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Iron(II) catalyzed reductive radical cyclization reactions of bromoacetals in the presence of $NaBH_4$: optimization studies and mechanistic insights

Sara H. Kyne [a,†], Christophe Lévêque [a], Shiwen Zheng [a], Louis Fensterbank [a,*], Anny Jutand [b,*], Cyril Ollivier [a,*]

[a] Institut Parisien de Chimie Moléculaire, UMR CNRS 8232, Sorbonne Universités, UPMC Univ Paris 06, 4 Place Jussieu, CC 229, F-75005 Paris, France
[b] Ecole Normale Supérieure – PSL Research University, Département de Chimie, Sorbonne Universités, UPMC Univ Paris 06, CNRS UMR 8640 PASTEUR, 24 Rue Lhomond, F-75231 Paris, Cedex 05, France

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ABSTRACT

5-*Exo*-trig radical reductive cyclization reactions of bromoacetals are catalyzed by iron in the presence of the reducing agent $NaBH_4$. Both iron(II) and iron(III) were found to effectively mediate these reactions. As shown by cyclic voltammetry, iron(III) can be reduced to an iron(II) precatalyst before passing through an identical reaction mechanism in which monoelectronic activation of the substrate would occur by an anionic hydridoiron(I) complex. Further studies have established that both the substrate (iodo- vs bromo-derivative) and the precatalytic mixture are decisive in determining the reaction outcome.

1. Introduction

Free radical processes are established as powerful and versatile tools for organic synthesis.[1] The notoriety of tin hydrides as reliable radical chain carriers and good hydrogen donors is well documented.[2] However, providing efficient alternatives that are less toxic and easier to remove at the end of the reaction is highly desirable for modern synthetic chemistry.[3]

In this context, intensive research has been conducted on the development of tin-free mediators, mainly focused on hydrides of main-group elements including silicon,[4] germanium,[5] boron[6] and phosphorus[7] derivatives. Besides these examples, interesting alternatives have been discovered with hydrides of gallium,[8] indium[8] and transition metal complexes including titanium,[9] zirconium[10] and chromium.[11] However most of these reactions require stoichiometric or substoichiometric amount of reagents, and challenges remain to develop catalytic alternatives.

A solution to this problem was the design of new metal/hydride systems that used a catalytic amount of metal complex. The story began with the work of Kuivila,[12] Corey[13] and Stork[14] who used catalytic amounts of tin hydride with a stoichiometric hydride source ($LiAlH_4$, $NaBH_4$, $NaBH_3CN$) for the simple reduction of halides. But to avoid the use of tin, other metal complexes based on gallium,[8] indium,[15] titanium,[9c,16] zirconium,[10] chromium,[17] cobalt[18] and nickel[19] associated with a reducing agent such as Red-Al or sodium borohydride have proven to be effective for such reductive transformations. Frequently, it has been proposed that under reducing conditions transition metal hydride species are formed, acting as the mediator for reductive radical reactions. However, the in situ formation of the hydrido transition metal species, and the subsequent reaction mechanism have both remained largely unexplored.

Of particular interest was the reactivity of iron for mediating reductive radical reactions since iron is abundant, cheap and has a low toxicity. Intermolecular radical reactions mediated by iron have been established.[20] However interestingly, there are considerably fewer examples of related iron-mediated reductive intramolecular radical reactions. The first example by Meunier reported the radical cyclization of 5-hexenyl bromide involving a single electron transfer process with a stoichiometric amount of an iron

* Corresponding authors. E-mail addresses: louis.fensterbank@upmc.fr (L. Fensterbank), anny.jutand@ens.fr (A. Jutand), cyril.ollivier@upmc.fr (C. Ollivier).
† Current address: School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Lincoln, LN6 7DL, UK.

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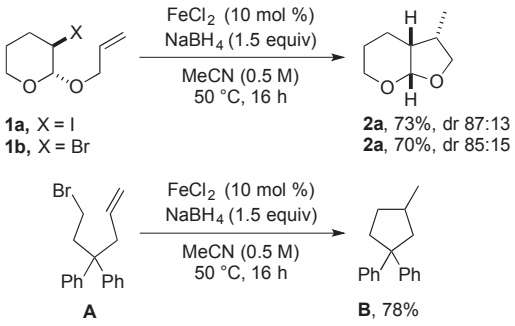
(II)—Grignard species, Cp(DIPHOS)FeMgBr.[21] Later, Oshima proposed catalytic conditions with the use of 5 mol % ferrous chloride and a Grignard reagent for the radical cyclization of iodo- and bromoalkenes to unsaturated or partially reduced tetrahydrofurans depending on the nature of the Grignard compound.[22]

To achieve a more effective system for catalytic reduction and thus avoid the formation of unsaturated products, a preliminary communication reported the reductive radical reactions of alkylhalides catalyzed by iron(II) dichloride (10 mol %) in the presence of sodium borohydride in acetonitrile (Scheme 1).[23] Direct reduction occurred in good yields, and unsaturated primary and secondary systems bearing either iodide or bromide radical precursors efficiently provided the corresponding products of tandem cyclization/reduction reactions.



Scheme 1. Iron(II)-mediated tandem cyclization/reduction reactions in the presence of $NaBH_4$ (previous work).[23]

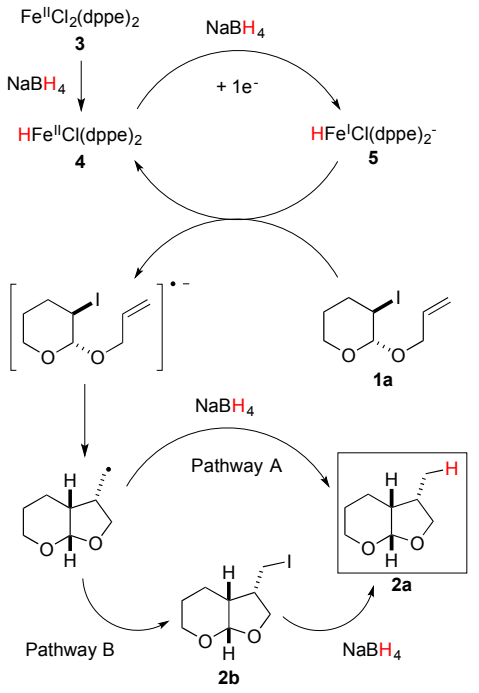
To gain more insight into the mechanism of these reactions, the iron(II) precatalyst $[FeCl_2(dppe)_2]$ (**3**) (dppe=1,2-bisdiphenylphosphinoethane) was selected as a probe due to the stabilizing effect imparted by the bis-phosphine ligands. Electrochemical studies on **3** in the presence of sodium borohydride clearly identified the formation of an iron monohydride $[HFe^{II}Cl(dppe)_2]$ (**4**) that upon reduction generated the anionic hydridoiron(I) $[HFe^{I}Cl(dppe)_2]^-$ (**5**). The catalytic activity of this species has been demonstrated by an increase of the observed reduction current of $[HFe^{II}Cl(dppe)_2]$ (**4**) with the number of iodoacetal **1a** equivalents (Scheme 2).

However during the preparative electrolysis of iodide **1a** (in the absence of $NaBH_4$), the formation of the bicyclic byproduct **2b** resulting from iodine atom transfer (ca. 10% yield) was observed. This could suggest, as also recently proposed by Curran and Studer,[24] that under the standard conditions given in Scheme 1, the cyclization process could involve iodine atom transfer, followed by nucleophilic substitution of the resulting primary iodide with the borohydride to give **2a** (Scheme 2, pathway B). In sharp contrast, the corresponding bromide (**1b**) is presumably not sufficiently reactive to undergo the equivalent bromine atom transfer, yet the reductive cyclization reaction takes place in similar yields from this substrate.[25] It is even more difficult to conceive a bromine atom transfer taking place in the cyclization of the primary bromide **A** to give **B** as shown in Scheme 1. To follow up on the mechanistic investigations carried out on **1a**, analysis was extended to the bromoacetal derivative **1b**. These studies have provided new insights into this interesting transformation.

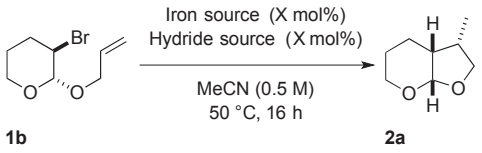
2. Results

2.1. Influence of reaction parameters

To complement the previous study, the influence of the iron and hydride sources and their respective loadings on the cyclization of bromoacetal **1b** was investigated as described in Scheme 3.



Scheme 2. Generation and reactivity of the anionic hydridoiron(I) active species ($[HFe^{I}Cl(dppe)_2]^-$) (**5**) for the reductive cyclization of **1a** via Pathway A (major) and Pathway B (iodine atom transfer. *Note*: Initiation by $NaBH_4$ alone is also possible).



Scheme 3. Iron(II)-mediated 5-exo-trig radical cyclization of unsaturated b-bromoacetal 1b in the presence of NaBH4.

2.1.1. Influence of the iron source. A variety of iron salts and iron complexes were screened under the general reaction conditions shown in Scheme 3 and a selection of the results are shown in Table 1 (see the Supplementary data for the complete table of results for bromoacetal **1b**, and results for iodoacetal **1a**). The bromoacetal **1b** was found to be more sensitive to the iron source than the corresponding iodoacetal **1a**: for example, while iodoacetal **1a** reacted well (62–65% yield) in the presence of iron(II) dichloride (98%), no reaction was observed with bromoacetal **1b** (Entry 1) or iron(III) trichloride (98%, Entry 4). In contrast, reaction with high purity iron(II) and (III) chlorides proceeded in similar, good yields (Entries 2 and 5), interestingly the results with high purity iron(II) dichlorides were dependent on the commercial

Table 1
Reactivity of **1b** in the presence of [Fe] or [Cu] (10 mol %) and sodium borohydride (150 mol %)[a]

Entry	[M], M=Fe, Cu	Purity%	Yield% (**2a**)
1	$FeCl_2$	98	0
2	$FeCl_2$[b]	99.99	78
3	$FeCl_2$[c]	99.99	39
4	$FeCl_3$	98	0
5	$FeCl_3$	99.99	80
6	$[FeCl_2(dppe)_2]$ (**3**)	N.D.	78
7	$CuCl_2$	99.995	14

[a] Reaction conditions: **1b** (1.0 mmol, 0.5 M CH_3CN), [M] M=Fe, Cu (10 mol %), $NaBH_4$ (150 mol %), 50 °C, 16 h.
[b] Commercial supplier: Sigma–Aldrich.
[c] Commercial supplier: Alfa Aesar.

supplier as shown in Entries 2 and 3 (see Supplementary data). A 78% yield was obtained from the phosphine dichloro complex [$Fe^{II}Cl_2(dppe)_2$] (**3**), confirming that the ligand could be employed without any adverse effect on the reaction outcome (Entry 6). Copper(II) dichloride also mediated the reaction with bromoacetal **1b** however the yield was very low (Entry 7). In this case, a new side product (14% yield) was also observed arising from the direct reduction of the substrate.

Following these results, the differences in reactivity of the iron(II) dichloride sources were investigated in more detail. Samples of $FeCl_2$ (99.99%) and $FeCl_2$ (98%) purity were studied first by high resolution ESI mass spectrometry. Spectra were collected in positive-ion mode at +50 V and +120 V cone voltage, and negative-ion mode at −50 V and −80 V cone voltage. No significant differences in the two samples were observed in either mode (see Supplementary data). These samples were analyzed by ICP mass spectroscopy and full details of the results are reported in the Supplementary data. The samples were found to be almost identical and no large impurities were found in either. The $FeCl_2$ (99.99%) sample contained an iron purity measured at 99.98%, while the $FeCl_2$ (98%) was found to contain a slightly higher purity, at 99.99%. The next most significant results were that of manganese and nickel which were detected at 0.0079% and 0.0038% for $FeCl_2$ (99.99%), and 0.0061% and 0.0070% for $FeCl_2$ (98%), respectively, most elements were below detection levels. Therefore, there is not a major elemental impurity in the iron source hindering reaction. However, these results do not preclude the possibility that an anion present in one of the samples has a significant impact on the outcome of the reaction.

2.1.2. Reducing agent. The suitability of different reducing agents for the reaction of bromoacetal **1b** in the presence of iron(II) dichloride (99.99%) was investigated (Table 2). Alternative counterions to sodium were first tested. While reduction with lithium borohydride (Entry 2) gave a 70% yield of bicyclic product **2a**, the corresponding potassium reagent (Entry 3) did not. Milder sodium based borohydrides were tested without success (Entries 4–6). The reaction proceeded with tetrabutylammonium borohydride, in a 59% yield (Entry 7). In the presence of iron(III) trichloride (99.99%) similar yields were obtained with $NaBH_4$ and nBu$_4$NBH$_4$ (Entries 9 and 11) however in the presence of $LiBH_4$ (Entry 10) the yield decreased to 31% without any obvious explanation.

These results show that reducing agents of lower reactivity, for example, cyanoborohydride, are not effective reagents for the reaction. Mayr and co-workers have established a hydride donor scale, which reveals that amine-boranes have comparable reactivity to cyanoborohydrides, while silanes are significantly less active.[26] Therefore neither of these reagents was tested in our study. Our results suggest that formation of an insoluble co-product from the reaction may assist to drive the reaction to completion. In the case of sodium and lithium borohydride, the co-product of the reaction (sodium or lithium bromide) is insoluble in acetonitrile.

Table 2
Reactivity of **1b** in the presence of [Fe] (10 mol %) and reducing agent (X mol %)[a]

Entry	[Fe]	Reducing agent	mol %	Yield% (**2a**)
1	$FeCl_2$	$NaBH_4$	150	78
2	$FeCl_2$	$LiBH_4$	150	70
3	$FeCl_2$	KBH_4	150	0
4	$FeCl_2$	$NaBH_3CN$	150	0
5	$FeCl_2$	$NaBH_3CN$	600	0
6	$FeCl_2$	$NaBH(OAc)_3$	150	0
7	$FeCl_2$	nBu$_4$NBH$_4$	150	59
8	$FeCl_2$	nBu$_4$NBH$_3$CN	150	0
9	$FeCl_3$	$NaBH_4$	150	80
10	$FeCl_3$	$LiBH_4$	150	31
11	$FeCl_3$	nBu$_4$NBH$_4$	150	59

[a] Reaction conditions: **1b** (1.0 mmol, 0.5 M CH_3CN), [Fe] (10 mol %), reducing agent (X mol %), 50 °C, 16 h.

2.1.3. Iron(II) dichloride loading. It is desirable to decrease the iron(II) and (III) chloride (99.99%) loading for the reaction of bromoacetal **1b** (Table 3). The loading of both iron salts could be decreased to 5 mol % and a comparable product yield was obtained (Entries 1 and 3). Any further decreases in iron loading rapidly resulted in incomplete conversion and subsequent loss in yield (Entry 2 and 4).

Table 3
Reactivity of **1b** in the presence of [Fe] (X mol %) and sodium borohydride (150 mol %)[a]

Entry	[Fe]	mol %	Yield% (**2a**)
1	$FeCl_2$	5	67
2	$FeCl_2$	2	17
3	$FeCl_3$	5	74
4	$FeCl_3$	2	13

[a] Reaction conditions: **1b** (1.0 mmol, 0.5 M CH_3CN), [Fe] (X mol %), $NaBH_4$ (150 mol %), 50 °C, 16 h.

2.1.4. Sodium borohydride loading. It is desirable to decrease the sodium borohydride loading for the reaction of bromoacetal **1b** to improve the potential substrate scope (Table 4). Employing iron(II) dichloride (99.99%) revealed that decreasing the sodium borohydride loading resulted in a drop in product yields. The yield was respectable in the presence of 100 mol % and 75 mol % sodium borohydride (Entries 2 and 3), however attempts to decrease the loading further resulted in incomplete reaction and low isolated yield (Entry 4). Similar conditions were tested for reactions with iron(III) trichloride (99.99%). A comparable yield was obtained from 100 mol % sodium borohydride (Entry 6) as under our standard reaction conditions. However, decreasing the loading any further once again resulted in incomplete reactions and low isolated yield (Entries 7 and 8).

Table 4
Reactivity of **1b** in the presence of [Fe] (X mol %) and sodium borohydride (X mol %)[a]

Entry	[Fe]	mol %	$NaBH_4$ mol %	Yield% (**2a**)
1	$FeCl_2$	10	150	78
2	$FeCl_2$	10	100	65
3	$FeCl_2$	10	75	65
4	$FeCl_2$	10	50	42
5	$FeCl_3$	5	150	80
6	$FeCl_3$	5	100	78
7	$FeCl_3$	5	75	55
8	$FeCl_3$	5	50	43

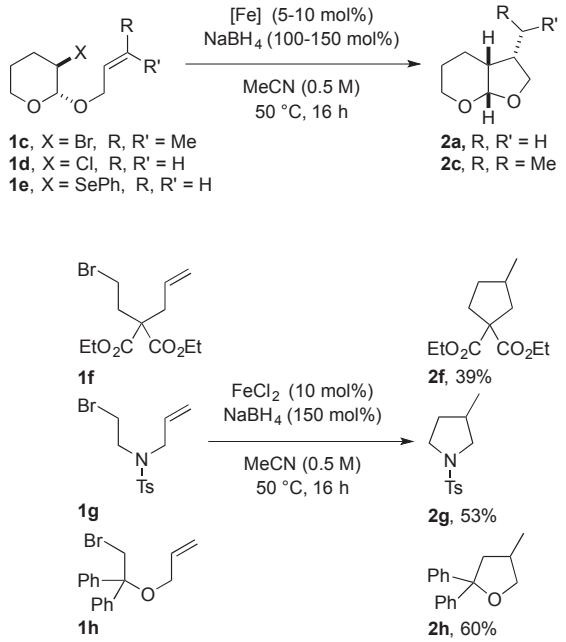
[a] Reaction conditions: **1b** (1.0 mmol, 0.5 M CH_3CN), [Fe] (X mol %), $NaBH_4$ (X mol %), 50 °C, 16 h.

In conclusion the optimization studies have revealed the best experimental conditions to be: iron(II) dichloride (99.99%, 10 mol %) in the presence of sodium borohydride (150 mol %) or iron(III) trichloride (99.99%, 5 mol %) in the presence of sodium borohydride (100 mol %). Reactivity of the substrate was observed in the presence of both iron(II) and iron(III) chlorides and therefore the initial oxidation state of the iron source is not critical to the reaction outcome. Indeed it appears that the oxidation state of the catalytically active species is available from both sources, as explored in detail in Section 2.3 (vide infra).

2.2. Reaction scope

To explore the potential of these catalytic systems, additional unsaturated halides and phenylseleno derivatives were tested.

2.2.1. Unsaturated β-haloacetals and primary alkyl bromides. A variety of unsaturated β-haloacetals (**1c**–**e**) and unsaturated primary alkyl bromides (**1f**–**h**) substrates were reacted under the standard reactions conditions shown in Scheme 4. The unsaturated β-haloacetals were reacted with iron(II) and iron(III) chloride to verify whether the oxidation state impacted the reaction. Results are given in Table 5.



Scheme 4. Iron(II)-mediated 5-exo-trig radical cyclization of unsaturated b-haloacetals and unsaturated primary alkyl bromides in the presence of NaBH4.

Table 5
Reactivity of haloacetal **1** in the presence of [Fe] (X mol %) and sodium borohydride (X mol %)[a]

Entry	Acetal	[Fe]	mol %	$NaBH_4$ mol %	Yield% (**2**) (***1*** *recovered%*)
1	**1c**	$FeCl_2$	10	150	55
2	**1c**	$FeCl_3$	5	100	23 (*25*)
3	**1c**	(**3**)	10	150	60
5	**1d**	$FeCl_2$	10	150	0 (*59*)
6	**1d**	$FeCl_3$	5	100	0 (*>95*)
7	**1e**	$FeCl_2$	10	150	0
8	**1e**	$FeCl_3$	5	100	0 (*>95*)

[a] Reaction conditions: **1** (1.0 mmol, 0.5 M CH_3CN), [Fe] (X mol %), $NaBH_4$ (X mol %), 50 °C, 16 h.

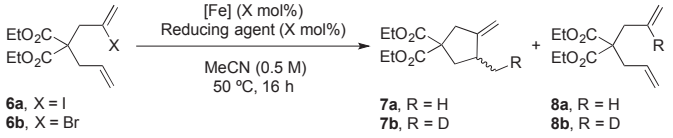
Previously 3-methyl-2-(2-propenoxy)-3-iodotetrahydropyran was shown to undergo cyclization (51% yield).[23] Similarly, 3-methyl-2-(2-propenoxy)-3-bromo-tetrahydropyran (**1c**)[7] was converted cleanly to the corresponding bicyclic product (**2c**)[7] by iron(II) dichloride and [$FeCl_2$(dppe)$_2$] (**3**) (Entries 1 and 3). In contrast only a 23% yield was observed for the reaction with iron(III) trichloride (Entry 2).

In contrast to iodide and bromide substrates, less activated haloacetal radical substrates were not reactive using either iron(II) or iron(III) chloride. Only substrate was recovered from the reaction with 2-allyloxy-3-chlorotetrahydropyran (**1d**)[27] (Entries 5 and 6). Reaction with 2-allyloxy-3-(phenylseleno)tetrahydropyran (**1e**)[28] resulted in significant substrate degradation, however no conversion to the product was observed in these reactions either (Entries 7 and 8).

Primary alkyl radicals were generated from the corresponding bromides under the optimized conditions, subsequently the primary radical underwent 5-*exo*-trig cyclization and reduction to give the cyclic product. Three different substrates **1f**, **1g**, and **1h** were tested and furnished the respective five-membered rings in 39%, 53% and 60% yields (Scheme 4).

2.2.2. Vinyl halides. The reaction system was efficient at generating alkyl radicals from reactive halides (iodide and bromide). Next, the generation of vinyl radicals[29] starting from the corresponding iodide or bromide was investigated to effect 5-*exo*-trig cyclization reactions. The high reactivity of vinyl radicals has been exploited in cascade radical reactions to build multiple new bonds in a single step, giving rise to polycyclic natural product scaffolds.[30] It has also been used to achieve high degrees of stereocontrol in radical reactions.[31]

Diethyldiallyl malonates **6a** and **6b** were screened under the standard reaction conditions with both iron(II) and iron(III) chloride and further experiments were conducted based on these results. Two products could be identified from these reactions: the cyclized product (**7**) and the product (**8**) arising from direct reduction of the substrate (Scheme 5).



Scheme 5. Iron mediated cyclization and reduction of diethyldiallyl malonates.

The reactivity of 2-iodo-4,4-(dicarbethoxy)-1,6-heptadiene (**6a**) was screened first and the results are given in Table 6. In the presence of iron(II) dichloride and sodium borohydride conversion was complete (Entry 1). A 50% yield of products was obtained as an inseparable mixture of cyclized **7a** and directly reduced product **8a**. The reduced product was favored, with a 12:88 ratio of products (**7a**:**8a**) estimated by ^{1}H NMR. In an attempt to favor cyclization, sodium borodeuteride was employed which is supposed to have a slower rate of deuterium delivery than the corresponding hydride.[32] Indeed, selectivity for the cyclized product **7b** increased, albeit not significantly with a 28:72 ratio of **7b**:**8b** obtained (Entry 2). Also to favor cyclization, the reaction was tested in the presence of sodium cyanoborohydride, however once again this reagent was not an effective reducing agent for this reaction (Entry 3).

Table 6
Reactivity of iodoacetal **6a** in the presence of [Fe] (X mol %) and reducing agent (X mol %)[a]

Entry	[Fe]	mol %	Reducing agent	mol %	Yield% (ratio 7:8)
1	$FeCl_2$	10	$NaBH_4$	150	50 (12:88)[b]
2	$FeCl_2$	10	$NaBD_4$	150	42 (28:72)[b]
3	$FeCl_2$	10	$NaBH_3CN$	150	0
4[b]	$FeCl_3$	5	$NaBH_4$	100	38 (30:70)[b]
5[c]	$FeCl_3$	5	$NaBD_4$	100	60(19:81)[c]
6	$FeCl_3$	10	$NaBH_3CN$	100	0
7	(**3**)	10	$NaBH_4$	150	40 (0:100)

[a] Reaction conditions: **6a** (1.0 mmol, 0.5 M in CH_3CN), [Fe] (X mol %), reducing agent (X mol %), 50 °C, 16 h.
[b] Products not separable by column chromatography.
[c] Substrate and product not separable by column chromatography; Yields are estimated based on the isolated yield and integration of the ^{1}H NMR.

Iron(III) trichloride mediated the reaction in the presence of sodium borohydride. As shown in Entry 4, a mixture of products was again obtained favoring the uncyclized product **8a**, with a 30:70 ratio of **7a**:**8a**. Conversion was incomplete in the presence of sodium deuteride (Entry 5). Interestingly in the presence of iron(III) trichloride and sodium cyanoborohydride, the reaction failed completely (Entry 6). Finally, the phosphine dichloroiron

complex (**3**) mediated the reaction, with complete selectivity for the directly reduced product **8a** (Entry 7).

The mixture of products arising from the reaction of 2-iodo-4,4-(dicarboethoxy)-1,6-heptadiene (**6a**) contrasts with the selectivity for cyclization observed in the reaction of 6-bromo-4,4,diphenylhex-1-ene (**A**). These contrasting results may originate from organometallic mediated heterolytic pathways.

The corresponding 2-bromo-4,4-(dicarboethoxy)-1,6-heptadiene (**6b**)[33] was screened under similar conditions to the iodide **6a**, and the results are given in Table 7. Unlike the iodide, only the directly reduced product **8** was observed in any of these reactions, never the cyclized product **7**.

Table 7
Reactivity of bromoacetal **6b** in the presence of [Fe] (X mol %) and reducing agent (X mol %)[a]

Entry	[Fe]	mol %	Reducing agent	mol %	Yield% (**8**)
1	$FeCl_2$	10	$NaBH_4$	150	58
2	$FeCl_2$	10	$NaBD_4$	150	65[b]
3	$FeCl_2$	10	$NaBH_3CN$	150	0
4	$FeCl_3$	5	$NaBH_4$	100	65[b]
5	$FeCl_3$	5	$NaBD_4$	100	68[b]
6	$FeCl_3$	10	$NaBH_3CN$	100	0
7	(**3**)	10	$NaBH_4$	150	49

[a] Reaction conditions: **6b** (1.0 mmol, 0.5 M in CH_3CN), [Fe] (X mol %), reducing agent (X mol %), 50 °C, 16 h.
[b] Substrate and product not separable by column chromatography; yield not determined, approximate yield given based on crude ^1H NMR.

Iron(II) dichloride and the phosphine dichloroiron complex (**3**) mediated the reaction giving the directly reduced product **8b** in 58% and 49% yields, respectively (Entries 1 and 7). Conversion was incomplete when sodium borohydride was employed with iron(III) chloride (Entry 4) and sodium borodeuteride with either iron(II) or iron(III) chloride (Entries 2 and 5). No reactivity was observed in the presence of sodium cyanoborohydride (Entries 3 and 6). Only substrate was recovered from these reactions in 69% and 49% yields, respectively, indicating that some degradation had occurred.

2.3. Mechanistic studies: formation of the hydridoiron precatalyst

In the preliminary report, electrochemical studies formed the basis of the proposed reaction mechanism. This technique, along with additional information obtained from multi-nuclear NMR experiments has provided us with a more complete understanding of the reaction system presented herein and the subsequent mechanistic implications. These results are discussed below.

2.3.1. Cyclic voltammetry. First, it was necessary to establish whether iron(II) and iron(III) chloride were acting via the same mechanism. To achieve this, the reaction with $[Fe^{III}Cl_3]$ was studied via cyclic voltammetry (CV) to compare with previous results for the reaction mediated by $[Fe^{II}Cl_2]$.[23]

The CV of $[Fe^{III}Cl_3]$ in acetonitrile (4 mM) exhibited a reversible reduction peak at E^P_{R1}=+0.04 V versus the standard calomel electrode (SCE; Fig. 1a). An oxidation peak characteristic of an electrogenerated iron(II) species was observed on the reverse scan (O_1, Fig. 1a). Two equivalents of 1,2-bis(diphenylphosphino)ethane (dppe) ligand were added to $[Fe^{III}Cl_3]$ in acetonitrile (4 mM) and a new reduction peak was observed at E^P_{R2}=−1.45 V (Fig. 1b). This peak was assigned to $[Fe^{II}Cl_2(dppe)_2]$ (**3**) by comparison with an authentic sample (E^P=−1.47 V). $[Fe^{III}Cl_3]$ was still present in the CV (R_1, Fig. 1b) which indicates that $[Fe^{III}Cl_3]$ does not react directly with dppe, but a reaction takes place with the electrogenerated iron(II) species to generate $[Fe^{II}Cl_2(dppe)_2]$ (**3**).

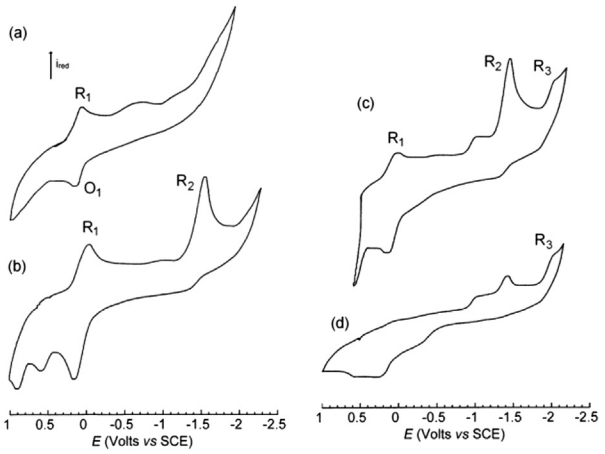


Fig. 1. Cyclic voltammetry performed at a gold disk electrode (d=1 mm) at 22 °C in acetonitrile containing nBu$_4$NBF$_4$ (0.3 M) as the supporting electrolyte at a scan rate of 5 V s^{-1}: (a) Reduction of $Fe^{III}Cl_3$ (4 mM); (b) Reduction of $Fe^{III}Cl_3$ (4 mM) in the presence of dppe (2 equiv); (c) Reduction of $Fe^{III}Cl_3$ (4 mM) and dppe (2 equiv) in the presence of $NaBH_4$ (1 equiv); (d) Reduction of $Fe^{III}Cl_3$ (4 mM) and dppe (2 equiv) in the presence of $NaBH_3CN$ (8 equiv).

When 1 equiv of $NaBH_4$ was added to a mixture of $[Fe^{III}Cl_3]$ (4 mM) and dppe (2 equiv) in acetonitrile, the reduction peak of $[Fe^{III}Cl_3]$ (R_1) partly decreased (Fig. 1c). The reduction peak at R_2 corresponding to $[Fe^{II}Cl_2(dppe)_2]$ (**3**) was once again observed (compare Fig. 1b and c). A new reduction peak was observed at E^P_{R3}=−2.05 V (Fig. 1c). The peak at R_3 was assigned to the hydridoiron(II) complex $[HFe^{II}Cl(dppe)_2]$ (**4**) by comparison with an authentic sample of the known complex (E^P=−2.08 V).[34] One equivalent aliquots of $NaBH_4$ were successively added to the mixture to determine the stoichiometry required to completely reduce iron(III). The reduction peak at E^P_{R1}=+0.04 V completely disappeared upon addition of 4 equiv of $NaBH_4$. At the same time, the reduction peak at E^P_{R2}=−1.42 V was observed to decrease while the reduction peak at E^P_{R3}=−2.03 V increased. This confirms that the chemical reduction of $[Fe^{III}Cl_3]$ by $NaBH_4$ generates an iron(II) species which leads to formation of $[HFe^{II}Cl(dppe)_2]$ (**4**) after reaction with $NaBH_4$.

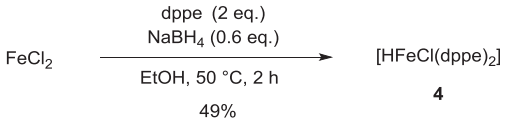
For interest, the ability of sodium cyanoborohydride to reduce iron(III) trichloride to the hydridoiron(II) complex **4** was tested. One equivalent aliquots of $NaBH_3CN$ were added to a mixture of $[Fe^{III}Cl_3]$ (4 mM) and dppe (2 equiv) in acetonitrile. The reduction peak of $[Fe^{III}Cl_3]$ at R_1 completely disappeared after the addition of 8 equiv of $NaBH_3CN$ (Fig. 1d). The reduction peak corresponding to R_2 was hardly observed, whereas the reduction peak at E^P_{R3}=−2.07 V was, confirming the formation of $[HFe^{II}Cl(dppe)_2]$ (**4**).

These results suggest that iron(III) trichloride in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) is able to undergo reduction by a strong reducing agent to form the hydridoiron(II) complex $[HFe^{II}Cl(dppe)_2]$ (**4**). Our previous studies revealed that $[Fe^{II}Cl_2]$ in the presence of dppe reacts with $NaBH_4$ to form the same complex. In conclusion, the cyclization reaction mediated by either iron(II) or iron(III) chloride occurs via an identical mechanism.

These studies successfully characterized the formation of the hydridoiron complex (**4**) by CV in the reaction of either iron(II) or iron(III) chloride with sodium borohydride in the presence of the dppe ligand. The next goal was to observe the formation of this species in situ by spectroscopic techniques, then to study its reactivity.

*2.3.2. Synthesis and characterization of trans-[HFeCl(dppe)$_2$] (**4**).* The hydridoiron complex (**4**) was synthesized following the procedure reported by Sacco and co-workers, except that

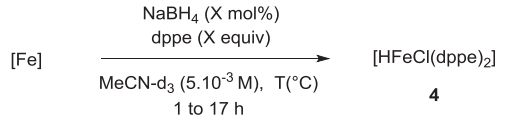
anhydrous iron(II) dichloride was employed, giving a pink-red solid in 49% yield (Scheme 6).[34]



Scheme 6. Synthesis of [HFeCl(dppe)$_2$] (**4**).

NMR spectra recorded in chloroform-*d* matched literature reports of the complex and confirmed the *trans* geometry.[34,35] In acetonitrile-d_3, the ^{1}H NMR signal for the H ligand on iron was shifted slightly upfield compared to the spectrum in chloroform-*d* (δ CD_3CN=−29.0 ppm, quintet, $^2J_{P\text{-}H}$=49.1 Hz vs δ $CDCl_3$=−26.8 ppm, quintet, $^2J_{P\text{-}H}$=49.1 Hz) while no such effect was observed in the $^{31}P\{^1H\}$ NMR, with the signal observed at δ=81.5 ppm (doublet, $^2J_{P\text{-}H}$=49.1 Hz) for both solvents.

*2.3.3. Formation of [HFeCl(dppe)$_2$] (**4**) by ^{1}H and $^{31}P\{^1H\}$ NMR.* The formation and subsequent fate of [HFeCl(dppe)$_2$] (**4**) in situ was followed by ^{1}H and $^{31}P\{^1H\}$ NMR spectroscopy under a variety of conditions (Scheme 7). Reactions were set up as follows: a mixture of the appropriate iron complex (0.005 mmol) and sodium borohydride (0.0 mmol, 0.015 mmol or 0.17 mmol) were prepared in a screw cap NMR tube before acetonitrile-d_3 (1.0 mL) was added under argon. The progress of the reaction was monitored via alternating ^{1}H and $^{31}P\{^1H\}$ NMR spectra (vide infra and Supplementary data for full details). The following results refer to the $^{31}P\{^1H\}$ NMR spectra observed.



Conditions A: $NaBH_4$ (0 mol%), rt
Conditions B: $NaBH_4$ (0 mol%), 50 °C
Conditions C: $NaBH_4$ (1500 mol%), rt
Conditions D: $NaBH_4$ (300 mol%), rt
Conditions E: $NaBH_4$ (1500 mol%), 50 °C
Conditions F: $NaBH_4$ (300 mol%), 50 °C

Scheme 7. Formation of [HFeCl(dppe)$_2$] (**4**) under various conditions.

2.3.3.1. From iron(II) dichloride (0.005 M) and dppe ligand (2.0 equiv). The formation of [HFeCl(dppe)$_2$] (**4**) in the presence of excess sodium borohydride directly from $FeCl_2$ and 2 equiv of dppe was first investigated. After 1 h [HFeCl(dppe)$_2$] (**4**) was observed in the $^{31}P\{^1H\}$ NMR spectrum at δ CD_3CN=84.0 ppm, along with free dppe ligand (δ CD_3CN=−13.7 ppm) under all the conditions tested in Scheme 7 (Conditions A–F). [$FeCl_2$(dppe)$_2$] (**3**, δ CD_3CN=51.0 ppm) was never detected in this series of reactions. Reactions at room temperature were fairly clean (Conditions C and D). Additional signals were detected when the reaction was heated to 50 °C (Conditions E and F). Each of these species was positively identified by first synthesizing authentic samples of postulated products, and taking the NMR spectra in acetonitrile-d_3. The signals observed upon heating (Scheme 7) were compared to the spectra of authentic samples to confirm their identity. $^{31}P\{^1H\}$ signals at δ CD_3CN=101.7 and 90.7 ppm observed in Conditions E correspond to the *cis*-dihydridoiron complex [H_2Fe(dppe)$_2$] (**9**).[35] A $^{31}P\{^1H\}$ NMR signal at δ CD_3CN=31.8 ppm was identified as 1,2-bis(diphenylphosphine oxide)ethane (**10**)[36] presumably formed by traces of oxygen present in the reaction (Conditions E and F) and a signal at δ CD_3CN=18.3 ppm corresponded to 1,2-bis(diphenylphosphino) ethane bisborane (**11**)[37] (Conditions D, E and F).

*2.3.3.2. From trans-dichlorodi{1,2-bis(diphenylphosphino)ethane}iron (**3**) (0.005 M).* The stability of the phosphine dichloroiron complex (**3**) to the reaction conditions was next investigated by NMR. Interestingly, in the absence of sodium borohydride the complex was no longer observed after 4 h at room temperature or 2 h at 50 °C (Conditions A and B, respectively). The mechanistic implications of this finding are discussed in detail, vide infra. A $^{31}P\{^1H\}$ signal at δ CD_3CN=51.0 ppm corresponds to *trans*-[$FeCl_2$(dppe)$_2$] (**3**). The $^{31}P\{^1H\}$ signal at δ CD_3CN=74.9 ppm observed in both cases was tentatively assigned to a [$Fe(NCCH_3)_2$(dppe)$_2$]Cl_2 complex, by analogy with a report from DuBois and Miedaner.[38] In their synthesis of *trans*-[$Fe(NCCH_3)_2$(dppe)$_2$]$(BF_4)_2$ they reported that the crude reaction mixture consisted of two products, with $^{31}P\{^1H\}$ signals observed at δ CD_3CN=74.2 ppm (minor) and δ CD_3CN=50.6 ppm (major) in acetonitrile-d_3. The later corresponded to the *trans* product which they were able to characterize, the minor complex was not isolated. Two related compounds, *trans*-[$Fe(NCCH_3)_2$(dppe)$_2$]$(ClO_4)_2$ and *trans*-[$Fe(NCCH_3)_2$(depe)$_2$]BPh_4, have been reported in the literature but neither were characterized by NMR spectroscopy.[39]

To verify that [HFeCl(dppe)$_2$] (**4**) was formed from [$FeCl_2$(dppe)$_2$] (**3**) in the presence of reducing agent, the same series of NMR reactions as described above was repeated starting from [$FeCl_2$(dppe)$_2$] (**3**). After 1 h the phosphine dichloro complex (**3**) was completely consumed in the presence of sodium borohydride and 1,2-bis(diphenylphosphino)ethane bisborane (**10**, δ CD_3CN=18.3 ppm) was formed in each case as observed in the $^{31}P\{^1H\}$ NMR spectra. The hydridoiron complex (**4**, δ CD_3CN=84.0 ppm) was formed after 1 h in the presence of 1500 mol % sodium borohydride (Conditions C and D). The complex was still present in the reaction after 17 h (Conditions C, D and F). 1,2-bis(diphenylphosphinyl)ethane (**10**, δ CD_3CN=32.9 ppm) was once again observed (Conditions C and F) and was the major product at 50 °C. Free dppe (δ CD_3CN=−12.6 ppm) was observed at 50 °C under conditions F, indicating that elevated temperature also causes the iron complexes to degrade to some extent. Fig. 2 illustrates the $^{31}P\{^1H\}$ NMR spectra for: (a) the reaction mixture from conditions C, after 1 h; (b) the reaction mixture from conditions C, after 17 h; (c) an authentic sample of the hydridoiron complex (**4**); (d) an authentic sample of dppe; (e) an authentic sample of 1,2-bis(diphenylphosphine oxide)ethane (**10**); (f) an authentic sample of 1,2-bis(diphenylphosphino)ethane bisborane (**11**); (g) an authentic sample of 1,2-bis(diphenylphosphino)ethane bisborane (**11**) after heating to 50 °C for 17 h.

*2.3.3.3. Trans-hydridochlorodi{1,2-bis(diphenylphosphino)ethane} iron (**4**) (0.005 M).* The stability of the hydridoiron complex (**4**) to the reaction conditions was explored employing the series of NMR reactions detailed in Scheme 7. In the absence of sodium borohydride the complex was stable even for 18 h at 50 °C (Conditions B). In the presence of sodium borohydride, the hydridoiron complex (**4**, δ CD_3CN=84.0 ppm) was still present after 1 h, along with free dppe (δ CD_3CN=−13.7 ppm) in each case (Conditions C–F) as observed in the $^{31}P\{^1H\}$ NMR spectra. At room temperature the hydridoiron complex (**4**, δ CD_3CN=84.0 ppm) was observed after 17 h (Conditions C and D), however at elevated temperature this species disappears after 9–12 h (Conditions E and F, respectively). Therefore, the hydridoiron complex (**4**) is sufficiently stable to act as the precatalyst for the length of the reaction, but not for longer periods. 1,2-Bis(diphenylphosphino)ethane bisborane (**11**, δ CD_3CN=18.7 ppm) was detected in most cases, however 1,2-bis(diphenylphosphinyl)ethane (**10**, δ CD_3CN=32.9 ppm) was detected only at elevated temperature (Conditions E and F), in none of these reactions were these observed as the major products. The dihydridoiron complex (**9**, δ CD_3CN=101.3, 90.4 ppm) was detected only at room temperature (Conditions C and D).

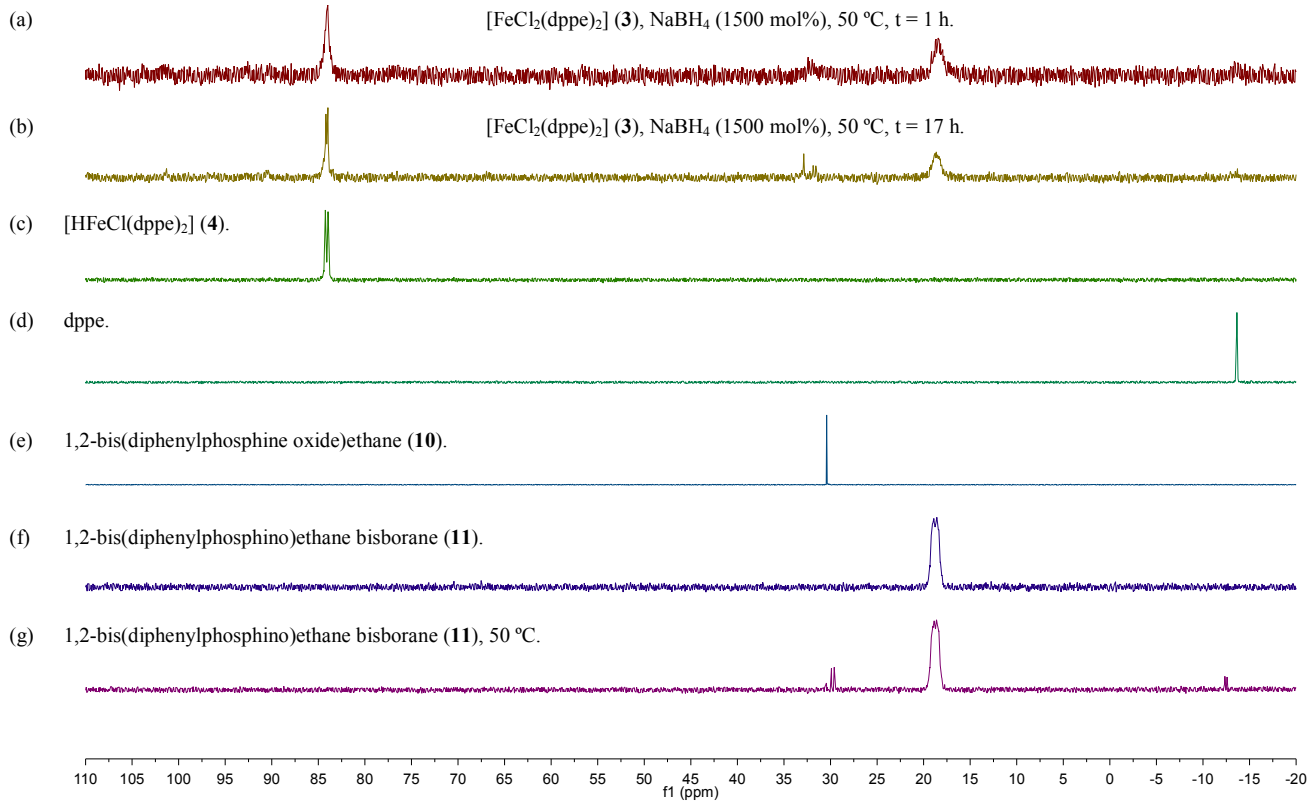
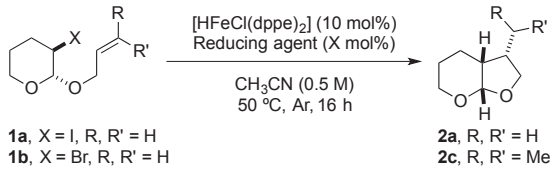


Fig. 2. Reaction of $[FeCl_2(dppe)_2]$ (**3**) in the presence of $NaBH_4$ (1500 mol %) at 50 °C. $^{31}P\{^1H\}$ NMR spectra of: (a) reaction mixture (1 h, conditions E); (b) reaction mixture (17 h, conditions E); (c) $[HFeCl(dppe)_2]$ (**4**); (d) dppe; (e) dppe oxide (**10**); (f) dppe boron trihydride (**11**); and (g) dppe boron trihydride (**11**, 50 °C, 17 h).

In conclusion, this series of experiments has shown that $[HFeCl(dppe)_2]$ (**4**) is formed in situ starting from either $[FeCl_2(dppe)_2]$ (**3**) or from free $FeCl_2$ and dppe. In reactions at room temperature and 1500 mol % reducing agent, $[H_2Fe(dppe)_2]$ (**9**) could also be observed as a minor product. $[HFeCl(dppe)_2]$ (**4**) was found to be stable under the standard reaction conditions for more than 9 h at 50 °C and can therefore by used as a precatalyst with the appropriate substrate.

2.4. Reactivity of *trans*-hydridochlorodi{1,2-bis(diphenylphosphino)ethane} iron precatalyst (4)

The reactivity of the $[HFeCl(dppe)_2]$ (**4**) was explored with iodoacetal **1a** as shown in Scheme 8.



Scheme 8. Reaction of iodoacetal **1a** in the presence of $[HFeCl(dppe)_2]$ (**4**) under various conditions.

Table 8, Entries 1 and 2 show that 10 mol % **4** promotes the complete reaction with iodoacetal **1a** in the presence of stoichiometric loadings of $NaBH_4$. One equivalent of $NaBH_4$ furnished the bicyclic product in comparable yield to the standard conditions given in Scheme 2 (i.e., $FeCl_2/NaBH_4$ compared to Entry 2). The amount of reducing agent employed in the reaction was decreased further, as shown in Entries 3 and 4, substoichiometric loadings were able to promote reaction, however conversions were incomplete. A milder reducing agent was once again tested for reactivity, as it was possible that formation of $[HFeCl(dppe)_2]$ (**4**) required a strong reducing agent with the subsequent hydrogen atom transfer reaction proceeding in the presence of a weaker agent. However, even in the presence of a large excess of sodium cyanoborohydride, no reactivity was observed (Entries 5 and 6).

Table 8
Reactivity of **1a** in the presence of $[HFeCl(dppe)_2]$ (**4**) (10 mol %) and reducing agent (X mol %)[a]

Entry	Reducing agent	mol %	Yield% (**2a**)
1	$NaBH_4$	150	63[23]
2	$NaBH_4$	100	70
3	$NaBH_4$	20	45
4	$NaBH_4$	10	55
5	$NaBH_3CN$	600	0
6	$NaBH_3CN$	10	0

[a] Reaction conditions: **1a** (1.0 mmol, 0.5 M CH_3CN), $[HFeCl(dppe)_2]$ (**4**) (10 mol %), reducing agent (X mol %), 50 °C, 16 h.

Next the reactivity of bromoacetal **1b** with $[HFeCl(dppe)_2]$ (**4**) was explored. In contrast to iodoacetal **1a**, bromoacetal **1b** was completely unreactive and $[HFeCl(dppe)_2]$ (**4**) was unable to promote reaction irrespective of the catalyst loading (10–50 mol %), the nature of the reducing agent ($NaBH_4$ or $NaBH_3CN$) or the amount of reducing agent employed (10–150 mol %).

3-Methyl-2-(2-propenoxy)-3-bromotetrahydropyran (**1c**) was reacted with $[HFeCl(dppe)_2]$ (**4**) in the presence of stoichiometric $NaBH_4$, however once again no reaction was observed.

The ability of $[HFeCl(dppe)_2]$ (**4**) to promote reduction of the chloroacetal **1d**, phenylselenoacetal **1e** and the vinyl halides (**6a** and **6b**) used early in this study was tested. These reactions were unsuccessful, and $[HFeCl(dppe)_2]$ (**4**) was not sufficiently active to promote reaction with any of these substrates.

2.5. Mechanistic studies: role of substrate

The difference in the observed reactivity between the iodo- and bromacetal substrates raised an important question over the nature of the precatalyst, the hydridoiron(II) complex (**4**), and the catalytically active species that warranted detailed exploration.

2.5.1. Cyclic voltammetry. CV had been used effectively in the earlier studies of [HFe^{II}Cl(dppe)$_2$] (**4**) to prove the catalytic activity of anionic hydridoiron(I) catalyst [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) in the presence of iodoacetal **1a**.[23] Therefore electrochemistry was employed to explore the reactivity of 2-allyloxy-3-bromotetrahydropyran (**1b**). The reduction potential of bromoacetal **1b**, analyzed as a solution in acetonitrile, could not be measured as the substrate was not reduced before the solvent at −2.7 V at a scan rate of 5 V s^{-1}. As shown in Fig. 3a, the reduction of [HFe^{II}Cl(dppe)$_2$] (**4**) in the presence of iodoacetal **1a** results in a lack of reversibility at a scan rate of 5 V s^{-1}. The reduction peak (R_3) of [HFe^{II}Cl(dppe)$_2$] (**4**) increases noticeably with increasing aliquots of iodoacetal **1a** (1–4 equiv, Fig. 3a) confirming that [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) reacts with **1a** to generate [**1a**]$^{\bullet -}$ and regenerate [HFe^{II}Cl(dppe)$_2$] (**4**). Interestingly, when the experiment was conducted with bromoacetal **1b**, the current peak (R_3) was observed to only slightly increase (1–6 equiv, Fig. 3b). However, this effect was considerably attenuated in the presence of bromoacetal **1b**, in comparison with iodoacetal **1a** even if the timescale of the CV was longer (0.5 V s^{-1} vs 5 V s^{-1}). Based on these results, the rate of reduction of **1b** by the anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) is insufficient to maintain the catalytic cycle.

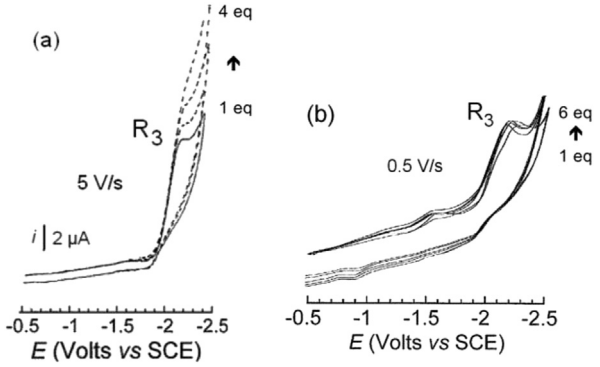
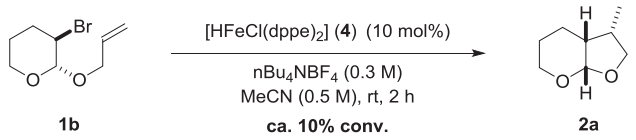


Fig. 3. Cyclic voltammetry performed at a gold disk electrode (d=1 mm) at 22 °C in acetonitrile containing nBu$_4$NBF$_4$ (0.3 M) as the supporting electrolyte: (a) Reduction of [HFe^{II}Cl(dppe)$_2$] (4 mM) at a scan rate of 5 V s^{-1} in the presence of increasing amounts of **1a** (1 equiv, solid line; 2, 3, and 4 equiv, dashed lines); (b) Reduction of [HFe^{II}Cl(dppe)$_2$] (4 mM) at a scan rate of 0.5 V s^{-1} in the presence of increasing amounts of **1b** (1 equiv, solid line; 2, 3, 4, 5 and 6 equiv, dashed lines).

2.5.2. Preparative electrolysis. A preparative-scale electrolysis of a solution of bromoacetal **1b** (0.4 mmol) in the presence of [HFeCl(dppe)$_2$] (**4**) in acetonitrile was performed at the controlled reduction potential of [HFeCl(dppe)$_2$] (−2 V, Scheme 9). After the passage of 23 Cb (0.27 F) the electrolysis gave the bicyclic product **2a** in <10% yield.



Scheme 9. Electrolysis of **1b** in the presence of [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**).

For the reaction to proceed to completion, 85 Cb (2.2 F) would be required to reduce the precatalyst **4** to active catalyst **5** and reduce the substrate. However, only 23 Cb (0.27 F) were passed before the reaction ceased. Therefore, there has only been sufficient current passed to reduce the precatalyst and a small amount of substrate prior to deactivation of the precatalyst **4**. Bromoacetal **1b** is less reactive than the corresponding iodoacetal **1a**, and thus the catalytic cycle breaks down. The active catalyst (**5**) is likely to be unstable in solution and this result provides evidence to support a competing degradation pathway for the active catalyst.

2.6. Role of the substrate on anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (5) catalytic activity

The following reactions were carried out to help explain the observed reactivity difference between bromoacetal **1b** and iodoacetal **1a** in the presence of the precatalyst [HFe^{II}Cl(dppe)$_2$] (**4**).

2.6.1. Competition reactions. Competition reactions were devised to verify that the same catalytically active species was formed from the reaction when the substrate was either iodoacetal **1a** or bromoacetal **1b**. In these reactions, 0.5 equiv of each substrate were reacted with the different iron complexes used throughout this study. As shown in Table 9, Entries 1 and 2, in the presence of $FeCl_2$ or $FeCl_3$ both substrates underwent 100% conversion and good yields of the bicyclic product (**2a**) were obtained. However, in the presence of [HFeCl(dppe)$_2$] (**4**) bromoacetal **1b** did not react (Entry 5). In this case bicyclic product **2a** and bromoacetal **1b** (72% recovery from **1b**) were isolated from the reaction, while no iodoacetal **1a** could be detected. This provides further evidence that the same catalytically active species is formed in the presence of either substrate, however anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) would not be sufficiently active to promote reaction with bromoacetal **1b**.

Table 9
Reactivity of haloacetal mixtures (**1a** and **1b**) in the presence of [Fe] (X mol %) and sodium borohydride (X mol %)[a]

Entry	Haloacetal	[Fe]	mol %	$NaBH_4$ mol %	Yield% (***1b*** *recovered*)
1	**1a**/**1b**	$FeCl_2$	10	150	51
2	**1a**/**1b**	$FeCl_3$	5	100	68
3	**1a**/**1b**	(**3**)	10	150	59
4	**1a**/**1b**	(**3**)	5	150	43
5	**1a**/**1b**	(**4**)	5	150	30 (*36*)

[a] Reaction conditions: **1a** (0.5 mmol, 0.5 M in CH_3CN), **1b** (0.5 mmol, 0.5 M in CH_3CN), [Fe] (X mol %), $NaBH_4$ (X mol %), 50 °C, 16 h.

2.6.2. Order of reagent addition. CV studies revealed that anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) exhibited quite poor reactivity with bromoacetal **1b** (Fig. 3b). If the active catalyst did not react rapidly with substrate, then alternative reaction pathways might dominate the reaction outcome. Indeed if the active species rapidly degraded or underwent alternative side reactions, this would hinder reaction with less activated substrates and result in poor product yield. To explore this possibility further, the order of addition of each reagent was studied sequentially on the reaction to observe if this had any impact. Unfortunately, no dramatic differences were observed in the reaction outcome (Table 10).

*2.6.3. Reactivity of [HFeCl(dppe)$_2$] synthesized in acetonitrile (**4***).* One hypothesis was that the synthetic procedure employed to give the authentic [HFeCl(dppe)$_2$] (**4**) (as compared with the in situ generated species) effected the reactivity. This could be caused by the presence and/or use of ethanol in the synthesis of the complex, the solvent, or the stabilizer present in the solvent. To verify if this was the case, isolation of the hydridoiron species under conditions closely replicating the standard reaction conditions was carried out. Iron(II) dichloride and dppe (2 equiv) were heated to 50 °C in

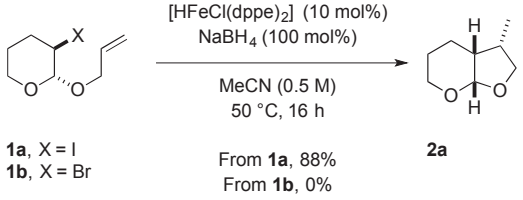
Table 10
Order of reagent introduction: reactivity of bromoacetal **1b** in the presence of [HFeCl(dppe)$_2$] (**4**) (10 mol %) and sodium borohydride (150 mol %)[a]

Entry	1	2	3	4	Observation (NMR)
1[a]	(**4**)	**1b**	$NaBH_4$	50 °C	**1b**
2[a]	(**4**)	**1b**	$NaBH_4$	rt	**1b**
3[a]	$NaBH_4$	**1b**	(**4**)	50 °C	**1b** + **2a**[c]
4[a]	$NaBH_4$	**1b**	(**4**)	rt	**1b**
5[b]	(**4**)	$NaBH_4$	**1b**	rt	**1b**
6[b]	(**4**)	$NaBH_4$	**1b**	50 °C	**1b**

[a] Reaction conditions: 1+2 neat, +3 in CH_3CN, 16 h.
[b] Reaction conditions: 1+2 in CH_3CN, after 15 min +3 in CH_3CN, 16 h.
[c] Traces of bicyclic product **2a** observed.

acetonitrile and sodium borohydride (0.6 equiv) added, after 2 h an orange powder was isolated in 24% yield. This species (**4***) exhibited identical characteristic ^1H and $^{31}P\{^1H\}$ NMR signals to the authentic complex (**4**).

Under standard reaction conditions, this species (**4***) gave an 88% of bicyclic product **2a** starting from iodoacetal **1a** (Scheme 10). Once again the bromoacetal **1b** was unreactive, and no conversion was observed. Therefore, the authentic and in situ generated species exhibit the same reactivity. This validates the synthetic procedure to give [HFeCl(dppe)$_2$] (**4**).



Scheme 10. Reaction of haloacetals **1** in the presence of [HFeCl(dppe)$_2$] (**4***).

2.6.4. Additives to promote reaction. A number of other reactions were tested to promote reactivity. Potentially, bromoacetal **1b** requires a large excess of reducing agent to favor reaction and sustain the catalytic cycle. In the presence of 10 equivalents of $NaBH_4$ and iron(II) dichloride (10 mol %), bromoacetal **1b** was once again found to be unreactive and no cyclized product **2a** was observed. There was also the possibility that the substrate and hydridoiron precatalyst may undergo halogen exchange. In this case, the catalytically active species would be [HFe^{I}**X**(dppe)]$^-$. In the presence of iodoacetal **1a**, the hydridoiron iodide [HFe^{I}**I**(dppe)]$^-$ could be formed, which would be more reactive that the equivalent bromide. Potentially, bromoacetal **1b** in the presence of an iodide source could form the postulated iodide active species to promote the catalytic cycle. Two crystals of iodine were added to the standard reaction conditions however no conversion was observed after the reaction. The electrochemistry studies had revealed that bromoacetal **1b** promoted limited catalytic activity of [HFeCl(dppe)$_2$] (**4**), and it was therefore possible that the supporting electrolyte benefited the reaction. $^nBu_4NBF_4$ (0.3 M) was added to the standard reaction conditions but once again no conversion was observed.

2.6.5. Phosphine iron complex mixtures. The reaction was carried out in the presence of both [Fe^{II}Cl$_2$(dppe)$_2$] (**3**) and [HFe^{II}Cl(dppe)$_2$] (**4**). In this case, bromoacetal **1b** was reacted with 5 mol % of each **3** and **4** under otherwise standard reaction conditions. 100% conversion of the substrate was observed, and the bicyclic product **2a** isolated in 76% yield. This suggests that the reactive species which can activate bromoacetal **1b** is not the anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) (which is generated from both [Fe^{II}Cl$_2$(dppe)$_2$] (**3**) and [HFe^{II}Cl(dppe)$_2$] (**4**)) but another species which is more reactive with **1b** than the anionic complex **5**.

3. Discussion

From these experiments one concludes that [Fe^{II}Cl$_2$(dppe)$_2$] (**3**) is a more efficient precatalyst than [HFe^{II}Cl(dppe)$_2$] (**4**), as clearly demonstrated by the reactions involving bromoacetal **1b**.

As shown in Fig. 4, when [Fe^{II}Cl$_2$(dppe)$_2$] (**3**) is used as the precatalyst it reacts with $NaBH_4$ to form [HFe^{II}Cl(dppe)$_2$] (**4**), and borane is formed as the by-product of the reaction. Borane is known to react rapidly with free phosphine to form a very stable phosphane–borane complex in an irreversible reaction.[40] Under standard reaction conditions, any dppe that is liberated will react rapidly with borane to form 1,2-bis(diphenylphosphino)ethane bisborane (**11**) (as observed by $^{31}P\{^1H\}$ NMR, vide supra). Moreover specific $^{31}P\{^1H\}$ NMR experiments conducted on [HFe^{II}Cl(dppe)$_2$] with of BH_3.THF (1 and 4 equiv) showed the rapid formation 1,2-bis(diphenylphosphino)ethane bisborane (**11**) after 30 min (see Supplementary data) and the amount did not change over 16 h. Borane may participate in the dissociation of dppe from the iron centre and subsequent complexation of the free ligand leading to formation of compound (**11**) (see $^{31}P\{^1H\}$ NMR spectra in Supplementary data). As a consequence of borane complexing with dppe, a new phosphine-free complex, [HFe^{II}Cl(NCCH$_3$)$_2$] (**12**), may be formed. This complex could undergo reduction with $NaBH_4$ to generate the phosphine-free anionic [HFe^{I}Cl(NCCH$_3$)$_2$]$^-$ (**13**) species which will be able to activate bromoacetal (**1b**). In competition, the precatalyst [HFe^{II}Cl(dppe)$_2$] (**4**) may also react with $NaBH_4$ to form the anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) species and BH_4• radical.[41]

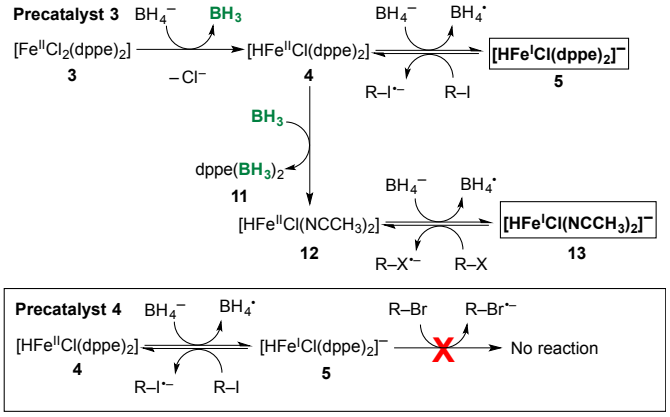


Fig. 4. Reactions leading to the generation of active catalysts in the presence of borohydride.

In the same manner, when starting from [HFe^{II}Cl(dppe)$_2$] (**4**) as the precatalyst, the anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) species and the BH_4• radical are formed (Fig. 4). However, as the hydride transfer step is not required, no borane is formed in this reaction. Thus any dppe liberated in this reaction will remain in solution, unable to form bis(diphenylphosphino)ethane bisborane (**11**).

These details suggest that formation of borane is critical to success: the reaction between borane and free dppe is rapid and irreversible which acts as a driving force for the reaction. Dissociation of dppe ligand is favored, leaving the iron centre with vacant coordination sites that may be readily filled by solvent molecules, further dissociation would give [HFe^{II}Cl(NCCH$_3$)$_2$] (**12**). Studies on the formation and reactivity of this species are ongoing and will be reported in due course.

In contrast, the precatalyst [HFeCl(dppe)$_2$] (**4**) is in equilibrium with the 19 electron anionic [HFe^{I}Cl(dppe)$_2$]$^-$ (**5**) species. Without

borane formation in this reaction, there is also no driving force for dppe dissociation from the iron species and thus $[HFe^{I}Cl(dppe)_2]^-$ (**5**) is an active catalyst for the reaction with iodooacetal **1a** but not sufficiently reactive with bromoacetal **1b**.

4. Conclusions

Work is underway to further explain these results with theory and to explore effective methods to stabilize the anionic hydrido(I) species. This will facilitate the design of potentially more efficient precatalysts to be used in a wider range of radical reactions starting from different radical precursors.

5. Experimental section

5.1. General procedure for the preparation of haloacetal substrates

A mixture of *N*-halosuccinimide (76 mmol) and alcohol (74 mmol) in dichloromethane (40 mL) was cooled to −10 °C, then 3,4-dihydro-2*H*-pyran (6.8 mL, 75 mmol) added dropwise under argon. The reaction mixture was allowed to warm to room temperature over 3 h and stirred at this temperature overnight. The reaction was diluted with dichloromethane (40 mL) and washed with saturated sodium thiosulfate (3×20 mL). The combined aqueous phase was extracted with dichloromethane (3×20 mL) and the combined organic phase washed with brine (20 mL), dried (phase separation paper) and the solvent removed in vacuo. The residue was purified by column chromatography (20% diethyl ether/pentane) to afford the title compound. The product was filtered through neutral alumina prior to use.

5.2. General procedure for the cyclization of haloacetal substrates

The iron complex (0.1 mmol) and reducing agent were added to a screw cap tube in the glovebox (the tube was capped with a suba seal). Acetonitrile (1.5 mL) was added under argon, and the mixture stirred for 15 min at room temperature. A solution of haloacetal (1.0 mmol) in acetonitrile (0.5 mL) was added under argon, the suba seal replaced by a screw cap and the reaction heated to 50 °C overnight. The reaction was cooled to room temperature, quenched with water (20 mL) and the aqueous phase extracted with dichloromethane (3×20 mL). The combined organic phase was washed with brine (30 mL), dried (phase separation paper) and the solvent removed in vacuo. The residue was purified by flash chromatography (5–20% diethyl ether/pentane).

5.3. Cyclic voltammetry set up

Cyclic voltammetry (CV) was performed in a three-electrode cell connected to a Schlenk line (under argon) at room temperature. The working electrode was a steady gold disk (d=1 mm), the counter electrode a platinum wire (ca. 0.2 cm^2 apparent area). The reference was a saturated calomel electrode (SCE) separated from the solution by a bridge filled with tetrabutylammonium tetrafluoroborate in acetonitrile solution (0.3 M, 2 mL). The same solution (0.3 M, 12 mL) was used as the solvent in the electrochemical cell for all CV experiments reported herein.

5.4. General procedure for cyclic voltammetry to measure reduction potentials

Substrate (0.048 mmol, 4 mM) was added to the electrochemical cell containing a solution of tetrabutylammonium tetrafluoroborate in acetonitrile (0.3 M, 12 mL), the mixture was stirred briefly and the CV performed immediately at a scan rate of 5 V s^{-1} (towards the reduction potential).

5.5. NMR set up

NMR spectra were acquired on a Bruker AV400 instrument fitted with a QNP probe and the temperature was set to 300 K or 323 K for all experiments described herein. Spectra acquisition settings were as follows for ^{1}H NMR; NS=64 scans; D1=1.0 s; SW=150 ppm; TD=32,768, AQ=0.27 s and O1P=25 ppm; for $^{31}P\{^1H\}$ NMR: NS=1024; TD0=8; D1=2.0 s; SW=400 ppm; O1P=−50 ppm. The sample remained in the instrument for the duration of the experiment (to maintain temperature). The samples were analyzed at fixed intervals using the Bruker Topspin spooler.

5.6. General procedure for NMR reactions

The iron complex (0.005 mmol) and sodium borohydride (if required) were added to a screw cap NMR tube in the glovebox. Acetonitrile-d_3 (1.0 mL) was added under argon, the NMR tube inserted immediately into the magnet and the time noted. The reaction was allowed to equilibrate for ca. 15 min then the first proton-decoupled ^{31}P NMR spectrum taken. Alternate ^{1}H and $^{31}P\{^1H\}$ NMR spectra were recorded each 30 min for 18 h.

Full experimental details, procedures, analytical data including NMR (^{1}H, ^{13}C spectra), ESI-MS, ICP-MS and additional Tables are given in the Supplementary data.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.08.039.

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