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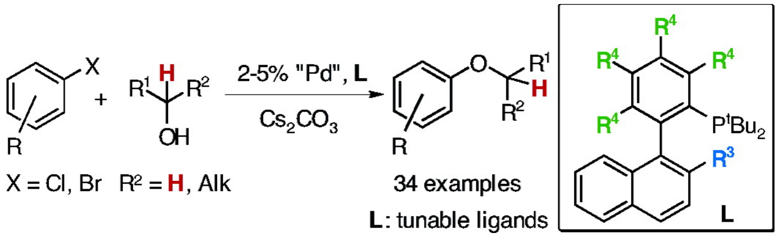

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Use of Tunable Ligands Allows for Intermolecular Pd-Catalyzed C−O Bond Formation

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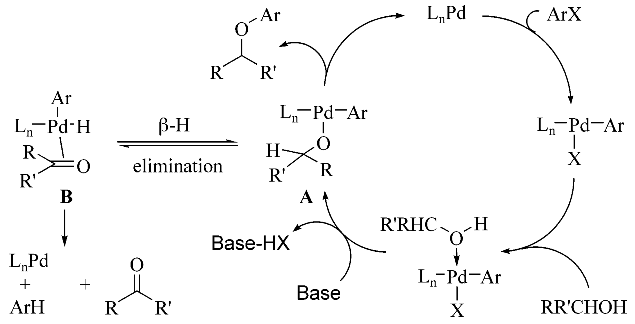
Abstract: Bulky biaryl phosphine ligands facilitate Pd-catalyzed C−O coupling reactions of aryl halides with primary and secondary alcohols by promoting reductive elimination at the expense of β-hydride elimination. The key to their success is the ability to match the size of the ligand to that of the combination of substrates. The efficient coupling of a number of unactivated aryl chlorides and bromides with cyclic and acyclic secondary alcohols was achieved. This included the coupling of allylic alcohols for the first time in a Pd-catalyzed coupling process.

The Pd-catalyzed formation of C−N bonds has become a general method for the preparation of aniline derivatives from the reaction of aryl halides or sulfonates and amines.[1] The analogous process for the addition of alcohols to produce aromatic ethers has also been successfully accomplished.[2] However, except for intramolecular C−O bond-forming processes,[2a,g] the success of the method greatly depends on the partitioning of the alkoxide intermediate **A** between aryl ether product or the product of β-hydride elimination, **B** (Scheme 1). Thus, while coupling with tertiary alcohols,[2b,e,f,h] phenols,[2c,d] and silanols[2f] is not affected by this dichotomy, the reactions of primary and secondary alcohols often produce large amounts of arene byproduct. In 2001 we reported[3] the first examples of Pd-catalyzed coupling of primary alcohols with unactivated aryl chlorides and bromides. Excellent results were obtained with aryl halides with one or two ortho-substituents, which facilitate the rate of reductive elimination from **A**. In the absence of such ortho-substitution, however, the reactions of unactivated aryl halides gave only poor to moderate yields. In all of these cases it was necessary to use **L2** to achieve satisfactory results. Unfortunately, we do not have an efficient synthesis of this ligand. Attempts to extend our method to include secondary alcohol substrates were successful only in reactions with ortho,-ortho′-disubstituted aryl halides.[3] A mild catalytic method for the preparation of aryl *sec*-alkyl ethers would complement existing techniques including Mitsunobu processes[4] and the copper-catalyzed coupling of aryl iodides and secondary alcohols,[5] since the former is often complicated by formation of byproducts and the latter suffers from slow reaction rates. Precedent existed[2,3] to indicate that bulky ligands could facilitate Pd-catalyzed C−O coupling reactions by promoting reductive elimination at the expense of β-hydride elimination. However, the need to accomplish this and yet accommodate coupling partners of various sizes has made the search for general ligands for these processes difficult. The general notion of devising modular syntheses of ligands that allow the tuning of steric and electronic properties to accommodate a given substrate combination has been used to advantage in many instances.[6] Herein we disclose the development of such a ligand system for Pd-catalyzed C−O coupling of primary and secondary alcohols, including allylic alcohols, with unactivated aryl chlorides and bromides. The key to our success is the ability to match the size of the ligand to that of the combination of substrates.

Scheme 1. Pd-Catalyzed C−O Coupling of Primary and Secondary Alcohols



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10.1021/ja050471r CCC: $30.25

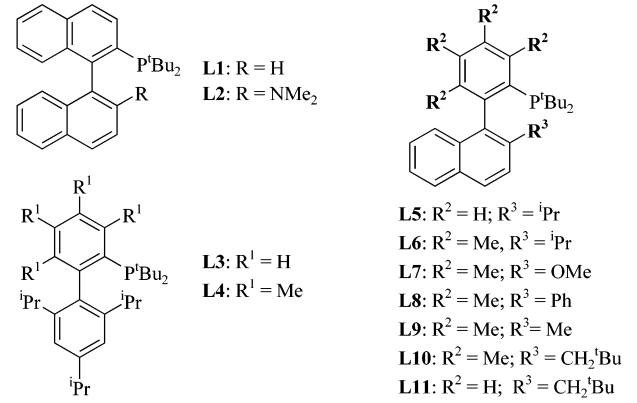
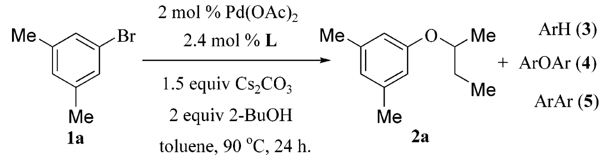


Figure 1. Ligands for Pd-catalyzed C−O coupling.

Table 1. Coupling of 5-Bromo-*m*-xylene with 2-Butanol[a,b]

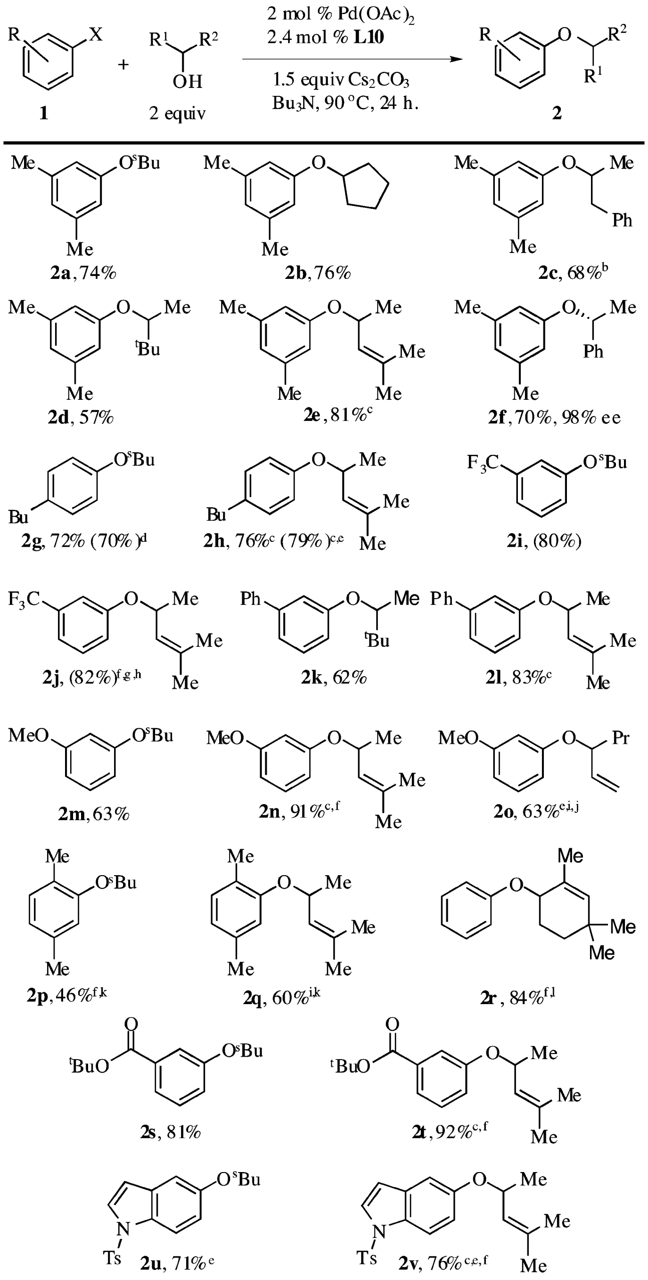


entry	ligand	**1a**, %	**2a**, %	**3**, %	**4**, %	**5**, %
1	L1	−	1	94	−	−
2	L2	−	48	42	4	2
3	L3	−	7	80	4	3
4	L4	26	4	14	31	12
5	L5	−	31	60	2	−
6	L6	−	42	27	19	6
7	L7	13	19	38	4	10
8	L8	16	25	26	15	7
9	L9	2	26	49	7	5
10	L10	−	53	31	7	5
11[c]	L10	−	76	5	4	6

[a] Conditions: 2 mol % of $Pd(OAc)_2$, 2.4 mol % of **L**, 2 equiv of 2-BuOH, 1.5 equiv of Cs_2CO_3, toluene, 90 °C, 24 h. [b] GC yields. [c] In Bu_3N.

An initial screen was performed using **L1**−**L6** (Figure 1) for the coupling reaction of **1a** and 2-BuOH. This produced, in addition to the desired coupling product (**2a**), side products: arene (**3**), diaryl ether[7] (**4**), and biaryl (**5**) (Table 1).[8] Use of ligands **L1**, **L3**, and **L5** led to the extensive formation of **3** (entries 1, 3, 5). Presumably, these were insufficiently bulky to render reductive elimination faster than β-H elimination from **A**. The results with **L4** (entry 4) were disappointing, and while employing **L2** and **L6** gave moderate yields of the coupling product **2a** (entries 2 and 6), further modification of the ligand was obviously necessary. Having increased the size of the top ring by the addition of four methyl groups, we examined the effect of changing the size of R^3. Ligands **L7**, **L8**, **L9**, with R^3 = OMe, Ph, and Me, respectively, were prepared but found to be less efficient than **L6** as supporting ligands (entries 7−9). Interestingly, replacement of isopropyl group as R^3 of **L6** by a methyl group in **L9** led to the formation of a smaller amount of diaryl ether **4** (entry 6 vs 9). Unfortunately, the decreased steric bulk in **L9** produced a lower ratio of **2a**:**3**. This ratio was improved using **L10**, in which $R^3 = CH_2{}^tBu$ (entry 10). With **L10** the formation of **3** can be almost completely suppressed if Bu_3N is used as a solvent[9] instead of toluene (entry 11). Thus, simply changing R^3 from isopropyl to neopentyl along with a solvent switch is enough to produce a synthetically useful catalyst system.

Table 2. Coupling of Aryl Halides with Secondary Alcohols[a]



[a] Isolated yields: X = Br (X = Cl). [b] 3% Pd, 3.6% **L10**. [c] 50 °C, 18 h. [d] 100 °C. [e] 5% Pd, 6% **L10**. [f] In toluene. [g] 50 °C, 8 h. [h] 1.2 equiv of Cs_2CO_3. [i] 70 °C, 18 h. [j] 1.2 equiv of alcohol. [k] With **L11**. [l] 70 °C, 24 h.

With the best conditions in hand, we examined the reaction of a number of unactivated aryl bromides and chlorides with cyclic and acyclic secondary alcohols (Table 2), which proceed in good yields. However, for more hindered 3,3-dimethylbutan-2-ol, less efficient coupling to afford **2d** and **2k** was realized. Of note, allylic alcohols, which previously were not viable substrates for these processes, are readily transformed to products, usually at a lower temperature and in higher yields

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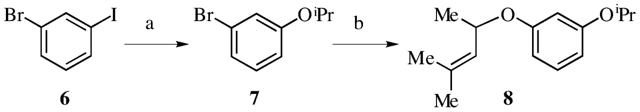
(7) The mechanism for the formation of diaryl ether **4** is not completely understood. When ^{18}O-labeled 1-phenylethanol was reacted with **1** using **L4** as a ligand, ^{18}O-**2d** (8%) and **4** (45%) were formed, the latter product without ^{18}O enrichment. Therefore, it is likely that residual H_2O and/or Cs_2CO_3 are involved in this side reaction.

(8) See Supporting Information for the details

(9) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397.

Scheme 2. Cu- and Pd-Catalyzed Sequential C−O Coupling[a]



[a] Conditions: (a) 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, 2 equiv of Cs_2CO_3, ^{i}PrOH neat, 110 °C, 24 h, 81%; (b) 3 mol % of Pd $(OAc)_2$, 3.6 mol % of **L10**, 1.5 equiv of Cs_2CO_3, Bu_3N, 50 °C, 18 h, 84%.

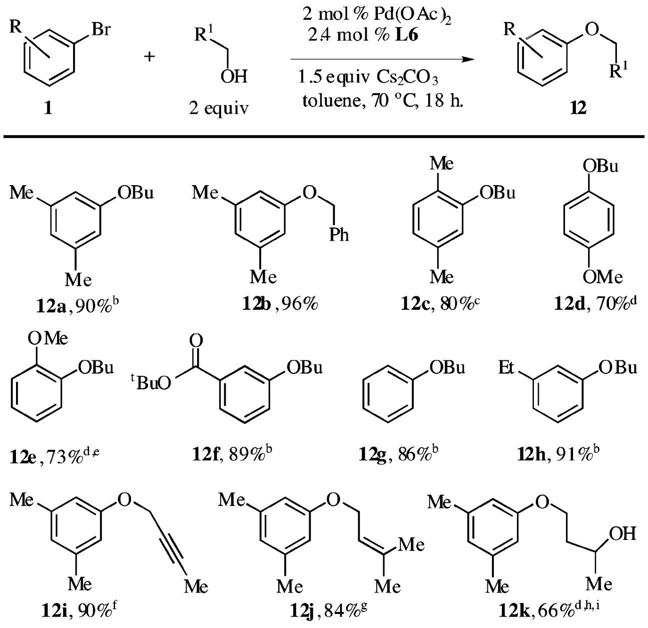
than seen with saturated alcohols. This method avoids the regiochemical issues that arise in Pd-[10] and Rh-catalyzed[11] allylic alkylation reactions of phenols. Yields were lower for the coupling of a monosubstituted allylic alcohol than for a trisubstituted one (compare **2n** and **2o**). Functional group tolerance for substituents on the aryl bromides was moderate and allowed for the formation of ester- and heterocycle-containing products **2s**−**v**. Although the reactions of most meta- and para-substituted aryl halides that we examined were well-behaved, little progress was realized with more electron-rich *o*- and *p*-bromoanisoles due to the extensive formation of arene and diaryl ether side products. Success with ortho-substituted aryl halides required the use of ligand **L11**, which is a less hindered analogue of **L10**. But even then the yields of **2p** and **2q** were only moderate, with the rest of the mass balance being **3** and **4**. Coupling of (*R*)-1-phenylethanol (98% ee) gave the product (*R*)-**2f** (98% ee) without racemization.

As was the case with C−N bond formation,[12] Pd- and Cu-catalyzed reactions can be used to advantage when performed in a tandem manner. Thus, the latter methodology allows for the selective coupling of bromoiodide **6** with ^{i}PrOH. The resulting bromide **7** can then be further transformed by treatment with secondary alcohol as shown (Scheme 2).

Major improvements in the coupling reaction of primary alcohols were achieved when the bulkier ligand, **L6**, was used in place of **L2**, which was previously the best ligand[3] (Table 3). Reduction was suppressed, where necessary, by running the reactions in Bu_3N. For *ortho*-substituted aryl bromides, **L5** must be utilized (**12c**). The most challenging substrates, electron-rich *p*- and *o*-bromoanisole, gave good yields of the coupling products **12d** and **12e** using exceptionally hindered **L4**; poor yields had previously been seen[3] with **L2**. With **L4**, the selective arylation of the primary hydroxyl of 1,3-dihydroxybutane was also possible (**12k**), without detectable coupling of the secondary hydroxyl.

The choice of ligand for Pd-catalyzed C−O bond formation is based on the nature of substrate combination being coupled (Table 4). Thus, as previously described,[3] ortho,ortho′-disubstituted aryl halides can be easily coupled using **L1** as a supporting ligand (entry 1). Less hindered *ortho*-substituted aryl halides (except for R = EDG) require the bulkier ligands **L2** or **L5** for the successful reaction with primary alcohols and **L11** with secondary alcohols (entry 2). Electron-rich aryl halides are the most challenging substrates. Their coupling with primary alcohols works moderately well using **L4**. The analogous reaction, however, with secondary alcohols could not be achieved (entries 3, 4). For all other meta- and para-substituted aryl halides, the use of **L6** and **L10** is recommended, with primary and secondary alcohols, respectively (entry 5).

Table 3. Coupling of Aryl Bromides with Primary Alcohols[a]



12a, 90%[b] **12b**, 96% **12c**, 80%[c] **12d**, 70%[d]

12e, 73%[d,e] **12f**, 89%[b] **12g**, 86%[b] **12h**, 91%[b]

12i, 90%[f] **12j**, 84%[g] **12k**, 66%[d,h,i]

[a] Isolated yields. [b] In Bu_3N. [c] With **L5**. [d] With **L4**. [e] $Pd_2(dba)_3$ (1%) was used. [f] Slow addition of the alcohol. [g] 50 °C. [h] 24 h. [i] 5% Pd, 6% **L4**.

In summary, we have developed a tunable ligand system for the coupling of primary and secondary alcohols with aryl halides. These ligands, in combination with Bu_3N as a solvent, suppress the β-H elimination pathway, allowing for the first time for the efficient coupling of secondary, including allylic, alcohols. All of these ligands are accessible by variations of our benzyne route.[13] The most general ligands **L6** and **L10** have been prepared on >10 g scale without the need for chromatographic purification. We hope to have these as well as **L4** and **L5** commercially available soon.

Experimental Section

General Procedure for the Intermolecular Coupling of Alcohols with Aryl Halides. An oven-dried Schlenk tube was cooled in vacuo, back-filled with argon, and charged with $Pd(OAc)_2$, ligand, and Cs_2CO_3. The Schlenk tube was fitted with rubber septum, evacuated, and back-filled with argon. The aryl halide and alcohol were added through the septum via syringe, followed by the solvent. The septum was replaced with a Teflon screw cap under a counterflow of argon, and the tube was sealed and placed in an oil bath. The reaction was conducted under the conditions indicated in Tables 2 and 3. After the reaction mixture was allowed to cool to room temperature, it was filtered through a layer of Celite with the aid of ethyl acetate. In the cases where toluene was used as the solvent, the filtrate was concentrated in vacuo and the crude product was purified chromatographically (silica gel). In the cases where Bu_3N was used as the solvent, the filtrate was extracted with 10% HCl. The organic layer was isolated and the aqueous layer was back-extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, and the crude product was purified chromatographically (silica gel). The yields of the coupling products are indicated in Tables 2 and 3. Three representative examples are shown below.

1-(1,3-Dimethylbut-2-enyloxy)-3,5-dimethylbenzene (2e). The general procedure was followed using $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), **L10** (11.4 mg, 0.024 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), 5-bromo-*m*-xylene

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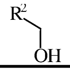
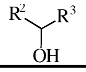
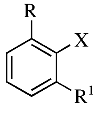
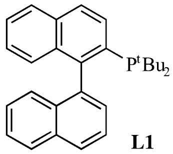
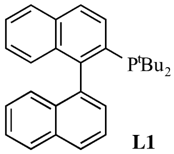
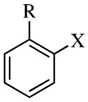
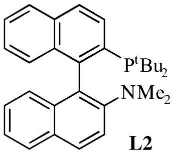
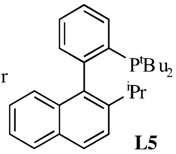
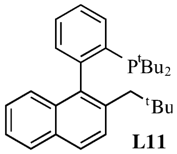
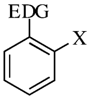
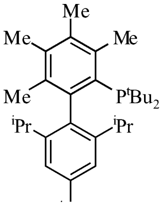
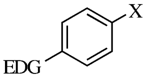
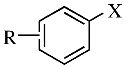
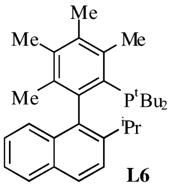
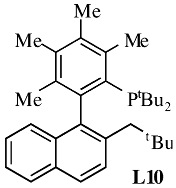
Table 4. Choice of Ligand for C−O Bond Formation[a]

entry	ArX	alcohol	
			
1		 L1	 L1
2		 L2 or  L5	 L11
3		 L4	—
4	or 		
5		 L6	 L10

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[a] EDG, electron-donating group; R ≠ EDG.

(185 mg, 1 mmol), and 4-methylpent-3-en-2-ol (200 mg, 2 mmol), with Bu_3N (2 mL) as solvent, for 18 h at 50 °C. The filtrate was extracted with 10% HCl (2 × 35 mL). Chromatographic purification (1% ethyl acetate in hexane) provided **2e** (colorless liquid, 165 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.50 (s, 2H), 5.20−5.24 (m, 1H), 4.93−5.01 (m, 1H), 2.26 (m, 6H), 1.73 (d, 3H, J = 1.3 Hz), 1.72 (d, 3H, J = 1.3 Hz), 1.35 (d, 3H, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.9, 134.0, 127.1, 122.1, 113.5, 70.7, 25.6, 21.4, 21.3, 18.2. IR (neat, cm^{-1}) 2975, 1595, 1448, 1292, 1155, 1067, 827, 688. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.95; H, 9.84.

1-*sec*-Butoxy-3-methoxybenzene (2m). The general procedure was followed using $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), **L10** (11.4 mg, 0.024 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), 1-bromo-3-methoxybenzene (187 mg, 1 mmol), and 2-butanol (148 mg, 2 mmol), with Bu_3N (1 mL) as solvent, for 24 h at 90 °C. The filtrate was extracted with 10% HCl (2 × 20 mL). Chromatographic purification (2% ethyl acetate in hexane) provided **2m** (colorless liquid, 114 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, 1H), 6.45−6.51 (m, 3H), 4.28 (sextet, 1H, J = 6.2 Hz), 3.79 (s, 3H), 1.69−1.80 (m, 1H), 1.56−1.67 (m, 1H), 1.29 (d, 3H, J = 6.1 Hz), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.4, 129.8, 107.9, 105.9, 102.2, 74.9, 55.1, 29.1, 19.2, 9.8; IR (neat, cm^{-1}) 2972, 1601, 1492, 1377, 1286, 1201, 1150, 1043, 1001, 837, 763, 688. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 9.11.

1-Butoxy-3,5-dimethylbenzene (12a). The general procedure was followed using $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), **L6** (10.7 mg, 0.024 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), 5-bromo-*m*-xylene (185 mg, 1 mmol), and butanol (148 mg, 2 mmol), with Bu_3N (2 mL) as solvent, for 18 h at 70 °C. The filtrate was extracted with 10% HCl (2 × 35 mL). Chromatographic purification (hexane, followed by 2% ethyl acetate in hexane) provided **12a**[3] (colorless liquid, 161 mg, 90%). ^{1}H and ^{13}C NMR data were consistent with those of the previously reported compound.

Acknowledgment. We thank the National Institutes of Health (GM58160) for funding this work and Merck and Novartis for further support. We are grateful to Chemetall and FMC Lithium for the generous gifts of Cs_2CO_3 and $^tBu_2PCl$.

Supporting Information Available: Full experimental details and characterizaton of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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