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Iron-Catalyzed Highly Enantioselective Hydrosilylation of Unactivated Terminal Alkenes

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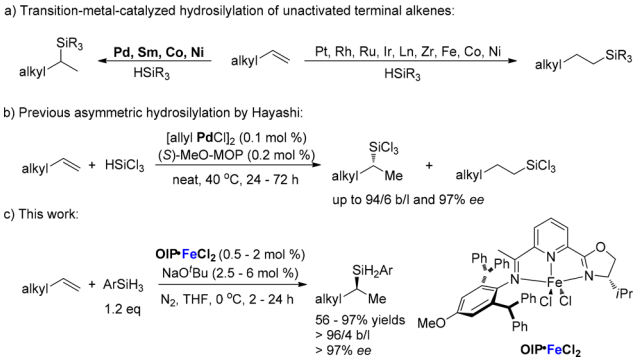
Supporting Information

ABSTRACT: The iron-catalyzed highly Markovnikov-type selective and enantioselective hydrosilylation of terminal aliphatic alkenes with good functional group tolerance is developed. This operationally simple protocol uses earth-abundant transition metal catalyst, readily available aliphatic alkenes and hydrosilanes to construct valuable chiral organosilanes with better than 99% ee in most cases. The chiral aliphatic alkan-2-ol and chiral dihydroxysilane as an analogue of ketone could be efficiently synthesized via further derivatization of chiral organosilanes without any racemization.

Asymmetric alkene transformation is one of the most powerful strategies for efficient construction of valuable chiral molecules, which has been widely used in industry and academia.[1] However, the unactivated terminal alkenes, which are readily available from large-scale industrial processes, are much less applied in efficient catalytic asymmetric transformation.[2] There are three main reasons for this phenomenon. First, unactivated terminal alkenes have few electronic effects without any chelating groups or directing groups, which leads to the difficulty of controlling regioselectivity. Second, the difficulty in differentiating two enantiotopic faces in prochiral substrates leads to the difficulty of controlling enantioselectivity. Third, active catalytic species would be favored to chelate functional groups rather than simple alkenes, which is the reason why the functional group toleration is quite limited in the successful cases. So the development of highly regio- and enantioselective transformation with good functional group toleration of readily available unactivated terminal alkenes is quite challenging and highly desirable.

Chiral organosilanes have widespread applications in organic synthesis,[3] silicon-based materials science,[4] and silasubstitution in medicinal chemistry.[5] Compared to other methods to prepare highly enantiopure organosilanes, such as desymmetrization of silanes for silicon-stereogenic silanes,[6] and asymmetric silicon-hydride bond insertions,[7] asymmetric alkene hydrosilylation is one of the most efficient methods for construction of nonracemic carbon-stereogenic silanes.[8,9a] Although the recent earth-abundant transition metal-catalyzed hydrosilylation of alkenes offers an atom-economic and efficient method to produce organosilanes (Scheme 1a); however, the Markovnikov-type selective reaction of aliphatic alkenes is still a challenge.[9] In 1991, Hayashi and co-workers reported the first successful highly enantioselective palladium-catalyzed hydrosilylation of aliphatic terminal alkenes (Scheme 1b).[10] The reaction provided chiral silanes with excellent enantioselectivity (up to 97% ee) and moderate to good regioselectivity (66/34−94/6 b/l). Although many research groups tried to improve this protocol using various noble transition metal catalysts and chiral phosphine ligands, so far no better results have been reported. Meanwhile, $HSiCl_3$ has to be used, which limited functional group tolerance. Recently, Buchwald group[11] and our group,[12] respectively, successfully reported the copper or cobalt-catalyzed asymmetric hydrosilylation of styrenes with nonhalogen hydrosilanes; however, the reactions of simple alkenes were not reported or did afford the products with less than 88% ee.

Scheme 1. Highly Enantioselective Hydrosilylation of Aliphatic Terminal Olefins



Iron, as an earth-abundant, nontoxic, lower cost, and biocompatible transition metal, has been great attractive in various applications.[13] Chirik and co-workers reported ligand-promoted iron-catalyzed hydrosilylation of alkenes,[14] which accelerated the development of hydrosilylation chemistry.[15] However, the asymmetric iron-catalyzed Markovnikov selective hydrosilylation of aliphatic alkenes is quite challenging. Additionally, even the racemic example has not been reported. Herein, we report a highly regio- and enantioselective iron-catalyzed Markovnikov-selective hydrosilylation of aliphatic terminal olefins (Scheme 1c).

At the beginning of screening, simple hex-5-en-1-yl methanesulfonate (**1a**) and phenylsilane (**2a**) were chosen as model substrates. Chiral oxazolineiminopyridine (OIP) iron complex[16] and sodium *tert*-butoxide[15f] were used as a precatalyst and a mild activator, respectively. The reaction was conducted using **1a** (0.5 mmol), **2a** (0.5 mmol), **La**·$FeCl_2$

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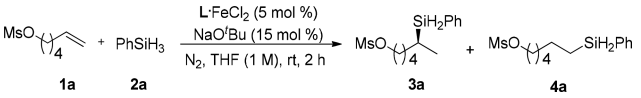
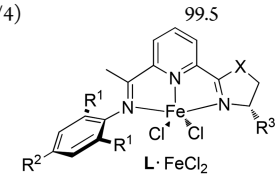
(5 mol %) and NaO^{t}Bu (15 mol %) in a solution of THF at room temperature for 2 h to afford the branched product **3a** and the linear product **4a** in 62% combined yield with 23/77 b/l and 33% ee (entry 1). The use of more sterically hindered 2,6-diisopropyl imine (**Lb**) led to dramatical increase in the regio- and enantioselectivities to 73/27 and 93%, respectively (entry 2). An exciting result with 97/3 b/l and 99.3% ee was obtained using much larger substituent on imine (**Lc**) (entry 3). Neither increasing nor decreasing the steric hindrance on oxazoline did improve the yield and regiomeric ratio (entries 3−5). The imidazoline iminopyridine (IIP, **Lf**)[17] could also promote this reaction to afford **3a** in a higher yield (83%) and regioselectivity (98/2), with slightly lower enantioselectivity (98.7%) (compared entry 6 to 3). Reducing the reaction temperature to 0 °C and slightly increasing the amount of phenylsilane to 1.2 equiv could improve the yield up to 99% with similar high regio- and enantioselectivities (entries 7 and 8). Using 2 mol % catalyst loading on 1 mmol scale, the reaction underwent smoothly to afford **3a** in 95% isolated yield with 96/4 b/l and 99.5% ee (entry 9). The standard conditions were identified as using alkene (1.0 mmol), phenylsiliane (1.2 equiv), **Lc**·FeCl$_2$[18] (2 mol %) and NaO^{t}Bu (6 mol %) in a solution of THF (1 M) at 0 °C for 2 h (Table 1).

Table 1. Optimizations for Asymmetric Hydrosilylation[a]



Entry	L·FeCl$_2$	Yield of **3a**+**4a** (%)[b] (b/l)	ee of **3a** (%)[c]
1	**La**	62 (23/77)	33
2	**Lb**	63 (73/27)	93
3	**Lc**	79 (97/3)	99.3
4	**Ld**	72 (92/8)	97.7
5	**Le**	55 (69/31)	99.4
6	**Lf**	83 (98/2)	98.7
7[d]	**Lc**	91 (96/4)	99.7
8[d,e]	**Lc**	99 (96/4)	99.6
9[d,e,f]	**Lc**	95 (96/4)	99.5

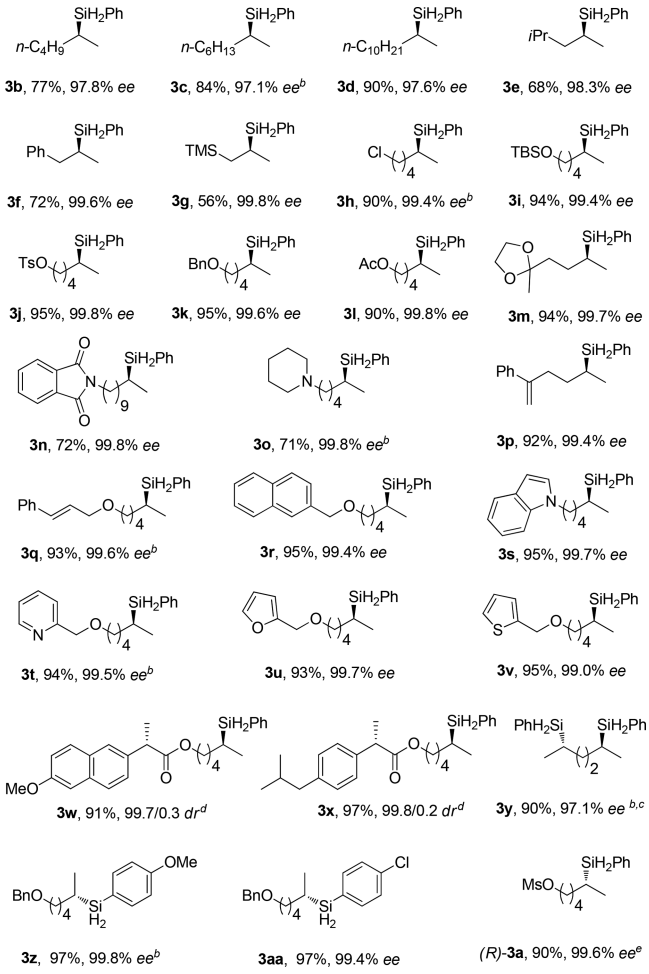
La: R^1 = Me, R^2 = H, R^3 = *i*Pr, X = O
Lb: R^1 = *i*Pr, R^2 = H, R^3 = *i*Pr, X = O
Lc: R^1 = CHPh$_2$, R^2 = OMe, R^3 = *i*Pr, X = O
Ld: R^1 = CHPh$_2$, R^2 = OMe, R^3 = Me, X = O
Le: R^1 = CHPh$_2$, R^2 = OMe, R^3 = *t*Bu, X = O
Lf: R^1 = CHPh$_2$, R^2 = OMe, R^3 = *i*Pr, X = NPh



[a]The reaction was conducted using **1a** (0.5 mmol), **2a** (0.5 mmol), **L**·FeCl$_2$ (5 mol %), NaO^{t}Bu (15 mol %) and THF (0.5 mL) at rt for 2 h. [b]Determined by ^{1}H NMR using mesitylene as an internal standard. [c]Determined by chiral HPLC. [d]0 °C. [e]**1a**/**2a** = 1/1.2. [f]1 mmol scale, **Lc**·FeCl$_2$ (2 mol %), isolated yield.

Under the optimized conditions, the substrate scope is explored in Table 2. The regiomeric ratios and ee values of all reactions were better than 96/4 and 97%, respectively. The reaction of 1-hexene, which is one of the most simple liquid terminal alkenes at room temperature, afforded **3b** with 97/3 b/l and 97.8% ee, which is better than the previously reported Pd-catalyzed result (89/11 b/l and 94% ee).[10] The regio- and enantioselectivities were not obviously influenced by the length of the alkyl chain (**3b**−**3e**). Various functional groups were well tolerated, such as ether, silyl, halide, protected alcohol, ester, acetal, amide and amine. The reaction of alkenes containing 1,1- and 1,2-disubstituted olefins could afford **3p** and **3q** with

Table 2. Scope of Chiral Silanes[a]



[a]Standard conditions: alkenes (1.0 mmol), ArSiH$_3$ (1.2 mmol), **Lc**·FeCl$_2$ (0.02 mmol), NaO^{t}Bu (0.06 mmol), THF (1 mL), 0 °C, 2 h. Isolated yield. Without noted, b/l > 97/3. [b]b/l = 96/4. [c]Using 2.4 mmol of PhSiH$_3$, 96/4 dr. [d]Chiral substrates were used. [e]Using (*R*)-**Lc** as a ligand.

excellent chemoselectivity. Otherwise, polycycles and heterocycles, such as 2-naphthalene, indole, pyridine and furan, were well tolerated to afford the corresponding products in excellent yields with better than 99% ee. In particular, the reaction of sulfur-containing thiophene afforded **3v** in 95% yield with 99.0% ee, which used to be suppressing deactivation by coordination with sulfur compounds in rubber industry.[6b] In addition, the late-stage functionalization of terminal alkenes bearing bioactive molecules, such as naproxen and buprofen, were also presented to deliver **3w** and **3x** in 91% and 97% yield, respectively. The reaction of 1,5-hexadiene with 2.4 equivent of PhSiH$_3$ could afford a disilyl product (**3y**) with 90% yield, 96/4 dr and 97.1% ee. Both the electron-donating and electron-withdrawing groups on phenylsilane were well tolerated to afford **3z** and **3aa** in excellent yields with better than 99% ee. The opposite enantiomer (*R*)-**3a** could be easily obtained using (*R*)-**Lc** as a ligand. The absolute configuration was confirmed by X-ray diffraction of **5f**[19] (the corresponding dihydroxysilane from oxidation[20] of **3f**), and the other products were then assigned by analogy to **5f**.

The gram scale reaction using 0.5 mol % catalyst loading for 24 h could be smoothly performed to afford **3k** in 94% yield

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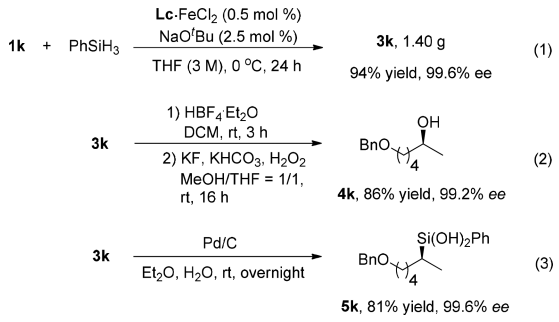
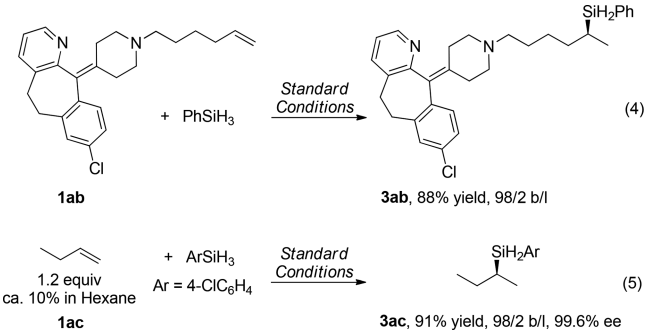
with 99.6% ee (eq 1). The chiral silanes could be further derivatized without any racemization (eqs 2 and 3). The silane



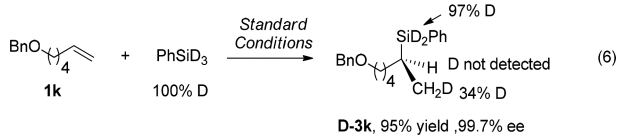
3k could undergo Fleming-Tamao oxidation[21] to afford chiral aliphatic alkan-2-ol **4k** in 86% yield, which is quite challenging to be synthesized. The chiral dihydroxysilane **5k** as an analogue of ketone could be obtained in 81% yield via Pd/C catalytic oxidation.[20]

The reaction could be used to modify complicated drug molecules. Terminal alkene bearing desloratadine was converted to **3ab** in 88% yield with 98/2 b/l (eq 4). Not only



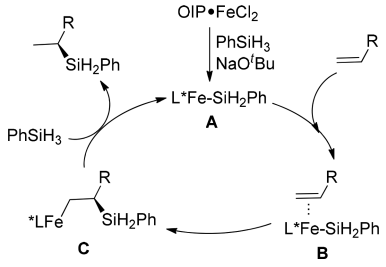
complicated molecules but also very simple alkenes proved to be suitable for this catalytic system. 1-Butene, which is the most simple substrate for this transformation, could be delivered to **3ac** in 91% yield with 99.6% ee (eq 5). To the best of our knowledge, this is the best result on efficient regio- and enantioselective transformation of 1-butene so far.

To probe the possible mechanism of the asymmetric hydrosilylation of terminal aliphatic olefins, the reaction of **1k** with $PhSiD_3$ was performed under standard conditions to afford **D-3k** in 95% yield and 99.7% ee with a deuterium atom on silane stoichiometrically transferring into the methyl group on the hydrosilylation product (eq 6). If the iron-hydride species



were proposed, the alkene insertion to iron-hydride bond would generate secondary alkyl iron species which used to undergo β-hydride elemination due to steric influence of the alkyl group.[22] So the iron silyl species was more possible.[23] The predicted models for stereochemical outcome are proposed in SI. The proposed mechanism for this protocol is shown in Scheme 2. The iron silyl species (**A**) obtained from reducing OIP·$FeCl_2$ by NaO*t*Bu and $PhSiH_3$ coordinate with alkene to generate iron species (**B**). Then alkene inserted into Fe−Si

Scheme 2. Proposed Mechanism



bond to generate iron alkyl species (**C**), which reacted with $PhSiH_3$ to regenerate iron−silicon species and afford the hydrosilylation product. More studies were continuous undergoing in our laboratory to gain an accurate understanding of the mechanism.

In summary, we developed an iron-catalyzed highly Markovnikov-selective and enantioselective hydrosilylation of aliphatic terminal olefins to afford valuable chiral organosilanes. Both simple terminal alkenes and ones containing various functional groups are suitable. This operationally simple and atom-economic protocol could be easily scaled-up in a gram-scale using 0.5 mol % catalyst loading. The development of more asymmetric iron-catalyzed reactions is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01638.

Experimental procedures, characterization data for all compounds (PDF)
X-ray diffraction of **Lc**·$FeCl_2$ (CIF)
X-ray diffraction of **5f** (CIF)

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Notes

The authors declare no competing financial interest.

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