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Hydrosilylation

Enantioselective Hydrosilylation of β,β-Disubstituted Enamides to Construct α-Aminosilanes with Vicinal Stereocenters

*Wen-Wen Zhang and Bi-Jie Li**

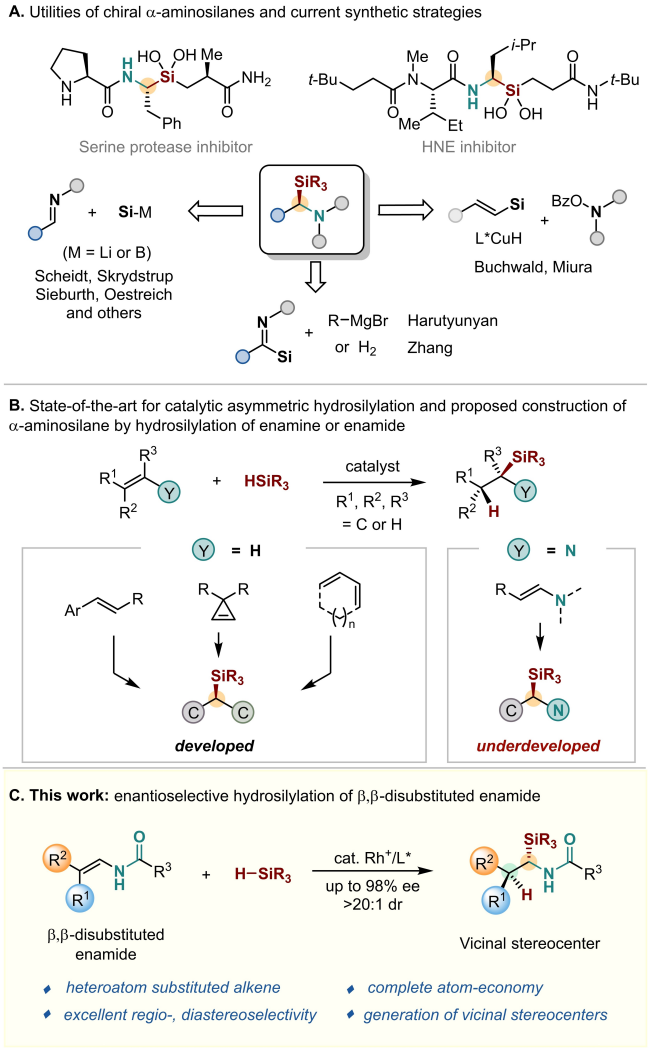
Abstract: Despite the advances in the area of catalytic alkene hydrosilylation, the enantioselective hydrosilylation of alkenes bearing a heteroatom substituent is scarce. Here we report a rhodium-catalyzed hydrosilylation of β,β-disubstituted enamides to directly afford valuable α-aminosilanes in a highly regio-, diastereo-, and enantioselective manner. Stereodivergent synthesis could be achieved by regulating substrate geometry and ligand configuration to generate all the possible stereoisomers in high enantio-purity.

Introduction

Chiral organosilanes have diverse applications in organic synthesis, as they undergo a variety of useful transformations.[1] In addition, sila-substitution has gained increasing attention in medicinal chemistry because silicon-containing molecules exhibit low toxicity and favorable metabolic profiles that complement those of their carbon analogues.[2] Among the diverse array of organosilicon compounds, chiral α-aminosilanes have been a particularly attractive subclass. They serve as mimics of natural α-amino acids and have been incorporated into peptide isosteres.[3] Additionally, chiral α-aminosilanes are key structural motifs in various potent protease inhibitors (Scheme 1A).[4] Consequently, the development of practical methods to construct chiral α-aminosilanes is highly desirable.[5]

However, enantioselective approaches to this structural motif are rather limited.[5,6] Current approaches usually involve the use of a stoichiometric amount of chiral reagent or auxiliary.[7] Very recently, a few notable catalytic enantioselective methods have emerged, including nucleophilic silyl addition to imines,[8] hydroamination of vinylsilanes,[9] and enantioselective addition to aryl silyl imines (Scheme 1A).[10] Nevertheless, these methods have the limitation of substrate availability, product diversity or by-product formation and generate chiral α-aminosilanes containing a single stereocenter.

We reasoned that metal-catalyzed regio- and enantioselective hydrosilylation[11] of alkenes bearing a nitrogen substituent would provide a unique opportunity to access chiral α-aminosilanes with complete atom-economy. How-



Scheme 1. Enantioselective hydrosilylation of heteroatom substituted alkenes to construct α-aminosilanes.

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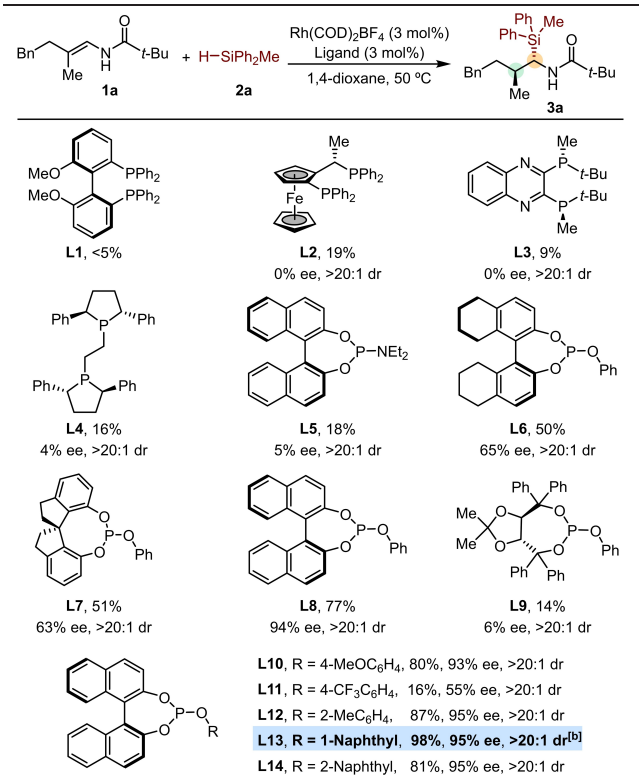
ever, compared to the progresses made in asymmetric hydrosilylation of styrenes,[12] dienes,[13] strained alkenes,[14] enynes,[15] and allenes,[16] much less attention has been paid to the metal-catalyzed hydrosilylation of alkenes bearing a heteroatom such as nitrogen[17] and oxygen[17c,e,g,18] that forms a stereogenic center. To our knowledge, metal-catalyzed highly enantioselective hydrosilylation of enamines or enamides has not been developed so far, despite the distinct structures and notable utilities of the resulting products (Scheme 1B). The key challenge is to identify a chiral catalyst that could enable the hydrosilylation of such heteroatom substituted alkenes while simultaneously control the regio- and enantioselectivities during the C–Si bond-forming process.

We have been interested in the catalytic hydrofunctionalization of enamides,[19] because the resulting chiral amides are versatile compounds in organic synthesis. Importantly, the two-point binding of an enamide to the metal center[20] facilitates the control of regio- and enantioselectivity, which has been demonstrated in the corresponding asymmetric hydrogenation reactions.[21] Inspired by these pioneering work, we have developed coordination-assisted[22] hydrofunctionalization of substituted enamides, including enantioselective C–C[23] and C–B[24] bond-forming reactions. In this context, we sought to further exploit this coordination-assistance to construct C–Si bond to deliver chiral α-aminosilanes, through effective control of the regio- and stereoselectivities. Here we report a rhodium-catalyzed diastereo- and enantioselective hydrosilylation of β,β-disubstituted enamides under mild conditions (Scheme 1C). Starting from readily available substrates, the hydrosilylation proceeds with high stereocontrol and complete atom-economy to afford chiral α-aminosilanes with two stereogenic centers. Moreover, through modulating substrate geometry and ligand configuration, all the possible stereoisomers are readily accessible in high enantio-purity. Mechanistic studies suggest that C–Si forming reductive elimination is turnover-limiting and determines the enantioselectivity.

Results and Discussion

We began our investigation by testing the rhodium-catalyzed hydrosilylation of β,β-disubstituted enamide **1a** with commercially available hydrosilanes **2a** (Table 1). When MeO-BIPHEP **L1** was used as a ligand, no hydrosilylation product was observed. In the presence of electron-rich bisphosphines such as Josiphos **L2**, QuinoxP* **L3** and Ph-BPE **L4**, we started to observe the hydrosilylation product, however, with low ee. Thus, we turned to electron-deficient ligands. Although similarly low ee was observed with phosphoramidite ligand **L5**, significantly improved yield and ee were obtained when we switched to phosphite **L6**. The ligand backbone has an important impact on the enantioselectivity, as revealed by the reactions using ligands **L6**–**L9**. Good yield, high ee and complete diastereoselectivity were obtained when using **L8** as a ligand. Further variation of the aryl group on the phosphite (**L10**–**L14**) indicated that 1-naphthyl substituted ligand **L13** further increased the catalytic activity without compromising the ee.

Table 1: Optimization study.[a]



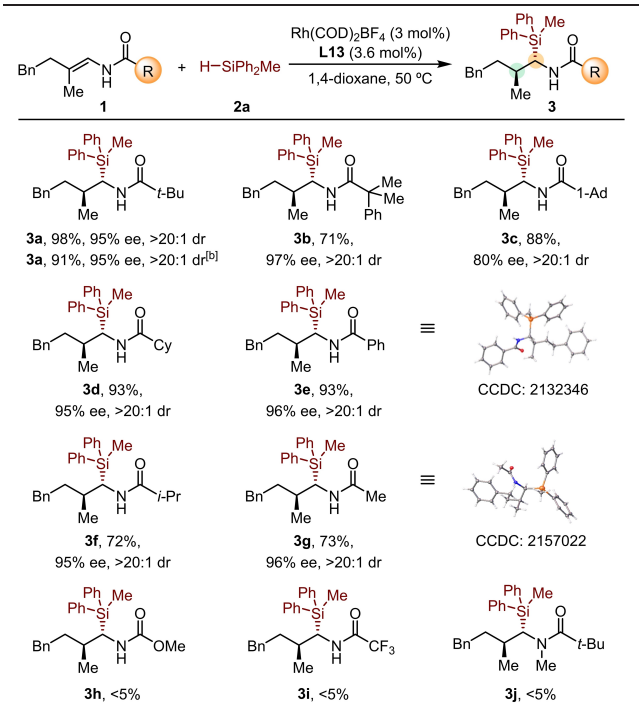
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), Rh(COD)$_2$BF$_4$ (3 mol%) and ligand (3 mol%) in 1,4-dioxane at 50 °C for 15 hours. The dr values were determined by crude ^{1}H NMR. The ee values were determined by chiral HPLC. Isolated yields are reported. [b] Ligand (3.6 mol%), 24 hours.

We explored the scope of the asymmetric hydrosilylation of β,β-disubstituted enamides (Table 2). First, we varied the substituents on the amide group. It appears that the reaction is not sensitive to the steric hindrance, as demonstrated by high ee's obtained for various amides (**3a**–**3g**). However, hydrosilylation of amides **3h** and **3i** failed to deliver the product, indicating that the amide coordination is crucial for the reactivity. In addition, a free NH group is important for the catalytic reaction (see Supporting Information for explanations). The absolute configurations were determined by X-ray structure of **3e** and **3g**.

Subsequently, the scope of the hydrosilane was examined (Table 3). Trialkylsilanes with various chain length were compatible with the reaction conditions (**3k**–**3l**). $PhMe_2SiH$ and $(TMSO)_2MeSiH$ also reacted to afford the hydrosilylation products (**3m**–**3n**), although the enantioselectivities were lower. Further investigation showed that catalytic hydrosilylation with diphenylalkylsilane (**3o**–**3p**) proceeded with lower yields, but high diastereo- and enantio-selectivities.

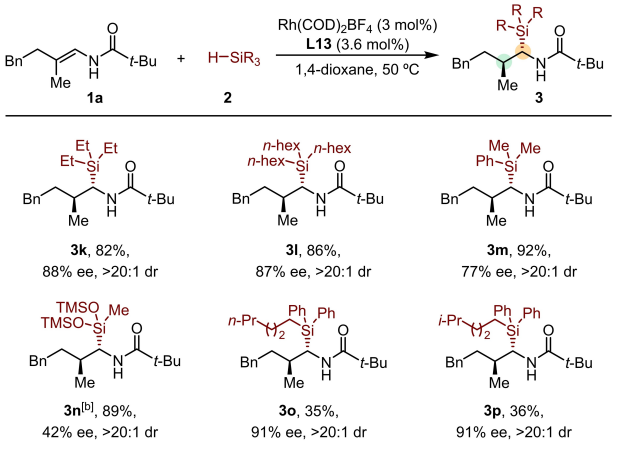
This catalytic hydrosilylation is applicable to diverse β,β-disubstituted enamide substrates (Table 4). Functional groups including aryl halides (**4h**) and aryl ether (**4i**) were

Table 2: Variation of the substituents on the amide group.[a]



[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.15 mmol), $Rh(COD)_2BF_4$ (3.0 mol%) and **L13** (3.6 mol%) in 1,4-dioxane at 50 °C for 24 hours. [b] 1.0 equivalent of **2a**.

Table 3: Substrate scope of hydrosilanes.[a]



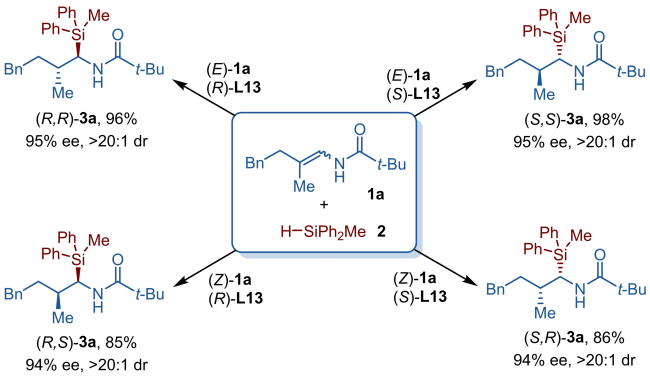
[a] Reactions were performed on 0.10 mmol scale. [b] **L12** (3.6 mol%).

compatible with the catalytic conditions. In addition, functional groups at the alkyl substituents were also tolerated. Enamides containing alkyl halide, ester, acetal, silyl ether, tosylate, phthalimide and carbonate groups (**4j**–**4q**) underwent the catalytic hydrosilylation in good yields and high regio- and enantioselectivities. Furthermore, enantioselective hydrosilylation of a β-ethyl enamide (**4r**) occurred with similar efficiency. In all these cases, complete diastereoselectivities were observed due to the stereospecificity of the catalytic hydrosilylation process.

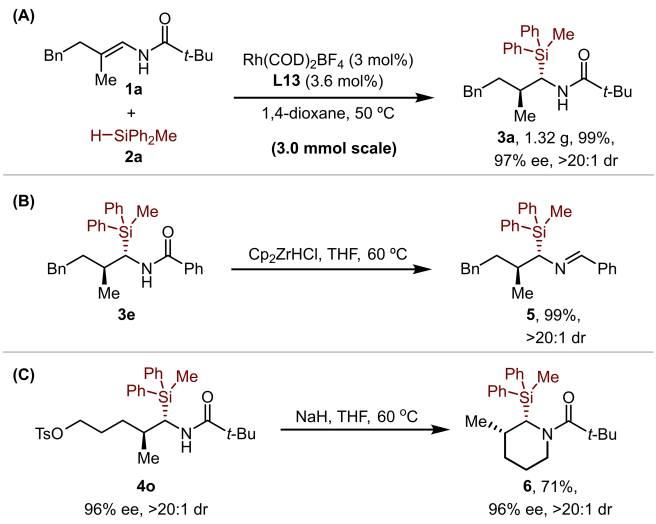
The stereospecificity of the catalytic hydrosilylation provided an opportunity for the stereodivergent synthesis of all possible stereoisomers (Scheme 2).[25] By changing the olefin geometry, the two diastereomers could be obtained in high diastereoselectivities. By switching to the other ligand enantiomer, the other two enantiomers of the hydrosilylation product were generated. Therefore, the four possible stereoisomers of **3a** could be obtained in high diastereo- and enantioselectivities, respectively.

To demonstrate the practicability of this method, a gram-scale reaction was conducted. Product **3a** was obtained without deterioration of yield, diastereo- and enantioselectivity when the reaction was conducted on a 3.0 mmol scale (Scheme 3A). Furthermore, an imine with vicinal stereocenter (**5**) was afforded through the reduction of the amide, which could be hydrolyzed to generate a free aminosilane compound (Scheme 3B). In addition, the hydrosilylation product **4o** underwent an intramolecular cyclization to deliver useful piperidine compound **6** containing α and β stereocenters in good yield and complete diastereocontrol (>20:1) (Scheme 3C).

To assess the metal to ligand ratio during catalysis for this hydrosilylation, the non-linear effect was probed (Fig-

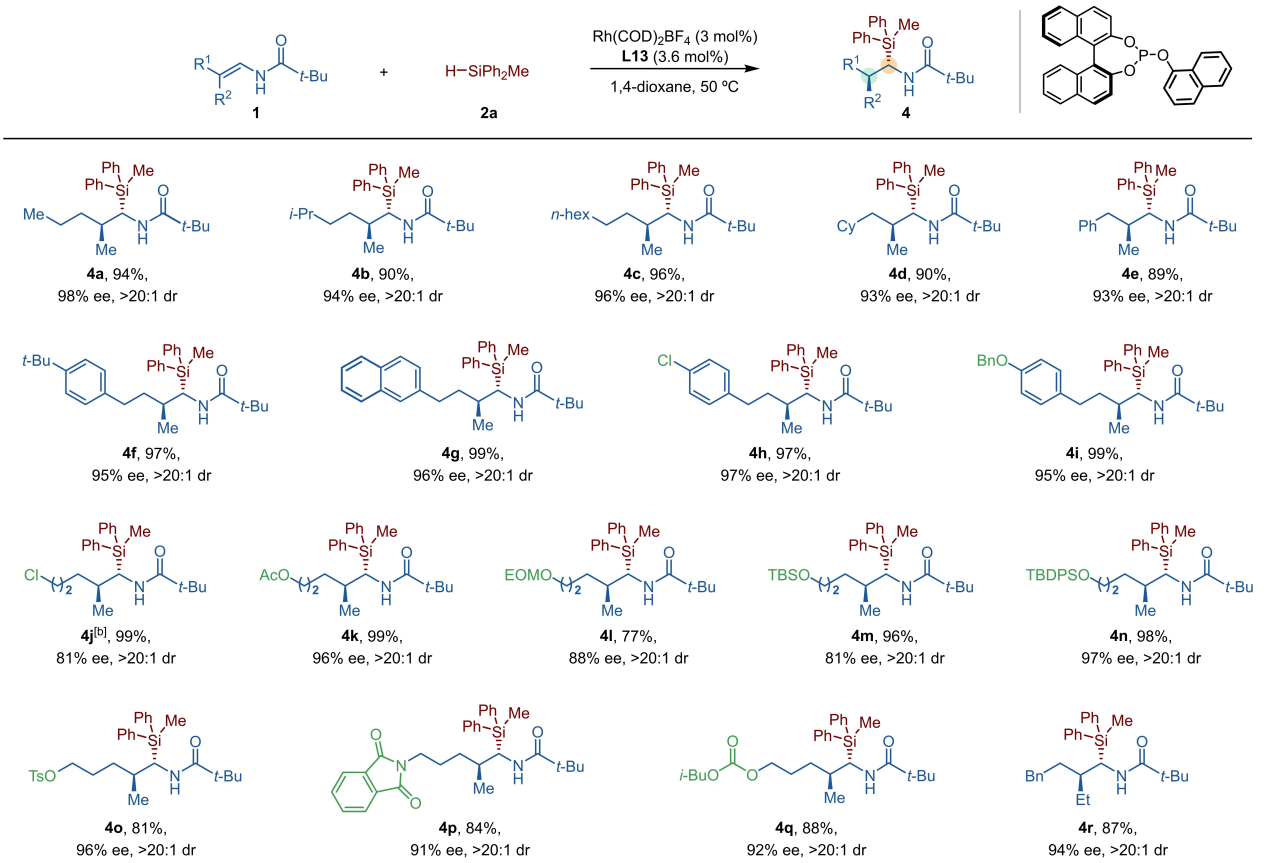


Scheme 2. Stereodivergent synthesis.



Scheme 3. Synthetic applications.

Table 4: Substrate scope of enamides.[a]

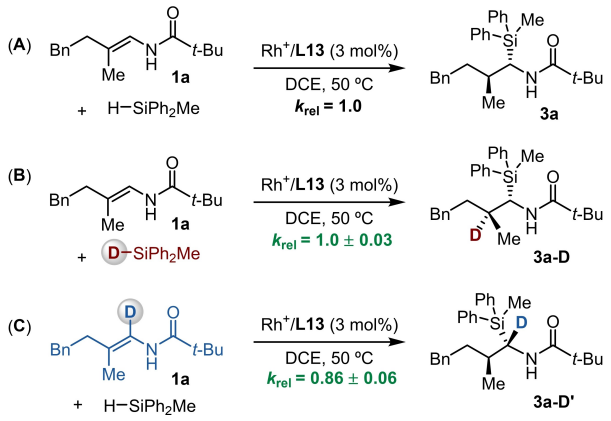


[a] Reactions were performed on 0.10 mmol scale. [b] $Rh(COD)_2BF_4$ (5 mol%), **L13** (6 mol%).

ure 1A). The absence of a non-linear effect likely suggests a 1:1 metal to ligand ratio during catalysis. We further monitored the kinetic behavior of two catalytic reactions using 1:1 and 1:2 M/L ratios. No significant difference was observed (Figure 1B). This is consistent with a 1:1 M/L ratio in the catalytic reaction.

To gain further insight into the mechanism, the kinetic orders with respect to each component were measured using initial-rate method (see Supporting Information for details). The reaction exhibits a first order to enamide, a zeroth order to hydrosilane, and a fractional order to the catalyst (Figure 1C–E). These results suggest that the hydrosilane reacts with the catalyst prior to a turnover-limiting step (TLS) involving the enamide. In addition, the fractional order of the catalyst[26] indicates that a dimeric or polymeric silyl rhodium hydride species was likely involved. Formation of dimeric silyl rhodium hydride through the reaction of hydrosilane with a rhodium complex has been frequently observed,[27] although the attempt to isolate such complex in our system has been unsuccessful so far.

To further distinguish the turnover-limiting step, kinetic isotopic effect (KIE) was measured (Figure 1F and Scheme 4). When $DSiPh_2Me$ was used, a KIE of 1.0 ± 0.04 was obtained (Scheme 4B). This is consistent with a fast reaction of the rhodium catalyst with hydrosilane. To see whether migratory insertion of the alkene into the rhodium hydride bond is turnover-limiting, the initial rate of the reaction of a deuterium labeled enamide was measured (Scheme 4C). However, an inverse KIE was not observed, which indicated that the migratory insertion is not turnover-limiting. Thus, we propose that the C–Si forming reductive elimination is the TLS of the catalytic reaction. The secondary KIE of 1.2 ± 0.1 obtained when using a deuterium labeled enamide as the substrate is consistent with this proposal (Scheme 4C).



Scheme 4. Deuterium labeling experiments.

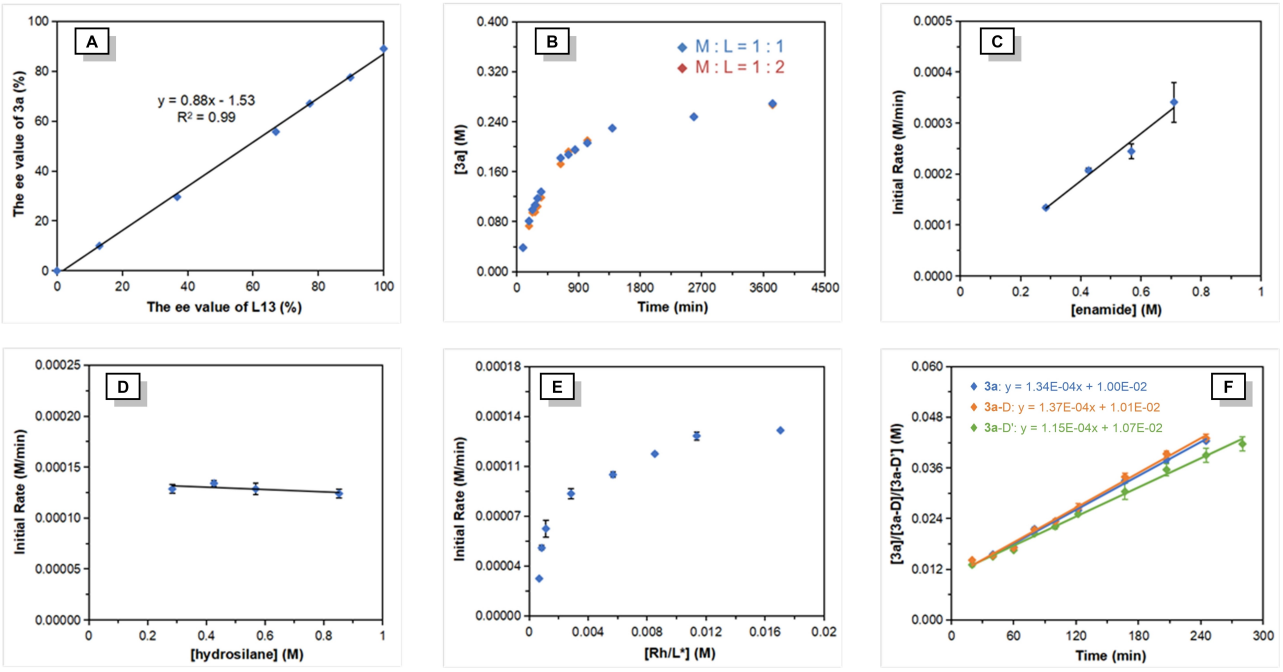
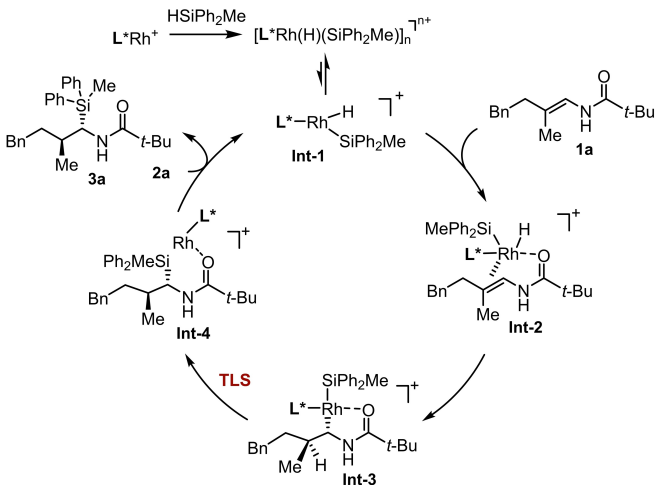


Figure 1. A) Absence of a non-linear effect. B) Catalytic reactions with 1 : 1 and 1 : 2 M/L ratios. C) Kinetic order of enamide. D) Kinetic order of hydrosilane. E) Kinetic order of the catalyst. F) Kinetic isotope effects.

Because the silyl group is directly attached to the metal center during TLS, the identity of the silane would impact the overall reaction rate. To do so, we measured the initial rates of the catalytic reactions with various hydrosilanes. Indeed, the rates of the catalytic reactions are dependent on the hydrosilanes, with a nearly five-fold increase using $HSi(OTMS)_2Me$ (Table 5). These results are consistent with C–Si forming reductive elimination being the TLS.

Table 5: Initial rates of various hydrosilanes.

Hydrosilane	Initial Rate (M/min)	Relative Rate
$H\text{-}SiPh_2Me$	8.8×10^{-5}	1.0
$H\text{-}SiEt_3$	1.1×10^{-4}	1.2
$H\text{-}SiPhMe_2$	1.2×10^{-4}	1.4
$H\text{-}Si(n\text{-}hex)_3$	1.5×10^{-4}	1.7
$H\text{-}SiMe(OTMS)_2$	4.1×10^{-4}	4.6



Scheme 5. Proposed mechanism.

Based on these mechanistic data, the following catalytic cycle was proposed (Scheme 5). Oxidative addition of hydrosilane **2a** to the metal center generates a silyl rhodium hydride intermediate, which likely forms a dimeric or polymeric species. Then enamide **1a** coordinates to the metal center (**Int-2**) before it undergoes migratory insertion into the rhodium hydride bond. The resulting alkyl rhodium intermediate (**Int-3**) is stabilized by internal amide coordination. Finally, a turnover-limiting C–Si forming reductive elimination delivers the hydrosilylation product. It is likely that this step also controls the enantioselectivity.

Conclusion

In conclusion, we have developed a catalytic asymmetric hydrosilylation of β,β-disubstituted enamides. Using a cationic rhodium catalyst bearing a phosphite ligand, this protocol enables the formation of chiral α-aminosilanes with two stereogenic centers in high diastereo- and enantioselectivities. The reaction occurs under mild reaction conditions with readily available substrates. Further understanding of the reaction mechanism and development of asymmetric hydrosilylation of other heteroatom substituted alkenes are ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Alkene Hydrofunctionalization · Hydrosilylation · Rhodium Catalysis · Substrate Directed Reaction · α-Aminosilane

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