Iron Catalysis

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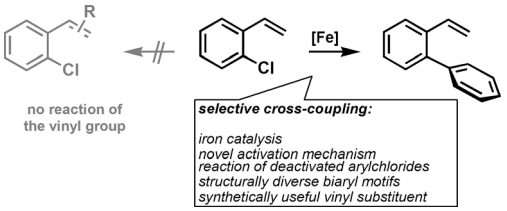
Chlorostyrenes in Iron-Catalyzed Biaryl Coupling Reactions**

*Samet Gülak and Axel Jacobi von Wangelin**

Palladium- and nickel-catalyzed cross-coupling reactions are among the most versatile methods for the assembly of biaryl compounds, which constitute important structural motifs of fine chemicals, materials, pharmaceuticals, and natural products. Suzuki–Miyaura reactions between arylboronic acids and aryl halides are carried out under especially mild conditions and exhibit high functional-group tolerance.[1,2] The constantly increasing world market price of palladium,[3] the toxicity of nickel compounds,[4] and the laborious synthesis of arylboronic acids[5] are prompting the search for powerful alternatives, especially for industrial processes. The past years have witnessed the development of iron-catalyzed protocols, which boast high operational practicality and synthetic efficiency: the precatalysts are cheap and nontoxic iron salts; complex, air-sensitive ligands are not required; the mild reaction conditions tolerate various functional groups.[6] To date, iron-catalyzed biaryl syntheses from aryl Grignard species and aryl (pseudo)halides proved rather unselective.[7] Furthermore, only one protocol that largely suppressed the competing homocoupling has been reported for the effective utilization of cheap but sluggish aryl chlorides. This method requires a special precatalyst combination of iron(II) fluoride and a carbene ligand, the generation of the catalytically active species in a prior step, and elevated reaction temperatures.[8]

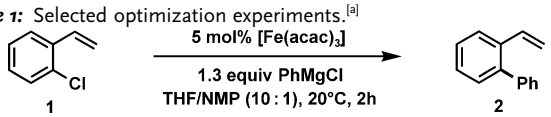
During our research program directed at iron-catalyzed biaryl syntheses, we became interested in the role of activating substituents. Electronegative heteroatom-based groups at the electrophile generally enhance its reactivity.[9] Hydrocarbons, however, have received only little attention as activating substituents.[10] Based upon the rich coordination chemistry of olefins with iron in low oxidation states, we postulated a novel mode of activation for olefin-substituted aryl chlorides.[11] We assumed that sequential olefin coordination at the catalyst and haptotropic migration could effect C–Cl bond activation of chlorostyrenes. Herein, we report an efficient iron-catalyzed biaryl synthesis by exploiting this unprecedented activation mechanism. The reaction of aryl Grignard species with chlorostyrenes proceeds under mild and practical reaction conditions in the presence of iron(III) tris(acetylacetonate) [Fe(acac)$_3$] as precatalyst. Competitive reactions at the vinyl group (e.g., polymerization, carbometalation, and substitution) do not occur (Scheme 1).[12]



Scheme 1. Selective iron-catalyzed biaryl coupling with chlorostyrenes.

Our initial optimizations of the model reaction between *ortho*-chlorostyrene (**1**) and phenylmagnesium chloride (PhMgCl) are summarized in Table 1. Moderate yields of *ortho*-vinylbiphenyl (**2**) were obtained with iron(III) salts as precatalysts in a THF/NMP solvent mixture (NMP = *N*-methyl-2-pyrrolidone, Table 1, entries 1–3).[13] Nickel, copper, and palladium salts showed no activity (< 2% of **2**). The absence of NMP as well as the use of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)[14] resulted in major consumption of **1** by polymerization (Table 1, entries 4 and 5, respectively). The addition of TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) gave a slight increase of selectivity, as radical reaction pathways (e.g., homo-biaryl formation, catalyst deactivation, polymerization) were suppressed (Table 1,

Table 1: Selected optimization experiments.[a]



Entry	Precatalyst	Variation of standard conditions	Yield [%][b]
1	[Fe(acac)$_3$]	–	46 (60)
2	[Fe(acac)$_3$] [c]	–	47 (61)
3	$FeCl_3$	–	36 (50)
4	[Fe(acac)$_3$]	no NMP	3 (99)
5	[Fe(acac)$_3$]	THF/TMEDA (10/1)	3 (100)
6	[Fe(acac)$_3$]	Et_2O/NMP (10/1)	5 (20)
7	[Fe(acac)$_3$]	with 5 mol% TEMPO	54 (60)
8	[Fe(acac)$_3$]	with 1 equiv LiCl	41 (45)
9	[Fe(acac)$_3$]	30°C	56 (61)
10	[Fe(acac)$_3$]	PhMgBr addition (20 min)[d]	74 (90)
11	[Fe(acac)$_3$]	as entry 10, 30°C	89 (98)
12	[Fe(acac)$_3$] [e]	as entry 11	85 (87)
13	[Fe(acac)$_3$]	as entry 11	82[f] (91)
14	[Fe(acac)$_3$]	as entry 11[g]	78 (87)

[a] [Fe(acac)$_3$] (5 mol%, > 98%), **1** (1 mmol) in THF/NMP (10/1 v/v, 4.4 mL), PhMgCl (1.3 mmol, 0.5 M in THF), 20°C, 2 h. [b] Yields determined by GC analysis, conversion of **1** in brackets. [c] 99.99% purity. [d] Slow addition of PhMgCl over 20 min. [e] 1 mol% [Fe(acac)$_3$]. [f] 10 mmol scale, yield of isolated product. [g] Addition of 1 equiv ethyl benzoate.

[*] Dipl.-Chem. S. Gülak, Prof. Dr. A. Jacobi von Wangelin
Institute of Organic Chemistry, University of Regensburg
Universitätsstr. 31, 93053 Regensburg (Germany)
E-mail: axel.jacobi@ur.de

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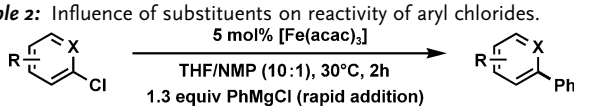
entry 7).[15] The addition of lithium chloride proved detrimental to the reaction (Table 1, entry 8).[16]

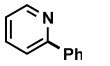
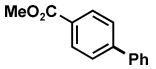
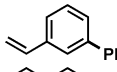
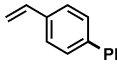
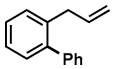
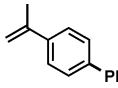
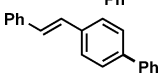
A slightly elevated reaction temperature (30 °C) and slow addition of the Grignard species were highly beneficial, the latter preventing catalyst aggregation (Table 1, entries 9–11).[17] The selectivity of the reaction was significantly increased by the use of 1 mol% of [Fe(acac)$_3$] (Table 1, entry 12). A 10-fold increase in the reaction scale afforded **2** in 82% yield of isolated product (Table 1, entry 13). The addition of ethyl benzoate resulted in slightly lower selectivity (Table 1, entry 14),[7e] while ketones were not tolerated.

Table 2 shows the influence of the stereoelectronic properties and positions of various substituents on the reactivity of chloroarenes under modified standard conditions (rapid addition of PhMgBr). The arylation of activated chloroarenes (4-benzoate, 2-pyridyl) was already reported by Fürstner et al. (Table 2, entries 1 and 2).[7e] Without electronegative or with electron-donating substituents, no conversion was observed (Table 2, entries 4–6). Alkenyl groups had a slightly deactivating effect because of their electron-rich π systems, yet we postulate an olefin coordination to the catalyst followed by haptotropic[18] migration along the conjugated π systems into proximal position to the C–Cl bond.

Unlike 2-chlorostyrene, the 3- and 4-chloro isomers showed no selective activation of the C–Cl bonds (Table 2, entries 7–9). This effect is attributed to a strong coordination of the distal vinyl groups which inhibits haptotropic migration. On the other hand, the (slight) steric hindrance of *ortho*-chlorostyrene (**1**) favors a migration of the iron species. α-Methyl substitution of the *ortho*-vinyl group effects a twisting of the olefin and aryl planes, thus breaking the conjugated system and prohibiting C–Cl activation (Table 2, entry 10). Our hypothesis of an essential coordination and migration along the conjugated π systems is also manifested in the reactivity of substituted 4-chlorostyrenes. The installation of an α-methyl- or a β-phenyl group in combination with low steric hindrance and retention of planarity led to clean arylation of the distal C–Cl bond (Table 2, entries 13 and 14). This comparative study shows that, besides electron-withdrawing moieties (as in 2-chloropyridine and ethyl-4-chlorobenzoate),[7e] olefins with proper substitution and positioning facilitate the activation of aryl chlorides. Phenylations of 2-chlorostyrene, 1-chloro-4-isopropenylbenzene, and 4-chlorostilbene each proceeded with product selectivities greater than 90% (Table 2, entries 7, 13, and 14). This new mode of activation has then been exploited for the synthesis of diverse hetero-biaryl compounds (Tables 3 and 4).

Table 2: Influence of substituents on reactivity of aryl chlorides.



Entry	Aryl chloride	Biaryl	Yield [%][a]
1[b]	2-pyridyl		73
2[b]	4-$MeCO_2CC_6H_4$		28
3[c]		 R′ = F	0
4[c]		H	1
5[c]		OMe	0
6[c]		Me	0
7	2-vinylphenyl		56 (61)
8	3-vinylphenyl		1 (16)
9	4-vinylphenyl		3 (20)
10	2-*iso*-propenylphenyl		12 (13)
11[d]	2-allylphenyl		0 (30)
12[c]	2-cyclopropylphenyl		0
13	4-*iso*-propenylphenyl		48 (49)
14	4-β-styrylphenyl		46 (51)

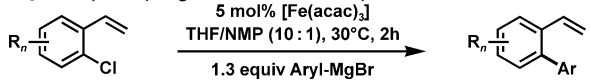
[a] Yields determined by GC analysis, conversion of aryl chloride in brackets. [b] Ref. [7e]. [c] < 8% conversion. [d] Isomerization to 1-chloro-2-propenylbenzene (20%).

The aryl Grignard reagents were prepared from aryl bromides and magnesium ribbons in THF at room temperature.[19] The cross-coupling reactions were conducted under argon at 30 °C, with the Grignard species (0.5 M in THF) being slowly added over a period of 20 min. Fluoro-substituted arylmagnesium bromides gave better yields upon rapid addition (Table 3, entries 5–7, 11, 14, 16, and 18). Such less basic Grignard reagents showed low propensity to undergo homo-biaryl coupling and reductive catalyst deactivation/aggregation.[17] The reaction conditions tolerate amine-, ether-, fluoro-, chloro-, acetal-, and alkene functions. Both aryl components can bear electron-withdrawing or electron-donating substituents. Aryl Grignard reagents with *ortho*-substituents afforded low yields (< 35%), with major formation of the homo-biaryl compound.

Aryl chlorides with *para*- and *meta*-alkenyl substituents exhibited similar reactivities under identical conditions (Table 4), however, substrates that carry isopropenyl substituents were subject to slow deprotonation at the allylic methyl group.[20] Cross-coupling of the resultant anionic chlorostyrenes did not occur under the reaction conditions. Slow addition of the arylmagnesium bromide solution over 40 minutes resulted in suppression of deprotonation and a selective cross-coupling reaction (Table 4, entries 1–3 and 7–9). Strongly basic Grignard reagents (Table 4, entries 5 and 6), an excess of ArMgBr (Table 4, entries 4 and 6) or their rapid addition (< 1 min, Table 4, entry 10) led to nonproductive deprotonation and recovery of the aryl chloride (> 50%) after aqueous work-up. 2-Chloronaphthalene showed only minimal reactivity (Table 4, entry 11).

For the first time, iron-catalyzed hetero-biaryl coupling reactions of deactivated aryl chlorides with aromatic Grignard reagents have been realized in good yields under

Table 3: Biaryl coupling with *ortho*-chlorostyrenes.[a]

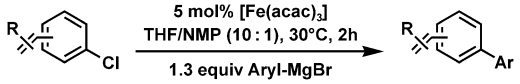


Entry	Chlorostyrene	Biaryl		Yield [%]
1			R′ = H	89[b]
2			NMe_2	72
3			OMe	73[b]
4			Me	82[b]
5[c]			OCF_3	81
6[c]			F	81
7[c]				83[b]
8				82
9				75
10				72[b]
11[c]			R′ = F	83
12			NMe_2	73
13			OMe	91
14[c]				84
15				78[d]
16[c]				77
17				69[d]
18[c]				76
19				69[b]

[a] 2 mmol scale reactions, addition of Grignard species over 20 min, see the Supporting Information. [b] Yields determined by GC analysis. [c] Direct addition of Grignard species. [d] Yield determined by NMR spectroscopy.

mild conditions. A new mechanism involving coordination of the vinyl substituent to the iron catalyst and subsequent haptotropic migration to the site of C–Cl bond activation is decisive. The significant secondary kinetic isotope effect

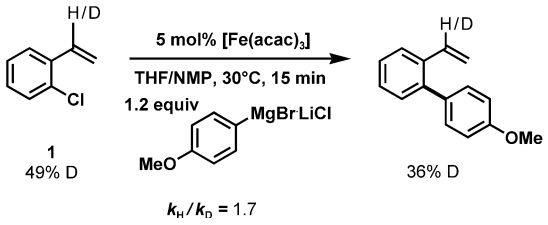
Table 4: Biaryl coupling with *meta*- and *para*-chlorostyrenes.[a]



Entry	Chlorostyrene	Biaryl		Yield [%]
1			R′ = F	93[b]
2			OCF_3	83[b]
3			H	86[b]
4[c]			H	45[b]
5			OMe	45[b]
6[c]			OMe	25[b]
7				82
8				69[b]
9			R′ = F	85
10[d]			H	20[b]
11				< 10

[a] 2 mmol scale reactions, addition of Grignard species over 40 min, see the Supporting Information. [b] Yields determined by GC analysis. [c] 2.3 equiv ArMgBr. [d] Direct addition of Grignard species.

(k_H/k_D=1.7, average of two reactions) in the reaction of an equimolar mixture of **1** and [D_1]-**1** is indicative of a rate-determining olefin–iron coordination (Scheme 2). The general procedure is highly practical (ligand-free, THF/NMP, 20–30 °C, 2 h) and based on [Fe(acac)$_3$] (1–5 mol %) as cheap precatalyst. Unlike conventional auxiliaries, alkenyl substituents permit various opportunities for further functionalization.



Scheme 2. Secondary kinetic isotope effect.

Experimental Section

General procedure (rapid addition of Grignard reagent): A 25 mL round bottom flask was charged with [Fe(acac)$_3$] (17 mg, 0.05 mmol, 5 mol %) and purged with argon (1 min). Absolute THF and NMP (4.4 mL, 10/1, v/v) were added, followed by 2-chlorostyrene (1 mmol) and freshly prepared 4-fluorophenylmagnesium bromide (1.3 mmol, 0.5 M in THF) at room temperature. The mixture was stirred for 2 h at 30 °C. Then, saturated aqueous $NaHCO_3$ (5 mL) was added, the

mixture extracted with ethyl acetate (3 × 5 mL), and the organic phases dried (Na_2SO_4). Volatile components were removed in vacuo and the residue was subjected to flash chromatography (SiO_2, pentane, ethyl acetate) to give 4′-fluoro-2-vinylbiphenyl in 81% yield (GC yield 86%). R_f 0.29 (SiO_2, *n*-pentane); MS (EI, 70 eV): *m*/*z* 198, 183, 170, 152, 143, 133, 120, 107, 98, 74, 63, 50; HRMS: 198.085 (calcd 198.0845); IR (ATR) $1/\lambda = 3058$ (m), 2952 (m), 2357 (w), 1890 (w), 1823 (w), 1763 (w), 1625 (m), 1598 (m), 1490 (s), 1220 (s), 1155 (s), 911 (s), 756(s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.68–7.61$ (m, 1H), 7.55–7.45 (m, 1H), 7.40–7.22 (m, 4H), 7.17–7.05 (m, 3H), 6.67 (dd, 1H, 10.9/6.4 Hz), 5.70 (dd, 1H, 17.5/1.1 Hz), 5.21 ppm (dd, 1H, 11.0/1.1 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 163.9$, 139.9, 136.0, 135.8, 125.9, 116.0, 115.7, 115.1, 114.9 ppm.

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