

Iron-Catalyzed Alkylations of Aryl
Sulfamates and Carbamates

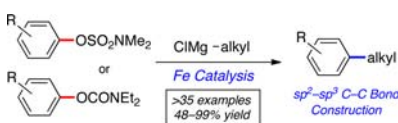
Amanda L. Silberstein, Stephen D. Ramgren, and Neil K. Garg*

Department of Chemistry and Biochemistry, University of California, Los Angeles,
California 90095-1569, United States

neilgarg@chem.ucla.edu

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ABSTRACT



The alkylation of aryl sulfamates and carbamates using iron catalysis is reported. The method constructs sp^2 – sp^3 carbon–carbon bonds and provides synthetically useful yields across a range of substrates (>35 examples). The directing group ability of sulfamates and carbamates, accompanied by their low reactivity toward conventional cross-couplings, renders these substrates useful for the synthesis of polyfunctionalized arenes.

As one of the most abundant, inexpensive, and nontoxic elements on earth, iron has been hailed as an ideal metal for the development of catalytic transformations.¹ Various Fe-based methods to promote C–C bond formation have been reported since the seminal publications of Kharasch² and Kochi,³ with many key advances being described in the past decade.¹ One especially promising area is iron-catalyzed cross-coupling reactions of aryl electrophiles,^{4,5} largely pioneered by Fürstner,^{4a,b} which nicely complements the most commonly used Pd- and Ni-based methods for forging C–C bonds. The use of iron-mediated coupling reactions in natural product and drug synthesis

is testament to the promise of this developing field of research.⁶

With the aim of discovering iron-promoted reactions for use in synthesis, we explored iron-catalyzed reactions of aryl sulfamate and carbamate substrates. These substrates have recently garnered significant attention in cross-coupling reactions because of their ease of preparation, pronounced stability to a variety of reaction conditions, including conventional transition metal catalysis, and their directing group ability for arene functionalization.^{7,8} Sulfamates and carbamates have primarily been used in

(1) (a) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364. (c) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (d) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *2*, 396. (e) Ritter, S. K. *Chem. Eng. News* **2008**, *86*, 53.

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(8) For reviews, see: (a) Knappke, C. E. I.; Jacobi von Wangelin, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3568. (b) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (c) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728. (d) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, B.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

Ni-catalyzed arylation,^{7–9} amination,¹⁰ and deoxygenation¹¹ reactions, but their use in iron-catalyzed couplings holds much promise for enabling alkylative processes. No examples of iron-catalyzed sulfamate alkylation have been reported, and only a single example of a carbamate alkylation is known.^{12,13}

Herein, we report the alkylations of aryl sulfamates and carbamates using alkyl Grignard reagents¹⁴ and iron catalysis to generate sp^2 – sp^3 C–C bonds (Figure 1). The transformation enables the alkylation of a broad range of substrates, including electron-rich arenes, heterocycles, and ortho-substituted aromatics. This promising synthetic tool should prove generally useful for the synthesis of sp^2 – sp^3 C–C bonds¹⁵ and also expands the repertoire of highly sought after iron-catalyzed cross-coupling reactions.

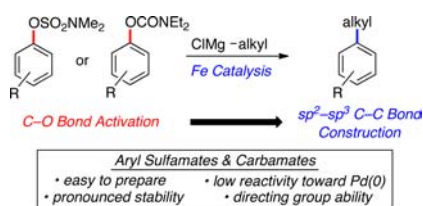


Figure 1. Iron-catalyzed alkylation of aryl sulfamates and carbamates.

Alkyl Grignard reagents were considered to be ideal coupling partners for the intended alkylation of aryl sulfamates and carbamates. Despite their high reactivity, conventional Grignard reagents are widely available and extensively utilized across a host of modern synthetic applications.¹⁴ An extensive survey of reaction conditions

(9) Although most C–C bond-forming reactions of aryl sulfamates and carbamates construct sp^2 – sp^2 linkages, there are a few examples of sp^2 – sp^3 couplings using nickel, rather than iron, catalysis; see ref 7a for the coupling of aryl carbamates with $TMSCH_2MgCl$ and ref 7d for the coupling of cyclic sulfamate substrates. Previous attempts to couple aryl carbamates with n -BuMgCl using Ni catalysis were unsuccessful because of competitive aryl C–O bond reduction (see ref 7a). No general methodology for the alkylation of aryl sulfamates or carbamates is known.

(10) (a) Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2171–2173. (b) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Fine Nathel, N. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766. (c) Ackermann, L.; Sandmann, R.; Song, W. *Org. Lett.* **2011**, *13*, 1784.

(11) Mesganaw, T.; Fine Nathel, N. F.; Garg, N. K. *Org. Lett.* **2012**, *14*, 2918.

(12) An Fe-catalyzed alkylation of a 2-naphthyl carbamate substrate was reported by Shi (see ref 5); however, attempts to apply these reaction conditions to other carbamate substrates led to low yields (see the Supporting Information). No other examples of Fe-catalyzed aryl carbamate couplings are known.

(13) For an iron-catalyzed arylation of a sulfamate substrate, see ref 4c.

(14) (a) Silverman, G. S.; Rakita, P. S. *Handbook of Grignard Reagents*; CRC Press: New York, 1996. (b) Inoue, A.; Oshima, K. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH Verlag: Weinheim, 2005; pp 51–154.

(15) sp^2 – sp^3 carbon–carbon bonds are commonly observed in natural products, pharmaceuticals, agrochemicals, ligands for catalysis, and materials.

(16) The use of *N*-hexylmagnesium bromide in THF gave comparable yields of coupled product **2**.

was undertaken to effect the alkylative coupling of carbamate **1** with *n*-hexylmagnesium chloride¹⁶ to afford alkylated product **2** (see the Supporting Information). Although most reaction conditions based upon literature procedures for iron-catalyzed Kumada couplings were unsuccessful, a modification of Shi's conditions^{5,12} using the NHC ligand **3**¹⁷ delivered the alkylated product (Figure 2). Of note, the addition of substoichiometric quantities of CH_2Cl_2 was critical in order to obtain good yields and consistent results.^{18,19} Experiments conducted in the absence of $FeCl_2$ gave < 15% product with or without the addition of copper, palladium, or nickel salts (see the Supporting Information).^{20,21}

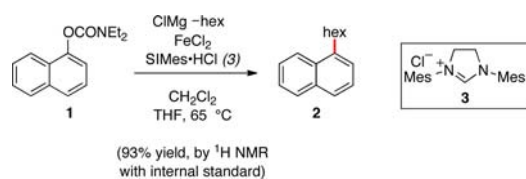


Figure 2. Optimal results obtained after extensive optimization.

Having discovered conditions for the iron-catalyzed coupling of naphthylcarbamate **1**, we examined several other carbamate substrates, in addition to aryl sulfamates (Table 1).²² The parent 1-naphthyl and phenyl systems underwent smooth reaction to give good isolated yields of product (entries 1 and 2). An electron-withdrawing *p*-trifluoromethyl substituent was examined and was found to be tolerated by the methodology (entry 3). Substrates containing the electron-donating *p*-methoxy and *p*-methyl groups also participated in the reaction, although yields obtained from the carbamate substrates were generally higher compared to those from the corresponding sulfamate substrates (entries 4 and 5). These results are notable, as iron-catalyzed alkylation reactions of electron-rich aryl chlorides and tosylates typically do not proceed efficiently.^{4a,b} The use of substrates derived from *m*-cresol also gave useful yields of coupled product (entry 6).

(17) For the preparation and characterization of iron–NHC complexes, see: (a) Przyojski, J. A.; Arman, H. D.; Tonzetich, Z. J. *Organometallics* **2012**, *31*, 3264. (b) Danopoulos, A. A.; Braunstein, P.; Wesolek, M.; Monakhov, K. Y.; Rabu, P.; Robert, V. *Organometallics* **2012**, *31*, 4102.

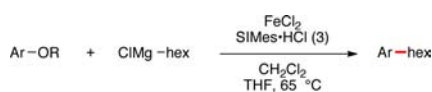
(18) The use of CH_2Cl_2 as solvent returned unreacted substrate. The unique beneficial role of CH_2Cl_2 as an additive is not presently understood (see the Supporting Information for additional additive studies).

(19) For the use of a dichloroalkane (i.e., 1,2-dichloro-2-methylpropane) as an additive in an unrelated Fe-catalyzed coupling, see: Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian J.* **2011**, *6*, 3059.

(20) For discussions of metal contaminants in iron-catalyzed reactions, see: (a) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586. (b) Thomé, I.; Nijis, A.; Bolm, C. *Chem. Soc. Rev.* **2012**, *41*, 979. (c) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407. (d) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.

(21) > 98.0% anhydrous $FeCl_2$ (Strem, 25 g or 0.2 mol = \$66 USD) was employed in all experiments, although the use of > 99.998% anhydrous $FeCl_2$ (Sigma-Aldrich) gave comparable results.

(22) For the subsequent data shown in Tables 1–3, reaction times are 3 h (nonoptimized for individual substrates).

Table 1. Iron-Catalyzed Coupling of Aryl Carbamates and Sulfamates with *n*-Hexylmagnesium Chloride^a

entry	Ar	OR	product	yield ^b
1a		-OSO ₂ NMe ₂		84% ^c
1b		-OCONEt ₂		78% ^c
2a		-OSO ₂ NMe ₂		85%
2b		-OCONEt ₂		82%
3a		-OSO ₂ NMe ₂		67%
3b		-OCONEt ₂		66%
4a		-OSO ₂ NMe ₂		67%
4b		-OCONEt ₂		90%
5a		-OSO ₂ NMe ₂		63%
5b		-OCONEt ₂		90%
6a		-OSO ₂ NMe ₂		53%
6b		-OCONEt ₂		92%

^a Reaction conditions: FeCl₂ (5 mol %), **3** (15 mol %), *n*-hexMgCl (1.5–2.0 equiv), CH₂Cl₂ (15–60 mol %), 3 h. ^b Isolated yields. ^c Isolated with naphthalene; see the Supporting Information for details.

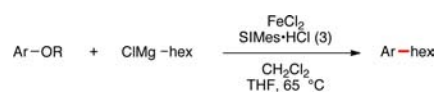
As shown in Table 2, the scope of the methodology includes heterocyclic substrates in addition to ortho-substituted substrates that are typically not tolerated in related iron-catalyzed couplings.^{1c,4} Of note, ortho-substituted aryl carbamates and sulfamates are readily accessible using ortho-metalation^{7c,23} or through transition-metal-catalyzed carbamate functionalization processes.²⁴ *o*-Cresol derivatives underwent the desired coupling (entry 1), as did substrates possessing an ortho phenyl substituent (entry 2). An *o*-methoxy group could also be employed (entry 3). Moreover, a bulky trimethylsilyl substituent was tolerated (entry 4). Heterocycles were also examined. Indole and dihydrobenzofuran carbamate derivatives coupled successfully (entries 5b and 6b), although coupling of the corresponding sulfamates proved difficult (entries 5a and 6a). Pyridine-containing substrates also participated in the desired transformation (entries 7a and 8).²⁵

The scope of the methodology with respect to the Grignard reagent is highlighted in Table 3. Alkyl Grignard

(23) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002; pp 330–367. (c) Macklin, T.; Snieckus, V. In *Handbook of C–H Transformations*; Dyke, G., Ed.; Wiley-VCH: New York, 2005; pp 106–119.

(24) (a) Bedford, R. B.; Webster, R. L.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 4853. (b) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (c) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978. (d) Yamazaki, K.; Kawamorita, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978. (e) Feng, C.; Loh, T.-P. *Chem. Commun.* **2011**, *47*, 10458. (f) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235.

(25) Attempts to couple the 2-carbamoylpyridine derivative (Table 2, entry 7b) led to cleavage of the carbamate.

Table 2. Coupling of Ortho-Substituted and Heterocyclic Substrates^a

entry	Ar	OR	product	yield ^b
1a		-OSO ₂ NMe ₂		82%
1b		-OCONEt ₂		84%
2a		-OSO ₂ NMe ₂		85%
2b		-OCONEt ₂		82%
3a		-OSO ₂ NMe ₂		56%
3b		-OCONEt ₂		52%
4a		-OSO ₂ NMe ₂		67%
4b		-OCONEt ₂		64%
5a		-OSO ₂ NMe ₂		<5% ^e
5b		-OCONEt ₂		48%
6a		-OSO ₂ NMe ₂		<30% ^e
6b		-OCONEt ₂		63%
7a ^c		-OSO ₂ NMe ₂		72%
7b ^d		-OCONEt ₂		–
8a ^c		-OSO ₂ NMe ₂		79%
8b		-OCONEt ₂		62%

^a Reaction conditions: FeCl₂ (5 mol %), **3** (15 mol %), *n*-hexMgCl (1.5–4.0 equiv), CH₂Cl₂ (15–60 mol %), 3 h. ^b Isolated yields. ^c 0 °C. ^d 23 °C. ^e Yield determined by ¹H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard.

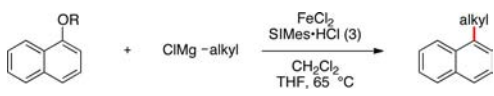
reagents possessing pendant ether or acetal functional groups were suitable coupling partners (entries 1 and 2). In addition, use of a furan-containing reagent provided the corresponding alkylated product (entry 3). The influence of branching near the Mg center was also evaluated. As demonstrated by the coupling of isobutylmagnesium chloride (entry 4), β -branching was tolerated. Finally, when Grignard reagents with substituents on the α -carbon were tested, coupling proceeded smoothly (entries 5 and 6). These latter two examples showcase the methodology's utility to construct C–C linkages between sp² and secondary sp³ centers, which remains a significant challenge in cross-coupling chemistry.²⁶

The iron-catalyzed sp²–sp³ C–C bond formation using aryl carbamates and sulfamates holds much promise for the synthesis of polyfunctionalized aromatic compounds. A demonstration of this attribute is shown in Figure 3, involving the functionalization of *p*-chlorophenyl carbamate **4**,

(26) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314.

(27) Chlorination of *N,N*-diethylphenyl carbamate using trichloroisocyanuric acid gave **4** in 71% yield (¹H NMR with internal standard), albeit with formation of the corresponding ortho substituted isomer in 29% yield.

Table 3. Coupling of 1-Naphthyl Carbamate and Sulfamate Substrates with Various Alkyl Grignard Reagents^a



entry	ClMg-alkyl	OR	product	yield ^b
1a		-OSO ₂ NMe ₂		59%
1b		-OCONEt ₂		78%
2a		-OSO ₂ NMe ₂		84%
2b		-OCONEt ₂		93%
3a		-OSO ₂ NMe ₂		58%
3b		-OCONEt ₂		52%
4a		-OSO ₂ NMe ₂		93%
4b		-OCONEt ₂		99%
5a		-OSO ₂ NMe ₂		82%
5b		-OCONEt ₂		80%
6a ^c		-OSO ₂ NMe ₂		54% ^d
6b ^c		-OCONEt ₂		60% ^d

^a Reaction conditions: FeCl₂ (5 mol %), **3** (15 mol %), alkyl-MgCl (2.0 equiv), CH₂Cl₂ (15–60 mol %), 3 h. ^b Isolated yields. ^c Grignard reagent exists as a mixture of endo/exo isomers; see the Supporting Information for details. ^d Isolated as a mixture of endo/exo isomers; see the Supporting Information for details.

which, in turn, can be prepared by carbamoylation of *p*-chlorophenol or through electrophilic chlorination of *N,N*-diethylphenyl carbamate.²⁷ Regioselective lithiation directed by the carbamate²³ and subsequent quenching with iodomethane afforded trisubstituted arene **5** in excellent yield, without disturbing the aryl chloride. Next, a Ni-catalyzed Suzuki–Miyaura coupling²⁸ led to the selective functionalization of the aryl chloride moiety (**5**→**6**). It should be emphasized that no evidence of competitive carbamate coupling was detected under these conditions.²⁹ With the *o*-functionalized carbamate **6** in hand, we tested the iron-catalyzed coupling. Using cyclohexylmagnesium

(28) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.

(29) The analogous coupling using the *des*-methyl derivative of **5** also led to selective coupling of the aryl chloride in high yield.

chloride, the desired coupling proceeded smoothly to furnish the alkylated product **7** in 72% yield.

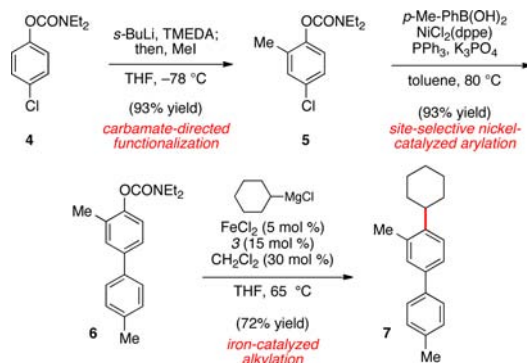


Figure 3. Sequential site-selective couplings and assembly of **7**.

In summary, the iron-catalyzed coupling of aryl sulfamates and carbamates with alkyl Grignard reagents provides a versatile means for the construction of sp²–sp³ C–C bonds. The methodology complements the more established methods for aryl sulfamate and carbamate functionalization achieved through arylation⁷ and amination¹⁰ processes. Considering the attractive features of sulfamate and carbamate substrates, the coupling reaction's broad scope, and the many virtues of iron-catalysis, we expect this methodology will prove useful in multistep synthesis and will further encourage the development of iron-promoted synthetic transformations.

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Supporting Information Available. Experimental details and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.