

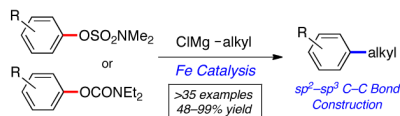
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Iron-Catalyzed Alkylations of Aryl Sulfamates and Carbamates

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

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, render these substrates useful for the synthesis of polyfunctionalized arenes.

As one of the most abundant, inexpensive, and non-toxic 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 Ni-catalyzed arylation,^{7,8,9} 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 bonds,¹⁵ and also expands the repertoire of highly sought after iron-catalyzed cross-coupling reactions.

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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>.

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 was undertaken to effect the alkylative coupling of carbamate **1** with *n*-hexylmagnesium chloride¹⁶ to afford alkylated product **2** (see SI). Although most reaction conditions based upon literature procedures for ironcatalyzed 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 CH₂Cl₂ was critical in order to obtain good yields and consistent results.^{18,19} Experiments conducted in the absence of FeCl₂ gave <15% product with or without the addition of copper, palladium, or nickel salts (see SI).^{20,21}

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).

As shown in Table 2, the scope of the methodology includes heterocyclic substrates, in addition to orthosubstituted substrates that are typically not tolerated in related iron-catalyzed couplings.^{1c,4} Of note, orthosubstituted aryl carbamates and sulfamates are readily accessible using ortho-metallation^{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 ortho 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 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 sp^2 and secondary sp^3 centers, which remains a significant challenge in cross-coupling chemistry.²⁶

The iron-catalyzed sp^2 – sp^3 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**, 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 chloride, the desired coupling proceeded smoothly to furnish the alkylated product **7** in 72% yield.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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 reference 7a for the coupling of aryl carbamates with $TMSCH_2MgCl$ and reference 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 reference 7a). No general methodology for the alkylation of aryl sulfamates or carbamates is known.
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15. sp^2 – sp^3 carbon-carbon bonds are commonly observed in natural products, pharmaceuticals, agrochemicals, ligands for catalysis, and materials.
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22. For the subsequent data shown in Tables 1–3, reaction times are 3 h (non-optimized for individual substrates).
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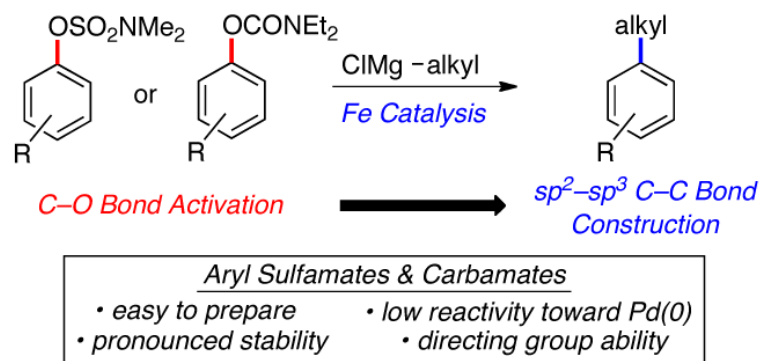


Figure 1. Iron-catalyzed alkylation of aryl sulfamates and carbamates.

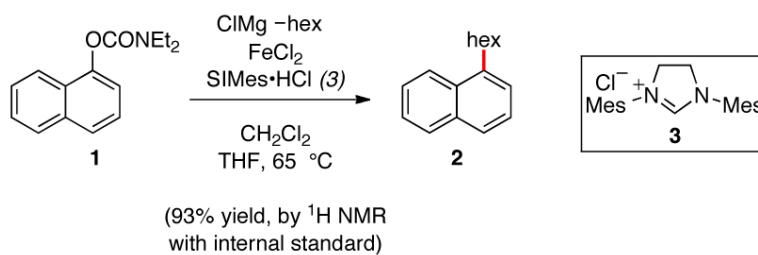


Figure 2.
Optimal result obtained after extensive optimization.

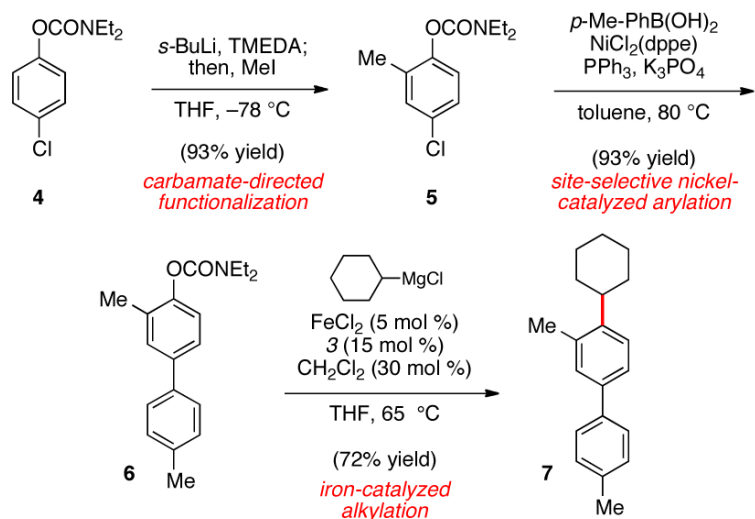
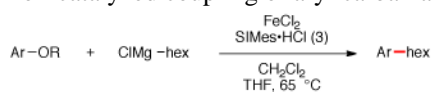


Figure 3.
Sequential site-selective couplings and assembly of 7.

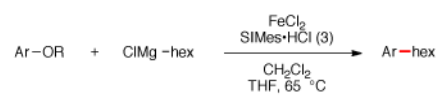
Table 1

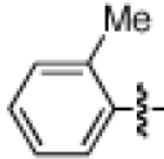
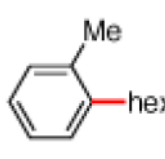
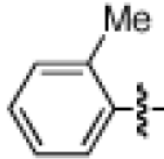
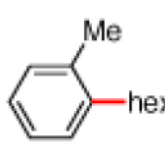
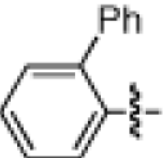
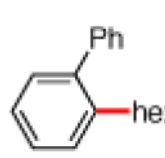
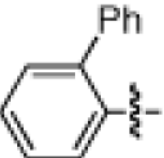
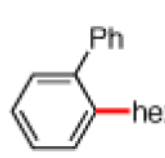
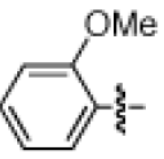
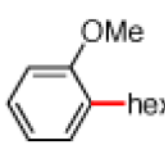
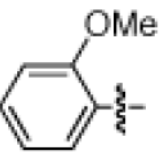
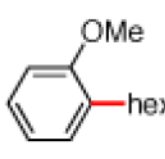
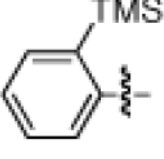
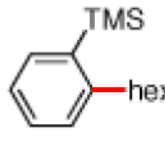
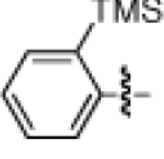
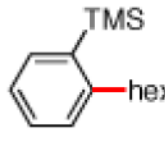
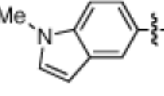
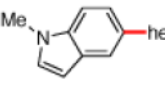
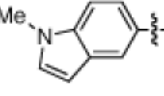
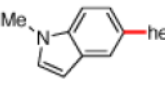
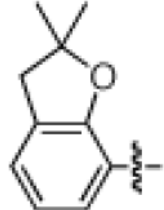
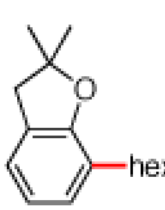
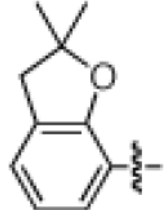
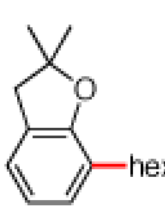
Iron-catalyzed coupling of aryl carbamates and sulfamates with *n*-hexylmagnesium chloride.^a

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%

^aReaction conditions: FeCl₂ (5 mol %), **3** (15 mol %), *n*-hexMgCl (1.5–2.0 equiv), CH₂Cl₂ (15–60 mol %), 3 h.^bIsolated yields.^cIsolated with naphthalene; see Supporting Information for details.

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%

entry	Ar	OR	product	yield ^b
7a ^c 7b ^d		-OSO ₂ NMe ₂ -OCONEt ₂		72% -
8a ^c 8b		-OSO ₂ NMe ₂ -OCONEt ₂		79% 62%

^aReaction conditions: FeCl₂ (5 mol %), **3** (15 mol %), *n*-hexMgCl (1.5–4.0 equiv), CH₂Cl₂ (15–60 mol %), 3 h.

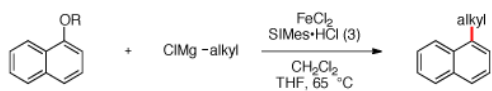
^bIsolated yields.

^c0 °C.


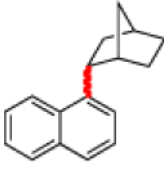
^d23 °C.

^eYield determined by ¹H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard.

Table 3

Coupling of 1-naphthyl carbamate and sulfamate substrates with various alkyl Grignard reagents.^a

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

entry	CIMg alkyl	OR	product	yield ^b
6a ^c 6b ^c		-OSO ₂ NMe ₂ -OCONEt ₂		54% ^d 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 SI for details.

^d Isolated as a mixture of endo:exo isomers; see Supporting Information for details.