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Palladium-Catalyzed Cross-Coupling of Cyclopropylmagnesium Bromide with Aryl Bromides Mediated by Zinc Halide Additives

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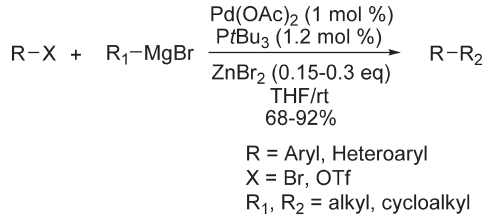

The key Pd-catalyzed cross-coupling of aryl bromides or triflates and cyclopropylmagnesium bromide in the presence of substoichiometric amounts of zinc bromide produces cyclopropyl arenes in good to excellent yields. The cross-coupling of other alkyl, cycloalkyl, and aryl Grignard reagents with aryl bromides under the same conditions gives the corresponding substituted arenes in good yields.

The cyclopropyl group is a common structural motif in natural products and pharmaceutical molecules,[1] and its incorporation via Pd-catalyzed coupling has been extensively studied mainly using boron-,[2] zinc-,[3] and bismuth-based[4] reagents. These soft organometallic reagents offer wide functional group compatibility, but their high cost severely limits their attractiveness for large-scale synthesis. The less expensive cyclopropylmagnesium bromide (**1**), on the other hand, suffers from poor functional group tolerance and low reactivity (in cross-coupling reactions) due to the "hardness" of the magnesium species.[5] Even though these issues can be partially addressed by premixing Grignard reagents with *stoichiometric* amounts of zinc halides to form the zinc reagents prior to the coupling reaction[6] and a new protocol for the synthesis of cyclopropylarenes by cross-coupling of cyclopropylzinc bromide with aryl halide,[7] an improved coupling of cyclopropylmagnesium halides using a catalytic amount of zinc reagents would be a useful addition to the current available methodologies. A successful catalytic process would also be applicable for the coupling of other Grignard reagents. Reported herein is our finding that the addition of a *substoichiometric* amount of zinc bromide, even as low as 0.15 equiv, can effectively "soften" the Grignard reagent[8] and significantly improve the Pd-catalyzed coupling reaction of aryl and heteroaryl halides/triflates with **1**.

We began our study with *p*-bromobenzonitrile (**2a**) as a model substrate for coupling with **1** in THF at room temperature (Table 1). The initial screening revealed that the selection of appropriate catalysts and ligands is important for the success of this reaction (entries 1−4). Among the catalyst systems that we examined, the combination of palladium acetate and tri-*tert*-butylphosphine[9] gave the best reaction. The Pd/phosphine ratio also had no significant impact on the reaction (entries 4−6). We next examined the effect of *in situ* formation of the zinc reagent with substoichiometric amounts of zinc halide additives (entries 7−10). In these experiments, **1** was added slowly to a premixed solution of **2a**, zinc halide, and catalyst. We were pleased to find that the use of 0.3−0.6 equiv of zinc bromide provided better yield than the premixing approach (entries 7, 8). Here the use of $P(t\mathrm{Bu})_3$, an electron-rich and bulky phosphine ligand, is important, as it greatly accelerates the coupling reaction.[10] Reducing the amount of additive further to 0.15 equiv (entry 9) caused a slight decrease in yield, although the result is still comparable to that obtained with the premixing approach. Use of zinc chloride gave decreased conversion to product, demonstrating again the importance of halide counterion (entry 10). Finally the control experiment with no additive gave significantly lower yield (entry 11). In all experiments, the use of excess **1** (1.8 equiv) was necessary to achieve a complete coupling by consuming all the starting material **2a**.

After establishing the optimum conditions for this reaction, we turned our attention to exploring the reaction scope. As shown in Table 2, a wide range of aryl and heteroaryl bromides were suitable substrates. Electron-rich substrates **2b** and **2c** gave the desired products **3b** and **3c** in excellent yields (entries 1, 2). Reactions with the substrates **2d**−**f**,

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(8) For a related example of using Grignard nucleophiles together with substoichiometric amount of zinc halide, see: Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999.

(9) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555–1564.

(10) (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158–163. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724.

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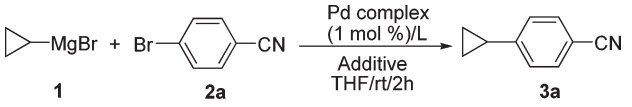
TABLE 1. Screening of Cross-Coupling between 1 and 2a



entry	Pd/ligand (mol ratio)	additive (equiv)[a]	zinc reagent	yield (%)[b]
1	$Pd(OAc)_2/PPh_3$ (1/1.2)	$ZnBr_2$ (1.2)	preformed	72
2	$Pd(OAc)_2/PCy_3$ (1/1.2)	$ZnBr_2$ (1.2)	preformed	19
3	$Pd(dppf)Cl_2$	$ZnBr_2$ (1.2)	preformed	73
4	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/1.2)	$ZnBr_2$ (1.2)	preformed	89
5	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/2.4)	$ZnBr_2$ (1.2)	preformed	90
6	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/3.6)	$ZnBr_2$ (1.2)	preformed	89
7	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/1.2)	$ZnBr_2$ (0.6)	*in situ*	95
8	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/1.2)	$ZnBr_2$ (0.3)	*in situ*	95 (92 [c])
9	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/1.2)	$ZnBr_2$ (0.15)	*in situ*	88
10	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/1.2)	$ZnCl_2$ (0.3)	*in situ*	82
11	$Pd(OAc)_2/P(t\text{Bu})_3$ (1/1.2)	none	*in situ*	71

[a]Stoichiometry relative to Grignard **1**. [b]Wt % assay yield based on HPLC quantification. [c]Isolated yield.

bearing sensitive ester and lactone groups, afforded the products in moderate yields (entries 3, 4). The cross-coupling of thioether **2g** gave a satisfactory result with 70% yield of **3g** (entry 6). Pyridyl and quinolinyl substrates **2i** and **2j** underwent cross-coupling reactions to give **3i** and **3j** in excellent yields, respectively (entries 8, 9). The study also showed that the coupling reaction was highly dependent on the choice of halide. It is noteworthy to mention that a slow addition of **1** to the mixture of aryl halides (especially for those substrates bearing sensitive functional groups) and $ZnBr_2$ (typically 30 min for 5−10 mmol scale) is necessary to ensure no accumulation of **1** occurs during the reaction; that is, the rate of addition of the reagent is lower than that of transmetalation and cross-coupling. In the absence of $ZnBr_2$, the yields for **3d**,**e** and **3j** fell to 40−50% due to side reactions such as addition of Grignard reagent to sensitive functional groups. Whereas the coupling of triflates **2k**,**n** produced **3k**,**b** in reasonable yields (entries 10, 13), both chloride **2l** and iodide **2m** afforded very poor product yields (entries 11, 12). In the former case, the low reactivity of aryl chloride resulted in clean but low conversion (< 20%) to **3a** even after extended reaction time, whereas in the latter case, the high reactivity of iodide resulted in a significant amount of deiodinated byproduct (> 30%).

Besides cyclopropylmagnesium bromide (**1**), alkyl, cycloalkyl, and aryl Grignard reagents **4** were also studied (Table 3). Primary *n*-propyl Grignard reagents **4a** and **4b** were subjected to coupling with **2b** (entries 1, 2). Interestingly, the counterion (Br vs Cl) had a significant effect on the reaction yield. On the other hand, the isopropyl and *tert*-butyl Grignard reagents **4c** and **4d** did not afford the desired product (entries 3, 4). Instead *n*-propyl- and isobutyl-(*p*-methoxy)-benzenes **5a** and **5d** were isolated as the major products, presumably from the competing Pd−H scrambling pathway.[5] The coupling reaction of cyclohexyl Grignard reagents **4e** and **4f** with bromide afforded the desired product with excellent yield and purity. In this case, the counterion (Br vs Cl) had a slight impact on the reaction yield. Aryl Grignard reagent **4g** reacted similarly to afford the desired product in excellent yield under the same conditions (entry 7).

In summary, we have developed a general and mild Pd-catalyzed cross-coupling reaction between aryl bromides/triflates and cyclopropylmagnesium bromide using a substoichiometric zinc bromide additive. The scope of nucleophiles was further extended to other alkyl, cycloalkyl, and aryl Grignard reagents with good results.

Experimental Section

General Procedure of Pd-Catalyzed Cross-Coupling. To a suspension of aryl halide/triflate (2.3 mmol, 1.0 equiv) and tri-*tert*-butylphosphonium tetrafluoroborate (0.14 mmol, 41 mg, 0.06 equiv) in THF (2.5 mL) under N_2 were added $Pd(OAc)_2$ (0.11 mmol, 25 mg, 0.05 equiv) and zinc bromide solution (27.6 wt % solution in THF, 0.57 g, 0.7 mmol, 0.3 equiv). Cyclopropylmagnesium bromide (0.50 M in THF, 7.36 mL, 3.68 mmol, 1.6 equiv) was added slowly over 30 min while maintaining the temperature at 20−25 °C. The reaction mixture was stirred at room temperature for an additional 2 h and monitored by HPLC. Upon completion (> 99% conversion), the reaction was cooled to 0 °C, and water (8.0 mL) was added slowly while maintaining the temperature below 15 °C. Ethyl acetate (10 mL) was added, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude mixture was purified by chromatography (silica gel, ethyl acetate/hexanes) to afford the purified product.

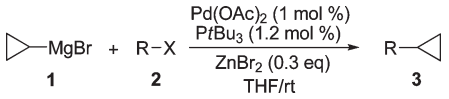
4-Cyclopropylbenzonitrile (3a). Following the general procedure, the title compound was obtained in 92% yield (303 mg) from **2a** or 81% yield (267 mg) from **2j** as a yellow oil.[2c] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (ABq, J = 8.4 Hz, 2H), 7.12 (ABq, J = 8.4 Hz, 2H), 1.96−1.90 (m, 1H), 1.11−1.06 (m, 2H), 0.78−0.74 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 150.4, 132.3, 126.3, 119.4, 109.0, 16.0, 10.8.

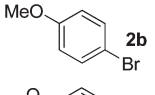
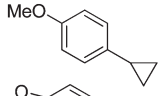
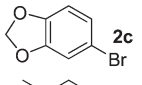
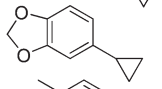
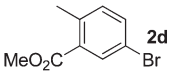
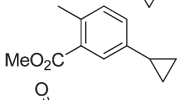
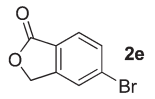
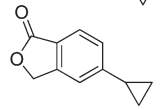
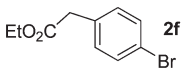
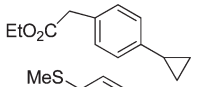
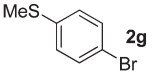
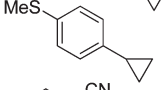
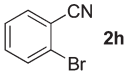
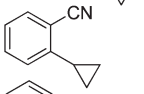
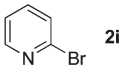
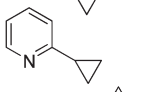
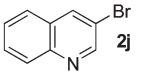
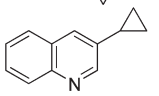
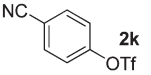
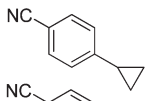
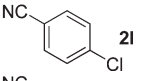
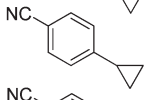
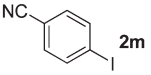
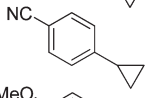
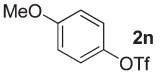
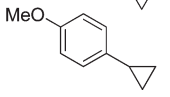
1-Cyclopropyl-4-methoxybenzene (3b). Following the general procedure, the title compound was obtained in 88% yield (300 mg) as a yellow oil.[2c] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (ABq, J = 8.8 Hz, 2H), 6.83 (ABq, J = 8.8 Hz, 2H), 3.79 (s, 3H), 1.89−1.85 (m, 1H), 0.93−0.88 (m, 2H), 0.65−0.61 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 157.9, 136.1, 127.0, 114.0, 55.5, 14.8, 8.7.

5-Cyclopropylbenzo[*d*][1,3]dioxole (3c). Following the general procedure, the title compound was obtained in 82% yield (266 mg) as a colorless oil.[4a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0, 1H), 6.55 (s, 1H), 5.91 (s, 2H), 1.89−1.81 (m, 1H), 0.91−0.88 (m, 2H), 0.63−0.60 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 147.9, 145.6, 138.0, 119.2, 108.2, 106.5, 101.0, 15.46, 8.9.

Methyl 3-Cyclopropyl-4-methylbenzoate (3d). Following the general procedure, the title compound was obtained in 68%

TABLE 2. Coupling of Aryl Halides with Cyclopropylmagnesium Bromide (1)



entry	RX **2**	product **3**	yield of **3**[a]
1	 **2b**		88%(**3b**)
2	 **2c**		82%(**3c**)
3	 **2d**		68%(**3d**)
4	 **2e**		75%(**3e**)
5	 **2f**		78%(**3f**)
6	 **2g**		70%(**3g**)
7	 **2h**		68%(**3h**)
8	 **2i**		92%(**3i**)
9	 **2j**		83%(**3j**)
10	 **2k**		81%(**3a**)
11	 **2l**		20%(**3a**)[b]
12	 **2m**		35%(**3a**)[b]
13	 **2n**		85%(**3b**)

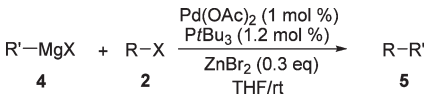
[a]Isolated yield by flash chromatography on silica gel. [b]Wt % assay yield by GC.

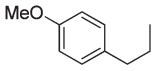
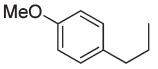
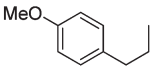
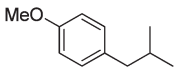
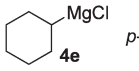
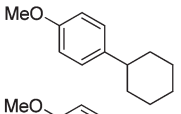
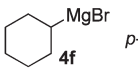
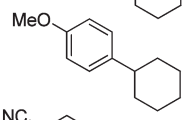
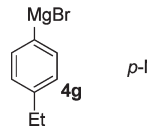
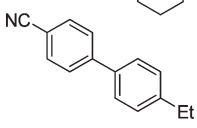
yield (298 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H), 3.88 (s, 3H), 2.47 (s, 3H), 1.89−1.86 (m, 1H), 0.98−0.94 (m, 2H), 0.70−0.66 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.6, 143.8, 141.8, 129.8, 127.9, 127.1, 126.9, 52.1, 20.1, 13.6, 7.1. HRMS: calcd for $[C_{12}H_{14}O_2 + H]^+$ 191.1077, found 191.1086.

5-Cyclopropylisobenzofuran-1(3*H*)-one (3e). Following the general procedure, the title compound was obtained in 75% yield (301 mg) as a beige powder.[4a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 5.25 (s, 2H), 2.03−1.99 (m, 1H), 1.14−1.09 (m, 2H), 0.83−0.79 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 171.3, 152.2, 147.4, 126.9, 125.8, 123.2, 118.8, 69.6, 16.3, 10.9.

Ethyl (4-Cyclopropylphenyl)acetate (3f). Following the general procedure, the title compound was obtained in 78% yield (318 mg) as a beige powder.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (ABq, J = 8.0 Hz, 2H), 7.04 (ABq, J = 8.0 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.57 (s, 2H), 1.91−1.87 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.98−0.94 (m, 2H), 0.71 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.8, 142.8, 121.1, 129.1, 125.9, 60.8, 41.0, 15.1, 14.2, 9.2.

TABLE 3. Coupling of Aryl Bromides with Grignard Reagents 4



entry	RMgX **4**	RX **2**	product **5**	yield of **5**[a]
1	*n*-PrMgBr **4a**	*p*-MeOPhBr **2b**		88%(**5a**)
2	*n*-PrMgCl **4b**	*p*-MeOPhBr **2b**		63%(**5a**)
3	*i*-PrMgBr **4c**	*p*-MeOPhBr **2b**		72%(**5a**)
4	*t*-BuMgCl **4d**	*p*-MeOPhBr **2b**		86%(**5d**)
5	 **4e**	*p*-MeOPhBr **2b**		77%(**5e**)
6	 **4f**	*p*-MeOPhBr **2b**		80%(**5e**)
7	 **4g**	*p*-NCPhBr **2m**		84%(**5g**)

(3-Cyclopropylphenyl)(methyl)sulfide (3g). Following the general procedure, the title compound was obtained in 70% yield (172 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 2.49 (s, 2H), 1.91−1.85 (m, 1H), 0.99−0.95 (m, 2H), 0.73−0.69 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 144.7, 138.2, 128.7, 124.3, 123.7, 122.5, 15.9, 15.3, 9.1.

2-Cyclopropylbenzonitrile (3h). Following the general procedure, the title compound was obtained in 68% yield (224 mg) as a colorless oil.[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.0, 1H), 2.31−2.24 (m, 1H), 1.16−1.11 (m, 2H), 0.80−0.77 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 148.0, 133.0, 132.7, 126.0, 124.5, 118.5, 113.2, 14.3, 9.7.

3-Cyclopropylquinoline (3j). Following the general procedure, the title compound was obtained in 83% yield (280 mg) as a colorless oil.[2a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.07 (t, J = 8.0 Hz, 1H), 7.71 (m, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.62−7.60 (m, 1H), 7.51−7.45 (m, 1H), 2.09−2.03 (m, 1H), 1.12−1.07 (m, 2H), 0.86−0.82 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 150.6, 146.6, 136.7, 130.9, 129.1, 128.4, 128.1, 127.2, 126.6, 13.4, 9.2.

1-Methoxy-4-propylbenzene (5a). Following the general procedure, the title compound was obtained in 88% yield (264 mg) from *n*PrMgBr, 63% yield (189 mg) from *n*PrMgCl, and 72% yield (216 mg) from *i*PrMgCl as a colorless oil.[14] ^{1}H NMR

(11) Kusuyama, Y.; Ikeda, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 204–207.
(12) Lazzaroni, S.; Dondi, D.; Fagnoni, M.; Albini, A. *Eur. J. Org. Chem.* **2007**, *26*, 4360–4365.
(13) Shono, T.; Nishiguchi, I. *Tetrahedron* **1974**, *30*, 2183–2190.

(400 MHz, $CDCl_3$): δ 7.01 (ABq, J = 8.8 Hz, 2H), 6.74 (ABq, J = 8.8 Hz, 2H), 3.73 (s, 3H), 2.45 (t, J = 7.4 Hz, 2H), 1.52 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 157.8, 135.0, 129.5, 113.83, 55.5, 37.4, 25.0, 14.0.

1-Isobutyl-4-methoxybenzene (5d). Following the general procedure, the title compound was obtained in 86% yield (282 mg) as a yellow oil.[5b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (ABq, J = 8.8 Hz, 2H), 6.83 (ABq, J = 8.8 Hz, 2H), 3.79 (s, 3H), 2.42 (d, J = 7.2 Hz, 2H), 1.82 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 157.9, 134.0, 130.2, 113.7, 55.4, 44.74, 30.6, 22.5.

1-Cyclohexyl-4-methoxybenzene (5e). Following the general procedure, the title compound was obtained in 77% yield (293 mg) from **4e** and 80% yield (304 mg) from **4f** as a white foam.[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (ABq, J = 8.7 Hz, 2H), 6.84 (ABq, J = 8.7 Hz, 2H), 3.79 (s, 3H), 2.45 (m, 1H), 1.84 (m, 4H), 1.73 (m, 1H), 1.39 (m, 4H), 1.26 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 157.9, 140.6, 127.8, 113.9, 55.4, 43.9, 34.9, 27.17, 26.4.

4′-Ethylbiphenyl-4-carbonitrile (5g). Following the general procedure, the title compound was obtained in 84% yield (435 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−7.65 (m, 4H), 7.51 (ABq, J = 8.2 Hz, 2H), 7.31 (ABq, J = 8.2 Hz, 2H), 2.70 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.80, 145.26, 136.67, 132.74, 128.84, 127.67, 127.34, 119.23, 110.71, 28.75, 15.77. HRMS: calcd for $[C_{15}H_{13}N + H]^+$ 208.1126, found 208.1138.

Acknowledgment. We thank Dr. John Proudfoot and Dr. Jonathan Reeves for discussions.

Supporting Information Available: Copies of ^{1}H/^{13}C NMR spectra for compounds **3a**−**j**, **5a**, and **5d**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Maras, N.; Polanc, S.; Kocevar, M. *Tetrahedron* **2008**, *64*, 11618–11624.

(15) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364–4366.