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Chemo-, regio-, and stereoselective iron-catalysed hydroboration of alkenes and alkynes†‡

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The highly chemo-, regio-, and stereoselective synthesis of alkyl- and vinyl boronic esters with good functional group tolerance has been developed using *in situ* activation of a bench-stable iron(II) pre-catalyst and pinacolborane (16 examples, 45–95% yield, TOF up to 30 000 mol h^{-1}). The first iron-catalysed alkene hydrogermylation is also reported.

Boronic acid derivatives have become ubiquitous in chemical synthesis. The facile stereospecific transformation of these diversely functionalised building blocks into a wide variety of functional groups has made them key intermediates in organic syntheses.[1] Alkyl boronic esters are generally easy to isolate, purify and store, and can be used in a wide variety of transformations including Suzuki–Miyaura cross-coupling reactions for the generation sp^3–sp^2 C–C bonds (Fig. 1).[2] Alkyl boronic esters are commonly prepared by reaction of alkyllithium and magnesium reagents with a boron source;[1a] however these methods are limited by poor functional-group tolerance and atom economy. Transition-metal-catalysed processes have the potential to overcome these problems. Direct borylation of alkanes using Rh, Ir, Ru, and Re catalysts under photochemical or thermal conditions has been reported,[3] but these methods can suffer from forcing reaction conditions. Rhodium and iridium complexes are known to catalyse the addition of catechol- and pinacolborane to olefins under mild conditions, and with good functional group tolerance.[4] Many regio- and enantioselective examples have been reported,[4,5] however competitive dehydroboration,[6] and the relative instability of catecholborane[5b,7] can effect synthetic utility. The copper-catalysed synthesis of alkyl boronic esters from primary and secondary alkyl halides has been reported with good functional group tolerance,[2e] however long reaction times, excess B_2pin_2, and relatively high catalyst loadings were required.

Iron offer significant advantages as a catalyst due to its low toxicity, low cost, natural abundance and sustainable long-term commercial availability.[8] Ritter reported the 1,4-hydroboration of terminal 1,3-dienes using an iron(II) iminopyridine complex, which was reduced to an active catalyst *in situ* using elemental magnesium.[9] Good to excellent regioselectivity and excellent stereoselectively were demonstrated. Enthaler has shown that $Fe_2(CO)_9$ can catalyse the hydroboration of terminal and internal alkynes with pinacolborane to give vinyl boronic esters in up to 99 : 1 dr.[10] Recently, Huang[11] and Chirik[12] have reported the iron-catalysed hydroboration of alkenes using pinacolborane. Huang found that a bipyridyl phosphine iron(II) complex activated with sodium triethylborohydride produced a highly active catalyst for the hydroboration of terminal, and 1,1-disubstituted alkenes. Chirik reported that bis(imimo)pyridine iron(0) bis(dinitrogen) complexes[13] would catalyse the addition of pinacolborane to terminal-, 1,1- and 1,2-disubstituted alkenes. Functional group tolerance has been demonstrated for tertiary amine, silyl, ether, acetal and tosyl-protected alcohol substrates; however both methods suffer from the use of highly air- and moisture sensitive pre-catalysts.

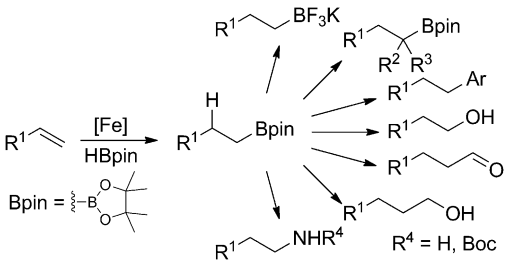

Fig. 1 Selected synthetic transformations of alkylboronic esters.[1,2]

Herein we report the iron-catalysed hydroboration of alkenes and alkynes using a bench stable iron(II) pre-catalyst and pinacolborane to give alkyl and vinyl boronic esters directly. Iron(II) salts are reduced to highly active, low-valent species by reaction with a Grignard reagent,[14] which we speculated may provide simple access to catalysts for hydroboration. Using 4-phenylbutene as a model substrate, initial studies focussed on hydroboration using pinacolborane (HBpin), bis(imino)pyridine iron(II) complex [**1**-$FeCl_2$][15] (5 mol%), and tolylmagnesium

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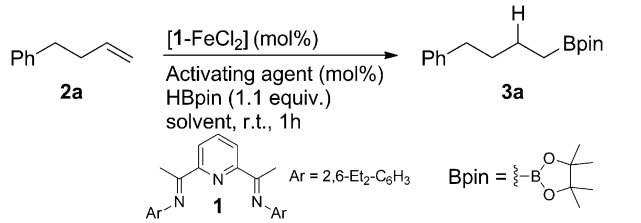
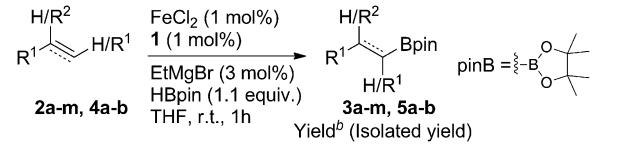
Table 1 Optimisation of iron-catalysed hydroboration: solvent and activating agent[a]

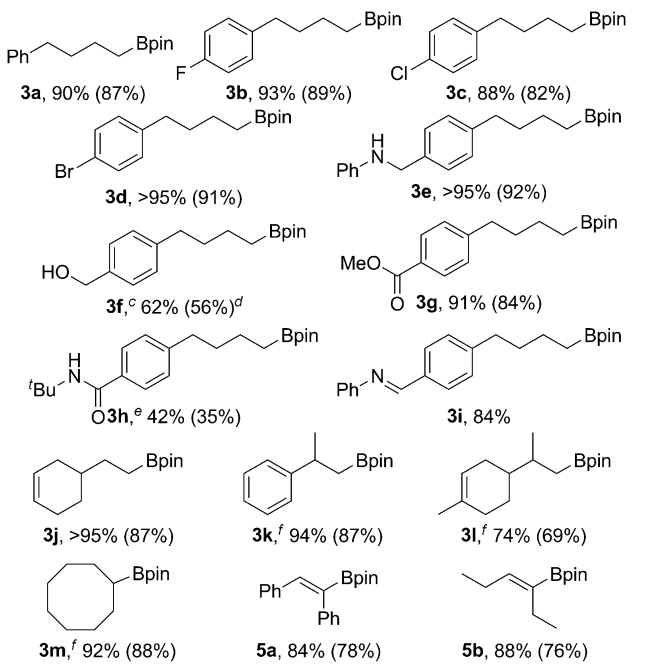


Entry	[Fe] (mol%)	Activating agent (mol%)	Solvent	Yield[b] (%)
1	5	TolMgBr (5)	THF	18
2	5	TolMgBr (10)	THF	92
3	5	TolMgBr (15)	THF	91
4	5	TolMgBr (25)	THF	52
5[c]	1	EtMgBr (3)	THF	90
6[c]	1	TolMgBr (3)	THF	89
7[d]	1	*n*-BuLi (3)	Toluene	92
8[e]	0.2	*n*-BuLi (0.6)	'Solvent-free'	94[f]

[a] Conditions: 4-phenylbutene (0.7 mmol), [**1**-$FeCl_2$] (5 mol%), activating agent (*x* mol%), HBpin (1.1 equiv.), solvent (0.25 M), 1 h, r.t. [b] Yield determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [c] $FeCl_2$ (1 mol%) and **1** (1 mol%) complexed *in situ* in place of [**1**-$FeCl_2$]. [d] [**1**-$FeCl_2$] (1 mol%). [e] Conditions: 4-phenylbutene (7.33 mmol), [**1**-$FeCl_2$] (0.2 mol%), *n*-BuLi (0.6 mol%), HBpin (1.1 equiv.), 1 min, r.t. [f] Isolated yield (1.80 g).

Table 2 Iron-catalysed hydroboration of olefins: scope and functional group tolerance[a]

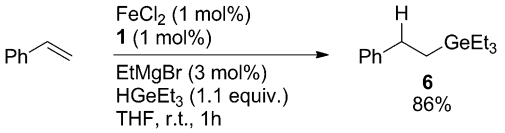




[a] Conditions: olefin (0.7 mmol), $FeCl_2$ (1 mol%), **1** (1 mol%), EtMgBr (3 mol%), HBpin (1.1 equiv.), THF (0.25 M), 1 h, r.t. [b] Yield determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard, isolated yield given in parentheses. [c] TolMgBr (105 mol%) used. [d] Product isolated as the diol following oxidation. [e] $FeCl_2$ (5 mol%), **1** (5 mol%), EtMgBr (15 mol%) used. [f] Conditions: olefin (0.7 mmol), [**1**-$FeCl_2$] (1 mol%), *n*-BuLi (3 mol%), HBpin (1.1 equiv.), 1 h, r.t.

bromide (TolMgBr) as activating agent in tetrahydrofuran. Using 5 mol% TolMgBr gave only a low yield of the linear boronic ester **3a** (Table 1, entry 1); however 10 and 15 mol% TolMgBr gave the linear boronic ester **3a** directly in excellent yield and complete regioselectivity (entries 2 and 3). Use of 25 mol% TolMgBr, led to a decreased yield of **3a** (entry 4). The system was equally active using 1 mol% pre-catalyst, which could be prepared *in situ* by simple combination of $FeCl_2$ (1 mol%) and free bis(imino)pyridine ligand **1** (1 mol%) prior to the addition of substrate and activator. Activation with EtMgBr (3 mol%) gave equal results to that using TolMgBr (entries 5 and 6). To demonstrate increased industrial applicability, the hydroboration was developed to operate in both toluene and under 'solvent-free' conditions.[16] A suspension of iron complex [**1**-$FeCl_2$] (1 mol%) in either toluene, or neat alkene,[17] could be activated for alkene hydroboration by the addition of *n*-BuLi (3 mol%) (entry 7). Using 'solvent-free' reaction conditions, the gram-scale hydroboration of 4-phenylbutene **2a** with pinacolborane was complete within 1 minute using just 0.2 mol% catalyst, corresponding to a catalyst turnover frequency of 30 000 mol h^{-1} (entry 8). To the best of our knowledge this represents the most efficient iron catalyst reported to date for the hydroboration of olefins. Activation (reduction) of the iron(II) pre-catalyst [**1**-$FeCl_2$] using TolMgBr allowed the average oxidation state of iron to be calculated by quantifying the formation of bitolyl. Maximum catalytic activity corresponded to an average oxidation state of iron(I).[18,19]

The functional group tolerance of the hydroboration was then investigated using the *in situ* complexation of $FeCl_2$ (1 mol%) and **1** (1 mol%) in tetrahydrofuran, and activation with EtMgBr (3 mol%) (Table 2). Aryl fluoride, chloride and bromide substituted alkenes **2b–d** were tolerated under the reaction conditions giving linear boronic esters **3b–d** in excellent yield and regioselectivity, with no cleavage of the aryl-halide bond observed.[14b,20] Unprotected amine **2e** and alcohol **2f** were successfully hydroborated, and gave linear boronic esters **3e** and **3f** with complete control of regiochemistry and in excellent and moderate yield, respectively. Substrates containing more than one unsaturated group were then investigated. Ester substituted alkene **2g** was chemoselectively hydroborated in excellent yield and regioselectivity, with no observed C–O bond cleavage,[21] or ester reduction. Secondary amide **2h** reacted to give only a moderate yield of the linear boronic ester **3h**, along with unreacted starting material, suggesting catalyst deactivation. Aldimine substituted alkene **2i** was chemoselectively hydroborated at the alkene, with less than 10% aldimine reduction observed. 4-Vinylcyclohexene **2j** was also chemoselectively hydroborated at the terminal alkene giving linear boronic ester **3j** in excellent yield and regioselectivity, with the internal alkene intact. Using 'solvent-free' reaction conditions, 1,1- and 1,2-disubstituted alkenes were also suitable substrates for hydroboration. Boronic esters **3k–m** were isolated in good to excellent yield, and in the case of **3k** and **3l** with perfect regioselectivity for the linear boronic ester product.



Scheme 1 Iron-catalysed hydrogermylation of styrene.

The developed methodology was also applied to the hydroboration of alkynes. (*Z*)-Vinyl boronic esters **5a** and **5b** were stereoselectively synthesised in excellent yield within one hour, with no observed *anti*-addition of pinacolborane, representing the most active and stereoselective iron catalyst reported for the hydroboration of alkynes.

Finally, the developed methodology was applied to the hydrogermylation of styrene using commercially available triethylgermanium hydride, giving the linear hydrogermylation product **6** in 86% isolated yield and with complete control of regiochemistry (Scheme 1). To the best of our knowledge, this is the first example of an iron-catalysed alkene hydrogermylation,[22] but more significantly illustrates the generality of this iron catalyst in the activation of small molecules, and indicates the potential for further synthetic applications.

In summary, we have reported a highly functional group tolerant, operationally simple, chemo-, regio- and stereoselective iron-catalysed hydroboration of alkenes and alkynes, which uses just 1 mol% iron catalyst [$FeCl_2$ (1 mol%), ligand **1** (1 mol%)] and 1.1 equivalents of pinacolborane at room temperature. All reagents used were commercially available, easy to handle and store, and the active iron catalyst was generated *in situ*. Terminal, 1,1- and 1,2-disubstituted aryl and alkyl alkenes and alkynes bearing an unprecedented diversity of functional groups were successfully hydroborated with excellent control of all aspects of selectivity (chemo, regio and stereochemistry). The methodology was shown to operate under 'solvent-free' conditions and on gram-scale, improving industrial applicability and the ease of product isolation. Preliminary mechanistic experiments suggest that an iron(I) catalyst may be formed under the reaction conditions. The use of an *in situ* generated iron catalyst greatly simplifies practical requirements, and should allow the non-expert to fully utilise this synthetic methodology.

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