Palladium-Catalyzed Suzuki–Miyaura Reactions of Potassium Aryl- and Heteroaryltrifluoroborates with Aryl- and Heteroaryl Triflates

Gary A. Molander,* Daniel E. Petrillo, Nicole R. Landzberg, John C. Rohanna, Betina Biolatto

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, USA
Fax +1(215)5737165; E-mail: gmolandr@sas.upenn.edu

Received 23 March 2005

Abstract: The Suzuki–Miyaura cross-coupling of potassium aryl- and heteroaryltrifluoroborates with aryl- and heteroaryl triflates is reported. The catalyst system provides good to excellent yields using sterically hindered and electronically diverse coupling partners.

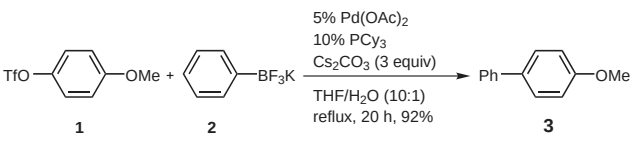
Key words: Suzuki–Miyaura, palladium, cross-coupling, biaryls, aryltrifluoroborates, aryl triflates

The Suzuki–Miyaura reaction is one of the most effective and reliable methods of forming biaryl compounds.[1] Although the synthesis of biaryls via cross-coupling procedures can be carried out using a variety of organometallic reagents, organoboron compounds possess several advantages including their ease of preparation by a variety of methods and low toxicity. Competent aryl electrophiles for the Suzuki–Miyaura reaction include aryl halides (iodides, bromides, and chlorides) and trifluoromethanesulfonates (triflates). A wide variety of functionality is tolerated in the coupling process using organoborons, making the process amenable to complex molecule synthesis.

Recently, organotrifluoroborates have been demonstrated to be effective partners in the Suzuki–Miyaura reaction as well as other carbon–carbon bond-forming reactions.[2] These reagents offer many advantages over other organoborons such as boronic acids, boronate esters and trialkylboranes. The organotrifluoroborates are easily prepared in large quantities and are indefinitely bench-stable. In contrast to boronic acids, they are monomeric species, making the determination of stoichiometry very reliable. The trifluoroborates are more atom economical than boronate esters, and the exclusive production of inorganic by-products makes work up of their coupling reactions more facile as well.

In 1996 Genêt reported the coupling of potassium aryl- and alkenyltrifluoroborates with arenediazonium tetrafluoroborates.[3] In 1999, Xia used diaryliodonium salts as electrophiles under the same conditions.[4] The coupling of tetrabutylammonium aryltrifluoroborates with aryl iodides and bromides was first described by Batey in 2001.[5] In 2002, we reported the palladium-catalyzed reaction of aryl- and heteroaryl trifluoroborates with aryl- and heteroaryl halides under ligandless[6] and ligand-assisted[7] conditions. Herein we report an expansion of this method to the synthesis of biaryl- and heterobiaryl systems using aryl triflates as electrophiles.

In a previous study of Suzuki–Miyaura couplings under ligandless conditions that was optimized for aryl halide electrophiles [0.5 mol% $Pd(OAc)_2$, K_2CO_3. MeOH],[6] only electron-poor aryl triflates underwent coupling with potassium aryltrifluoroborates. When these conditions (as well as the ligand-assisted conditions[7]) were applied to the coupling of electron rich *p*-methoxyphenyl triflate (**1**) with potassium phenyltrifluoroborate (**2**), only traces of product were seen. Because of the importance of aryl triflates as substrates for biaryl coupling, targeted optimization for these electrophiles was undertaken. A screen of catalysts, ligands, bases, and solvents led to the combination of $Pd(OAc)_2$, PCy_3, Cs_2CO_3 and THF–H_2O which produced an 80% assay yield (GC) of product in the coupling between phenyltrifluoroborate and *p*-methoxyphenyl triflate. Further optimization of catalyst loading and concentration led to a 92% isolated yield of **3** using 5 mol% $Pd(OAc)_2$, 10 mol% PCy_3, 3 equivalents of Cs_2CO_3, and a total concentration of 0.2 M in THF–H_2O (10:1, Scheme 1).



Scheme 1

To test the generality of these conditions, various aryl triflates were then coupled to potassium phenyltrifluoroborate (Table 1).

Electron-rich (entry 1), electron-poor (entries 3 and 8), and electronically neutral (entry 4) triflates all coupled in good to excellent yields with potassium phenyltrifluoroborate. Sterically hindered (entry 5) and naphthyl triflates (entries 2 and 6) coupled smoothly. Additionally, a heteroaryl triflate (entry 9) underwent the coupling reaction, giving 8-phenylquinoline in good yield.

Interestingly, when the bromophenyl triflate (entry 7) was used as the electrophile, coupling occurred at the bromide rather than the triflate. However, when the chlorophenyl triflate (entry 8) was subjected to the optimized conditions, coupling occurred at the triflate. This is consistent

SYNLETT 2005, No. 11, pp 1763–1766
Advanced online publication: 14.06.2005
DOI: 10.1055/s-2005-871544; Art ID: Y00205ST

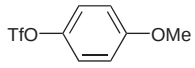
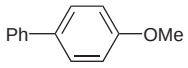
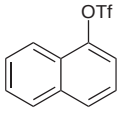
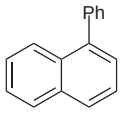
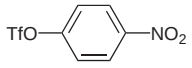
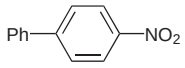
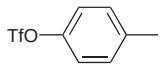
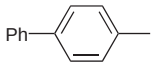
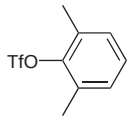
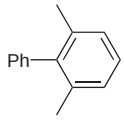
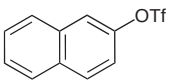
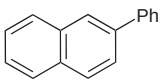
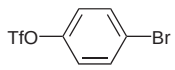
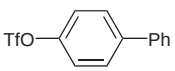
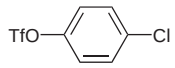
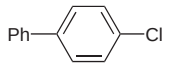
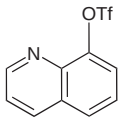
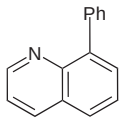
with our previous observations for the cross-coupling of potassium alkyltrifluoroborates with aryl electrophiles, in which the order of reactivity is Br > OTf > Cl.[8]

Electronically diverse potassium aryltrifluoroborates were then reacted under the optimized conditions (Table 2).

Electron-rich (entry 2), electron-poor (entries 4 and 6), and electronically neutral (entry 3) aryltrifluoroborates all coupled, providing good to excellent yields of the desired products. A heteroaryltrifluoroborate (entry 1) coupled to **1** in good yield as well.

In summary, potassium aryltrifluoroborates are readily prepared, easily handled, and stable to indefinite storage. Their outstanding physical properties and synthetic utility as described herein, combined with the facile preparation of aryl triflates from phenol derivatives, allows an important new entry to a wide array of functionalized biaryls.

Table 1 Reaction of Potassium Phenyltrifluoroborate with Aryl Triflates[a]

Entry	ArOTf	Product	Yield of Product (%)
1			92
2			86
3			65
4			94
5			83
6			92
7			43
8			82
9			81

[a] Conditions: $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), Cs_2CO_3 (3 equiv), THF–H_2O (10:1), reflux.

4-Methoxybiphenyl[9] – General Procedure A for Suzuki Coupling of Potassium Aryltrifluoroborates with Aryl Triflates

Tricyclohexylphosphine (0.10 mmol, 0.028 g) was added to a dry, 2-neck 25 mL flask equipped with a stirbar, reflux condenser and septum in a glove box. The flask was removed from the glove box and placed under nitrogen gas. Potassium phenyltrifluoroborate[10] (1.20 mmol, 0.221 g), Cs_2CO_3 (3.00 mmol, 0.975 g), and palladium acetate (0.050 mmol, 0.011 g) were sequentially added to the flask. After addition, the flask and condenser were evacuated and refilled with nitrogen. 4-Methoxyphenyl triflate (1.00 mmol, 0.256 mL) and THF–H_2O (4.55 mL:0.45 mL) were then added to the flask. The mixture was heated at reflux for 20 h at which point GC-MS indicated consumption of the triflate. The resulting mixture was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (4 × 10 mL), and the organic layer was then washed with brine. The organic layer was then dried with $MgSO_4$ and concentrated. The resulting product was purified by flash chromatography (0.5% EtOAc–hexanes) to give 0.169 g (92%) of 4-methoxybiphenyl. Product appearance: white solid; mp 87.5–88.5 °C; R_f = 0.37 (5% EtOAc–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (t, *J* = 6.7 Hz, 4 H), 7.49 (t, *J* = 8.0 Hz, 2 H), 7.38 (t, *J* = 6.7 Hz, 1 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.3, 55.3.

4-(3-Thienyl)anisole[11] – General Procedure B for Suzuki Coupling of Aryltrifluoroborates with Aryl Triflates

In a glove box, tricyclohexylphosphine (0.20 mmol, 0.056 g) was added to a dry, 10 mL flask or 20 mL vial. The flask was removed from the glove box and the phosphine was dissolved in THF (1 mL) under nitrogen gas. Potassium 3-thienyltrifluoroborate (2.40 mmol, 0.456 g), Cs_2CO_3 (6.00 mmol, 1.95 g), and palladium acetate (0.10 mmol, 0.022 g) were sequentially added to a separate 25 mL, 2-neck round-bottomed flask. After addition, the flask was evacuated and refilled with nitrogen. 4-Methoxyphenyl triflate (2.00 mmol, 0.512 g), THF (8 mL), and H_2O (0.9 mL) were added to the flask. The solution of the phosphine was then added via double-ended needle to the reaction vessel. The mixture was heated at reflux for 48 h at which point GC-MS revealed consumption of starting material. The resulting mixture was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (4 × 20 mL) and the organic layer was washed with brine, dried with $MgSO_4$, and concentrated. The resulting product was purified by flash chromatography (1.0% EtOAc–hexanes) to give 0.300 g (79%) of 4-thienylanisole. Product appearance: yellow solid; mp 123–125 °C; R_f = 0.15 (1% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.52 (m, 2 H), 7.38–7.34 (m, 3 H), 6.95–6.93 (m, 2 H), 3.84 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 142.2, 128.9, 127.7, 126.4, 126.2, 119.1, 55.5.

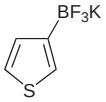
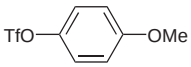
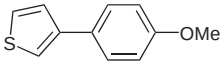
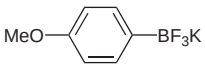
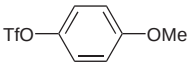
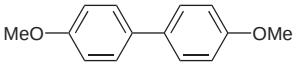
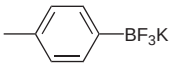
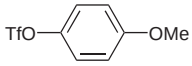
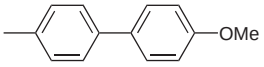
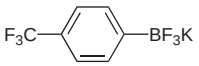
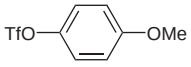
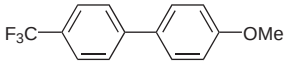
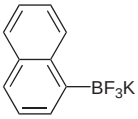
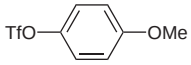
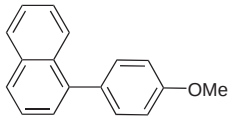
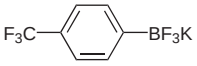
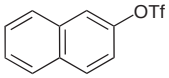
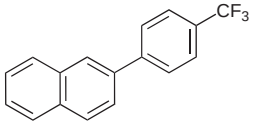
1-Phenylnaphthalene[12]

General procedure A was used, but the reaction was heated at reflux for 22 h. Yield 86%. Product appearance: colorless oil. R_f = 0.33 (0.5% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.5 Hz, 1 H), 8.19 (d, *J* = 8.6 Hz, 1 H), 8.13 (d, *J* = 7.7 Hz, 1 H), 7.83–7.69 (m, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.9, 140.4, 133.9, 131.8, 130.2, 128.8, 128.4, 128.3, 127.7, 127.3, 127.0, 126.1, 125.8, 125.5.

4-Nitrobiphenyl[13]

General procedure A was used, but the reaction was heated at reflux for 4 h. Yield 65%. Product appearance: yellow solid; mp 107.5–108.0 °C; R_f = 0.35 (5% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.3 Hz, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 7.64–7.62 (m, 1 H), 7.53–7.44 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6, 147.1, 138.8, 129.2, 129.0, 127.8, 127.4, 124.1.

Table 2 Reaction of Potassium Aryltrifluoroborates with Aryl Triflates[a]

Entry	$ArBF_3K$	ArOTf	Product	Yield (%)
1				79
2				76
3				66
4				59
5				71
6				92

[a] Conditions: $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), Cs_2CO_3 (3 equiv), THF–H_2O (10:1), reflux.

4-Methylbiphenyl[12]
General procedure B was used, but the reaction was heated at reflux for 22 h. Yield 94%. Product appearance: white solid; R_f = 0.32 (hexanes); mp 43.5–44.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 7.7 Hz, 2 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 7.37 (t, *J* = 7.7 Hz, 1 H), 7.30 (d, *J* = 7.7 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.3, 138.5, 137.2, 129.6, 128.8, 127.1, 127.1, 21.2.

2,6-Dimethylbiphenyl[14]
General procedure B was used, but the mixture was heated for 72 h. Yield 83%. Product appearance: colorless oil; R_f = 0.33 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.12 (m, 8 H), 2.05 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.0, 141.2, 136.2, 129.2, 128.6, 127.4, 127.2, 126.7, 21.0.

2-Phenylnaphthalene[15]
General procedure A was used, but the reaction was heated at reflux for 20 h. Yield 92%. Product appearance: white solid; mp 100–101 °C; R_f = 0.27 (5% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.1 (s, 1 H), 7.98–7.91 (m, 3 H), 7.84–7.77 (m, 3 H), 7.60–7.52 (m, 4 H), 7.47–7.43 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.3, 138.7, 133.8, 132.8, 129.0, 128.6, 128.3, 127.8, 127.6, 127.5, 126.4, 126.0, 125.9, 125.7.

4-Trifluoromethylsulfonyloxybiphenyl[16]
General procedure B was used, but the mixture was heated for 48 h. Yield 43%. Product appearance: yellow solid; mp 57–61 °C. R_f = 0.22 (1% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.34 (m, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.1, 141.9, 139.5, 129.1, 129.0, 128.2, 127.4, 121.8, 118.9 (q, J_{CF} = 321.4 Hz).

4-Chlorobiphenyl[17]
General procedure B was used, but the reaction was heated at reflux for 24 h. Yield 82%. Product appearance: white solid; mp 76.0–76.5 °C; R_f = 0.34 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57–7.35 (m, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.2, 139.8, 133.5, 129.1, 129.0, 128.5, 127.7, 127.1.

8-Phenylquinoline[18]
General procedure B was used, but the mixture was heated for 24 h. Yield 81%. Product appearance: brown oil; R_f = 0.16 (5% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.97 (dd, *J* = 4.2, 1.8 Hz, 1 H), 8.21 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.83 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.76–7.73 (m, 3 H), 7.61 (t, *J* = 7.3 Hz, 1 H), 7.53–7.50 (m, 2 H), 7.44–7.40 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.4, 146.2, 141.1, 139.7, 136.4, 130.4, 130.4, 128.9, 128.1, 127.7, 127.5, 126.4, 121.1.

4-4′-Dimethoxybiphenyl[19]
General procedure A was used, but the reaction was heated at reflux for 38 h. Yield 76%. Product appearance: off-white solid; mp 172–173 °C; R_f = 0.27 (2.5% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.4 Hz, 4 H), 6.98 (d, *J* = 8.8 Hz, 4 H), 3.86 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 133.6, 127.9, 114.3, 55.5.

4-Methoxy-4′-methylbiphenyl[20]
General procedure A was used, but the reaction was heated at reflux for 21 h. Yield 66%. Product appearance: white solid. Recrystallization from EtOH gave an analytical sample (42%); mp 107–108 °C; R_f = 0.32 (2.5% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 9.6 Hz, 2 H), 7.55 (d, *J* = 7.9 Hz, 2 H), 7.32 (d, *J* = 7.7 Hz, 2 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 3.91 (s, 3 H), 2.48 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 138.1, 136.5, 133.9, 128.1, 126.7, 114.3, 55.5, 21.2.

4-Methoxy-4′-(trifluoromethyl)biphenyl[21]
General procedure B was used, but the mixture was heated for 40 h. Yield 59%. Product appearance: white solid; mp 117–121 °C; R_f = 0.14 (1% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ =

7.68–7.64 (m, 4 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 144.4, 132.3, 128.8 (q, J_{CF} = 32.6 Hz), 128.5, 127.0, 125.8 (q, J_{CF} = 3.8 Hz), 125.6 (q, J_{CF} = 271.6 Hz), 114.6, 55.5.

1-(4-Methoxyphenyl)naphthalene[21]

General procedure A was used, but the reaction was heated at reflux for 3.5 h. Yield 71%. Product appearance: off-white solid; mp 113–115 °C; R_f = 0.11 (1% EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.9 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.59–7.45 (m, 6 H), 7.11–7.08 (m, 2 H), 3.94 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 140.0, 134.0, 133.3, 132.0, 131.2, 128.4, 127.5, 127.0, 126.2, 126.0, 125.8, 125.5, 113.9, 55.4.

2-(4-Trifluoromethylphenyl)naphthalene

General procedure A was used, but the reaction was heated at reflux for 24 h. Yield 92%. Product appearance: white solid; mp 127–129 °C; R_f = 0.35 (EtOAc–hexanes 1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.99–7.89 (m, 3 H), 7.85–7.77 (m, 5 H), 7.60–7.53 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.8, 137.2, 133.7, 133.1, 129.5 (q, J_{CF} = 32.6 Hz), 128.9, 128.5, 127.8, 127.8, 126.7, 126.6, 126.5, 125.9 (q, J_{CF} = 3.8 Hz), 125.3, 124.5 (q, J_{CF} = 271.6 Hz). IR (KBr): 3062, 2368, 1926, 1617, 1595, 1503, 1436, 1408, 1339, 1114, 1076, 1009 cm^{-1}. Anal. Calcd for $C_{17}H_{11}F_3$: C, 74.99; H, 4.07. Found: C, 75.04; H, 3.98.

Acknowledgment

The authors wish to thank the NIH, Johnson & Johnson, Merck Research Laboratories, and Amgen for their support of this program. We thank Johnson-Matthey for the generous donation of palladium catalysts used in this study.

References

(1) (a) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, **1998**. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(2) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313.
(3) (a) Darses, S.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4394. (b) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875.
(4) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457.
(5) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099.
(6) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
(7) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
(8) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.
(9) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276.
(10) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.
(11) Rieke, R. D.; Kim, S.-H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921.
(12) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266.
(13) Wallow, T. L.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.
(14) Kamikawa, T.; Hayashi, T. *Synlett* **1997**, 163.
(15) Kim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049.
(16) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(17) Klement, I.; Rottlander, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201.
(18) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.
(19) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205.
(20) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058.
(21) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357.