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Domino Iron Catalysis: Direct Aryl–Alkyl Cross-Coupling**

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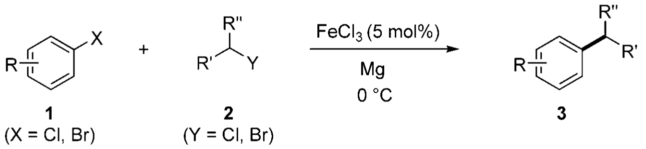
In memory of Jay K. Kochi

Over the past decade, transition-metal-catalyzed cross-coupling reactions have matured into an indispensable class of reactions for organic synthesis.[1] Palladium and nickel complexes, in particular, boast high catalytic activity for a wide range of substrates and high functional-group tolerance. In view of potential industrial applications,[2] the drive towards higher levels of efficiency and sustainability remains unabated. The high costs[3] associated with the use (and removal) of palladium and nickel catalysts as well as toxicological aspects[4] have limited the more general use of such protocols in large-scale production. Based upon the pioneering work by Kharasch[5a] and Kochi,[5] and recent developments of iron-catalyzed cross-coupling procedures using cheap and non-toxic iron catalysts by Fürstner,[6] Knochel,[7] Nakamura,[8] Cahiez,[9] Bolm,[10] and others[11] have addressed these sustainability issues.[12] Despite the economic use of simple iron salt/amine precatalysts, the employment of hazardous organomagnesium reactants inC−C coupling reactions still imposes stringent and elaborate safety precautions for the overall process.[13] As part of our research program, we rose to the challenge to develop a sustainable methodology for the direct cross-coupling of aryl halides **1** with alkyl halides **2** which obviates the presence of large quantities of hard-to-handle and sensitive Grignard reagents. We report herein on a new, operationally simple, one-pot synthesis of substituted arenes **3** by iron-catalyzed cross-coupling under mild conditions (Scheme 1).



Scheme 1. Direct iron-catalyzed cross-coupling.

Bogdanovic et al. demonstrated earlier that formal [Fe-$(MgX)_2$] complexes catalyze the formation of Grignard species from aryl halides and magnesium.[14] Electronically analogous complexes have also been postulated by Fürstner and others to be catalytically competent in cross-coupling reactions of organomagnesium halides with organohalides.[6,9c,15] The obvious involvement of low-valent iron–magnesium complexes in both the formation of organomagnesium species and the cross-coupling with organohalides raises the question whether domino catalysis for the direct cross-coupling of two electrophilic organohalides is feasible. We chose the reaction of *p*-tolyl bromide (**1a**) with cyclohexyl bromide (**2a**) in the presence of magnesium as our model system.[16a] Although the components are electronically differentiated, potential (catalyzed) transmagnesiation from the kinetic (alkyl–MgX) to the thermodynamic (aryl–MgX) Grignard species, competitive reductive processes, and thermodynamically favored biaryl coupling could deplete the selectivity for the cross-coupling product.

Initial experiments documented the feasibility of such direct cross-coupling reactions with unexpectedly high selectivities. In the presence of $FeCl_3$ as the precatalyst and stoichiometric amounts of magnesium turnings and *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA) as an additive, the cross-coupling product was obtained in up to 73% yield in a practical one-pot reaction (Table 1).[16a] The best results were obtained in THF and 2-methyl-THF, while other ether solvents inhibited the reaction. Primary amines and pyridine as additives gave no conversion under the reaction conditions. Interestingly, the THF/*N*-methylpyrrolidinone (NMP) solvent mixture[6,9] favored by Fürstner and Cahiez resulted in low conversion. The best selectivities were obtained in dilute solution (0.1–0.2 M) which also reduces competitive biaryl formation. Higher precatalyst loadings (> 5 mol%) enhanced the occurrence of side reactions. The inherent formation of a low-valent iron–magnesium catalyst by reduction of $FeCl_3$ with in situ formed alkylmagnesium halide accounts for the need for a slight excess of alkyl halide.[6] When a larger excess of one component was employed, yields were slightly increased albeit at the cost of reduced selectivities.

We screened various commercial iron salts as precatalysts.[16a] The comparable activities of $FeCl_3$ and $FeCl_2$ are in accordance with the literature.[6b] Interestingly, FeF_2 and FeI_2 were inactive. Diketone complexes [Fe(acac)$_3$] and [Fe(bzac)$_3$] (acac = acetylacetonate, bzac = benzoylacetonate) gave only slightly lower yields than $FeCl_3$. Iron(II) phthalocyanine exhibited low activity, and iron powder was not a competent catalyst.[6a] The preformed homobimetallic complex [$(FeCl_3)_2$(tmeda)$_3$] described by Cahiez et al.[9c] resulted

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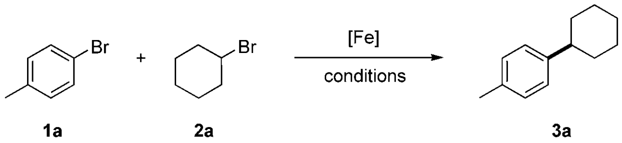
Table 1: Selected optimization experiments.



T [°C]	Solvent	Additive[a]	$FeCl_3$ [mol %]	**1a**/**2a**	Yield [%][b]
20	Et_2O	TMEDA	5	1:1.2	0 (0)
	MTBE				0 (0)
	dioxane				< 10 (0)
	$c\text{-}C_6H_{12}$				0 (0)
	THF				65 (9)
	2-Me-THF				65 (6)
0	THF	TMEDA	5	1:1.2	70 (9)
45					53 (10)
0	THF	TMEDA	7.5	1:1.2	72 (14)
			10		75 (14)
			15		69 (14)
0	THF	–	5	1:1.3	27 (8)
		py			0 (0)
		phen			0 (0)
		DMA			31 (9)
		NEt_3			32 (15)
		DACH			0 (0)
		Me_4-DACH			38 (12)
		NMP[c]			< 5 (0)

[a] py = pyridine, phen = 1,10-phenanthroline, DMA = *N*,*N*-dimethylaniline, DACH = 1,2-diaminocyclohexane, Me_4-DACH = *N*,*N*,*N*′,*N*′-tetramethyl-DACH. [b] Yield of **3a** (in brackets: 4,4′-bitolyl). [c] THF/NMP = 10:1.

in moderate yield of the cross-coupling product accompanied by large amounts of unwanted 4,4′-bitolyl (**4b**) under the reaction conditions.

The selectivity of the cross-coupling reactions was found to depend significantly on the amount of TMEDA, which potentially stabilizes the complexes of both metals (Fe, Mg) (Figure 1).[16a] In the absence of TMEDA, reduction to toluene (ArH) was dominant. The cross-coupling product **3b** was favorably formed with increasing TMEDA concentrations, which can be explained by the slower formation of the Grignard reagent. Reductive dehalogenation (to ArH) and biaryl coupling (to **4b**) were minimized upon addition of 1.2 equivalents of TMEDA.

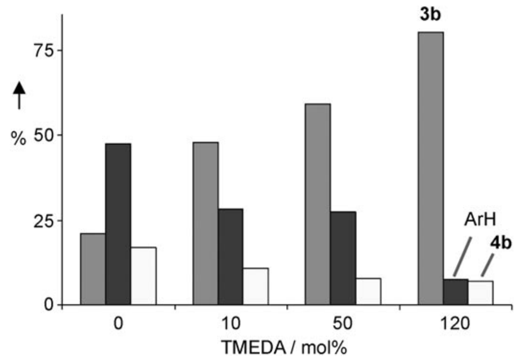


Figure 1. TMEDA dependence of the model system *p*-tolyl bromide (**1a**) and *n*-dodecyl bromide (**2b**). ArH = toluene.

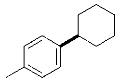
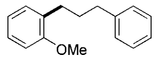
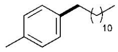
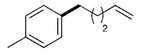
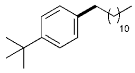
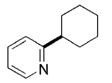
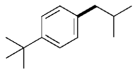
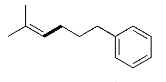
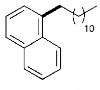
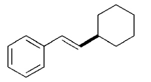
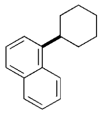
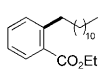
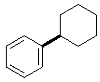
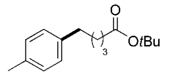
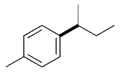
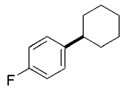
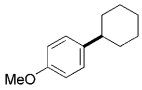
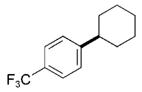
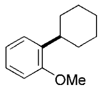
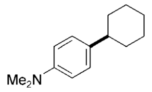
Table 2 shows a series of 18 aryl–alkyl and 2 alkenyl–alkyl cross-coupling products synthesized under one-pot conditions from the corresponding organohalides.[16a] Aryl and heteroaryl bromides bearing alkyl, alkoxy, fluoro, and amine substituents exhibited good reactivities with primary and secondary alkyl bromides (**3a**–**k**, **3r**–**t**). Tertiary alkyl bromides gave only minimal conversion under the standard conditions (< 10 %). No isomerization of primary alkyl bromides to the more stable secondary isomers was observed; terminal olefins showed no double-bond migration (**3l**). The resultant ω-arylalkenes constitute versatile substrates for additional transformations of the olefin moiety.

Vinyl bromide gave a complex mixture of products, but higher homologues such as dimethylvinyl bromide and β-bromostyrene afforded the corresponding internal olefins in moderate yields (**3n**, **3o**). Surprisingly, low conversion (< 15 %) was observed with ester and cyano substituents in either component. Here, consumption of the magnesium was inhibited, probably as a result of surface deactivation.[17] Employment of a larger excess of Mg turnings (> 1.5 equiv) or powder (1.2 equiv) and catalytic TMEDA resulted in moderate conversions at longer reaction times (**3p**, **3q**). Whereas chloroarenes and chloroalkanes (**3g**, **3j**, **3m**) exhibited only low conversions under standard conditions (3 h, 0 °C), a two-step protocol (preformation of the catalyst at 0 °C, coupling at 20 °C) resulted in significantly increased yields in reactions with alkyl chlorides (**3a**, **3j**). The corresponding alkanes and arenes (formed by hydrodehalogenation,[18] each < 15 %), alkenes (β-hydride elimination, < 10 %), and biaryls (mostly < 6 %) are general by-products. Notably, a major portion of these by-products stem from the necessary in situ reduction of the $FeCl_3$ to the postulated cross-coupling catalyst $[Fe(MgX)_2]$.[19]

Apart from the high practicality of the one-pot protocol and the direct employment of simple organohalides as starting materials, this novel cross-coupling methodology also boasts high selectivity of the underlying domino reaction. Despite the expected thermodynamic preference for homocoupling to give the biaryl, the reaction displays high selectivity for the cross-coupling product. In all cases only minimal amounts of the biaryl were formed (< 9 %).[20]

Although the electronic differentiation of the two organohalides should favor magnesiation of the alkyl bromide (weaker $C_{(sp^3)}$–Br bond, reversible Mg→π*(ArBr) electron transfer),[21] we postulate the intermediacy of both Grignard species under the reaction conditions. Bogdanovic et al. reported on the iron-catalyzed Grignard formation from aryl halides catalyzed by an iron–magnesium complex under similar conditions.[14] Our results support the operation of iron-catalyzed Grignard-forming reactions for both model substrates (1-bromonaphthalene (**1f**) and cyclohexyl bromide (**2a**), Figure 2). In the absence of $FeCl_3$ the induction period for the magnesiation of the alkyl– and aryl–Br bonds was observed to be three times longer. Upon addition of 5 mol % $FeCl_3$ both organohalides were rapidly consumed.[16] Our one-pot reaction is thus based upon a novel sequence of iron-catalyzed Grignard formation and iron-catalyzed cross-coupling. This constitutes the first example of a domino iron catalysis for cross-coupling reactions.

Table 2: Synthesis of aryl–alkyl and vinyl–alkyl cross-coupling products.

Aryl/vinyl–X	Alkyl–Y	Product		Yield [%]	Aryl/vinyl–X	Alkyl–Y	Product		Yield [%]
Br Br	Br Cl		**3a**	70 75[a]	Br	Br		**3k**	74[c]
Br	Br		**3b**	80	Br	Br		**3l**	50
Br	Br		**3c**	81	Br Cl	Br Br		**3m**	58 38
Br	Br		**3d**	67	Br	Br		**3n**	52
Br	Br		**3e**	75	Br	Br		**3o**	54
Br	Br		**3f**	67	Br	Br		**3p**	51[d]
Br Cl Br	Br Br Cl		**3g**	77 20[b] 25	Br	Br		**3q**	38[d]
Br	Br		**3h**	62	Br	Br		**3r**	48
Br	Br		**3i**	65	Br	Br		**3s**	68[e]
Br Br Br	Br Cl Cl		**3j**	66 39 63[a]	Br	Br		**3t**	72

[a] Aryl–Br/alkyl–Cl 1.2:1, 2 h at 0°C, then 2 h at 20°C. [b] 3 h at 20°C. [c] Yield determined by GC methods. [d] 1.6 equiv Mg, 20 mol% TMEDA, 10 h. [e] Yield determined by NMR spectroscopy.

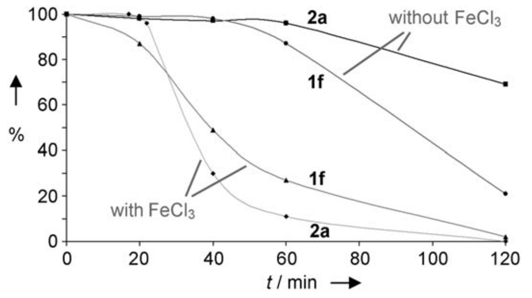


Figure 2. Iron-catalyzed Grignard formation from 1-bromonaphthalene (**1f**) and cyclohexyl bromide (**2a**).

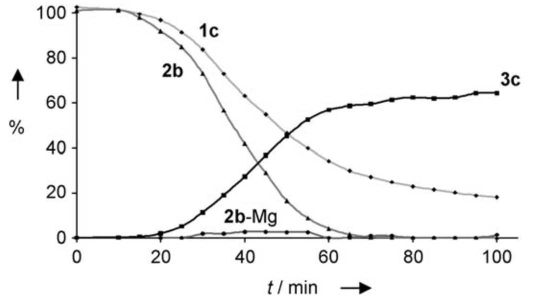


Figure 3. Concentration–time plots for the model reaction of 4-*tert*-butylbromobenzene (**1c**) and dodecyl bromide (**2b**) with intermediate **2b**–Mg.

Concentration–time plots (Figure 3) illustrate the faster consumption of alkyl bromide **2b**, possibly because of the rapid reduction of $FeCl_3$ by intermediate alkyl-MgBr. Furthermore, quenching experiments[16a] documented the existence of minimal and rather constant (quasi-stationary) concentrations of alkyl-MgBr over the course of the reaction ($<4\%$). The Grignard-forming step thus appears to be rate-determining and the subsequent coupling reaction relatively fast. This impedes an induction period, which is known to entail spontaneous heat release and rapid unselective reactions in conventional Grignard-forming protocols (RX + Mg).[13,16a] Unlike classical methodologies, our one-pot protocol obviates the need for stoichiometric amounts of hazardous Grignard compounds, and hence, contributes to the safer performance of such reactions.

We have demonstrated, for the first time, the concept of domino iron catalysis in cross-coupling reactions. The reaction uses a single cheap precatalyst ($FeCl_3$). We postulate the formation of both organomagnesium species under the reaction conditions. Preliminary results showed that both organohalides undergo rapid oxidative addition[22] to a [Fe-

$(MgBr)_n$] complex.[23] The reasons for the unexpectedly high cross-coupling selectivities under one-pot conditions as well as mechanistic details are currently being investigated. We regard the underlying general concept of domino iron catalysis as a viable template for numerous related direct coupling reactions between two electrophiles.[24] Extension of this methodology to aryl–aryl coupling reactions is currently in progress.

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Keywords: cross-coupling · domino reactions · Grignard reactions · iron · sustainable chemistry

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