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Palladium–Phosphinous Acid-Catalyzed NaOH-Promoted Cross-Coupling Reactions of Arylsiloxanes with Aryl Chlorides and Bromides in Water

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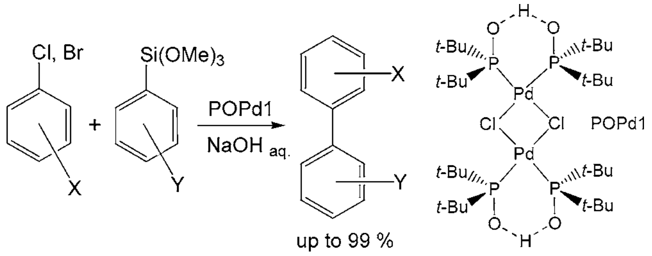
ABSTRACT



A palladium–phosphinous acid-catalyzed and NaOH-promoted coupling method using arylsiloxanes and aryl halides in water has been developed. The POPd1-catalyzed reaction between aryl chlorides or bromides and arylsiloxanes is compatible with various functional groups and affords biaryls in up to 99% yield. This cross-coupling reaction does not require additives such as surfactants or organic cosolvents and proceeds under air, which greatly facilitates operation and catalyst handling.

Palladium-catalyzed cross-coupling methods utilizing aryl halides and boronic acids, organostannanes, organosiloxanes, organozinc compounds, or Grignard reagents have found widespread popularity in synthetic chemistry.[1] One of the major remaining limitations to most currently available cross-coupling methods is the need for highly toxic and reactive organometallic substrates that require inert reaction conditions and anhydrous solvents. The replacement of expensive, hazardous, and flammable organic solvents by water is highly desirable for reducing costs and for developing environmentally benign synthetic processes. To date, few examples of aqueous Suzuki,[2] Buchwald−Hartwig,[3] Sonogashira,[4] Stille,[5] and Heck reactions[6] have been reported.[7] The introduction of amphiphilic resin-supported palladium catalysts and microwave-assisted Suzuki couplings using palladium acetate has provided new means for time-efficient and versatile high-throughput cross-coupling reactions in aqueous solutions.[8] Since Hiyama introduced arylfluorosilanes to the Pd-catalyzed coupling reaction with aryl iodides,[9] others have employed alkenylalkoxysilanes in fluoride-promoted coupling reactions of alkenyl and aryl halides.[10] Lee and co-workers reported efficient cross-couplings of aryl chlorides and bromides with phenyl- or vinyltrimethoxysilane mediated

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[1] (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Miyaura, N., Ed. *Cross-Coupling Reactions*; Springer: Berlin, 2002.

[2] (a) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170−7173. (b) Uozomi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. (c) Gelpke, A. E. S.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Hiemstra, H. *Tetrahedron* **1999**, *55*, 6657−6670. (d) Paetzold, E.; Oehme, G. *J. Mol. Catal. A: Chem.* **2000**, *152*, 69−76. (e) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *3*, 1555−1557. (f) Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757−2759. (g) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523−6526. (h) Ueda, M.; Nishimura, M.; Miyaura, N. *Synlett* **2000**, 856−858. (i) Botella, L.; Najera, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 179−181. (j) Botella, L.; Najera, C. *J. Organomet. Chem.* **2002**, *663*, 46−57. (k) Alonso, D. A.; Najera, C.; Pacheco, M. A. *J. Org. Chem.* **2002**, *67*, 5588−5594. (l) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466−467. (m) Li, C.-J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4856−4858.

[3] Wuellner, G.; Jaensch, H.; Kannenberg, S.; Schubert, F.; Boche, G.; *Chem. Commun.* **1998**, 1509−1510.

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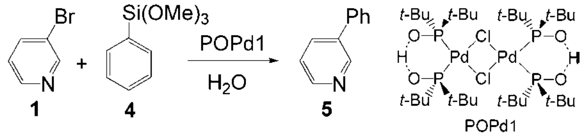
by palladium acetate in the presence of an imidazolium chloride.[11] DeShong at al. employed vinyl and aryl halides, aryl triflates, and allylic benzoates in Pd-catalyzed cross-coupling reactions with hypervalent siloxanes.[12] Notably, Denmark and others have developed a variety of Lewis base-promoted stereoselective reactions utilizing hypervalent silicates as active intermediates.[13] Because of the increasing availability and remarkable reactivity in conjugate additions to α,β-unsaturated carbonyl compounds or Hiyama-like coupling reactions,[14] organosiloxanes have recently been employed in aqueous transition metal-catalyzed C−C bond-forming reactions using 10−40% water in dioxane.[15] However, aqueous Hiyama-type coupling procedures developed to date require aryl bromides and substantial amounts of organic cosolvents but do not proceed with less reactive aryl chlorides.

Recently, we and others reported the use of highly active palladium−phosphinous acid complexes in various C−C, C−N, and C−S bond-forming reactions using a wide range of aryl halides.[16] Because of the remarkable stability of this class of catalysts to air and water and on the basis of our previously reported findings that palladium−phosphinous acid complex $[[(t\text{-Bu})_2P(OH)(t\text{-Bu})_2PO)]PdCl]_2$ (POPd1) catalyzes Hiyama-type reactions of aryl halides in the presence of tetrabutylammonium fluoride in organic solvents in good to high yields,[16e] we decided to employ POPd1 in cross-coupling reactions between aryl chlorides or bromides and arylsiloxanes using water as the solvent. Initially, we employed 3-bromopyridine, **1**, 3-chloropyridine, **2**, and 2-methyl-4-chloroquinoline, **3**, and various arylsiloxanes in optimization studies to elucidate the feasibility of palladium−phosphinous acid-catalyzed Hiyama-type cross-coupling in water (Scheme 1).

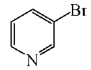
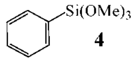
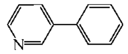
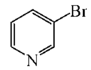
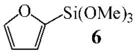
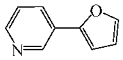
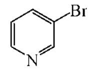
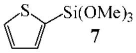
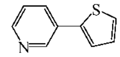
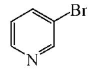
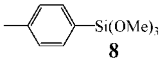
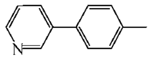
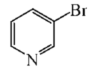
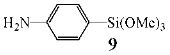
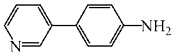
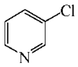
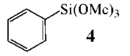
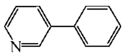
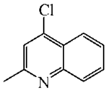
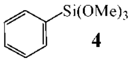
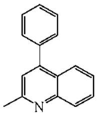
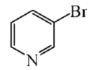
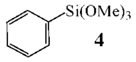
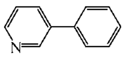
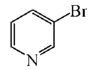
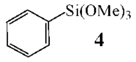
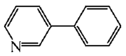
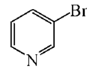
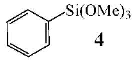
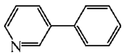
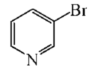
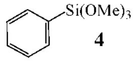
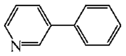
Scheme 1. POPd1-Catalyzed Cross-Coupling of 3-Bromopyridine, **1**, and Phenyltrimethoxysilane, **4**[a]



[a] Typical cross-coupling procedure. A mixture of 100 mg of **1**, 2 equiv of **4**, and 7 mol % of POPd1 was stirred in 5 mL of 0.5 M NaOH at 135 °C for 24 h. All reactions were carried out using a high-pressure vessel (i.d. 31.7 cm) made of 4.0 mm Pyrex 7740 heavy wall glass and equipped with a 4 mm bore valve and Aegis backing O-ring.

We were pleased to find that **1** and **4** afford 3-phenylpyridine, **5**, in 95% yield in the presence of 7 mol % POPd1 and 1 equiv of TBAF dissolved in deionized water (Table 1, entry 1). Replacement of **4** by 2-furan-, 2-thiophen-, 4-tolyl-, and 4-anilinotrimethoxysilane, **6**−**9**, gave the corresponding cross-coupling products **10**−**13** in 61−90% yield (entries 2−5). As expected, aryl chorides give lower yields than bromides (compare entries 1 and 6). It has been assumed

Table 1. Screening of Aqueous Hiyama-Type Cross-Coupling Reaction Conditions[a]

entry	aryl halide	arylsiloxane	product	yield (%)
1[b]	 **1**	 **4**	 **5**	95
2[b]	 **1**	 **6**	 **10**	61
3[b]	 **1**	 **7**	 **11**	73
4[b]	 **1**	 **8**	 **12**	90
5[b]	 **1**	 **9**	 **13**	75
6[b]	 **2**	 **4**	 **5**	69
7[b]	 **3**	 **4**	 **14**	73
8[c]	 **1**	 **4**	 **5**	90
9[d]	 **1**	 **4**	 **5**	99
10[d,e]	 **1**	 **4**	 **5**	80
11[d,f]	 **1**	 **4**	 **5**	90

[a] General conditions: A mixture of 100 mg of aryl halide, 2.0 equiv of arylsiloxane, and 7 mol % POPd1 in 5 mL of deionized water was heated to 135−140 °C for 24 h in a closed vessel. [b] In the presence of 1 equiv of TBAF. [c] In the presence of 0.1 M NaOH. [d] In the presence of 0.5 M NaOH. [e] Performed with 1 equiv of **4**. [f] $T = 100$ °C.

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(4) (a) Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829−39. (b) Hessler, A.; Stelzer, O.; Dibowski, H.; Worm, K.; Schmidtchen, F. P. *J. Org. Chem.* **1997**, *62*, 2362−2369. (c) Lopez-Deber, M. P.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, *3*, 2823−2826.

(5) (a) Roshchin A. I.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, *36*, 125−128. (b) Rai, R.; Aubrecht, K. B.; Collum, D. B. *Tetrahedron Lett.* **1995**, *36*, 3111−3114. (c) Kang, S.-K.; Baik, T.-G.; Song, S.-Y. *Synlett* **1999**, *3*, 327−329.

(6) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715−717.

(7) (a) Genet, P. J.; Savignac, M. *J. Organometallic Chem.* **1999**, *576* (1-2), 305−317. (b) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997−1999. (c) Najera, C.; Gil-Molto, J.; Karlstrom, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451−1454.

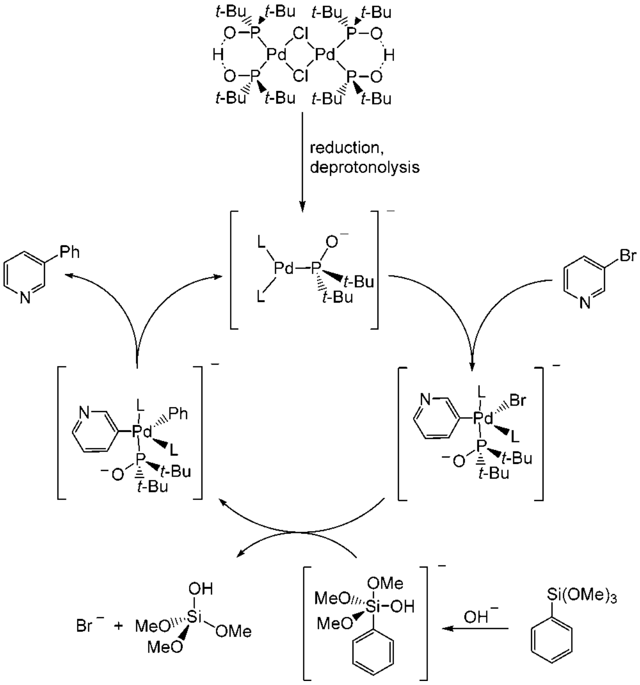
(8) (a) Uozomi, Y.; Nakai, Y. *Org. Lett.* **2002**, *4*, 2997−3000. (b) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888−892.

(9) (a) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711−1714. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471−1478. (c) Hagiwara, E.; Gouda, K.-I.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439−442. (d) Gouda, K.-I.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232−7233. (e) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58−61.

(10) (a) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051−6054. (b) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309−1310. (c) Hanamoto, T.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 6354−6359.

(11) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053−2055.

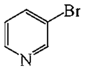
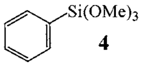
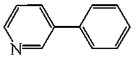
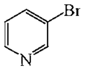
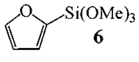
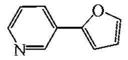
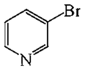
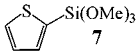
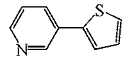
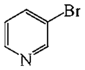
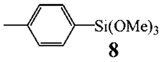
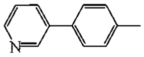
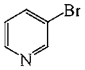
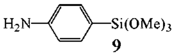
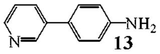
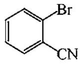
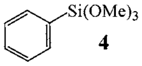
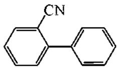
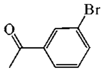
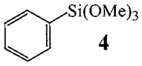
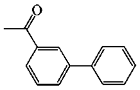
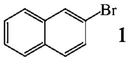
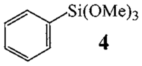
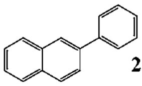
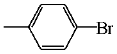
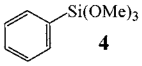
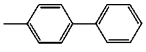
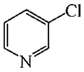
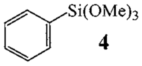
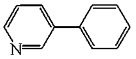
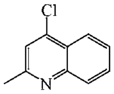
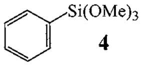
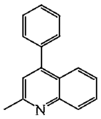
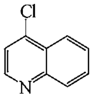
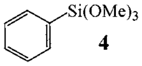
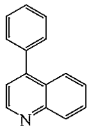
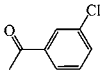
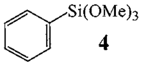
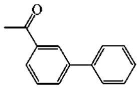
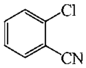
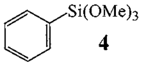
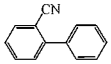
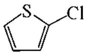
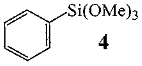
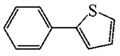
Scheme 2. Proposed Catalytic Cycle of the NaOH-Promoted POPd1-Catalyzed Cross-Coupling Reaction



that palladium−phosphinous acids undergo reduction and deprotonolysis in the presence of a base to form a highly active anionic Pd(0) complex.[16] We rationalized that generation of such an electron-rich phosphine-containing Pd complex should proceed in the presence of aqueous sodium hydroxide. In addition, formation of a pentavalent silicate should also be feasible under basic aqueous conditions through nucleophilic attack of a hydroxide ion at the arylsiloxane (Scheme 2). It is well-known that cross-coupling reactions require subsequent oxidative addition of the aryl halide to the catalyst, transmetalation, and reductive elimination to form the biaryl product and to regenerate the catalytically active species. Because arylsiloxanes are less reactive than their corresponding stannanes or boronic acids, they need to be activated to undergo transmetalation with the palladium complex. This can be accomplished via formation of a hypervalent sp^{3}d-hybridized siloxane in the presence of TBAF or hydroxide ions. Thus, sodium hydroxide would fulfill two fundamental functions, i.e., activation of the catalyst for oxidative addition and activation of the arylsiloxane for the transmetalation step.

Indeed, we obtained biaryl **5** using 0.1 M NaOH solution in 90% yield, and further optimization of the NaOH concentration increased the yield to 99% (Table 1, entries 8 and 9). It is noteworthy that this procedure does not require any surfactant additives or organic cosolvents and proceeds under air, which greatly facilitates operation and catalyst handling. Employing equimolar amounts of **4** in the coupling reaction with **1** or reducing the reaction temperature to 100 °C reduced the yields of biaryl **5** to 80 and 90%, respectively (Table 1, entries 10 and 11).

Table 2. Cross-Coupling of Arylsiloxanes and Aryl Halides in Water[a]

entry	aryl halide	arylsiloxane	product	yield (%)
1	 **1**	 **4**	 **5**	99
2	 **1**	 **6**	 **10**	66
3	 **1**	 **7**	 **11**	75
4	 **1**	 **8**	 **12**	92
5	 **1**	 **9**	 **13**	77
6	 **15**	 **4**	 **23**	81
7	 **16**	 **4**	 **24**	90
8	 **17**	 **4**	 **25**	77
9	 **1**	 **4**	 **26**	71
10	 **2**	 **4**	 **5**	72
11	 **3**	 **4**	 **14**	81
12	 **19**	 **4**	 **27**	88
13	 **20**	 **4**	 **24**	90
14	 **21**	 **4**	 **23**	77
15	 **22**	 **4**	 **28**	44

[a] All reactions were carried out with 100 mg of aryl halide, 2.0 equiv of arylsiloxane, and 7 mol % POPd1 in 5 mL of 0.5 M NaOH at 135−140 °C for 24 h using a closed vessel.

To demonstrate the scope of NaOH-promoted POPd1-catalyzed C−C bond formation we applied our optimized procedure to a variety of aryl halides and arylsiloxanes (Table 2). Coupling of bromide **1** with siloxanes **4** and **6**−**9** in 0.5 M NaOH gave slightly better results than we had obtained using aqueous TBAF solutions (entries 1−5). We observed that ortho-substituted aryl halides **15** and **21** undergo coupling in 77−81% yield, and cyano, ketone, amino, and heteroaryl groups are well tolerated (entries 2, 3, 5−7, 13−15).

As expected, electron-deficient pyridyl and quinolyl chlorides readily undergo POPd1-catalyzed cross-coupling in 72−88% yields (Table 2, entries 10−12). Unactivated, electron-rich aryl chlorides are commonly known to reluctantly undergo oxidative addition to transition metals and therefore provide low yields in cross-coupling reactions. Accordingly, we obtained relatively low yields for the synthesis of 2-phenylthiophene, **28**, from 2-chlorothiophene, **22** (entry 15). However, the availability of siloxanes **6**, **7**, and **9** provides a successful cross-coupling strategy for the preparation of biaryls exhibiting an electron-rich aryl ring (entries 2, 3, and 5).

In summary, a variety of aryl halides and arylsiloxanes have successfully been employed in NaOH-promoted POPd1-catalyzed cross-coupling reactions to afford biaryls in good to high yields. This facile coupling reaction proceeds in 0.5 M aqueous NaOH solution under air and in the absence of commonly used additives such as CsF and TBAF or other surfactants. We have thus developed an environmentally benign cross-coupling method that utilizes an air-stable palladium−phosphinous acid complex in water while avoiding toxic reagents such as stannanes and the use of hazardous organic cosolvents. The mechanism of the catalytic process, including the structure of the resting state of the active palladium catalyst and the role of NaOH in activating the palladium−phosphinous acid and in promoting transmetalation of arylsiloxanes, is currently under investigation in our laboratories.

Acknowledgment. We thank Combiphos Catalysts, Inc., New Jersey (www.combiphos.com) for POPd1.

Supporting Information Available: Experimental procedures and full characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Brescia, M.-R.; DeShong, P. *J. Org. Chem.* **1998**, *63*, 3156−3157. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688. (c) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137−2140. (d) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem.* **2000**, *72*, 1655−1658. (e) Riggleman, S.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 8106−8109. (f) Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159−7165. (g) Hoke, M., E.; Brescia, M.-R.; Bogaczyk, S.; DeShong, P.; King, B. W.; Crimmins, M. T. *J. Org. Chem.* **2002**, *67*, 327−335.

(13) (a) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448. (b) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *115*, 6392−6393. (c) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407−408. (d) Denmark, S. E.; Winter, S. B. D.; Su, X. P.; Wong, K. T. *J. Am. Chem. Soc.* **1996**, *118*, 7404−7405. (e) Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333−2334. (f) Denmark, S. E., Winter, S. B. D. *Synlett* **1997**, 1087−1089. (g) Denmark, S. E.; Stavenger, R. A.; Wong, K. T.; Su, X. P. *J. Am. Chem. Soc.* **1999**, *121*, 4982−4991. (h) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837−8847. (i) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3473−3476. (j) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477−3480. (k) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846.

(14) (a) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569−8571. (b) Murata, S.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, *40*, 9255−9257. (c) Denmark, S. E.; Amishiro, N. *J. Org. Chem.* **2003**, *68*, 6997−7003.

(15) (a) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667−669. (b) Huang, T. S.; Li, C. J. *Chem. Commun.* **2001**, 2348−2349. (c) Murata, M.; Shimazaki, R.; Watanabe, S.; Masuda, Y. *Synthesis* **2001**, 2231−2233.

(16) (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. (b) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677−8681. (c) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643−3650. (d) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077−7084. (e) Wolf, C.; Lerebours, R.; Tanzini, E. H. *Synthesis* **2003**, 2069−2073. (f) Yang, W.; Wang, Y.; Corte, J. R. *Org. Lett.* **2003**, *5*, 3131−3134. (g) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551−7554.