Markovnikov-Selective, Activator-Free Iron-Catalyzed Vinylarene Hydroboration

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Supporting Information Placeholder

ABSTRACT: Two series of structurally related alkoxy-tethered NHC iron(II) complexes have been developed as catalysts for the regioselective hydroboration of alkenes. Significantly, Markonikov selective alkene hydroboration with HBpin has been controllably achieved using an iron catalyst (11 examples 35-90% isolated yield) with up to 37:1 branched:linear selectivity. *anti*-Markovnikov selective alkene hydroboration was also achieved using HBcat and modification of the ligand backbone (6 examples, 44-71% yields). In both cases, ligand design has enabled activator-free low oxidation-state iron catalysis.

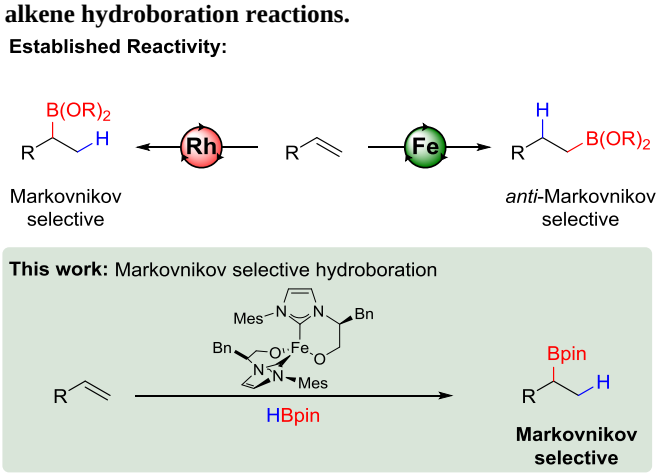
Keywords: ***iron, catalysis, hydroboration, Markovnikov selectivity, NHC ligands***

Boronic esters are ubiquitous in chemical synthesis due to the vast number of bond-forming reactions able to selectivity transform these stable reagents into a wide-range of functionalities.[1–4] The hydroboration of alkenes using boranes is a well-established method for the synthesis of alkyl boranes, which can be converted to the bench-stable boronic esters in a straightforward manner.[5,6] In contrast, the hydroboration of alkenes using boronic esters leads directly to the alkyl boronic esters, but requires the use of a precious metal catalyst, most commonly rhodium (Scheme 1).

Although high chemoselectivity, regioselectivity and enantioselectivity can be achieved using precious-metals,[7–9] there is still limited precedent for the direct generation of bench-stable pinacol boronic esters by use of pinacol borane (HBpin),[10–12] and precious metals suffer from inherent toxicity, cost and sustainability concerns. To address these concerns, earth abundant metal species have been developed as potential alternatives.[13,14]

A number of iron catalysts have been developed for the hydroboration using HBpin, or formal hydroboration using B_2Pin_2 and an alkoxide, of alkene and alkynes to give the pinacol boronic esters directly (Scheme 1).[15–24] In all cases these hydroboration reactions are either highly *anti*-Markovnikov selective or give the Markovnikov product as a mixture with the *anti*-Markovnikov product. Recently reported by Webster and coworkers, the highest Markovnikov:*anti*-Markovnikov selectivity ranges from 60:40 to 70:30 for styrene derivatives.[23] Thus, there is a clear need for earth abundant metal-catalyzed hydroboration reactions that proceeds with Markovnikov selectivity.[25,26,27]

Scheme 1. The current state-of-the-art in metal-catalyzed alkene hydroboration reactions.

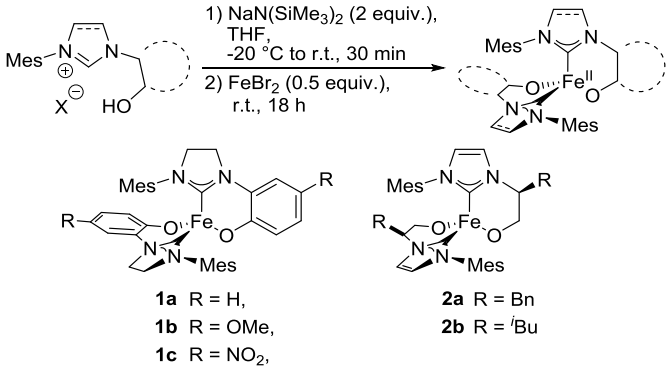


To this end, we sought to develop a Markovnikov selective iron-catalyzed hydroboration reaction. Ideally, this would be achieved using operationally simple conditions: easily handled reagents and without the need for an external activator. As part of our continuing research efforts on the development of novel activation modes for earth abundant metal pre-catalysts, and given that alkoxy-tethered NHC ligands have been reported for the hydrosilylation of carbonyl derivatives,[28,29] we postulated that ligand assistance could be used to enable both pre-catalyst and boronic ester activation.

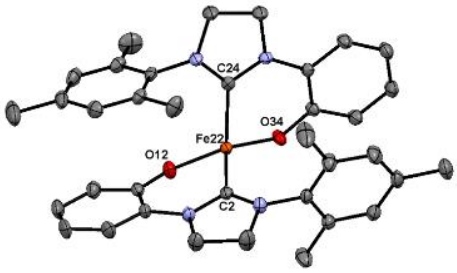
Three aryloxy-functionalized imidazolinium salts were synthesized,[30] along with two alkoxy-functionalized imidazolium salts produced using a one-pot protocol.[31] These were deprotonated and reacted with $FeBr_2$ to give the five iron(II) complexes **1a-c** and **2a**, **b**, respectively (Scheme 2).[32,33] It is worth noting at this point, that even with ligand synthesis, these iron catalysts were prepared in 2-steps and at considerably less cost than even commercially available Wilkinson's catalyst.[34]

Single-crystal X-ray analysis revealed that these bis-ligated complexes all adopted a similar distorted tetrahedral structure featuring an anchoring iron-carbene bond and the potentially activating group in the Fe-O motif (see ESI for details).

Scheme 2. Synthesis of novel Fe(II) complexes 1a-c and 2a,b. Molecular structure of 1a.



1a

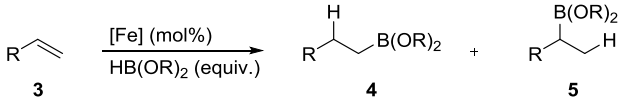


50% probability ellipsoids; Hydrogen atoms and solvent molecules omitted for clarity; Grey = C, Blue = N, Red = O, Orange = Fe. CCDC 1487368-1487371 contains the supplementary crystallographic data for complexes **1a-c** and **2a**.

Initial investigations into alkene hydroboration found success using catecholborane (HBcat). HBcat is known to perform alkene hydroboration at elevated temperatures, but the reaction proceeds only very slowly at room temperature (Table 1, Entry 1).[35,36] In the presence of HBcat, complexes **1a-c** were shown to be catalytically active for the linear hydroboration of terminal alkenes in THF at room temperature (Entry 2, see ESI for further details). Using 5 mol% of aryloxy-tethered NHC-Fe^{II} complex **1a** the *anti*-Markovnikov hydroboration product **4** was obtained, following oxidation to give the linear alcohol **6a**,[10] in 81% yield. Interestingly, variation of the electronic character of the aryloxy-substituent on the catalyst led to diminished hydroboration yields (see ESI for further details). Alkoxy-tethered NHC-Fe^{II} complexes **2a**, **b** were considerably less active under these conditions (Entry 3, see ESI for further details).

Initial testing of aryloxy- and alkoxy-tethered NHC-Fe^{II} complexes **1a-c** and **2a**, **b** for alkene hydroboration using pinacolborane (HBpin) resulted in alkene isomerization and hydrogenation only (Table 1, entries 4 and 5, for full details see ESI). By performing the hydroboration of styrene derivatives with HBpin in the absence of solvent, mixtures of the secondary **5** and primary **4** alkylboronic ester products could be obtained (Entries 6-9, see ESI for further details). Significantly, the Markovnikov (branched) product was favored in all cases. Alkoxy-tethered NHC complex **2a** gave the best Markovnikov selectivity and yield of the secondary hydroboration product **5** (Entries 7). Yields of the secondary boronic ester **5** could be increased for aryloxy-tethered NHC complex **1a**, but only by performing the reactions in an excess of the styrene derivative (Entry 8). This was not necessary for alkoxy-tethered NHC complex **2a** which gave synthetically useful isolated yields of the secondary boronic ester product using 1.25 equivalents of HBpin (Entry 9). Further variation of HBpin and catalyst loading gave no significant increase in yield (see ESI for full details). Application of HBcat to the neat reaction conditions using alkoxy-tethered complex **2a**, led to formation of the linear hydroboration product (Entries 10 and 11). These reaction mixtures were colorless and contained aggregates and the product mixtures were indistinguishable from uncatalyzed control reactions. This suggests that the alkoxy-tethered complex **2a** is decomposed by HBcat under these conditions, and that the background, *anti*-Markovnikov selective, reaction proceeds in this case.

Table 1. Reaction optimization for the hydroboration of styrene derivatives[a]



3 **4** **5**

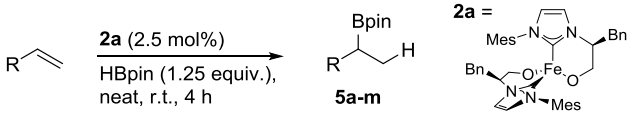
Entry	[Fe] (mol%)	R	$HBOR_2$ (equiv.)	Yield (%)[b] 4	5
1[c]	none	$PhCH_2CH_2$	HBcat (1.5)	25	-
2[c]	**1a** (5.0)	$PhCH_2CH_2$	**HBcat** (1.5)	**81**	8
3[c]	**2a** (5.0)	$PhCH_2CH_2$	HBcat (1.5)	30	-
4	**1a** (5.0)	$PhCH_2CH_2$	HBpin (2.0)	-	-
5	**1a** (2.5)	4-^{t}Bu-C_6H_4	HBpin (2.0)	-	6
6[d]	**1a** (2.5)	4-^{t}Bu-C_6H_4	HBpin (2.0)	5	26[e]
7[d]	**2a** (2.5)	4-^{t}Bu-C_6H_4	HBpin (2.0)	3	25[e]
8[d,f]	**1a** (2.5)	4-^{t}Bu-C_6H_4	HBpin (1.0)	2	67[e]
9[d]	**2a** (2.5)	4-^{t}Bu-C_6H_4	**HBpin** (1.25)	8	**70**[e]
10[d]	**2a** (2.5)	4-^{t}Bu-C_6H_4	HBcat (1.25)	37[e]	-
11[d]	**2a** (2.5)	$PhCH_2CH_2$	HBcat (1.25)	65[e]	-

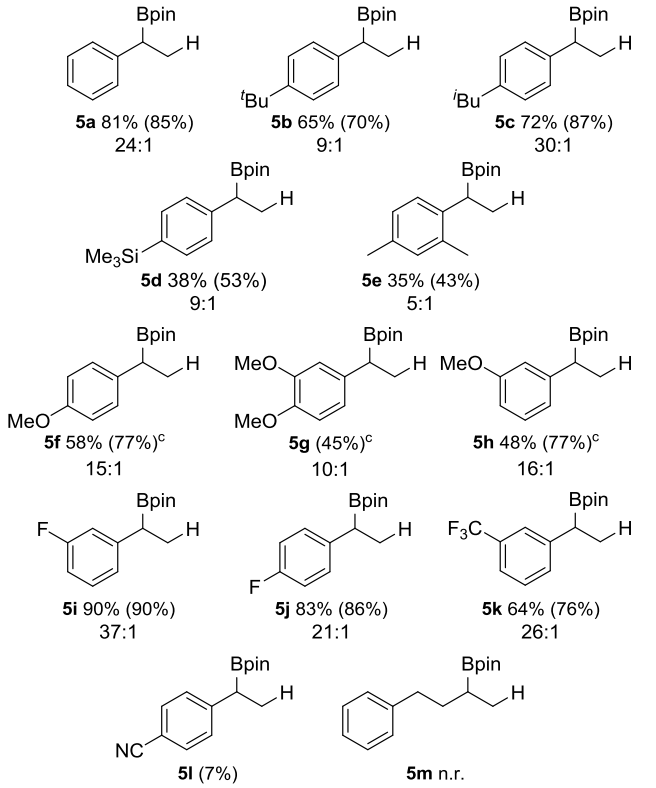
[a]Conditions: Boronic ester (equiv.), [Fe] (2.5 to 5.0 mol%) and alkene (1 equiv.) in THF (0.5 M), r.t.. [b]Yields determined by ^{1}H NMR relative to 1,3,5-trimethoxybenzene internal standard. [c]Isolated as the corresponding alcohols following oxidation with basic H_2O_2(aq). [d]Conditions: neat. [e]Conversions determined by integrals of benzylic product peaks in ^{1}H NMR relative to the limiting reagent. [f]4-*tert*-butylstyrene (5 equiv.).

The scope of the Markovnikov selective hydroboration reaction was investigated using a range of electronically differentiated styrene derivatives, alkoxy-tethered NHC-Fe^{II} **2a** (2.5 mol%) and HBpin (1.25 equivalents) (Table 2). Styrene proved to be an excellent substrate giving the secondary boronic ester **5a** in 81% isolated yield, and a 24:1 branched:linear ratio, significantly increased regioselectivity compared to those previously reported.[23] Styrene derivatives bearing alkyl- and trialkylsilyl-substituents reacted in good yields (**5b**-**5d**, 38-72%) and branched:linear selectivities (9:1 to 30:1). Alkyl substituents could also be tolerated in the *ortho* position, with synthetically useful yields and branched:linear selectivities achieved (**5e**). Styrene derivatives bearing electron-donating aryl-substituents underwent successful hydroboration in moderate to good yields (35-72%) and selectivities (5:1 to 30:1) to give the branched boronic esters **5b**-**5g**. Styrene derivatives bearing electron-withdrawing aryl-substituents including fluoro- and trifluoromethyl groups gave the secondary alkyl-boronic esters **5h**-**5k** in good yields (48-90%) and excellent branched:linear ratios (16:1 to 37:1). Using 4-cyanostyrene resulted in only 7% of the alkene hydroboration product **5l**, along with a mixture of alkene and nitrile hydrogenation products. Alkyl-alkenes, such as 4-phenyl-1-butene gave no conversion to the Markovnikov hydroboration product **5m** under these conditions with only starting material and a mixture of alkene isomerization products recovered from these reactions. Styrene derivates bearing substituents at the α- or β- position, such as

α-methylstyrene, β-methylstyrene, and indene were all unreactive under the developed conditions.

Table 2. Iron-catalyzed Markovnikov selective hydroboration of styrene derivatives using 2a.[a,b]

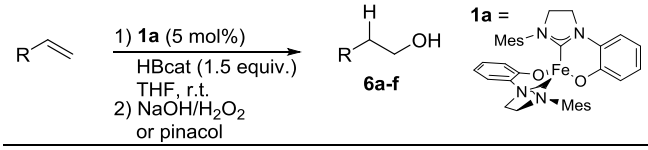


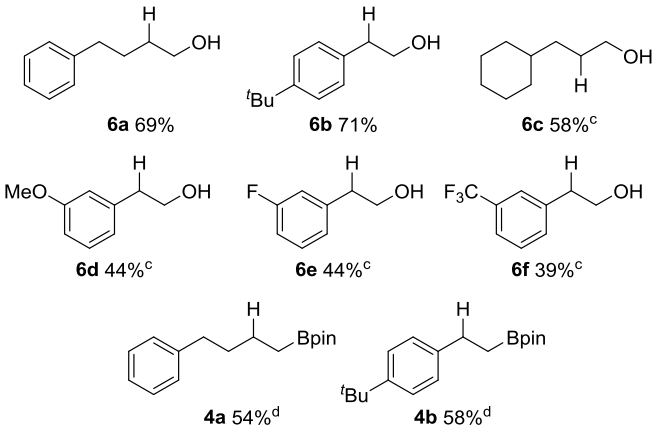


[a]Conditions: HBpin (1.25 equiv.) added in a single portion to **2a** (2.5 mol%), followed after ~15 s by alkene (1 equiv.), r.t., 4 h. [b]Isolated yields following flash column chromatography. Conversions in parentheses, and branched:linear ratios calculated from relative integrals of starting material and product peaks in ^{1}H NMR, average of at least 2 runs. [c]Product unstable on silica gel.[37]

The substrate scope of the hydroboration to give primary alkylboronic esters was next investigated with aryloxy-tethered NHC catalyst **1a** (5 mol%), HBcat (1.5 equivalents) and various alkenes (Table 3). Successful catalysis was achieved for terminal alkyl- and aryl- alkenes to give the primary alcohol products **6a-6f**, following oxidation with basic hydrogen peroxide. Alternatively, the catechol-boronic esters could be transesterified with pinacol to give the primary alkyl- boronic ester products **4a** and **4b**. Styrene derivatives bearing both electron-withdrawing and -donating arene substituents gave the primary alcohol products in roughly equal yields, albeit decreased from that obtained with alkyl-substituted alkenes.

Table 3. Iron-catalyzed *anti*-Markovnikov selective hydroboration of terminal alkenes using 1a.[a,b]

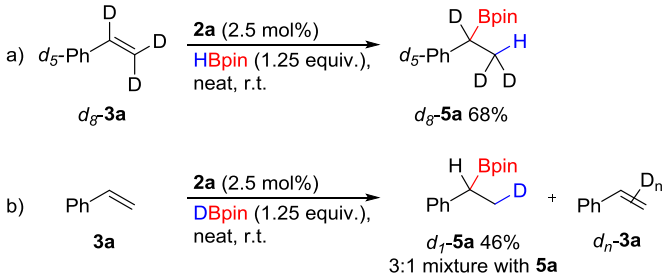




[a]Conditions: HBcat (1.5 equiv.) was added in a single portion to a solution of **1a** (5 mol%) and an alkene (1 equiv.) in THF (0.5 M), r.t., 5 h. Then an aqueous H_2O_2/NaOH solution was added in a single portion, 0 °C, 0.5 h. [b]Isolated yields following flash column chromatography. [c]Yield measured by ^{1}H NMR of crude reaction product relative to 1,3,5-trimethoxybenzene internal standard. [d]Instead of oxidation, pinacol (1 equiv.) was added, r.t., 18 h.

In order to gain insight into the mechanism of the alkene hydroboration with HBpin, deuterium labeling experiments were performed. Catalytic hydroboration of d_8-styrene with HBpin gave the mono-protio-boronic ester d_8-**5a** exclusively with H incorporation at the terminal methyl group (Scheme 3, a). When DBpin was used for the hydroboration of styrene the mono-deuterated boronic ester d_1-**5a** formed in a 3:1 mixture with the fully protio-boronic ester **5a** accompanied by deutero-styrene d_n-**3a**, (Scheme 3, b). This suggests that hydrometallation precedes C-B bond formation. In addition, the returned deutero-styrene showed deuterium at both alkene carbons suggesting β-hydride elimination occurs following hydrometallation, as an alternative to B-C bond formation. This β-hydride elimination accounts for the formation of fully protio-boronic ester observed when using DBpin.

Scheme 3. Deuterium labeling studies of Marknovnikov selective alkene hydroboration. Isolated yields following flash column chromatography.



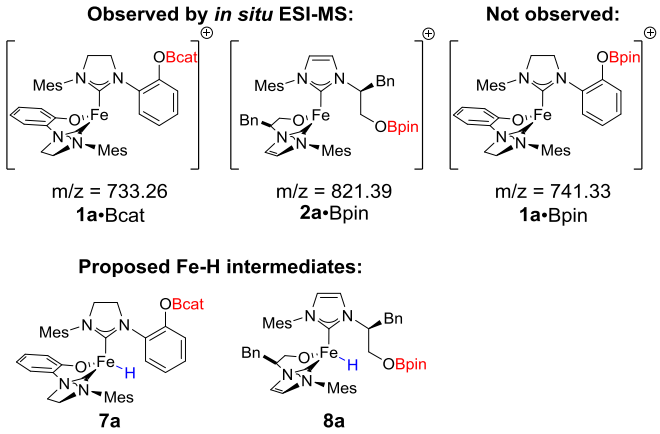
Reaction monitoring by ^{11}B NMR provided no evidence of any boron containing species other than the product and HBpin in the reaction mixtures. Oxidation of the branched hydroboration prod-

uct, followed by chiral HPLC analysis revealed no enantioenrichment of the secondary alcohol products, despite the enantioenriched ligand (see ESI for details).

To further probe the mechanism, and given the lack of any enantioselectivity, the catalytic hydroboration of styrene with HBpin was performed in the presence of radical inhibitors TEMPO and galvinoxyl free radical. In both cases, increased loading of radical inhibitor was needed to considerably attenuate catalytic activity (see ESI for details). The formation of neither alkyl-TEMPO nor alkyl-galvinoxyl adducts were observed. Diminished yields in the presence of free radical additives may simply be due to reactions between the additive and the iron catalyst.[38,39]

Having proposed that the alkoxy-tethered NHC ligands could act in conjunction with the Fe^{II} center to activate the boronic esters, investigation into the identity of the catalytic intermediates was paramount. ESI-MS was used to directly probe the reaction mixtures of both the *anti*-Markovnikov- and Markovnikov selective hydroboration of styrene **3g** (Scheme 4).

Scheme 4: *In situ* reaction monitoring by ESI-MS.



Reactions of the *anti*-Markovnikov selective catalyst **1a** with HBcat showed cleavage of H-B bond to give an adduct bearing a borylated ligand (**1a**·Bcat m/z = 733.26). The analogous reaction with HBpin lead to no such borylation product being observed. However when the Markovnikov selective catalyst **2a** was used, HBpin was cleaved and borylated complexes **2a**·Bpin and **2a**·$(Bpin)_2$ (m/z = 821.39 and 948.48 respectively) were observed. The alkoxy-tethered complex **2a**, when treated with HBcat, gave only products of ligand dissociation and complex decomposition. This is in keeping with the results above, which indicted that **2a** is not a stable catalyst for hydroboration with HBcat.

That the reaction conditions effectively catalyze the isomerization of terminal alkyl-substituted alkenes (*vide supra*) strongly implies that the reaction proceeds by alkene hydrometallation by an iron-hydride complex. The observed borylated iron complexes **1a**·Bcat, **2a**·Bpin (Scheme 4) are presumably derived from the corresponding iron-hydride complexes **7a** and **8a** respectively on ionization. We propose that the alkoxy-tethered ligand is more able to activate Bpin, promoting the formation of the required iron-hydride species and in contrast to the analogous reaction with HBcat which only leads to catalysts decomposition. The low activity of **1a** in the hydroboration of alkenes with HBpin is presumably due to the low reactivity of this ligand towards the activation of HBpin. It is not clear whether these reactions proceed by a single catalytic iron-hydride species or an ensemble thereof.

The regioselectivity of the Markovnikov selective hydroboration of styrene derivatives with HBpin and alkoxy-tethered complex **2a** can be rationalized by the formation a stabilized benzyl-iron intermediate following hydrometallation. For the *anti*-Markovnikov selective hydroboration reactions with the more electrophilic HBcat, where catalyst decomposition is observed, a Lewis acid/base promoted,[40] or radical hydrogen-atom transfer[41] reactions cannot be ruled out. However, we also cannot exclude the formation of a kinetically favored terminal alkyl-iron intermediate when using HBcat. Further mechanistic investigations, in order to investigate the regioselectivity switch, and allow refinement of the catalyst design and expansion of the reaction scope, are still ongoing.

In summary we have developed a series of novel Fe(II) catalysts bearing alkoxy-tethered NHC ligands that are catalytically active for the hydroboration of terminal alkenes with controlled and switchable regioselectivity. Alkoxy-tethered NHC-Fe^{II} complex **2a** is the first reported iron catalyst that is effective for the Markovnikov (branched) selective hydroboration of styrene derivatives using HBpin. Additionally, aryloxy-tethered NHC-Fe^{II} complex **1a** has been shown to be an effective catalyst for the *anti*-Markovnikov (linear) selective hydroboration of terminal alkenes using HBcat. Mechanistic investigations suggest that the innovative ligand design facilitates a ligand-assisted catalyst activation. The proposed catalytically active hydride species enable iron-catalyzed hydroboration reactions to proceed in short reaction times at ambient temperatures and, most significantly, in the absence of any external activator.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data including crystallographic data for compounds **1a**, **1b**, **1c** and **2a** in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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