

Homogeneous Catalysis

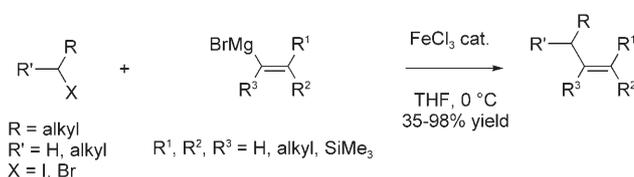
Iron-Catalyzed Cross-Coupling of Alkyl Halides with Alkenyl Grignard Reagents

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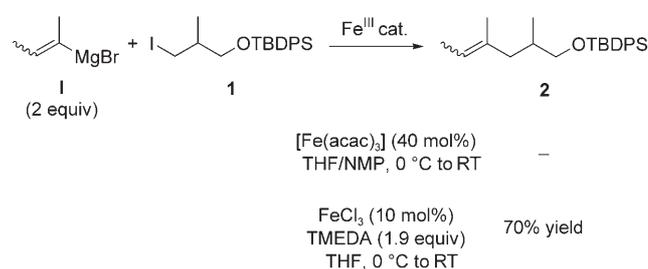
Transition-metal-catalyzed C–C bond coupling between vinyl metal reagents and unactivated alkyl halides is a useful reaction^[1–3] that can be realized using copper,^[4] palladium, nickel, or cobalt complexes as catalysts.^[1–3,5] For example, primary alkyl bromides can be coupled with alkenyl tin reagents using a palladium-catalyzed Stille coupling.^[6] Negishi cross-coupling reactions of alkyl halides with alkenyl zinc reagents^[7] or with alkenyl zirconium species^[8] also proceeded in the presence of palladium complexes. Recently, [Co(acac)₃] (acac = acetylacetonate) was used as a catalyst for the cross-coupling reaction of primary and secondary alkyl halides with 1-(trimethylsilyl)ethenylmagnesium.^[9] This reaction was shown to proceed through a radical pathway, and the cross-coupling products were obtained in good to excellent yields. Nevertheless, 20 to 40 mol% of the cobalt complex were required, and no reaction occurred with other alkenyl Grignard reagents.^[9]

As synthetic organic methods are increasingly concerned with the growing importance of sustainable chemistry, iron-catalyzed cross-coupling reactions are one of the promising research areas for the construction of C–C bonds, since iron is inexpensive and more environmentally friendly than palladium, cobalt, or nickel.^[10,11] After the pioneering works of Kochi and co-workers in the 1970s,^[12,13] only recently have the groups of Cahiez,^[14] Fürstner,^[15] and Nakamura,^[16] extended the scope of iron-catalyzed processes, notably by developing efficient cross-coupling reactions between aromatic Grignard reagents and alkyl halides.^[17] Although coupling reactions between vinyl bromide derivatives and alkyl Grignard reagents have been reported using the iron catalyst [Fe(acac)₃],^[14c] to our knowledge, the iron-catalyzed cross-coupling reaction between alkyl halides and alkenyl Grignard reagents has never been reported. Herein, we report that FeCl₃ efficiently catalyzes cross-coupling reactions between various alkyl halides and alkenyl Grignard reagents in good to excellent yields (Scheme 1).

We first turned our attention to [Fe(acac)₃] as the catalyst (40 mol%).^[18] When alkyl iodide **1** was treated with 1-methyl-1-propenylmagnesium bromide **I** (7:3 mixture of (*E*)- and (*Z*)-isomers, 2 equiv) in THF/NMP (NMP = *N*-methyl-2-pyrrolidone) from 0 °C to room temperature for 2 h, no conversion was observed (Scheme 2). We next examined the conditions developed by Nakamura for the cross-coupling reaction between aromatic Grignard reagents and alkyl halides.^[16]



Scheme 1. Cross-coupling between alkenyl Grignard reagents and alkyl halides catalyzed by FeCl₃.

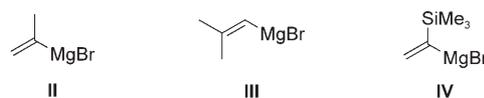


Scheme 2. Influence of the Fe^{III} source on catalysis of the cross-coupling between alkenyl Grignard **I** and alkyl iodide **1**.

When the reaction was performed in the presence of FeCl₃ (10 mol%) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 1.9 equiv) in THF at 0 °C for 10 min and then at room temperature for 30 min, compound **2** was obtained in 70% yield as a mixture of (*E*)- and (*Z*)-isomers (Scheme 2).^[19] To ensure full conversion of the starting material, dropwise addition of the alkenyl Grignard reagent at 0 °C over 1 h was essential.

In order to simplify the analysis of the cross-coupled products, three other alkenylmagnesium bromides **II**, **III** (commercially available), and **IV** (prepared from the corresponding bromide,^[9] Scheme 3) of a single configuration were examined in the FeCl₃-catalyzed alkenylation of halides **1–15**.

When a solution of alkenylmagnesium bromide **II** (2 equiv) and TMEDA (1.9 equiv) in THF was slowly added over 1 h at 0 °C (at a rate of around 5 mL h⁻¹) to a solution of alkyl iodide **1** and FeCl₃ (10 mol%) in THF, olefin **16** was formed in 87% yield. This coupling reaction appeared to be general, as alkyl halides **2–6** and **9–12** were transformed to the corresponding olefinic compounds **17–21** and **22–25** using the above-mentioned conditions (Table 1). Olefin **17** was isolated



Scheme 3. Alkenyl Grignard reagents examined in the FeCl₃-catalyzed cross-coupling reaction with halides **1–15**.

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Table 1: FeCl₃-catalyzed cross-coupling reaction of alkenyl Grignard **II** with halides **1–15**.^[a]

Entry	Halide	Product (yield of isolated product)
1		 16 (87%)
2 ^[b]		 17 (98%)
3		 18 (88%)
4		 19 (80%)
5		 20 13:1 (86%)
6 ^[b]		 21 (50%)
7		
8		
9		 22 (62%)
10 ^[c]		 23 (94%)
11 ^{[b][d]}		 24 7:2:1 (70%)
12 ^{[c][d]}		 25 1.9:1.6:1 (98%)
13 ^[e]		
14		
15		

[a] See the Experimental Section for general procedure; TBDPS = *t*BuPh₂Si, TIPS = *i*Pr₃Si, Cbz = benzyloxycarbonyl. [b] Reaction carried out using 5 mol % of FeCl₃. [c] Yield determined by NMR spectroscopy. [d] Ratio determined by GC–MS analysis. [e] Reactions with alkyl chlorides are sluggish and lead to complex reaction mixtures.

in an excellent yield (98 %) from phenethyl iodide **2**. When alkyl bromides were used, the cross-coupling reaction was still efficient; olefins **18–20** were obtained in yields around 80 % from bromides **3–5**. In the case of (3-bromo-butoxy)benzene (**5**), olefin **20** was isolated as a 13:1 mixture with the elimination product **20'**. The coupling reaction is also

compatible with polar functionalities, as bromoacetal **6** could be transformed to the olefinic acetal **21** in 50 % yield. Concerning bromoesters **7–9**, the position of the ester group relative to the halide showed an important influence on the outcome of the cross-coupling reaction. When α -bromoester **7** or β -bromoester **8** was examined, complex reaction mixtures were observed with no trace of the cross-coupling product. Nevertheless, when the ester functionality was present at the δ -position, ethyl 5-bromovalerate (**9**) was converted to the olefinic ester **22** in good yield (62 %).

The cross-coupling reaction with secondary alkyl bromides was also effective. Cycloheptyl bromide (**10**) was transformed into the corresponding alkene **23** in 94 % yield (Table 1, entry 10).^[20] Benzyl 4-bromopiperidine-1-carboxylate (**11**) was transformed to **24**, which was isolated along with the elimination product **24'** and the reduction product **24''** in 70 % yield and a ratio of 7:2:1 (for the origin of these byproducts, see the proposed mechanism below). However, when the linear secondary alkyl bromide **12** was treated with Grignard **II**, the cross-coupling product **25** was isolated as a mixture with the elimination products **25'** and **25''**. Alkyl chlorides and aryl halides are unreactive under the reaction conditions (Table 1, entries 13–15).

To evaluate the scope of this cross-coupling, alkenyl Grignard reagents **III** and **IV** were reacted with alkyl halides **1–3**, **5**, **9** and **26** under the same reaction conditions but with 5 mol % FeCl₃.^[21] These results are summarized in Table 2. The olefinic compounds **27–32** resulting from the cross-

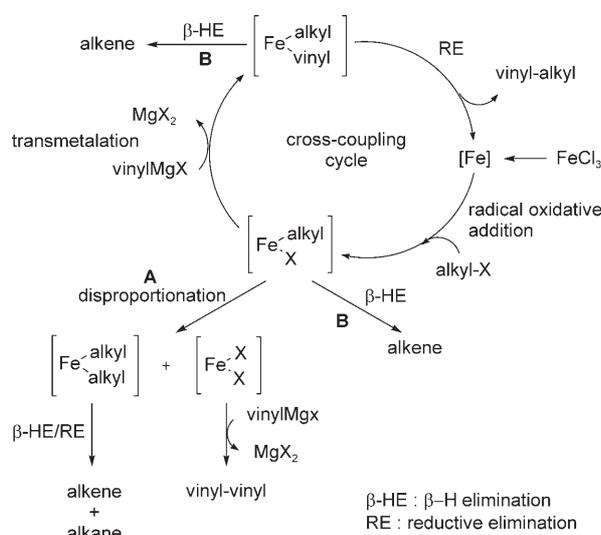
Table 2: FeCl₃-catalyzed cross-coupling reaction of alkenyl Grignard **III** and **IV** with alkyl halides.^[a]

Entry	Alkenyl Grignard Halide	III Product (yield)	IV Product (yield)
1		 27 (80%)	 33 3:1 (38%)
2		 28 (67%)	
3		 29 (88%)	 34 6:2:2 (86%) 35
4		 30 (91%)	 36 5.5:1 (68%)
5 ^[b]		 31 (98%)	 37 (40%)
6 ^[c]		 32 (64%)	

[a] Reactions carried out according to the general procedure using 5 mol % of FeCl₃. [b] Reaction carried out using 10 mol % of FeCl₃. [c] Yield determined by NMR spectroscopy.

coupling reaction between **1–3**, **5**, **9**, and **26** with reagent **III** were isolated in yields similar to those obtained with alkenyl Grignard **II**, except for compound **31**, which was obtained in higher yield (98%) from ethyl 5-bromovalerate (**9**).

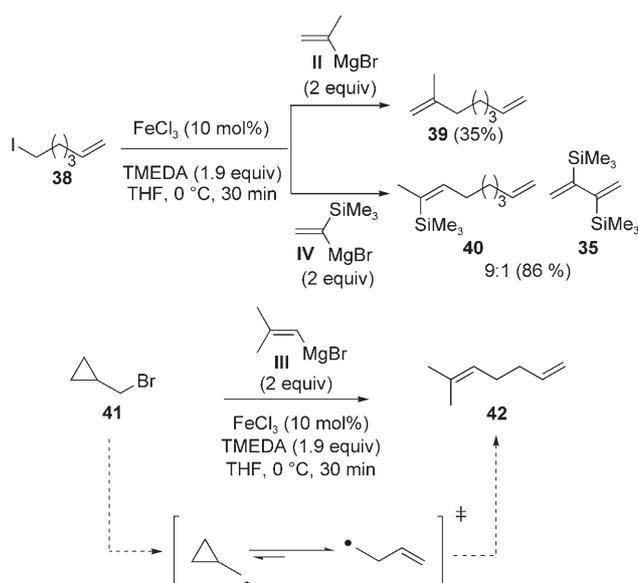
Concerning the alkenyl Grignard reagent **IV**, which was prepared from the commercially available (1-bromovinyl)trimethylsilane,^[9] the yields obtained for the cross-coupling products were in general lower than those previously obtained with reagents **II** or **III**. Moreover, cross-coupling products **34** and **36** were isolated along with the elimination and reduction products, and the analyses of the crude reaction mixtures for compounds **33**, **34**, **36**, and **37** showed the formation of the homocoupled product 2,3-bis(trimethylsilyl)-buta-1,3-diene (**35**). The formation of these byproducts is probably the result of a competitive pathway (disproportionation, pathway **A** in Scheme 4), which can be rationalized by the mechanism for the coupling of aryl Grignards and alkyl



Scheme 4. Plausible mechanism for the alkenyl-alkyl coupling.

halides proposed by Hayashi (Scheme 4).^[17a] In the original Hayashi mechanism,^[17a] the oxidative addition step proceeds through a concerted pathway, contrary to the mechanism recently proposed by Cahiez in which the iron-catalyzed coupling of aryl Grignard and alkyl halides would occur through a two-step single-electron transfer.^[14e]

To determine if a radical pathway was operational under our cross-coupling conditions, we first turned our attention to iodo olefin **38** (Scheme 5). Indeed, it has been shown that δ -unsaturated alkyl halides could afford 5-*exo-trig* cyclization prior to the cross-coupling with aryl Grignard reagents.^[15b,23] The treatment of iodo olefin **38** under our reaction conditions with reagents **II** or **IV** produced direct cross-coupling products **39** and **40**, respectively, and no trace of the cyclized product was observed (Scheme 5). However, this result is inconclusive, since Martin and Fürstner reported that 5-*exo-trig* cyclization prior to the cross-coupling reaction was highly substrate-dependant.^[15b] Consequently, we studied the reaction with cyclopropylmethyl bromide (**41**), which is a faster



Scheme 5. Cross-coupling between alkenyl Grignard reagents and alkyl halides **38** and **41**.

radical clock than iodo olefin **38**. When **41** and Grignard **III** were allowed to react, the major compound observed by GC-MS and ¹H NMR spectroscopy of the crude product was the linear cross-coupling product **42** derived from the radical opening of the cyclopropyl ring prior to the cross-coupling with Grignard **III** (Scheme 5).

This result suggests that the iron-catalyzed cross-coupling of alkenyl Grignard reagents with alkyl halides probably proceeds by a radical pathway (single electron transfer mechanism) for the oxidative addition step (Scheme 4). However, the mechanism of this reaction remains obscure and both organometallic and radical pathways could be operational.^[22]

In summary, we have reported the first iron-catalyzed cross-coupling reaction between alkyl halides and alkenyl Grignard reagents. This FeCl₃-mediated reaction is selective, as no coupling products were observed with aryl halides. The reaction also tolerates various functionalities such as ethers, acetals, esters, amides, and silyl ethers. This C–C bond coupling reaction catalyzed by the inexpensive and environmentally friendly FeCl₃ seems to proceed by a radical mechanism.

Experimental Section

General procedure: A solution of the alkenyl Grignard reagent (0.5 M in THF, 2 equiv) and TMEDA (1.9 equiv) was added dropwise (at a rate of around 5 mL h⁻¹) using a syringe pump to a solution of alkyl halide (1 equiv) and FeCl₃ (10 mol%) in THF at 0 °C. After further 30 min at 0 °C, the reaction mixture was quenched by adding an aqueous saturated NH₄Cl solution. After extractive workup, the crude product was purified by silica-gel chromatography.

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