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Iron-Catalyzed, Markovnikov-Selective Hydroboration of Styrenes

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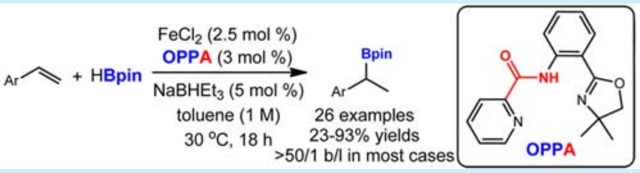
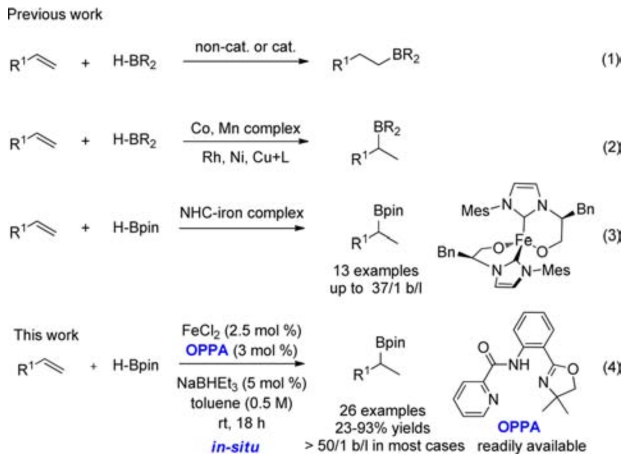
S *Supporting Information*

ABSTRACT: A highly Markovnikov-selective, iron-catalyzed hydroboration of styrenes is reported using available oxazolinylphenyl picolinamide as the ligand to afford the branched hydroboration products with up to >50/1 b/l. This reaction is operationally simple and could be carried out in gram scale.



Iron, as an earth-abundant, cheap, less toxic, and environmentally benign transition metal, arouses chemists' interest in exploring versatile iron catalysts for organic synthesis.[1] Alkylboronates are very important organic intermediates because their C−B bonds could be readily transformed to C−N, C−O, C−X, or C−C bonds in a stereospecific manner.[2] Hydroboration of alkenes is an efficient and atom-economical method to construct alkylboronates.[3] Generally, the direct hydroboration of alkenes is used to afford *anti*-Markovnikov products (Scheme 1, eq 1).[3,4] Transition-metal-catalyzed hydroboration provides the possibility to achieve the sterically hindered Markovnikov selectivity (Scheme 1, eq 2). Although highly Markovnikov-selective hydroboration of alkenes has been achieved using precious metals,[5] the growing interest in sustainable metal catalysis leads to the possibility of using earth-abundant transition metal catalysis to replace precious metal catalysis.[1,6] To date, Markovnikov-type hydroboration reactions of alkenes using earth-abundant metals, such as copper,[7] nickel,[8] cobalt,[9] and manganese,[10] have been described; however, the examples are still rare, and there are some drawbacks, such as the intolerance of halogenated substrates,[8] moderate regioselectivity,[11] and preparation of air-sensitive metal complexes.[9,10] In particular, there are only two examples using iron catalysis. Webster and co-workers reported an iron-catalyzed Markovnikov hydroborationof styrenes with a ratio of branched and linear products (b/l) from 60/40 to 70/30.[11a] The Thomas group described an iron-catalyzed Markovnikov hydroboration of sytrenes with an up to 37/1 b/l using an NHC iron complex (Scheme 1, eq 3);[11b] however, the difficulties in separating two regioisomers, as well as the additional step needed for preparation of the iron complex using a glovebox technique, limit the utility of this transformation. Thus, it is still highly desirable to develop an iron-catalyzed, highly Markovnikov-selective hydroboration of alkenes using readily available ligands.

Scheme 1. Hydroboration of Styrenes



Tridentate ligands containing imine or amine groups have presented unique properties for the hydroboration of alkenes. However, to our knowledge, the use of amide-based tridentate ligands in catalytic hydroboration of alkenes is still unknown. Here, we report an iron-catalyzed, highly Markovnikov-selective hydroboration of styrenes (>50/1 b/l in most cases) by using a readily available oxazolinylphenyl picolinamide ligand (Scheme 1, eq 4).

We began our studies by choosing the hydroboration of styrene **1a** with pinacolborane (HBpin) as a model reaction. The OIP·FeCl$_2$complex (**La**·FeCl$_2$), OAP ligand **Lb**, and IPOPA ligand **Lc** developed in our laboratory[4h,12] were first used (Table 1, entries 1−3). The reaction using complex **La**·FeCl$_2$ afforded a mixture of branched and linear products with 14/19 b/l. Next, a slightly better result with 38% yield and 38/24 b/l was found using **Lb**. However, no product was observed using **Lc**. Based on these results, we predicted that imine or amine groups were not suitable for the iron-catalyzed Markovnikov-type hydroboration of styrene. Our group is particularly interested in designing nitrogen-based ligands for earth-abundant transition metal catalysis; herein, the amide moiety was introduced as a chelated arm. A readily available oxazolinylpicolinamide ligand **Ld** was synthesized according to the previously reported literature[13] (two steps, 76% yield) and evaluated in this reaction. Encouragingly, **2a** was obtained in 65% yield with excellent Markovnikov selectivity (>50/1 b/l) using FeCl$_2$ as a catalyst

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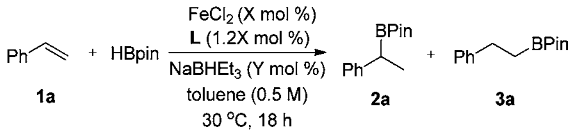
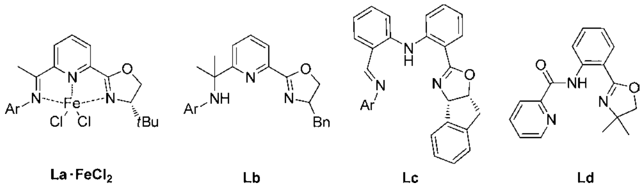
(entry 4). Various iron salts, solvents, amounts of styrene and HBpin, catalyst loadings, and reaction temperature were investigated, and no significant improvements of yield were observed (entries 5−8 and Table S1). The control experiments without ligand or reductant gave no product that indicated the necessity of these two elements (entries 9 and 10). Interestingly, when the concentration of **1a** was increased to 1 M, **2a** was found in 77% yield (entry 11). When the catalyst loading was lowered to 2.5 mol % with 5.0 mol % of NaBHEt$_3$, **2a** was also formed in 74% isolated yield with excellent branched selectivity (entry 13). When the catalyst loading was as low as 0.1 mol %, 44% of **2a** was observed with no deterioration in regioselectivity (entry 14). The standard conditions were identified as alkene (1.0 mmol), HBpin (1.2 equiv), FeCl$_2$ (0.025 equiv), **Ld** (0.03 equiv), and NaBHEt$_3$ (0.05 equiv) in a solution of toluene (1.0 M) at 30 °C for 18 h.

Table 1. Optimization for Synthesis of 2°-Alkylboronate[a]



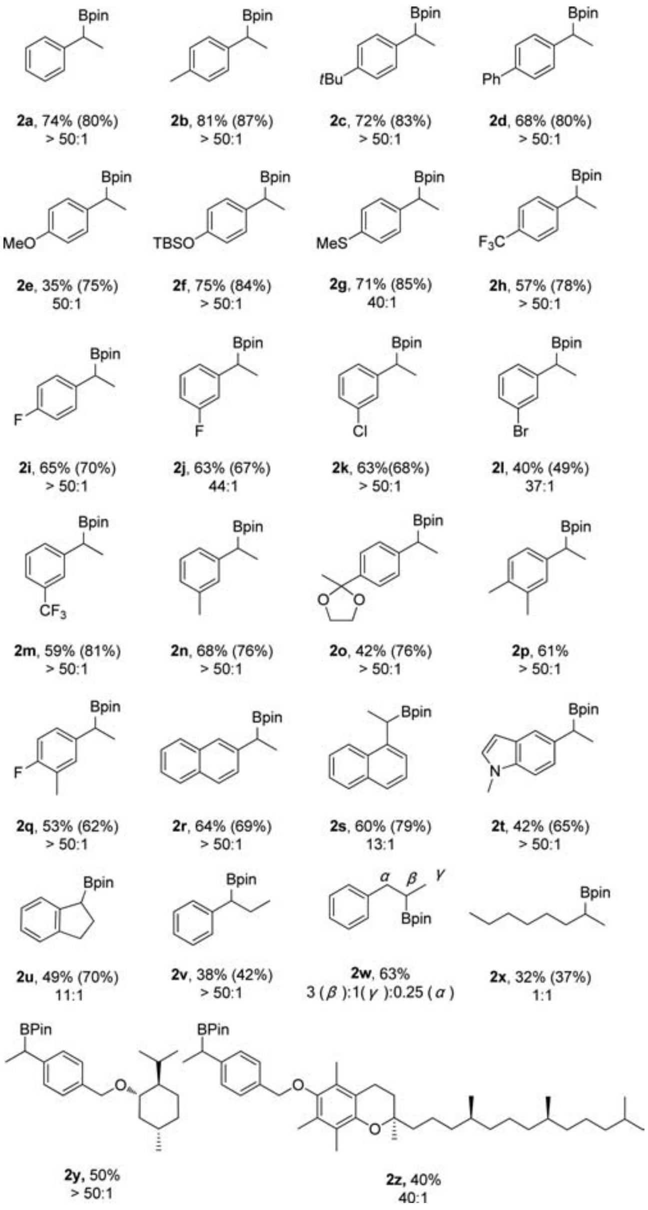
			yield (%)[b]	
entry	FeX$_2$	ligand	2a	3a
1	**La**·FeCl$_2$	–	14	19
2	FeCl$_2$	**Lb**	38	24
3	FeCl$_2$	**Lc**	–	2
4	FeCl$_2$	**Ld**	65	0.8
5	Fe(OAc)$_2$	**Ld**	12	1
6	Fe(acac)$_2$	**Ld**	37	1.2
7	Fe(OTf)$_2$	**Ld**	54	1
8	FeBr$_2$	**Ld**	50	0.5
9	FeCl$_2$	–	–	–
10[c]	FeCl$_2$	**Ld**	–	–
11[d]	FeCl$_2$	**Ld**	77	1.1
12[d,e]	FeCl$_2$	**Ld**	77	1.2
13[d,f]	FeCl$_2$	**Ld**	80(74)	1.0
14[d,g]	FeCl$_2$	**Ld**	44	0.4

[a] Reactions were conducted using **1** (0.5 mmol), HBpin (0.6 mmol), iron salts (5 mol %), ligand (6 mol %), and NaBHEt$_3$ (15 mol %) in a solution of toluene (1 mL) at 30 °C under N$_2$ atmosphere for 18 h. [b] Yields were determined using TMSPh as an internal standard. [c] Without NaBHEt$_3$. [d] **1** (1 mmol), toluene (1 M). [e] FeCl$_2$ (2.5 mol %), NaBHEt$_3$ (7.5 mol %). [f] FeCl$_2$ (2.5 mol %), NaBHEt$_3$ (5 mol %). [g] FeCl$_2$ (0.1 mol %). Ar = 2,6-di*i*PrC$_6$H$_3$.



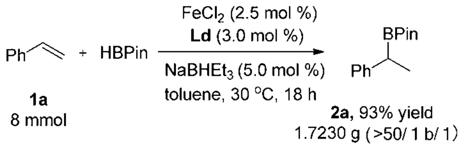
With the standard conditions in hand, the scope of the substrate was explored in Scheme 2. Styrenes bearing both electron-donating and electron-withdrawing groups at *para*- or *meta*-positions could be delivered to the corresponding products **2b**−**2q** in moderate to good yields (35−81%) with excellent Markovnikov selectivities (37/1 → 50/1 b/l), which indicated that the branched selectivity was not dramatically affected by the electronic nature of the substrate. Notably, styrenes with halides, trifluoromethyl, silyl ether, thioether, and ketal can be tolerated.

Scheme 2. Products of Hydroboration of Alkenes[a]



[a] Standard conditions: FeCl$_2$ (2.5 mol %), **Ld** (3.0 mol %), NaBHEt$_3$ (5.0 mol %), alkene (1 mmol), HBpin (1.2 equiv), toluene (1 mL), rt, 18 h. Isolated yields, NMR yields in parentheses.

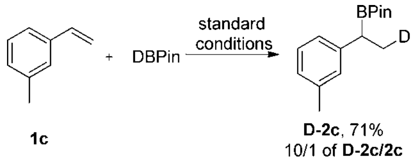
However, the *ortho*-substituted styrenes, such as 2-methylstyrene, 2-bromostyrene, or 2-chlorostyrene, were not compatible with these reaction conditions, and only a trace amount of product was detected. Polycycles and heterocycles, such as 1- or 2-naphthyl and 5-indolyl, were suitable for this reaction system (**2s** and **2t**). 1,2-Disubstituted styrenes, such as indene and *β*-methylstyrene, which were challenging substrates in the previous methods,[10,11] can be also converted to products **2u** and **2v** in moderate to excellent selectivities (11/1 → 50/1 b/l). Additionally, the reactions of aliphatic alkenes, such as allylbenzene and 1-octene, can also afford the branched products in moderate yields, albeit with poor regioselectivities (1/1−3/1 b/l). Furthermore, the late-stage functionalizations of styrenes bearing bioactive molecules were also presented. Styrenes bearing (+)-menthol or vitamin E were converted to the corresponding products **2y** and **2w** in moderate yields with excellent branched selectivities. A gram-scale



(5)

reaction of **1a** was smoothly performed to afford **2a** in a even better yield (93%) with excellent branched selectivity (>50/1 b/l) (eq 5).

To probe the mechanism of this hydroboration reaction, the deuterium experiment using DBpin was conducted to afford



(6)

D-2c and **2c** in 71% combined yield with 10/1 ratio of **D-2c**/**2c** (eq 6).[14] There is a possibility of an alkene insertion into the iron-hydride species and the occurrence of β-hydride elimination during this transformation. More experimental and computational studies should be further performed to gain an accurate understanding of the origin of the high regioselectivity.

In summary, we report an iron-catalyzed, highly Markovnikov-selective hydroboration of styrenes using readily available oxazolinylphenyl picolinamide ligands. A variety of styrenes bearing both electron-donating group and electron-withdrawing groups are suitable for this reaction system to be converted to the branched alkylboronates in excellent regioselectivities (>50/1 b/l in most cases). This amide-based tridentate ligand shows a unique property for an efficient Markovnikov selectivity. The oxazolinyl moiety also offers the possibility for asymmetric transformation by introducing chirality. The asymmetric reaction is being studied in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00227.

> Experimental details, characterization data of all compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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