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Heteroaromatic Sulfonates and Phosphates as Electrophiles in Iron-Catalyzed Cross-Couplings

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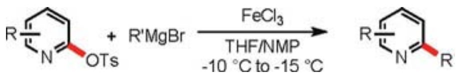
ABSTRACT



Employment of heteroaromatic tosylates and phosphates as suitable electrophiles in iron-catalyzed cross-coupling reactions with alkyl Grignard reagents is reported. These reactions are performed at low temperature allowing good functional group tolerance and full conversion is achieved within minutes. In addition, an aryl−aryl cross-coupling utilizing a heteroaryl sulfamate electrophile is reported.

Heteroaromatic systems are important constituents of a wide range of natural products, pharmaceuticals, and fine chemicals, and hence methods for their functionalization are of high interest.[1,2] Transition-metal-catalyzed transformations represent a central strategy in this respect, and in particular Pd-catalyzed reactions for the introduction of ring substituents have demonstrated their worth.[3] On the other hand, iron-catalyzed cross-couplings employing heteroaromatic electrophiles have been described to a lesser extent, with primary focus on heteroaryl halides and a few triflates, even though such catalytic protocols for coupling reactions with Grignard reagents have been successfully applied to isocyclic aromatic ring systems.[4]

Heterocyclic alcohols represent interesting precursors to such Fe-catalyzed coupling reactions as they allow for the possibility of exploiting another class of commercially available substrates with orthogonal substitution patterns compared to the aryl halides.[5] However, the use of the more common aryl triflates suffers from certain drawbacks such as their instability and the use of expensive triflating agents for their preparation. Hence, replacement of the heteroaromatic triflate electrophiles with the corresponding and more stable tosylates or phosphates would increase the utility of such compounds.[6−9]

In this communication we report on the introduction of 2-pyridyl and 2-pyrimidyl tosylates and phosphates as viable electrophiles in Fe-catalyzed cross-coupling reactions with alkyl Grignard reagents. These reactions are performed under conditions allowing good functional group tolerance.

Initial studies were focused on the coupling of *n*-hexylmagnesium bromide with the crystalline 4,6-dimethylpyrimidin-2-yl tosylate **1a** prepared from the corresponding alcohol with tosyl chloride.[3g] Using similar reaction conditions as reported by the groups of Fürstner and Cahiez with

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(1) (a) Roth, H. J.; Kleemann, A. In *Pharmaceutical Chemistry, Volume 1: Drug Synthesis*; John Wiley and Sons: New York, 1988. (b) Sha, F.; Huang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458. (c) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (d) Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6951.

(2) For some recent reviews, see: (a) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. (b) Hill, M. D.; Movassaghi, M. *Chem. Eur. J.* **2008**, *14*, 6836.

(3) (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Kakiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 9032. (d) Sasada, T.; Kobayashi, F.; Sakai, N.; Konakahara, T. *Org. Lett.* **2009**, *11*, 2161. (e) Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715. (f) Peréz-Balado, C.; Willemsens, A.; Ormerod, D.; Aelterman, W.; Mertens, N. *Org. Process. Res. Dev.* **2007**, *11*, 237. (g) Gøgsig, T. M.; Lindhardt, A. T.; Dekhane, M.; Grouleff, J.; Skrydstrup, T. *Chem. Eur. J.* **2009**, *15*, 5950.

(4) (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) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844. (d) Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547.

(5) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565.

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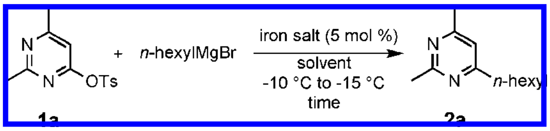
$Fe(acac)_3$ as the catalyst in a solvent mixture of THF/NMP, the desired coupling product **2a** could be isolated in a satisfactory 88% yield (Table 1, entry 1).[4,10]

Table 1. Optimization of the Catalytic System



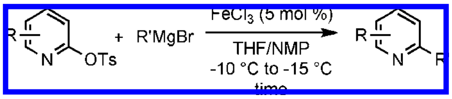
entry[a]	iron salt	solvent	time (min)	yield (%)[b]
1	$Fe(acac)_3$	THF/NMP	15	88
2	$Fe(acac)_3$	THF	60	not complete[c]
3	None	THF/NMP	240	not complete[c]
4	$Fe(acac)_3$	THF/NMP	60	not complete[c,d]
5	$Fe(acac)_3$	DME	45	73
6	$FeCl_3$	THF/NMP	15	98
7	$FeCl_2$	THF/NMP	15	94
8	FeF_3	THF/NMP	60	no reaction
9	$FeCl_3$	THF/NMP	20	90[e]
10	$FeCl_3$	THF/NMP	15	96[f]

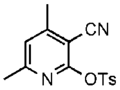
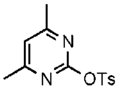
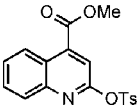
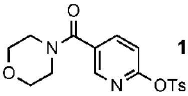
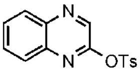
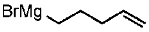
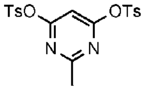
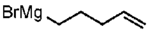
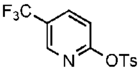
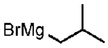
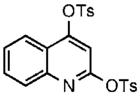
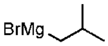
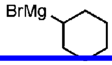
[a] **1a** (0.6 mmol), NMP (5.4 mmol), and *n*-hexylmagnesium bromide (1.1 mmol) in THF (2.5 mL). [b] Isolated yields. [c] Yield not determined due to complex ^1H NMR spectrum of crude reaction mixture. [d] Reaction run with $Fe(acac)_3$ (1 mol %). [e] Reaction run with *n*-hexylmagnesium bromide (0.8 mmol). [f] Reaction run with *n*-hexylmagnesium bromide (0.9 mmol).

Lowering the catalytic loading or changing the solvent system was nonrewarding and facilitated the formation of undesired byproducts (entries 2−5). As observed by the group of Cahiez, the presence of NMP as a cosolvent proved imperative for the coupling to occur (entry 2).[10] Turning to the iron(III) chloride salt improved the reaction, and a nearly quantitative yield could be secured after column chromatography (entry 6). An essentially identical yield was obtained when *n*-hexylmagnesium bromide (1.5 equiv) was added to the reaction mixture, attaining full conversion within only 15 min (entry 10). On the other hand, no reaction was observed when iron(III) fluoride was applied, resulting in a sluggish reaction mixture, without the formation of the characteristic dark brown solution upon addition of the Grignard reagent (entry 8).

With these successful reaction conditions in hand, we set out to test the generality of this iron-catalyzed cross-coupling reaction, employing a variety of substituted heteroaromatic tosylates as depicted in Table 2.

Table 2. Heteroaromatic Tosylates in Iron-Catalyzed Cross-Couplings



entry[a]	tosylate	R'MgBr	time(min)	yield(%)[b]
1	 **1b**	*n*-$C_6H_{13}MgBr$	15	85 **2b**
2	 **1c**	*n*-$C_6H_{13}MgBr$	10	91 **2c**
3	 **1d**	*n*-$C_6H_{13}MgBr$	10	80 **2d**
4	 **1e**	*n*-$C_6H_{13}MgBr$	10	80 **2e**
5	**1a**		10	92 **2f**
6	 **1f**		9	84 **2g**
7	**1b**		20	73 **2h**
8	 **1g**		14	96 **2i**[c]
9	**1d**		16	77 **2j**
10	**1e**		15	76 **2k**
11	 **1h**		10	83 **2l**
12	 **1i**		10	76 **2m**[d]
13	**1a**		15	77 **2n**[e]

[a] **1a** (0.6 mmol), NMP (5.4 mmol), and alkylmagnesium bromide (0.9 mmol) in THF (2.5 mL). [b] Isolated yields. [c] Reaction run with 4-pentenyl magnesium bromide (1.8 mmol). [d] Reaction run with isobutyl-magnesium bromide (1.8 mmol). [e] Reaction run with Fe(salen)Cl (5 mol %) and cyclohexylmagnesium bromide (1.2 mmol) at 0 °C.

Functional groups such as nitriles, esters, and amides are well tolerated under the applied conditions, and the alkylated products could be isolated in excellent yields (entries 1, 3 and 4). Switching from a pyridyl- to a pyrimidyl-based aromatic core did not influence the outcome of the reaction (entry 2). Alkenyl Grignard reagents represented by 4-pentenylmagnesium bromide demonstrated equal reactivity toward the heteroaromatic tosylates as described above (entries 5, 7, 9, and 10). In addition, 2-quinaxolinyl tosylate performed well, and a satisfactory 84% yield was obtained (entry 6). A double coupling of the pyrimidyl ditosylate shown in entry 8 was attempted, resulting in a nearly

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(6) For applications of tosylate electrophiles, see: (a) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. (b) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (c) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. (d) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (e) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457.

(7) For applications of phosphate electrophiles, see: (a) Hansen, A. L.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464. (b) Gauthier, D.; Beckendorf, S.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536. (c) Mousset, D.; Gillaizeau, I.; Sabatié, A.; Bouyssou, P.; Coudert, G. *J. Org. Chem.* **2006**, *71*, 5993.

(8) Activated aryl tosylates have in a few examples been demonstrated to be compatible in iron-catalyzed cross-couplings; see refs 4a and 4b.

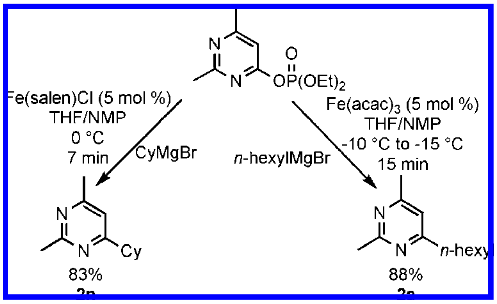
(9) Cahiez and coworkers have recently described the coupling of dienol phosphates with Grignard reagents under Fe-catalysis: Cahiez, G.; Habiak, V.; Gager, O. *Org. Lett.* **2008**, *10*, 2389.

(10) (a) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53. (b) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.

quantitative yield in only 14 min. Increasing the steric bulk on the organomagnesium species did not influence the outcome of the cross-coupling reaction (entries 11−13). Despite the fact that 3 equiv of isobutylmagnesium bromide was added to the reaction mixture, only the monoalkylated quinoline-4-yl tosylate was detected (entry 12). Employment of the more reactive Fe(salen)Cl complex was necessary in order to obtain successful coupling when switching to a secondary alkylmagnesium reagent (entry 13).[4b] Finally, substrates such as vinyl-, allyl-, (1,3-dioxolan-2-yl-methyl)-, and 3-(dimethylamino)-propylmagnesium halides did not participate in this reaction. In the latter case, it may be conceived that a coordination of the amine moiety to the magnesium nucleus could possibly impede the desired coupling. As reported by the group of Fürstner an ethylene spacer between the magnesium and the functional group appears to be vital in order to obtain productive reactivity.[4b]

Enol phosphates derived from the corresponding ketones or aldehydes have been shown to readily undergo iron-catalyzed cross-coupling reactions with both alkyl and aryl Grignard reagents.[10,11] Thus, exploiting the same optimized reaction conditions, we examined the utility of pyrimidyl phosphates as coupling partners. As illustrated in Scheme 1, diethyl phosphates can be effectively employed to give coupling products in excellent yields. These results demonstrate to the best of our knowledge the first examples of aryl phosphates as viable electrophiles in iron catalysis.

Scheme 1. Heteroaromatic Phosphates in Iron-Catalyzed Cross-Couplings

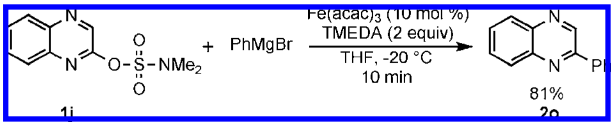


Finally, we studied the ability of the heteroaromatic tosylates and phosphates to perform cross-coupling with phenylmagnesium chloride. Unfortunately, severe formation of undesired byproduct was detected (results not shown). In addition to the expected homocoupling of the aryl Grignard reagent,[12] the formation of phenol was also observed, potentially originating from a nucleophilic attack on the sulfur center. In order to overcome this side reaction, we set forth to search for an alternative electrophile. In this respect, we examined the corresponding heteroaryl sulfamate because of the recent application of such derivatives in palladium-catalyzed Suzuki−Miyaura and Negishi cross-couplings in which they have been demonstrated to exhibit increased reactivity compared to that of the corresponding tosylates.[13]

In the coupling with phenylmagnesium bromide, the precatalyst Fe(acac)$_3$ proved superior compared to FeCl$_3$, and NMP had a detrimental effect on the coupling yield. Instead, a premixed solution of the Grignard reagent in THF and TMEDA (*N*,*N*,*N*',*N*'-tetramethylethylene-diamine) added slowly to the cooled reaction mixture turned out to be crucial to attain full conversion.[14] Gratifyingly, this resulted in a satisfying 81% isolated yield. Running the reaction at −40 °C produced the exact same result after only 10 min, proving this cross-coupling to be very effective.

In conclusion we have demonstrated the usefulness of heteroaromatic tosylates in iron-catalyzed alkylation reactions with good functional group tolerance. Furthermore, we have introduced heteroaromatic phosphates as viable electrophiles displaying comparable reactivities as the corresponding tosylates, and a single example of an effective aryl−aryl coupling with a heterocyclic sulfamate was achieved. Work is now underway in our laboratories to investigate the scope of both aryl phosphates and sulfamates, which will be reported in due time.

Scheme 2. Heteroaromatic Sulfamate in Iron-Catalyzed Cross-Couplings



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Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all the coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Cahiez, G.; Gager, O.; Habiak, V. *Synthesis* **2008**, 2636. (b) Larsen, U. S.; Martiny, L.; Begtrup, M. *Tetrahedron Lett.* **2005**, *46*, 4261.

(12) For papers regarding homocoupling of Grignard reagents, see: (a) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788. (b) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943. (c) Xu, X.; Cheng, D.; Pei, W. *J. Org. Chem.* **2006**, *71*, 6637. (d) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491. (e) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1654, and references therein.

(13) Albaneze-Walker, J.; Raju, R.; Vance, J. A.; Goodman, J. A.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P. A.; Espino, P.; Andrews, D. R. *Org. Lett.* **2009**, *11*, 1463, and references therein.

(14) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521.