Catalytic Double C–Cl Bond Activation in CH₂Cl₂ by Iron(III) Salts with Grignard Reagents

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Abstract: Cross-coupling of Grignard reagents with dichloromethane is achieved using iron(III) catalysts. Aryl- and benzylmagnesium bromides show a range of activity toward double C–Cl bond activation resulting in the insertion of methylene fragments between two equivalents of the nucleophilic partner.

Key words: cross-coupling, iron, catalysis, arylation, Grignard reagent

Transition-metal-catalyzed C-C cross-coupling is a powerful tool in organic synthesis and significant advances have been made using aryl and alkenyl halides and pseudohalides as electrophiles.1 Unactivated alkyl halides, however, continue to pose a challenge,² and only a few examples of C-C catalysis using alkyl chlorides in particular have been reported.3-5 Even fewer reports exist of catalytic coupling of di- or polychloroalkanes with organometallic nucleophiles. Particularly noteworthy is the amidobis(amine) [NN₂]Ni-catalyzed activation of CH₂Cl₂ and CHCl₃ leading to selective C–C bond formation with alkyl Grignard reagents.⁶ Related amidobis(phosphine) [NP₂]Ni(II) alkyl complexes can react slowly with CH₂Cl₂ (765 equiv) at 110 °C, but no organic product was identified.7 Furthermore, [tpb]Ag-catalyzed insertion of a carbene into one C-Cl bond of CH₂Cl₂, CHCl₃ and CCl₄ forming a new C–C bond has also been reported ([tbp] =tris(pyrazolyl)borate).8 Stoichiometric double C-Cl oxidative addition reactions have been reported for basic Rh(I) complexes. A recent report involving Rh(I) with Pfunctionalized aminopyridine ligands describes both single and double C-Cl activation to give terminal CH₂Cl and CH₂ groups simultaneously.⁹

The use of iron for catalytic C–C cross-coupling is undergoing a renaissance and various iron-based processes have been described.^{3,10–12} Iron is cheap, non-toxic and environmentally benign; therefore, the use of readily prepared iron catalysts that are easily handled is extremely desirable. Particularly tantalizing is the use of iron for C– C bond formation using dichloroalkane electrophiles.¹³ Herein we report the first example of double C–Cl bond cleavage in dichloromethane with aryl and benzyl Grignard reagents by Fe(III) under mild conditions.

SYNLETT 2011, No. 6, pp 0852–0856 Advanced online publication: 16.03.2011 DOI: 10.1055/s-0030-1259922; Art ID: S09810ST © Georg Thieme Verlag Stuttgart · New York

We have recently found that the amine-bis(phenolate) iron complex (µ-dichloro)bis[(n-propylamino-N,N-bis(2methylene-4-tert-butyl-6-methylphenoxo)iron], abbreviated $\{(\mu-Cl)[O_2N]Fe\}_2$, (1; Scheme 1) is an effective catalyst for the cross-coupling of aryl and benzyl Grignard reagents with primary and secondary alkyl halides, including chlorides. However, when dihalogenated substrates, such as 1,4-dichlorobutane, were used, only arylation at one chloride position was observed.¹⁴ We were therefore surprised to find over the course of that investigation that addition of aryl Grignards to dichloromethane solutions of complex 1 resulted in the formation of diarylmethane and diarylethane compounds (Scheme 1). A study of catalyst loading, ratio of Grignard to dichloromethane, addition rate and temperature effects was performed using o-tolylmagnesium bromide (1.0 M in THF; Table 1). Yield of diarylmethane (Product A) based on the Grignard reagent increased upon increasing catalyst loading from 1.0 mol% to 2.5 mol% Fe versus Grignard at 25 °C, with a Grignard reagent-to-dichloromethane ratio of 1:12.5 (entries 1 and 2). Increasing the loading of 1 to 5.0% and 10.0% versus the aryl Grignard reagent actually decreased the yields of diarylmethane formed (entries 3 and 4). It has been proposed that ironcatalyzed cross-coupling of Grignard reagents with electrophiles proceeds by the formation of reduced Fe as the active species, which is generated by excess Grignard.¹¹ Higher catalyst loading consumes more Grignard reagent, which is the limiting reagent since the alkyl halide (dichloromethane) is present in large excess. Therefore, the optimum loading of 1 was found to be 2.5 mol% Fe versus Grignard (entry 2) giving 83% yield of cross-coupled product. The absence of 1 gave no cross-coupled products (entry 5).15

Increasing the CH₂Cl₂-to-Grignard ratio also lowered the yield of diarylmethane (entry 6). A 2:1 loading of Grignard to CH₂Cl₂ resulted in much lower yields of diarylmethane and no diarylethane (entry 7). Slow addition of Grignard reagent over a period of 20 minutes using a syringe pump (entries 8 and 9) decreased the yield of diarylmethane regardless of catalyst loading, as did conducting the reaction at 0 °C (entry 10).

Simple iron salts, such as FeCl₃ and Fe(acac)₃, both with and without the use of additives, have been shown to be efficient catalysts for the cross-coupling of aryl Grignard reagents with alkyl halides.^{12,16} However, trace impurities of copper, palladium and other metals have also been





Scheme 1 General dichloromethane activation cross-coupling reactions

Table 1	Effect of Catalyst Loading of 1, Ratio of Nucleophile to
Electrophi	ile, and Grignard Addition Rate

Entry	Loading (mol%)	RMgBr	Ratio ^a	Yield (%) o product A	of Yield (%) of product B
1	1.0	o-tolyl	1:12.5	56	7
2 ^b	2.5	o-tolyl	1:12.5	83	13
3 ^b	5.0	o-tolyl	1:12.5	72	7
4 ^b	10.0	o-tolyl	1:12.5	69	7
5	0	o-tolyl	1:12.5	0	0
6	2.5	o-tolyl	1:25	51	10
7	2.5	o-tolyl	2:1	27	0
8 ^{b,c}	2.5	o-tolyl	1:12.5	56	10
9 ^{b,c}	5.0	o-tolyl	1:12.5	58	14
10 ^d	2.5	o-tolyl	1:12.5	48	9

^a Ratio of Grignard reagent to CH₂Cl₂.

^b Average of two runs.

^c Grignard reagent (3.8 mmol) was added dropwise by syringe pump over 20 min.

^d Reaction temperature was 0 °C.

shown to strongly influence the yields of cross-coupling reactions where iron salts were used as catalysts.¹⁷ Therefore, we studied a variety of other simple metal salts and additives for their ability to perform this reaction (Table 2). Anhydrous FeCl₃ (2.5 mol% vs. Grignard) was extremely effective at coupling *o*-tolylmagnesium bromide with CH_2Cl_2 at room temperature (entry 1). Surprisingly, phenylmagnesium bromide led to much lower yields of diphenylmethane and approximately equal quantities of 1,2-diphenylethane. Microwave heating of the reaction to 100 °C led to a slightly improved yield of diphenylmethane (entry 2). Interestingly, using FeBr₃ gave lower yields of diarylmethane (entry 3) than the chloride salt, and no diarylethane was observed. Using additives such as TMEDA, DMF and olefins with FeCl₃ led

to considerably inferior yields compared to FeCl₃ alone (entries 4–7). Using FeCl₂, however, was also less effective (entry 8), whereas CuCl and CuBr₂ (entries 9 and 10) gave no yield of either product A or B. Using Fe(acac)₃ with and without TMEDA did not catalyze cross-coupling of phenyl Grignard reagent with CH₂Cl₂ (entries 11 and 12), but these conditions were effective when *o*-tolyl Grignard reagent reacted with CH₂Cl₂ (entries 13 and 14). Using PdCl₂ and Pd(OAc)₂ gave moderate yields when *o*tolyl Grignard reagent reacted with CH₂Cl₂ (entries 15 and 16). It is worth noting that Pd catalysts produced product B, diarylethane, as the major products.

With these results in hand, we screened a number of Grignard reagents using **1** and anhydrous FeCl₃ as the catalysts (Table 3). When phenyl- and *p*-tolylmagnesium bromide solutions were added to solutions of **1** in CH₂Cl₂ at room temperature, only poor yields of diarylmethane were obtained (entries 2 and 3). The presence of the *ortho*-methyl group may be important to the stability of Fe-aryl intermediates. Use of secondary and primary alkyl Grignard nucleophiles (entries 4 and 5) gave little or no cross-coupled products, contrary to results obtained using [NN₂]Ni(II) complexes where good yields of cross-coupling products were observed using alkyl nucleophiles but no conversion was shown for aryl nucleophiles.⁶ Benzyl Grignard reagents reacted with CH₂Cl₂ and gave good yields of diarylpropane cross-coupling products (entries 5 and 6).

Anhydrous FeCl₃ (3.0 mol%) showed poor yields and selectivity for cross-coupling of *p*-tolylMgBr, but *o*-tolyl Grignard gave excellent results (entries 8 and 9). 2,6-Dimethylphenyl gave negligible yields of diarylmethane, instead producing diarylethane, the yield of which improved slightly upon microwave heating to 100 °C (entry 11). Other nucleophiles such as anisyl and 4-fluorophenyl Grignards all gave modest yields and selectivity (entries 12–15). It is worth noting that reaction of 4-methoxyphenylmagnesium bromide with CH₂Cl₂ produced 1,3-diarylpropane and 1,4-diarylbutane in addition to diarylmethane and diarylethane. Also, heating of entry 13 to 100 °C led to lower yields of cross-coupled products. 1-Naphthyl Grignard reagent only gave product A in modest yield (entry 16) whereas 2-methyl-1-naphthylmagnesium bromide (entry 17) gave no detectable products. For 4-methoxybenzyl Grignard reagent (entry 18), 1 is a more effective catalyst than FeCl₃ and allyl Grignard showed no cross-coupling products (entry 19).

It is worth noting that 1,2-dichloroethane has been shown to be an effective oxidant for FeCl₃-catalyzed homocoupling of arylmagnesium bromides.¹⁸ Indeed, homocoupling is the main side reaction of iron-catalyzed crosscoupling between aryl Grignards and alkyl halides possessing β -hydrogens.^{3,10–12,14} For the reaction of dichloromethane with Grignard reagents, we propose a possible mechanism (Scheme 2) based on the mechanism proposed by Hayashi.¹⁸ Hayashi suggests dichloroethane oxidatively adds to a low valent iron complex, generated by the reaction of FeCl₃ with Grignard reagent (producing biaryls in the process). The same can occur with dichlo-

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Table 2 Differe	nt Metal Sal	ts and Use	of Additives
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Entry	Catalyst	Loading (mol%)	RMgBr	Yield (%) of pro	oduct A Yield (%) of product B
1	FeCl ₃	2.5	o-tolyl	90	<1
2	FeCl ₃	2.5	Ph	21 43ª	25 27ª
3	FeBr ₃	2.5	o-tolyl	56	0
4 ^b	FeCl ₃ + TMEDA	2.5	o-tolyl	17	25
5 ^b	$FeCl_3 + DMF$	2.5	o-tolyl	16	5
6 ^b	$\text{FeCl}_3 + 1$ -octene	2.5	o-tolyl	33	17
7	$\text{FeCl}_3 + \text{cod}$	2.5	o-tolyl	25	21
8	FeCl ₂	2.5	o-tolyl	12	10
9	CuCl	2.5	o-tolyl	0	0
10	CuBr ₂	5.0	o-tolyl	0	0
11	Fe(acac) ₃	5.0	Ph	<1	<1
12 ^c	$Fe(acac)_3 + TMEDA$	5.0	Ph	<1	<1
13	Fe(acac) ₃	5.0	o-tolyl	90	<1
14 ^c	$Fe(acac)_3 + TMEDA$	5.0	o-tolyl	81	7
15	$Pd(OAc)_2$	5.0	o-tolyl	23	51
16	PdCl ₂	5.0	o-tolyl	13	31

^a Microwave-assisted, 100 °C, 10 min.

^b Ligand (1 equiv) to Grignard reagent.

^c Additives (10 mol%) were added to Grignard reagent.

romethane (cycle A). These first two steps are generally believed to be key to cross-coupling as they lead to alkyl iron halides, which can undergo transmetallation with the Grignard to give alkylaryliron complexes. Reductive elimination gives the desired cross-coupled product, but side reactions may ensue from the alkyliron halide. For example, in Hayashi's system β -hydride elimination would lead to the formation of chloroethene, whereas β chloride elimination would lead to a dichloroiron species and ethane. The dichloroiron can now be again reduced by the aryl Grignard, and thus produce another equivalent of biaryl. In the case of dichloromethane, neither β -hydrogens nor β -chlorides are present; therefore transmetallation with aryl Grignard to form an alkylaryliron complex becomes favored. Cross-coupling at this stage leads to the formation of benzylhalide, which is capable of oxidative addition (OA) at a reduced iron centre (cycle B), which leads to product A, as well as single electron transfer (SET). The occurrence of the latter is reasonable taking into account the formation of product B with many of the aryl Grignards in Table 3.

In summary, iron complex 1 and simple iron salts can catalyze multiple C–Cl activation in CH_2Cl_2 .¹⁹ Under similar conditions, simple Pd and Cu salts were less selective and productive, respectively. The effect of Grignard reagent on cross-coupling was screened; however, only *o*-tolyl Grignard reagent gives high yield of double cross-coupling products. For the remaining Grignard reagents attempted, biaryl homocoupling products were observed. The formation of diarylethane in the cross-coupling of CH_2Cl_2 suggests the formation of arylmethyl radical, which subsequently undergoes radical coupling. Since yields of the diarylmethane products are favored under optimized conditions, the reaction of arylmethyl radicals with aryl nucleophiles proceeds faster than homocoupling, particularly if the concentration of Grignard versus Fe (and alkyl radical) is high. Further studies to extend the scope of this method and to gain detailed mechanistic in-



Scheme 2 Mechanism leading to the formation of products A and B

Entry	Catalyst	RMgBr	Yield (%) of product A	Yield (%) of product B
1 ^b	1	o-tolyl	83	13
2	1	Ph	11	22
3	1	<i>p</i> -tolyl	21	10
4	1	cyclohexyl	1.3	0.8
5	1	<i>n</i> -Bu	0	0
6	1	4-methoxybenzyl	71	9
7	1	4-fluorobenzyl	60	0
8	FeCl ₃	<i>p</i> -tolyl	14	10
9°	FeCl ₃	o-tolyl	90	<1
10 ^c	FeCl ₃	Ph	21 43 ^d	25 27 ^d
11	FeCl ₃	2,6-dimethylphenyl	<1	16 40 ^d
12	FeCl ₃	2-methoxyphenyl	36	19
13	FeCl ₃	3-methoxyphenyl	18	18
14	FeCl ₃	4-methoxyphenyl	23	13
15	FeCl ₃	4-fluorophenyl	33 18 ^d	10 7 ^d
16	FeCl ₃	1-naphthyl	35	0
17	FeCl ₃	2-methyl-1-naphthyl	0	0
18	FeCl ₃	4-methoxybenzyl	38	9
19	FeCl ₃	allyl	0	0

 Table 3
 Effect of Grignard Reagent on Cross-Coupling Catalyzed by 1 and FeCl₃^a

^a Ratio of Grignard reagent to $CH_2Cl_2 = 1:12.5$, [Fe] loading = 2.5 mol%.

^b Taken from Table 1.

^c Taken from Table 2.

^d Microwave-assisted, 100 °C, 10 min.

sight (including the role of the ligand in complex 1) are currently underway.

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Acknowledgment

We thank Memorial University, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation and the Government of Newfoundland and Labrador for funding. We are grateful to Prof. F. M. Kerton for use of the GC– MS instrument.

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(19) General Experimental Conditions: Unless otherwise stated, all manipulations were performed under an atmosphere of anhyd oxygen-free nitrogen by means of standard Schlenk or glove box techniques. Dichloromethane was purified using an MBraun Solvent Purification System. Reagents were purchased from Aldrich, Alfa Aesar or Strem and used without further purification. Grignard reagents were titrated prior to use and analyzed by GC–MS after being quenched with dilute HCl (aq) to quantify biaryl complexes or other impurities present prior to their use in catalyst runs. Complex 1 was prepared according to the previously published procedure.¹⁴ Anhydrous FeCl₃ (97%) from Aldrich was used for the synthesis of 1 and for crosscoupling catalysis experiments.

General Conditions for Room-Temperature Reactions; For 2.5 mol% [Fe] Loading with a 12.5-Fold Excess of CH₂Cl₂ to ArMgBr (Table 1, Entry 2): Complex 1 (50.1 mg; 0.1 mmol of Fe) was added to a flask and dissolved in CH₂Cl₂ (4.24 g, 3.2 mL, 50 mmol). To this stirred solution was added o-tolylmagnesium bromide (4.0 mL, 1.0 M in THF, 4.0 mmol). The reaction mixture was stirred for 30 min, after which time it was quenched by adding HCl (2.0 M, 5.0 mL) and filtered through a 10 cm silica column. The products were detected and quantified using GC-MS (relative to standard curves) with dodecane as the internal standard. Reported yields were confirmed by ¹H NMR on isolated product mixtures. Complete separation of products A and B was not possible given their structural similarity, hence the NMR spectra consistently showed contamination with minor products. Yields are reported with respect to Grignard reagent. Since the Grignard reagents are obtained in THF or Et₂O solutions, the addition of Grignard is concomitant with the addition of solvent, e.g. 4.0 mmol of a 1.0 M o-tolylmagnesium bromide solution results in the addition of 4.0 mL THF to the reaction.

Catalytic Method for Microwave Heating: In a glove box, **1** (25.0 mg, 0.05 mmol) or FeCl₃ (8.1 mg, 0.05 mmol) and a magnetic stir bar were added to a BiotageTM microwave vial, which was sealed with a septum cap. To this vial was injected CH₂Cl₂ (2.13 g, 25.0 mmol), followed by slow injection of the Grignard reagent (2.0 mmol). The mixture was heated in a Biotage InitiatorTM Microwave Synthesizer using the following parameters: time = 10 min; temperature = 100 °C; prestirring = off; absorption level = high; fixed hold time = on. Upon completion, dodecane (1.9 mmol) was added to the mixture followed by 1 M HCl (aq; 5 mL). The product yields were quantified by GC–MS and for highyielding reactions by ¹H NMR as described for the general method. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.