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Asymmetric Catalysis Hot Paper

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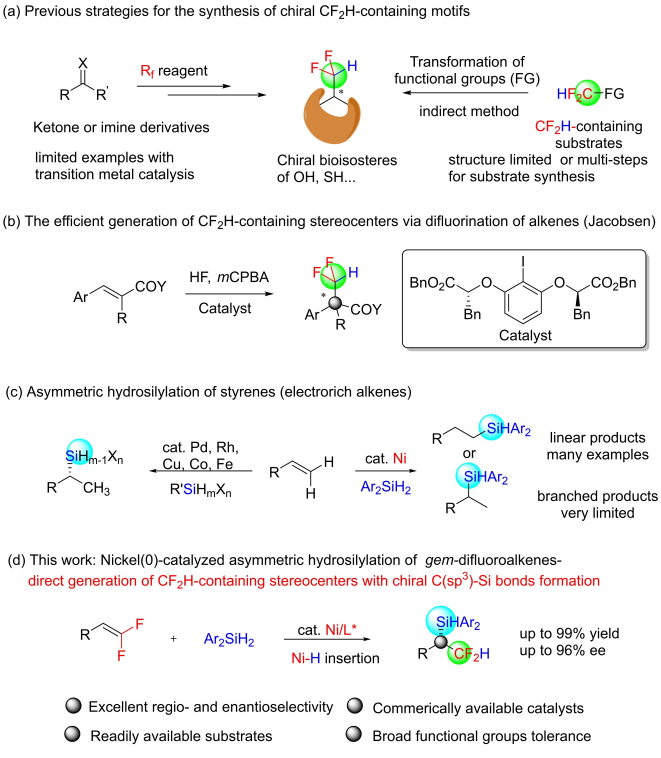
Highly Regio- and Enantioselective Hydrosilylation of *gem*-Difluoroalkenes by Nickel Catalysis

Dachang Bai, Fen Wu, Lingna Chang, Manman Wang, Hao Wu, and Junbiao Chang**

Abstract: *The synthesis of small organic molecules with a difluoromethylated stereocenter is particularly attractive in drug discovery. Herein, we have developed an efficient method for the direct generation of difluoromethylated stereocenters through Ni^0-catalyzed regio- and enantioselective hydrosilylation of gem-difluoroalkenes. The reaction also represents the enantioselective construction of carbon-(sp^3)–silicon bonds with nickel catalysis, which provides an atom- and step-economical synthesis route of high-value optically active α-difluoromethylsilanes. This protocol features readily available starting materials and commercial chiral catalysis, broad substrates spanning a range of functional groups with high yield (up to 99 % yield) and excellent enantioselectivity (up to 96 % ee). The enantioenriched products undergo a variety of stereospecific transformations. Preliminary mechanistic studies were performed.*

The incorporation of fluorinated motifs into organic molecules is of great value in drug discovery and functional materials development.[1] The difluoromethyl group (CF_2H) is an important fluoroalkyl group and notable with a slightly acidic C–H, which has emerged to improve metabolic stability, lipophilicity and bioavailability of molecules.[2] Moreover, the difluoromethyl group has been recognized as a more-lipophilic isostere of hydroxyl or thiol groups in drug design. Particularly, the chiral CF_2H-containing molecules can provide unique hydrogen-bonding interactions with chiral receptors like enzymes or proteins to enhance binding selectivity and biological activity.[1,2] Although a number of methodologies have been developed for the direct incorporation of the CF_2H group into small organic molecules,[3] the enantioselective version still mainly relied on the reactions of ketone or imine derivatives with difluoromethyl synthons R_f (the active group needed to be removed in a separate operation) or the transformations of functional groups in the pre-installed CF_2H-containing substrates (limitations of the specified substrates synthesis) (indirect method, Scheme 1a).[4] In 2016, the Jacobsen group developed an efficient synthesis route to difluoromethylated carbonyl compounds via an asymmetric difluorination of alkenes with easily available reagents and a chiral iodide catalyst (Scheme 1b).[5] An efficient, straightforward and economical approach for the generation of CF_2H-containing stereocenters is very appealing.

On the other hand, chiral organosilicons have been widely applied in organic synthesis and have gradually gained use in medicinal chemistry because of the unique properties and low toxicity of the silicon atom.[6] The transition-metal catalyzed asymmetric hydrosilylation of alkenes is one of the most useful methods for the construction of chiral organosilanes.[7,8] Recently, Hayashi,[8a] Buchwald,[8b] Nishiyama[8c] and Lu[8d,e] and their groups developed the asymmetric Markovnikov hydrosilylation of simple styrenes with different transition metal catalysis



Scheme 1. The generation of CF_2H-containing stereocenters.

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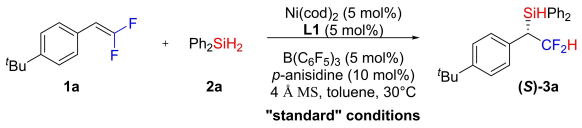
(Scheme 1c). The efficient enantioselective construction of chiral silanes with multi-substituted olefins is still highly desirable. With nickel catalysis, linear products were usually observed using monosubstituted olefins,[9] thus, the regio- and/or enantioselective hydrosilylation is a challenge.[10]

Taking advantage of the fluorine effect, herein, we report the Ni^0-catalyzed enantioselective hydrosilylation of *gem*-difluoroalkenes with silanes for the synthesis of chiral α-difluoromethylsilanes, achieving the direct generation of CF_2H-substituted stereogenic centers combined with enantioselective $C(sp^3)$–Si bond formation using a commercially available chiral ligand (Scheme 1d). Over the past two decades, the versatile and easily available *gem*-difluoroalkenes have been used for the synthesis of complex fluorinated molecules.[11] Diverse nucleophiles have been developed to attack the α-carbon of the alkenes and typically gave monofluoroalkenes via the β-fluorine elimination process. The generation of an α-fluoroalkyl-containing stereocenter from a *gem*-difluoroalkene is still limited.[12] The metal–hydride (M–H) addition to the *gem*-difluoroalkenes would be an attractive strategy to access molecules bearing a CF_2H group, while, up to now, the catalytic enantioselective variant is still unexplored.[13] To avoid the thermodynamically favored β-fluorine elimination and the control of enantioselectivity would be the key challenges of this strategy.[11]

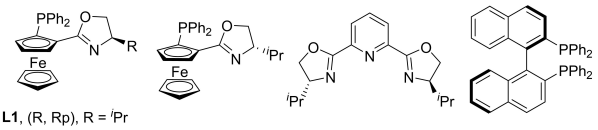
We began our study by identifying chiral Ni catalysts and suitable conditions for the hydrosilylation of *gem*-difluoroalkenes. After systematic investigations of the reaction parameters using *gem*-difluoroalkenes **1a** and Ph_2SiH_2 **2a** as model substrates (Table 1), we found that the desired α-difluoromethylsilane **3a** could be obtained in 99 % yield and 95 % ee (Table 1, entry 1). Notably, no β-F elimination product was observed, nor was any other regioisomer detected. Control experiments showed the $Ni(cod)_2$ was essential for the transformation (entry 2), and no Si–H insertion product **3a** was detected under the air or upon the addition of H_2O respectively (entries 3 and 4). The *p*-anisidine and $B(C_6F_5)_3$ were important for the efficiency, which might accelerate the oxidative addition of Ni^0 to Si–H bond (entries 5–7).[7e] Solvent screening for this hydrosilylation showed that toluene gave the best result (entries 8–12). Both the yield and enantioselectivity were sensitive to skeleton of chiral ligands (entries 13–17). The ligand **L2** with Ph on the oxazoline gave slightly low enantioselectivity and the ^{t}Bu substituted ligand (**L3**) provided the product **3a** in moderate yield with 20 % ee (entries 13 and 14). The absolute configuration of α-difluoromethylsilane **3a** was controlled by the chirality of the oxazoline substituent in the ligand (entry 1 vs. entry 15). Pybox ligand (**L5**) and (*R*)-BINAP (**L6**) didn't promote the transformation (entries 16 and 17).

Having established the optimal conditions, we next explored the scope of this asymmetric hydrosilylation reaction (Scheme 2). The catalyst system turned out to be broadly applicable for *gem*-difluoroalkenes bearing diverse functional groups at the *para* position of the benzene ring (**3a**–**3f**), giving consistently excellent yield (86–99 % yield) and good to excellent enantioselectivity (77–95 % ee). High activity was realized for most substrates. The reaction also worked smoothly for *meta*- and *ortho*-substituted aryl difluoroalkenes (**3g**–**3i**, 50–88 % yield and 86–92 % ee) with slightly lower efficiency, possibly due to steric effects. Other (hetero)aryl-substituted difluoroalkenes gave the corresponding products in 98–99 % yield and 90–95 % ee (**3j**–**3m**). Difluoroalkene containing a *N*-methyl-indolyl group gave the corresponding product **3n** in 42 % yield and 85 % ee. As biaryl compounds are presented in a large number of biologically active natural products,[14] various biaryl *gem*-difluoroalkenes containing electro-withdrawing or electro-donating groups were synthesized. These substituted biaryl difluoroalkenes gave the corresponding α-difluoromethylsilanes in high yield and excellent enantioselectivity (**3o**–**3x**, 74–99 % yield, 90–96 % ee). The absolute configuration of **3q** was confirmed to be (S) by X-ray crystallography (CCDC 2100482).[15] Moreover, difluoroalkenes bearing heterobiaryls such as phenyl substituted thiophenes also worked well to afford the desired products (**3ma**–**3md**, 75–99 % yield, 83–94 % ee). The Lewis basic pyridine product **3na** was obtained with slightly low enantioselectivity (73 % yield, 71 % ee). Replacing the phenyl group with different substituted benzene ring in silanes also tolerated (**3aa**–**3ad**, 44–99 % yield, 91–95 % ee). The more challenging conjugated *gem*-difluoroalkenes was also applicable in the cata-

Table 1: Investigation of reaction conditions.[a]



entry	Variation from the "standard" conditions	yield (%)	ee (%)
1	none	99	95
2	no $Ni(cod)_2$	<1	--
3	under the air	<1	--
4	H_2O (2.0 eq) added	<1	--
5	no *p*-anisidine	21	81
6	no $B(C_6F_5)_3$	74	91
7	no $B(C_6F_5)_3$ and *p*-anisidine	10	79
8	MeO^{t}Bu instead of toluene	86	93
9	Dioxane instead of toluene	89	81
10	THF instead of toluene	95	93
11	DCE instead of toluene	<1	--
12	DMA instead of toluene	<1	--
13	**L2** instead of **L1**	84	87
14	**L3** instead of **L1**	74	20
15	**L4** instead of **L1**	94	-95
16	**L5** instead of **L1**	<1	--
17	**L6** instead of **L1**	<1	--



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Ni(cod)_2$ (5 mol%), L* (5 mol%), $B(C_6F_5)_3$ (5 mol%), p-anisidine (10 mol%), 30 °C in solvent (2.0 mL) under argon, 24 h, isolated yield. The ee was determined by HPLC on a chiral stationary phase.

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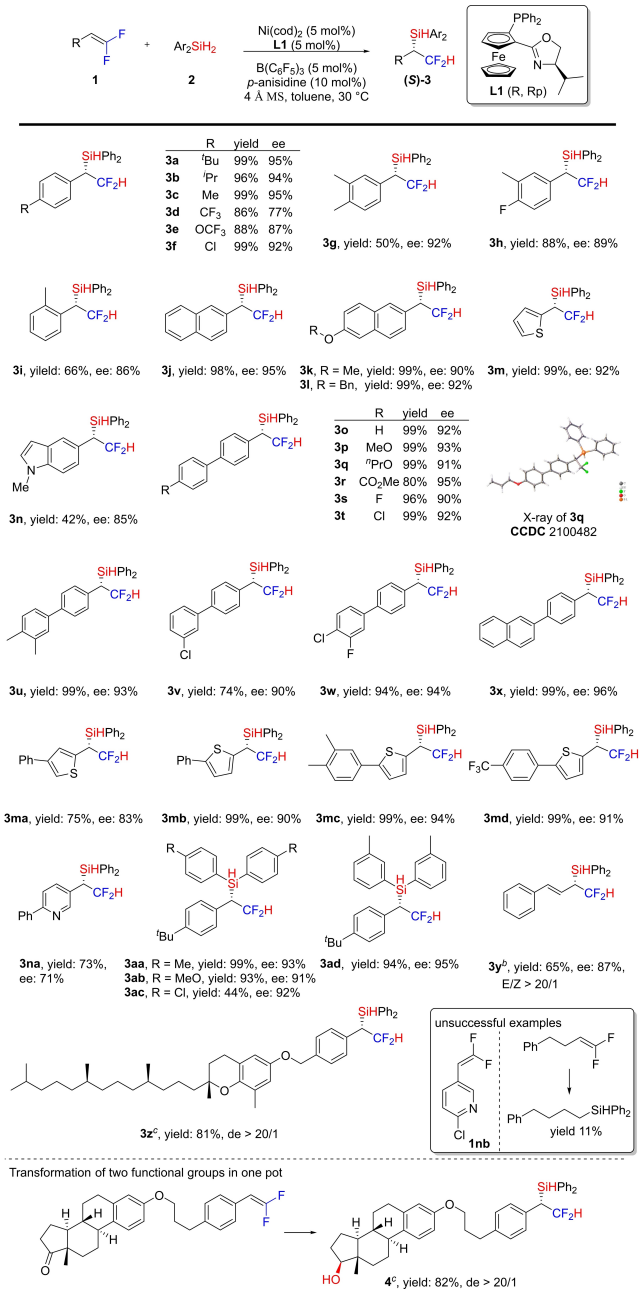
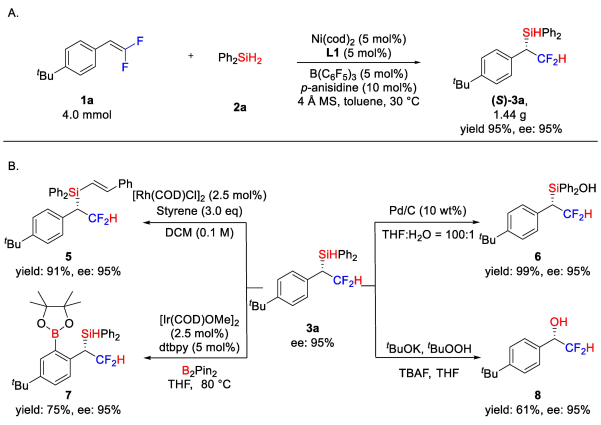


Scheme 2. Scope of the asymmetric hydrosilylation reaction.[a] [a] Reaction conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Ni(cod)_2$ (5 mol%), **L1** (5 mol%), $B(C_6F_5)_3$ (5 mol%), *p*-anisidine (10 mol%), 30 °C, toluene (2.0 mL), isolated yields. [b] 0 °C in MeO^{t}Bu (2.0 mL). [c] $Ni(cod)_2$ (10 mol%), **L1** (10 mol%), $B(C_6F_5)_3$ (10 mol%), *p*-anisidine (20 mol%), THF (2.0 mL), isolated yields.

lytic system under the slightly revised reaction conditions, affording the difluoromethylated allylic silane **3y** with high chemo- and stereoselectivity (65% yield, $E/Z > 20/1$, 87% ee), thus significantly extending the scope of the reaction.[16] Remarkably, this method is well suited for the construction of difluoromethylated stereocenter on complex drug-like molecules with excellent stereoselectivity (**3z**, 81% yield, de > 20/1). Notably, the difluoromethylated stereocenter containing steroid molecule **4** can be prepared by hydrosilylation of the *gem*-difluorovinyl moiety and reduction of carbonyl group in one pot with excellent stereoselectivity (82% yield, de > 20/1). These transformations demonstrate the considerable potential for modifications of bioactive molecules in drug discovery programs. However, the 6-chloropyridin-3-yl substituted *gem*-difluoroalkene **1nb** was found to be unreactive with starting materials recovered. The reaction of 1,1-difluoro-4-phenyl-1-butene gave complex results with 11% yield of the diphenyl(4-phenylbutyl)silane, presumably due to the competitive β-F elimination process, indicating the limitation of this reaction system.

Synthetic utility of this asymmetric hydrosilylation of *gem*-difluoroalkenes has been briefly elaborated (Scheme 3). The reaction was successfully performed on a gram scale, affording 1.44 gram of product **3a** in 95% yield and 95% ee (Scheme 3A). The dehydrogenative silylation of the chiral silane **3a** with styrene in presence of Rh^I catalysis gave product **5** in 91% yield and 95% ee with excellent chemoselectivity. The silane **3a** could be oxidized to monohydroxysilane **6** in 99% yield without erosion of enantiopurity. The borylated product **7**, which is a useful synthetic intermediate, could be obtained in 75% yield and 95% ee through the Ir^I-catalyzed borylation of aromatic C–H bond with the silyl-directing group.[17] As the vicinal fluoro alcohols (fluorohydrins) are useful building blocks and present interesting properties as liquid crystals and bioactive molecules,[1,11] we performed the Fleming–Tamao oxidation of **3a** giving the corresponding chiral α-difluoromethylated alcohol **8** in 61% yield and 95% ee, which provide a noble transition-metal catalysis free approach for the synthesis of difluoromethyl alcohols with excellent enantioselectivity (Scheme 3B).[18]

To gain insights of this hydrosilylation reaction mechanism, some experiments were carried out (Scheme 4). When styrene was used under optimal conditions, linear product **9** was obtained with altered regioselectivity, indicating the electro-withdrawing effect of fluorine atom in *gem*-difluoroalkenes might control the regioselectivity (Scheme 4a). When 1,1-diphenylethylene was used as an additive, the product **3a** was obtained in 68% yield with slightly lower ee (76% ee), showing the 1,1-diphenylethylene might coordi-



Scheme 3. Scale-up reaction and derivatization.

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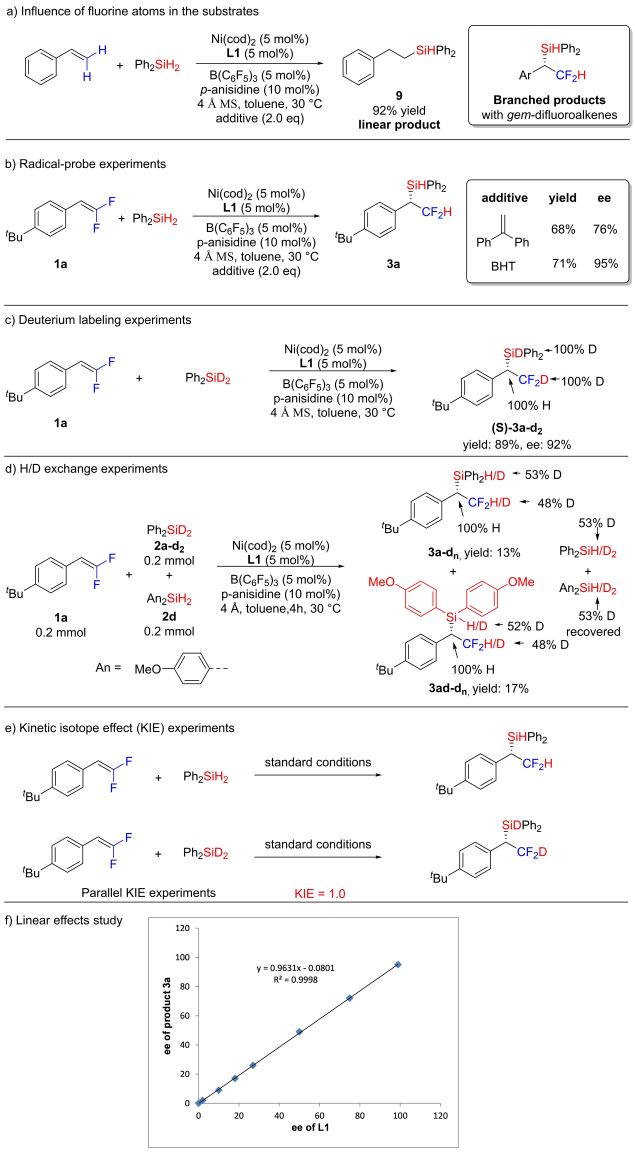
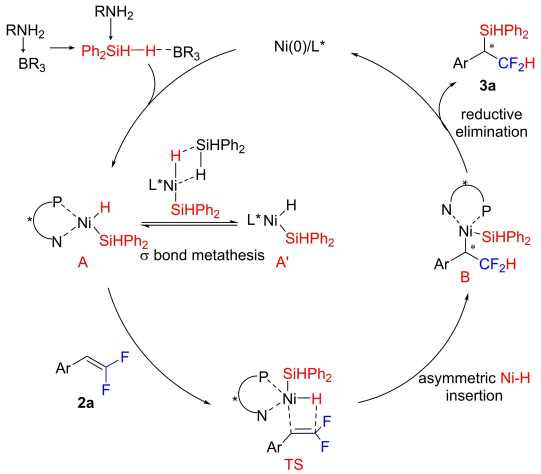


Scheme 4. Mechanistic studies.

nate to the nickel center in the enantio-determining step, which suggested the coordination of *gem*-difluoroalkene to the chiral nickel center involved in the enantio-determining step. In addition, the presence of BHT didn't affect the reaction in terms of yield and enantioselectivity. These results indicated that the reaction proceeded through a Chalk–Harrod pathway instead of a radical pathway (Scheme 4b). To investigate the source of hydrogen, deuterium-labeling experiments were conducted using the deuterated silane Ph_2SiD_2, the deuterated product **3a-d$_2$** was obtained with >95 % D in the difluoromethyl group (Scheme 4c). For the three-component reaction of difluoroalkenes **1a**, Ph_2SiD_2 and **2d**, the approximately 50 % H/D exchange was observed in the difluoromethyl group and Si–H group of both products **3a-d$_n$** and **3ad-d$_n$**, indicating the process of H/D exchange proceeded quickly to equilibrium and might be reversible (Scheme 4d). Moreover, the competition experiments of a deuterium kinetic isotope effect (KIE) study revealed a KIE value of 1.0, suggesting the cleavage of a Si–H bond might not be involved in the turnover-limiting step (Scheme 4e). These results indicated the H/D exchange process reached equilibrium before the generation of benzylic nickel species, and the subsequent C(sp^3)–Si bond formation might be the rate-determining step, which was faster than the β-fluorine elimination. A linear correlation between the enantiomeric excesses of the chiral ligand **L1** and that of the product **3a** suggested a 1:1 coordination of the nickel center with the chiral ligand **L1** in the enantiodetermining transition state (Scheme 4f). In addition, the reaction of Ni/**L1** with Ph_2SiH_2 was performed in toluene-d_8 and monitored by ^{1}H NMR spectroscopy. A new Ni–H signal was observed at −15.8 ppm, indicating the presence of Ni–H intermediates (for details see Supporting Information).

On the basis of the above mechanistic studies and previous reports in the nickel-catalyzed hydrosilylation of alkenes, we proposed the plausible mechanism (Scheme 5).[7,19] The oxidative addition of Ni^0 to Ph_2SiH_2 gave the intermediate **A**. The anisidine and $B(C_6F_5)_3$ might form a frustrated Lewis pair and open the N–B linkage to accelerate the oxidative addition of Ni^0 to the Si–H bond.[20] The hydrogen in the Ni–H species (intermediate **A**) could be exchanged quickly with that of Ph_2SiH_2 through σ-bond metathesis. The insertion of Ni–H species into the α-carbon of the *gem*-difluoroalkene owing to the σ-withdrawing induced effect by fluorine atoms, giving the chiral α-difluoromethylated intermediate **B**, the by-product diphenyl(4-phenylbutyl)silane from the 1,1-difluoro-4-phenyl-1-butene in Scheme 2 indicated the formation of intermediate **B**. Subsequent reductive elimination of intermediate **B** gave the final product **3a** and regenerated the Ni^0 catalyst.

In summary, we have developed an efficient and economical method for the direct generation of difluoromethylated stereocenters through nickel(0)-catalyzed enantioselective hydrosilylation of *gem*-difluoroal-



Scheme 5. Proposed mechanism.

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kenes with commercially available chiral ligands, affording various chiral α-difluoromethylsilanes in good to excellent enantioselectivity (71–96 % ee). These reactions are highly efficient for most substrates (42–99 % yield) and highly regioselective. Mechanistic studies including linear effects and deuterium-labeling studies have been performed. This method may provide insight for further development of enantioselective construction of $C(sp^3)$–Si bonds and generation of CF_2H-containing stereocenters. The detailed mechanism of this transformation including the role of anisidine and novel difluoromethylated stereocenters synthesis 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 supplementary material of this article.

Keywords: α-Difluoromethylsilanes · Enantioselectivity · *gem*-Difluoroalkenes · Hydrosilylation · Nickel

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