# Cross-Coupling of Alkyl Halides with Aryl Grignard Reagents Catalyzed by a Low-Valent Iron Complex**

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While palladium- and nickel-catalyzed cross-coupling reactions of aryl and vinyl halides have evolved over decades into mature tools for advanced organic synthesis,[1] it was only recently that extensions of this chemistry to *alkyl* halides as the substrates have been possible.[2–7] The use of special ligands and additives as well as careful optimization of the reaction conditions were necessary to overcome the reluctance of alkyl halides to undergo oxidative addition and to suppress the proclivity of the resulting alkyl metal reagents for destructive β-hydride elimination.[2–7] Therefore it may come as a surprise that bare, low-valent iron species under "ligand-free" conditions offer a simple and powerful alternative. Prompted by recent reports in the literature,[8] we disclose our results on the remarkable efficiency and excellent selectivity profile of alkyl–aryl cross-coupling reactions catalyzed by a well-defined Fe$^{-II}$ complex.

Encouraged by early reports of Kochi et al.,[9] our group has launched a program to explore in more detail the potential of iron catalysts as substitutes for palladium and nickel. Various types of substrates were found to undergo effective cross-coupling reactions with Grignard reagents in the presence of FeX$_n$ ($n = 2, 3$; X = Cl, acac (acac = acetyl-acetonate)) as precatalysts.[10–17] 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. Although the mechanisms are far from clear, it was speculated that highly reduced iron–magnesium clusters of the formal composition [Fe(MgX)$_2$]$_n$[18] generated in situ may play a decisive role in the catalytic cycle.[10,12]

To probe this hypothesis, we investigated whether the reactivity of these presumed clusters can be emulated by structurally well-defined complexes containing an Fe$^{-II}$ center. Of these, the tetrakis(ethylene)ferrate complex [Li(tmeda)]$_2$[Fe(C$_2$H$_4$)$_4$] (**1**) (tmeda = *N,N,N′,N′*-tetramethyl-ethylenediamine) described by Jonas et al.[19] seemed to be most promising. Its highly reduced metal center is only

weakly ligated by four ethylene molecules, and strong ion-pair interactions between the ferrate unit and the peripheral lithium cations are observed in the solid state. Since these structural features are somewhat reminiscent of the assumed bonding situation in the intermetallic cluster [Fe(MgX)$_2$]$_n$, complex **1** could qualify as a catalyst for similar purposes.

As can be seen from Scheme 1, this is indeed the case. Thus, reaction of chloride **2** with hexylmagnesium bromide in THF/NMP (NMP = N-methylpyrrolidone) at 0 °C proceeded within minutes, delivering the desired product **3** in 85 % yield. This outcome compares well to the result obtained under "in situ" conditions.[10]
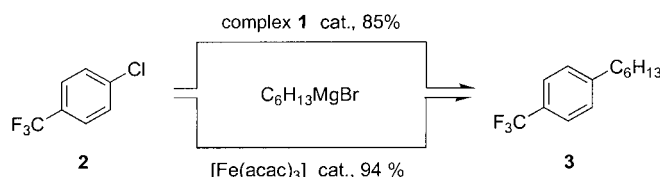
*Scheme 1.*

Even more gratifying is the fact that complex **1** also catalyzes the cross-coupling of alkyl halides and various aryl Grignard reagents or phenyllithium with exceptional ease (Scheme 2). Primary alkyl iodides and secondary alkyl
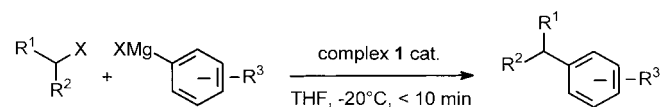
*Scheme 2.*

bromides, as well as propargyl and allyl halides react smoothly, affording the desired arylated products in virtually quantitative yields in most cases; only tertiary halides and alkyl chlorides were found to be inert. Since these reactions usually proceed within minutes even at −20 °C, they compare favorably to the palladium- and nickel-based procedures for alkyl–aryl cross-coupling known to date[2–7] and are clearly more effective than related arylations employing stoichiometric amounts of organocopper reagents.[20]

The unprecedented rate of productive cross-coupling of alkyl halides in the presence of complex **1** translates into an excellent chemoselectivity profile. Although one might assume that the use of organomagnesium reagents as the nucleophiles inherently restricts the functional-group tolerance of the method, the results compiled in Table 1 show that this is not the case. The iron-catalyzed activation of the alkyl halide turned out to be significantly faster than the uncatalyzed attack of the Grignard reagent to various other polar groups in the substrates, thus leaving ketones, esters, enoates, chlorides, nitriles, isocyanates, ethers, acetals, and trimethylsilyl groups intact. Moreover, tertiary amines do not interfere with productive C–C bond formation. This remarkable tolerance allowed us, for example, to convert even ethyl α-

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**Table 1:** Cross-coupling reactions of alkyl halides catalyzed by [Li(tmeda)]$_2$[Fe(C$_2$H$_4$)$_4$] (**1**) (5 mol%). All reactions were performed in THF at −20°C unless stated otherwise.

| Entry | Substrate | RMgX/RLi | Product | Yield [%] |
|---|---|---|---|---|
| 1 | | PhMgBr | | 94/89[a] (X=H) |
| 2 | | PhLi | | 92 (X=H) |
| 3 | | p-MeOC$_6$H$_4$MgBr | | 95 (X=OMe) |
| 4 | | p-ClC$_6$H$_4$MgBr | | 67 (X=Cl)[b] |
| 5 | | p-PhC$_6$H$_4$MgBr | | 93 (X=Ph)[b] |
| 6 | | m-(Me$_3$Si)$_2$NC$_6$H$_4$MgBr | | 88 (X=NH$_2$)[b,c] |
| 7 | | p-MeC$_6$H$_4$MgBr | | 95 |
| 8 | | PhMgBr | | 96 (X=I) |
| 9 | | PhMgBr | | 61 (X=Br) |
| 10 | | 2,4-(CH$_3$)$_2$C$_6$H$_3$MgBr | | 94 |
| 11 | | PhMgBr | | 74[b] |
| 12 | | PhMgBr | | 93 |
| 13 | | PhMgBr | | 89 |
| 14 | | PhMgBr | | 84 |
| 15 | | PhMgBr | | 91 |
| 16 | | PhMgBr | | 88 |
| 17 | | PhMgBr | | 83 (X=I) |
| 18 | | PhMgBr | | 90 |
| 19 | | PhMgBr | | 86 |
| 20 | | PhMgBr | | 87 (X=H) |
| 21 | | p-PhC$_6$H$_4$MgBr | | 85 (X=Ph)[b] |
| 22 | | PhMgBr | | 95 |
| 23 | | PhMgBr | | 87 |
| 24 | | PhMgBr | | 94 |
| 25 | | PhMgBr | | 93 |
| 26 | | PhMgBr[d] | | 96 |
| 27 | | PhMgBr | | 87 |
| 28 | | PhMgBr | | 97 |
| 29 | | PhMgBr[d] | | 98 |
| 30 | | PhMgBr | | 93[e] |
| 31 | | PhMgBr | | 96[f] |
| 32 | | PhMgBr | | 87[g] |

bromobutyrate into ethyl 2-phenylbutyrate in excellent yield within minutes (entry 23).[21] Substrates bearing more than one halide function are subject to exhaustive arylation (entries 26, 29; for an exception see entry 19).

Despite previous reports in the literature on iron-catalyzed transformations of allylic phosphates,[22] effective cross-coupling of the more abundant allylic halides have not yet been described. Entries 14 and 24–29, however, show that complex **1** is highly adequate for this purpose. In all cases investigated, the aryl group is introduced regioselectively at the least hindered site of the allylic system. Propargyl bromides behave equally well; only minor amounts, if any, of allenic by-products are formed under the chosen conditions (entries 30–32).

Although the development of this method was driven by the assumption that the ferrate complex **1** might mimic the behavior of the alleged iron clusters that supposedly operate under "in situ" conditions,[8,10] a concise mechanistic interpretation of the results outlined above is not yet possible. While the complete loss of optical purity in the reaction of (R)-2-bromooctane (98% ee) with PhMgBr (entry 12) could be explained by either an organometallic or by a radical pathway, the fact that the 2-iodoacetal derivative shown in entry 33 undergoes ring-closure prior to cross-coupling seems to indicate radical intermediates in this particular case.[23] Care, however, must be taken in generalizing this, because several other compounds set up for analogous 5-exo-trig pathways do not cyclize under otherwise identical conditions (cf. entries 13, 14, 25, 32). Moreover, tertiary halides remain unchanged, although they would afford the most stabilized alkyl radicals. In further studies we aim to unravel the mechanistic basis of this versatile iron-catalyzed alkyl–aryl coupling process and fully explore its preparative scope.

## Experimental Section

Representative example: Table 1, entry 26: A solution of 2-benzoyl-6-bromo-2-(4-bromo-but-2-enyl)-hex-4-enoic acid ethyl ester (228 mg, 0.5 mmol) in THF (1 mL) was added to a solution of [Li(tmeda)]$_2$[Fe(C$_2$H$_4$)$_4$] (**1**) (9 mg, 5 mol%) in THF (3 mL) at −20°C under argon, causing an immediate color change from green to red. At that point, PhMgBr (1M in THF, 1.2 mL, 1.2 mmol) was added dropwise, and the resulting mixture was stirred at −20°C for 5 min. Quenching of the reaction with saturated aq NH$_4$Cl followed by a

**Table 1:** (Continued)

| Entry | Substrate | RMgX/RLi | Product | Yield [%] |
|---|---|---|---|---|
| 33 |  | PhMgBr |  | 85[b] |
| 34 |  | PhMgBr |  | 77[h] |

[a] Only 1 mol% of complex **1** was used. [b] The reaction was performed at 0°C. [c] After hydrolytic work-up. [d] Using 2 equiv of PhMgBr. [e] 15:1 mixture with 1,1-diphenylallene. [f] 5:1 mixture with 1-phenyl-1-trimethylsilylallene. [g] No allene by-product detected in the crude mixture. [h] No incorporation of the phenyl group was observed.

standard extractive work-up and flash chromatography (hexanes/ethyl acetate 4:1) of the crude product afforded 2-benzoyl-6-phenyl-2-(4-phenyl-but-2-enyl)-hex-4-enoic acid ethyl ester as a colorless solid (217 mg, 96%). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 0.92$ (t, $J = 6.8$ Hz, 3H), 1.98 (m, 2H), 2.37 (m, 2H), 3.44 (m, 2H), 3.89 (m, 4H), 4.61 (d, $J = 6.2$ Hz, 2H), 5.23 (m, 2H), 7.31 ppm (m, 15H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 13.6, 30.8, 30.9, 52.8, 52.9, 60.3, 60.4, 77.8, 77.9, 124.86, 124.9, 125.0, 126.3, 126.6, 127.8, 127.9, 128.7, 128.8, 143.6, 143.7, 146.7, 175.8, 175.8$ ppm; IR (film): $\tilde{v} = 3066, 2941, 1771, 1743, 1646, 1617, 1448, 1265, 1150, 1048, 906, 791$ cm$^{-1}$; elemental analysis calcd for C$_{31}$H$_{32}$O$_3$: C 82.27, H 7.13; found: C 82.35, H 7.30.

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