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On direct iron-catalyzed cross-coupling reactions*

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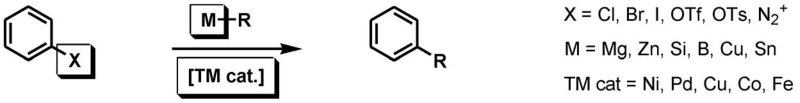
Abstract: A new methodology for the direct cross-coupling reaction between aryl halides and alkyl halides under iron catalysis is described. Unlike conventional protocols, the direct cross-coupling obviates the need for the preformation of stoichiometric amounts of Grignard species and thus exhibits a reduced hazard potential. The underlying one-pot reaction involves iron-catalyzed Grignard formation followed by a rapid cross-coupling step. Mechanistic data on the role of *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) as additive, the concentration of intermediates, and the nature of the catalyst species are discussed.

Keywords: arylhalide; catalysis; cross-coupling reactions; Grignard reaction; iron.

INTRODUCTION

Catalysts for cross-coupling reactions

Carbon–carbon bond-forming cross-coupling reactions are substitution reactions between an organic electrophile bearing a leaving group and an organometallic nucleophile in the presence of a transition-metal catalyst (Scheme 1). Best understood and most widely used are palladium and nickel catalysts, which offer a flurry of advantages, such as wide scope and high functional group tolerance [1]. However, their economic and ecological properties are detrimental to a more general use of such protocols: palladium is rather expensive, nickel compounds suffer from a high toxicity [2]. Both metals also require the presence of sensitive and costly ligands with high molecular weight. On the other hand, simple iron salts that were lately discovered as competent precatalysts for carbon–carbon bond-forming cross-coupling reactions boast a superior economic and ecological profile (Fig. 1) [3].



Scheme 1 Carbon–carbon bond-forming cross-coupling reaction with an aryl electrophile.

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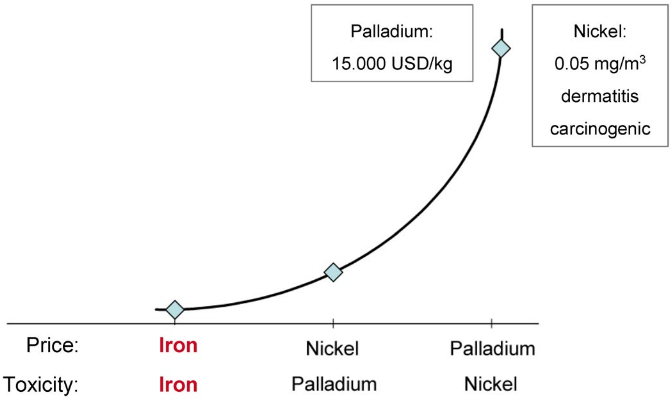
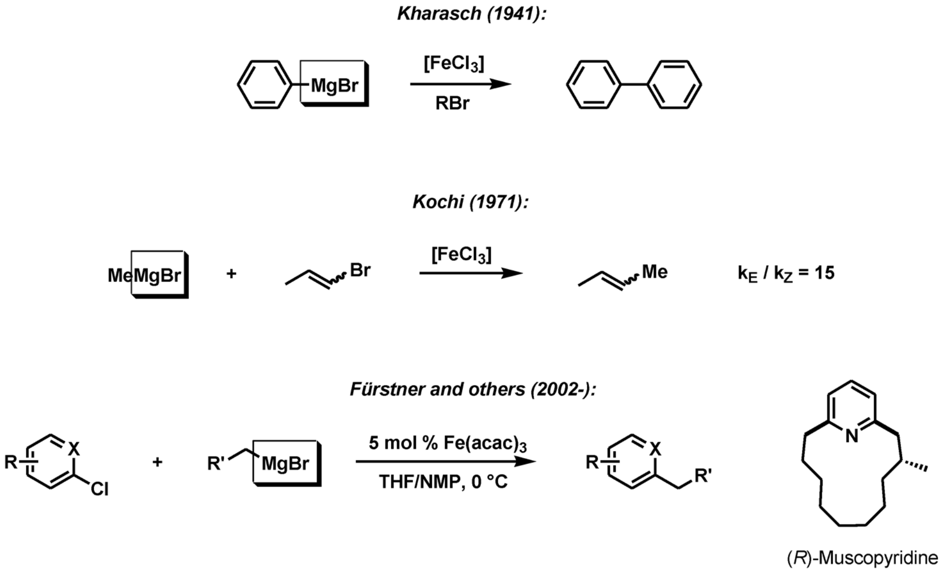


Fig. 1 An abstract economic and environmental evaluation of catalyst metals [2].

Iron-catalyzed cross-coupling reactions

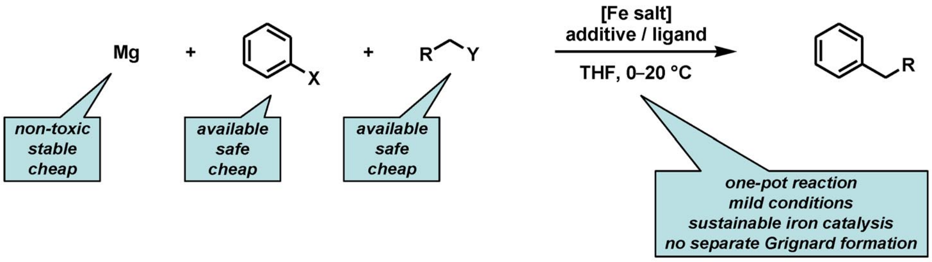
The history of iron-catalyzed carbon–carbon bond-forming cross-coupling reactions can be traced back to 1941 when Kharasch and Fields reported on the oxidative dimerization of arylmagnesium halides in the presence of catalytic $FeCl_3$ and an organohalide as oxidant [4]. It is important to note that this methodology is not only considered as the first iron-catalyzed coupling reaction but also frequently occurs as side reaction when aryl halides are present (Scheme 2, top). Thirty years later, Kochi and co-workers put forward a series of mechanistic and synthetic publications expanding the scope and understanding of iron-catalyzed cross-coupling reactions (Scheme 2, center) [5].



Scheme 2 Historical milestones of iron-catalyzed (cross)-coupling reactions.

This research area then lay dormant for almost another 30 years until the groups of Fürstner (Scheme 2, bottom) [6], Cahiez [7], Nakamura [8], and others [9] embarked on this field and reported a series of efficient and mild reaction conditions for selective iron-catalyzed cross-coupling reactions between various organomagnesium halides and organohalides. The potential of such reactions has also been harnessed in complex molecule synthesis (e.g., muscopyridine) [6c], however, applications on larger or even industrial scales shy away from the use of (super)stoichiometric amounts of Grignard reagents. The hazards associated with their flammability, corrosiveness, and air and moisture sensitivity translate into stringent safety arrangements and higher overall costs [10].

Two years ago, we set out to start a research program directed at the use of iron salts as simple and cheap catalysts for direct cross-coupling reactions. Unlike conventional protocols that employ excess amounts of preformed organomagnesium reagents, we rather resorted to a more efficient protocol where two electrophiles will be directly reacted under reductive conditions. Our first model system involved the direct cross-coupling of aryl bromides and alkyl bromides (Scheme 3). Both electrophiles are ubiquitously available, much cheaper, and operationally safer than any organometallic species. Magnesium ribbons act as safe and cheap in situ reductant, $FeCl_3$ as catalyst. Obviously, selectivity issues arise from the fact that both intermediate organomagnesium species might be formed under the reaction conditions and the iron-catalyzed carbon–carbon bond formation can involve homo and hetero coupling. An abstract evaluation based upon thermodynamic data (reduction potentials, bond dissociation energies, orbital stabilization of organoiron complexes) would suggest a rapid magnesiation of the alkyl bromide (vs. ArBr) and major formation of the aryliron species (vs. alkyl-Fe) [11].



Scheme 3 Direct aryl-alkyl cross-coupling reactions as model system.

RESULTS AND DISCUSSION

Direct aryl-alkyl coupling

We were delighted to observe rather selective cross-coupling in the model reaction between *p*-tolyl bromide and 1-dodecyl bromide in the presence of 5 mol % $FeCl_3$ in tetrahydrofuran (THF) with stoichiometric magnesium ribbons at 0 °C after 1 h [12]. In the presence of 120 mol % *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA), the alkylated arene (**3a**) was formed almost exclusively with only marginal reduction to toluene (ArH) and homo-coupling to 4,4'-bitolyl (**4a**, Fig. 2). From these and more detailed experimentations, we deduced that TMEDA acts as a ligand for the catalyst species and magnesium. The employment of stoichiometric TMEDA suppresses the β-hydride elimination of alkene, reduces the amount of homo-coupling, but most importantly lowers the rate of the in situ Grignard formation. Further increase of the TMEDA concentration did not lead to increased selectivities. A slow formation of the intermediate Grignard species is key to a high cross-coupling selectivity. One can view this as a built-in pseudo-dropwise addition of the organometallic while conventional protocols require the operationally laborious addition by syringe pump. The direct cross-coupling presented herein is truly a one-pot domino process where all starting materials, reagents, and catalyst are added in one go, obviating the need for laborious preformation and reagent addition.

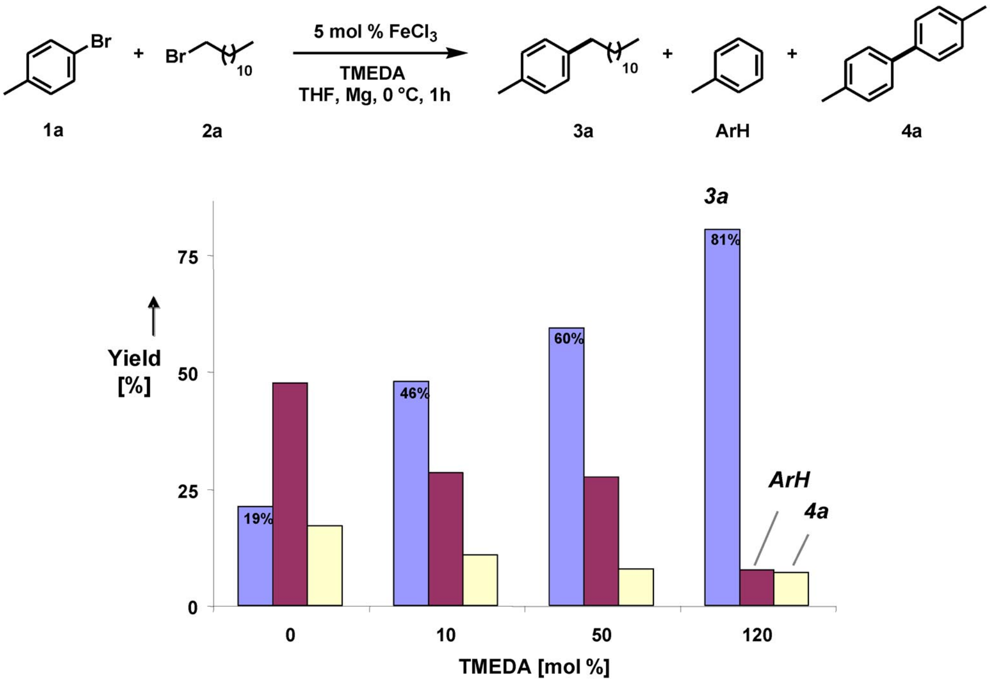
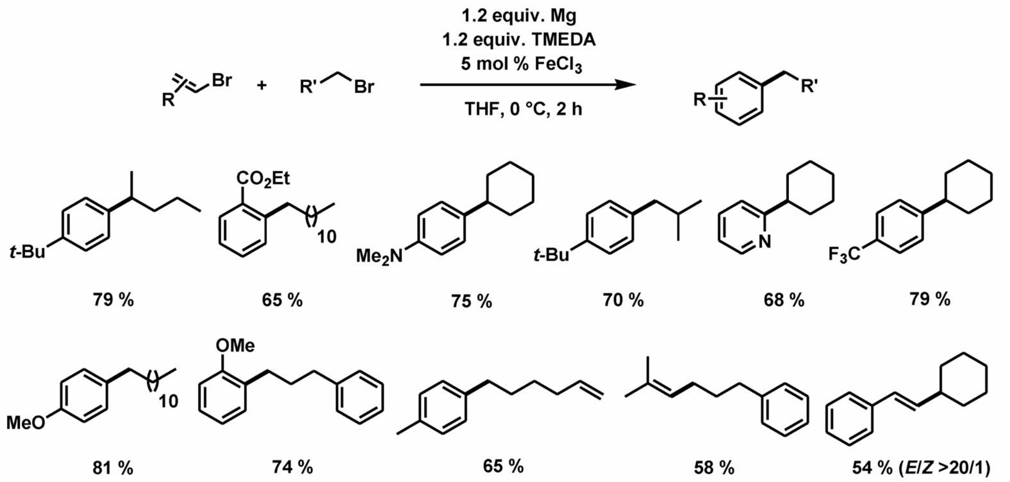


Fig. 2 TMEDA-dependent selectivity: Cross-coupling vs. reduction vs. homo-coupling.

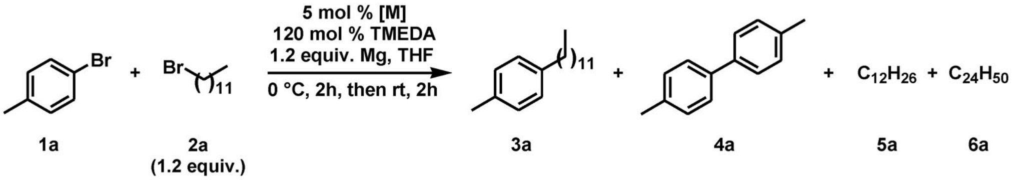
Standard conditions involve reaction of an aryl or alkenyl bromide with an alkyl bromide or chloride (1.2 equiv) with 1.2 equiv Mg, 120 mol % TMEDA, 5 mol % $FeCl_3$ in THF at 0 °C in 2 h. The protocol is chemoselective for the conversion of arylbromides; arylchlorides exhibited only marginal consumption. Primary and secondary alkylbromides were equally reactive substrates, while secondary alkylchlorides required extended reaction times (6 h). The reaction conditions tolerate alkyl, alkoxy, amino, fluoro, trifluoromethyl, pyridyl, ester, and alkene functions [12]. Polar functional groups on either of the organohalides, such as pyridyl and carbonyl moieties, resulted in sluggish magnesiation due to surface inhibition and slightly lower yields (Scheme 4).



Scheme 4 Standard conditions and substrate scope (isolated yields given; newly formed bonds are sketched **bold**).

In view of recent controversy on the role of impurities in iron-catalyzed cross-coupling reactions [13], we also examined the efficacy of other transition metals as catalysts (Table 1). The commercial 99.99 % $FeCl_3$ (from Aldrich) clearly was the most active catalyst; $NiCl_2$ exhibited only moderate reactivity in the underlying domino reaction. While Kumada reactions of preformed alkylmagnesium halides with aryl bromides under nickel catalysis have been known for a long time, the prerequisite formation of the intermediate Grignard species from the alkyl bromide starting material is slow under the reaction conditions. Other metal chlorides, including $CuCl_2$ and $PdCl_2$, showed poor activity. Low-valent iron complexes are undoubtedly the true catalysts for carbon–carbon bond-forming cross-coupling reactions with organomagnesium nucleophiles [14]. The catalytic role of copper impurities is thus limited to carbon–heteroatom bond-forming reactions [15].

Table 1 Alternative transition-metal chlorides as precatalysts.

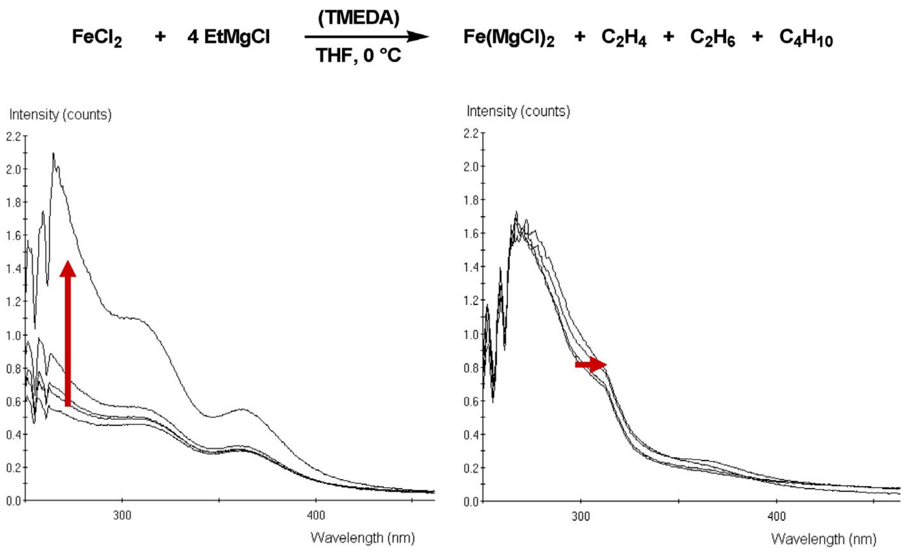


[M]	3a	4a	1a	5a	6a
$FeCl_3$	78 %	7 %	0 %	30 %	11 %
$CuCl_2$	7 %	0 %	23 %	28 %	26 %
$PdCl_2$	10 %	11 %	0 %	36 %	7 %
$NiCl_2$	41 %	18 %	0 %	23 %	28 %
$MnCl_2$	9 %	0 %	11 %	60 %	7 %
$CrCl_3$	1 %	0 %	21 %	42 %	8 %

Mechanistic investigations

With regard to the nature of the catalyst species, we assume that an initial reduction of the employed iron(III) chloride (or equally with $FeCl_2$) is operative when small amounts of alkylmagnesium halides form (Fig. 3, top) [6,16]. The resultant, but still elusive, reduced bimetallic complex has been viewed as a $[Fe^{-II}(MgX)_2]$ complex (inorganic Grignard) that is electronically equivalent to $[Ni^0]$ [17]. The catalyst solution generated upon reduction of $FeCl_2$ (or $FeCl_3$) with four (or five) equivalents of alkylmagnesium halide is generally dark brown and homogeneous in THF in the presence of TMEDA or other suitable amine additives. Dynamic light-scattering experiments showed no particles within the detection window (0.6–5000 nm) [18]. UV spectra documented the rapid aging of the catalyst species in the absence of TMEDA. After 17 h at 0 °C no catalytic activity was observed. With an analogous TMEDA/Fe (2/1) mixture, UV spectra exhibited no significant shift of the absorption bands, and the catalyst activity is retained for more than 17 h (Fig. 3, bottom).

A simple kinetic profile clearly shows the consumption of both substrates, with the alkyl bromide being consumed more rapidly due to the initial reduction of the iron salt to the catalyst species (Fig. 4). A small excess of the alkyl bromide is usually employed to assure high cross-coupling yields. Most interestingly, repetitive quenching experiments with benzaldehyde revealed a steady-state behavior of the concentration of the intermediate Grignard species. Most of the reactions studied exhibited constantly low concentrations of the alkylmagnesium species (detected as benzaldehyde adduct) over the whole reaction time [12]. This again is indicative of a slow Grignard forming step (due to the presence of TMEDA) and a rapid cross-coupling step. The fact that the reaction is largely free of organomagnesium species makes this protocol intrinsically safe and attractive for large-scale operations. Consistently, we



w/out TMEDA
(bottom to top: 0 min, 30 min, 45 min, 80 min, 17 h)

with TMEDA / [Fe] = 2/1
(left to right: 0 min, 30 min, 45 min, 80 min, 17 h)

Fig. 3 Reductive catalyst formation (top) and UV spectra of catalyst solutions (bottom).

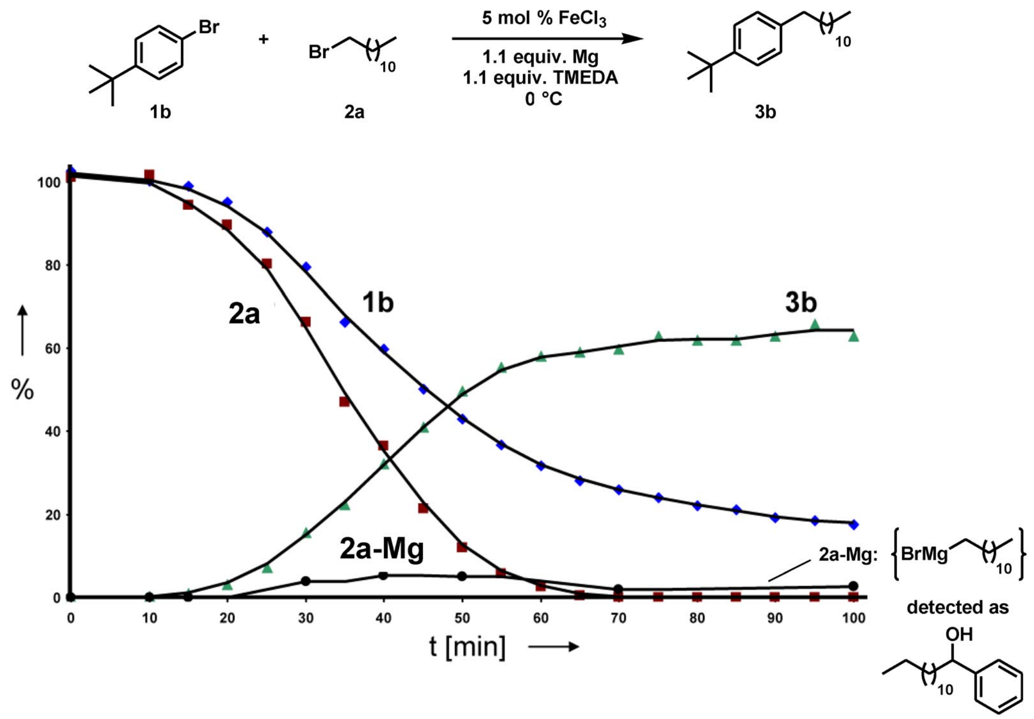
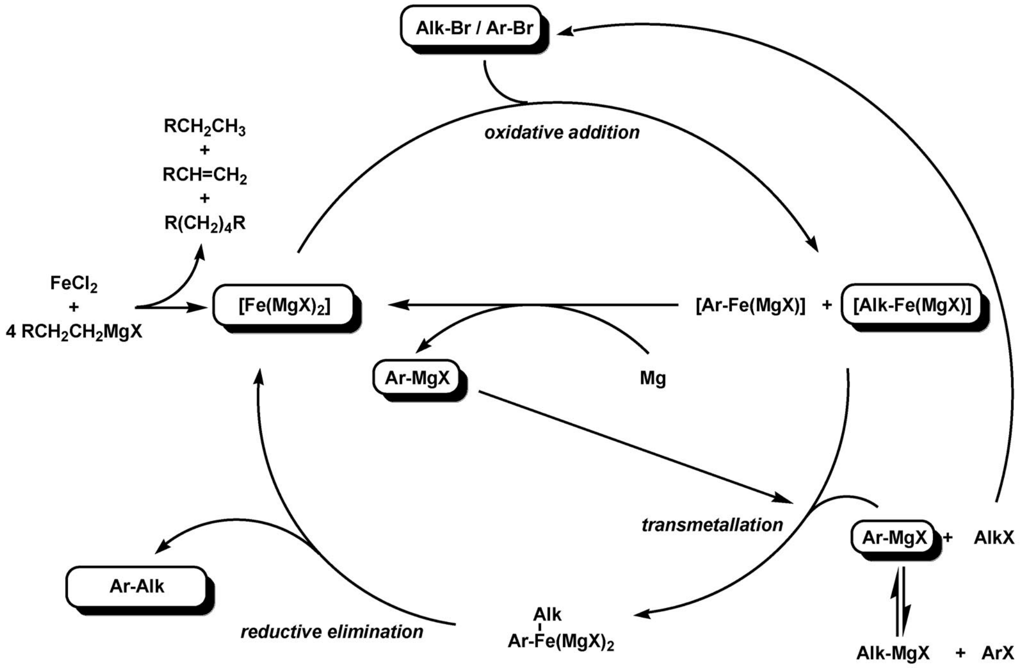


Fig. 4 Steady-state concentration of intermediate alkyl-Grignard species (**2a-Mg**).

observed only a slight decrease in cross-coupling yields (minus 10–15 %) when performing the reactions under aerobic conditions.

Mechanistic investigations have already been performed by the groups of Kochi [3], Cahiez [7], Fürstner [19], Nagashima [20], and others. However, the postulation of a concise mechanistic scenario is hampered by the unavailability of stable iron catalysts. Although evidence exists for the catalytic competence of aryliron(II) complexes as well as low-valent bimetallic [$Fe(MgX)_2$] species, iron-catalyzed cross-coupling reactions still lack a firm mechanistic framework [6f,19]. Based upon literature precedents [6,16], we postulate that the initial reduction of $FeCl_2$ (or equally $FeCl_3$) is prompted by small amounts of the alkylmagnesium halide. The low-valent iron catalyst, presumably in oxidation state –II, engages in rapid oxidative additions of both substrates, the aryl and alkyl bromide [12]. We believe that the aryliron species undergoes a magnesium-driven transmetallation to give ArMgX and the [$Fe(MgX)_2$] catalyst. The actual cross-coupling seems to occur between ArMgX and the residual alkyliron species (Scheme 5). We consider this simplified mechanistic postulate a working hypothesis that is consistent with most of our experimental data [21], but would like to emphasize that even slight alterations of the nature of the substrates, procedure of catalyst preformation and reaction conditions can exert significant changes of the mechanism. Competitive scenarios under the action of iron(I) or iron(II) catalysts have been discussed [19].



Scheme 5 Mechanistic postulate for the direct aryl-alkyl cross-coupling reaction.

SUMMARY

We developed a new one-pot methodology for the selective iron-catalyzed cross-coupling reaction between aryl halides and alkyl halides. The reaction conditions are highly sustainable as no preformation of the hazardous Grignard component is required and only minimal amounts of an intermediate organomagnesium species are formed during the course of reaction. $FeCl_3$ serves as cheap precatalyst. The unexpectedly high selectivity under one-pot conditions could spearhead the development of a yet untapped area of transition-metal-catalyzed direct cross-coupling reactions between two electrophiles in the presence of a metallating reagent [14,21,22].

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