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Selective Iron-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Enol Triflates, Acid Chlorides, and Dichloroarenes

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Cheap, readily available, air stable, nontoxic, and environmentally benign iron salts such as $Fe(acac)_3$ are excellent precatalysts for the cross-coupling of Grignard reagents with alkenyl triflates and acid chlorides. Moreover, it is shown that dichloroarene and -heteroarene derivatives as the substrates can be selectively monoalkylated by this method. All cross-coupling reactions proceed very rapidly under notably mild conditions and turned out to be compatible with a variety of functional groups in both reaction partners. A detailed analysis of the preparative results suggests that iron-catalyzed C−C bond formations can occur via different pathways. Thus, it is likely that reactions of methylmagnesium halides involve iron−ate complexes as the active components, whereas reactions of Grignard reagents with two or more carbon atoms are effected by highly reduced iron-clusters of the formal composition $[Fe(MgX)_2]_n$ generated in situ. Control experiments using the ate-complex $[Me_4Fe]Li_2$ corroborate this interpretation.

Introduction

Palladium- and nickel-catalyzed cross-coupling reactions are an indispensable tool for organic synthesis.[1−3] Despite the truly impressive application profile and maturity of this methodology, the search for possible alternatives might be rewarding, provided that catalysts can be found that are similarly effective, yet cheaper and/or less toxic. Early reports by Kochi et al. on the use of iron salts provide a particularly promising lead in this regard.[4] Surprisingly though, this method remained essentially restricted to alkenyl halides,[4,5] phosphates,[5a] and sulfones[6] as the substrates for a rather long period of time. Only recently was it possible to extend the scope of iron-catalyzed cross-coupling reactions beyond these types of electrophiles[7−12] and to implement the method into the synthesis of natural products and pharmaceutically relevant compounds.[13−15] These applications are distinguished by the low cost, ready availability, and benign character of the required iron salts as well as by exceptionally high reaction rates and notably mild conditions.

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[2] Selected reviews: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (e) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (f) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176 and literature cited therein.

[3] For selected contributions from this laboratory, see: (a) Fürstner, A.; Leitner, A. *Synlett.* **2001**, 290. (b) Fürstner, A.; Seidel, G. *Synlett* **1998**, 161. (c) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332. (d) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107. (e) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (f) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072.

[4] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (c) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599. (d) Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502. (e) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351. (f) Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11.

[5] (a) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (b) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53. (c) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901. (d) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (e) Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009. (f) Fakhakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131. (g) Ostergaard, N.; Pedersen, B. T.; Skjaerbaek, N.; Vedso, P.; Begtrup, M. *Synlett* **2002**, 1889. (h) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718. (i) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081.

[6] (a) Fabre, J.-L.; Julia, M.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2469. (b) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 111. (c) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 119.

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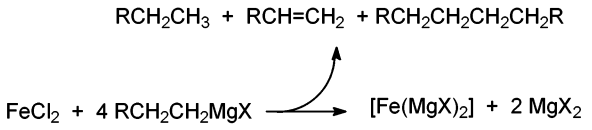
SCHEME 1



The available information suggests that the chosen iron precatalyst is reduced in situ by the Grignard reagent to form a highly nucleophilic entity of the formal composition $[Fe(MgX)_2]_n$ (Scheme 1);[16] this dark-brown, ether-soluble cluster species likely mediates the catalytic turnover.[7] As part of our ongoing studies in this field, we now report the first successful iron-catalyzed cross-couplings of enol triflates[17,18] and explore the scope of the iron-catalyzed reactions of acid chlorides in detail.[11,14] Moreover, the possibility of performing selective monoalkylation reactions of dihaloarenes is outlined. In addition to the preparative aspects, these results are also mechanistically relevant since they suggest that iron-catalyzed reactions may proceed along distinctly different pathways depending on the chosen nucleophile.

Results and Discussion

Alkenyl Triflates. As can be seen from the results compiled in Table 1, a variety of alkenyl triflates derived from ketones, β-keto esters, or cyclic 1,3-diketones can be efficiently cross-coupled with Grignard reagents in the presence of $Fe(acac)_3$ as the precatalyst of choice, affording the desired products in good to excellent yields in most cases (for exceptions see entries 7, 13, and 14). In line with previous observations,[7] the iron-catalyzed C−C bond formation outperforms the uncatalyzed attack of the Grignard reagent onto other electrophilic sites in the substrates, thus rendering the reaction compatible with functional groups such as esters, enones, ethers, carbamates, acetals, or lactones. Likewise, several functionalized organomagnesium halides bearing ether-, acetal-, alkyne-, trimethylsilyl-, or chloride entities on their backbones have been successfully employed. The method provides ready access to 4-alkyl-2(5*H*)-furanone derivatives (entries 17−23), some of which are effective calcium channel antagonists and have been patented for their specific antiinflammatory activity.[19] Furthermore, the product shown in entry 32 constitutes a key building block for the total synthesis of latrunculin B, a potent actin binding macrolide of marine origin.[14] A comparison of entries 1/4 and 11/14 makes clear that the iron-catalyzed reaction is sensitive to steric hindrance exerted by ortho substituents. In line with this, the formation of the menthone-derived alkene shown in entry 10 requires a high catalyst loading and is best carried our in a stoichiometric fashion (see below).

A closer inspection of the data summarized in Table 1 reveals certain reactivity trends that deserve further comment. First, *alkyl*magnesium halides perform particularly well and tend to give higher yields than their *aryl* counterparts.[20,21] Increasing the alkyl chain length results in somewhat lower yields; this effect is particularly pronounced with substrates bearing substituents ortho to the leaving group (cf. entries 12−14).

It is particularly important to note that even MeMgBr, MeLi,[22] and Me_3SiCH_2MgBr have been successfully cross-coupled, although these reagents cannot trigger the reduction of $Fe(acac)_3$ by the mechanism depicted in Scheme 1 due to the inability of a C1-donor to engender β-hydride elimination.[23] Their different behavior is reflected in a characteristic appearance of the reaction mixtures. Thus, addition of either MeMgBr, MeLi, or Me_3SiCH_2MgBr to $Fe(acac)_3$ in THF/NMP in the presence of a substrate leads to intensely yellow-colored homogeneous solutions, whereas any Grignard reagent with more than two carbon atoms instantaneously affords black/brown mixtures indicating the formation of $[Fe(MgX)_2]_n$ or related cluster species.[16]

Likewise, a look at the stoichiometry of the reactions substantiates the distinctly different behavior of methyl donors on one hand and higher *n*-alkyl-Grignard reagents on the other hand. Since the reduction process shown in Scheme 1 consumes 4 equiv of RMgX per Fe(II) center,[16] the catalyst loading should be low to avoid the need for an undue excess of the organomagnesium compound. The cross-coupling of MeMgBr, however, proceeds even if the loading of $Fe(acac)_3$ is increased to 100% (cf. entry 10).[24] This finding suggests that the scenario of Scheme 1 plays no essential role if *methyl* donors are employed and only

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[11] (a) Percival, W. C.; Wagner, R. B.; Cook, N. C. *J. Am. Chem. Soc.* **1953**, *75*, 3731. (b) Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805. (c) Dell'Anna, M. M.; Mastrorilli, P.; Nobile, C. F.; Marchese, G.; Taurino, M. R. *J. Mol. Catal. A: Chem.* **2000**, *161*, 239. (d) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700. (e) Ritter, K.; Hanack, M. *Tetrahedron Lett.* **1985**, *26*, 1285. (f) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 3595. (g) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053.

[12] (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

[13] Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308.

[14] Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5358.

[15] Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950.

[16] (a) Bogdanović, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610. (b) Aleandri, L. E.; Bogdanović, B. In *Active Metals: Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; p 299. (c) Aleandri, L. E.; Bogdanović, B.; Bons, P.; Dürr, C.; Gaidies, A.; Hartwig, T.; Huckett, S. C.; Lagarden, M.; Wilczok, U.; Brand, R. A. *Chem. Mat.* **1995**, *7*, 1153.

[17] For a review of enol triflate chemistry including various types of cross-coupling reactions, see: Ritter, K. *Synthesis* **1993**, 735.

[18] See the following for leading references on metal-catalyzed cross-coupling reactions of enol triflates with Grignard reagents and literature cited therein: (a) Miller, J. A. *Tetrahedron Lett.* **2002**, *43*, 7111. (b) Busacca, C. A.; Eriksson, M. C.; Fiaschi, R. *Tetrahedron Lett.* **1999**, *40*, 3101.

[19] Oomura, Y.; Shiraishi, T.; Takeoka, J. *Jpn. Kokai Tokkyo Koho* JP07,196,491, 1995; *Chem. Abstr.* **1995**, *123*, 246850.

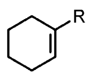
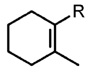
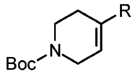
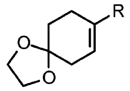
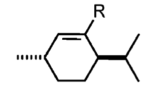
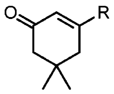
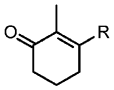
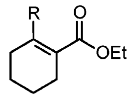
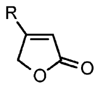
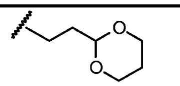
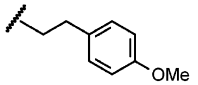
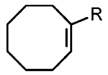
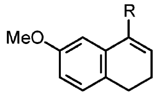
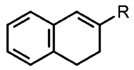
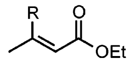
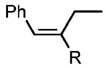
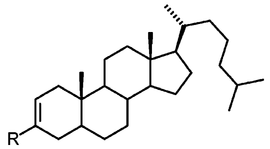
[20] Iron-catalyzed reactions of *aryl*magnesium halides in general are known to be more problematic because the catalytic homodimerization of the Grignard reagent can seriously compete with or even outperform effective cross coupling, cf. refs 7 and 21. In line with this, varying amounts of biphenyl or substituted biphenyls accompany the cross-coupling products shown in Table 1, which, however, are generally readily purified by flash chromatography.

[21] (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Constable: London, 1954. (b) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316. (c) Kharasch, M. S.; Nudenberg, W.; Archer, S. *J. Am. Chem. Soc.* **1943**, *65*, 495.

[22] Note that alkyllithium reagents in general were previously shown to be unsuitable for iron-catalyzed cross-coupling reactions, cf. ref 7.

[23] In this context, it is noteworthy that iron-catalyzed cross-couplings of MeMgX with aryl chlorides and triflates seem to be confined to special cases, cf. ref 9b.

TABLE 1. Iron-Catalyzed Cross Coupling Reactions of Alkenyl Triflates with Grignard Reagents[g]

Entry	Product	R	Yield
1		C_4H_9	80%
2		$C_{14}H_{29}$	67%
3		Ph	74%
4		C_4H_9	53%
5		C_6H_4OMe	62%
6		$C_{14}H_{29}$	73%
7		Ph	47%
8		$C_{14}H_{29}$	65%
9		Ph	68%
10		CH_3	88%[a]
11		$C_{14}H_{29}$	67%[b]
12		CH_3	73%
13		C_4H_9	45%
14		$C_{14}H_{29}$	17%
15		$C_{14}H_{29}$	79%[c]
16		Ph	53%[c]
17		CH_3	70%
18		C_6H_{13}	68%
19		$C_{14}H_{29}$	66%
20		CH_2SiMe_3	80%
21		Ph	51%
22			67%
23			84%
24		$C_{14}H_{29}$	60%[d]
25		Ph	61%
26		p-ClC_6H_4	66%
27		$C_{14}H_{29}$	64%
28		CH_3	89%
29		C_4H_9	88%
30		Ph	66%
31		$C_{14}H_{29}$	98%[e]
32		$CH_2CH_2C{\equiv}CMe$	97%[f]
33		Ph	83%[e]
34		p-$MeOC_6H_4$	51%
35		CH_3	87%
36		C_4H_9	90%
37		p-$MeOC_6H_4$	84%
38		CH_3	91%
39		$C_{14}H_{29}$	86%
40		Ph	76%
41		$(CH_2)_8$-OMOM	91%

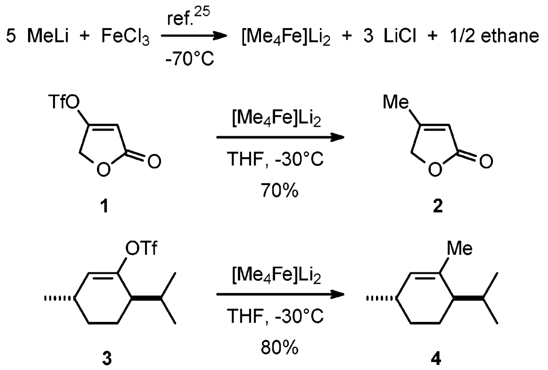
[a] Using 100 mol % of $Fe(acac)_3$. [b] Using Fe(salen)Cl as the catalyst. [c] Using 2.4 equiv of the Grignard reagent in combination with 10 mol % of $Fe(acac)_3$. [d] Using 2.4 equiv of $C_{14}H_{29}MgBr$ and 10 mol % of $Fe(acac)_3$. [e] Using 1.8 equiv of the Grignard reagent and 7 mol % of $Fe(acac)_3$. [f] Using 10 mol % of $Fe(acac)_3$ in THF (without NMP). [g] All reactions were performed using RMgX (1.1−1.3 equiv) and $Fe(acac)_3$ (5 mol %) in THF/NMP at −30 °C unless stated otherwise.

small amounts of MeMgBr—if any—are consumed prior to the actual cross-coupling.

In line with this notion, it is possible to prepare the ate-complex $[Me_4Fe][Li_2(OEt_2)_2]$ in analytically pure form as a thermolabile and highly air-sensitive orange solid by reaction of MeLi with $FeCl_3$.[25a,b] Treatment of triflates **1** and **3** with this defined reagent, which dissolves in THF with a characteristic yellow color, afforded the corresponding products **2** and **4** in yields similar to those obtained under "in situ" conditions (Scheme 2). Therefore, these control experiments suggest that ate-complexes act as the nucleophilic partners in *methylation* reactions of this type.

Together with the results of previous investigations, the available data seem to indicate that iron-catalyzed C−C-bond formations can occur via different pathways, which likely involve "iron−ate" complexes [10h,24,25] in the case of methyl donors but highly reduced metal clusters such as $[Fe(MgX)_2]_n$ when Grignard reagents with two or more carbon atoms are employed.

SCHEME 2



Acid Chlorides. Despite some scattered reports on the efficiency of iron salts as catalysts for the cross-coupling of Grignard reagents with acid chlorides,[11,26] the relevance of this method has not been fully explored (Scheme 3). Due to the good compatibility of iron-

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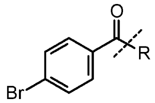
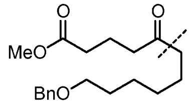
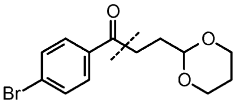
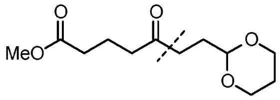
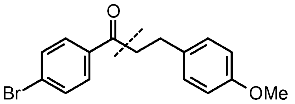
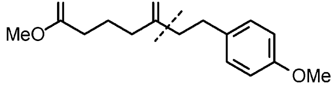
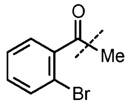
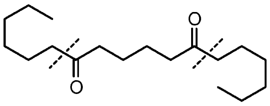
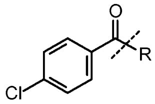
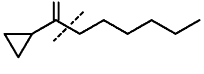
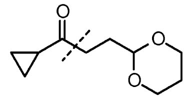
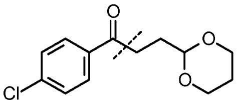
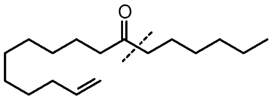
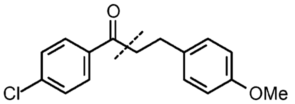
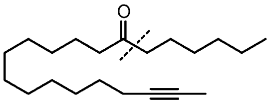
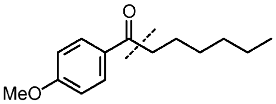
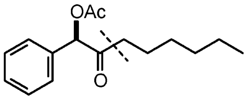
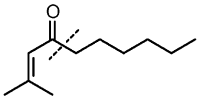
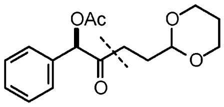
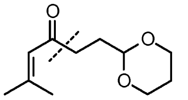
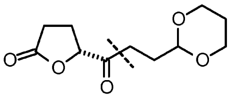
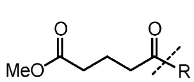
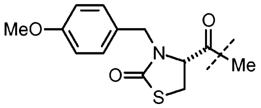
(24) For alkylations of alkenyl halides with stoichiometric amounts of organoiron reagents of different *formal* compositions formed in situ, see: (a) Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, *11*, 315. (b) Kauffmann, T.; Laarmann, B.; Menges, D.; Neiteler, G. *Chem. Ber.* **1992**, *125*, 163.

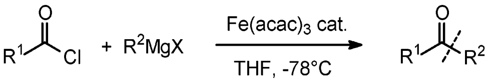
(25) (a) Spiegl, H. J.; Groh, G.; Berthold, H. J. *Z. Anorg. Allg. Chem.* **1973**, *398*, 225. (b) Jacob, K.; Pietzner, E.; Vastag, S.; Thiele, K.-H. *Z. Anorg. Allg. Chem.* **1977**, *432*, 187. (c) Sarry, B.; Noll, S. *Z. Anorg. Allg. Chem.* **1972**, *394*, 141. (d) Bazhenova, T. A.; Lobkovskaya, R. M.; Shibaeva, R. P.; Shilova, A. K.; Gruselle, M.; Leny, G.; Deschamp, E. *J. Organomet. Chem.* **1983**, *244*, 375.

TABLE 2. Iron-Catalyzed Cross-Coupling Reactions of Acid Chlorides or Diacid Dichlorides with Grignard Reagents According to Scheme 3[h]

Entry	Product	Yield	Entry	Product	Yield
1 2 3		86% (R = Me)[b] 89% (R = Et) 84% (R = Hexyl)	17		88%[e]
4		69%[e]	18		76%[e]
5		90%[e]	19		95%
6		85%[a]	20		95%[e]
7 8 9		81% (R = Me) 87% (R = Et) 97% (R = Hexyl)	21		92%
			22		88%
10		83%[e]	23		95%[e]
11		96%[e]	24		79%
12		99%[e]	25		43%[d,f]
13		90%[e]	26		78%[f]
14		80%	27		59%[g]
15 16		95% (R = Hexyl)[b,e] 65% (R = Ph)	28		80%[c]

[a] Small amounts (7%, GC) of 2-methylacetophenone formed as byproduct by cross-coupling at the bromide function of the substrate. [b] The product was purified by Kugelrohr distillation. [c] The ee of the crude product was only 87%; however, one recrystallization from hexane suffices to bring the ee to 99%. [d] Two byproducts formed were identified as 1-phenyl-2-octanone (5%) and 1-acetoxy-1,4-diphenyl-3-hexylbutan-2,4-dione (13%). [e] "Inverse addition" protocol, cf. the text. [f] ee > 99% (HPLC). [g] ee = 94% (GC). [h] The newly formed bond is indicated by a dotted line. All reactions were performed using RMgX (1.3 equiv) and Fe(acac)$_3$ (3 mol %) in THF at −78 °C unless stated otherwise.

SCHEME 3



catalyzed processes in general with a variety of functional groups in both reaction partners, we anticipated that the scope of this particular ketone synthesis might extend beyond the barely functionalized cases previously reported in the literature.[11]

As can be seen from the results compiled in Table 2, a host of aromatic and aliphatic acid chlorides react

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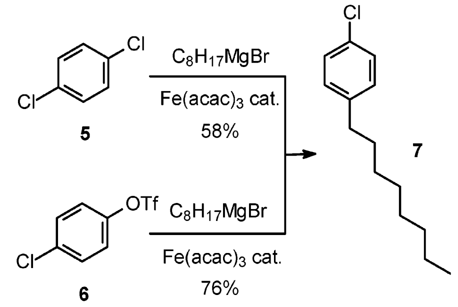
(26) For a general review on the acylation of organometallic reagents, see: Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.

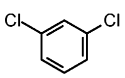
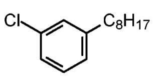
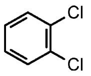
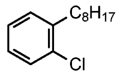
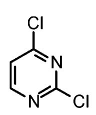
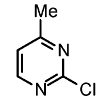
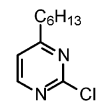
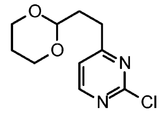
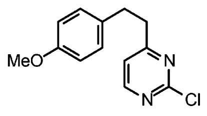
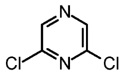
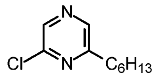
SCHEME 4



smoothly with various alkyl- as well as arylmagnesium halides to give the corresponding ketones in good to excellent yields. The reactions proceed very rapidly at −78 °C (<15 min), require only a low catalyst loading, and can also be performed by "inverse addition" (a solution of the acid chloride is added to a cold solution containing Fe(acac)$_3$ and the Grignard reagent). Under these conditions, the uncatalyzed attack of the Grignard reagent to the resulting ketone is negligible. The integrity of the cyclopropyl group makes radical intermediates rather unlikely. Since different functional groups turned out to be compatible and stereogenic centers in the substrate are not racemized,[27] the method should qualify for target-oriented synthesis. Notable is the fact that even chloride or bromide substituents in the substrates do not interfere (cf. entries 1−11), thus showing that the iron-catalyzed reaction of an acid chloride is even faster than the otherwise very rapid cross-coupling of aryl halides.[7]

Selective Monoalkylation of Dichloroarenes. While the iron-catalyzed alkylation of electron-deficient aryl chlorides and aryl sulfonates has been studied in some detail in the recent past,[7,9,13] the possibility to perform selective monoalkylation reactions of arenes bearing more than one leaving group has not yet been fully explored. To this end, the behavior of 1,4-dichlorobenzene **5** was investigated first, since a literature search revealed that nickel-catalyzed reactions of this particular substrate tend to give mixtures favoring the dialkylation products,[28] whereas conventional palladium catalysts are largely unreactive.[29] So far, best results were obtained with PdCl$_2$(dppf) in the presence of excess ligand (dppf: Pd = 2−3:1) at high temperatures and extended reaction times.[30] We were pleased to find that the iron-catalyzed cross-coupling process constitutes an attractive and much cheaper alternative which provides multigram amounts of the monoalkylation product **7** in good to excellent yield and purity. Once again, the reaction proceeds rapidly even at ambient temperature (Scheme 4). In line with our expectations,[7,13] triflate **6** is an even better substrate for this purpose.

TABLE 3. Iron-Catalyzed Monoalkylation Reactions of Dichloroarene Derivatives with Grignard Reagents[c]

Entry	Substrate	Product	Yield
1			77%[a]
2			39%[a,b]
3			51%
4			83%
5			70%
6			71%
7			66%

[a] Performed in THF/NMP at ambient temperature. [b] The product formed is difficult to separate from unreacted starting material and hexadecane formed by oxidative dimerization of the Grignard reagent. [c] All reactions were performed in THF at −78 °C unless stated otherwise.

As can be seen from Table 3, iron-catalyzed selective monosubstitution reactions can be performed with a variety of different substrates and Grignard reagents. Despite this favorable profile and reasonably wide scope, however, some limitations also became apparent during our studies. Most notable is the fact that 1,2-dichlorobenzene—in contrast to its regioisomers—reacts rather sluggishly, providing only 39% of the desired product which is difficult to separate from unreacted starting material and hexadecane formed by oxidative dimerization of the Grignard reagent (cf. Table 3, entry 2). This outcome is in line with to the finding described above that alkenyl triflates bearing ortho substituents are problematic substrates. Furthermore, *functionalized* organomagnesium compounds generally show a significantly lower reactivity in the presence of iron catalysts as evident from the comparison depicted in Scheme 5.

While commercially available (1,3-dioxane-2-yl-ethyl)-magnesium bromide efficiently reacts with highly activated substrates such as 2,4-dichloropyrimidine **8** in the presence of Fe(acac)$_3$ furnishing the monoalkylation product **9** in good yield, this particular donor does not

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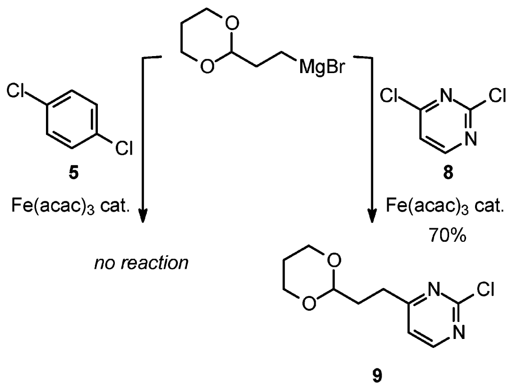
(27) Note that the loss of enantiomeric purity in the conversion of the cysteine derived acid chloride to the corresponding methyl ketone depicted in entry 28 is not caused by the iron-catalyzed cross-coupling but reflects the inherent configurational lability of amino acid chlorides; compare also footnote c in Table 2.

(28) (a) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1958. (b) Reddy, G. S.; Tam, W. *Organometallics* **1984**, *3*, 630. (c) Eapen, K. C.; Dua, S. S.; Tamborski, C. *J. Org. Chem*. **1984**, *49*, 478.

(29) For related palladium-catalyzed monoalkylation reactions of dibromobenzene, chlorobromobenzene, or chlorofluorobenzene, see: (a) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem*. **1977**, *125*, 281. (b) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett*. **1980**, *21*, 845.

(30) (a) Katayama, T.; Umeno, M. *Chem. Lett*. **1991**, 2073. (b) Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem*. **2002**, *653*, 288.

SCHEME 5



engage in cross coupling with 1,4-dichlorobenzene **5** under otherwise identical conditions. The reasons for this distinct behavior are not yet clear and are subject to further investigations.

In summary, the present study helps to define the scope and limitations of iron-catalyzed cross couplings with various types of electrophiles and illustrates some of the major advantages of this method. Investigations aiming at a further expansion of this powerful technique, its implementation into target oriented synthesis, and the refinement of the as yet incomplete mechanistic understanding are actively pursued in our laboratory and will be reported in due course.

Experimental Section

Representative Procedure for the Iron-Catalyzed Reaction of Enol Triflates with Grignard Reagents: 8-Tetradecyl-1,4-dioxaspiro[4.5]dec-7-ene (Table 1, Entry 8). A solution of $C_{14}H_{29}MgCl$ (1 M in THF, 0.6 mL, 0.6 mmol) was rapidly added to a solution of trifluoromethanesulfonic acid 1,4-dioxaspiro[4.5]dec-7-en-8-yl ester (154 mg, 0.5 mmol) and Fe(acac)$_3$ (9 mg, 5 mol %) in THF (10 mL) and NMP (0.46 mL) at −30 °C under argon, causing an immediate color change from orange-red to brown/black. The mixture was stirred for 15 min at that temperature before it was quenched with NH_4Cl (5 mL). The aqueous phase was repeatedly extracted with Et_2O, the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. Purification of the residue by flash chromatography on silica (hexanes/EtOAc, 30:1) provided 8-tetradecyl-1,4-dioxaspiro[4.5]dec-7-ene (110 mg, 65%) as a colorless oil. ^1H NMR (400 MHz, CD_2Cl_2): δ 5.27 (m, 1H), 3.92 (s, 4H), 2.19 (m, 2H), 2.11 (m, 2H), 1.95 (m, 2H), 1.71 (t, $J = 6.5$ Hz, 2H), 1.38 (m, 2H), 1.27 (m, 22H), 0.88 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 118.1, 108.4, 64.6, 37.5, 36.0, 32.3, 31.6, 30.1, 30.1, 30.0, 29.9, 29.8, 29.8, 28.2, 27.9, 23.1, 14.3. IR (film): 2924, 2853, 1671, 1377, 1119, 1060, 947, 861, 722 cm^{-1}. MS (EI): *m/z* (rel int.) 336 (34 [M$^+$]), 254 (4), 153 (9), 139 (5), 99 (7), 86 (100), 81 (3),67 (4), 55 (4), 43 (8). HRMS: calcd for $C_{22}H_{40}O_2$ 336.302830, found 336.302668.

All other compounds were prepared analogously. Their analytical and spectroscopic data are compiled in the Supporting Information.

Preparation of [Me$_4$Fe][Li$_2$(OEt$_2$)$_2$].[25a] A solution of anhydrous $FeCl_3$ (2.0 g, 12.3 mmol) in Et_2O (40 mL) was added dropwise at −78 °C to a solution of MeLi (38.4 mL, 1.6 M in Et_2O, 61.5 mmol) in Et_2O (40 mL). The dark brown reaction mixture was stirred at −78 °C for 12 h, and stirring was continued for an additional 10 h at −30 °C. During this period of time, the color changed from dark brown to orange with concomitant formation of a white precipitate. The reaction mixture was allowed to reach 0 °C before the precipitated LiCl was rapidly filtered off under inert atmosphere. Removal of the solvent at −78 °C in high vacuum afforded the title complex as a dark red solid. CAUTION: [Me$_4$Fe][Li$_2$(OEt$_2$)$_2$] is highly moisture sensitive and can ignite when exposed to air. It can be stored at −78 °C for several month without noticeable decomposition.

Representative Procedure for the Reaction of Enol Triflates with [Me$_4$Fe][Li$_2$(OEt$_2$)$_2$]: (6*R*)-Isopropyl-1,3(*S*)-dimethylcyclohexene (4). A chilled, golden-yellow solution of [Me$_4$Fe][Li$_2$(OEt$_2$)$_2$] (135 mg, 0.49 mmol) in THF (4 mL) was added to a solution of trifluoromethanesulfonic acid 6-isopropyl-3-methylcyclohex-1-enyl ester **3** (139 mg, 0.49 mmol) in THF (5 mL) at −30 °C, causing an immediate color change to orange. After being stirred for 15 min at this temperature, the reaction was carefully quenched with NH_4Cl (5 mL) and diluted with Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. Purification of the residue by flash chromatography on silica (pentane) provided the title compound as a colorless oil (60 mg, 80%). $[\alpha]^{20}_D = +5.2$ ($c = 2.33$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.30−5.29 (m, 1H), 2.12−1.96 (m, 3H), 1.79−1.73 (m, 1H), 1.69−1.61 (m, 4H), 1.32−1.22 (m, 1H), 1.04−0.95 (m, 1H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.68 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 131.2, 44.3, 31.8, 30.9, 27.7, 22.3, 21.9, 21.7, 20.7, 15.6. IR (film): 3025, 2958, 2926, 2868, 2851, 1454, 1385, 842 cm^{-1}. MS (EI): *m/z* (rel int) 152 (27 [M$^+$]), 137 (12), 109 (100), 95 (15), 82 (31), 79 (8), 67 (51), 55 (13), 41 (14), 27 (4). HRMS: calcd for $C_{11}H_{20}$ 152.156500, found 152.156542.

Representative Procedure for Iron-Catalyzed Reactions of Acid Chlorides with Grignard Reagents. Heneicos-2-yn-15-one (Table 2, Entry 24). A solution of hexylmagnesium bromide (2 M in Et_2O, 0.65 mL, 1.3 mmol) was added via syringe to a solution of pentadec-13-ynoic acid chloride (257 mg, 1.0 mmol) and Fe(acac)$_3$ (11 mg, 0.03 mmol) in THF at −78 °C under argon, causing an immediate color change from bright red to dark brown/black. After being stirred for 15 min at that temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with *tert*-butyl methyl ether (3 × 20 mL) after reaching ambient temperature. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated, and the residue was purified by flash chromatography on silica (hexanes/EtOAc, 100/1 → 30/1) providing the title compound as a white solid (243 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.38 (t, $J = 7.5$ Hz, 4H), 2.11 (m, 2H), 1.78 (t, $J = 2.5$ Hz, 3H), 1.55 (m, 4H), 1.46 (quint, $J = 7.2$ Hz, 2H), 1.31 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.9, 79.6, 75.4, 43.0, 31.8, 29.7 (*2), 29.6 (*2), 29.4, 29.3, 29.2, 29.1 (*2), 24.1, 24.0, 22.7, 18.8, 14.2, 3.6. IR (film): 2953, 2927, 2914, 2849, 2254, 1701, 1471, 1420, 909, 734. MS (EI): *m/z* (rel intensity) 306 ([M$^+$], 18), 291 (2), 249 (8), 239 (26), 221 (24), 211 (2), 141 (11), 129 (12), 113 (79), 97 (13), 95 (46), 85 (28), 79 (11), 68 (57), 67 (32), 58 (31), 55 (53), 43 (100), 41 (44). HRMS: calcd 306.292265, found 306.292584. Anal. Calcd for $C_{21}H_{38}O$: C, 82.28; H, 12.50. Found: C, 82.15; H, 12.59.

Representative Procedures for Selective Monoalkylation Reactions. 1-Chloro-4-octylbenzene (7). Method A. A solution of octylmagnesium bromide (0.4 M in THF, 120 mL) was added over 15 min to a solution of 1,4-dichlorobenzene **5** (4.67 g, 31.8 mmol) and Fe(acac)$_3$ (1.13 g, 3.2 mmol) in THF (200 mL) and NMP (15 mL), causing an immediate color change from red to dark brown/black and a slight increase in temperature (ca. 40 °C). After the mixture was stirred for 30 min, additional octylmagnesium bromide (0.4 M in THF, 22 mL) and Fe(acac)$_3$ (565 mg, 1.6 mmol) were introduced, and stirring was continued for 30 min. The reaction was quenched with dilute HCl, the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by distillation (bp 65 °C, 10^{-4} Torr) to give product **7** as a colorless liquid (4.34 g, 58%, GC purity ≥95%, remainder is hexadecane). **Method B.** A solution of octylmagnesium bromide (0.45 M in THF, 26 mL) was added over 45 min to a solution of 4-(trifluoromethylsulfonyloxy)-1-chlorobenzene (1.71 g, 6.6 mmol) and Fe(acac)$_3$ (247 mg, 0.7 mmol) in THF (20 mL) and NMP (3 mL), causing an immediate color change from red to dark brown/black. After the mixture was stirred for 30 min, the reaction was quenched with dilute HCl, the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were dried (Na$_2$SO$_4$) and evaporated, and the residue was purified by distillation (bp 65 °C, 10^{-4} Torr) to give product **7** as a colorless liquid (1.27 g, GC purity ≥90%, remainder is hexadecane, corresponds to 76% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.21 (d, $J = 8.5$, 2 H), 7.07 (d, 2 H). 2.55 (t, $J = 7.6$, 2 H), 1.57 (m, 2 H), 1.38−1.20 (m, 10 H), 0.88 (t, $J = 6.9$, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.3, 131.2, 129.7, 128.3, 35.3, 31.9, 31.4, 29.5, 29.4, 29.3, 29.2, 14.1; MS: m/z (rel intensity) 224 ([M$^+$], 51), 189 (3), 167 (2), 138 (5), 125 (100), 103 (6), 91 (24), 71 (5), 57 (31), 43 (16), 41 (14), 29 (8). Anal. Calcd for C$_{14}$H$_{21}$Cl: C, 74.81; H, 9.42. Found: C, 74.75; H, 9.30.

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Supporting Information Available: Procedures for the preparation of the enol triflates used and spectroscopic and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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