 Å powdered molecular sieves (0.1 g), triethylamine (4 equiv), and THF (1.0 mL). Note: Powdered sieves gave dramatically improved yields relative to pellets. The heterogeneous mixture was mixed for 3 h. The resin was filtered and washed alternately with THF (7×) and DCM (5×), followed by THF (5×), and charged with fresh reagents. The reaction mixture was again mixed for 3 h. The washing procedure was repeated, and the resin was charged again with fresh reagents and shaken overnight. The washing procedure was repeated as above. The product was cleaved from the solid support by treatment with 50% TFA in DCM for 1 h. The resin was filtered and washed with DCM. The combined filtrates were evaporated to dryness. Percent conversions are based on the HPLC analysis at 220 nm of the unpurified material. Isolated yields are given after purification on preparative HPLC.

The following compounds were prepared according to the procedure described above.

4a: 65% conversion; 45% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.26 (m, 2H, Ar.), 7.12 (d, 2H, Ar), 6.83 (d, 3H, Ar), 6.74 (d, 2H, Ar), 4.41 (d, 2H, CH_2), 3.90 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 2.98 (s, 3H, CH_3); HRMS *m*/*e* calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1603, found 285.1603.

4b: 72% conversion; 65% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.13 (d, 2H, Ar.), 6.83 (d, 4H, Ar), 6.72 (d, 2H, Ar), 4.40 (d, 2H, CH_2), 3.82 (s, 2H, CH_2) 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.92 (s, 3H, CH_3); HRMS *m*/*e* calcd for $C_{18}H_{23}N_2O_3$ $[M + H]^+$ 315.1709, found 315.1708.

4c: 86% conversion; 65% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H, Ar), 7.46 (t, 1H, NH), 7.10 (d, 2H, Ar), 6.81 (d, 2H, Ar), 6.72 (d, 2H, Ar), 4.40 (d, 2H, CH_2), 3.98 (s, 2H, CH_2) 3.78 (s, 3H, OCH_3), 3.07 (s, 3H, CH_3); HRMS *m*/*e* calcd for $C_{18}H_{20}F_3N_2O_2$ $[M + H]^+$ 353.1477, found 353.1502.

4d: 35% conversion; 21% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, 1H, NH), 7.12 (m, 6H, Ar), 6.85 (d, 2H, Ar), 4.44 (d, 2H, CH_2), 3.80(s, 3H, OCH_3), 3.65 (s, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); HRMS *m*/*e* calcd for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1760, found 299.1760.

5a: 66% conversion; 45% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.09 (d, 2H, Ar), 6.82 (m, 4H, Ar), 6.58 (d, 2H, Ar), 4.45 (dd, 1H, CH_2), 4.29 (dd, 1H, CH_2), 3.99 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.58 (m, 1H, CH_2), 3.17 (m, 1H, CH_2), 2.27 (m, 2H, CH_2), 1.98 (m, 2H, CH_2); HRMS *m*/*e* calcd for $C_{20}H_{25}N_2O_3$ $[M + H]^+$ 341.1865, found 341.1865.

5b: 86% conversion; 65% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, 2H, Ar), 7.4 (t, 1H, NH), 7.07 (d, 2H, Ar), 6.82 (d, 2H, Ar), 6.58 (d, 2H, Ar), 4.43 (dd, 1H, CH_2), 4.29 (dd, 1H, CH_2), 4.14 (t, 1H, CH), 3.77 (s, 3H, OCH_3), 3.58 (m, 1H, CH_2), 3.26 (m, 1H, CH_2), 2.27 (m, 2H, CH_2), 1.98 (m, 2H, CH_2); HRMS *m*/*e* calcd for $C_{20}H_{22}F_3N_2O_2$ $[M + H]^+$ 379.1633, found 379.1653.

5c: 39% conversion; 25% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.07 (m, 4H, Ar), 6.80 (m, 2H, Ar), 6.54 (d, 2H, Ar), 4.50 (dd, 1H, CH_2), 4.24 (dd, 1H, CH_2), 4.02 (t, 1H, CH), 3.77 (s, 3H, OCH_3), 3.59 (m, 1H, CH_2), 3.17 (m, 1H, CH_2), 2.27(m, 2H, CH_2), 1.98 (m, 2H, CH_2); HRMS *m*/*e* calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ 325.1916, found 325.1916.

6a: 75% conversion; 52% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.40 (s, 5H, Ar), 7.23 (d, 2H, Ar), 6.90 (d, 2H, Ar), 4.40 (d, 2H, CH_2), 3.94 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.64 (bs, 1H, CH), 3.39 (m, 2H, CH_2),

2.64 (t, 1H, CH), 2.17 (m, 5H, CH_3, CH_2); HRMS *m*/*e* calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ 325.1916, found 325.1916.

6b: 90% conversion; 65% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 2H, Ar), 7.4 (t, 1H, NH), 7.23 (d, 2H, Ar), 7.00 (d, 2H, Ar), 6.88 (d, 2H, Ar), 4.40 (d, 2H, CH_2), 3.94 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.65 (bs, 1H, CH), 3.45 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 2.40 (m, 2H, CH_2); HRMS *m*/*e* calcd for $C_{21}H_{27}N_2O_3$ $[M + H]^+$ 355.2022, found 355.1910.

6c: 48% conversion; 31% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 2H, Ar), 7.4 (t, 1H, NH), 7.28 (d, 2H, Ar), 7.21 (d, 2H, Ar), 6.85 (d, 2H, Ar), 4.37 (d, 2H, CH_2), 3.86 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.64 (bs, 1H, CH), 3.39 (m, 2H, CH_2), 2.64 (t, 1H, CH), 2.17 (m, 5H, CH_3, CH_2); HRMS *m*/*e* calcd for $C_{21}H_{26}N_2O_2$ $[M + H]^+$ 339.2073, found 339.2073.

10: 66% conversion; 47% yield; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (t, 1H, NH), 7.07 (d, 2H, Ar), 7.04 (d, 4H, Ar.), 6.87 (d, 4H, Ar), 6.82 (d, 2H, Ar), 4.24 (s, 2H, CH_2), 4.20 (d, 2H, CH_2), 3.65 (s, 3H, OCH_3), 2.22 (s, 6H, 2 CH_3); HRMS *m*/*e* calcd for $C_{24}H_{27}N_2O_2$ $[M + H]^+$ 375.2073, found 375.2072.

11a: 60% conversion; 40% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.20 (m, 2H, Ar), 7.18 (d, 2H, Ar), 6.82 (m, 3H, Ar), 6.60 (d, 2H, Ar), 4.42 (dd, 1H, CH_2), 4.28 (dd, 1H, CH_2), 3.87 (q, 1H, CH), 3.77 (s, 3H, OCH_3), 1.54 (d, 3H, CH_3); HRMS *m*/*e* calcd for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1603, found 285.1603.

11b: 82% conversion; 55% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.08 (d, 2H, Ar), 6.83 (m, 6H, Ar), 4.39 (dd, 1H, CH_2), 4.29 (dd, 1H, CH_2), 3.99 (q, 1H, CH), 3.78 (s, 6H, OCH_3), 1.50 (d, 3H, CH_3); HRMS *m*/*e* calcd for $C_{18}H_{23}N_2O_3$ $[M + H]^+$ 315.1709, found 315.1709.

11c: 62% conversion; 41% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (t, 1H, NH), 7.14 (m, 5H, Ar), 6.79 (m, 3H, Ar), 6.51 (d, 1H, NH), 4.48 (dd, 1H, CH_2), 4.27 (dd, 1H, CH_2), 3.88 (q, 1H, CH), 3.78 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3), 1.59 (d, 3H, CH_3); HRMS *m*/*e* calcd for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1760, found 299.1759.

References and Notes

(1) Evrard, D. A.; Harrison, B. L. Recent Approaches to Novel Antidepressant Therapy. *Annu. Rep. Med. Chem.* **1999**, *34*, 1−10.

(2) Robichaud, A. J.; Largent, B. L. Recent Advances in Selective Serotonin Receptor Modulation. *Annu. Rep. Med. Chem.* **2000**, *35*, 11−20 (Chapter 2).

(3) Schaus, J. M.; Bymaster, F. P. Dopaminergic Approaches to Antipsychotic Agents. *Annu. Rep. Med. Chem.* **1998**, *33*, 1−10.

(4) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. Solid Supported Aryl/Heteroaryl C−N Cross-Coupling Reactions. *Tetrahedron Lett.* **1999**, *40*, 1623−1626.

(5) Combs, A. P.; Rafalski, M. N-Arylation of Sulfonamides on Solid Supports. *J. Comb. Chem.* **2000**, *2*, 29−32.

(6) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-Arylation with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.

(7) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.

(8) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New Aryl/Heteroaryl C−N Bond Cross-Coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation. *Tetrahedron Lett.* **1998**, *39*, 2941−2944.

(9) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. Copper-Promoted C−N Bond Cross-Coupling with Hypervalent Aryl Siloxanes and Room-Temperature N-Arylation with Aryl Iodide. *J. Am. Chem. Soc.* **2000**, *122*, 7600−7601.

(10) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. Copper Promoted Aryl/Saturated Heterocyclic C−N Bond Cross-Coupling with Arylboronic Acid and Arylstannane. *Synlett* **2000**, 674−676.

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