ORGANIC LETTERS

2013
Vol. 15, No. 1
96–99

Iron-Catalyzed Cross-Coupling Reactions of Alkyl Grignards with Aryl Sulfamates and Tosylates

Toolika Agrawal and Silas P. Cook*

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102, United States

sicook@indiana.edu

Received November 13, 2012

ABSTRACT

The iron-catalyzed cross-coupling of aryl sulfamates and tosylates has been achieved with primary and secondary alkyl Grignards. This study of iron-catalyzed cross-coupling reactions also examines the isomerization and β-hydride elimination problems that are associated with the use of isopropyl nucleophiles. While a variety of iron sources were competent in the reaction, the use of $FeF_3 \cdot 3H_2O$ was critical to minimize nucleophile isomerization.

Palladium-catalyzed cross-coupling reactions represent over 60% of the carbon−carbon bond-forming reactions used in medicinal chemistry today.[1] This majority virtually guarantees that every new clinical candidate will require a process-scale implementation of a cross-coupling reaction. The use of palladium raises the issue of residual contamination that may affect subsequent transformations or even the health of patients.[2] As such, chemists need to investigate new cross-coupling reactions catalyzed by more benign metals. Iron, a historically important metal in cross-coupling reactions,[3] offers an appealing alternative to palladium due to its low cost, broad availability, and low toxicity (Figure 1).[4] Combined with an environmentally friendly electrophile, iron-catalyzed cross-coupling reactions could become the obvious alternative to palladium-mediated processes.

The use of C−O-based electrophiles provides an attractive cross-coupling partner that has been used widely with Ni,[5] and to a lesser extent with Pd.[6] The ubiquity of phenols and ketones combined with their favorable environmental impact when compared to halogen substrates confers clear advantages in using C−O electrophiles. While triflates and tosylates make up the majority of C−O cross-coupling

(1) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.
(2) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.
(3) (a) Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599.
(4) (a) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061.
(5) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.
(6) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (c) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (d) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. (e) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (f) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. (g) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402.
(7) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750.
(8) (a) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437. (b) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (c) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884.
(9) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (b) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (c) Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2171. (d) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766. (e) Mesganaw, T.; Fine Nathel, N. F.; Garg, N. K. *Org. Lett.* **2012**, *14*, 2918. (f) Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4182.
(10) (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2010**, *133*, 389. (b) Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, *2011*, 2761. (c) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790. (d) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293.

10.1021/ol303130j
Published on Web 12/17/2012

substrates, other functional groups have also been investigated recently by the groups of Snieckus,[7] Shi,[8] Garg,[9] Jarvo,[10] and Watson,[11] among others. Both triflates and tosylates have been reported to function better than iodides and bromides in iron-catalyzed cross-coupling reactions,[12] but there are few reports of alternative C−O electrophiles in iron catalysis.[13] Shi and co-workers first reported the iron-catalyzed alkylation of alkenyl pivalates, but only one low yielding example of an aryl pivalate was described.[14] Very recently, Garg and co-workers reported the first study of iron-catalyzed sulfamate and carbamate alkylation.[15] In light of these recent developments, we thought it appropriate to report our findings regarding an iron-catalyzed cross-coupling with aryl sulfamates and tosylates (Figure 1). The methodology provides for the construction of C_{sp^2}−C_{sp^3} bonds by coupling C−O-based electrophiles with primary and secondary Grignard reagents.

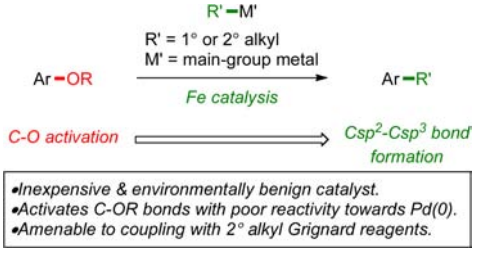
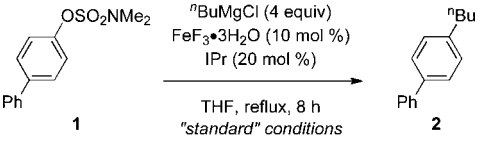


Figure 1. Iron-catalyzed C−O activation.

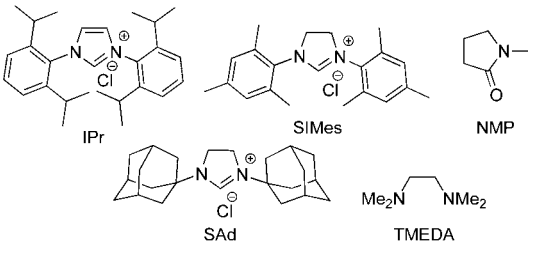
To begin our studies, a suitable activating group was required for the phenolic oxygen. Specifically, a functional group capable of conferring selectivity to the C−O bond while, at the same time, being stable to the reaction conditions was needed.[16] The evaluation of pivalate (CO^{t}Bu), diethylcarbamate ($CONEt_2$), diphenylphosphinate ($POPh_2$), Boc ($CO_2{}^t$Bu), and sulfamate (SO_2NMe_2) led quickly to the identification of sulfamate as the optimal activating group since nucleophilic displacement of the sulfamate by the Grignard reagent was not observed. Furthermore, the sulfamate moiety functions as an ideal directing group for the site-selective functionalization of arenes.[9c,17] With *p*-phenylphenol sulfamate **1** as the model substrate, reaction conditions were evaluated. In agreement with previous work,[14,15,18] N-heterocyclic carbene ligands were found to be uniquely effective for this transformation (entries 1, 5, and 6, Table 1) with 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) providing the optimal yield (entry 1, Table 1). Surprisingly, other ligands reported for iron-catalyzed cross-coupling reactions, such as TMEDA,[19] NMP,[20] and phosphines,[21] as well as other polydentate amines such as bipyridine and terpyridine, led to none of the desired product (entries 7−12, Table 1). The transformation also worked well with a number of alternative iron precatalysts (entries 2−4, Table 1), albeit in lower yield than with $FeF_3{\bullet}3H_2O$. While lower catalyst loadings led to slightly reduced yields, the exceptionally low cost of iron and ease of catalyst removal made the use of 10 mol % loading inconsequential. When 3 equiv of Grignard were used, the reaction consistently returned a 5−10% lower yield. Furthermore, the reaction proved unusually sensitive to temperature, generally providing 15−20% lower yields when reducing the temperature from 66 to 60 °C. During the preparation of this manuscript, Garg and co-workers reported the beneficial effect of DCM as an additive.[15] Here we found the reaction proceeded well in the absence of DCM.

Table 1. Deviation from Optimal Reaction Conditions



entry	variation from "standard" conditions	yield[a] (%)
1	none	90
2	$Fe(acac)_3$ (10 mol %) instead of FeF_3	84
3	$FeCl_3$ (10 mol %) instead of FeF_3	82
4	$FeCl_2$ (10 mol %) instead of FeF_3	66
5	SIMes (20 mol %) instead of IPr	80
6	SAd (20 mol %) instead of IPr	36
7	TMEDA (2 equiv) instead of IPr	0
8	THF:NMP (10:1) instead of THF	0
9	bipyridine (20 mol %) instead of IPr	0
10	terpyridine (10 mol %) instead of IPr	0
11	PPh_3 (30 mol %) instead of IPr	0
12	DIPHOS (20 mol %) instead of IPr	0
13	IPr (10 mol %) instead of 20 mol %	79
14	IPr (30 mol %) instead of 20 mol %	83
15	IPr (30 mol %), ^{n}BuMgCl (3 equiv)	81

[a] Yields obtained after silica gel chromatography.



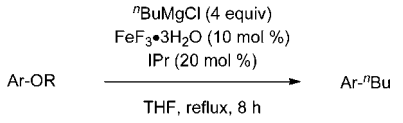
(11) Ehle, A. R.; Zhou, Q.; Watson, M. P. *Org. Lett.* **2012**, *14*, 1202.
(12) (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (d) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (e) Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950.
(13) (a) Cahiez, G.; Gager, O.; Habiak, V. *Synthesis* **2008**, 2636. (b) Hayashi, N.; Nakada, M. *Tetrahedron Lett.* **2009**, *50*, 232.
(14) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656.
(15) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796.
(16) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486.
(17) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352.
(18) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844.

After identifying $FeF_3 \bullet 3H_2O$ as the optimal iron precatalyst and IPr as the optimal NHC ligand, we turned our attention to the substrate scope (Table 2). Since aryl tosylates provide good yields in iron/NMP-catalyzed cross-coupling reactions[12a,b] and are considerably cheaper than sulfamates, we explored the relative reactivity of aryl tosylates and sulfamates. In general, naphthyl substrates (entries 9, 10, 17, and 19, Table 2) provided higher yields of the cross-coupled product than any of the phenyl substrates (entries 1−8, 11−14, Table 2). Sterically hindered electrophiles with a single *ortho* substituent provided low yields (entries 11−12, Table 2) while bis-*ortho* substituted substrates failed to react (entries 13−14, Table 2). Electron-rich aromatic rings (entries 1−2, Table 2) gave slightly lower yields than electron-deficient aromatic rings (entries 5−8, Table 2). Heterocyclic substrates also gave moderate yields under the reaction conditions (entries 15−16, Table 2). *All reactions with aryl sulfamates produced very few side products with nearly quantitative yields based on recovered starting material.* Attempts to suppress premature catalyst deactivation (e.g., slow Grignard addition, portionwise catalyst addition, etc.) were unsuccessful. In contrast, while reactions with aryl tosylates were much faster than those with aryl sulfamates, the aryl tosylates produced more side products and 5−10% of the corresponding phenol.

Previous work by Shi and co-workers found secondary Grignards, such as isopropyl magnesium chloride, failed in their iron-catalyzed cross-coupling reactions.[19] Garg and co-workers[15] reported secondary Grignards to be competent nucleophiles in their iron-catalyzed cross-coupling reactions with C−O electrophiles, and others have observed iron-catalyzed coupling reactions with secondary Grignards and aryl/vinyl chlorides.[12b,22] We were interested in the branched-to-linear ratios of secondary Grignards, an important problem in secondary alkyl cross-coupling chemistry[23] that has not been examined in iron-catalyzed variants. Both the tosylate and sulfamate proved competent electrophiles with cyclohexyl magnesium chloride to give moderate-to-good yields of the cross-coupled product (entries 2 and 5, Table 3). Interestingly, while isopropyl magnesium chloride provided moderate branched selectivity with the sulfamate (entry 3, Table 3), the selectivity was reversed with the corresponding tosylate (entry 6, Table 3). Since the iron-catalyzed cross-coupling reaction seemed relatively tolerant of different iron precatalysts (Table 1), we investigated the formation of the branched product as a function of the iron precatalyst (Table 4).

The branched-to-linear ratio was determined for the coupling of an aryl sulfamate with isopropyl magnesium chloride under the influence of different iron precatalysts. Surprisingly, while $FeF_3 \bullet 3H_2O$ (entry 8, Table 4) favored

Table 2. Substrate Scope of Aryl Tosylates and Sulfamates



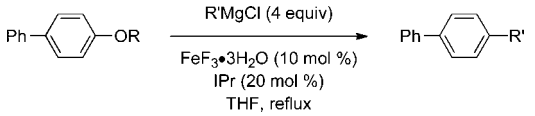
entry	Ar	R[a]	product	yield[b] (%)
1	MeO	-SO_2NMe_2	MeO, ^nBu	39
2		-Ts		45
3	MeS	-SO_2NMe_2	MeS, ^nBu	56
4		-Ts		62
5	F_3C, F_3C	-SO_2NMe_2	F_3C, ^nBu, F_3C	50
6		-Ts		62
7	F_3C	-SO_2NMe_2	^nBu, F_3C	65
8		-Ts		53
9		-SO_2NMe_2	^nBu	86
10		-Ts		81
11		-SO_2NMe_2	^nBu	35
12		-Ts		30
13		-SO_2NMe_2	^nBu	0
14		-Ts		trace
15	N	-SO_2NMe_2	N, ^nBu	50
16		-Ts		55
17	MeO	-SO_2NMe_2	MeO, ^nBu	81
18		-Ts		N/A[c]
19	MeO	-SO_2NMe_2	MeO, ^nBu	58
20		-Ts		N/A[c]

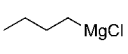
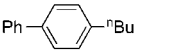
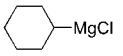
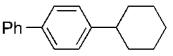
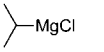
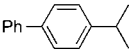
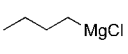
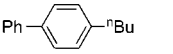
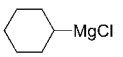
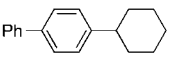
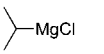
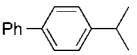
[a] All sulfamate reactions refluxed for 8 h, and tosylate reactions refluxed for 3 h. [b] Yields obtained after silica gel chromatography. [c] Starting tosylates were unstable.

branched selectivity by 6.5:1, $FeCl_3$ reversed the selectivity to favor the linear product by 1:5 (entries 1 and 2, Table 4). Furthermore, both acetylacetonate (entry 3, Table 4) and trifluoroborate (entry 5, Table 4) counterions exhibit selectivity for the linear product whereas the triflate counterion (entry 4, Table 4) shows almost equal formation of branched and linear products with only a slight selectivity for the linear product. These results suggest that the coordination of the counterion to the active iron species has an effect on the branched-to-linear selectivity. To corroborate this, silver salts were used to exchange the halide counterions of both $FeCl_3$ and FeF_3 in situ. If full counterion exchange with the noncoordinating counterion of SbF_6

(19) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.
(20) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.
(21) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2005**, *71*, 1104.
(22) Ottesen, L. K.; Ek, F.; Olsson, R. *Org. Lett.* **2006**, *8*, 1771.
(23) (a) Joshi-Pangu, A.; Ganesh, M.; Biscoe, M. R. *Org. Lett.* **2011**, *13*, 1218. (b) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 1871.

Table 3. Substrate Scope of Grignards

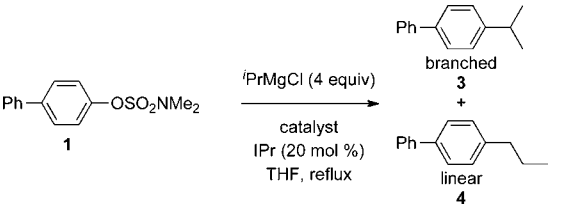


entry	R	R'MgCl	product	yield (%)
1	-SO_2NMe_2			90
2	-SO_2NMe_2			77
3	-SO_2NMe_2			65 (6.5:1)[a]
4	-Ts			74
5	-Ts			39
6	-Ts			50 (1:10)[a]

[a] Branched/linear ratio in parentheses.

could be realized, then both of these reactions should give similar yields and selectivity. When the reaction was run with $FeCl_3$ (10 mol %) and $AgSbF_6$ (30 mol %), there is virtually no change in yield relative to $FeCl_3$ alone (entry 6 vs 1, Table 4), whereas the reaction with $FeF_3•3H_2O$ (10 mol %) and $AgSbF_6$ (30 mol %) shows a marked decrease in branched selectivity when compared to $FeF_3•3H_2O$ alone (entry 7 vs 8, Table 4). The lack of complete selectivity reversal is likely due to incomplete AgF formation since it has considerable solubility in THF, unlike AgCl. This provides soluble fluoride ions that are available to coordinate with iron to enhance the branched-to-linear selectivity. A possible explanation for the unique branched-to-linear selectivity for $FeF_3•3H_2O$ is that the fluoride ion strongly coordinates to the iron center to prevent open coordination sites for β-agostic interactions, thereby slowing down the isomerization of the alkyl Grignard. It is noteworthy that reactions with $FeF_3•3H_2O$ are the slowest, requiring the full 8 h at reflux, whereas reactions with all other iron precatalysts are complete in 3 h or less. The slower rate is consistent with the posibility of fewer open coordination sites at iron with $FeF_3•3H_2O$ during the catalytic cycle.

Table 4. Iron Precatalyst Effects on Branched-to-Linear Selectivity



entry	catalyst	yield (%)[a]	**3:4**
1	$FeCl_3$ (10 mol %)	79	0.2:1
2	$FeCl_3•6H_2O$ (10 mol %)	70	0.3:1
3	$Fe(acac)_3$ (10 mol %)	85	0.2:1
4	$Fe(OTf)_2$ (10 mol %)	76	0.9:1
5	$Fe(BF_4)_2•6H_2O$ (10 mol %)	80	0.3:1
6	$FeCl_3$ (10 mol %), $AgSbF_6$ (30 mol %)	76	0.2:1
7	$FeF_3•3H_2O$ (10 mol %), $AgSbF_6$ (30 mol %)	43	1.1:1
8	$FeF_3•3H_2O$ (10 mol %)	65	6.5:1

[a] Yields obtained after silica gel chromatography.

In summary, the iron-catalyzed cross-coupling of aryl sulfamates and tosylates has been achieved. The reaction was shown to tolerate a number of iron precatalysts, but the iron counterions had a significant influence on branched-to-linear ratios with secondary Grignard reagents. While reactions with the sulfamates produced nearly quantitative yields based on recovered starting material, further investigations to determine the cause of catalyst deactivation will lead to highly effective cross-coupling reactions. The attractive features of C–O electrophiles, combined with cheap and environmentally friendly iron catalysis, provide clear advantages for this methodology over existing cross-coupling technology and should facilitate the development of other iron-promoted transformations.

Acknowledgment. Financial support for this work was provided by Indiana University.

Supporting Information Available. Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.