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 stereoselective 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 alkyl lithium and magnesium reagents with a boron source; 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 alkenes 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 $^5$ 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,$^7$ however long reaction times, excess B$_2$pin$_2$, 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 alkenes 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 alkene using pinacolborane. Huang found that a bipyridyl phosphate 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(imino)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.

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 [I-FeCl$_2$]$^{15}$ (5 mol%), and tolylmagnesium...
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 1 (1 mol%) complexed in situ in place of [FeCl$_2$]$_2$.[17] [FeCl$_2$] (1 mol%). Conditions: 4-phenylbutene (7.33 mmol), [FeCl$_2$] (1 mol%), -BuLi (3 mol%), HBpin (1.1 equiv.), solvent (0.25 M), 1 h, r.t. Yield determined by $^1$H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. FeCl$_2$ (1 mol%) and 1 (1 mol%) complexed in situ in place of [FeCl$_2$]$_2$. FeCl$_2$ (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. A suspension of -BuLi (0.6 mol%), HBpin (1.1 equiv.), 1 min, r.t. Isolated yield (1.80 g).

<table>
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<th>Entry</th>
<th>[Fe] (mol%)</th>
<th>Activating agent (mol%)</th>
<th>Solvent</th>
<th>Yield$^b$ (%)</th>
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<td>-BuLi (3)</td>
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<td>92</td>
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<tr>
<td>8$^d$</td>
<td>0.2</td>
<td>-BuLi (0.6)</td>
<td>-‘Solvent-free’</td>
<td>94$^f$</td>
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</table>

$^a$ Conditions: 4-phenylbutene (0.7 mmol), [FeCl$_2$] (5 mol%), activating agent (x mol%), HBpin (1.1 equiv.), solvent (0.25 M), 1 h, r.t. Yield determined by $^1$H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. $^b$ Isolated yield (1.80 g).

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. 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 3g was chemoselectively hydroborated in excellent yield and regioselectivity, with no observed C–O bond cleavage, 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% aldime 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.
Notes and references


17 In situ complexation of FeCl2 and I1 in toluene or neat alkoine not possible due to the low solubility of the Fe(a) complex.

18 See ES1 for further details.


