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Iron-Catalyzed Reductive Radical Cyclization of Organic Halides in the Presence of $NaBH_4$: Evidence of an Active Hydrido Iron(I) Catalyst**

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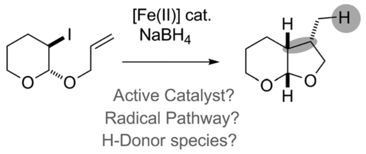
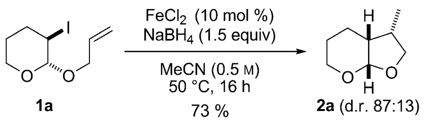
Radical chain reactions have become a very useful tool for organic synthesis.[1] Organotin hydrides stand out as the leading mediators for these processes. However, organotin hydrides generate toxic by-products that are extremely difficult to remove at trace level.[2] Currently, an actively pursued goal in radical chemistry is the discovery of alternatives to tin hydride mediators.[3–5] Hydrides of other main-group elements including silicon,[3a] boron,[3c,4e–h] gallium,[4b] and indium[4a–d] as well as hydrides of transition metals have been examined.[6]

In this context, we became interested in exploring the reactivity of iron hydrides. Iron is abundant, cheap, and has low toxicity. Although organoiron catalysis is a very active field,[7] iron hydride radical chemistry is still in its infancy.[8] Iron is known to accommodate low oxidation states,[9–12] and thus we decided to investigate iron(II) catalysts in the presence of $NaBH_4$ for the direct reduction and cyclization of organic halides. The mechanism of the reaction was investigated by means of electrochemistry (Scheme 1).



Scheme 1. Iron(II)-mediated reductive cyclization of 3-iodo-2-(allyloxy)-tetrahydropyran in the presence of $NaBH_4$.

In a typical experiment, a solution of iodoalkene **1a** in acetonitrile (0.5 M) was treated with $FeCl_2$ (10 mol%) and $NaBH_4$ (1.5 equivalents) at 50 °C under argon for 16 hours; the bicyclic product **2a** was isolated in 73% yield (Scheme 2). Control experiments with **1a** confirmed that both the iron salt and $NaBH_4$ were required for the transformation.



Scheme 2. Optimization of reaction conditions for the $FeCl_2$-mediated cyclization of iodoalkene **1a** in the presence of $NaBH_4$.

Secondary iodides **1b** and **1c** were converted into the corresponding bicyclic compounds **2b** and **2c** in good and moderate yields, respectively (Table 1, entries 1 and 2). A small amount of unsaturated acetal **2c′** was formed together with the expected product **2c**.[13] Primary iodoalkene **1d** gave the 5-*exo* product **2d** (70%; Table 1, entry 3). The *O*-homoallyl derivative **1e** gave the 6-*exo* product **2e** (Table 1, entry 4), which was obtained in relatively low yield, together with the directly reduced compound **2e′**, thus showing, as expected, that the 6-*exo*-trig cyclization is less favored than the 5-*exo*-trig cyclization.[14] The iodoalkyne **1f** gave **2f** through a 5-*exo*-dig cyclization (52%; Table 1, entry 5). The method was successfully extended to the reduction of tertiary iodide **1g** (94%; Table 1, entry 6) and aryl iodides **1h** (96%; Table 1, entry 7). Similarly, the ethyl 4-bromobutyrate **1i** and 4-bromopiperidine derivative **1j** gave the reduced ethyl butyrate **2i** and piperidine **2j** in 85% and 84% yield, respectively, (Table 1, entries 8 and 9).[15] The reaction of primary bromoalkene **1k** and secondary bromoalkene **1l** led to cyclopentane **2k** (78%; Table 1, entry 10) and hexahydrofuropyranyl derivative **2a** (70%; Table 1, entry 11), respectively.

The generation of bicycle **2a** (R′H) from **1a** (RI) probably proceeds through a mechanism involving the generation of a radical **3** ($R^\bullet$) by reduction of **1a** (Scheme 3), followed by a 5-*exo*-trig intramolecular attack of the radical onto the C=C bond; the resulting radical **4** ($R'^\bullet$) is then converted into the reduction product R′H.

When $NaBD_4$ was used as the stoichiometric reductant, [D]-**2a** was isolated with greater than 95% incorporation of

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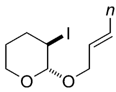
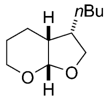
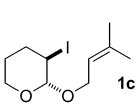
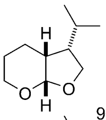
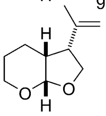
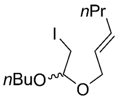
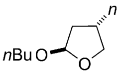
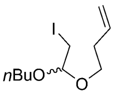
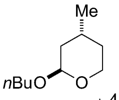
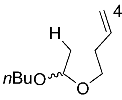
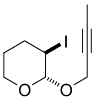
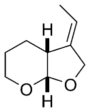
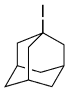
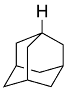
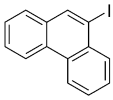
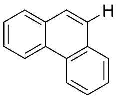
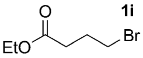
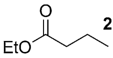
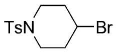
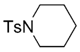
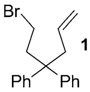
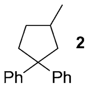
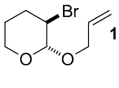
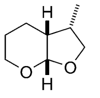
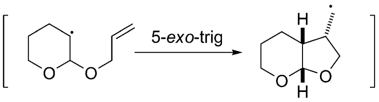
Table 1: Investigation of the reaction scope.

$$\underset{\mathbf{1}\ (\mathrm{X = I, Br})}{\mathrm{R{-}X}} \xrightarrow[\text{MeCN, 50 °C, 16 h}]{\text{FeCl}_2\text{ (10 mol \%)},\ \text{NaBH}_4\text{ (1.5 equiv)}} \underset{\mathbf{2}}{\mathrm{R'{-}H}}$$

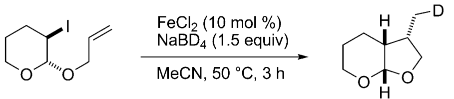
Entry	Substrate RX	Product[a]	d.r.[b]	Yield [%]
1	 **1b**	 **2b**	80:20	75
2	 **1c**	 **2c**	60:40	51[c]
		90:10		
		 **2c'**	60:40	
3	 **1d**	 **2d**	70:30	70
4	 **1e**	 **2e**	68:32	79
		44:56		
		 **2e'**	–	
5	 **1f**	 **2f**	60:40	52
6	 **1g**	 **2g**	–	94
7	 **1h**	 **2h**	–	96
8	 **1i**	 **2i**	–	85[d]
9	 **1j**	 **2j**	–	84
10	 **1k**	 **2k**	–	78
11	 **1l**	 **2a**	85:15	70

[a] The major diastereoisomer (as depicted) was assigned by analogy with literature data. [b] The diastereomeric ratio was determined by ^{1}H NMR analysis. [c] A 36:64 mixture of the product derived from the direct reduction of **1c** and a product derived from isomerization of **2c'** (8% yield overall) was also isolated. [d] Yield based on ^{1}H NMR analysis with sulfolene as an internal standard.



3 (R•) 4 (R'•)

Scheme 3. Radical pathway in the reductive cyclization of **1a**.



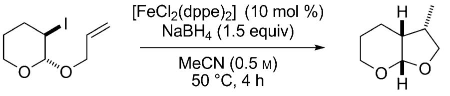
1a 67 % [D]-**2a** (d.r. 87:13)

Scheme 4. Deuterium-labelling experiment.

deuterium at one of primary C–H bonds (Scheme 4). In contrast, no deuterated product was detected when the reaction was carried out with NaBH$_4$ in CD$_3$CN. This rules out any hydrogen atom transfer from the solvent and suggests that the hydrogen atom in **2a** might come from BH$_4^-$ directly, from an in situ formed derivative of BH$_4^-$, or from an iron hydride generated by hydride transfer from BH$_4^-$ (see below).

The iron species that was responsible for the reaction was unknown. It could be either the Fe^{II} species that is added to the reaction or a reduced derivative that is generated in the presence of NaBH$_4$. Fe^{I},[9,10] Fe^{0},[10,11] and Fe^{-II}[12] species have been reported. Electrochemical techniques appeared well suited for obtaining insight into the mechanism of the reaction.[10,16] Indeed, iron complexes can be characterized by their reduction/oxidation potential. Moreover, their concentration in solution can be quantified by their oxidation/reduction current.[16]

The cyclic voltammetry (CV) of FeCl$_2$ in acetonitrile did not give a clean voltammogram because of the lack of stabilizing ligands. [FeCl$_2$(dppe)$_2$] (dppe = 1,2-bisdiphenylphosphinoethane)[17] was thus tested. The reaction of **1a** (1 mmol) with [FeCl$_2$(dppe)$_2$] (10 mol%) and NaBH$_4$ (1.5 equivalent) in acetonitrile was allowed to proceed for 4 hours at 50°C and led to the expected product **2a** in 77% yield (Scheme 5). This result suggests that [FeCl$_2$(dppe)$_2$] is a valid model catalyst for mechanistic investigation.



1a (RI) 77 % **2a** (R'H; d.r. 87:13)

Scheme 5. [FeCl$_2$(dppe)$_2$]-mediated reductive cyclization of iodoalkene **1a** in the presence of NaBH$_4$.

The CV of [FeCl$_2$(dppe)$_2$] in acetonitrile (4 mM) exhibited an irreversible reduction peak at $E^{p}_{R1} = -1.47$ V versus the standard calomel electrode (SCE; Figure 1a). A broad oxidation peak characteristic of an iron(0) species that is adsorbed at the electrode surface was observed at O$_1$ on the reverse scan (Figure 1a). The reduction peak of [FeCl$_2$(dppe)$_2$] ($E^{p}_{R1} = -1.47$ V) disappeared upon addition of NaBH$_4$ (1 equivalent) and a new reduction peak was observed at $E^{p}_{R2} = -1.99$ V. The new peak was assigned to the reduction peak of the 18 electron complex [HFeCl(dppe)$_2$] by comparison to an authentic sample (Figure 1b).[17] The latter was irreversible at the scan rate of 0.5 V s^{-1} but became partly reversible at a higher scan rate (5 V s^{-1}, see O$_2$ at $E^{p}_{O2} = -1.90$ V in Figure 1b). Therefore, [HFeCl(dppe)$_2$] undergoes a one-electron reduction to the anionic 19 electron

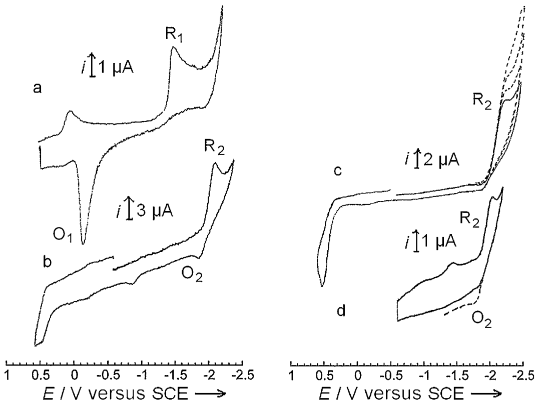
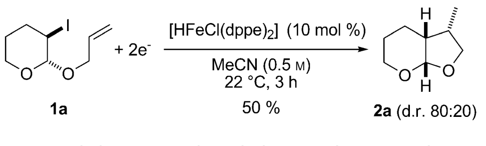


Figure 1. Cyclic voltammetry performed at a gold disk electrode ($d = 1$ mm) at 22 °C in acetonitrile containing $n\text{Bu}_4\text{NBF}_4$ (0.3 M) as the supporting electrolyte. a) Reduction of $[\text{FeCl}_2(\text{dppe})_2]$ (4 mM) at a scan rate of 0.5 V s^{-1}. b) Reduction of $[\text{HFeCl}(\text{dppe})_2]$ (4 mM) at a scan rate of 5 V s^{-1}. c) Reduction of $[\text{HFeCl}(\text{dppe})_2]$ (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). d) Reduction of $[\text{HFeCl}(\text{dppe})_2]$ (4 mM), (solid line); reduction of $[\text{HFeCl}(\text{dppe})_2]$ (4 mM) in the presence of NaBH_4 (2 mM) at a scan rate of 0.5 V.s^{-1} (dashed line).

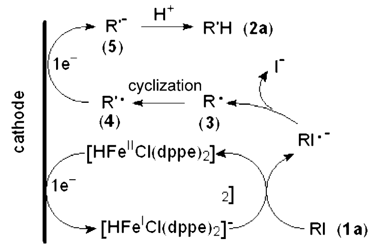
complex $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$, which is oxidized at the voltage corresponding to the O_2 peak and is moderately stable within the time scale of the CV.

Iodoalkene **1a**, analyzed as a solution in acetonitrile, was not reduced up until −2.5 V. The addition of **1a** to $[\text{HFeCl}(\text{dppe})_2]$ resulted in a lack of reversibility in reduction/oxidation events at a scan rate of 5 V s^{-1} (Figure 1c). The oxidation peak O_2 of $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$ disappeared whereas the reduction peak current of $[\text{HFeCl}(\text{dppe})_2]$ at R_2 increased with increasing amounts of **1a** (from one to four equivalents; Figure 1c). From these experiments, one deduces that the one-electron reduction of $[\text{HFeCl}(\text{dppe})_2]$ gives the anionic hydrido Fe^{I} complex $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$ which transfers one electron to **1a** to generate the radical anion $\mathbf{1a}^{\bullet-}$ and $[\text{HFeCl}(\text{dppe})_2]$. $[\text{HFeCl}(\text{dppe})_2]$ again undergoes reduction in the diffusion layer at the electrode, thus giving rise to a catalytic-reduction current, which is observed at R_2 (Figure 1c). A preparative-scale electrolysis of a solution of **1a** (0.4 mmol) in the presence of $[\text{HFeCl}(\text{dppe})_2]$ (10 mol %) in acetonitrile (12 mL) was performed at the controlled reduction potential of $[\text{HFeCl}(\text{dppe})_2]$ (−2 V, Scheme 6). After the passage of 85 Cb (2.2 F), the electrolysis gave the expected product **2a** in 50 % yield.



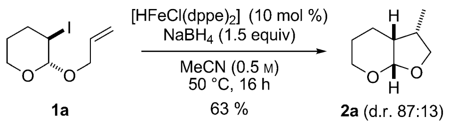
Scheme 6. $[\text{HFeCl}(\text{dppe})_2]$-mediated electroreductive cyclization of **1a**.

These results suggest that $[\text{HFeCl}(\text{dppe})_2]$ is a precatalyst, the reduction of which at the very beginning of the electrolysis to $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$ allows the activation of **1a** by electron transfer. A catalytic cycle is proposed for the cyclization of **1a** (Scheme 7). The passage of two electrons per mole of substrate indicates that the cyclized radical $\text{R}'^{\bullet}$ (**4**) is reduced at the cathode to generate the anion R'^- (**5**), which is then protonated to give **2a**. This mechanism is reminiscent of the radical cyclization of unsaturated α-bromoesters by electrochemically generated nickel(I) complexes.[18,19]



Scheme 7. Mechanism of the electroreductive cyclization of **1a** catalyzed by electrogenerated $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$ in CH_3CN.

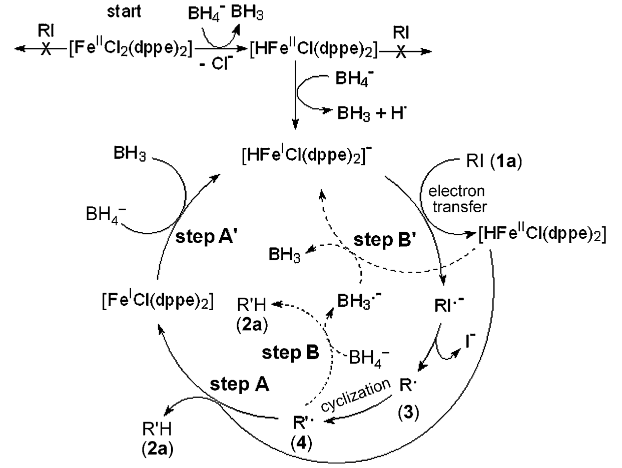
The mechanism of the catalytic reductive cyclization performed in the presence of the chemical reductant NaBH_4 was then investigated (Scheme 5). In the presence of a stoichiometric amount of $[\text{FeCl}_2(\text{dppe})_2]$ and in the absence of NaBH_4, **1a** did not undergo cyclization to give **2a**. In contrast, the cyclization did occur in the presence of a catalytic amount of $[\text{FeCl}_2(\text{dppe})_2]$ (10 mol %) and NaBH_4 (1.5 equivalents; Scheme 5). Thus, $[\text{FeCl}_2(\text{dppe})_2]$ is not the active catalyst. Similarly, no reaction was observed between $[\text{HFeCl}(\text{dppe})_2]$, present in a stoichiometric amount, and **1a**, thus also ruling out $[\text{HFeCl}(\text{dppe})_2]$ as being the active catalyst. As expected, **1a** underwent cyclization in the presence of a catalytic amount of $[\text{HFeCl}(\text{dppe})_2]$ (10 mol %) and NaBH_4 (1.5 equivalents), thus delivering **2a** in 63 % yield (Scheme 8).



Scheme 8. $[\text{HFeCl}(\text{dppe})_2]$-mediated cyclization of iodoalkene **1a** in the presence of NaBH_4.

These experiments show that $[\text{HFeCl}(\text{dppe})_2]$ only becomes active upon its reduction by NaBH_4. The addition of NaBH_4 (0.5 equivalents) to a solution of $[\text{HFeCl}(\text{dppe})_2]$ in acetonitrile (4 mM) resulted in an increase of the oxidation peak of $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$ at O_2 (Figure 1d), thus establishing that NaBH_4 transfers one electron to $[\text{HFeCl}(\text{dppe})_2]$ to generate the active species $[\text{HFe}^{\text{I}}\text{Cl}(\text{dppe})_2]^-$. This active species then activates **1a** by single electron transfer (SET) to give $\mathbf{1a}^{\bullet-}$ (Scheme 9), which eventually gives **2a**.

The formation of [D]-**2a** in the presence of NaBD_4 (Scheme 4) suggests that the radical $\text{R}'^{\bullet}$ (**4**), which is formed through intramolecular cyclization, abstracts a hydrogen atom from $[\text{HFe}^{\text{II}}\text{Cl}(\text{dppe})_2]$ (Scheme 9, step A) to generate **2a** and $[\text{Fe}^{\text{I}}\text{Cl}(\text{dppe})_2]$, which then presumably reacts with



Scheme 9. Mechanism of the $[HFe^{I}Cl(dppe)_2]^-$-catalyzed reductive cyclization of **1a** (RI) to **2a** (R'H) in the presence of $NaBH_4$ in CH_3CN.

BH_4^- to regenerate $[HFe^{I}Cl(dppe)_2]^-$ (Scheme 9, step A′). However, a direct hydrogen-atom transfer from BH_4^- to the radical **4** cannot be excluded (Scheme 9, step B).[6a,20]

Overall, the results suggest that $NaBH_4$ is involved in a number of steps in the catalytic cycle, namely it can i) donate hydride to $[FeCl_2(dppe)_2]$ in the very first step of the catalytic reaction, ii) donate hydride to $[Fe^{I}Cl(dppe)_2]$ in a catalyst-turnover step of the catalytic cycle (step A′) if step A takes place, iii) transfer one electron[21] to $[HFe^{II}Cl(dppe)_2]$ to generate the key complex $[HFe^{I}Cl(dppe)_2]^-$, or iv) transfer a hydrogen atom to substrate-derived radical **4** (step B; Scheme 9).

In conclusion, we have shown that unsaturated organic halides undergo a radical-based cyclization in the presence of an iron catalyst and $NaBH_4$ as the stoichiometric reductant. Data from electrochemical investigations suggest that the reaction proceeds though activation of the halide substrate by electron transfer. This electron transfer is mediated by an anionic hydrido iron(I) species, which is generated by reduction of the iron(II) precatalyst by $NaBH_4$. Future work will focus on the use of other radical precursors and the incorporation of this inexpensive and environmentally friendly reaction into cascade and asymmetric reactions.

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[19] The fact that the reduction peak R_2 of $[HFe^{II}Cl(dppe)_2]$ increases upon the addition of increasing amounts of RI establishes that $[HFe^{II}Cl(dppe)_2]$ is generated at each catalytic cycle. This rules out an alternative mechanism involving an oxidative addition of RI to the 15-electron complex $[HFe^{I}Cl(dppe)]^-$, which can be formed upon dissociation of one dppe ligand from the 19-electron complex $[HFe^{I}Cl(dppe)_2]^-$. This oxidative addition would generate $[HFe^{III}R(I)(Cl)(dppe)]^-$, which would be in equilibrium with $[HFe^{III}R(Cl)(dppe)]$. An intramolecular carboferration reaction of the latter involving the C=C bond would generate, after C–H reductive elimination, the product R′H and $[Fe^{I}Cl(dppe)]$; the latter species could then be transformed into $[HFe^{I}Cl(dppe)_n]^-$ ($n = 1$ or 2) after reaction with $NaBH_4$; $[Fe^{I}Cl(dppe)]$ would not be transformed into $[HFe^{II}Cl(dppe)_2]$ because of the reducing conditions. This sequence of chemical steps involving Fe^{I}, Fe^{III}, and Fe^{I} species would not be consistent with the observed behavior of the reduction peak R_2 of $[HFe^{II}Cl(dppe)_2]$.

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Communications

Iron Catalysis

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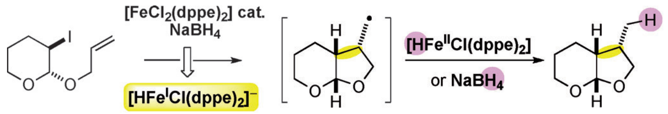
Iron-Catalyzed Reductive Radical Cyclization of Organic Halides in the Presence of $NaBH_4$: Evidence of an Active Hydrido Iron(I) Catalyst



Iron made'em: Iron(II) complexes such as $FeCl_2$ and $[FeCl_2(dppe)_2]$ (dppe = 1,2-bisdiphenylphosphinoethane) are efficient precatalysts for the radical cyclization of unsaturated iodides and bromides in the presence of $NaBH_4$ (see scheme). Cyclic voltammetry studies suggests that the reaction occurs through a radical mechanism via an anionic hydrido iron(I) species as the key intermediate for the activation of the substrates by electron transfer.