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Iron-Catalyzed Cross-Coupling of Alkyl Sulfonates with Arylzinc Reagents

Shingo Ito,[†] Yu-ichi Fujiwara, Eiichi Nakamura,[‡] and Masaharu Nakamura*

International Research Center for Elements Science (IRCELS), Institute for Chemical Research, and Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Uji, Kyoto 611-0011, Japan

masaharu@scl.kyoto-u.ac.jp

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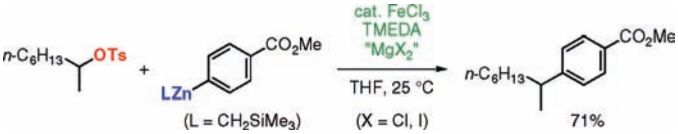
ABSTRACT



Iron-catalyzed cross-coupling reactions of primary and secondary alkyl sulfonates with arylzinc reagents proceed smoothly in the presence of excess TMEDA and a concomitant magnesium salt. The arylzinc reagents are prepared from the corresponding aryllithium or magnesium reagents with ZnI_2. The in situ formation of alkyl iodides and consecutive rapid cross-coupling avoids discrete preparation of the unstable secondary alkyl halides and also achieves high product selectivity.

The substitution reaction of alkyl sulfonates with a carbon nucleophile is a powerful method of carbon−carbon bond formation and has been widely used in organic synthesis. While organocuprates have long played a key role in the substitution reaction,[1] several catalytic methods using transition-metal catalysts, such as copper, nickel, or palladium, have been developed with various organometallic reagents.[2] Herein we report a new transition-metal-catalyzed substitution reaction of alkyl sulfonates: efficient cross-couplings of various primary and secondary[3] alkyl tosylates with arylzinc reagents are achieved by an iron catalyst, which is now re-emerging as an effective catalyst for cross-couplings of alkyl halides[4−7] after decades of dormancy.[8]

The cross-coupling reactions of alkyl sulfonates with arylzinc reagents catalyzed by $FeCl_3$[9] were examined using three different procedures[7e] (Scheme 1): Procedure A is the reaction with diarylzinc reagents prepared from ZnX_2(tmeda) and ArMgBr. Procedure B is the reaction with diarylzinc

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[†] Present address: Deparment of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.

[‡] Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

(1) (a) Whitesides, G. M.; Fischer, W. F., Jr.; San Filippo, J., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871–4882. (b) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777–7782. (c) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783–7788.

(2) (a) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82–83. (b) Burns, D. H.; Miller, J. D.; Chan, H.-K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133. (c) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223. (d) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912. (e) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890–891. (f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (g) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180–6182.

(3) Some copper catalysts were used for the cross-coupling reactions of secondary alkyl sulfonates albeit in low yield, see ref 2b.

(4) For reviews of transition-metal-catalyzed cross-couplings of unactivated alkyl electrophiles, see: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670, and references cited therein.

(5) For additional reports of other transition-metal-catalyzed cross-couplings of unactivated alkyl electrophiles, see the following. Pd catalysis: (a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340–11341. Ni catalysis: (b) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2007**, 825–827. Cu catalysis: (c) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086–2089.

(6) (a) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (c) Nakamura, M.; Ito, S. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 155−181. (d) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081–2091. (e) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624–629. (f) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108–1117. (g) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500–1511. (h) Bauer, E. B. *Curr. Org. Chem.* **2008**, *12*, 1341–1369.

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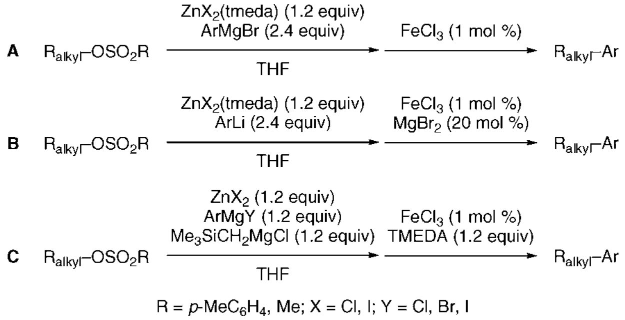
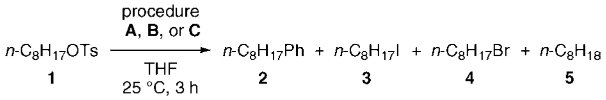
Scheme 1. Procedures for Iron-Catalyzed Cross-Coupling Reactions of Alkyl Sulfonates with Arylzinc Reagents



reagents prepared from ZnX_2(tmeda) and ArLi in the presence of 20 mol % of $MgBr_2$, which is added as a source of an essential cocatalyst for the cross-coupling reaction.[7e,10] Procedure C is the reaction with mixed diorganozinc reagents bearing a trimethylsilyl group as a nontransferable ligand[7e,11] in the presence of TMEDA.

We first examined octyl tosylate **1** and phenylzinc reagents under various conditions (Table 1). Previously reported conditions[7e] afforded the cross-coupling product **2** in 12% yield with the recovery of **1** in 70% yield (entry 1). Careful analysis of the byproducts revealed that 1-bromooctane **4** was obtained in 8%, which suggests that in situ formation of an alkyl halide might be responsible for the cross-coupling product.[12] Thus, it is expected that preparation of a diphenylzinc reagent from aryllithium or magnesium reagents and ZnI_2 would liberate a highly nucleophilic iodide ion, which could then efficiently convert alkyl tosylates to alkyl iodides under the reaction conditions. In fact, the use of ZnI_2 improved the yield of **2** to 88% (entry 2). While the cross-coupling reaction in the absence of a magnesium salt did not proceed (entry 3), the addition of a catalytic amount of $MgBr_2$ efficiently promoted the reaction to give **2** in quantitative yield (entry 4). A mixed diorganozinc reagent, $PhZnCH_2SiMe_3$, also gave **2** in high yield (entry 5).

Table 1. Cross-Coupling Reactions of Octyl Tosylate with Phenylzinc Reagents[a]



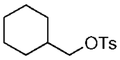
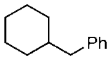
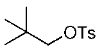
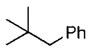
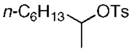
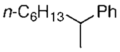
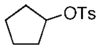
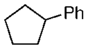
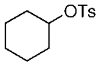
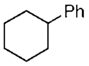
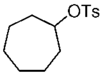
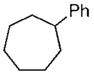
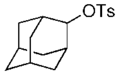
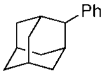
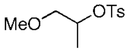
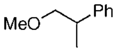
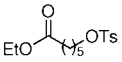
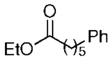
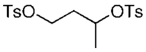
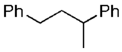
$$\underset{\mathbf{1}}{n\text{-}C_8H_{17}OTs} \xrightarrow[\text{THF, 25 °C, 3 h}]{\text{procedure } \mathbf{A}, \mathbf{B}, \text{ or } \mathbf{C}} \underset{\mathbf{2}}{n\text{-}C_8H_{17}Ph} + \underset{\mathbf{3}}{n\text{-}C_8H_{17}I} + \underset{\mathbf{4}}{n\text{-}C_8H_{17}Br} + \underset{\mathbf{5}}{n\text{-}C_8H_{18}}$$

entry	procedure	X	Ar	yield[b] (%) **2**	**3**	**4**	**5**	recovery of **1**[b] (%)
1[c]	**A**	Cl	Ph	**12**	0	8	7	70
2	**A**	I	Ph	**88**	0	0	8	0
3[d]	**B**	I	Ph	**0**	96	0	0	0
4	**B**	I	Ph	**99**	0	0	<1	0
5	**C**	I	Ph	**87**	0	0	8	0

[a] The reactions were carried out according to procedure A, B, or C shown in Scheme 1. [b] The yield was determined by GC or ^{1}H NMR analysis. [c] 1.5 equiv of the phenylzinc reagent and TMEDA and 5 mol % of $FeCl_3$ were used. [d] The reaction was carried out in the absence of $MgBr_2$.

The iron-catalyzed cross-coupling reactions of various alkyl tosylates with arylzinc reagents were investigated using procedures A and B (Table 2). The reactions of primary alkyl tosylates gave the coupling product in good yield (entries 1 and 2). However, neopentyl tosylate reacted sluggishly due

Table 2. Cross-Coupling Reactions of Various Alkyl Tosylates with Diphenylzinc Reagents[a]

entry	R–OTs	conditions	product	yield (%)[b] (**A**)	yield (%)[b] (**B**)
1	n-C_8H_{17}–OTs	**A** : 25 °C, 3 h **B** : 25 °C, 3 h	n-C_8H_{17}–Ph	88[c]	95
2		**A** : 25 °C, 24 h **B** : 25 °C, 12 h		95	86[c]
3		**A** : 50 °C, 12 h **B** : 50 °C, 12 h		19	5[c]
4		**A** : 25 °C, 6 h **B** : 25 °C, 1 h		90	86[c]
5		**B** : 25 °C, 1 h		---	91[c]
6		**A** : 25 °C, 24 h **B** : 25 °C, 12 h		13[c]	15[c]
7		**A** : 25 °C, 1 h **B** : 25 °C, 1 h		88	81
8		**A** : 40 °C, 12 h 60 °C, 6 h		57	---
9		**A** : 40 °C, 12 h **B** : 40 °C, 12 h		87[c,d]	---
10		**A** : 25 °C, 3 h **B** : 25 °C, 3 h		95	---
11[e]		**A** : 25 °C, 6 h		83	---

[a] The reactions were carried out according to procedure A or B shown in Scheme 1 (X = I; Ar = Ph). [b] Isolated yield. [c] 1H NMR yield. [d] The isomerized product, (1-methoxypropyl)benzene, was also obtained in 9% yield. [e] 2.4 equiv of the phenylzinc reagent and TMEDA were used.

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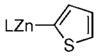
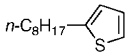
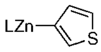
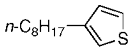
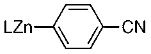
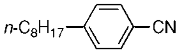
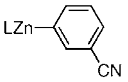
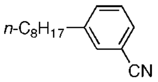
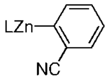
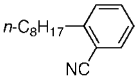
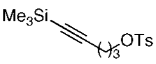
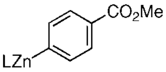
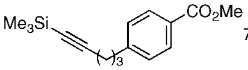
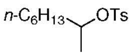
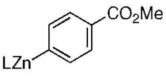
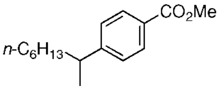
(7) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3786–3787. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299. (c) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822–2823. (d) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3952–3954. (e) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794–1798. (f) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161–4163. (g) Bica, K.; Gaertner, P. *Org. Lett.* **2006**, *8*, 733–735. (h) Bedford, R. B.; Betham, M.; Bruce, D. W.; Davis, S. A.; Frost, R. M.; Hird, M. *Chem. Commun.* **2006**, 1398–1400. (i) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104–1110. (j) Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015–1018. (k) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253–3254. (l) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364–4366. (m) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521–6524. (n) Rao Volla, C. M.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305–1307. (o) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787. (p) Nakamura, M.; Ito, S.; Fujita, A. Jpn. Kokai. Tokkyo Koho 2008214199, 2008. (q) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600–602. (r) Hatakeyama, T.; Kondo, Y.; Fujiwara, Y.; Takaya, H.; Ito, S.; Nakamura, E.; Nakamura, M. *Chem. Commun.* **2009**, 1216–1218.

to the steric congestion caused by the neighboring quaternary carbon center, which interferes the S_N2 reaction by an iodide ion (entry 3).[13] An acyclic secondary alkyl tosylate reacted efficiently to afford the desired product in good yield (entry 4). Five- and seven-membered cyclic seconday alkyl tosylates showed high reactivity (entries 5 and 7), while the reaction of a six-membered cyclic alkyl tosylate gave a poor result due to the sluggish substitution and relatively fast β-hydrogen elimination (entry 6).[14] Interestingly, a bulky 2-adamantyl tosylate, which possesses no β-hydrogen available for elimination, afforded the coupling product in 57% yield (entry 8). The oxygen functionality at the β-position of the tosylate group slightly affected the reactivity to afford a mixture of the cross-coupling product and the rearranged product, (1-methoxypropyl)benzene, in 87% and 9% yield, respectively (entry 9). Ester functionality was tolerated under the reaction conditions (entry 10). Furthermore, an alkyl 1,3-bistosylate was successfully converted to the diarylated compound by using 2.4 equivalents of phenylzinc reagents (entry 11).

The results of cross-couplings of alkyl tosylates with functionalized arylzinc reagents are summarized in Table 3.

Table 3. Cross-Coupling Reactions of Alkyl Tosylates with Functionalized Arylzinc Reagents[a]

entry	R–OTs	arylzinc reagent	product	yield (%)[b]
1[c]	1			72
2[d]	1			72
3	1			93
4[c]	1			93
5[d]	1			60
6				75
7				71

[a] The reactions were carried out according to procedure C shown in Scheme 1 (X = I). For the details, see the Supporting Information. [b] Isolated yield. [c] 3.0 equiv of TMEDA and 3 mol % of $FeCl_3$ were used. [d] 3.0 equiv of the arylzinc reagent and TMEDA and 5 mol % of $FeCl_3$ were used.

The functionalized arylzinc reagents were prepared according to the method reported by Knochel via a halogen−magnesium exchange reaction of aryl bromides or aryl iodides with i-PrMgCl·LiCl.[15] Competitive cross-coupling between the arylzinc reagents and the isopropyl halide (i-PrX) formed during the halogen-magnesium exchange reaction (ArX + i-PrMgCl·LiCl → ArMgCl·LiCl + i-PrX) could be avoided by thorough evaporation after transmetalation from magnesium to zinc and the subsequent treatment with Me_3SiCH_2MgCl. The cross-coupling reactions of heteroarylzinc reagents, such as 2- or 3-thienylzinc reagents, afford the products in 72% yields (entries 1 and 2). The reactions of the p- or m-cyanophenylzinc reagents with **1** gave the coupling products in excellent yield, while the reaction of the o-cyanophenylzinc reagent gave the product in 60% yield despite the use of 3.0 equiv of the arylzinc reagent and 5 mol % of $FeCl_3$. The arylzinc reagents possessing a p-methoxycarbonyl group reacted with primary and secondary alkyl halides to afford the products in 75 and 71% yield, respectively (entries 6 and 7).

The stereochemical environment of the leaving groups impacted the product distribution in the cross-coupling of substituted cyclohexyl tosylates: When *trans* isomer **6** was reacted with a diarylzinc reagent, the coupling product **8** was obtained in 60% yield along with the formation of olefin **9** in 40% yield (eq 1).[16] On the other hand, *cis* isomer **7** gave no coupling product and resulted in the quantitative formation of **9** (eq 2). Due to the antiperiplanar alignment of the leaving group and the β protons imposed by the bulky cyclohexyl substituent at the 4-position, E2 elimination of *cis* isomer **7** is significantly more rapid than S_N2 substitution by an iodide ion. In the case of the *trans* isomer **6**, S_N2 substitution is faster than β-elimination to afford the iodohexane, which undergoes a rapid iron-catalyzed cross-coupling reaction with arylzinc reagent via a radical mechanism.[17] The in situ generated iodide also possesses a β-hydrogen in the anti-periplanar relationship, and an elimination reaction from the iodide competes to give the elimination product **9** in 40%. These experiments demonstrate that the present cross-

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(8) Selected papers: (a) Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489. (b) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449–5452. (c) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53–60. (d) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199–1205. (e) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901–1904. (f) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863. (g) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (h) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928.

(9) Anhydrous $FeCl_3$ (>99.99%, Aldrich, Inc.) was used as a precatalyst throughout the present study. The iron salt has been reported rather free from the contamination of a trace amount of copper, see: Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586–5587.

(10) The similar effect of magnesium salts in organozinc coupling have been reported, see ref 2g.

(11) (a) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906–10907. (b) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed.* **1997**, *36*, 1496–1498.

(12) Place, P.; Roumestant, M.-L.; Gore, J. *Bull. Soc. Chim. Fr.* **1976**, 169–176.

(13) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3694–3697.

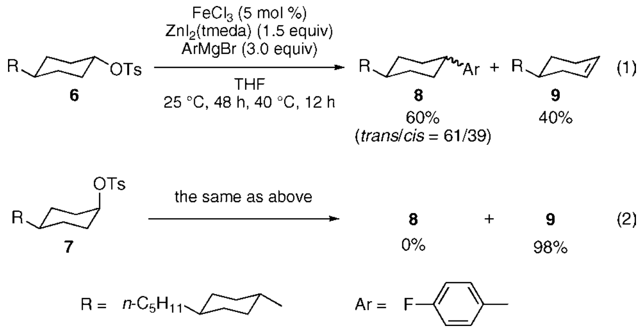
(14) It is known that nucleophilic substitution of cyclohexyl tosylate is generally slow and is often accompanied with elimination reaction; see: (a) Lambert, J. B.; Putz, G. J.; Mixan, C. E. *J. Am. Chem. Soc.* **1972**, *94*, 5132–5133. (b) Nordlander, J. E.; McCrary, T. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5133–5135, and references cited therein.

(15) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.

(16) The substitution reaction procceded in a non-stereospecific manner to afford a 61:39 mixture of the diastereomers, representing the characteristic reactivity profile of iron-catalyzed haloalkane cross-coupling reaction (cf. ref 7a,e).

(17) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078–6079.

coupling reaction proceeds from the in situ generated alkyl iodides and not from the sulfonates.



In summary, we have developed the first iron-catalyzed cross-coupling reactions using alkyl sulfonates as a substrate. The primary and secondary alkyl sulfonates reacted with arylzinc reagents derived from zinc iodide and Grignard reagents in the presence of $FeCl_3$ and TMEDA to give the coupling products in good yield. Key to the successful cross-coupling is in situ formation of alkyl iodides from the corresponding alkyl sulfonates and consecutive rapid catalytic cross-coupling.

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

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