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Iron-Catalyzed Cross-Coupling Reactions of Alkyl-Grignard Reagents with Aryl Chlorides, Tosylates, and Triflates**

Alois Fürstner* and Andreas Leitner

Classical cross-coupling processes such as the Kumada–Corriu, Negishi, Stille, or Suzuki reaction are of utmost importance for modern organic synthesis.^[1] These transformations are usually catalyzed by palladium or nickel complexes, although no inherent restriction to these late transition metals exists. Aryl iodides and bromides are the best substrates; only recently have special ligands been designed that allow the scope of these methods to be extended to aryl chlorides.^[2] Aryl triflates represent yet another class of suitable starting materials, whereas less expensive sulfonates have hardly been used so far because of their lack of activity in most cases.^[3]

Herein we describe initial studies on the development of an alternative cross-coupling procedure which allows the attachment of alkyl groups to arenes in a very efficient way.^[4] This method is distinguished by a number of notable advantages:

- 1) expensive noble metal catalysts are replaced by cheap, stable, commercially available and toxicologically benign iron salts
- 2) aryl chlorides and triflates provide a priori better results than the corresponding bromides or iodides
- 3) aryl tosylates turned out to be suitable starting materials as well
- 4) the reaction is performed under “ligand-free” conditions
- 5) the reaction times are usually very short.

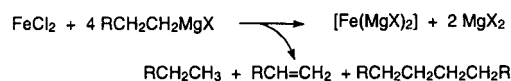
Although iron salts were proposed as catalysts for cross-coupling reactions by Kochi et al. as early as 1971,^[5] they attracted little attention in the following decades.^[6] Their scope remained essentially limited to reactions of Grignard reagents with *alkenyl* halides.^[6, 7] Successful applications to other types of substrates, in particular to *aryl* halides, have not been reported. Moreover, the mechanism of the iron-catalyzed reactions remained rather obscure, whereas detailed insights into most of the prominent palladium-catalyzed processes have been gained over the years.^[1] It has been proposed that Fe⁰ or Fe^I species constitute the catalytically relevant intermediates,^[5] although no secured information as to their structure or mode of action could be obtained. Alternatively, “super-ate” complexes of Fe^{II} have been suggested as the active species.^[8]

Taking recent advancements in the field of “inorganic Grignard reagents” into consideration,^[9] however, these hypotheses seem to be highly unlikely and called for a re-evaluation of iron-catalyzed cross-coupling chemistry. It is now well established that FeCl₂ reacts with *four* equivalents of

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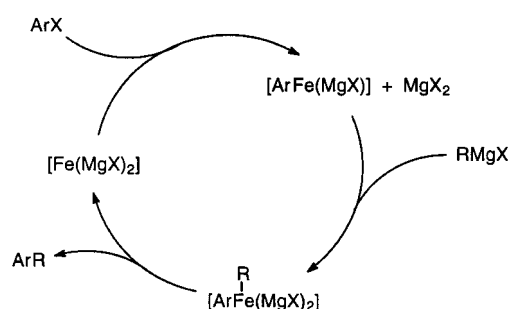
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RMgX to give a new species of the formal composition $[\text{Fe}(\text{MgX})_2]$.^[10] This implies that the reduction process does not stop once a zerovalent iron species “Fe⁰” is formed, but rather generates Fe^{-II} centers (Scheme 1),^[9, 11] which are



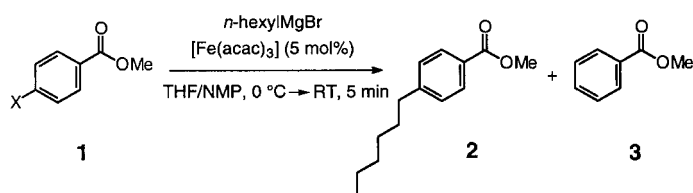
Scheme 1. Known stoichiometry for the formation of an inorganic Grignard reagent of iron.^[9, 11]

capable of oxidatively inserting into aryl halides due to their highly nucleophilic character.^[11, 12] We anticipated that the ensuing Fe⁰ complexes might again be alkylated by a suitable Grignard reagent.^[13] Subsequent reductive coupling should then form the desired product and regenerate the catalytically active $[\text{Fe}(\text{MgX})_2]$ species (Scheme 2).^[10, 14]



Scheme 2. Proposed formal catalytic cycle for the iron-catalyzed cross-coupling process.^[14]

Initial attempts to verify this concept using aryl iodide **1a** (X = I; Scheme 3) or aryl bromide **1b** (X = Br) were only partly successful. Although we were able to detect the cross-coupling product **2** in the reaction mixture, the reduction of the substrates with formation of compound **3** prevailed (Table 1). In marked contrast, however, the use of chloride **1c** as the starting material led to the almost quantitative formation of the desired alkylbenzoic acid ester **2**; notably, the



Scheme 3. Optimization of the iron-catalyzed cross-coupling reaction of substrate **1**, (see Table 1). NMP = *N*-methylpyrrolidone.

Table 1. Screening of different substrates in the iron catalyzed cross coupling reaction depicted in Scheme 3.

Entry	X	Yield [GC, %]	2	3
1	I	27	46	
2	Br	38	50	
3	Cl	> 95	–	
4	OTf	> 95	–	
5	OTs	> 95	–	

conversion is quantitative after a reaction time of less than 5 minutes, and no competing attack of the Grignard reagent on the methyl ester function of the substrate **1c** has been observed.^[15] It turned out that the corresponding triflate **1d** (X = OTf) and even the tosylate **1e** (X = OTs) perform equally well, providing product **2** in excellent yields and high reaction rates.

The reaction is virtually independent of the chosen iron salt (Table 2, entries 1–4, 7–9).^[5, 6] The cheap and non-hygroscopic $[\text{Fe}(\text{acac})_3]$ is the most convenient precatalyst from the practical point of view. Only for secondary alkyl Grignard reagents the use of $[\text{Fe}(\text{salen})\text{Cl}]$ is recommended (Table 2, entry 9). The method, however, was found to be highly responsive to the chosen nucleophile. In addition to *n*-alkyl- and *sec*-alkylmagnesium halides with ≥ 2 carbon atoms, which uniformly react without incident, trialkylzincates also constitute suitable reagents (Table 2, entry 16). The use of an organolithium compound, however, failed to afford any cross-coupling product (Table 2, entry 17). We tentatively ascribe

Table 2. Screening of the performance of different iron salts and nucleophiles in cross-coupling reactions with two different aryl chlorides.^[a]

Entry	ArCl	RM	Fe salt [5 %]	ArR [%] ^[b]
1		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{acac})_2]$	90
2		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{acac})_3]$	91
3		<i>n</i> -C ₆ H ₁₃ MgBr	FeCl ₃	88
4		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{salen})\text{Cl}]$	96
5		C ₂ H ₅ MgBr	$[\text{Fe}(\text{acac})_3]$	> 95
6		<i>n</i> -C ₆ H ₁₃ MgBr	$[\text{Fe}(\text{acac})_3]$	> 95
7		<i>n</i> -C ₆ H ₁₃ MgBr	FeCl ₂	> 95
8		<i>n</i> -C ₁₄ H ₂₉ MgBr	$[\text{Fe}(\text{acac})_3]$	> 95
9		<i>i</i> -C ₃ H ₇ MgBr	$[\text{Fe}(\text{salen})\text{Cl}]$	59
10			$[\text{Fe}(\text{acac})_3]$	91 ^[c]
11			$[\text{Fe}(\text{acac})_3]$	88 ^[c]
12			$[\text{Fe}(\text{acac})_3]$	85 ^[c]
13		H ₂ C=CHMgBr	$[\text{Fe}(\text{acac})_3]$	0
14		H ₂ C=CHCH ₂ MgBr	$[\text{Fe}(\text{acac})_3]$	0
15		C ₆ H ₅ MgBr	$[\text{Fe}(\text{acac})_3]$	28
16		Et ₃ ZnMgBr	$[\text{Fe}(\text{acac})_3]$	93
17		<i>n</i> -C ₄ H ₉ Li	$[\text{Fe}(\text{acac})_3]$	0

[a] acac = acetylacetonato, salen = *N,N*-ethylenebis(salicylideneamidato), MOM = methoxymethyl. [b] GC yields unless stated otherwise. [c] Yield of isolated product.

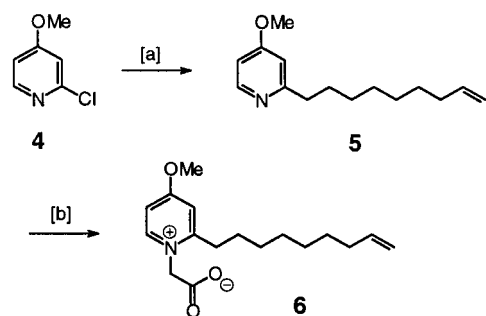
this distinct behavior to the need to form a rather covalent Fe–M (M = Mg, Zn) bond in the active species.^[9, 11, 16] In stark contrast to the successful use of alkylmagnesium halides, all aryl-, allyl- and alkenyl-Grignard reagents investigated invariably led to poor results (Table 2, entries 13–15). This might be caused by a competing catalytic decomposition of such organometallic species in the presence of transition metal salts and aryl halides to form biaryls or dienes, respectively, as documented in a series of classical publications of Kharasch et al.^[17]

With regard to the substrate scope, the iron-catalyzed process turned out to be widely applicable. As can be seen from the results compiled in Table 3, all moderately electron-

Table 3. Yields [%] of iron-catalyzed cross-coupling reactions of alkyl-Grignard reagents with aryl chlorides, triflates, and tosylates.

Nr.	ArX	RMgX	X = Cl	X = OTf	X = OTs
1		$n\text{-C}_6\text{H}_{13}\text{MgBr}$	91	87	83
2		$n\text{-C}_6\text{H}_{13}\text{MgBr}$	91	80	74
3		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	94	72	75
4		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	0	81	0
5		$n\text{-C}_6\text{H}_{13}\text{MgBr}$	85 (R = O <i>i</i> Pr)		
6			94 (R = NiPr ₂)		
7		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	0	90	0
8		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$		81	
9		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	92	74	82
10		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	81 (R = H)		
11			95 (R = OMe)		
12		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	93		
13		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	41		
14		$n\text{-C}_{14}\text{H}_{29}\text{MgBr}$	68		

deficient aryl chlorides and tosylates investigated react with good to excellent yields. In the case of electron-rich arenes, however, the use of aryl triflates is necessary (Table 3, entries 4, 7, 8). In this way a host of different carbo- and heterocyclic products can be prepared. Of particular note among them are the long-chain alkylbenzene sulfonate shown in entry 5 of Table 3, which serves as a precursor for a biologically degradable detergent,^[18] as well as compound **5** (Scheme 4) as the key intermediate of a synthesis of the cytotoxic marine natural product montipyrindine **6**.^[19] The fact that this new method allows the attachment of unsaturated



Scheme 4. Synthesis of the cytotoxic natural product montipyrindine **6**. [a] 8-Nonylmagnesium bromide, $[\text{Fe}(\text{acac})_3]$ (5 mol %), THF/NMP, $0^\circ\text{C} \rightarrow \text{RT}$, 81%; [b] 1. $\text{BrCH}_2\text{COO}(t\text{Bu})$, 40°C ; 2. F_3CCOOH , Et_3SiH , CH_2Cl_2 , 74%.

side chains to arene rings (Table 2 and Scheme 4) complements existing methodology for the preparation of substrates suitable for our studies into alkene and alkyne metathesis.^[20, 21]

The assumed mechanistic scenario outlined above is substantiated by the following control experiments. Thus, it has been shown that even highly activated $\text{Fe}^{0(*)}$ powder^[22] does not readily insert into the C–Cl bond of substrate **1c** even at elevated temperatures. If, however, a suspension of $\text{Fe}^{0(*)}$ is stirred in the presence of an excess of $n\text{-C}_{14}\text{H}_{29}\text{MgCl}$, the slow dissolution of the solid material with formation of a dark brown to black, homogeneous solution is observed. The latter is able to efficiently catalyze the cross-coupling of added **1c** with the Grignard reagent. This finding is in line with the notion that Fe^0 centers can be alkylated by organomagnesium compounds and thereby get reduced to Fe species with formally negative oxidation states (e.g. $[\text{Fe}(\text{MgX})_2]$)^[10] which likely account for the observed catalytic turnover.^[13] Ongoing studies are aimed at corroborating these mechanistic assumptions, at improving the results in the cross-coupling of arylmagnesium halides with chloroarenes, and at implementing this novel methodology into natural product synthesis.

Experimental Section

A flame-dried two-necked flask was charged under argon with methyl 4-chlorobenzoate (**1c**; 1.00 g, 5.86 mmol), $[\text{Fe}(\text{acac})_3]$ (103 mg, 0.29 mmol), THF (35 mL), and NMP (3.3 mL). A solution of n -hexylmagnesium bromide (2 M in Et_2O , 3.5 mL, 7.00 mmol) was added by syringe to the resulting red solution, causing an immediate color change to dark brown and finally to violet. The resulting mixture was stirred for 5–10 min, the reaction was diluted with Et_2O and was carefully quenched upon addition of aqueous HCl (1 M, ca. 10 mL). Standard extractive work-up followed by flash chromatography of the crude product (hexanes/ethyl acetate, 30/1) provided compound **2** as a colorless syrup (1.24 g, 91%). ^1H 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, 51.8, 35.9, 31.2, 31.0, 28.9, 22.5, 13.9; IR: $\tilde{\nu}$ = 1724 cm^{-1} ; MS (EI): m/z (rel. intensity): 220 (50, $[\text{M}^+]$), 189 (39), 150 (100), 91 (54), 43 (17).

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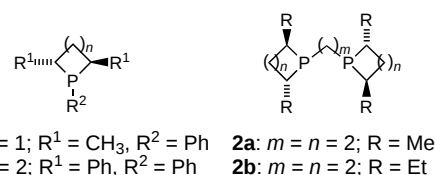
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Mono- and Bidentate Phosphinanes—New Chiral Ligands and Their Application in Catalytic Asymmetric Hydrogenations**

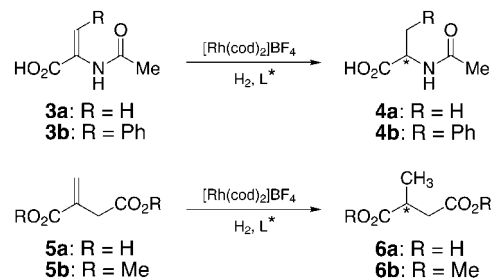
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Dedicated to Professor Dieter Hoppe
on the occasion of his 60th birthday

Chiral phosphanes possessing a modular make-up are important as ligands for asymmetric catalysis with transition metal complexes. The ethylene-bridged BPE ligands **2** and the 1,2-phenylene-bridged DuPHOS ligands,^[1] introduced by Burk et al., and analogues^[2] belong to the most effective ligands and were found to be particularly successful in enantioselective hydrogenations. Even with the monodentate phosphanes **1a** and **1b** enantiomeric excesses of up to 84 and 82 % *ee*, respectively, were achieved in the hydrogenation of



acetamidocinnamic acid (**3a**) (Scheme 1); however, only 12 % *ee* were obtained with **1a** in the case of substrate **5b**.^[3, 4] With the chelate ligands **2a** and **2b** hydrogenations of methyl 2-acetamidoacrylate furnished 91 and 98 % *ee*, respectively.^[1b]



Scheme 1. Asymmetric catalytic hydrogenations. cod = cycloocta-1,5-diene, L* = chiral ligand.

Upon inspection of the literature it was observed that phosphetanes^[5] (**1**, $n = 1$) and phospholanes^[1–4] (**1**, $n = 2$) had been studied intensively and phosphiranes^[6] marginally, surprisingly however, analogous phosphinanes (**1**, $n = 3$) were found to be unknown. Since there is a marked influence of ring size on the properties of ligands, we decided to fill this void in the arsenal of ligands. We now report the first ligands

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