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Ir-Catalyzed Enantioselective, Intramolecular Silylation of Methyl C–H Bonds

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Abstract

We report highly enantioselective intra-molecular, silylations of unactivated, primary C(sp^3)–H bonds. The reactions form dihydrobenzosiloles in high yields with excellent enantioselectivities by functionalization of enantiotopic methyl groups under mild conditions. The reaction is catalyzed by an iridium complex generated from $[Ir(COD)OMe]_2$ and chiral dinitrogen ligands that we recently disclosed. The C–Si bonds in the enantio-enriched dihydrobenzosiloles were further transformed to C–Cl, C–Br, C–I, and C–O bonds in final products. The potential of this reaction was illustrated by sequential C(sp^3)–H and C(sp^2)–H silylations and functionalizations, as well as diastereoselective C–H silylations of a chiral, natural-product derivative containing multiple types of C–H bonds. Preliminary mechanistic studies suggest that C–H cleavage is the rate-determining step.

Reactions that form carbon–silicon bonds are valuable because carbon–silicon bonds can be transformed to a variety of carbon–carbon and carbon–heteroatom bonds and because organosilicon compounds, themselves, have applications in material science,[2] agroscience,[3] and medicinal chemistry[4] (Figure 1). Among the reactions that form C–Si bonds,[1b,c,5] direct silylations of inert C–H bonds catalyzed by transition-metal complexes have been pursued because of the potential of this reaction to generate organosilanes under mild, neutral conditions from readily available starting materials.[6]

Although progress on the silylation of both aromatic and aliphatic C–H bonds has been made over the past two decades,[7,8] the development of enantioselective variants of these reactions, particularly enantioselective silylation of unactivated C(sp^3)–H bonds, has been limited (Scheme 1).[9] In 2013, Takai, Kuninubu, and co-workers published the first enantioselective silylation of aromatic C–H bonds.[10] The reaction was catalyzed by a rhodium complex ligated by a chiral diphosphine (Scheme 1a, left), forming chiral spirosila-bifluorenes in up to 90.5:9.5 er. In 2015, Shibata, He, and Takai independently reported

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Notes

The authors declare no competing financial interest.

Supporting Information

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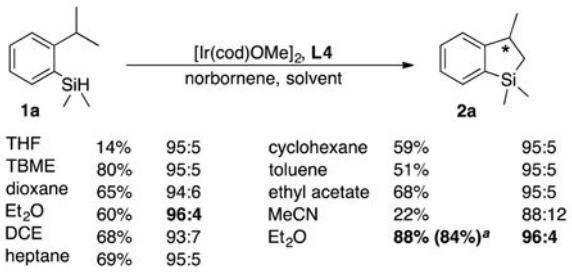
Experimental procedures and spectra for all new compounds. (PDF)

enantioselective silylations of aromatic C–H bonds that form chiral ferrocenes (Scheme 1a, middle) catalyzed by Rh complexes of chiral bisphosphine or diene ligands.[11] He et al. reported Rh-catalyzed tandem desymmetrizations of silacyclobutanes and silylations of C–H bonds to construct chiral tetraorganosilanes.[12] Our group reported Rh-catalyzed enantioselective silylations of aromatic C–H bonds in diarylmethanols (Scheme 1a, right)[13] and silylations of cyclopropyl C–H bonds (Scheme 1b, left).[14] The only enantioselective silylations of unactivated C(sp^3)–H bonds were reported by Takai and Murai, and these reactions occur with enantioselectivities below 70:30 er (Scheme 1b, right).[11b]

All of these prior enantioselective silylations of C–H bonds were catalyzed by Rh complexes ligated by chiral phosphine or diene ligands. Iridium complexes containing chelating, *N,N*-donor ligands, which have shown the most favorable combination of reactivity and functional group-compatibility in our studies in the C–H silylations,[7f,h,i] had not been applied to the enantioselective silylation of C–H bonds until our recent work on Ir-catalyzed silylation of aromatic C–H bonds to form diarylmethanols.[15]

Here, we report highly enantioselective silylations of unactivated C(sp^3)–H bonds. These reactions occur at one of two prochiral methyl groups with an Ir complex ligated by a chiral pyridyl oxazoline ligand (Scheme 1c). This process represents a rare example of the desymmetrization of an isopropyl group by a transition-metal-catalyzed C–H bond functionalization. In contrast to recently reported desymmetrizations of isopropyl groups to form C–C bonds,[16] the process we report forms carbon–silicon bonds that can be transformed to carbon–halogen and carbon–oxygen bonds.

To identify conditions for the Ir-catalyzed enantioselective silylation of unactivated C(sp^3)–H bonds, we tested Ir complexes derived from $[Ir(cod)OMe]_2$ and chiral *N,N*-donor ligands **L1**–**L4** for the intramolecular silylation of dimethylarylsilane **1a** in THF at 80 °C (Table 1, entries 1–4). Reactions with indane-fused oxazoline **L3** and **L4** formed product **2a** in higher yields (93% and 94%) and enantioselectivity (91:9 er and 92:8 er) than those with oxazoline-containing **L1** (80%, 74:26 er) and **L2** (20%, 74:26 er). The reaction with tetrahydroquinoline-based **L4** occurred with slightly higher enantioselectivity than that with quinoline-based **L3** (Table 1, entries 5 and 6), and the selectivities of the reactions catalyzed by complexes of **L3** and **L4** were further increased by running the reaction at 50 °C instead of 80 °C. Changes to the hydrogen acceptor and solvent further increased the yield and enantioselectivity (eq 1). The alkene serving as a hydrogen acceptor affected the yield without changing the enantioselectivity (Table 1, entries 6–10). Among the hydrogen acceptors tested, the reaction with norbornene occurred in the highest yield (73%). The solvent had a small effect on enantioselectivity, but reactions in ethers occurred with higher enantioselectivities than those in more polar and potentially coordinating solvents (eq 1). Among ethers, reactions conducted in diethyl ether occurred with the highest enantio-selectivity (96:4 er), but only 60% yield. Fortunately, the yield in eq 1 increased to 88% when the reaction time was prolonged from 12 to 24 h. The absolute configuration of compound **2a** was determined after oxidation under Tamao oxidation conditions to form the corresponding diol, for which the absolute configuration had been determined previously (see SI for details).[17]



(1)

Having identified conditions for the enantioselective silylation of compound **1a**, we assessed the scope of the reaction (Table 2). Reactions of dimethylarylsilanes containing a range of functional groups afforded the products of C–H silylation in high yields (up to 97%) and with excellent enantioselectivity (up to 98:2 er). Unsubstituted **1a** and alkyl- or aryl-substituted **1b** and **1c** gave the products **2a**–**2c** in good yields with excellent enantiomeric ratios (er). Various oxygen-containing functional groups, such as alkoxy ethers (**2d** and **2e**), a silyl ether (**2f**), a methylsulfonate ester (**2g**), a pivalate ester (**2h**), carbonates (**2i** and **2j**), and a carbamate (**2k**) were shown to be tolerated by the reaction. Reactions of substrates containing an aryl chloride (**1o**), alkyl chloride (**1p**), and ketal (**1q**) also occurred to afford products **2o**–**2q** in good yield with high enantiomeric ratios.

Substrates containing varied steric and electronic properties of the arenes were also tested. Varying the electronic properties of the arene did not significantly affect the yield or er of the reaction (**2l**–**2n**). Moreover, *meta*- and *ortho*-substituted **1r** and **1s** underwent silylation to form products **2r** and **2s** with excellent yields and er values. However, no reaction occurred when the very bulky 2,4,6-triisopropyl-substituted **1t** was subjected to the reaction conditions.

To determine if the reaction can be applied to the formation of products containing quaternary carbon centers with high enantioselectivity, we subjected compound **1u** to the silylation conditions. Compound **2u** was obtained in 90% yield and modest 86:14 er due to the small difference in steric hindrance between –Me and–CH_2OMOM groups. Replacement of the –CH_2OMOM group with a bulkier ethylene glycol-protected aldehyde afforded product **2v** in 97% yield and 95:5 er.

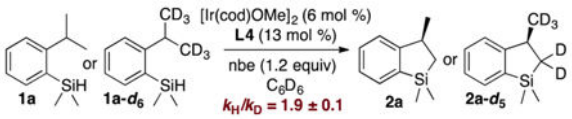
To demonstrate the potential applications of this reaction, the enantioselective silylation was conducted on a gram scale, and the resulting silole was converted to products containing a series of functional groups. The silylation of compound **1v** was conducted on a 4.0 mmol scale (1.1 g) with 0.50 mol % $[Ir(cod)OMe]_2$ and 1.1 mol % ligand. Under these conditions, product **2v** was isolated in 92% yield with the same enantio-selectivity (95:5 er) as that of the reaction conducted on a 0.20 mmol scale (Scheme 2). Product **2v** was then subjected to conditions that convert the C(sp^2)–Si bond to C–O, C–Cl, C–Br, and C–I bonds, giving products **3**–**6** in 81–98% yields.[1b,c,7d,e]

Compounds **3**–**6** obtained from **2v** can be transformed to further functionalized molecules. Compound **6** was oxidized to alcohol **7**, which contains a chiral quaternary carbon center at the β position of the hydroxyl group inaccessible by classic asymmetric hydrogenation. Under acidic conditions, compound **7** was deprotected to afford aldehyde **8** in 71% yield. Under Mitsunobu conditions, compound **3** was transformed to enantioenriched 3,3-disubstituted-2,3-dihydrobenzofuran **9** in 88% yield.

To underscore the ability of a silicon tether to enable the introduction of a series of functional groups, we conducted sequential silylations of C(sp^3)–H and C(sp^2)–H bonds, followed by functionalizations (Scheme 3). The enantioselective C(sp^3)–H silylation of **1a** was conducted on a 6.0 mmol scale, affording silole **2a** in 95% yield and 95:5 er. After chlorination of the C(sp^2)–Si bond of **2a** to form trialkylfluorosilane **10**, compound **10** was transformed to silole **12** in 59% yield over two steps by reduction of the Si–F bond in **10** and silylation of the C(sp^2)–H bond in compound **11**. The newly formed C–Si bond in compound **12** was converted to a C–I bond to form trialkylfluorosilane **13**. Compound **13** was then oxidized to alcohol **14** under Tamao oxidation conditions. By this series of sequential silylation reactions, a simple starting material (**1a**) was transformed to a product (**14**) containing one chiral tertiary carbon center and three new functionalities (C–Cl, C–I, and CO bonds).

The silylation with a chiral Ir catalyst was also applied to the functionalization of a biologically active natural product, dehydroabietic acid (Scheme 4). Aryldimethylsilane **16** was prepared from known bromide **15**[18] in 76% yield by a one-pot metalation and *in situ* nucleophilic substitution with dimethylchlorosilane. Under the C–H silylation conditions described above, compound **17** was obtained in 78% yield and 94:6 dr, this dr is close to the enantioselectivity of the reaction of related isopropylarylsilanes. This application demonstrates the potential to use the silylation to control diastereoselectivity for the diversification of analogues of biologically active compounds by late-stage C–H bond functionalization.

To gain insight into the mechanism of the reaction, we determined the kinetic isotopic effect (KIE) of separate reactions of protiated (**1a**) and deuterated (**1a-d_6**) substrates (eq 2). A KIE of 1.9 ± 0.1 was obtained from this set of experiments. This value is similar to that observed in our previous Ir-catalyzed silylation of secondary C(sp^3)–H bonds (2.0 ± 0.1)[7h] and Rh-catalyzed silylation of cyclopropyl C–H bonds (2.1 ± 0.1)[14] and implies that C–H cleavage is likely the rate-determining step of the reaction.[19]



(2)

In summary, we have developed a system for highly enantioselective silylations of unactivated C(sp^3)–H bonds. The silylation reaction is catalyzed by a combination of

$[Ir(cod)OMe]_2$ and chiral pyridyl oxazoline ligands and occurs in high yields and excellent enantioselectivity with substrates containing a wide range of functional groups. The C–Si bond in the enantioenriched dihydrobenzosiloles can be transformed to various functionalities, such as a hydroxyl group or a chloride, bromide, or iodide. Sequential silylations of $C(sp^3)$–H and $C(sp^2)$–H bonds and functionalizations, as well as diastereoselective silylations, show the potential of this process for diverse synthetic applications. Preliminary mechanistic studies suggest that C–H activation is likely the rate-determining step. Further studies of the scope and mechanism of the enantioselective silylation of C–H bonds are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Denmark, SE., Sweis, RF. Metal-Catalyzed Cross-Coupling Reactions. 2. De Meijere, A., Diederich, F., editors. Vol. 1. Wiley-VCH; Weinheim: 2004. p. 163-216.(b) Hartwig JF. Acc Chem Res. 2012; 45:864. [PubMed: 22075137] (c) Cheng C, Hartwig JF. Chem Rev. 2015; 115:8946. [PubMed: 25714857]
2. Jones, RG., Ando, W., Chojnowski, J. Silicon-Containing Polymers. Springer; Berlin: 2000.
3. Cash GG. Pestic Sci. 1997; 49:29.
4. (a) Franz AK. Curr Opin Drug Discovery Dev. 2007; 10:654.(b) Franz AK, Wilson SO. J Med Chem. 2013; 56:388. [PubMed: 23061607]
5. Patai, S., Rappoport, Z. The Chemistry of Organic Silicon Compounds. Wiley & Sons; New York: 2000.
6. (a) Yu, J-Q., Shi, Z-J. Topics in Current Chemistry. Vol. 292. Springer; Heidelberg: 2010. (b) Baudoin O. Chem Soc Rev. 2011; 40:4902. [PubMed: 21505712] (c) Gutekunst WR, Baran PS. Chem Soc Rev. 2011; 40:1976. [PubMed: 21298176] (d) McMurray L, O'Hara F, Gaunt MJ. Chem Soc Rev. 2011; 40:1885. [PubMed: 21390391] (e) Yamaguchi J, Yamaguchi AD, Itami K. Angew Chem, Int Ed. 2012; 51:8960.(f) Rouquet G, Chatani N. Angew Chem, Int Ed. 2013; 52:11726.(g) Girard SA, Knauber T, Li CJ. Angew Chem, Int Ed. 2014; 53:74.(h) Hartwig JF, Larsen MA. ACS Cent Sci. 2016; 2:281. [PubMed: 27294201] (i) Davies HML, Du Bois J, Yu JQ. Chem Soc Rev. 2011; 40:1855. [PubMed: 21390392] (j) He J, Wasa M, Chan KSL, Shao Q, Yu JQ. Chem Rev. 2017; 117:8754. [PubMed: 28697604]
7. (a) Kakiuchi F, Tsuchiya K, Matsumoto M, Mizushima E, Chatani N. J Am Chem Soc. 2004; 126:12792. [PubMed: 15469271] (b) Tsukada N, Hartwig JF. J Am Chem Soc. 2005; 127:5022. [PubMed: 15810828] (c) Ihara H, Suginome M. J Am Chem Soc. 2009; 131:7502. [PubMed: 19435323] (d) Kuznetsov A, Gevorgyan V. Org Lett. 2012; 14:914. [PubMed: 22272663] (e) Kuznetsov A, Onishi Y, Inamoto Y, Gevorgyan V. Org Lett. 2013; 15:2498. [PubMed: 23627807] (f) Cheng C, Hartwig JF. J Am Chem Soc. 2015; 137:592. [PubMed: 25514197] (g) Kanyiva KS, Kuninobu Y, Kanai M. Org Lett. 2014; 16:1968. [PubMed: 24646190] (h) Li B, Driess M, Hartwig JF. J Am Chem Soc. 2014; 136:6586. [PubMed: 24734777] (i) Li Q, Driess M, Hartwig JF. Angew Chem, Int Ed. 2014; 53:8471.(j) Xiao Q, Meng X, Kanai M, Kuninobu Y. Angew Chem, Int Ed. 2014; 53:3168.(k) Hua Y, Jung S, Roh J, Jeon J. J Org Chem. 2015; 80:4661. [PubMed: 25853682] (l) Hua Y, Asgari P, Avullala T, Jeon J. J Am Chem Soc. 2016; 138:7982. [PubMed: 27265033] (m) Li W, Huang X, You J. Org Lett. 2016; 18:666. [PubMed: 26847326] (n) Ghavtadze N, Melkonyan FS, Gulevich AV, Huang C, Gevorgyan V. Nat Chem. 2014; 6:122. [PubMed: 24451587]

8. (a) Furukawa S, Kobayashi J, Kawashima T. J Am Chem Soc. 2009; 131:14192. [PubMed: 19807175] (b) Toutov AA, Liu WB, Betz KN, Fedorov A, Stoltz BM, Grubbs RH. Nature. 2015; 518:80. [PubMed: 25652999] (c) Chen QA, Klare HFT, Oestreich M. J Am Chem Soc. 2016; 138:7868. [PubMed: 27303857] (d) Ma Y, Wang B, Zhang L, Hou Z. J Am Chem Soc. 2016; 138:3663. [PubMed: 26959863] (e) Yin Q, Klare HFT, Oestreich M. Angew Chem, Int Ed. 2016; 55:3204.
9. (a) Giri R, Shi BF, Engle KM, Maugel N, Yu JQ. Chem Soc Rev. 2009; 38:3242. [PubMed: 19847354] (b) Newton CG, Wang SG, Oliveira CC, Cramer N. Chem Rev. 2017; 117:8908. [PubMed: 28212007] (c) Nakanishi M, Katayev D, Besnard C, Kündig EP. Angew Chem, Int Ed. 2011; 50:7438.(d) Shi BF, Maugel N, Zhang YH, Yu JQ. Angew Chem, Int Ed. 2008; 47:4882.(e) Albicker MR, Cramer N. Angew Chem, Int Ed. 2009; 48:9139.(f) Würtz S, Lohre C, Fröhlich R, Bergander K, Glorius F. J Am Chem Soc. 2009; 131:8344. [PubMed: 19485322]
10. Kuninobu Y, Yamauchi K, Tamura N, Seiki T, Takai K. Angew Chem, Int Ed. 2013; 52:1520.
11. (a) Murai M, Matsumoto K, Takeuchi Y, Takai K. Org Lett. 2015; 17:3102. [PubMed: 26061112] (b) Murai M, Takeshima H, Morita H, Kuninobu Y, Takai K. J Org Chem. 2015; 80:5407. [PubMed: 25961415] (c) Shibata T, Shizuno T, Sasaki T. Chem Commun. 2015; 51:7802.(d) Zhang QW, An K, Liu LC, Yue Y, He W. Angew Chem, Int Ed. 2015; 54:6918.
12. Zhang QW, An K, Liu LC, Zhang Q, Guo H, He W. Angew Chem, Int Ed. 2017; 56:1125.
13. Lee T, Wilson TW, Berg R, Ryberg P, Hartwig JF. J Am Chem Soc. 2015; 137:6742. [PubMed: 25948056]
14. Lee T, Hartwig JF. Angew Chem, Int Ed. 2016; 55:8723.
15. Su B, Zhou TG, Li XW, Shao XR, Xu PL, Wu WL, Hartwig JF, Shi ZJ. Angew Chem, Int Ed. 2017; 56:1092.
16. Wu QF, Shen PX, He J, Wang XB, Zhang F, Shao Q, Zhu RY, Mapelli C, Qiao JX, Poss MA, Yu JQ. Science. 2017; 355:499. [PubMed: 28154075]
17. Chen J, Cheng B, Cao M, Lu Z. Angew Chem, Int Ed. 2015; 54:4661.
18. Esteves MA, Narender N, Gigante B, Marcelo-curto MJ, Alvarez F. Synth Commun. 1999; 29:275.
19. Simmons EM, Hartwig JF. Angew Chem, Int Ed. 2012; 51:3066.

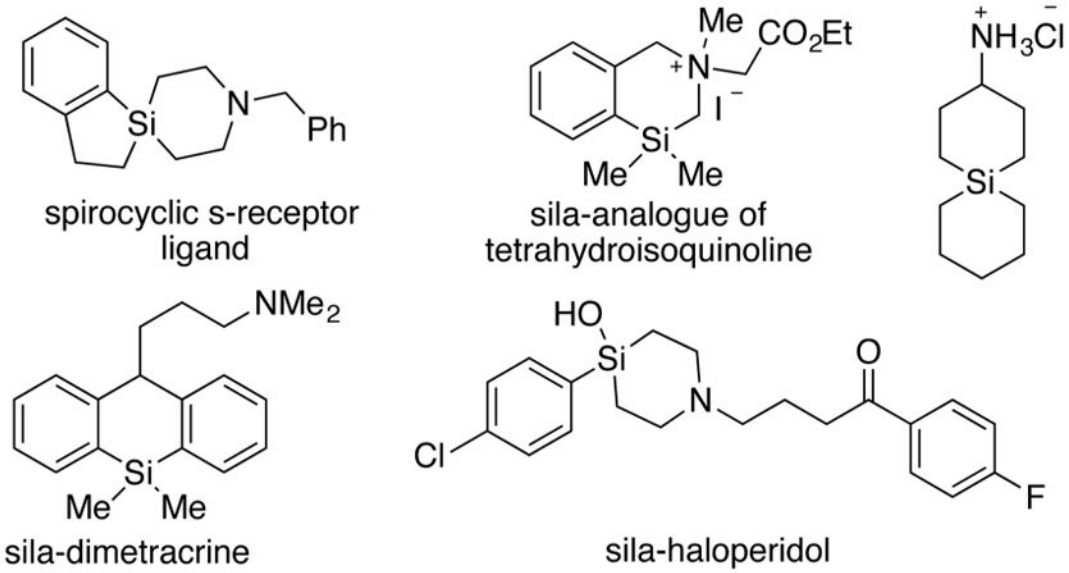
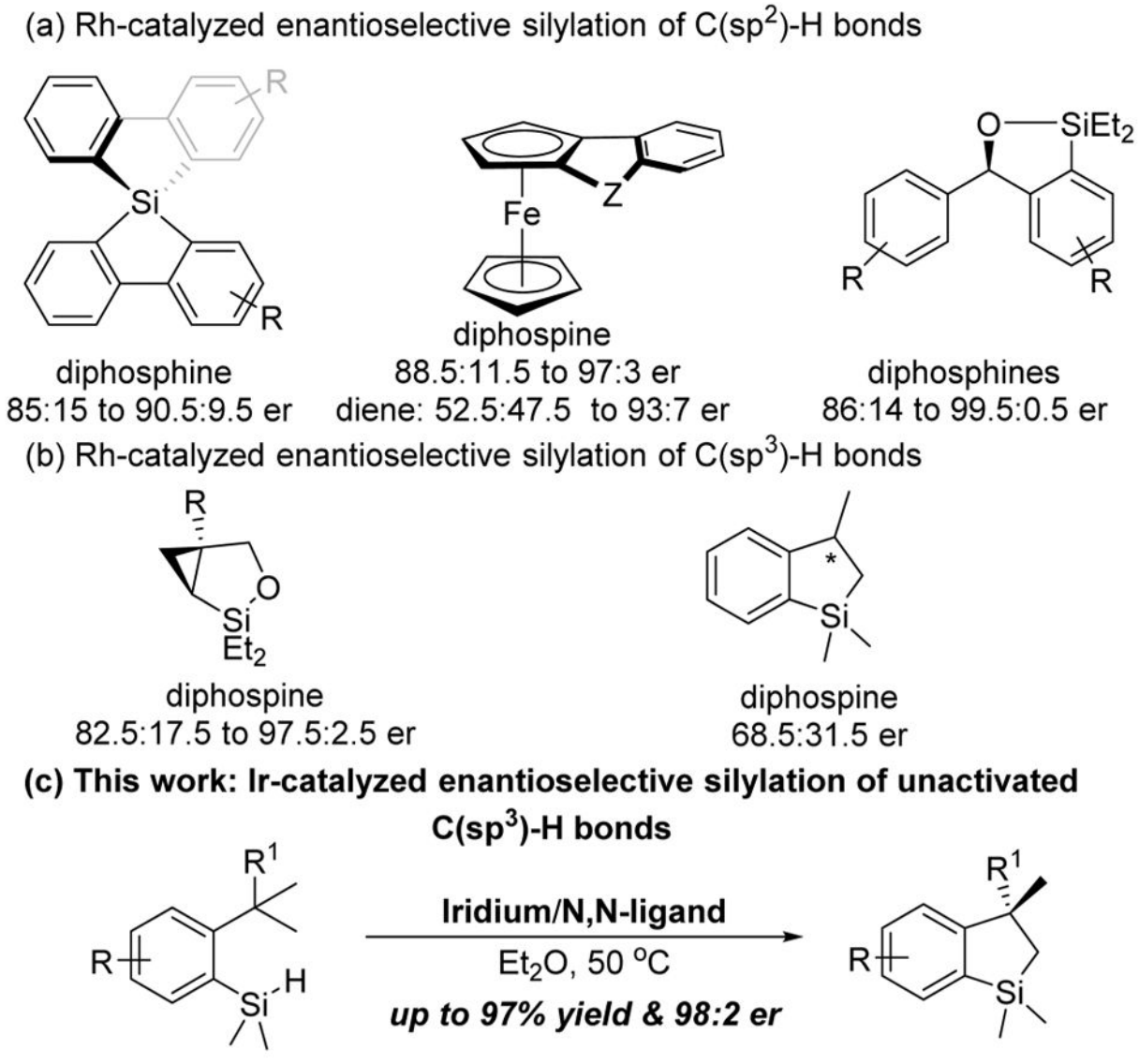
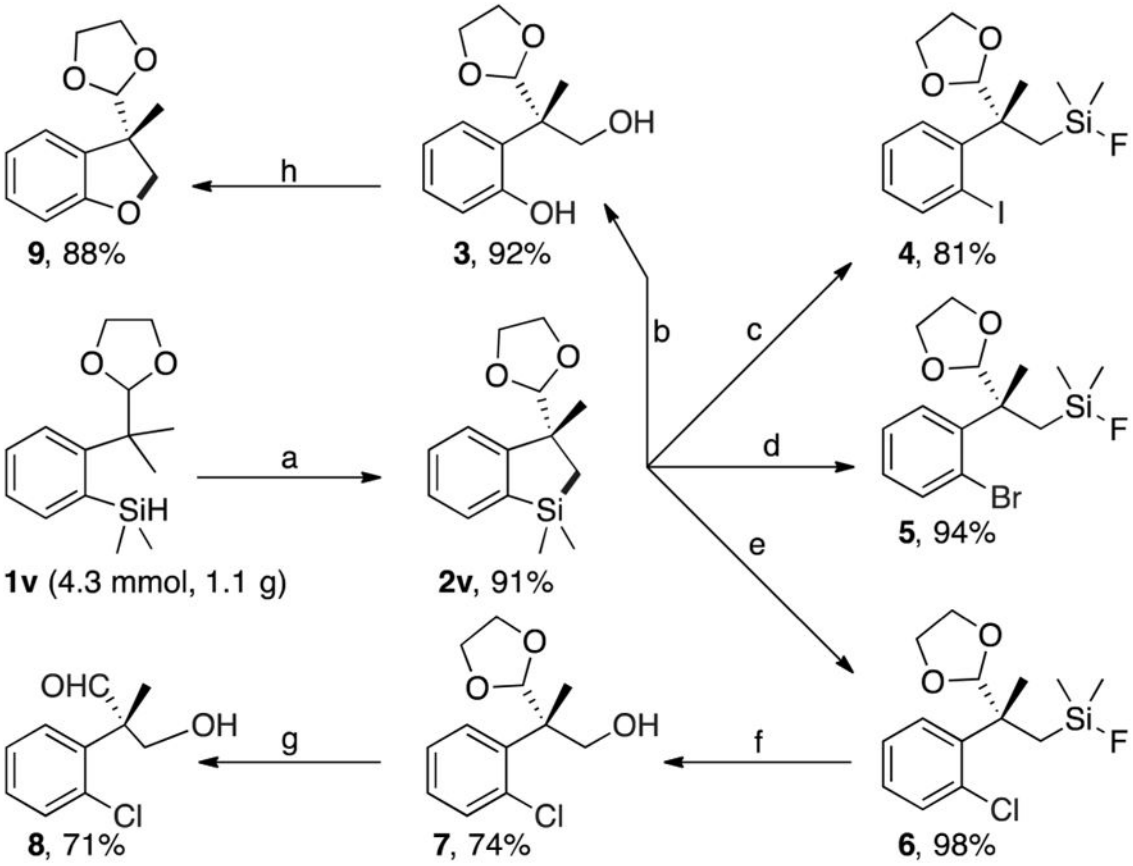


Figure 1.
Representative biologically active silicon-containing molecules.

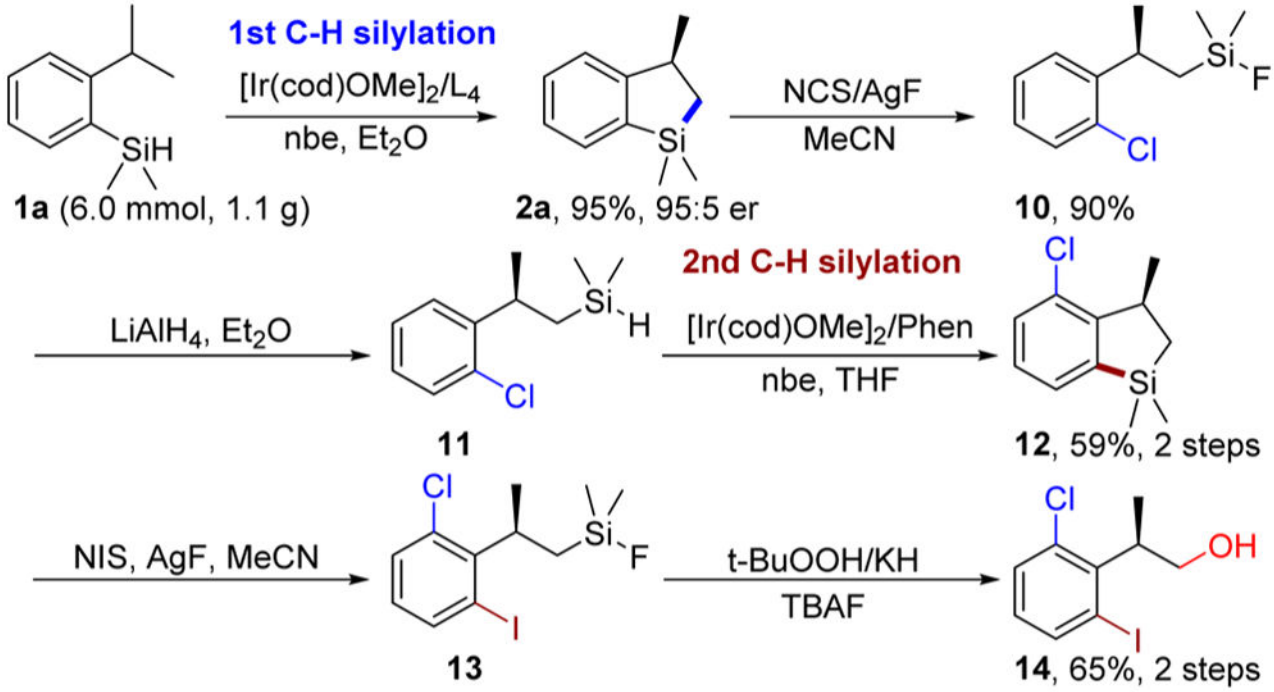


Scheme 1.
Transition-Metal-Catalyzed Enantioselective Silylations of C–H Bonds

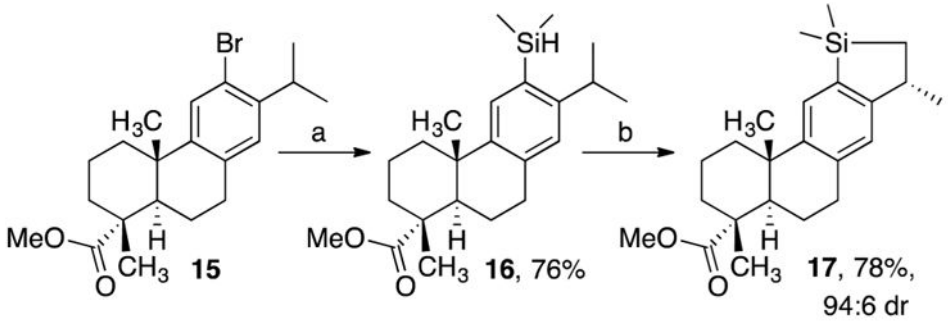


Scheme 2. Transformations of the Enantioenriched Dihydrobenzosiloles[a]

[a]Reaction conditions: (a) $[Ir(cod)OMe]_2$ (0.50 mol %), **L**$_4$, (1.1 mol %), nbe, Et_2O, 50 °C; (b) *t*-BuOOH, *t*-BuOK, TBAF; (c) NIS, AgF, MeCN; (d) NBS, AgF, MeCN; (e) NCS, AgF, MeCN; (f) *t*-BuOOH, KH, TBAF; (g) HCl, THF/H_2O; (h) DEAD, PPh_3, THF.



Scheme 3.
Sequential Silylations of C–H Bonds

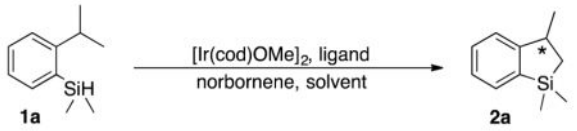


Scheme 4. Diastereoselective Silylation of the C(sp^3)–H Bond of Dehydroabietic Acid Derivative[a]

[a]Reaction conditions: (a) Mg, THF, Me_2SiHCl; (b) $[Ir(cod)OMe]_2$/**L_4**, nbe, Et_2O.

Table 1

Effect of Reaction Parameters on the Enantioselective Silylation of C(sp^3)–H Bonds[a]



entry	ligand	H_2 acceptor	temp (°C)	yield[b] (%)	er[c]
1	**L1**	norbornene	80	80	74:26
2	**L2**	norbornene	80	20	74:26
3	**L3**	norbornene	80	93	91:9
4	**L4**	norbornene	80	94	92:8
5	**L3**	norbornene	50	68	93:7
6	**L4**	norbornene	50	73	95:5
7	**L4**	cyclohexene	50	17	95:5
8	**L4**	1-hexene	50	70	95:5
9	**L4**	3,3-dimethylbutene	50	51	95:5
10	**L4**	none	50	14	95:5

[a]The reaction was conducted with **1a** (0.20 mmol), $[Ir(cod)OMe]_2$ (2.0 mol %), ligand (4.5 mol %), and norbornene (1.0 equiv) in THF (1.0 mL) for 12 h under N_2.

[b]The yield was determined by GC using dodecane as internal standard.

[c]The er value was determined by chiral GC.

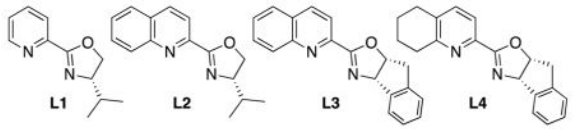
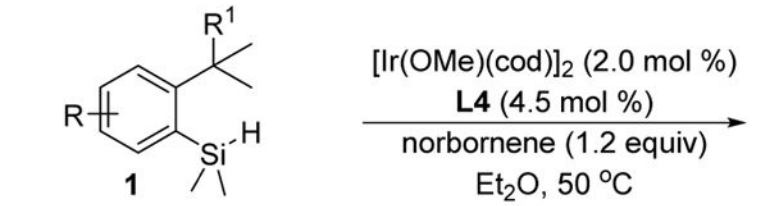
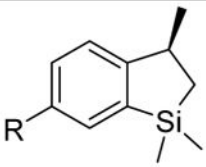


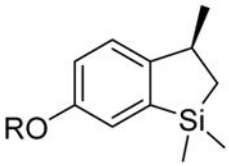
Table 2

Scope of the Enantioselective Silylation of C(sp^3)–H Bonds[a]

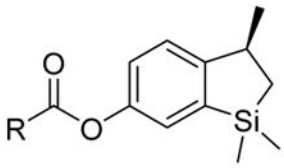




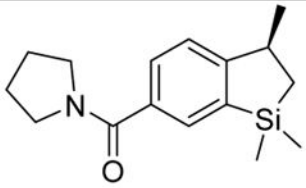
2a, R = H, 84%, 96:4 er
2b, R = *i*-Pr, 84%, 94:6 er
2c, R = 4-OMeC_6H_4
76%, 95:5 er



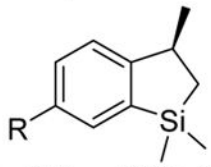
2d, R = Me, 86%, 93:7 er
2e, R = Bn, 90%, 95:5 er
2f, R = TBS, 83%, 95:5 er
2g, R = Ms, 88%, 95:5 er
2h, R = Piv, 87%, 95:5 er



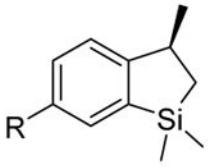
2i, R = OMe, 84%, 92:8 er
2j, R = OtBu, 81%, 95:5 er
2k, R = NEt_2, 88%, 97:3 er



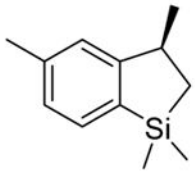
2l, 80%, 92:8 er



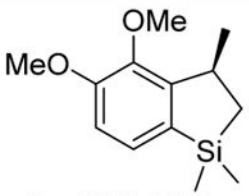
2m, R = NMe_2, 92%, 94:6 er
2n, R = CN, 89%, 94:6 er
2o, R = Cl, 84%, 95:5 er



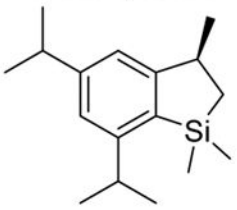
2p, R = OC_2H_4Cl
91%, 95:5 er
2q, R = CH_2OMOM
85% 95:5 er



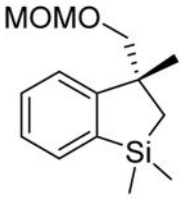
2r, 89%, 95:5 er



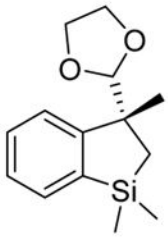
2s, 92%, 98:2 er



2t, no reaction



2u, 90%, 86:14 er



2v, 97%, 95:5 er

[a]The reaction was conducted for 24 h under N_2 unless otherwise noted. The yields refers to isolated yields and the er values were determined by chiral GC or HPLC.