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Iron-Catalyzed Cross-Coupling Reactions

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Abstract: Simple iron salts such as $FeCl_n$, $Fe(acac)_n$ ($n = 2,3$) or the salen complex **4** turned out to be highly efficient, cheap, toxicologically benign, and environmentally friendly precatalysts for a host of cross-coupling reactions of alkyl or aryl Grignard reagents, zincates, or organomanganese species with aryl and heteroaryl chlorides, triflates, and even tosylates. An "inorganic Grignard reagent" of the formal composition $[Fe(MgX)_2]$ prepared in situ likely constitutes the propagating species responsible for the catalytic turnover, which occurs in many cases at an unprecedented rate even at or below room temperature. Because of the exceptionally mild reaction conditions, a series of functional groups such as esters, ethers, nitriles, sulfonates, sulfonamides, thioethers, acetals, alkynes, and $-CF_3$ groups are compatible. The method also allows for consecutive cross-coupling processes in one pot, as exemplified by the efficient preparation of compound **12**, and has been applied to the first synthesis of the cytotoxic marine natural product montipyridine **8**. In contrast to the clean reaction of (hetero)aryl chlorides, the corresponding bromides and iodides are prone to a reduction of their C−X bonds in the presence of the iron catalyst.

Introduction

The importance of cross-coupling reactions for the formation of carbon−carbon bonds as well as carbon−heteroatom bonds can hardly be overestimated.[1−9] Within a few decades, this methodology evolved into a routine tool for the preparation of fine chemicals and pharmaceutically active compounds in the laboratory and on the industrial scale,[10] is widely appreciated in the context of parallel synthesis and combinatorial chemistry,[11] and plays a prominent role in a rapidly growing number of highly impressive total syntheses of target molecules of utmost complexity.[12,13]

While a variety of organometallic reagents and organic electrophiles can be joined by cross-coupling processes, this field is largely dominated by the use of palladium and nickel

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complexes as the catalysts.[14] They are distinguished by their wide scope and excellent compatibility with many functional groups and allow for the reliable transfer of stereochemical information from the substrates to the products. This profile usually overcompensates the disadvantages resulting from the high cost of the palladium precursors, from the need for ancillary ligands rendering the catalysts sufficiently reactive, from concerns about the toxicity of nickel salts, and from the extended reaction times, which are necessary in many cases.

The best substrates for palladium- and nickel-catalyzed cross-coupling reactions are aryl (alkenyl) iodides, bromides, and triflates. Only recently have special ligands been designed that allowed for the scope of these methods to extend to aryl chlorides, which are the most attractive starting materials due to their low cost and ready accessibility on a large scale.[15,16] Some of these ligands, however, are expensive and/or sensitive to oxygen and moisture. In view of the foregoing, there remains ample opportunity to improve upon existing cross-coupling methodology. In the following, we summarize our investigations aiming at the development of an alternative strategy based on the use of iron salts as simple yet highly effective substitutes for established palladium and nickel catalysts.[17] They are not only very cheap and toxicologically benign, account for short reaction times even if the cross-coupling reactions are carried out at or below room temperature, but also allow for activation of a host of aryl chlorides, triflates, and even tosylates under "ligand free" conditions.

Results and Discussion

Organometallic Background. Modern cross-coupling chemistry emerged in 1972, when Corriu et al. and Kumada et al. independendly described nickel-catalyzed reactions of Grignard reagents with alkenyl- and aryl halides.[18] The advantages gained upon replacing nickel by palladium have been discovered shortly thereafter.[19] These seminal disclosures, however, had been preceded by publications of Kochi et al., who proposed the use of iron salts for similar purposes.[20] Surprisingly though, the iron-based methodology attracted much less attention and remained essentially limited to cross-couplings of Grignard or organomanganese reagents with alkenyl halides,[21] alkenyl sulfones,[22] acid chlorides or thiolesters,[23] and allylic phosphates;[24,25] thereby, the contributions of Cahiez deserve particular mentioning, which include demonstrating the generality of the iron-catalyzed vinylation process and first recognizing the advantages associated with the use of NMP as a cosolvent.[21a−c] Successful applications to aryl halides as substrates, however, have not been reported.[26] Moreover, the mechanism of the iron-catalyzed cross-coupling remained rather obscure, whereas detailed insights into most of the prominent palladium- and nickel-catalyzed manifolds have been gained over the years.[1,14,27] It has been speculated that Fe(0) or Fe(+I) species constitute the catalytically relevant intermediates, although no secured information as to their structure or mode of action could be obtained.[20,28] Alternatively, "super-ate" complexes of Fe(+II) have been suggested as the active species.[29]

Recent advancements in the field of "inorganic Grignard reagents",[30] however, render these hypotheses highly unlikely and call for a re-evaluation of iron-catalyzed cross-coupling

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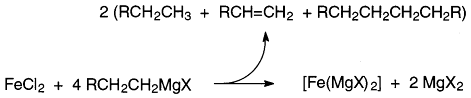
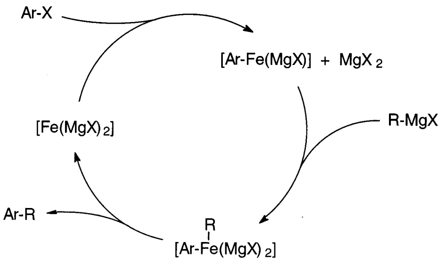
Scheme 1



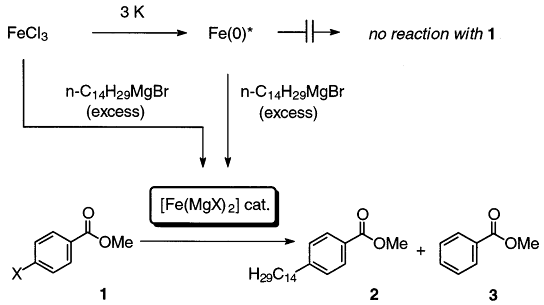
Scheme 2



chemistry in a broader context. It is now well established that $FeCl_2$ reacts with 4 equiv of R−MgX to give a new species of the *formal* composition $[Fe(MgX)_2]$, an "inorganic Grignard reagent", which is readily soluble in ethereal solvents such as THF (Scheme 1).[31] The available information suggests that $[Fe(MgX)_2]$ consists of small clusters incorporating magnesium and iron centers that are connected via fairly covalent intermetallic bonds. Although more structural details are not known to date,[32] the rigorously established stoichiometry of the reaction depicted in Scheme 1 implies that the reduction process does not stop once a zerovalent iron species, Fe(0), is formed but leads to species bearing a *formally negative charge at iron.* Such highly nucleophilic entities lacking any stabilizing ligands are able to oxidatively add to aryl halides.[31,33] The resulting organometallic iron compounds (formally Fe(0))[34] are again alkylated by the excess of the Grignard reagent in analogy to the case of the elementary steps passed through during the initial formation of $[Fe(MgX)_2]$ from $FeCl_2$ and RMgX. Subsequent reductive coupling of the organic ligands should then form the desired product and regenerate the propagating Fe(−II) species (Scheme 2). This suggests that iron-catalyzed cross-coupling reactions might be achieved that are far more general than those previously described.[20−24]

Although direct spectroscopic investigations of the actual intermediates involved in the formal catalytic cycle outlined above are hampered by various factors, most notably by their extremely high reactivity, thermal instability causing rapid aging, and paramagnetic character, experimental evidence for all of the basic features of such a scenario[32] is available. The assumption that formally negatively charged iron centers rather than Fe(0) complexes are the catalytically competent species is supported by the following results. Thus, cross-coupling of 4-chlorobenzoic acid methyl ester **1a** (X = Cl) with *n*-tetradecylmagnesium bromide in the presence of 5 mol % $FeCl_x$ ($x = 2, 3$) as the precatalyst is quantitative (>95% GC) within

Scheme 3[32]



less than 5 min at ambient temperature and proceeds even at −60 °C with similar ease. In striking contrast, highly dispersed and nonpassivated iron metal Fe(0)* powder[35] prepared by reduction of $FeCl_3$ with potassium does not insert at all into this substrate at room temperature and reacts only very reluctantly under more forcing conditions.[36] Even if one takes into account that the Fe(0)* slurry, though highly dispersed, might be kinetically handicapped as compared to its homogeneous counterpart, the immense difference in reactivities renders bare Fe(0) species as the actual carriers of the catalytic turnover highly unlikely.

More importantly, however, it was found that the suspension of finely dispersed Fe(0)* particles in THF *slowly dissolves on treatment with an excess of n*-$C_{14}H_{29}MgBr$ (Scheme 3). The resulting dark brown-black, homogeneous solution *catalyzes* the cross-coupling of substrate **1a** (X = Cl) with the residual Grignard reagent without incident. This experiment shows that Fe(0) reacts with organomagnesium reagents to give soluble species that likely contain the metal in formal oxidation states < 0, as postulated for $[Fe(MgX)_2]$. The fact that iron can exist in such low oxidatons states has ample precedence in the classical work of Collman, who has shown that the structurally well-defined Fe(−II) complex $Na_2Fe(CO)_4$ is a highly nucleophilic entity bearing a strong resemblance to an "inorganic Grignard reagent".[37−39]

It is reasonable to assume the presence of a covalent bond character between the Fe and Mg centers in such $[Fe(MgX)_2]$ clusters in view of the X-ray structure of [(Cp(dppe)Fe(MgBr)·3THF], a well-defined complex containing a covalent Fe−Mg bond of 2.593(7) Å length.[40] Further support comes from spectroscopic data on the closely related complex $[Cp(CO)_2Fe-$

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[34] Several Fe(0)-alkyl and -aryl compounds are known in the literature; for a review, see: Segnitz, A. In *Methoden der Organischen Chemie* (*Houben-Weyl*), 4th ed.; Segnitz, A., Ed.; Thieme: Stuttgart, Germany, 1986; Vol. 13/9a, p 175.

[35] (a) Rieke, R. D.; Sell, M. S.; Klein, W. R.; Chen, T.; Brown, J. D.; Hanson, M. V. In *Active Metals. Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, Germany, 1996; p 1. (b) Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164.

[36] It is known, however, that Fe(0)* inserts into C_6F_5I within 20 h to give solvated $(C_6F_5)_2Fe$ and FeI_2, cf.: (a) Kavaliunas, A. V.; Rieke, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 5944. (b) Kavaliunas, A. V.; Taylor, A.; Rieke, R. D. *Organometallics* **1983**, *2*, 377.

[37] (a) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA, 1987.

[38] $Na_2Fe(CO)_4$ oxidatively inserts into a variety of organic electrophiles, with the substrate reactivity resembling classical S_N2 reactions. However, it is not sufficiently reactive to insert into nonactivated aryl halides under mild conditions. Therefore, $Na_2Fe(CO)_4$ cannot substitute the structurally more elusive $[Fe(MgCl)_2]$ as a catalyst in cross-coupling reactions. Its lower reactivity is likely due to the partial back-bonding of the negative charge at iron into the empty π^* orbitals of the CO ligands.

[39] Another interesting similarity in the behavior of Collman's reagent $Na_2Fe(CO)_4$ and the presumed $[Fe(MgCl)_2]$ species is the pronounced effect of added NMP on their reactivity. It is known that the nucleophilicity of $Na_2Fe(CO)_4$ is 2×10^4 times higher in NMP than in THF.

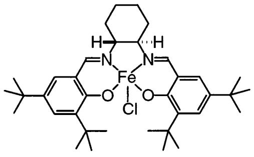
[40] (a) Felkin, H.; Knowles, P. J.; Meunier, B.; Mitschler, A.; Ricard, L.; Weiss, R. *J. Chem. Soc., Chem. Commun.* **1974**, 44. (b) Felkin, H.; Knowles, P. J.; Meunier, B. *J. Organomet. Chem.* **1978**, *146*, 151.

MgBr(THF)$_n$].[41] In this context, it should also be mentioned that several other transition metal−magnesium intermetallic complexes have been characterized in detail either by X-ray crystallography[42] or by in-depth EXAFS studies,[43] all of which indicate a strongly covalent character for the intermetallic bonds.

Catalyst Optimization and Screening of the Substrate Scope. Under the premise outlined above that the catalytically competent iron complexes are highly reduced species, one may anticipate an inherent competition between oxidative addition via two-electron-transfer processes and single-electron-transfer steps opening undesired radical manifolds.

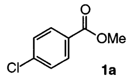
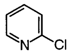
In line with this, the aryl bromide **1b** (X = Br) and iodide **1c** (X = I) mainly afford the reduced product **3** (50% and 46%, respectively) on treatment with n-C_6H_{13}MgBr in the presence of Fe(acac)$_3$ in THF/NMP, whereas the corresponding chloride **1a** (X = Cl) gives the desired cross-coupling product **2** in virtually quantitative yield (>95% GC); the isolated yield amounts to 91% on a gram scale (cf. Experimental Section). Not only is the conversion finished after less than 5 min of reaction time at 0 °C but it was also found that the uncatalyzed attack of the Grignard reagent onto the ester group of the substrate does not compete at all with the iron-catalyzed cross-coupling reaction. Gratifyingly, the corresponding triflate **1d** (X = OTf) and even the tosylate **1e** (X = OTs) perform equally well, providing product **2** in >95% yield (GC) at unprecedentedly high reaction rates. This is a significant advancement in view of the fact that inexpensive tosylates found hardly any application in conventional palladium- or nickel-catalyzed cross-coupling reactions because of their lack of reactivity.[44,45]

As can be seen from Table 1, the cross-coupling reactions of two representative substrates are hardly dependent on the chosen iron precatalyst, with Fe(+II) and Fe(+III) salts being equally effective; therefore, the cheap and nonhygroscopic Fe(acac)$_3$ is the most appropriate one from the practical point of view. Only for *sec*-alkyl Grignard reagents the use of Fe(salen)Cl **4**[46] is recommended (entry 2). The method, however, was found to be highly responsive to the nature of the nucleophile. In addition to n-alkyl- and *sec*-alkylmagnesium halides with ≥2 carbon atoms, which uniformly react without incident, trialkylzincates (entry 3) as well as all types of organomanganese reagents (RMnX, R_2Mn, R_3MnMgCl)[47] (entries 4−6) constitute equally suitable nucleophiles. In striking contrast, however, the use of n-BuLi or Et_3Al failed to afford any cross-coupling product.[48] We tentatively ascribe this distinct behavior to the need to form a rather covalent Fe−M (M = Mg, Zn, Mn) bond in the active species.



4

Table 1. Screening of Different Iron Precatalysts (5 mol %) and of Different Nucleophiles in Cross-Coupling Reactions with Two Representative Aryl Chlorides

Nr	Ar-Cl	R-M	Precatalyst	Ar-R (%)[a]
1	 **1a**	C_2H_5MgBr	Fe(acac)$_3$	>95
2		i-C_3H_7MgBr	Fe(salen)Cl[b]	59
3		Et_3ZnMgBr	Fe(acac)$_3$	93
4		$C_{14}H_{29}$MnCl	Fe(acac)$_3$	96
5		$(C_{14}H_{29})_2$Mn	Fe(acac)$_3$	>98
6		$(C_{14}H_{29})_3$MnMgCl	Fe(acac)$_3$	>98
7		C_6H_5MgBr	Fe(acac)$_3$	28
8	 **5**	n-C_6H_{13}MgBr	Fe(acac)$_2$	90
9		n-C_6H_{13}MgBr	Fe(acac)$_3$	91
10		n-C_6H_{13}MgBr	FeCl$_2$	85
11		n-C_6H_{13}MgBr	FeCl$_3$	88
12		n-C_6H_{13}MgBr	Fe(salen)Cl[b]	96
13		PhMgBr	Fe(acac)$_3$	73

[a] GC yields. [b] Fe(salen)Cl refers to complex **4**.

The behaviors of vinyl, allyl, and aryl Grignard reagents as nucleophiles are more complex.[26,49] While attempted cross-coupling reactions of vinyl- and allylmagnesium bromide with substrate **1a** were in vain, the use of phenylmagnesium bromide resulted in a low yield of the desired cross-coupling product but mainly led to biphenyl via oxidative dimerization of the Grignard reagent (entry 7). Importantly, however, the reaction of PhMgBr with the heterocyclic chloride **5** was found to be productive (entry 13); in this case, only small amounts of biphenyl have been detected in the crude mixture. It is well established in a series of classical papers of Kharasch et al. that aryl Grignard reagents are catalytically decomposed with the formation of biaryls in the presence of transition metal salts if aryl halides are present in the medium, which act as stoichiometric oxidizing agents under these conditions.[50] The different behaviors of aryl chloride **1a** and its heteroaryl congener **5** are

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(41) McVicker, G. B. *Inorg. Chem.* **1975**, *14*, 2087.

(42) (a) [Cp(H)Mo−MgBr(THF)]: Davies, S. G.; Green, M. L. H.; Prout, K. *J. Chem. Soc., Chem. Commun.* **1977**, 135. (b) [Cp(η^3-C_3H_5)Co−MgBr(THF)$_2$]: Jonas, K.; Koepe, G.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 923.

(43) (a) [Pt(MgCl)$_2$(THF)$_x$]: Aleandri, L. E.; Bogdanovic, B.; Dürr, C.; Huckett, S. C.; Jones, D. J.; Kolb, U.; Lagarden, M.; Rozière, J.; Wilczok, U. *Chem.−Eur. J.* **1997**, *3*, 1710. (b) [Ti(MgCl)$_2$(THF)$_x$]: Aleandri, L. E.; Bogdanovic, B.; Gaidies, A.; Jones, D. J.; Liao, S.; Michalowicz, A.; Rozière, J.; Schott, A. *J. Organomet. Chem.* **1993**, *459*, 87.

(44) For very recent examples, see: (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (b) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049. (c) Fu, X.; Zhang, S.; Yin, J.; McAllister, T. L.; Jiang, S. A.; Tann, C.-H.; Thiruvengadam, T. K.; Zhang, F. *Tetrahedron Lett.* **2002**, *43*, 573.

(45) For examples describing the activation of mesylates by Ni(0) complexes, see: (a) Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531. (b) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513. (c) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060.

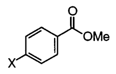
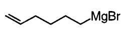
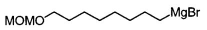
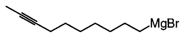
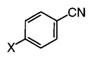
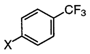
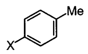
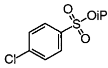
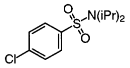
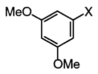
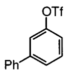
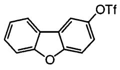
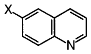
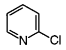
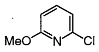
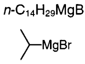
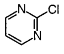
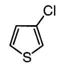
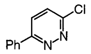
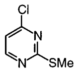
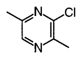
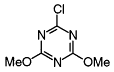
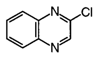
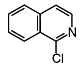
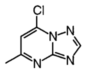
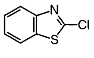
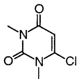
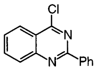
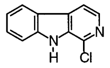
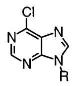
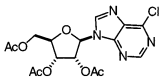
(46) Prepared in analogy to: Gerloch, M.; Lewis, J.; Mabbs, F. E.; Richards, A. *J. Chem. Soc. A* **1968**, 112. For a detailed procedure, see the Supporting Information.

(47) For reviews on organomanganese compounds, see: (a) Cahiez, G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; pp 925 and 3227. (b) Normant, J.-F.; Cahiez, G. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Sauerländer-Salle: Frankfurt, Germany, 1983; Vol. 3, p 173. (c) Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1.

(48) In this context, an early observation reported by Corey and Posner, who studied cross-coupling processes in the presence of stoichiometric amounts of FeI$_2$, is relevant. They found that the reaction proceeds with MeLi but invariably failed with n-butyllithium as the nucleophile, cf.: Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, *11*, 315.

(49) For a convenient and general method for the cross-coupling of vinyl, allyl, and alkynyl reagents, see ref 16g and: (a) Fürstner, A.; Seidel, G. *Synlett* **1998**, 161. (b) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165.

Table 2. Cross-Coupling Reactions of Alkyl Grignard Reagents R−MgBr with Aryl and Heteroaryl Chlorides, Tosylates, and Triflates (Ar−X)[a]

Entry	Ar–X	R–MgBr	Ar–R (Yield)
1 2 3		n-C_6H_{13}MgBr	91% (X = Cl) 87% (X = OTf) 83% (X = OTs)
4			91%
5			88%
6			85%
7 8 9		n-$C_{14}H_{29}$MgBr	91% (X = Cl) 80% (X = OTf) 74% (X = OTs)
10 11 12		n-$C_{14}H_{29}$MgBr	94% (X = Cl) 72% (X = OTf) 75% (X = OTs)
13 14		n-$C_{14}H_{29}$MgBr	0% (X = Cl) 81% (X = OTf)
15		n-C_6H_{13}MgBr	85%
16		n-C_6H_{13}MgBr	94%
17 18		n-$C_{14}H_{29}$MgBr	0% (X = Cl) 90% (X = OTf)
19		n-$C_{14}H_{29}$MgBr	81%
20		n-$C_{14}H_{29}$MgBr	81%
21 22 23		n-$C_{14}H_{29}$MgBr	92% (X = Cl) 74% (X = OTf) 82% (X = OTs)
24		n-$C_{14}H_{29}$MgBr	81%
25 26		n-$C_{14}H_{29}$MgBr 	95% 56%
27		n-$C_{14}H_{29}$MgBr	93%
28		n-$C_{14}H_{29}$MgBr	41%
29		n-$C_{14}H_{29}$MgBr	68%
30		n-$C_{14}H_{29}$MgBr	89%
31		n-$C_{14}H_{29}$MgBr	94%
32		n-$C_{14}H_{29}$MgBr	84%
33		n-$C_{14}H_{29}$MgBr	95%
34		n-$C_{14}H_{29}$MgBr	95%
35		n-$C_{14}H_{29}$MgBr	67%
36		n-$C_{14}H_{29}$MgBr	68%
37		n-$C_{14}H_{29}$MgBr	60%
38		n-$C_{14}H_{29}$MgBr	84%
39		n-C_2H_5MgBr	67%
40 41		n-$C_{14}H_{29}$MgBr	90% (R = Me) 85% (R = H)
42		n-$C_{14}H_{29}$MgBr	72%

[a] All reactions were carried out in THF/NMP using Fe(acac)$_3$ (5 Mol %) as the catalyst.

deemed to reflect the distinctly lower oxidizing potential of the latter. One might therefore expect the scope of iron-catalyzed aryl−aryl cross-coupling reactions to be limited to π-electron-deficient substrates. This profile will be mapped out in more detail below.

Iron-Catalyzed Alkyl−Aryl Cross-Coupling Reactions. With regard to the substrate scope, the iron-catalyzed cross-coupling process of alkylmagnesium halides and aromatic electrophiles turned out to be widely applicable.[51] As can be seen from the results compiled in Table 2, a host of moderately electron-deficient aryl chlorides and tosylates react with good to excellent yields. This includes various benzene derivatives substituted with electron-withdrawing substitutents such as esters, nitriles, sulfonates, sulfonamides, or −CF$_3$ groups as well as many heterocyclic compounds of the pyridine, pyrimidine, triazine, quinoline, isoquinoline, carbazole, purine, pyridazine, pyrazine, quinoxaline, quinazoline, uracil, thiophene, and even benzothiazole series.[52] Particularly noteworthy is the example shown in entry 42, in which the chloride function at C-6 of the per-*O*-acetylated purine-β-D-ribofuranoside is replaced by the alkyl group of the Grignard reagent in the presence of catalytic amounts of Fe(acac)$_3$ as the precatalyst. This example clearly illustrates that the uncatalyzed attack of the organomagnesium reagent on the rather labile ester protecting groups in this substrate obviously does not compete with the efficacy of the

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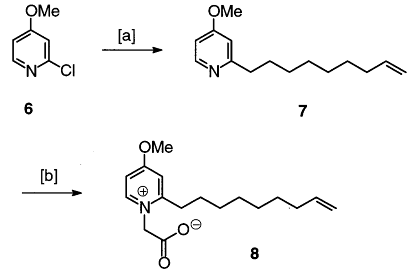
(50) (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice Hall: New York, 1954. (b) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316. (c) Kharasch, M. S.; Nudenberg, W.; Archer, S. *J. Am. Chem. Soc.* **1943**, *65*, 495.

(51) For a recent review showing the importance of alkyl−aryl cross-coupling chemistry, see: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (b) Tamao, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, p 435.

Scheme 4 [a]



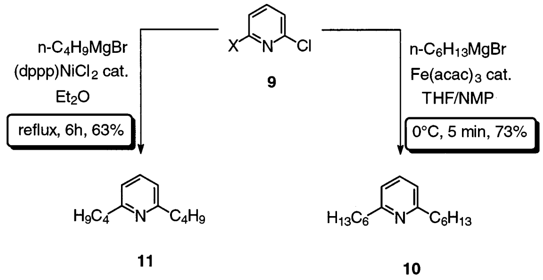
[a] (a) 8-Nonenylmagnesium bromide, Fe(acac)$_3$ (5 mol %), THF/NMP, 0 °C → rt, 81%. (b) (i) BrCH$_2$COOtBu, 40 °C; (ii) F$_3$CCOOH, Et$_3$SiH, CH$_2$Cl$_2$, 74%.

iron-catalyzed activation of the C−Cl bond.[53] Importantly, even the unprotected 6-chloropurine containing an acidic N−H bond undergoes efficient cross-coupling, although an extra equivalent of the Grignard reagent is necessary for the initial deprotonation of this site (entry 41); further support for this notion comes from the transformation of the *N*-unprotected chlorocarbazole[54] shown in entry 39 which is converted into the 1-ethyl derivative, an antimicrobially active natural product isolated from various sources such as the plant *Hannoa klaineana* and the bryozoa *Costaticella hastata* and *Cribricellina cribraria*.[55]

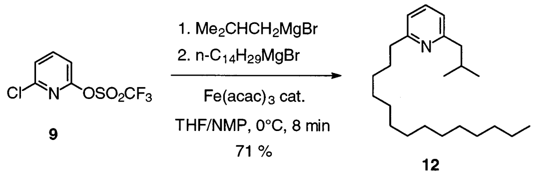
Yet, another favorable chemoselectivity aspect is evident from the example shown in entry 30. Whereas nickel-catalyzed Kumada−Corriu reactions of Grignard reagents are known to proceed with thioethers as the substrates,[56] the iron-catalyzed variant described herein rigorously distinguishes between the C−Cl and the C−S bonds, although the latter resides at an activated 2-position of the pyrimidine ring. Note, however, that, in the case of electron-rich arenes, the use of aryl triflates is necessary (entries 13/14, 17/18, 19, 20). The use to this leaving group allows for the cross-coupling of even rather unreactive substrates such as a resorcinol derivative (entry 18)[57] or the dibenzofuran (entry 20) in excellent yields.

Some of the products prepared by iron-catalyzed alkyl−aryl cross-coupling deserve further comment. As an example, the long chain alkylbenzene sulfonate, shown in entry 15, serves as a precursor for a biologically degradable detergent,[58] while Scheme 4 summarizes a convenient synthesis of the cytotoxic marine natural product montipyridine **8**.[59] The fact that this new method allows the attachment of unsaturated side chains to arene rings (Table 2 and Scheme 4) complements existing methodology for the preparation of substrates required for our ongoing studies on alkene and alkyne metathesis.[60]

Scheme 5



Scheme 6



Polysubstitution Reactions and Consecutive Cross-Coupling. Some preliminary experiments show that arenes bearing more than one leaving group X (X = Cl, OTf) can either be exhaustively or selectively cross-coupled with suitable Grignard reagents. Compound **9** (X = Cl, OTf) served as a prototype example (Scheme 5). Its treatment with an excess of *n*-C$_6$H$_{13}$-MgBr in the presence of Fe(acac)$_3$ affords the dihexylpyridine derivative **10** in 73% yield after just 5 min of reaction time. This outcome must be seen in the light of an experiment previously described in the literature, in which the reaction of **9** (X = Cl) with *n*-C$_4$H$_9$MgBr catalyzed by [NiCl$_2$(dppp)] required 6 h of reaction time in refluxing Et$_2$O to give 63% of the corresponding dialkylpyridine derivative **11**.[61] The obvious difference in the reaction rates of the iron- versus the nickel-catalyzed process is fairly representative.

The transformation depicted in Scheme 6 highlights another favorable aspect of the iron-based cross-coupling methodology. Isobutylmagnesium bromide (1.1 equiv) was added to a solution of substrate **9** (X = OTf) and Fe(acac)$_3$ catalyst in THF/NMP at 0 °C; after stirring for only 3 min at that temperature, a solution of *n*-C$_{14}$H$_{29}$MgBr was introduced and the reaction product was isolated after an overall reaction time of only 8 min, providing product **12** in 71% yield derived from the consecutive cross-coupling of the two different Grignard reagents. This example illustrates not only the exceptional efficiency of this new methodology but also opens new vistas for practical yet selective polyfunctionalization reactions to be carried out in "one pot".

Iron-Catalyzed Aryl−Heteroaryl Cross-Coupling Reactions. As outlined above, the iron-catalyzed cross-coupling of aryl Grignard reagents is more senstitive to the chosen elec-

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(56) Review: Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89.

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(58) Kosswig, K. In *Ullmann's Encyclopedia of Industrial Chemistry*; VCH: Weinheim, Germany, 1994; Vol. A25, p 747.

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(60) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem.*−*Eur. J.* **2001**, *7*, 5299. (c) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108 and literature cited therein.

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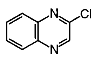
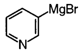
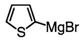
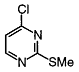
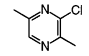
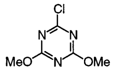
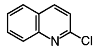
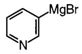
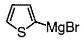
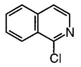
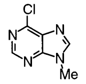
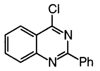
Table 3. Cross-Coupling Reactions of Aryl Grignard Reagents R−MgBr with Heteroaryl Chlorides Ar−Cl[c]

Entry	Ar–X	R–MgBr	Ar–R (Yield)[a]
1		PhMgBr	73%[b]
2			82%
3			69%
4		PhMgBr	53%
5		PhMgBr	64%
6		PhMgBr	63%
7		PhMgBr	71%
8			63%
9			63%
10		PhMgBr	57%
11		PhMgBr	60%
12		PhMgBr	66%

[a] Isolated yield. [b] Using Fe(salen)Cl **4** as the catalyst. [c] All reactions were carried out in THF using Fe(acac)$_3$ (5 mol %) as the catalyst unless stated otherwise.

trophile and is preferentially carried out in THF in the absence of NMP as cosolvent. While electron-rich aryl halides tend to fail, giving rise to the homocoupling of the Ar−MgX only, the reaction is applicable to various π-electron-deficient heterocycles.[26] This is evident from the data compiled in Table 3, which include examples from the pyrimidine, pyrazine, triazine, isoquinoline, quinoxaline, and quinazoline series. In all cases, varying amounts of biphenyl are formed as byproduct, which is easily separated by flash chromatography because of its different polarity. Likewise, cross-coupling with pyridine-3-magnesium bromide or 2-thienylmagnesium bromide has been achieved in good yield, whereas reaction with mesitylmagnesium bromide failed for steric reasons. The results must be seen in the context of the rapidly growing interest in azine and diazine natural products, pharmaceuticals, and building blocks for supramolecular chemistry or material science.[62] Special mentionings are deserved for 2-phenylquinoline (entry 7), as a simple alkaloid of the stem bark of *Galipea longiflora* with potential antileishmanial activity,[63] and the aryl quinoxalines (entries 1−3), which exhibit potency as inhibitors of platelet-derived growth factor receptor tyrosine kinase.[64] In terms of yields, the results compiled in Table 3 are comparable to those obtained in related palladium- or nickel-catalyzed cross-coupling reactions of aryl Grignard reagents with π-deficient heterocycles previously described in the literature,[52] whereas the reaction rates of the iron-catalyzed processes are usually much higher.

Conclusions and Outlook. The reducing ability of Grignard reagents is one of the major limiting factors in "standard" cross-coupling reactions of these nucleophiles in the presence of palladium complexes as catalysts, causing the precipitation of palladium black and, hence, the arrest of the catalytic turnover. In sharp contrast, this propensity is the key to success for the iron-catalyzed processes described herein. These reactions likely involve highly reduced iron−magnesium intermetallic species as the actual catalysts formed in situ and proceed at unprecedentedly high rates at ambient temperature or below. The fact that aryl chlorides, triflates, and tosylates are inherently better substrates than the corresponding bromides or iodides represents a major advantage in practical terms. The favorable profile of this new method is further increased by the low cost as well as the toxicologically and environmentally benign character of the iron salts used as precatalysts.

Although one may object that the high reactivity of the C−MgX bond restricts the scope of the iron-catalyzed cross-coupling methodology, the rapidly growing number of *functionalized* Grignard reagents[65] becoming readily available hold promise that the method presented herein may bring even polyfunctional products into reach. The same pertains to the yet not fully explored potential of functionalized zincates or manganese reagents as nucleophiles. Further work along those lines is currently in progress in this laboratory.

Experimental Section

General Procedures. For details, see the Supporting Information.

Representative Procedure for an Iron-Catalyzed Alkyl−Aryl Cross-Coupling Reaction. Synthesis of 4-Hexylbenzoic Acid Methyl Ester. A flame-dried two-necked flask is charged under argon with 4-chlorobenzoic acid methyl ester **1a** (1.00 g, 5.86 mmol), Fe(acac)$_3$ (103 mg, 0.29 mmol), THF (35 mL), and *N*-methylpyrrolidone (NMP, 3.3 mL). A solution of *n*-hexylmagnesium bromide (2 M in Et$_2$O, 3.5 mL, 7.00 mmol) is added via syringe to the resulting red solution, causing an immediate color change to dark brown and then finally to violet. The resulting mixture is stirred for 5−10 min, and the reaction is diluted with Et$_2$O and is carefully quenched upon the addition of aq HCl (1M, ~10 mL). Standard extraction followed by flash chromatography of the crude product (hexanes/ethyl acetate, 30:1) provides the title compound as a colorless syrup (1.24 g,

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91%). Its analytical and spectroscopic data are in excellent agreement with those published in the literature.[66] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 3.84 (s, 3H), 2.59 (t, $J = 7.7$ Hz, 2H), 1.57 (m, 2H), 1.21−1.29 (m, 6H), 0.84 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 148.4, 129.2, 128.7, 127.6, 51.8, 35.9, 31.2, 31.0, 28.9, 22.5, 13.9; IR ν 1724 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 220 (50, [M$^+$]), 189 (39), 150 (100), 91 (54), 43 (17).

Representative Procedure for an Iron-Catalyzed Aryl−Heteroaryl Cross-Coupling Reaction. Synthesis of 2-Phenylquinoxaline. A flame-dried two-necked round-bottom flask is charged under Ar with 2-chloroquinoxaline (300 mg, 1.82 mmol), the Fe(salen)Cl complex **4** (29 mg, 0.09 mmol), and THF (10 mL), and the mixture was cooled to −30 °C. A solution of phenylmagnesium bromide (1 M in THF, 4.2 mL, 4.2 mmol) is added via syringe to the resulting red solution, causing an immediate color change to dark brown-black. The resulting mixture is stirred for 10 min, and the reaction is then diluted with Et_2O and is carefully quenched with brine. Standard extraction followed by flash chromatography (hexanes/EtOAc, 13:1) provides the title compound as a colorless solid (275 mg, 73%). mp = 73−75 °C (lit.[67] 77−78 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.21−8.10 (m, 4H), 7.79−7.71 (m, 2H), 7.58−7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (DEPT) δ 151.79 (C), 143.26 (CH), 142.27 (C), 141.54 (C), 136.75 (C), 130.20 (CH), 130.12 (CH), 129.59 (CH), 129.47 (CH), 129.09 (CH), 127.51 (CH); IR ν 3061, 1545, 1488, 1486, 1313, 769, 750, 687 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 206 (100, [M$^+$]), 179 (36), 152 (5), 103 (12), 76 (19), 50 (9).

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Supporting Information Available: Compilation of the analytical and spectroscopic data of all new compounds. Procedure for the preparation of the iron−salen complex **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA027190T

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