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Iron-catalysed, hydride-mediated reductive cross-coupling of vinyl halides and Grignard reagents^{*,*,§}

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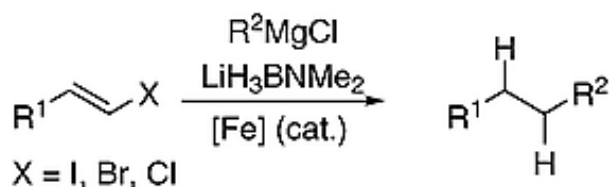
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Supporting information:

Electronic Supplementary Information (ESI) available – full experimental procedures and analytical data are available. See <http://dx.doi.org/10.1039/C1CC14622J>

Graphical abstract:



Synopsis:

An Iron-catalysed, hydride-mediated reductive cross-coupling has been developed and used to prepare a range of alkanes from vinyl halides and Grignard reagents.

Abstract

An iron-catalysed, hydride-mediated reductive cross-coupling reaction has been developed for the preparation of alkanes. Using a bench-stable iron(II) pre-catalyst, reductive cross-coupling of vinyl iodides, bromides and chlorides with aryl- and alkyl Grignard reagents successfully gave the products of formal sp^3 - sp^3 cross-coupling reactions.

Introduction

Metal-catalysed cross-coupling reactions have become ubiquitous in synthetic chemistry with palladium- and nickel-catalysed reactions used routinely in both academia and industry.¹ However, preceding the seminal discoveries of Heck² and Kumada,³ Kharasch⁴ and, later, Kochi reported the iron-catalysed cross-coupling of vinyl bromides and Grignard reagents.⁵ Iron-catalysed cross-coupling reactions have since been developed into a powerful method for the formation of carbon-carbon⁶ and carbon-heteroatom bonds.⁷

The last decade has seen a significant increase in the number of transformations achieved using iron catalysts.⁸ The iron-catalysed reduction of carbonyl groups by hydrosilylation, transfer-hydrogenation and hydrogenation are now well developed, with turnover frequencies equal to those of the best ruthenium-based catalysts and good enantioselectivities have been achieved for the reduction of ketones and imines.⁹ However, the reduction of olefins is only now being realised without the need for forcing reaction conditions. Chirik has developed a series of iron(0) complexes, based on the polymerisation catalysts of Gibson and Brookhart,¹⁰ which catalyse the hydrogenation of functionalised and unfunctionalised alkenes at low hydrogen pressure and with excellent activity.¹¹ de Vries has used iron nanoparticles as the catalyst for the hydrogenation of alkenes and alkynes.¹² However, both of these powerful methods use air- and moisture-sensitive iron species which require synthesis prior to the hydrogenation reaction. Iron porphyrin complexes and sodium borohydride,¹³ and iron chloride in conjunction with lithium aluminium hydride¹⁴ have also been used to reduce alkenes, α,β -unsaturated ketones and esters.

We recently reported the iron-catalysed, hydride-mediated reduction of alkenes using substoichiometric iron triflate and sodium triethylborohydride.¹⁵ Examination of the postulated catalytic cycles of the iron-catalysed hydrogenation¹¹ and cross-coupling¹⁶ reactions reveal common low-valent iron species. We therefore sought to combine both of these reactions into one transformation, catalysed by a single, bench stable, iron pre-catalyst. Reductive cross-coupling is proposed to proceed by iron-catalysed cross-coupling of the vinyl halide and Grignard reagent to give an alkene **2**. This alkene is then reduced *in situ* by an iron hydride to the alkane **3** (Figure 1). The iron

hydride is generated by the reaction of the iron salt with a stoichiometric hydride reagent. This transformation gives the product of an sp^3 - sp^3 cross-coupling without the problems associated with these reactions.¹ Furthermore, as the Grignard reagent needed for cross-coupling generates a low-valent iron species *in situ*, we will be able to use bench-stable iron(II) pre-catalysts.

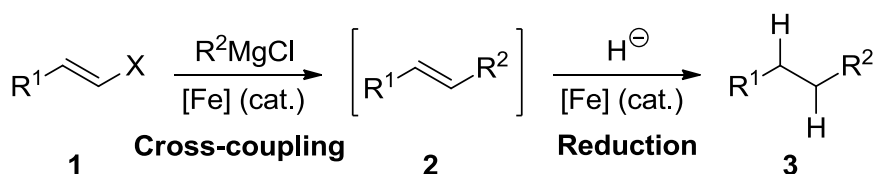
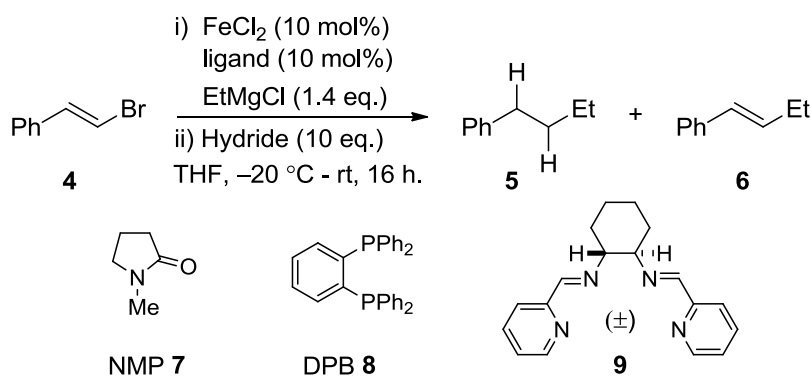


Figure 1. Iron-catalysed, hydride-mediated reductive cross-coupling.

In order to develop the reductive cross-coupling we chose commercially available β -bromostyrene **4** and ethyl magnesium chloride as model coupling partners and iron(II) chloride as the iron source (Table 1). Sodium triethylborohydride was initially used as the hydride source and *N*-methyl pyrrolidinone (NMP) **7** as a stabilising ligand due to the success we had with these reagents for the isolated reduction of alkenes.¹⁵ Using 10 mol% iron(II) chloride, 110 mol% NMP and 10 equivalents of NaHBET₃ gave the reduced cross-coupled alkane **5** in only 9% conversion and the cross-coupled alkene **6** in 53% (entry 1). This indicated that although cross-coupling was successful, the alkene was not being reduced under these conditions. We assumed that either the iron catalyst was not capable of mediating the hydrogenation or was degrading before hydrogenation could occur. To extend catalyst lifetime we screened multidentate ligands and found that the tetradentate dipyridyldiimino ligand **9** gave 56% conversion to the alkane **5** and 44% alkene **6** (entries 2 and 3). This showed that complete cross-coupling was achieved and the hydrogenation step now needed improvement. Thus, we screened a number of hydride sources (entries 4-12). Variation of the cation of the hydride source showed that KHB^sBu₃(K-Selectride) (entry 6) gave a similar conversion as NaHBET₃, but the use of reagents with a lithium counter ion gave the best conversions (entries 7-9). LiHBET₃ gave a 20% increase in alkane **5** (entry 7), compared to NaHBET₃, and lithium *N,N*-dimethylaminoborohydride¹⁷ gave quantitative conversion to the alkane **5** (entry 8). It should be noted that even in the absence of ligand the reductive cross-coupling proceeded, but only 61% of the alkane **5** and 24% alkene **6** were observed (Table 1, entry 9). Without iron(II) chloride no cross-coupling or reduction products were observed. To test if the reductive cross-coupling was catalysed by an iron species or a trace metal impurity,¹⁸ the reaction was carried out with added Cu, Ni and Co salts and with these metals in the absence of iron. No reductive cross-coupling was observed using Cu, Ni or Co salts alone and the yield of the reaction was not increased when these salts were added to the standard reaction conditions.¹⁹



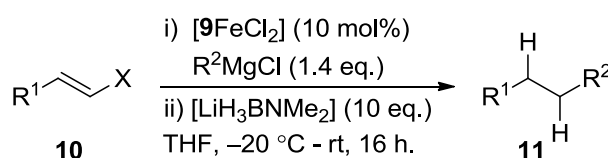
Entry	Hydride	Ligand	Conversion (%) ^b	
			Alkane 5	Alkene 6
1	NaHBET ₃	NMP 7 ^c	9	53
2	NaHBET ₃	DPB 8	2	91
3	NaHBET ₃	9	56	44
4	NaHB(OAc) ₃	9	-	78
5	LiHAl(O ^t Bu) ₃	9	25	73
6	KHB ^s Bu ₃	9	55	44
7	LiHBET ₃	9	73	27
8	LiH ₃ BNMe ₂	9	99	-
9	LiH ₃ BNMe ₂	-	61	24
10	NaBH ₄	9	-	93
11	LiAlH ₄	9	-	94
12	HSiEt ₃	9	-	87

^a Conditions: 1 mmol **4**, 10 mol% FeCl₂, 10 mol% ligand, THF (0.1 M), -20 °C, i) 1.4 eq. EtMgCl (2M in THF), 15 min, ii) 10 eq. hydride, warm to rt, 16 h. ^b Conversion measured by GC-MS of the crude reaction mixture by comparison to authentic samples. ^c 110 mol% NMP.

Table 1. Optimisation of the iron-catalysed, hydride-mediated reductive cross-coupling^a

Having developed optimised reaction conditions we investigated the scope and limitations of the reductive cross-coupling (Table 2). We began by using β-bromostyrene and a range of alkyl Grignard reagents (entries 1-6). Ethyl- and iso-propylmagnesium chloride both gave excellent conversions to the alkanes (entries 2 and 3). *tert*-Butyl- and phenylmagnesium chloride gave a moderate conversion to the alkane, but no alkene was observed (entries 4-5). Using Grignard reagents without a β-hydrogen was expected to give poor conversion as the formation of the key low-valent iron species is now not possible. However, methylmagnesium chloride gave moderate conversion to the alkane **11a** (entry 1). Presumably an anionic ferrate complex¹⁷ is the catalytically active iron species when using this Grignard reagent. Using allylmagnesium chloride introduced a second alkene to the reaction and this was also reduced under the reaction conditions to give the fully saturated alkane **11e**, albeit in low yield (entry 6).

We next turned our attention to the effect of varying the halide substituent of the vinyl halide (entries 7-12). Using the elegant methodology of Charette²⁰ we prepared a series of aryl-vinyl halides bearing differing aryl and vinyl functionality. β -Iodo- and β -bromo-4-methylstyrene gave equal conversions to the alkane **11f**, but β -chloro-4-methylstyrene gave 13% of the alkane **11f** and 46% of the alkene (entries 7-9). Electron-deficient aryl-vinyl halides showed no such dependence on the vinyl halide substituent. Both β -chloro- and β -bromo-4-chlorostyrene gave similar conversion to the alkane **5** (entries 10-11). However, proto-dehalogenation of the aromatic ring was observed in both cases, possibly suggesting a low-valent iron catalyst.²¹ Finally, we tested the electron-rich β -bromo-3,5-dimethoxystyrene and this gave comparable conversion to that observed when using the electron-neutral aryl-vinyl halides (entry 12).



Entry	R ¹	X	R ²	Alkane	Conversion (%) ^b
1	Ph	Br	Me	53	11a
2	Ph	Br	Et	99 (84 ^c)	5
3	Ph	Br	^t Pr	87	11b
4	Ph	Br	^t Bu	37 ^d	11c
5	Ph	Br	Ph	41 ^e	11d
6	Ph	Br	Allyl	35	11e^f
7	4-Me-Ph	I	Et	92 (87 ^c)	11f
8	4-Me-Ph	Br	Et	91	11f
9	4-Me-Ph	Cl	Et	13 ^g	11f
10	4-Cl-Ph	Cl	Et	60	5
11	4-Cl-Ph	Br	Et	66	5
12	3,5-MeO-Ph	Br	Et	81	11g

Conditions: 1 mmol **10**, 10 mol% [9FeCl₂], THF (0.1 M), -20 °C, i) 1.4 eq. R²MgCl (2M in THF), 15 min, ii) 10 eq. [LiH₃BNMe₂] (1.7 M in THF), warm to rt, 16 h. ^b Conversion measured by GC-MS of the crude reaction mixture by comparison to authentic samples. ^c Isolated yield. ^d 61% 1,4-diphenylbutane. ^e 40% biphenyl. ^f Complete reduction of R² observed in the reaction, product **11e** R² = *n*-propyl. ^g 46% alkene.

Table 2. Scope and limitation of the iron-catalysed, hydride-mediated reductive cross-coupling^a

At this point we were unsure why the low alkane conversions were not accompanied by significant amounts of the intermediary alkenes. In the cases with low conversion to the alkane **11**, careful examination of the crude reaction mixtures revealed that the vinyl halide **10** was undergoing reductive

homo-coupling to give the 1,4-diarylbutane **13**, presumably *via* the 1,4-diarylbutadiene **12** (Figure 2).

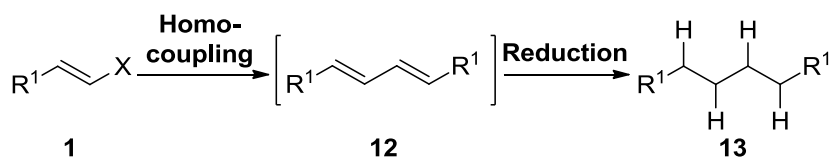
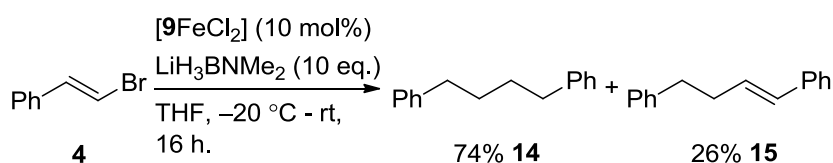


Figure 2. Proposed homocoupling of vinyl halides.

In order to address this we examined the time between Grignard and hydride addition, the time over which the Grignard reagent was added, and the initial temperature of the reaction. Under our standard reaction conditions using ⁱPrMgCl, variation of all these parameters led to very similar results with no increase in the conversion to the target alkane. We therefore suspected the hydride reagent was causing the low conversions. Carrying out the reaction in the absence of Grignard reagent confirmed this. Reaction of β -bromostyrene **4** with 10 mol% [**9**FeCl₂] and 10 equivalents of lithium *N,N*-dimethylaminoborohydride gave 74% conversion to the fully reduced homo-coupled product, 1,4-diphenylbutane **14**, and 26% of the mono-reduced homo-coupled alkene **15** (Scheme 1). Presumably when cross-coupling is slow, for example with ^tBuMgCl, the rate of hydride-mediated homo-coupling becomes competitive with the rate of Grignard-mediated cross-coupling. Thus, on addition of the hydride reagent any remaining vinyl halide **10** can either undergo reductive homo-coupling to give the diarylbutane **13** or reductive cross-coupling to alkane **11**. Further studies are ongoing to overcome and exploit this problem.



Scheme 1. Iron-catalysed, hydride-mediated homo-coupling of β -bromostyrene

In summary, we have developed an iron-catalysed, hydride-mediated reductive cross-coupling reaction for the preparation of alkanes from vinyl halides and Grignard reagents using a simple, bench-stable iron(II) pre-catalyst and commercially available reagents. This transformation gives the product of a formal sp^3 - sp^3 cross-coupling reaction by the *in situ* reduction of an intermediate alkene to the alkane. The scope and limitations of this reaction have been tested and moderate to excellent conversions have been observed in the reductive cross-coupling of vinyl bromides, iodides and chlorides with aryl and alkyl Grignard reagents.

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