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Activation Strategies for Earth-abundant Metal Catalysis

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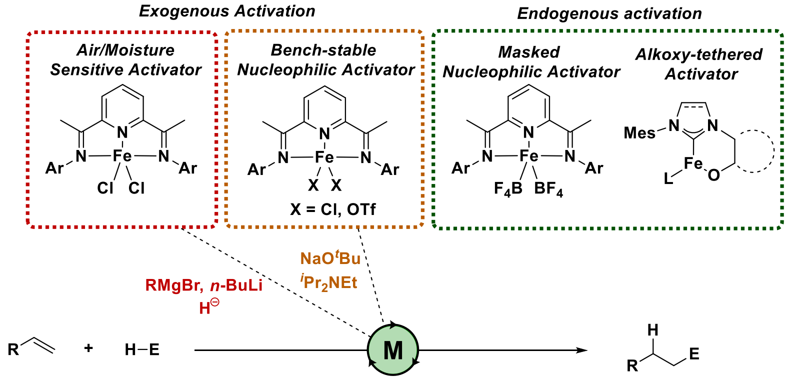

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Abstract The use of Earth-abundant metal-catalysed organic transformations has increased significantly in recent years. Where low oxidation-state catalysts are required, the *in situ* activation of metal(II/III) salts offers an operationally simple method to access these catalysts. Here we present the development of activation strategies from the use of reducing organometallic reagents to endogenous activation. Applications in alkene and alkyne hydrofunctionalisation reactions will be used to highlight the synthetic applications of the activation methods discussed.

1 Introduction
2 *in situ* Activation using Organometallic Reagents
3 *in situ* Activation using Non-organometallic Reagents
4 'Activator-Free' Systems
5 Conclusions

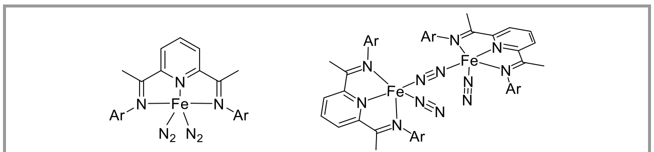
Key words alkene hydrofunctionalisation, low oxidation-state, activation, Earth-abundant metal catalysis

1. Introduction

Modern synthetic chemistry has been profoundly influenced by the use of organometallic catalysis, and is dominated by systems based on platinum-group metals.[1] Despite the huge success of precious metal systems, these catalytic processes suffer from long-term sustainability issues.[2] Firstly, the terrestrial deposits of platinum-group metals are rare, with major mines in Russia, South Africa and Montana, leading to price volatility and a lack of supply security.[3] The quantity of platinum-group metal exploitation declined by 20% between 2010 to 2015.[4] Secondly, platinum-group metals have high toxicity and the cost of removing these metals to low ppm levels from active pharmaceutical intermediates can be considerable.[5] These limitations have inspired the search for more sustainable and environmentally benign catalysts derived from Earth-abundant first-row transition metals such as iron, cobalt and manganese. However, many Earth-abundant catalytic protocols rely on the use of low oxidation-state precursors to facilitate productive catalysis.

Hydrofunctionalisation reactions are a class of reaction in which low oxidation-state Earth-abundant metal catalysts have been used as sustainable alternatives to late transition-metal catalysts. A number of strategies have been reported as a means to access these low oxidation-state species and enable successful chemical transformations.[6] This account will explore progress towards simple activation strategies for low oxidation-state Earth-abundant metal catalysis.

The potential application of Earth-abundant metal catalysis in hydrofunctionalisation reactions was shown by Chirik's seminal work using reduced analogs of Gibson[7a] and Brookhart's[7b] bis(imino)pyridine iron catalyst.[8] These low oxidation-state iron complexes were prepared by the reduction of the corresponding iron(II) complexes with strong reducing agents including sodium amalgam, sodium triethylborohydride and sodium naphthalene, under an atmosphere of nitrogen (**1**-**4**, Scheme 1).[9]



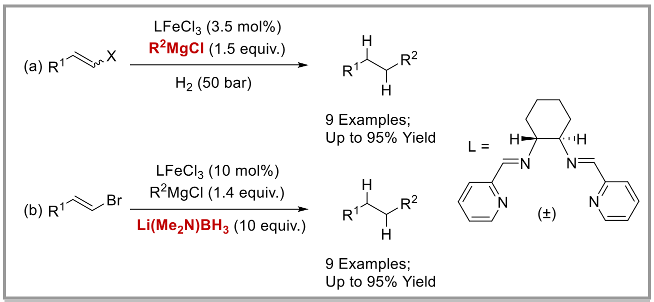
1 Ar = 2,6-$^{i}Pr_2$-C_6H_3
2 Ar = 2,6-Me_2-C_6H_3
3 Ar = 2,6-Me_2-C_6H_3
4 Ar = 2,6-Et_2-C_6H_3

Scheme 1 Examples of bis(imino)pyridine iron(0) dinitrogen complexes **1**-**4** used in alkene hydrofunctionalisation reactions developed by Chirik.

2. *in situ* Activation using Organometallic Reagents

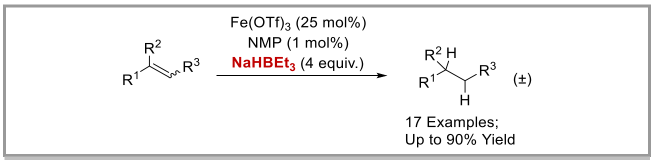
Despite the high reactivity achieved using well-defined low oxidation-state complexes, the translation of these systems to an industrial scale remains challenging. The highly air- and moisture sensitive nature of these low oxidation-state complexes requires special preparation and handling techniques. To overcome these limitations, *in situ* activation strategies have been developed.[6a-d, 10] This enables the use of iron(II/III) or cobalt(II/III) halide complexes by use of a strongly reducing reagent to generate the low oxidation-state species *in situ* which can then catalyse the reaction.

We began in this area by identifying a common low oxidation-state iron species in cross-coupling and hydrogenation reactions. We postulated that these common low oxidation-state species could be exploited in a tandem cross-coupling-hydrogenation reaction to remove the need to prepare the challenging formally iron(0) hydrogenation pre-catalysts. We were able to successfully perform a one-pot reductive cross-coupling of vinyl halides and Grignard reagents under hydrogen, by *in situ* generation of a low oxidation-state iron catalyst (Scheme 2a).[11] Grignard reagent was used in to act as both the pre-catalyst activating agent and also the nucleophilic coupling partner. We also investigated this iron pre-catalyst and Grignard activation in hydride-mediated reductive cross-coupling reactions (Scheme 2b).[12] β-Halostyrene derivatives were coupled with Grignard reagents using iron(III) chloride and a tetradentate ligand and the intermediate alkene reduced *in situ* to an alkane using superstoichiometric lithium aminoborohydride.



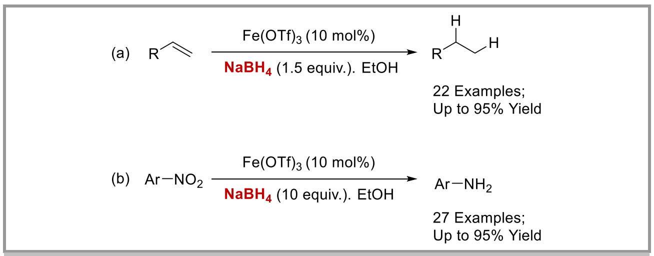
Scheme 2 (a) Iron-catalysed reductive cross-coupling of vinyl halides and Grignard reagents. (b) Iron-catalysed, hydride-mediated reductive cross-coupling of vinyl halides and Grignard reagents.

The iron-catalysed reduction of alkenes and alkynes was performed using sodium triethylborohydride as the stoichiometric hydride source.[13] The system was active for the formal hydrogenation of aryl- and alkyl alkenes and internal alkenes (Scheme 3). However, an attempt to make this reaction enantioselective by the replacement of the NMP with enantiopure ligands was not successful. Deuterium labelling experiments showed that both hydrogen atoms originated in the borohydride reagent.



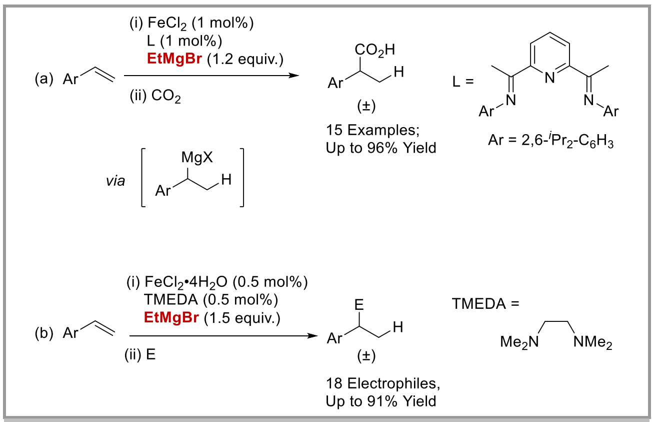
Scheme 3 Iron-catalysed, $NaHBEt_3$-mediated, formal hydrogenation of alkenes.

In a further simplification, we used air- and moisture stable iron(III) salts and sodium borohydride, in ethanol for the formal hydrogenation of terminal alkenes (Scheme 4a).[14] Use of radical traps completely inhibited alkene hydrogenation, but no trapped substrate was observed, indicating irreversibly binding to the catalyst. Deuterium labelling studies indicate that this reaction proceeds by an ionic rather than radical mechanism, but offer little information on either the identity of the catalytically active species or the mechanism of hydrogenation. A number of nitroarenes and heteroarenes were also successfully reduced using these simple reaction conditions (Scheme 4b).



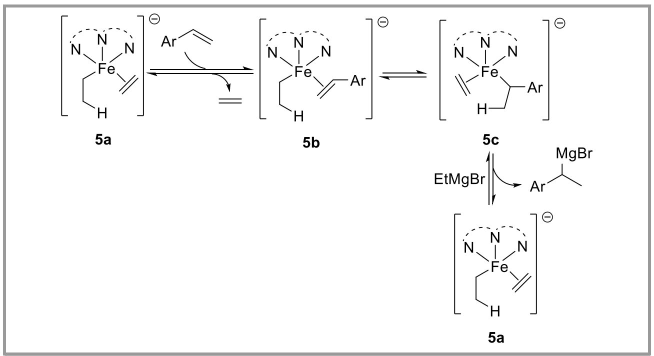
Scheme 4 (a) Iron-catalysed formal hydrogenation of alkenes using $Fe(OTf)_3$ and $NaBH_4$. (b) Iron-catalysed formal hydrogenation of nitroarenes using $Fe(OTf)_3$ and $NaBH_4$.

We reported an iron-catalysed formal hydrocarboxylation of styrene derivatives using stoichiometric ethyl magnesium bromide as the hydride source and *in situ* activator. proceeded by the hydromagnesiation of styrene derivatives to form a nucleophilic benzylic Grignard reagent (Scheme 5a).[15] The reaction gave the carboxylic acid products in excellent yields and regioselectivities. We also reported a simplified version of this procedure using tetramethylethylenediamine (TMEDA) instead of bis(imino)pyridine, which was applied to the reaction of 18 different electrophiles (Scheme 5b).[16]



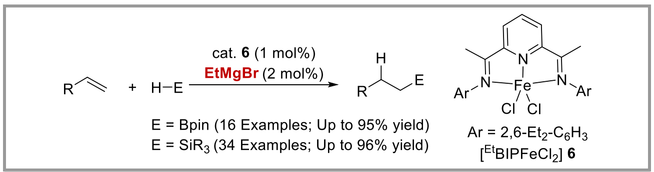
Scheme 5 (a) Iron-catalysed hydrocarboxylation of styrenes, using stoichiometric EtMgBr as hydride donor and activator. (b) The application of hydromagenesiation to the formal hydrofunctionalisation of aryl alkenes with different electrophiles.

After much effort, a formally Fe(0) 'ate' species $[^{iPr}BIPFe(Et)(ethene)]^{-1}$ **5a** was identified as the resting state in the hydromagnesiation. In contrast to our originality proposed iron-hydride intermediate, it was determined that a β-hydride of an ethyl ligand was the active hydrometallation species. The $[^{iPr}BIPFe(Et)(ethene)]^{-1}$ complex **5a** could loss ethylene and transiently coordinate the styrene derivative and mediate a rapid and reversible direct β-hydride transfer to give the benzylic iron species **5c**, negating the necessity of a discrete iron hydride intermediate. Catalyst turnover was achieved by transmetallation with ethylmaganesium bromide to regenerate $[^{iPr}BIPFe(Et)(ethene)]^{-1}$ **5a** and the benzylic Grignard reagent.[17]



Scheme 6 Proposed reaction mechanism for iron-catalysed hydromagenesiation of styrene derivatives

We next sought to identify an alternative hydride source to replace ethyl magnesium bromide and further simplify the hydromagnesiation reaction. When attempting to use silane (H-Si) or borane (H-B) reductants, we noted that instead of hydromagenesiation we observed hydrosilylation and hydroboration, respectively (Scheme 7).[18] A bis(imino)pyridine iron(II) complex **6** was *in situ* activated using substoichiometric ethylmagnesium bromide or *n*-butyllithium to generate a low oxidation-state active iron species, which catalysed the hydrofunctionalisation reactions.

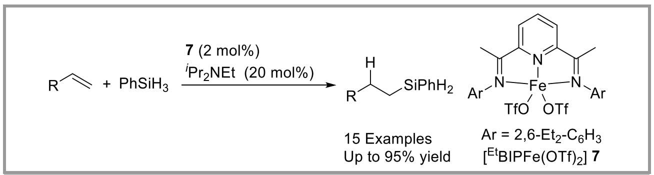


Scheme 7 Iron-catalysed *anti*-Markovnikov selective hydroboration, hydrosilylation and hydrogermylation using *in situ* activation by EtMgBr

3. *in situ* Activation using Non-organometallic Reagents

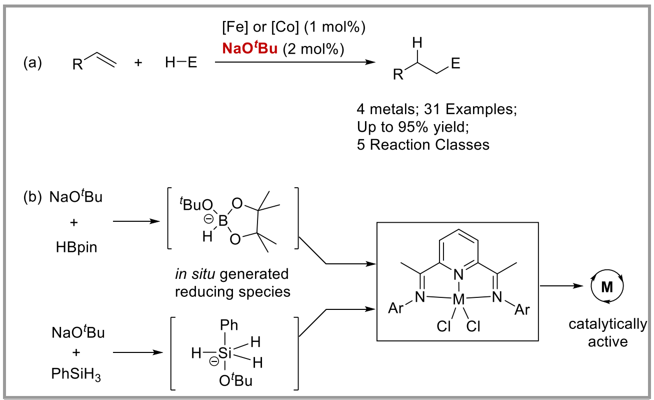
Although many strategies have been developed using organometallic activators, the air- and moisture sensitivity of the organometallic activators limits adoption by the wider community. Ideally, the development of activation strategies using readily available, bench-stable and easily-handled reagents as activators, instead of pyrophoric organometallic reagents, would allow access to low oxidation-state Earth-abundant metal catalysis in a highly operationally simple and safe manner.

We reported that the bis(imino)pyridine iron(II) triflate pre-catalyst **7**, could be activated *in situ* with a tertiary amine (Hünig's base) to catalyse the hydrosilylation of alkenes and alkynes (Scheme 8).[19] Significantly, these reactions proceeded in equal yield under air and inert reaction conditions. The use of triflate counterions was demonstrated to be crucial to the *in situ* generation of the active catalyst as the weak binding affinity of the anion makes the iron(II) precursor amenable to the amine-induced activation. Amines have been reported to reduce late transition metal complexes by coordination and *β*-hydride elimination.[20] However, the products of such a reaction, such as an aldehyde or imine, were not observed. In addition, no direct evidence for the formation of a silicon 'ate' complexes could be obtained.



Scheme 8 Iron-catalysed hydrosilylation reaction using *in situ* activation by Hünig's base.

In an attempt to minic the hydride transfer seen in the hydromagnesiation reaction, we next explore non-organometallic activating reagents bearing available *β*-hydrogens. Serendipity and an excellent PhD student led to the discovery of alkoxide activation.[21, 22] We found that commercially available, bench-stable and non-toxic alkoxide salts offered a generic activation strategy for Earth-abundant metal complexes across a range of transformations (Scheme 9a).[19] The activation was shown to proceed through the *in situ* generation of a hydridic boron or silicon 'ate' complex, which were observed by ^{11}B and ^{29}Si NMR spectroscopy, respectively. The boron or silicon 'ate' complexes activated the pre-catalyst by hydride transfer and reduction (Scheme 9b).



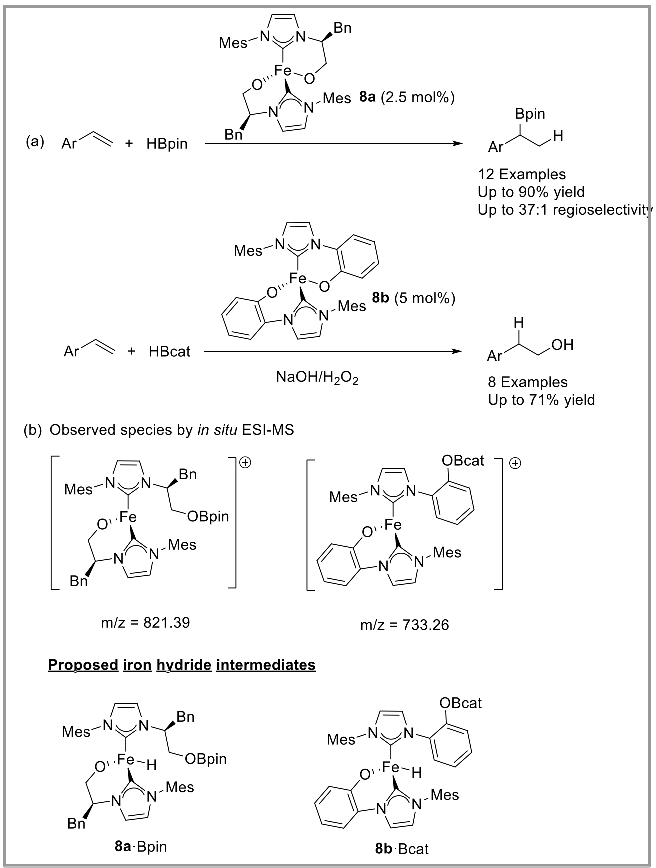
Scheme 9 (a) Earth-abundant metal-catalysed hydrofunctionalisation reactions using *in situ* activation by NaO^{t}Bu. (b) Proposed pre-catalyst activation pathway, by the generation of hydridic boron or silcon 'ate' species.

Using a combination of an alkoxide salt and pinacolborane allowed iron and cobalt pre-catalysts to be applied across hydrovinylation, hydrogenation and [2π+2π] cycloaddition reactions. We used the alkoxide activation to develope a cobalt-catalysed Markovnikov selective hydroboration of aryl alkenes[23] and a manganese-catalysed hydrofunctionalisation of alkenes.[24] Moreover, this activation protocol was applied to a number of Earth-Abundant metal-catalysed industrially relevant transformations.[25]

4. 'Activator-Free' Systems

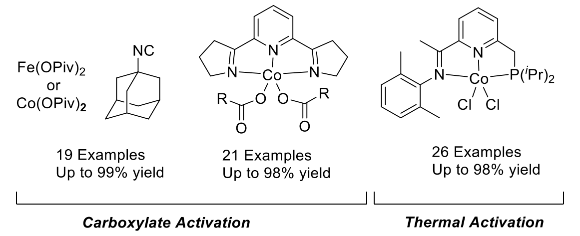
'Activator-free' hydrofunctionalisation systems have recently been reported, in which Earth-abundant metal pre-catalysts undergo activation without the need for external activators. This represents the state-of-the-art for Earth-abundant metal catalysis. Metal complexes bearing nucleophilic ligands are generally used in these 'activator-free' systems.

We developed a regioselective alkene hydroboration using two alkoxy-tethered NHC iron(II) complexes (Scheme 10a).[26] These iron(II) complexes **8a-b** were designed with aryl- or alkyl-oxy anions, which would react with borane (H-B) to give hydridic boron 'ate' complex and activate the pre-catalyst. This was supported by *in situ* reaction monitoring using mass spectrometry, in which the borylated iron complexes **8a**·Bpin, and **8b**·Bcat were observed (Scheme 10b). It was proposed that these species were derived from the corresponding iron hydride complexes. Markovnikov selective alkene hydroboration with pinacolborane was achieved for the first time using an iron(II) catalyst **8a**. *anti*-Markovnikov selective alkene hydroboration was observed using catecholborane and a modified ligand backbone.

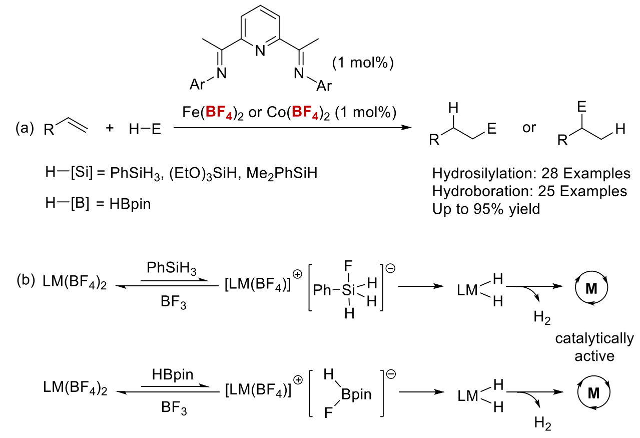


Scheme 10 (a) Iron-catalysed regiodivergent alkene hydroboration without the need for an external activator (b) *in situ* Reaction monitoring by ESI-MS

Iron- and cobalt carboxylate salts have been shown to act as pre-catalysts for 'activator free' alkene hydrosilylation.[27] Similarly, a tridentate PNN-cobalt(II) dichloride pre-catalyst could be *in situ* activated at elevated temperature for alkene hydrosilylation.[28] The carboxylate and thermal activation protocols were proposed to proceed by a σ-bond metathesis reaction between the metal carboxylate and silane (Scheme 11). We took a different approach and used tetrafluoroborate salts. We proposed that using tetrafluroborate counterion enable the pre-catalyst activation by release of fluoride for regiodivergent hydrosilylation and *anti*-Markovnikov hydroboration reactions were carried out without the need for an external activator, thus simplifying the procedure of hydrofunctionalisation reactions (Scheme 12a).[29] This endogenous activation was shown to proceed by the dissociation of fluoride from the metal tetrafluoroborate pre-catalysts, which led to the formation of a hydridic boron or silicon 'ate' complex. The 'ate' complex activated the metal pre-catalyst by hydride transfer, generating a metal hydride complex, which was followed by reductive elimination to generate the low oxidation-state species to catalyse the reaction (Scheme 12b).[27]



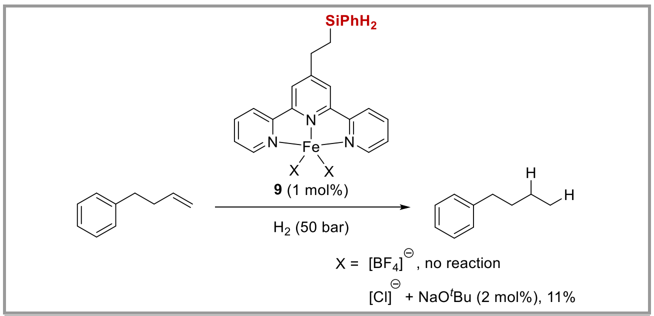
Scheme 11 Endogenous activation with iron- and cobalt complexes.



Scheme 12 (a) Iron- or cobalt-catalysed regiodivergent hydrosilylation and hydroboration of alkenes, using tetrafluroborate metal salts and bis(imino)pyridine ligands. (b) Proposed tetrafluroborate activation: hydridic 'ate' complex formation to reduce metal complex.

The use of the tetrafluoroborate activation as a general platform to access low oxidation-state, catalytically active species, was also investigated. The combination of tetrafluoroborate pre-catalysts and a hydrofunctionalisation reagent, such as phenylsilane and pinacolborane, produced a hydridic 'ate' complex, which gave a low oxidation-state catalyst capable of hydrogenation, [2π+2π] cycloaddition and C-H borylation reactions.

All the previously mentioned activation strategies proceed by the reaction of external hydride source (borane or silane) with either an external activator or internal activator to generate hydride species used to reduce iron- and cobalt pre-catalysts. A limitation of these strategies is the need for a reagent containing Si-H or B-H bonds to enable pre-catalyst activation. A more ideal scenario enables activation without the need of any external hydride. We proposed that a self-activating catalysis system could be achieved by incorporating hydride source onto the ligand and using iron and cobalt salts with nucleophilic counter ions. However, our initial investigations into this area have been hindered by challenging ligand syntheses and low reactivity (Scheme 13). ^{SiPhH2}TerpyFeCl$_2$ **9** was prepared with a SiH_2Ph group incorporated onto the terpyridine ligand. Endogenous activation failed, and even the addition of an alkoxide activator gave only low yields in alkene hydrogenation reactions.[30] However, the need to incorporate a silane of borane into a ligand severely limits this strategy going forward. Thus, there are still significant hurdles to overcome and novel synthetic strategies needed towards developing self-activating systems outwith hydroelementation reactions.



Scheme 13 Iron-catalysed hydrogenation of 4-phenyl-1-butene without using external hydride source

5. Conclusions

There are a growing number of methods using Earth-abundant metal catalysts, most commonly accessing low oxidation-state species to perform industrially relevant transformations. We report the evolution of activation protocols to access low oxidation-state active species. Iron(II) and cobalt(II) pre-catalysts are commonly activated by reduction using organometallic reducing agents. Once accessed, the low oxidation-state species have shown excellent catalytic activity across several hydrofunctionalisation reactions. However, organometallic reducing agents pose a barrier to wider use due to the need for specialist handling and high flammability. To overcome these limitations, we, and others, have developed a new class of safe, easy-to-handle and bench stable alternatives. Activators such as alkoxide salts and amines have enabled easier use of Earth-abundant metals for catalytic applications. In a further simplification endogenous activation protocols are now being developed, where the metal counter ions act as the nucleophilic activator, using both iron- and cobalt pre-catalysts. We have used iron and cobalt tetrafluoroborate salts in this context where a 'masked' fluoride was found to initiate pre-catalyst activation. Although these endogenous activation strategies offer excellent reactivity, they still require a reagent or additive with a hydridic bond. The next challenge will be to overcome this and develop pre-catalysts that undergo 'self-activation' by incorporating both the nucleophilic and hydridic elements of activation.

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Biosketches

	Jingying Peng was born in Harbin, China. She studied Applied Chemistry at East China University of Science and Technology, China, graduating in 2015. She went to Queen's University Belfast as a visiting student from September 2014 to June 2015. She moved to University of Edinburgh doing a Master by research in September 2016, funded by Tercentenary International Scholarship. Then she started her PhD in September 2016, funded by University of Edinburgh and China Scholarship Council under the supervision of Dr. Stephen Thomas. Her research are focused on developing Earth-Abundant metal catalysts for carbon-boron and carbon-carbon bond forming reactions.
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