Directed Ferration

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Preparation of Functionalized Aryl Iron(II) Compounds and a Nickel-Catalyzed Cross-Coupling with Alkyl Halides**

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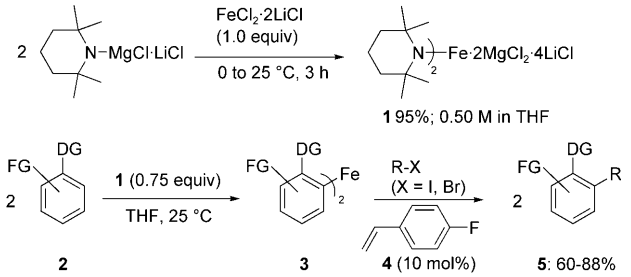
Iron-catalyzed cross-coupling reactions of organometallic reagents have found numerous applications in organic synthesis.[1] Although this method has found wide acceptance,[2] the mechanism of the cross-coupling is still not completely elucidated.[3] This goal may be achieved by preparing stoichiometric amounts of organometallic Fe compounds and studying their stability and reactivity towards electrophiles.[4] Although aryl Fe^{II} derivatives can be prepared by transmetalation[5] or by direct ferration using a tetramethylethylenediamine(tmeda)-stabilized sodium ferrate base,[6] no iron base has been reported that allows for the general preparation of organometallic aryl Fe^{II} compounds.

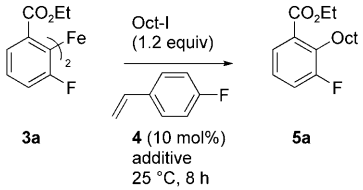
Building on our previous reports on LiCl-solubilized Mg,[7] Zn,[8] Al,[9] and Mn[10] tmp bases (tmp = 2,2,6,6-tetramethylpiperidyl), we now report a new convenient iron(II) base $tmp_2Fe{\cdot}2\,MgCl_2{\cdot}4\,LiCl$ (**1**), which allows room-temperature ferration of a broad range of functionalized arenes **2** to diaryl Fe^{II} derivatives **3**. A subsequent efficient cross-coupling with alkyl iodides (or bromides) and benzylic chlorides promoted by 4-fluorostyrene (**4**)[11] resulted in the formation of polyfunctional arenes **5** in 60–88% yield (Scheme 1). The importance of metallic impurities in $FeCl_2{\cdot}2\,LiCl$ was examined, and such impurities were found to catalyze this cross-coupling reaction.



Scheme 1. Preparation and reactions of **1**. DG: directing group; FG: functional group.

Thus, the reaction of tmpMgCl·LiCl[8] (2 equiv) with $FeCl_2{\cdot}2\,LiCl$[12] (1 equiv) at 0 °C and further stirring at 25 °C for 3 h produces quantitatively $tmp_2Fe{\cdot}2\,MgCl_2{\cdot}4\,LiCl$ (**1**). This base has excellent solubility in THF (0.5 M) and can be stored in solution without decomposition for at least eight weeks at 25 °C. The reaction of **1** with ethyl-3-fluorobenzoate (**2a**; 25 °C, 3 h) leads to the corresponding diaryl Fe^{II} species **3a**, which reacted smoothly with 1-iodooctane (1.2 equiv) to provide the 1,2,3-trisubstituted benzoate **5a** in 86% yield. The reaction time was 14 h, but by adding 4-fluorostyrene (**4**; 10 mol%), the cross-coupling was complete within 7 h at 25 °C (88% yield; Table 1, entry 1). 4-Fluorostyrene is known to promote Ni-catalyzed cross-coupling reactions.[11] It is assumed that it accelerates the reductive elimination step through a coordination of the electron-poor olefin to the metal center.

Table 1: Influence of the purity of $FeCl_2$ and additives on the cross-coupling yield.



Entry	Additive[a]	Yield [%][b]	Entry	Additive[a]	Yield [%]
1	–	95[c] (88)	10	$NiCl_2$, $MnCl_2$	88[d]
2	–	25[d]	11	$MnCl_2$, $FeCl_3$	18[d]
3	$MnCl_2$	20[d]	12	$NiCl_2$, $MnCl_2$, $FeCl_3$	74[d]
4	$CoCl_2$	34[d]	13	$CuCl_2$, $FeCl_3$	18[d]
5	$CuCl_2$	27[d]	14	$CuCl_2$, $NiCl_2$	85[d]
6	CuCl	23[d]	15	$CuCl_2$, $MnCl_2$	26[d]
7	$FeCl_3$	12[d]	16	$CuCl_2$, $NiCl_2$, $FeCl_3$	65[d]
8	**$NiCl_2$**	**94[d] (86)**	17	$CuCl_2$, $MnCl_2$, $FeCl_3$	17[d]
9	$NiCl_2$, $FeCl_3$	69[d]			

[a] 0.5% of the additive was used. In the case of several additives, equimolar amounts were used. [b] Yields in brackets refer to yield of isolated, analytically pure product. [c] $FeCl_2$ with a purity grade of 98% was used. [d] $FeCl_2$ with a purity grade of 99.998% was used.

Although the purity of $FeCl_2$ did not modify the metalation rate leading to **3a**, it considerably influences the cross-coupling step. Thus, we observed that by using $FeCl_2$ with a purity of 99.998%, the cross-coupling conversion to **5a** after a reaction time of 8 h is only 25% rather than the 95% achieved using 98% pure $FeCl_2$ (Table 1, entries 1 and 2).

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Since atomic absorption analysis revealed that the commercial sample of 98% pure $FeCl_2$ contains traces of Mn, Ni, Co, and Cu, small amounts (0.5%) of the corresponding chlorides were intentionally added to $FeCl_2$ (99.998%).[13]

Whereas $FeCl_3$, $CoCl_2$, $MnCl_2$, $CuCl_2$, and CuCl only moderately changed the cross-coupling rate (Table 1, entries 3–7), the addition of 0.5% $NiCl_2$ restored the full cross-coupling rate observed with 98% pure $FeCl_2$ (entry 8). Interestingly, combinations of two or three metallic chlorides produced intermediate cross-coupling rates (entries 9–17). In conclusion, the presence of 0.25% Ni in commercial $FeCl_2$ is certainly responsible for the observed cross-coupling reaction rate. From a practical point of view, $FeCl_2$ (98% pure) has been used for preparing tmp_2Fe (**1**), and most of the subsequent cross-coupling reactions were performed in the presence of 4-fluorostyrene (**4**; 10 mol%).[11]

Starting from ethyl-3-fluorobenzoate (**2a**), the cross-coupling of **3a** proceeds well with octyl iodide (Table 2, entry 1). Octyl bromide reacts more slowly, providing after 20 h at 25°C the product **5a** in 74% yield (entry 2). Also, secondary alkyl iodides and bromides such as *i*Pr–Br, *c*Hex–I, and *c*Hex–Br lead to the corresponding cross-coupling products **5b**,**c** in 60–83% yield (entries 3–5). In the absence of 4-fluorostyrene (**4**), an efficient reaction with benzyl chloride was observed, furnishing the benzylated arene **5d** in 88% yield (entry 6). Remarkably, various functionalized alkyl iodides undergo smooth cross-coupling reactions. Thus, the reaction of **3a** with ethyl-4-iodobutyrate (1.2 equiv) leads to the desired diester **5e** in 80% yield (entry 7). Diethyl iodomethylphosphonate reacts rapidly with **3a** at −10°C in the absence of 4-fluorostyrene (**4**) to give the phosphonate **5f** in 68% yield (entry 8). Interestingly, the dihalide 1-chloro-6-iodohexane undergoes only a substitution of the carbon–iodine bond, providing the benzoate **5g** in 85% yield (entry 9). Surprisingly, the reaction of **3a** with 6-iodohex-1-ene provided only the alkenylated product **5h** in 77% yield without any cyclization product (entry 10).[14]

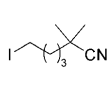
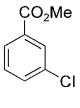
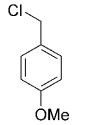
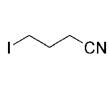
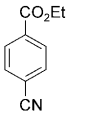
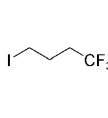
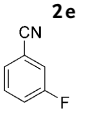
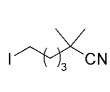
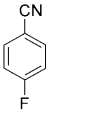
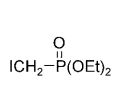
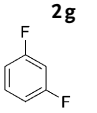
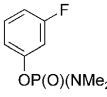
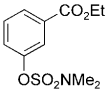
Table 2: Cross-coupling of **3a** with organic halides in the presence of **4** leading to the substitution products **5a–h**.

Entry	Substrate	Halide	Product	Yield [%][a]
				
1	**3a**	Oct–I	**5a**: R = Oct	88
2	**3a**	Oct–Br	**5a**: R = Oct	74
3	**3a**	*i*Pr–Br	**5b**: R = *i*Pr	70
4	**3a**	*c*Hex–I	**5c**: R = *c*Hex	83
5	**3a**	*c*Hex–Br	**5c**: R = *c*Hex	60
6	**3a**	$PhCH_2Cl$	**5d**: R = Bn	88[b]
7	**3a**	$I(CH_2)_3CO_2Et$	**5e**: R = $(CH_2)_3CO_2Et$	80
8	**3a**	$ICH_2P(O)(OEt)_2$	**5f**: R = $CH_2P(O)(OEt)_2$	68[b]
9	**3a**	$I(CH_2)_6Cl$	**5g**: R = $(CH_2)_6Cl$	85
10	**3a**	$I(CH_2)_4CH{=}CH_2$	**5h**: R = $(CH_2)_4CH{=}CH_2$	77

[a] Yield of isolated, analytically pure product. [b] No **4** was added.

Remarkably, this tandem metalation/cross-coupling procedure could be extended to various organic halides. Thus, the ferration of ethyl-3-chlorobenzoate (**2b**) and methyl-3-chlorobenzoate (**2c**) using **1** proceeds within 36 h at 25°C, and the subsequent couplings with an alkyl iodide and a benzylic chloride, respectively, provide the desired products **5i**,**j** in 71 and 66% yield (Table 3, entries 1 and 2). Similarly, the cyano-substituted ethyl benzoates **2d**,**e** are metalated at 25°C within 18 and 48 h, respectively. Subsequent cross-coupling reactions with aliphatic iodides furnish the alkylated products **5k**,**l** in 75 and 65% yield (entries 3 and 4). Fluoro-substituted benzonitriles are also excellent substrates. Thus, the metalation of 3-

Table 3: Preparation of diaryl Fe^{II} derivatives and cross-coupling with various organic halides in the presence of **4** (10 mol%) leading to the products of type **5**.

Entry	Substrate	*t* [h]	Halide	Product Yield [%][a]
				
1	**2b**	36		**5i**: 71
				
2	**2c**	36		**5j**: 66[b]
				
3	**2d**	18		**5k**: 75
				
4	**2e**	48		**5l**: 65
				
5	**2f**	9		**5m**: 70
				
6	**2g**	18		**5n**: 72[b]
		Dec–I		
7	**2h**	10		**5o**: 77
		Oct–I		
8	**2i**	30		**5p**: 85
		Hex–I		
9	**2j**	60		**5q**: 66

[a] Yield of isolated, analytically pure product. [b] No **4** was added.

fluorobenzonitrile (**2f**) with **1** (0.75 equiv, 25 °C) is completed within 9 h, whereas the metalation of 4-fluorobenzonitrile (**2g**) requires 18 h. Alkylation with 6-iodo-2,2-dimethylhexanenitrile and diethyl iodomethylphosphonate produces the functionalized benzonitriles **5m**,**n** in 70 and 72% yield (entries 5 and 6). Interestingly, the metalation of 1,3-difluorobenzene (**2h**) is completed within 10 h and the reaction with 1-iododecane leads to the alkylated benzene **5o** in 77% yield (entry 7). Moreover, the protected phenols **2i** and **2j** are deprotonated by tmp_2Fe at 25 °C within 30 and 60 h, respectively. After alkylation reactions with 1-iodooctane or 1-iodohexane, the substituted products **5p**,**q** are obtained in 85 and 66% yield (entries 8 and 9).

To gain some mechanistic insight into the reactivity of organometallic Fe intermediates, we treated tmpMgCl·LiCl (3.0 equiv) with $FeCl_3$ (1.0 equiv) in THF. Surprisingly, Mössbauer spectroscopy (see the Supporting Information) indicated that the product is mainly an Fe^{II} amide (70% yield compared to 95% yield for the preparation of **1** starting from $FeCl_2$·2 LiCl). This reagent **6** has a comparable stability to **1** and induces smooth deprotonation (0.75 equiv, 25 °C, 3 h) of ethyl-3-fluorobenzoate (**2a**), leading to the corresponding iron(II) derivative. Its cross-coupling with octyl iodide in the presence of 4-fluorostyrene (**4**) proceeds with similar rate as the analogous reaction with Fe^{II} base **1** and provides the corresponding cross-coupling product **5a** in 72% yield (compared to 88% with **1**, Table 1, entry 1).

In summary, we have described a convenient directed ferration of various polyfunctional aromatics. This metalation procedure tolerates many functional groups (methyl and ethyl esters, halogen atoms, nitriles) and proceeds at 25 °C. Moreover, we reported that the subsequent cross-coupling reaction with functionalized organic halides is catalyzed by the Ni impurities of commercial $FeCl_2$. Further studies on the reaction scope of this cross-coupling are currently underway.

Experimental Section

1: In a dry and argon-flushed 250 mL Schlenk flask, freshly titrated tmpMgCl·LiCl (100 mmol, 1.18 M, 85 mL) was purged and cooled to 0 °C. Then, $FeCl_2$·2 LiCl (1 M in THF, 50 mL, 50 mmol) was added over 5 min. The resulting mixture was stirred for 30 min at 0 °C, warmed to 25 °C, and stirred for another 3 h. The resulting solution of **1** was concentrated in vacuo and was titrated prior to use at 0 °C with benzoic acid (0.2 M in THF) using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.5 M in THF was obtained (95% yield).

5a: A dry and argon-flushed 25 mL Schlenk tube, equipped with a magnetic stirring bar and septum was charged with a solution of **2a** (336 mg, 2 mmol) in anhydrous THF (1 mL). Compound **1** (0.5 M in THF, 3.0 mL, 1.5 mmol) was added dropwise, and the reaction mixture was stirred at 25 °C for 3 h. Then, **4** (24 mg, 0.2 mmol) was added and subsequently 1-iodooctane (576 mg, 2.4 mmol). The mixture was stirred for 7 h at 25 °C. After standard workup, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (SiO_2; pentane/diethyl ether 100:1) to give **5a** (493 mg, 88% yield) as a colorless liquid.

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