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Iridium-Catalyzed, β-Selective C(sp^3)−H Silylation of Aliphatic Amines To Form Silapyrrolidines and 1,2-Amino Alcohols

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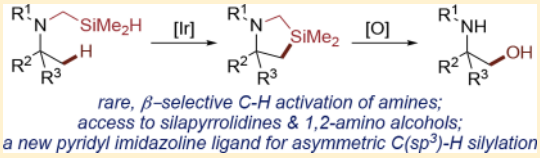
Supporting Information

ABSTRACT: The functionalization of unactivated C(sp^3)−H bonds of aliphatic amines catalyzed by transition-metal complexes is important because amine-based functionality is present in a majority of biologically active molecules and commercial pharmaceuticals. However, such reactions are underdeveloped and challenging to achieve in general because the basicity and reducing properties of alkylamines tends to interfere with potential reagents and catalysts. The functionalization of C−H bonds β to the nitrogen of aliphatic amines to form prevalent 1,2-amino functionalized structures is particularly challenging because the C−H bond β to nitrogen is stronger than the C−H bond α to nitrogen, and the nitrogen in the amine or its derivatives usually directs a catalyst to react at more distal γ- and δ-C−H bonds to form 5- or 6-membered metallacyclic intermediate. The enantioselective functionalization of a C−H bond at any position in amines also has been vexing and is currently limited to reactions of specific, sterically hindered, cyclic structures. We report iridium-catalyzed, β-selective silylations of unactivated C(sp^3)−H bonds of aliphatic amines to form silapyrrolidines that are both silicon-containing analogs of common saturated nitrogen heterocycles and precursors to 1,2-amino alcohols by Tamao−Fleming oxidation. These silylations of amines are accomplished by introducing a simple methylene linker between the heteroatom and silicon that has not been used previously for the silylation of C−H bonds. The reactions occur with high enantioselectivity when catalyzed by complexes of new chiral, pyridyl imidazoline ligands, and the rates of reactions with catalysts of these highly basic ligands are particularly fast, occuring in some cases at or even below room temperature.



INTRODUCTION

Aliphatic amines are important organic compounds that are commonly found in natural products and pharmaceuticals,[1] including almost half of the top 200 drugs by prescriptions in the US in 2016.[2] Therefore, methods that enable efficient synthesis or selective functionalization of aliphatic amines have been pursued intensively. Among various approaches to the synthesis of functionalized aliphatic amines, site-selective functionalization of traditionally unreactive C−H bonds catalyzed by transition metals is attractive because this process can occur with reactants that contain fewer functional groups than those typically needed to prepare products containing amino groups, and it can introduce functional groups at sites that are usually unreactive in amines.

However, the development of site-selective functionalization of C−H bonds of aliphatic amines has been limited because of the challenges associated with this process. For example, functionalizations of the C−H bonds in aliphatic amines often occur at highly activated C−H bonds α to nitrogen,[3] rather than the stronger C−H bonds more distal to nitrogen.[4] In addition, the oxidative conditions of many C−H functionalization processes lead to *N*-oxides, and amines can bind strongly to transition metals, thereby deactivating the catalyst.[5]

Various strategies have been explored to address these challenges and achieve the site-selective functionalization of C−H bonds in aliphatic amines (Figure 1a). One of the most common strategies is to convert the free amine to an amide or imine.[6,7] The installation of such auxiliary moieties can prevent the deactivation of the catalyst and the oxidation of the amine, facilitate the coordination of substrate to the catalyst, and direct the functionalization to specific sites. Reactions of such amine derivatives by coordination of the metal to this nitrogen atom usually provide products from functionalization of the C−H bonds γ or δ to the amino group by forming a five- or six-membered metallacyclic intermediate (i of Figure 1a).[6−8] A second strategy involves the complexation of the amine to a Brønsted acid or Lewis acid. This complexation deactivates the C−H bonds proximal to the nitrogen and directs the reaction to occur at C−H bonds more distal to this atom (ii of Figure 1a).[9] A third strategy involves the installation of a removable linker between the nitrogen of the aliphatic amine and the functional group that is being introduced, thereby rendering the process intramolecular (iii of Figure 1a).[10] This strategy has led to the metal-catalyzed insertion of nitrenes into C−H bonds, most commonly into tertiary or activated secondary C−H bonds.[10a,b]

We considered that the silylation of C−H bonds could enable the selective functionalization of amines because hydrosilanes are reducing and would not oxidize the amine nitrogen.[11] In addition, the oxidative addition of an Si−H bond would likely occur in the presence of amines, render the subsequent C−H bond silylation intramolecular, and address both deactivation of the catalysts by free amines and overcome

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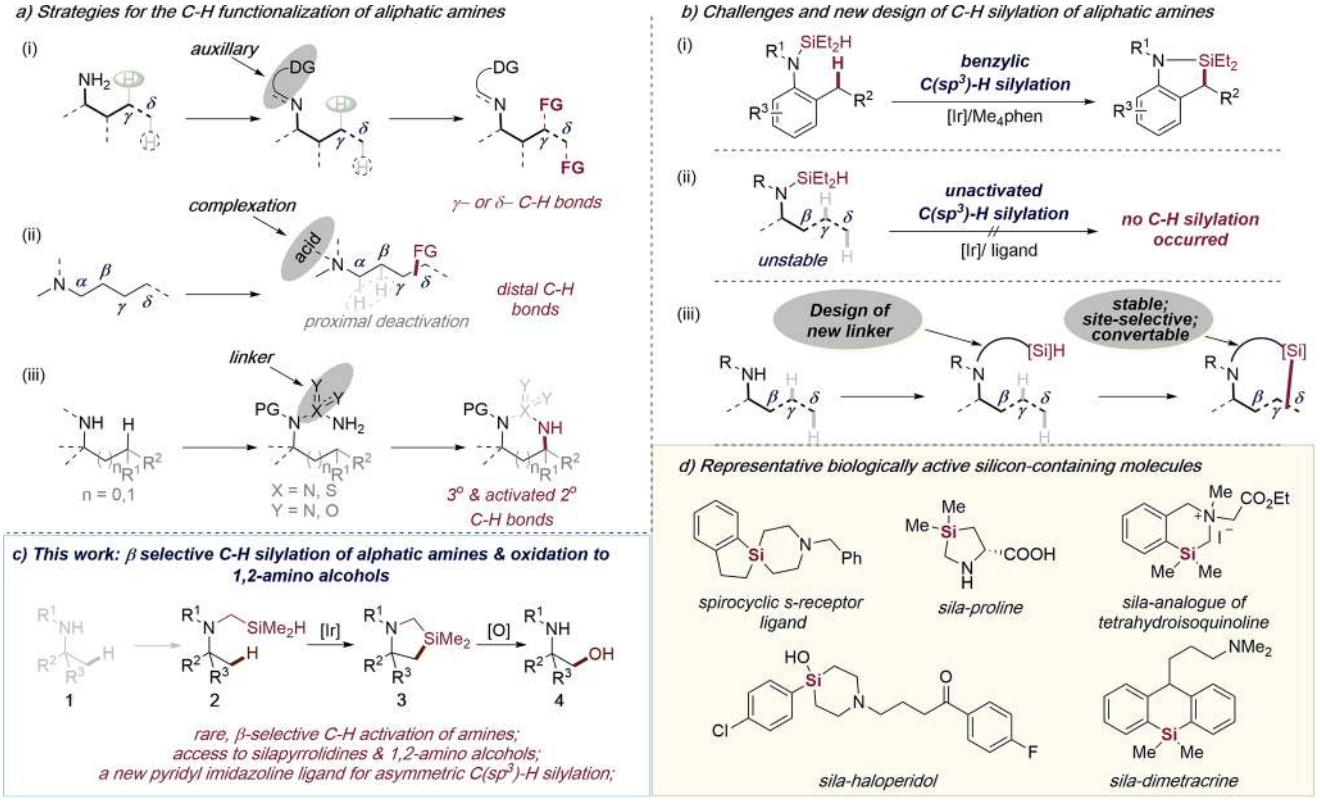

Figure 1. Strategies, challenges, conception, realization, and potential applications of C−H functionalization of aliphatic amines.

the tendency of metal complexes to react at the C−H bond α to nitrogen. Previously, our group reported metal-catalyzed intramolecular silylations of unactivated C(sp^3)−H bonds by first forming an O−Si bond between the alcohol and a silane.[12] However, efforts to develop the silylation of C(sp^3)−H bonds in amines by first forming an N−Si bond led to functionalizations of only activated benzylic C(sp^3)−H bonds in aniline derivatives (i of Figure 1b).[13] Reactions of hydrosilyl amines derived from aliphatic amines underwent disproportionation and decomposition due to the instability of the N−Si linker (ii of Figure 1b). Therefore, a different approach to link the nitrogen and silicon that would withstand the conditions of the C−H bond functionalization process was needed for the silylation of alkylamines to occur in high yield (iii of Figure 1b).

Enantioselective functionalizations of C−H bonds[14−16] in aliphatic amines at any site are rare, perhaps because poorly selective catalysts can form by coordination of the achiral amine reactants. Only one enantioselective functionalization of a C(sp^3)−H bond in an aliphatic amine has been reported,[16e] and this reaction requires a cyclic secondary amine that possesses two adjacent fully substituted carbons.

We report an iridium-catalyzed, β-selective silylation of unactivated C(sp^3)−H bonds of aliphatic amines (Figure 1c). The reaction is enabled by linking a hydrosilyl unit to the nitrogen by a methylene group, which is easily prepared by alkylation of the amine with a chloromethylsilane.[17] The reaction occurs enantioselectively at one of two enantiotopic methyl groups when conducted with a pyridyl imidazoline ligand. Such ligands have rarely been used in asymmetric catalysis, but were evaluated because they make the metal center more electron rich than those in complexes of more common chiral, nitrogen-based ligands.[18] The silapyrrolidine products are known to possess unique physical and chemical properties for medical chemistry (Figure 1d)[19] and are precursors to 1,2-amino alcohols after oxidation of the Si−C bond.

RESULTS AND DISCUSSION

1. Initial Silylations of Aliphatic Amines. Our studies on the silylation of C−H bonds in aliphatic amines began with reactions of silylmethylamines. This substrate was selected because the silylmethylamine would be more stable to hydrolysis and disproportionation than a silylamine, cyclization would form five-membered ring products that have been studied as silicon-containing analogs of pyrrolidine derivatives, and oxidation would generate a hemiaminal that would hydrolyze to an amino alcohol. This amino alcohol would result from an overall hydroxylation β to the amino group. Such hydroxylations have been limited to hydrazone derivatives that require over six steps to prepare or secondary amines that contain two hindered tertiary alkyl groups on the nitrogen in a ring.[6i,20]

To identify conditions for the iridium-catalyzed, β-selective silylation of the alkyl C−H bond of a silylmethylamine, the reactions of (silylmethyl)amine **2a** with various iridium catalysts generated from [Ir(cod)OMe]$_2$ and dinitrogen ligands **L1**−**L6** were evaluated (Table 1). The reaction conducted with 4,4′-di-*tert*-butylbipyridine **L1** as the ligand and norbornene as the hydrogen acceptor at 100 °C formed silapyrrolidine **3a** in 46% yield (entry 1). Higher yields were obtained from the reactions with catalysts containing phenanthroline ligands **L2**−**L5** than with those containing 4,4′-di-*tert*-butylbipyridine **L1** (entries 2−5). Among these phenanthroline ligands, sterically hindered 2-substituted phenanthrolines **L4** and **L5**, used previously for the iridium-

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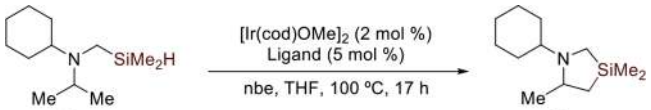
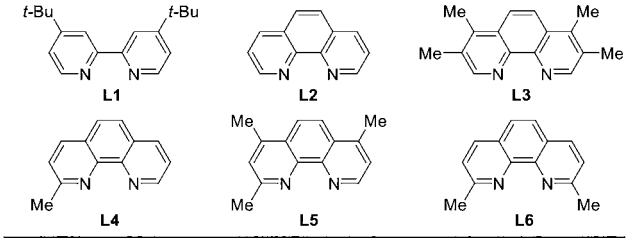
Table 1. Evaluation of Conditions for the Intramolecular C−H Silylation of 2a[a]



entry	ligand	conversion (%)	yield (%)
1	**L1**	>99	46
2	**L2**	>99	85
3	**L3**	>99	86
4	**L4**	>99	90
5	**L5**	>99	90
6	**L6**	98	26
7	none	70	6
8[b]	**L5**	>99	91



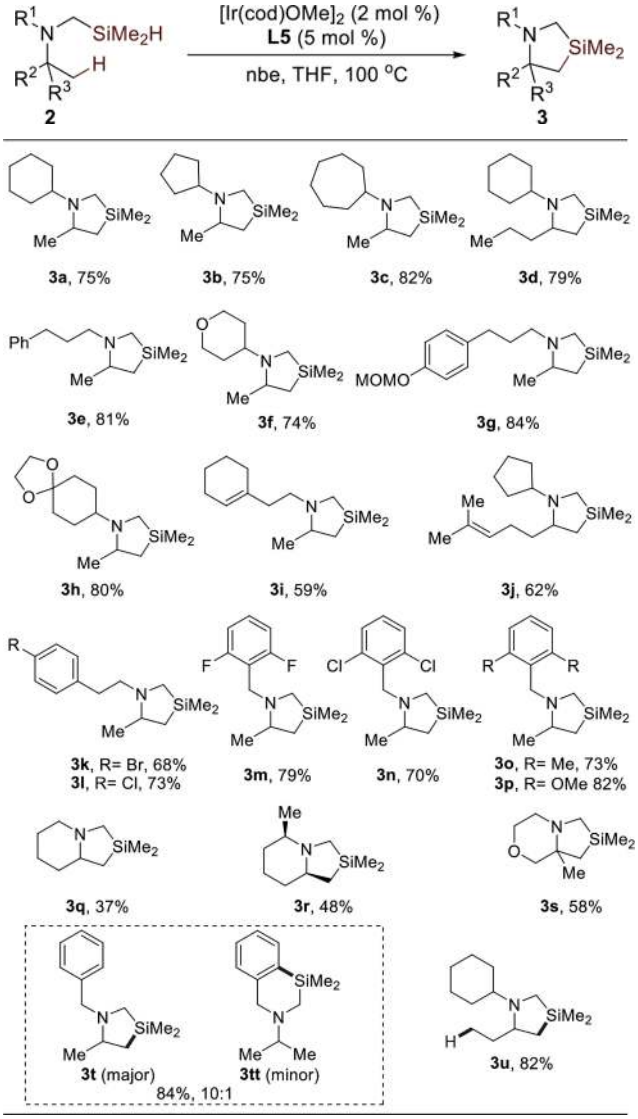
[a]Reactions were conducted on a 0.10 mmol scale in an N_2-filled glovebox, and the yields refer to ^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [b]Reaction was conducted on a 0.25 mmol scale using a standard air-free technique outside an N_2-filled glovebox.

catalyzed, intermolecular silylation of aromatic C−H bonds,[21] formed more active catalysts than did **L2** and **L3**. However, 2,9-disubstituted phenanthroline **L6**, which is more sterically hindered than **L4** and **L5**, generated a less active catalyst (entry 6). In the absence of any dinitrogen ligand, the reaction gave the silylation product **3a** in a very low yield (6%, entry 7), indicating that (silylmethyl)amine **2a** itself cannot serve as a ligand to generate an active iridium catalyst for this C−H bond functionalization. Although we typically assembled our silylation reactions in an N_2-filled glovebox, a high yield of the silapyrrolidine product **3a** was obtained from the reaction conducted by standard air-free techniques without a glovebox (entry 8).

2. Scope of the Silylation of Aliphatic Amines. Having established conditions for the silylation of (silylmethyl)amine **2a**, we investigated the scope of the reaction (Table 2). β-Selective silylations of amines that contain various cyclic or acyclic alkyl groups proceeded smoothly, affording silapyrrolidines **3a**−**3e** in high yields (75−82%). A wide range of functional groups, such as a cyclic ether (**3f**), ketals (**3g** and **3h**), cyclic and linear alkenes (**3i** and **3j**), various aryl halides (**3k**−**3n**), and a methoxy group (**3p**) were tolerated. Fused silapyrrolidines **3q**−**3s** also were obtained. The unique properties of silicon-containing pyrrolidine derivatives have been highlighted, but current methods for their preparation require both enamine and ester groups in the precursors to the silaproline derivatives,[22] whereas the catalytic method we report provides silapyrrolidines from amines without the need for additional functionality in the reactant.

To investigate the selectivity of the silylation process toward β- and γ-C−H bonds, the silylation of amines **2t** and **2u** containing γ-C−H bonds that are aliphatic and aromatic were conducted. Although aromatic C−H bonds are generally more reactive than alkyl C−H bonds toward functionalizations

Table 2. Scope of the Intramolecular C−H Silylation of Aliphatic Amine[a]



[a]Yields refer to isolated yields, and the reactions were conducted on a 0.10−0.25 mmol scale.

through organometallic intermediates, the reaction of amine **2t** gave silapyrrolidine **3t** from silylation of the β-C(sp^3)−H bond as the major product over benzosilapiperidine **3tt**, which would form from silylation of the γ-C(sp^2)−H bond. Reaction of **2u**, which contains primary β- and γ-C(sp^3)−H bonds and secondary β-C(sp^3)−H bonds, formed the sole product **3u** from silylation of the primary β-C(sp^3)−H bond.

3. Formation of 1,2-Amino Alcohols. 1,2-Aminoalcohols are common substructures and precursors to natural products and pharmaceuticals and could be envisioned to form by hydroxylation of aliphatic amines. Part of our design of the silylmethylamine substructure for the silylation of C−H bonds was based on the anticipated Tamao-Fleming oxidation of the silapyrrolidine to an aminal that would hydrolyze to the 1,2-amino alcohol. However, this process requires conditions in which the Si−C bond oxidizes in preference to the amine nitrogen.

To identify conditions for the Tamao-Fleming oxidation of silapyrrodine **3**, we conducted reactions with various oxidants

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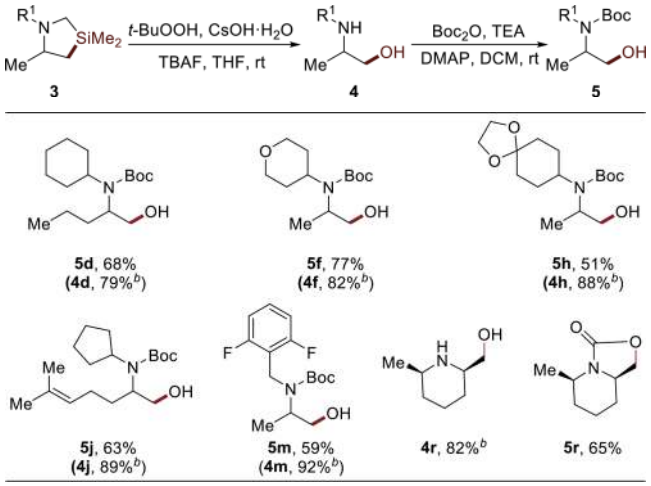
and additives. These experiments showed that the oxidation of **3** formed amino alcohol **4** in good yields (79−92%), as determined by NMR spectroscopy, without oxidation of the amino group in **4** when conducted with *tert*-butyl hydroperoxide (TBHP), cesium hydroxide, and tetrabutylammonium fluoride (TBAF) in THF at room temperature.

Examples of the formation of 1,2-amino alcohols are shown in Table 3. Functional groups, such as a cyclic ether (**4f**), a ketal (**4h**), an alkene (**4j**), and a fluoroaryl group (**4m**), were tolerated under the oxidation conditions. To facilitate the isolation by silica-gel chromatography, amino alcohols **4** from the oxidation of silapyrrolidines **3** were converted to the corresponding carbamate **5** by treatment with di-*tert*-butyl carbonate and base.

Table 3. 1,2-Amino Alcohols Derived from C−H Silylation Products[a]



[a]The yields of **5** refer to isolated yields over two steps. [b]The yields of **4** refer to ^{1}H NMR yields with CH_1Br_2 as internal standard.

To demonstrate the applicability of the combined C−H bond silylation and C−Si bond oxidation to the functionalization of more complex amines, the hydroxylation of a derivative of propranolol, one of the top 200 drugs by prescription in 2016 in US, was conducted (Figure 2). Under our conditions for the β-selective silylation of C(sp^3)−H bonds of aliphatic amines, silapyrrolidine **7** was obtained in 90% yield. Oxidation of silapyrrolidine **7** formed amino alcohol **8**, which was then transformed to carbamate **9** in 54% yield over 2 steps.

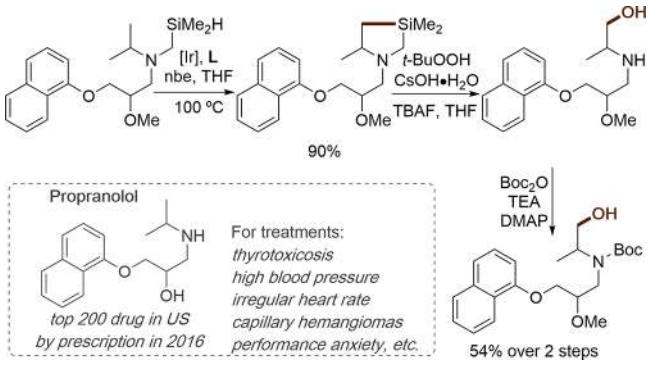
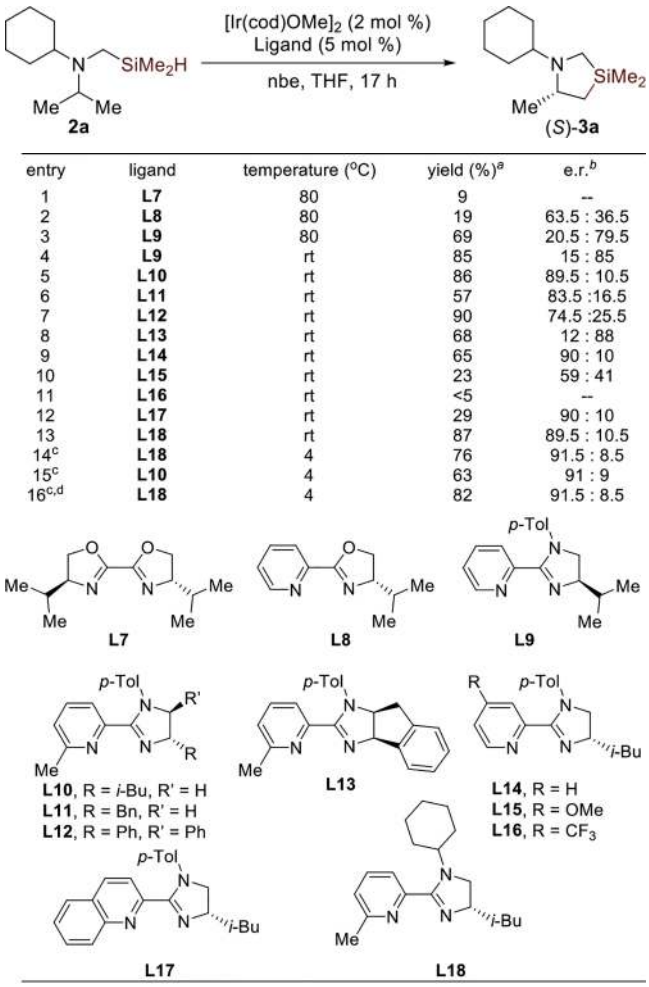


Figure 2. Modification of pharmaceutical molecule via C−H silylation and C−Si oxidation.

4. Enantioselective Silylation of Aliphatic Amines. To develop a catalyst for the site-selective and enantioselective silylation,[11d23] of unactivated C(sp^3)−H bonds of aliphatic amines, iridium complexes of a variety of chiral *N*,*N*-ligands were investigated as catalysts for the silylation of amine **2a** (Table 4). An initial survey with chiral, nitrogen-based ligands that are commonly used in asymmetric catalysis, such as bis(oxazoline) ligands (e.g., **L7**, entry 1) and pyridyl oxazoline ligands (e.g., **L8**, entry 2) that formed highly enantioselective catalysts in our prior silylation of both C(sp^2)−H and C(sp^3)−H bonds,[23e23f] showed that the reactivity and enantioselectivity of catalysts formed from these common classes of chiral *N*,*N*-based structures were low.

Table 4. Evaluation of Asymmetric C−H Silylation of 2a[a]



entry	ligand	temperature (°C)	yield (%)[a]	e.r.[b]
1	**L7**	80	9	--
2	**L8**	80	19	63.5 : 36.5
3	**L9**	80	69	20.5 : 79.5
4	**L9**	rt	85	15 : 85
5	**L10**	rt	86	89.5 : 10.5
6	**L11**	rt	57	83.5 :16.5
7	**L12**	rt	90	74.5 :25.5
8	**L13**	rt	68	12 : 88
9	**L14**	rt	65	90 : 10
10	**L15**	rt	23	59 : 41
11	**L16**	rt	<5	--
12	**L17**	rt	29	90 : 10
13	**L18**	rt	87	89.5 : 10.5
14[c]	**L18**	4	76	91.5 : 8.5
15[c]	**L10**	4	63	91 : 9
16[c,d]	**L18**	4	82	91.5 : 8.5

[a]Determined by ^{1}H NMR analysis with 1,3,5,-trimethoxybenzene as an internal standard. [b]Determined by chiral GC and the absolute configuration of (*S*)-**3a** was determined by comparion with known compound after trasformation (see SI). [c]72 h. [d][Ir(cod)Cl]$_2$ instead of [Ir(cod)OMe]$_2$.

We hypothesized that ligands containing an imidazoline unit might generate more active catalysts than those containing an oxazoline unit because the imidazoline unit is more basic than an oxazoline.[18] This greater basicity of the imidazoline group would lead to more electron-rich catalysts than those containing an oxazoline donor and to higher reactivity toward the oxidative addition of C−H bonds.

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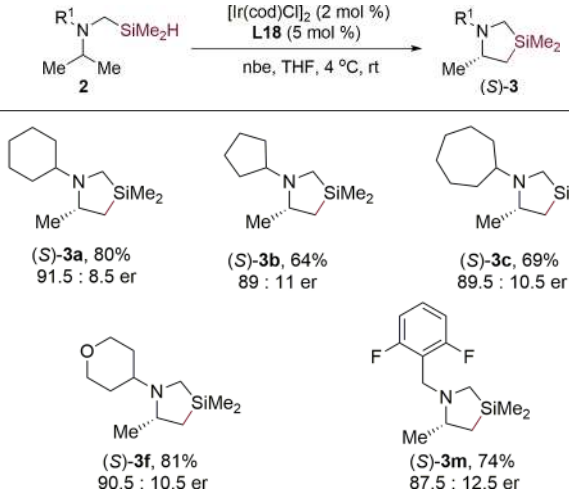
To test this hypothesis, pyridyl imidazoline **L9** was synthesized. Indeed, the silylation of **2a** with **L9** occurred in a higher yield and a higher enantioselectivity than that with pyridyl oxazoline **L8** (entry 2 and 3). The enantioselective silylation of the C−H bond occurred even at room temperature to give **3a** in a higher yield (85%) and a higher e.r. (15:85) than those from the analogous reaction at 80 °C (entry 4). This reactivity of the catalyst derived from the new pyridyl imidazoline ligand **L9** was higher than that of any prior metal-catalyzed silylation of a C−H bond.

To increase the enantioselectivity of the site-selective silylation of amine **2a** further, we prepared various pyridyl imidazoline ligands (**L10**−**L16**, **L18**) and a quinolinyl imidazoline ligand **L17** and studied the reactivity and enantioselectivity of the catalysts derived from those ligands. Investigation of the effect of substituents on the imidazoline fragment of the ligand (**L10**−**L13**) showed that the enantioselectivity of the reaction with **L10** as ligand was a higher 89.5:10.5 (entry 5−8). Modification of the pyridine fragment of the ligand (entry 9−12, **L14**−**L17**) showed that the reaction with the quinolinyl imidazoline **L17** formed the product with high enantioselectivity, but in only 29% yield (entry 12). However, the reaction catalyzed by the complex generated from the *N*-alkyl imidazoline **L18** occurred with both high reactivity and selectivity (entry 13). The reaction catalyzed by this complex occurred in a good yield (76%), even below room temperature, to provide the silylation product in a high e.r. (89.5:10.5) (entries 14 and 15). The yield of **3a** increased to 82% from 76% without decrease of the enantioselectivity by using $[Ir(cod)Cl]_2$ as the source of iridium, rather than $[Ir(cod)OMe]_2$ (entry 16). These results represent the first examples in which pyridyl imidazoline ligands have been used for a catalytic reaction that occurs with high enantioselectivity.[24]

Having identified conditions for the site- and enantioselective silylation of an aliphatic C−H bond in **2a**, the enantioselectivity of the reactions of other aliphatic amines was examined (Table 5). (Silylmethyl)amines containing a cyclohexyl group (**2a**), a cyclopentyl group (**2b**), and a cycloheptyl group (**2c**) were converted to the corresponding silapyrrolidines (*S*)-**3a**−**3c** with high enantioselectivity (89:11 to 91.5:8.5 e.r.) in good yields. In addition, the reaction of amine **2f**, bearing an oxygen-containing six-membered ring, and amine **2m**, containing a less sterically bulky 2,6-difluorobenzyl group, gave the chiral, silapyrrolidines (*S*)-**3f** and (*S*)-**3m** in high yields with good enantioselectivity. Thus, the reaction can tolerate a saturated heteroaryl ring, does not require a secondary alkyl group on nitrogen, and can be conducted with a removable group (2,6-difluorobenzyl group) from the nitrogen to generate a chiral, cyclic secondary silapyrrolidine poised for further modifications at nitrogen.

Table 5. Scope of the Asymmetric C−H Silylation of Aliphatic Amines[a]



[a]Yields refer to isolated yields, the enantiomeric values were determined by chiral GC analysis or ^{1}H NMR analysis with (*S*)-*O*-acetylmandelic acid.

CONCLUSIONS

Prior studies on the functionalization of aliphatic amines required the amines to be very sterically hindered or to be transformed to amides or imines. A series of features of the substrate and catalyst in the current work have overcome these limitations and enabled regioselective functionalization of an alkylamine by a hydrosilyl unit with unusual selectivity for the C−H bond located β to nitrogen. First, the incorporation of a methylene linker between the nitrogen of the amine and the silyl group using a chloromethylsilane as reagent address the instability of the N−Si bond observed during prior studies of the silylation of amines and leads to a rare β-selectivity for the functionalization of C−H bonds in aliphatic amines due to the size of the intermediate metallacycle. Second, the use of a silane as the functionalizing reagent avoids metal binding or oxidation at the electron pair of nitrogen that usually occurs during the functionalization of C−H bonds in amines under oxidative conditions, and oxidation of the C−Si bonds in the presence of the amine unit allows the 1,2-amino alcohol to be generated, representing a formal β-hydroxylation of alkylamines. Third, linking of silicon to the nitrogen atom avoids deactivation of the catalyst by the amines and prevents reaction at the weaker α C−H bond because reaction at this position would form a strained, four-membered azasiletidine. Finally, the design of modular, chiral, imidazoline ligands led to enantioselective catalysts that are highly reactive, thereby enabling reactions to occur at or below room temperature and enhancing stereoselectivity. Further applications of these principles and new ligands for catalytic enantioselective reactions are 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.8b10428.

Experimental procedures, characterization data, NMR spectra for new compounds (PDF)

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Notes
The authors declare no competing financial interest.

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■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257.

(2) (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348. (b) https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/2016Top200PharmaceuticalPrescriptionSalesPosterLowResV2.pdf. Retrieved October 19, 2018.

(3) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. Direct α-alkylation of primary aliphatic amines enabled by CO2 and electrostatics. *Nat. Chem.* **2018**, *10*, 1037.

(4) (a) Li, C.-J. Cross-Dehydrogenative Coupling (CDC): Exploring C−C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. New Strategic Reactions for Organic Synthesis: Catalytic Asymmetric C−H Activation α to Nitrogen as a Surrogate for the Mannich Reaction. *J. Am. Chem. Soc.* **2003**, *125*, 6462. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322.

(5) Smalley, A. P.; Gaunt, M. J. Mechanistic Insights into the Palladium-Catalyzed Aziridination of Aliphatic Amines by C−H Activation. *J. Am. Chem. Soc.* **2015**, *137*, 10632.

(6) (a) Shao, Q.; Wu, Q.-F.; He, J.; Yu, J.-Q. Enantioselective γ-C(sp^3)−H Activation of Alkyl Amines via Pd(II)/Pd(0) Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 5322. (b) Kapoor, M.; Liu, D.; Young, M. C. Carbon Dioxide-Mediated C(sp^3)−H Arylation of Amine Substrates. *J. Am. Chem. Soc.* **2018**, *140*, 6818. (c) Cabrera, P. J.; Lee, M.; Sanford, M. S. Second-Generation Palladium Catalyst System for Transannular C−H Functionalization of Azabicycloalkanes. *J. Am. Chem. Soc.* **2018**, *140*, 5599. (d) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. Buttressing Salicylaldehydes: A Multipurpose Directing Group for C(sp^3)−H Bond Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 1073. (e) Liu, Y.; Ge, H. Site-selective C−H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017**, *9*, 26. (f) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. Catalytic C(sp^3)−H Arylation of Free Primary Amines with an exo Directing Group Generated In Situ. *Angew. Chem., Int. Ed.* **2016**, *55*, 9084. (g) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. Pd-Catalyzed γ-C(sp^3)−H Arylation of Free Amines Using a Transient Directing Group. *J. Am. Chem. Soc.* **2016**, *138*, 14554. (h) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. Palladium-catalysed transannular C−H functionalization of alicyclic amines. *Nature* **2016**, *531*, 220. (i) Huang, Z.; Wang, C.; Dong, G. A Hydrazone-Based exo-Directing-Group Strategy for β C−H Oxidation of Aliphatic Amines. *Angew. Chem., Int. Ed.* **2016**, *55*, 5299. (j) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. Ligand-enabled cross-coupling of C(sp^3)−H bonds with arylboron reagents via Pd(II)/Pd(0) catalysis. *Nat. Chem.* **2014**, *6*, 146. (k) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. Efficient Alkyl Ether Synthesis via Palladium-Catalyzed, Picolinamide-Directed Alkoxylation of Unactivated C(sp^3)−H and C(sp^2)−H Bonds at Remote Positions. *J. Am. Chem. Soc.* **2012**, *134*, 7313.

(7) (a) Nadres, E. T.; Daugulis, O. Heterocycle Synthesis via Direct C-H/N-H Coupling. *J. Am. Chem. Soc.* **2012**, *134*, 7. (b) Chuentragool, P.; Parasram, M.; Shi, Y.; Gevorgyan, V. General, Mild, and Selective Method for Desaturation of Aliphatic Amines. *J. Am. Chem. Soc.* **2018**, *140*, 2465.

(8) Xu, Y.; Dong, G. sp^3 C−H activation via exo-type directing groups. *Chem. Sci.* **2018**, *9*, 1424.

(9) (a) Lee, M.; Sanford, M. S. Platinum-Catalyzed, Terminal-Selective C(sp^3)−H Oxidation of Aliphatic Amines. *J. Am. Chem. Soc.* **2015**, *137*, 12796. (b) Chen, K.; Wang, D.; Li, Z.-W.; Liu, Z.; Pan, F.; Zhang, Y.-F.; Shi, Z.-J. Palladium catalyzed C(sp^3)-H acetoxylation of aliphatic primary amines to γ-amino alcohol derivatives. *Org. Chem. Front.* **2017**, *4*, 2097.

(10) (a) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. Expanding the substrate scope for C-H amination reactions: Oxidative cyclization of urea and guanidine derivatives. *Org. Lett.* **2006**, *8*, 1073. (b) Olson, D. E.; Du Bois, J. Catalytic C-H amination for the preparation of substituted 1,2-diamines. *J. Am. Chem. Soc.* **2008**, *130*, 11248. (c) Osberger, T. J.; White, M. C. N-Boc Amines to Oxazolidinones via Pd(II)/Bis-sulfoxide/Brønsted Acid Co-Catalyzed Allylic C−H Oxidation. *J. Am. Chem. Soc.* **2014**, *136*, 11176. (d) Strambeanu, I. I.; White, M. C. Catalyst-Controlled C-O versus C-N Allylic Functionalization of Terminal Olefins. *J. Am. Chem. Soc.* **2013**, *135*, 12032.

(11) For other selected silylation of unactivated C-H bonds, see: (a) Tsukada, N.; Hartwig, J. F. Intermolecular and Intramolecular, Platinum-Catalyzed, Acceptorless Dehydrogenative Coupling of Hydrosilanes with Aryl and Aliphatic Methyl C−H Bonds. *J. Am. Chem. Soc.* **2005**, *127*, 5022. (b) Ghavtadze, N.; Melkonyan, F. S.; Gulevich, A. V.; Huang, C.; Gevorgyan, V. Conversion of 1-alkenes into 1,4-diols through an auxiliary-mediated formal homoallylic C−H oxidation. *Nat. Chem.* **2014**, *6*, 122. (c) Frihed, T. G.; Pedersen, C. M.; Bols, M. Synthesis of All Eight L-Glycopyranosyl Donors Using C-H Activation. *Angew. Chem., Int. Ed.* **2014**, *53*, 13889. (d) Murai, M.; Takeshima, H.; Morita, H.; Kuninobu, Y.; Takai, K. Acceleration Effects of Phosphine Ligands on the Rhodium-Catalyzed Dehydrogenative Silylation and Germylation of Unactivated C(sp^3)−H Bonds. *J. Org. Chem.* **2015**, *80*, 5407. (e) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. Silylation of C-H bonds in aromatic heterocycles by an Earth-abundant metal catalyst. *Nature* **2015**, *518*, 80. (f) Chen, Q.-A.; Klare, H. F. T.; Oestreich, M. Brønsted Acid-Promoted Formation of Stabilized Silylium Ions for Catalytic Friedel−Crafts C−H Silylation. *J. Am. Chem. Soc.* **2016**, *138*, 7868. (g) Yin, Q.; Klare, H. F. T.; Oestreich, M. Friedel−Crafts-Type Intermolecular C−H Silylation of Electron-Rich Arenes Initiated by Base-Metal Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 3204. (h) Ma, Y.; Wang, B.; Zhang, L.; Hou, Z. Boron-Catalyzed Aromatic C−H Bond Silylation with Hydrosilanes. *J. Am. Chem. Soc.* **2016**, *138*, 3663. (i) Ma, X.; Kucera, R.; Goethe, O. F.; Murphy, S. K.; Herzon, S. B. Directed C−H Bond Oxidation of (+)-Pleuromutilin. *J. Org. Chem.* **2018**, *83*, 6843.

(12) (a) Simmons, E. M.; Hartwig, J. F. Catalytic functionalization of unactivated primary C−H bonds directed by an alcohol. *Nature* **2012**, *483*, 70. (b) Li, B.; Driess, M.; Hartwig, J. F. Iridium-Catalyzed Regioselective Silylation of Secondary Alkyl C-H Bonds for the Synthesis of 1,3-Diols. *J. Am. Chem. Soc.* **2014**, *136*, 6586. (c) Karmel, C.; Li, B.; Hartwig, J. F. Rhodium-Catalyzed Regioselective Silylation of Alkyl C−H Bonds for the Synthesis of 1,4-Diols. *J. Am. Chem. Soc.* **2018**, *140*, 1460.

(13) Li, Q.; Driess, M.; Hartwig, J. F. Iridium-Catalyzed Regioselective Silylation of Aromatic and Benzylic C-H Bonds Directed by a Secondary Amine. *Angew. Chem., Int. Ed.* **2014**, *53*, 8471.

DOI: 10.1021/jacs.8b10428
J. Am. Chem. Soc. 2018, 140, 18032−18038

(14) For reviews of enantioselective C−H functionalization, see: (a) Davies, H. M. L.; Beckwith, R. E. J. Catalytic Enantioselective C−H Activation by Means of Metal−Carbenoid-Induced C−H Insertion. *Chem. Rev.* **2003**, *103*, 2861. (b) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908. (c) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. Enantioselective C(sp^3)−H bond activation by chiral transition metal catalysts. *Science* **2018**, *359*, No. eaao4798.

(15) For early examples of enantioselective C(sp^2)−H functionalization, see: (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective Activation of C(sp^2)-H and C(sp^3)-H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Albicker, M. R.; Cramer, N. Enantioselective Palladium-Catalyzed Direct Arylations at Ambient Temperature: Access to Indanes with Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2009**, *48*, 9139. (c) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. Pd(II)-Catalyzed Enantioselective C−H Olefination of Diphenylacetic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 460. (d) Anas, S.; Cordi, A.; Kagan, H. B. Enantioselective synthesis of 2-methyl indolines by palladium catalysed asymmetric C(sp^3)-H activation/cyclisation. *Chem. Commun.* **2011**, *47*, 11483. (e) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. Fused Indolines by Palladium-Catalyzed Asymmetric C-C Coupling Involving an Unactivated Methylene Group. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (f) Chu, L.; Xiao, K.-J.; Yu, J.-Q. Room-temperature enantioselective C-H iodination via kinetic resolution. *Science* **2014**, *346*, 451.

(16) For selected examples of enantioselective C(sp^3)−H functionalization, see: (a) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. Palladium(II)-Catalyzed Enantioselective C(sp^3)−H Activation Using a Chiral Hydroxamic Acid Ligand. *J. Am. Chem. Soc.* **2014**, *136*, 8138. (b) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. Ligand-accelerated enantioselective methylene C(sp^3)−H bond activation. *Science* **2016**, *353*, 1023. (c) Wang, H.; Tong, H.-R.; He, G.; Chen, G. An Enantioselective Bidentate Auxiliary Directed Palladium-Catalyzed Benzylic C−H Arylation of Amines Using a BINOL Phosphate Ligand. *Angew. Chem., Int. Ed.* **2016**, *55*, 15387. (d) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. Enantioselective amine α-functionalization via palladium-catalysed C−H arylation of thioamides. *Nat. Chem.* **2017**, *9*, 140. (e) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. Palladium-Catalyzed Enantioselective C−H Activation of Aliphatic Amines Using Chiral Anionic BINOL-Phosphoric Acid Ligands. *J. Am. Chem. Soc.* **2017**, *139*, 1412. (f) Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. Formation of α-chiral centers by asymmetric β-C(sp^3)−H arylation, alkenylation, and alkynylation. *Science* **2017**, *355*, 499. (g) Pedroni, J.; Cramer, N. Enantioselective C−H Functionalization−Addition Sequence Delivers Densely Substituted 3-Azabicyclo[3.1.0]hexanes. *J. Am. Chem. Soc.* **2017**, *139*, 12398.

(17) Labrecque, D.; Nwe, K. T.; Chan, T. H. Synthesis of (aminomethyl)silanes with the use of an easily cleavable carbon-silicon bond. *Organometallics* **1994**, *13*, 332.

(18) Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Smyth, M. P. A Novel General Route for the Preparation of Enantiopure Imidazolines. *J. Org. Chem.* **2002**, *67*, 3919.

(19) (a) Franz, A. K.; Wilson, S. O. Organosilicon Molecules with Medicinal Applications. *J. Med. Chem.* **2013**, *56*, 388. (b) Barraza, S. J.; Denmark, S. E. Synthesis, Reactivity, Functionalization, and ADMET Properties of Silicon-Containing Nitrogen Heterocycles. *J. Am. Chem. Soc.* **2018**, *140*, 6668.

(20) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. Palladium-catalysed C-H activation of aliphatic amines to give strained nitrogen heterocycles. *Nature* **2014**, *510*, 129.

(21) Cheng, C.; Hartwig, J. F. Iridium-Catalyzed Silylation of Aryl C−H Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 592.

(22) Chung, J. Y. L.; Shevlin, M.; Klapars, A.; Journet, M. Asymmetric Synthesis of N-Boc-(R)-Silaproline via Rh-Catalyzed Intramolecular Hydrosilylation of Dehydroalanine and Continuous Flow N-Alkylation. *Org. Lett.* **2016**, *18*, 1812.

(23) (a) Lee, T.; Wilson, T. W.; Berg, R.; Ryberg, P.; Hartwig, J. F. Rhodium-Catalyzed Enantioselective Silylation of Arene C−H Bonds: Desymmetrization of Diarylmethanols. *J. Am. Chem. Soc.* **2015**, *137*, 6742. (b) Murai, M.; Matsumoto, K.; Takeuchi, Y.; Takai, K. Rhodium-Catalyzed Synthesis of Benzosilolometallocenes via the Dehydrogenative Silylation of C(sp^2)−H Bonds. *Org. Lett.* **2015**, *17*, 3102. (c) Zhang, Q.-W.; An, K.; Liu, L.-C.; Yue, Y.; He, W. Rhodium-Catalyzed Enantioselective Intramolecular C-H Silylation for the Syntheses of Planar-Chiral Metallocene Siloles. *Angew. Chem., Int. Ed.* **2015**, *54*, 6918. (d) For an example of enantioselective C−H silylation of cyclopropane derivatives, see: Lee, T.; Hartwig, J. F. Rhodium-Catalyzed Enantioselective Silylation of Cyclopropyl C−H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 8723. (e) Su, B.; Hartwig, J. F. Ir-Catalyzed Enantioselective, Intramolecular Silylation of Methyl C−H Bonds. *J. Am. Chem. Soc.* **2017**, *139*, 12137. (f) Su, B.; Zhou, T.-G.; Li, X.-W.; Shao, X.-R.; Xu, P.-L.; Wu, W.-L.; Hartwig, J. F.; Shi, Z.-J. A Chiral Nitrogen Ligand for Enantioselective, Iridium-Catalyzed Silylation of Aromatic C−H Bonds. *Angew. Chem., Int. Ed.* **2017**, *56*, 1092.

(24) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. Chiral pyridylimidazolines: synthesis, arene ruthenium complexes and application in asymmetric catalysis. *J. Chem. Soc. Perkin. Trans. 1* **2001**, 1500.

DOI: 10.1021/jacs.8b10428
J. Am. Chem. Soc. 2018, 140, 18032−18038