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Iron-Catalysed Reduction of Olefins using a Borohydride Reagent

Tom S. Carter,[a] Léa Guiet,[a] Dominik J. Frank,[b] James West,[a]
and Stephen P. Thomas[b],*

[a] School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.
[b] School of Chemistry, University of Edinburgh, Joseph Black Building, West Mains Road, Edinburgh EH9 3JJ, U.K.
Fax: (+44)-(0)-131-650-6543; e-mail: stephen.thomas@ed.ac.uk

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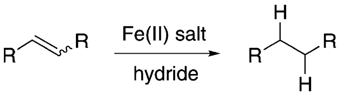
Abstract: The iron-catalysed reduction of olefins has been achieved using a simple iron salt and sodium triethylborohydride. A wide range of mono- and *trans*-1,2-disubstituted alkenes have been reduced (91–100%) using 25 mol% iron(II) triflate, 1 mol% *N*-methyl-2-pyrrolidinone and 4 equivalents of sodium triethylborohydride. The reduction of alkynes to alkanes is also reported (up to 84%). Significantly, the reduction of trisubstituted alkenes has also been achieved (60–86%).

Keywords: catalysis; hydrogenation; iron; olefins; reduction

Iron catalysis has undergone a rebirth in the last decade becoming a powerful and commonly used tool in synthetic chemistry.[1] Following the seminal works of Kharasch[2] and Kochi,[3] iron-catalysed cross-couplings have been significantly developed into highly robust and practical methods for carbon-carbon[4] and carbon-heteroatom[5,6] bond formations, and the reduction of carbonyl groups.[7] However, the reduction of olefins has received significantly less attention. Building upon earlier work using forcing reaction conditions,[8] Chirik and co-workers developed a series of iron(0) catalysts capable of mediating the hydrogenation of both functionalised and unfunctionalised alkenes at low hydrogen pressure (1–4 atm).[6,9] de Vries and co-workers have shown that iron nanoparticles are capable of catalysing the hydrogenation of alkenes and alkynes, albeit at higher hydrogen pressures (>10 atm).[10] Both of these powerful methods proved excellent for the reduction of mono- and disubstituted alkenes, but were not active in the hydrogenation of trisubstituted alkenes and used catalysts which are highly air- and-moisture sensitive.[9f] Iron-porphyrin complexes in conjunction with $NaBH_4$ have been used to catalyse the reduction of electron-deficient alkenes,[11] including α,β-unsaturated esters,[11b,12] and Ashby and co-workers showed that stoichiometric amounts of iron(II) chloride and $LiAlH_4$ would reduce mono- and disubstituted alkenes in good yield.[13] Most recently Boger and co-workers have used superstoichiometric amounts of an iron salt and borohydride reagent for the reductive functionalisation of alkenes with electrophiles.[14]

Having reported an iron-catalysed, hydride-mediated, reductive cross-coupling reaction,[15] we were keen to exploit the second step of this reaction (alkene hydrogenation) and develop an operationally simple iron-catalysed, hydride-mediated alkene reduction (Scheme 1). Significantly, the low-valent, active iron catalyst would now need to be generated by the hydride source, not a Grignard reagent.[16]

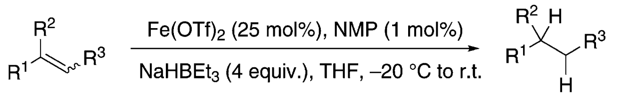


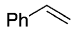
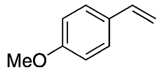
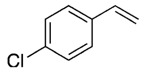
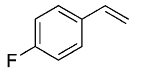
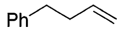
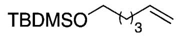
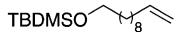
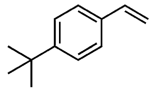
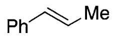
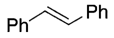
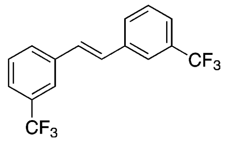
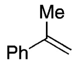
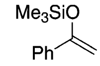
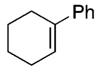
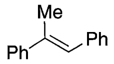
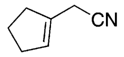
Scheme 1. Iron-catalysed, hydride-mediated reduction of alkenes.

Using stilbene as a model olefin, we found that $Fe(OTf)_2$ and $FeCl_2$ offered the highest reactivity and that the use of *N*-methylpyrrolidinone (NMP)[4c,e] allowed substoichiometric amounts of iron salt to be used. Interestingly, using just 1 mol% NMP, 25 mol% $Fe(OTf)_2$ and 4 equivalents of $NaHBEt_3$ gave the highest amounts of stilbene reduction.[17] Of the hydride sources tested, $NaHBEt_3$ gave the best reduction yields, with $LiAlH_4$ and $NaBH_4$ showing no activity. Importantly, the same level of reduction was achieved when 99.99% purity iron salts were used.[17]

Having developed the reaction conditions we sought to test the scope of this iron-catalysed alkene

Table 1. Iron-catalysed, hydride-mediated reduction of alkenes.[a]



Entry	Substrate		Conversion [%][b]
1		**1a**	100
2		**1b**	100
3		**1c**	100
4		**1d**	100
5		**1e**	100
6		**1f**	100
7		**1g**	94
8		**1h**	100
9		**1i**	98
10		**1j**	91
11		**1k**	54
12		**1l**	100
13		**1m**	100
14		**1n**	100
15		**1o**	61
16		**1p**	69
17		**1q**	86

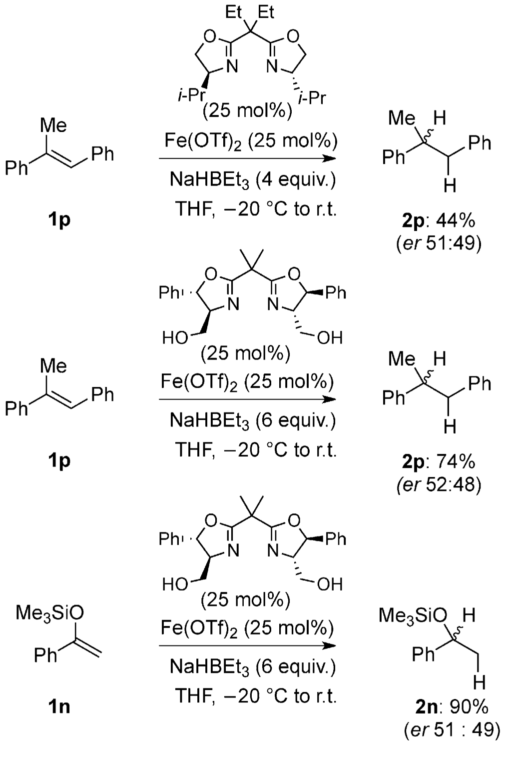
[a] *Conditions:* 1 mmol alkene, 4 mmol NaHBEt$_3$ (1M in THF), 25 mol% Fe(OTf)$_2$, 1 mol% NMP, THF (0.1M), −20 °C to room temperature, 16 h.

[b] Determined by GC-MS and ^{1}H NMR of the crude reaction mixture.

reduction (Table 1). Aryl- and alkyl-substituted terminal alkenes were all reduced with quantitative or near quantitative conversions (entries 1–7). Variation of the electronic properties of the styrene derivatives **1b–d** showed that electron-rich and electron-deficient substrates were equally reactive (entries 1–4). In the case of 4-chlorostyrene **1c** no dehalogenation was observed (entry 3), possibly indicating that the reaction is not catalysed by a low-valent iron species.[18] Alkyl-substituted terminal alkenes **1e–g** as well as 4-*tert*-butylstyrene **1h** were also reduced with excellent conversions (entries 5–8) and the reaction was found to be compatible with *tert*-butyldimethylsilyl-protected alcohols **1f** and **1g** (entries 6 and 7). Aryl-alkyl and aryl-aryl *trans*-1,2-disubstituted alkenes **1i–l** were all successfully reduced, including the bis-trifluoromethyl-substituted stilbene **1l** (entries 9–12). *cis*-Stilbene **1k** gave the lowest conversion of the alkenes tested (entry 11) and the recovered starting material had been isomerised to the *trans*-isomer exclusively. A similar decrease in catalyst activity has been observed using iron-porphyrin complexes[11a] and iron nanoparticles[10b] for the reduction of *cis*-stilbene compared to *trans*-stilbene. Presumably in our case, isomerisation occurs by hydrometallation of the *cis*-alkene, rapid C–C bond rotation and β-hydride elimination to give *trans*-stilbene.[19]

The reduction of α-methylstyrene **1m** has been previously observed to occur at a decreased rate compared to styrene[6a] or with homocoupling of the alkene to give 2,3-dimethyl-2,3-diphenylbutane.[11a] Under our reaction conditions both α-methylstyrene **1m** and α-(trimethylsilyloxy)styrene **1n** were reduced quantitatively after the standard reaction time (entries 13 and 14).

Most significantly, we were able to reduce three trisubstituted alkenes, **1o**, **1p** and **1q** with good conversion and even in the presence of a potentially sensi-



Scheme 2. Reduction of prochiral alkenes using enantioenriched ligands.

tive nitrile group **1q** (entries 15–17). To the best of our knowledge, these results represent the highest yields obtained to date for the reduction of an unfunctionalised trisubstituted alkene using an iron catalyst.[9f]

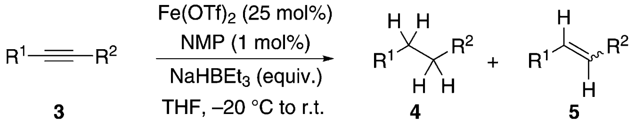
Having successfully applied our reduction protocol to trisubstituted alkenes, we were keen to attempt an enantioselective reduction of these prochiral substrates (Scheme 2). We naively presumed that replacing the NMP with a stoichiometric amount of enantiopure ligand, with respect to iron salt, would result in an enantioselective reduction. However, consistent with the reactions occurrence in the absence of ligand (NMP), racemic reduction was observed in all cases when using α-methylstilbene **1p** and α-(trimethylsilyloxy)styrene **1n**. Although these reactions were not enantioselective, using the hydroxy-BOX ligand gave a particularly high reduction yield for α-methylstilbene **1p** (74%).

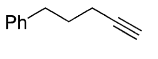
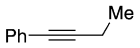
We next turned our attention to alkynes (Table 2). In this case we varied the amount of hydride used in the reaction to investigate if a selective reduction to either the alkane **4** or alkene **5** could be achieved.[20] Simply doubling the amount of borohydride reagent used, to 8 equivalents, gave a practically useful alkyne reduction to the alkane for the terminal alkyne **3a** and internal alkyne **3b** (entries 4 and 7). However, in the case of diphenylacetylene **3c** a selective reduction to the alkenes **5c** was achieved (entries 8–10). Even using 8 equivalents of NaHBEt$_3$ only gave the alkenes **5c**. As with our earlier results showing that *cis*-stilbene is reduced with far lower conversion than *trans*-stilbene (Table 1, entries 10 and 11), the majority of the alkene produced in the reduction of diphenylacetylene **3c** was the *cis*-isomer *cis*-**5c**. However it is unclear why the *cis*-alkene produced is not isomerised to the *trans*-alkene in this case. Decreasing the amount of NaHBEt$_3$ used did not give the alkenes **5a–c** for any of the alkynes tested **3a–c** (entries 1, 2, 5 and 8), except in the case of diphenylacetylene **3c**.

To probe if this olefin reduction is heterogeneous or homogeneous, we measured the initial rate of the reaction at different concentrations.[17] The rate of reaction was found to be directly proportional to the reaction concentration indicating a homogeneous active catalyst. To further support this, the reaction supernatant was found to be catalytically active (Scheme 3, A). Following the reduction of *trans*-stilbene under standard conditions (without work-up), the reaction supernatant was collected by filtration and used, with additional borohydride, to catalyse the reduction of a further equivalent of *trans*-stilbene. The yield of both reductions was found to equal that of the isolated reduction.

To confirm the origin of the added hydrogen, quenching the reaction with methanol-d_4 (Scheme 3, B) and carrying out the reaction in THF-d_8 (Scheme 3, C) showed no deuterium incorporation in the reduced product. This indicates that a mechanism passing through an intermediate organometallic species, arising from hydrometallation, that is quenched (protodemetallation) on work-up or by solvent is unlikely to be operating. Reduction of styrene-d_8 in THF-d_8 using NaHBEt$_3$ (as a solution in THF-d_8) showed, exclusively, the addition of hydrogen at the α- and β- positions (Scheme 3, D), indicating that both hydrogens originate from NaHBEt$_3$.

Table 2. Iron-catalysed, hydride-mediated reduction of alkynes.[a]



Entry	Substrate	Equiv. of NaHBEt$_3$	Conversion [%][b,c] 4	5
1	 **3a**	2.5	50	50
2		4	68	32
3		6	69	31
4		8	61	39
5	 **3b**	2.5	35	65
6		6	68	32
7		8	84	16
8	Ph—≡—Ph **3c**	2.5	6	60[d]
9		6	9	91
10		8	14	86

[a] *Conditions:* 1 mmol alkyne, NaHBEt$_3$ (1M in THF), 25 mol% Fe(OTf)$_2$, 1 mol% NMP, THF (0.1M), –20 °C to room temperature, 16 h.

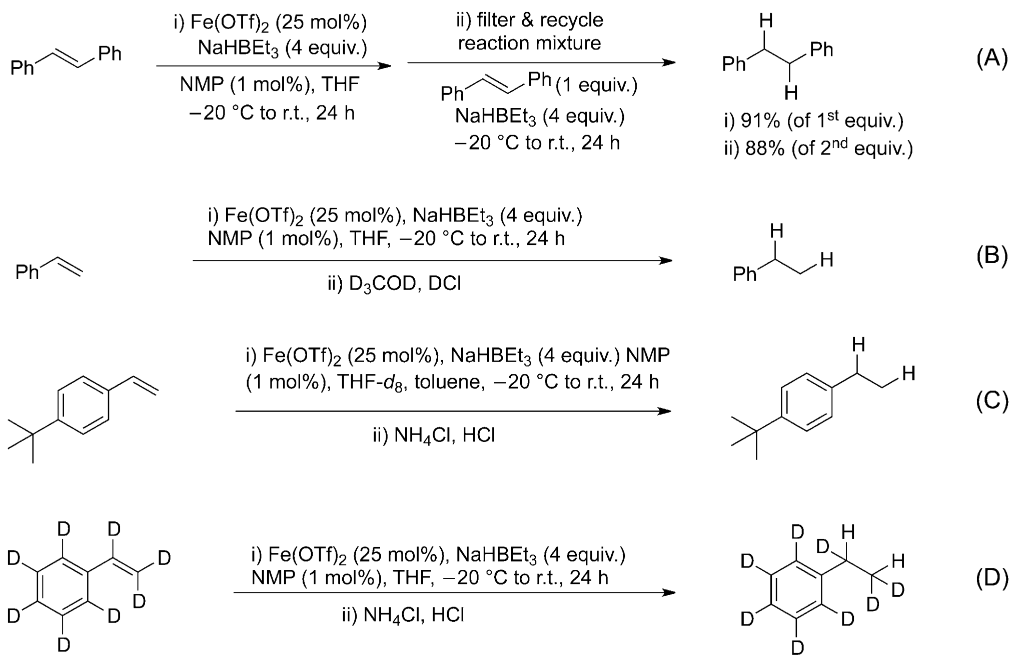
[b] Determined by GC-MS of the crude reaction mixture.

[c] As a mixture of *cis*- and *trans*-alkenes. See the Supporting Information for details.

[d] 34% recovered starting material.

Finally to investigate if the reaction was proceeding through a radical pathway, the reduction of 4-*tert*-butylstyrene was carried out in the presence of TEMPO to give no reduction product, suggesting a radical pathway. However, and in contrast, the reduction of *N*-tosyldiallylamine proceeded without ring-closure, but with concurrent loss a single or both allyl groups, suggesting an ionic pathway.[17]

In summary, we have developed an operationally simple iron-catalysed olefin reduction using a commercially available iron salt and sodium triethylborohydride. A wide range of unfunctionalised mono- and disubstituted alkenes have been reduced with excellent conversion. Most significantly, the reduction of three trisubstituted alkenes is reported. The reaction has been applied to the reduction of a terminal and internal alkyne to give the corresponding alkanes with good conversion.



Scheme 3. Recycling of catalyst solution in the reduction of *trans*-stilbene (A) and mechanistic investigations (B)-(D).

Experimental Section

General Procedure for Catalytic Reduction of Alkenes

A reaction tube (Radleys carousel 12 reaction station) was loaded with iron catalyst (25 mol%), NMP (1 mol%) and alkene (1 equiv.) in anhydrous THF (10 mL). The solution was cooled to −20 °C before the addition of sodium triethylborohydride (1.0 M in THF, 4 equiv.) and stirred for 16 h while warming to room temperature. Ammonium chloride (150 mg) was then added with a few drops of water. A sample of the reaction mixture was filtered, dried ($MgSO_4$) and diluted with THF before GC-MS analysis.

All hydrogenation products are known, were identified by GC-MS, and characterised by comparison with authentic samples and spectral data.

In order to determine isolated yields, the reaction mixture was concentrated under vacuum, and diethyl ether (20 mL) added. The solution was then washed with aqueous HCl (2.0 M, 3 × 20 mL), followed by brine (25 mL). The organic phase was collected and dried ($MgSO_4$), followed by concentration under vacuum to give the product. The sample was analysed by ^{1}H and ^{13}C NMR spectroscopy.

Acknowledgements

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