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Ligand-Free Iron-Catalyzed Regioselectivity-Controlled Hydroboration of Aliphatic Terminal Alkenes

Wei Su,*, † Rui-Xiao Qiao,‡ Yuan-Ye Jiang,# Xiao-Li Zhen,† Xia Tian,† Jian-Rong Han,† Shi-Ming Fan,‡ Qiushi Cheng, † Shouxin Liu*, ‡

† School of Science, Hebei University of Science and Technology, Shijiazhuang, 050022, China

‡ Hebei Key Laboratory of Molecular Chemistry for Drug, Hebei University of Science and Technology, Shijiazhuang, 050022, China

School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu, 273100, China

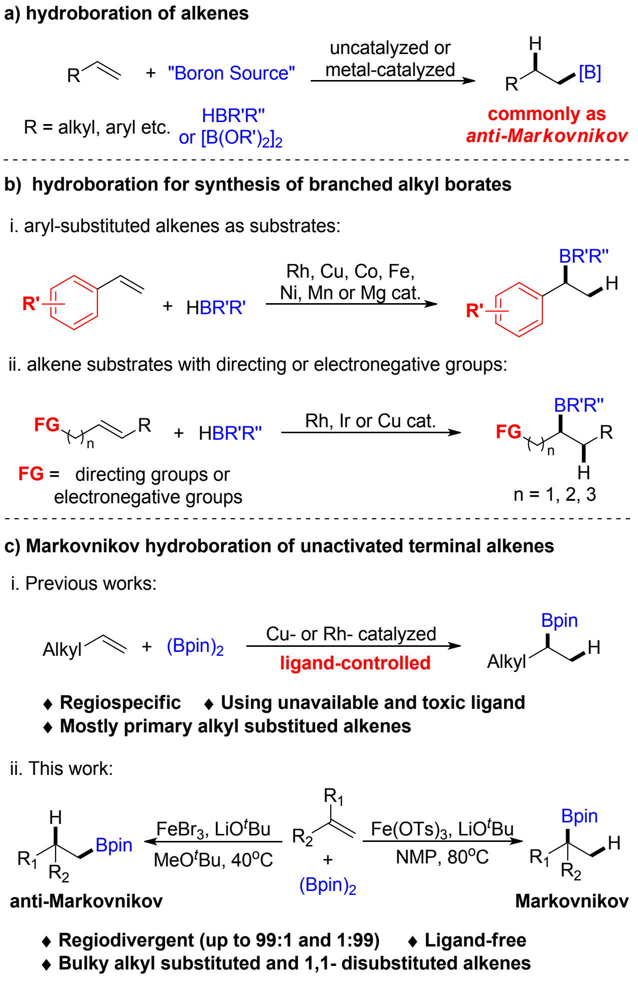
ABSTRACT: The control of regioselectivities has been recognized as the elementary issue for alkene hydroboration. Despite considerable progress, the specificity of alkene substrates or the adjustment of ligands were necessary for specific regioselectivities, which restrict the universality and practicability. Herein, we report a ligand-free iron-catalyzed regiodivergent hydroboration of aliphatic terminal alkenes that obtains both Markovnikov and anti-Markovnikov hydroboration products in high regioselectivities. Notably, solvents and bases were shown to be crucial factors influencing the regioselectivities and further studies suggested the iron-boron alkoxide ate complex is the key intermediate that determines the unusual Markovnikov regioselectivity. Terminal alkenes with diverse structures (mono-substituted and 1,1-disubstituted, open-chain and exocyclic) underwent the transformation smoothly. The reaction does not require the addition of auxiliary ligands and it can be performed on a gram scale, thus providing an efficient and sustainable method for the synthesis of primary, secondary, and tertiary alkyl borates.

Key Words: iron catalysis, hydroboration, alkenes, alkyl borates, regioselectivity, ligand-free

INTRODUCTION

Alkylboron compounds are not only widely employed as intermediates in organic synthesis[1], they are also applied in the field of pharmaceuticals because of their intrinsic biological activities[2]. Therefore, synthetic methods that can be used to construct alkylboron compounds in an efficient and sustainable manner have been studied widely[3]. Since the seminal work reported by Brown in 1956[4], the hydroboration of alkenes has evolved into the most powerful strategy for the synthesis of alkylboron compounds. As the elementary factor influencing product structures, the control of the regioselectivity has always been the core issue in hydroboration of alkenes. In most of the catalyzed and uncatalyzed approaches[5], alkene hydroboration commonly follows anti-Markovnikov regioselectivity to afford the corresponding linear alkylboron compounds (Scheme 1a). However, the metal-catalyzed hydroboration of aryl-substituted alkenes gave the reverse Markovnikov regioselectivity with catecholborane (HBcat) or pinacolborane (HBpin) as hydrogen and boron source, mainly because of the electronic bias of the vinyl group (Scheme 1b, i)[6]. Furthermore, the regiospecific hydroboration of internal alkenes was achieved through the introduction of directing groups[7] or remote electronic effects[8] in alkene substrates (Scheme 1b, ii). Despite these results, Markovnikov hydroboration of aliphatic terminal alkenes that can be obtained from petrochemical feedstocks or synthesized in a straightforward manner remain elusive. Very recently, the research groups of Ito[9,10], Montgomery[11], Aggarwal[12], and Shi[13] independently realized Cu- or Rh-catalyzed Markovnikov hydroboration of aliphatic alkenes based on the addition of metal-boron intermediates to alkenes (Scheme 1c, i). Although these efforts provide elegant methods for the synthesis of branched alkyl borates, the scope of the reactions with respect to alkenes are generally limited to monosubstituted alkenes, and they require either expensive and multi-step synthesized phosphine ligands or carbene ligands. To advance beyond these limitations, the development of new efficient and practical hydroboration reaction systems remains in demand.

Scheme 1. Markovnikov Hydroboration of Aliphatic Terminal Alkenes

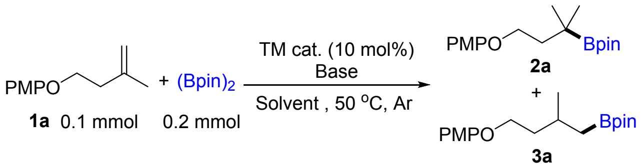


In recent years, iron-catalyzed transformations have attracted renewed interest not only because of its high natural abundance, low cost, and limited toxicity, but also because its catalytic properties differ from those of other transition metals[14]. Especially in the field of olefin functionalization, a series of unprecedented and practical transformation have been achieved by iron-catalysis[15]. Regarding the hydroboration of alkenes, since Ritter reported iron-catalyzed 1,4-hydroboration of 1,3-dienes in 2009[16a], a variety of iron catalysts have been developed, providing sustainable and efficient tools for alkene hydroboration by using HBpin[16] or $(Bpin)_2$[17] as boron source. Nevertheless, in terms of substrate range or selectivity, these iron-catalyzed hydroboration reactions did not surpass the effects achieved by other metals (Scheme 1a & 1b). Given the unique nature and enormous potential of iron catalysis,[18] we envisioned that iron-catalysis would be a feasible strategy to expand the concept of alkene hydroboration, both in the scope of alkene substrates and the regulatory mechanism of regioselectivities. Herein, we describe a ligand-free iron-catalyzed regiodivergent hydroboration of aliphatic terminals alkenes (Scheme 1c, ii). Either Markovnikov or anti-Markovnikov hydroboration products could be obtained in high regioselectivities (98:2 vs. 2:98) by regulation of solvent, base, and other reaction parameters. Interestingly, the adoption or not of the ate form of iron-boron intermediates was suggested to be a key factor that determines the regioselectivity. Finally, a series of terminal alkenes with a range of structures including primary, secondary, and tertiary alkyl substituted alkenes, 1,1-disubstituted alkenes and even 2-methylideneadamantane, were found to be compatible with this reaction.

RESULTS AND DISCUSSION

Development of iron-catalyzed hydroboration of aliphatic alkenes. We initially attempted iron-catalyzed hydroboration using *p*-methoxyphenyl protected 3-methyl-3-buten-1-ol (**1a**) as the substrate and $(Bpin)_2$ as the boron source (Table 1). When the substrates were treated with $FeCl_2$ and LiO^{t}Bu in 1,4-dioxane at 50 °C for 18 h, the hydroboration product was obtained in 51% GC yield with good anti-Markovnikov regioselectivity (**2a**/**3a** = 10:90, entry 1). On this basis, the solvent effect was tested. With ethers as solvent, the hydroboration tended to follow anti-Markovnikov regioselectivity (entries 1–3). In particular, with MeO^{t}Bu as solvent, excellent anti-Markovnikov regioselectivity was achieved (37%, **2a**/**3a** = 3:97, entry 3). Upon optimization of the reaction conditions, the anti-Markovnikov hydroboration product was obtained in improved yield and regioselectivity (67%, **2a**/**3a** = 2:98, entry 6). In contrast, the more desirable Markovnikov hydroboration product was predominantly obtained using amide solvents (entries 4 and 5). By increasing the amount of both $(Bpin)_2$ and LiO^{t}Bu and elevating the temperature, the yield and Markovnikov regioselectivity were both improved to excellent levels (78%, **2a**/**3a** = 98:2, entry 7). We also test the effect of iron salts, and the anions of iron salts were shown to have little influence on the regioselectivity (page S6-S7). $Fe(OTs)_3$ was found to be the best choice in NMP (entry 8). Notably, both the anion and cation in the base play important roles in determining the yield and regioselectivity (entries 8–12), which suggests the involvement of an iron alkoxide ate as a key catalytic intermediate[18c, 19] (entries 8-10). The reaction proceeded with undiminished yield and regioselectivity using high-purity $FeCl_2$ (99.99%) (entry 13, 14), while the use of other metal chlorides (copper, nickel, cobalt, manganese and palladium) led to low reactivities, and anti-Markovnikov product was mainly obtained with NMP as solvent (see SI, Page S13-S14). To exclude the possible borane-catalyzed process[20], the reactions with BH_3 as catalyst or HBpin as boron source were also conducted, and no hydroboration products were obtained (see SI, Page 13). Lastly, when iron salts were omitted in both MeO^{t}Bu and NMP, hydroboration products were not obtained (entries 15, 16), and the diboration of alkenes was obseverd in NMP while not in MeO^{t}Bu. According to previous work[19], the diboration of **1a** in NMP should be promoted by the alkoxide base LiO^{t}Bu at the relatively high temperature. From the above results, both regioselective outcomes clearly can be achieved in excellent levels and the course of the reaction can be determined by the choice of conditions in the iron-catalyzed system. The effect of trace amounts of other metals in the iron salts on the reaction was ruled out.

Table 1. Optimization of Reaction Conditions[a]

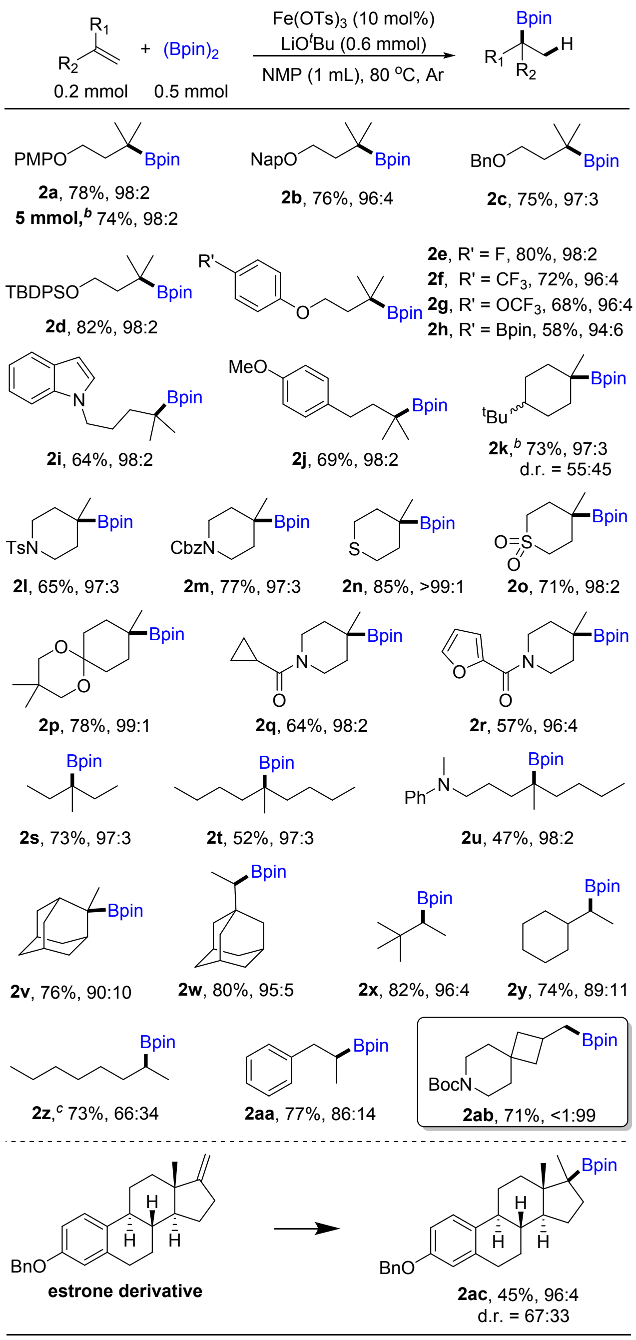


Entry	Fe cat.	Base (equiv)	Solvent	Yield (%)[b]	2a/3a[c]
1	$FeCl_2$	LiO^{t}Bu (2)	Dioxane	51	10:90
2	$FeCl_2$	LiO^{t}Bu (2)	THF	23	16:84
3	$FeCl_2$	LiO^{t}Bu (2)	MeO^{t}Bu	37	3:97
4	$FeCl_2$	LiO^{t}Bu (2)	DMA	63	83:17
5	$FeCl_2$	LiO^{t}Bu (2)	NMP	65	89:11
6[d]	**$FeBr_3$**	**LiO^{t}Bu (1.5)**	**MeO^{t}Bu**	**67**	**2:98**
7[e]	$FeCl_2$	LiO^{t}Bu (3)	NMP	78	98:2
8[e]	**$Fe(OTs)_3$**	**LiO^{t}Bu (3)**	**NMP**	**95**	**98:2**
9[e]	$Fe(OTs)_3$	LiOMe(3)	NMP	29	43:57
10[e]	$Fe(OTs)_3$	LiO^{i}Pr (3)	NMP	34	55:45
11[e]	$Fe(OTs)_3$	NaO^{t}Bu (3)	NMP	62	76:24
12[e]	$Fe(OTs)_3$	KO^{t}Bu (3)	NMP	18	74:26
13[e,f]	$FeCl_2$	LiO^{t}Bu (3)	NMP	77	98:2
14[d,f]	$FeCl_2$	LiO^{t}Bu (1.5)	MeO^{t}Bu	50	2:98
15[d]	–	LiO^{t}Bu (1.5)	MeO^{t}Bu	0	–
16[e]	–	LiO^{t}Bu (3)	NMP	0	–

[a] Reaction conditions: alkene **1a** (0.1 mmol), $(Bpin)_2$ (0.2 mmol), iron salt or other metal salt (0.01 mmol), and base were stirred in solvent (0.5 mL) at 50 °C for 18 h. [b] Combined yields of **2a** and **3a** determined by GC analysis. [c] Determined by GC analysis of the crude reaction mixtures. [d] Using $FeBr_3$ (0.02mmol), 40 °C for 36 h. [e] Using $(Bpin)_2$ (0.25mmol), 80 °C. [f] Using $FeCl_2$ (99.99%) purchased from Sigma–Aldrich.

Substrate scope of aliphatic alkenes. With the optimum conditions in hand, the generality of the Markovnikov hydroboration was investigated (Scheme 2). We found that Markovnikov hydroboration generally proceeded with a range of yields and regioselectivities that correlated with the steric hindrance imparted by the substituents on the vinyl group. The 1,1-disubstituted open-chain alkenes containing a methyl group were converted into the corresponding tertiary alkyl borates with excellent yields and regioselectivities (**2a**–**j**). Methylene substituted cycloalkanes also reacted in high yield and regioselectivity in the Markovnikov hydroboration (**2k**–**r**); however, methylene substituted cyclobutane gave complete anti-Markovnikov regioselectivity (**2ab**). Diminished yields were observed when the substituents on the vinyl group presented more steric bulk (**2s**, **2t**, **2u**), although the regioselectivity remained excellent. Interestingly, 2-methylene adamantine gave the corresponding product in good yield and regioselectivity. In addition to 1,1-disubstituted alkenes, mono-substituted alkenes were also investigated. The regioselectivity reduced from excellent (**2w**, **2x**) to good (**2y**), and then to moderate (**2z**, **2aa**), when the alkyl substituent was changed from 3° to 2° and to 1°, respectively. In contrast, for the Cu- and Rh-catalyzed versions, 1° alkyl substituted alkenes usually gave good regioselectivities, whereas 2° and 3° alkyl substituted alkenes reacted with lower regioselectivities[9-13]. Furthermore, the reaction tolerated a variety of functional groups, including phenyl ether (**2a**, **2e**–**h**), 2-methylnaphthalene ether (**2b**), benzyl ether (**2c**), silicon ether (**2d**), fluoro (**2e**), trifluoromethyl (**2f**), trifluoromethoxy (**2g**), phenylborate (**2h**), sulfonamide (**2l**), amide (**2m**, **2q**, **2r**), amine (**2u**), thioether (**2n**), sulfone (**2o**), and ketal (**2p**) groups, as well as some pharmaceutically important cycles, such as indole (**2i**), furan (**2r**), cyclopropane (**2q**), and amantadine (**2v**, **2w**). Benefiting from the good functional group tolerance, an estrone derivate could also be converted into the corresponding tertiary alkyl borate derivative, albeit with moderate diastereomeric ratio (d. r. = 67:33). Finally, the hydroboration of **2a** could be scaled up to 5 mmol with a reduced iron-catalyst loading of 2.5%, thereby demonstrating the robustness and practical application of this method.

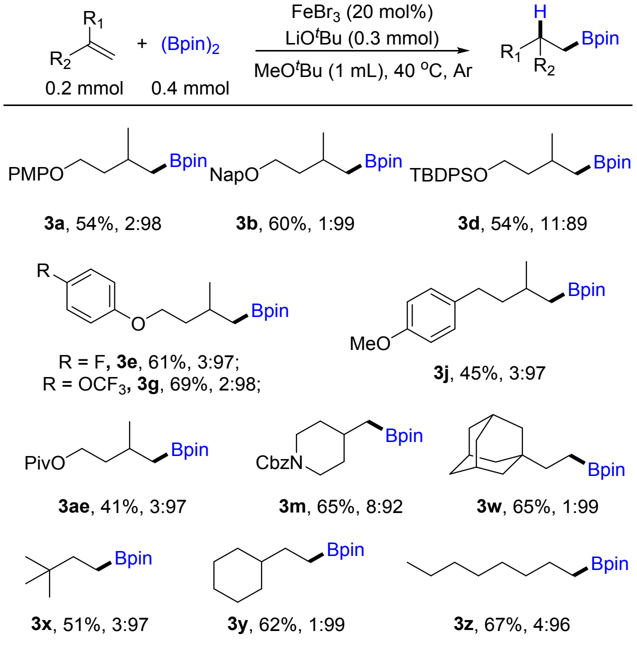
Scheme 2. Iron-Catalyzed Markovnikov Hydroboration[a]



[a]Reaction conditions: alkene (0.2 mmol), $(Bpin)_2$ (0.5 mmol), $Fe(OTs)_3$ (0.02 mmol), LiO^tBu (0.6 mmol) were stirred in NMP (1 mL) at 80 °C for 18 h. Isolated yields are shown here and the products is partially decomposed during isolation process. The regioselectivity was determined by GC analysis of the crude reaction mixtures. [b]$Fe(OTs)_3$ (2.5 mol%) was used.

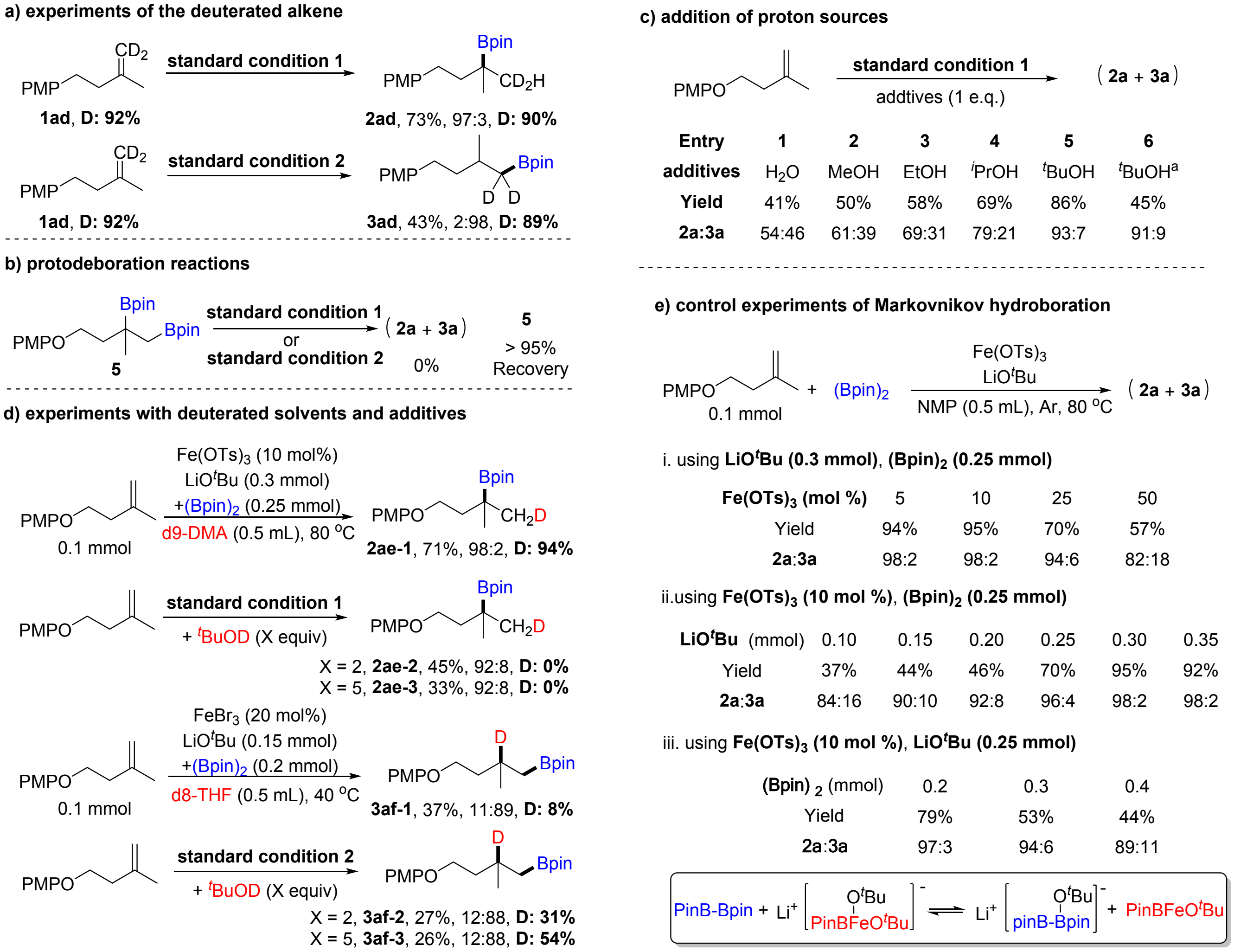
We then tested the scope of the iron-catalyzed anti-Markovnikov hydroboration (Scheme 3). All the 1,1-disubstituted, 1°, 2°, and 3° alkyl mono-substituted terminal alkenes reacted in moderate yield with high regioselectivity. Although many anti-Markovnikov hydroboration strategies have been established, the reaction described herein offers a further alternative method.

Scheme 3. Iron-Catalyzed anti-Markovnikov Hydroboration[a]



[a]Reaction conditions: alkene (0.2 mmol), $(Bpin)_2$ (0.4 mmol), $FeBr_3$ (0.04 mmol), LiO^tBu (0.3 mmol) were stirred in MeO^tBu (1 mL) at 40 °C for 36 h. Isolated yields are shown here and the products is partially decomposed during isolation process. The regioselectivity was determined by GC analysis of the crude reaction mixtures.

Scheme 4. Mechanism Studies



Standard conditions 1 as shown in Scheme 2. Standard conditions 2 as shown in Scheme 3. ^{a} ^{t}BuOH (2 equiv) was used.

Mechanistic investigations. To gain insight on the reaction mechanism, several additional experiments were performed. When deuterated alkene **1ad** was used as the reaction substrate, no migration of deuterium was observed under either of the standard conditions used for Markovnikov or anti-Markovnikov regioselectivities (Scheme 4a). This result suggested that elimination of iron and β-H followed by the addition of [FeH] to alkenes is unlikely.

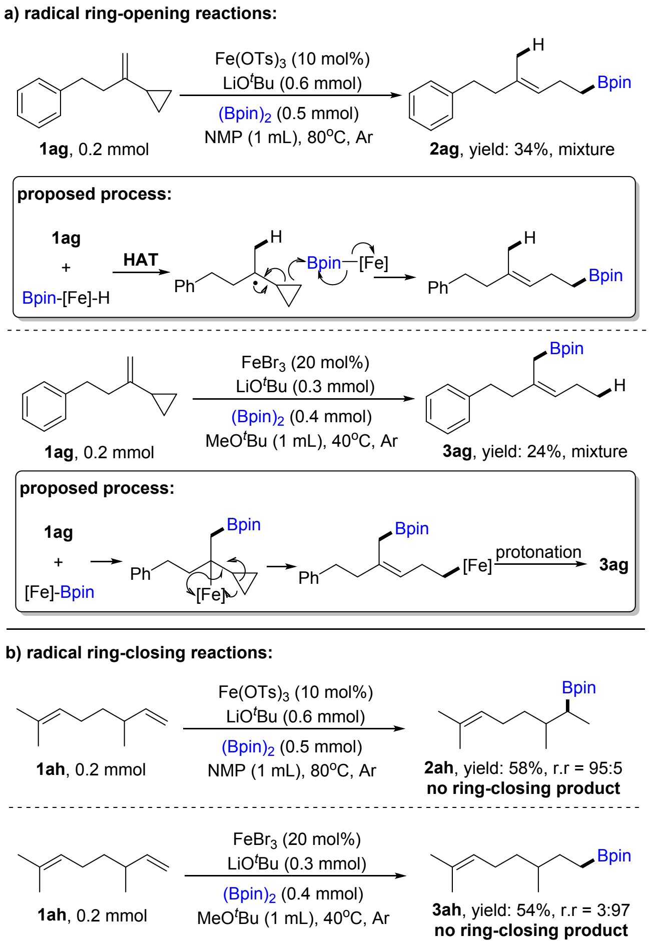
Next, we submitted alkene diboration substrate **5** to the reaction under both two standard conditions and observed no protodeboration products (Scheme 4b); thus, a diboration–protodeboration mechanism was excluded[9, 21].

Different from Cu- or Rh-catalyzed hydroboration in which alcohols just acted as proton sources[9-13], in iron-catalyzed Markovnikov hydroboration, additional H_2O or alcohols have significant effects on the yield and regioselectivity (Scheme 4c): a) on the whole, both of yield and Markovnikov regioselectivity decreased when proton sources were added; b) From ^{t}BuOH to ^{i}PrOH, EtOH, MeOH and H_2O, the yield and Markovnikov regioselectivity gradually decreased (entries 1-5); c) the more proton source was added, the more the yield decreased (entries 5, 6). The result indicates that the alcohol can undergo anion exchange with the reaction intermediate, and the anion influences yield and regioselectivity significantly.

To make clear the source of the hydrogen, we performed the reactions in deuterated solvents or with tBuOD as the deuterated additive (Scheme 4d). With d^9-DMA as solvent, the deuteration rate of Markovnikov product **2ae-1** was 94%, and either 0.2 mmol or 0.5 mmol tBuOD was added, the deuteration rates of **2ae-2** and **2ae-3** were both 0% in NMP. These results illustrated that, in Markovnikov hydroboration, the “H atom” is coming from the amide solvent and hydrogen atom transfer (HAT) is preferred to be underwent rather than boration-protonation. To our knowledge, the common hydrogen sources in iron-catalyzed HAT are hydrosilicon compounds[15b-f], and amides are the first time to be indicated as the hydrogen source. However, with d^8-THF as solvent, the deuteration rate of anti-Markovnikov product **3af-1** was 8%, while when 0.2 mmol or 0.5 mmol tBuOD were added in MeOtBu, the deuteration rates of **3af-2** and **3af-3** were respectively 31% and 54%, which indicated that the hydrogen has a multiple source in the anti-Markovnikov hydroboration.

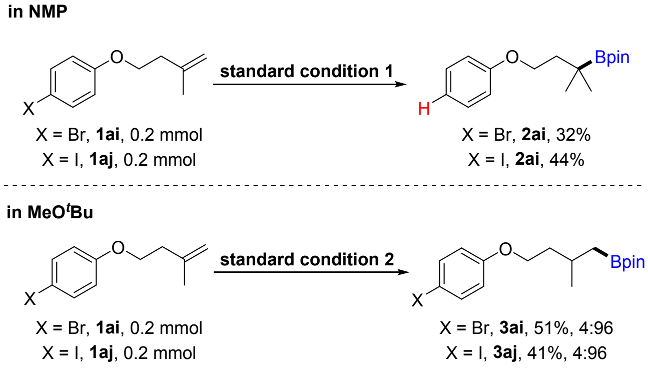
A series of control experiments were performed to clarify how the reaction was influenced by each parameter subtly (Scheme 4e). When $Fe(OTs)_3$ (10 mol%) was used, only the Markovnikov regioselectivity increased with an increase in the amount of LiO^{t}Bu. When LiO^{t}Bu (0.3 mmol) was used, the Markovnikov regioselectivity decreased with an increase in the amount of $Fe(OTs)_3$. These results indicate that an increase in the amount of LiO^{t}Bu relative to the amount of $Fe(OTs)_3$ led to better Markovnikov regioselectivity. Together with the results presented in Table 1, entries 8–12, we propose that an iron-boron alkoxide ate is the key intermediate that determines the Markovnikov regioselectivity and that the generation of a non-ate iron-boron intermediate mainly leads to the formation of the anti-Markovnikov products. To confirm the inference, control experiments in which $(Bpin)_2$ competed with iron-boron intermediate in forming the ate salt with LiO^{t}Bu were performed. The results showed that an increase in the amount of $(Bpin)_2$ led to a reduction in the level of Markovnikov regioselectivity, which is consistent with our proposed mechanism.

Scheme 5. Radical Clock Reactions



Furthermore, we performed the radical clock reations. The radical ring-opening reactions were conducted by using **1ag** as substrate (Scheme 5a). With NMP or MeO^{t}Bu as solvent, the ring-opening products **2ag** or **3ag** was respectively detected from the isolated mixture by ^{1}H-NMR and ^{13}C-NMR. The product **2ag** was proposed to be formed by the iron-catalyzed hydrogen atom transform of **1ag** and followed three-membered ring-opening boration process. The product **3ag** was proposed to be formed by initiated migration insertion of [FeBpin] intermediate to the vinyl of **1ag**, and followed ring-opening and protonation process. These results suggested that the Markovnikov regioselectivity was dictated by HAT process, while the anti-Markovnikov regioselectivity was controlled by the addition of [FeBpin] to alkenes. However, the radical-closing reactions with **1ah** only gave the straightforward hydroboration products **2ah** and **3ah** (Scheme 5b). These results were coursed by the slower rate of ring-closing process compared to the boration (Markovnikov) and protonation (anti-Markovnikov).

Scheme 6. Reactions of Substrates Containing Aryl Bromide/Iodide



Standard conditions 1 as shown in Scheme 2. Standard conditions 2 as shown in Scheme 3.

Unexpected results were observed with the substrates containing aryl bromide/iodide (Scheme 6). In MeO^{t}Bu, the aryl bromid and iodide (**1ai** & **1aj**) underwent the anti-Markovnikov hydroboration to give the corresponding products **3ai**, **3aj**; however, in NMP, both **1ai** and **1aj** gave the dehalogenated hydroboration product **2ai**. The dehalogenation was proposed to be initialed by the single electron transfer[22], which illustrated the ironboron intermediate formed in NMP is capable of the ability to catalyze single electron transfer process; meanwhile, the dehalogenation via iron-hydride intermediate is also possible[23].

Based on the above results and Uchiyama's previous work in which $KFe(O^tBu)_3$ was proven as a single-electron-transfer catalyst[19a], we propose a plausible reaction mechanism (see SI, page S30). Initially, iron(II or III) salts react with $(Bpin)_2$ and LiOtBu to form the iron(II)-boron di-*tert*-butoxide ate intermediate **A1** $Li^+[FeBpin(O^tBu)_2]^-$ in NMP and iron(II)-boron *tert*-butoxide intermediate **B1**[FeBpinO^{t}Bu] in MeO^{t}Bu. We propose that the ate ironboron intermediate **A1** could be stabilized by coordination of the carbonyl oxygen atoms of NMP to the lithium ion[24]. In MeO^{t}Bu, intermediate **B1** adds to the alkene to produce the intermediate **B2** with Bpin on the terminal carbon and iron on the internal carbon, then the organoiron intermediate **B2** undergo protonation to form the anti-Markovnikov product. In NMP, the ate intermediate **A1** performs as the single-electron-transfer catalyst and reacts with NMP to generate the iron hydride intermediate **A2** $H\cdot[FeBpin(O^tBu)_2]$. The HAT occurs with **A2** to the alkene to form the more stabilized tertiary radical and $FeBpin(O^tBu)_2$ (**A3**), then the tertiary radical reacts with intermediate **A3** to give the Markovnikov hydroboration product. Given the diversity of oxidation, spin states and coordination modes accessible by iron, especially in the ligand-free environment, the mechanism presented now is sketchy and the detailed version needs further efforts to elucidate[25].

CONCLUSION

In summary, we have developed an iron-catalyzed regiodivergent hydroboration methodology that can be applied to aliphatic terminal alkenes. The regioselectivity was shown to be determined by the solvent and base used, and further studies revealed that the iron-boron alkoxide ate salt was the vital intermediate for Markovnikov regioselectivity. We believe that these results provide crucial examples that expand our understanding of mechanisms involving iron catalysis. The phosphine- and carbene-ligand-free reaction features abundant, low cost, and low-toxicity iron catalyst, and offers wide scope with respect to terminal alkenes, which provides an efficient and sustainable method for synthesizing all primary, secondary, and tertiary alkyl borates. Further studies on iron-catalyzed alkene boration functionalization and related mechanism are under way.

ASSOCIATED CONTENT

Supporting Information

This information is available free of charge on the ACS Publications website.

Supplementary data, experimental procedures, and analytical data for all new compounds.

AUTHOR INFORMATION

Corresponding Author

Email for Wei Su: weisu@hebust.edu.cn;

Email for Shouxin Liu: chlsx@hebust.edu.cn.

Note

The authors declare no competing financial interest.

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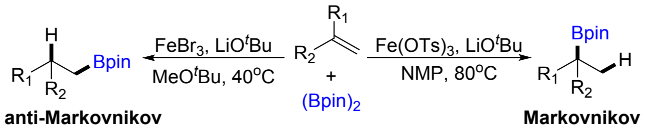

♦Regiodivergent (up to 99:1 and 1:99) ♦Ligand-free
♦Bulky alkyl substituted and 1,1- disubstituted alkenes