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Iridium-Catalyzed, Site-Selective Silylation of Secondary C(sp³)−H Bonds in Secondary Alcohols and Ketones

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Abstract

We report the iridium-catalyzed, stereoselective conversion of secondary alcohols or ketones to *anti*-1,3-diols by the silylation of secondary C–H bonds γ to oxygen and oxidation of the resulting oxasilolane. The silylation of secondary C–H bonds in secondary silyl ethers derived from alcohols or ketones is enabled by a catalyst formed from a simple bisamidine ligand. The silylation occurs with high selectivity at a secondary C–H bond γ to oxygen over distal primary or proximal secondary C–H bonds. Initial mechanistic investigations suggest that the source of the newly achieved reactivity is a long catalyst lifetime resulting from the high binding constant of the strongly electron-donating bisamidine ligand.

Selective functionalizations of C–H bonds by transitionmetal complexes are generating new strategies for the synthesis and derivatization of organic molecules.[1–3] Among such functionalizations, the silylation of C–H bonds has been valuable because the organosilane products can be isolated readily and derivatized by a variety of selective transformations.[4–7]

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c03127.
Experimental procedures, spectra for all new compounds, and crystallographic data (PDF)

Accession Codes

CCDC 2249056–2249058 and 2249060 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/ cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The catalytic silylation of alkyl C–H bonds occurs intermolecularly or intramolecularly.[7–13] The intramolecular reactions occur with rates and functional-group tolerance appropriate for synthetic applications.[14–17] High regioselectivity has been achieved by reactions at terminal C–H bonds to form cyclic silanes,[18] including those β, γ, and δ to an alcohol to form 1,2-diols, 1,3-diols, and 1,4-diols, respectively, after oxidation (Scheme 1A).[19–21] Intramolecular silylations of secondary C(sp^3)–H bonds are less developed but would be synthetically valuable because of the ubiquity of methylene C–H bonds and the potential to install a secondary alcohol stereoselectively.

However, the silylation of secondary C–H bonds is more challenging than that of primary C–H bonds because the oxidative addition of secondary C–H bonds is slower than that of primary C–H bonds.[22,23] We previously reported intramolecular silylation of secondary C–H bonds, but the reactants were limited to those derived from tertiary alcohols or those with carbocyclic substituents β to oxygen that would provide a Thorpe–Ingold effect on cyclization. Reactions of (hydrido)silyl ethers derived from secondary alcohols or ketones in most cases did not give oxasilolane products (Scheme 1B).[24] Thus, a more advanced catalyst is needed to achieve the silylation of the secondary C–H bonds of secondary alcohols and ketones.

We show that $[Ir(cod)OMe]_2$ and a simple, tricyclic bisamidine ligand catalyze the silylation of secondary γ-C–H bonds in silyl ethers derived from secondary alcohols and ketones to form the corresponding oxasilolanes with high site selectivity and diastereoselectivity (Scheme 1C). This reaction and the subsequent oxidation transform secondary alcohols and ketones into *anti*-1,3-diols. The method complements radical-mediated oxidations that form *syn* or achiral 1,3-diols at benzylic or tertiary C–H bonds preferentially[25] and is enabled by the increased stability of the catalyst containing the simple, but rarely used, bisamidine.

To achieve the silylation of secondary C–H bonds in a secondary (hydrido)silyl ether, we studied the reaction of (hydrido)silyl ether 1 with $[Ir(cod)OMe]_2$ and a variety of bidentate N,N ligands in the presence of norbornene (nbe) as a hydrogen acceptor (Table 1). Prior silylations of C–H bonds in silyl ethers were achieved with catalysts bearing phenanthroline ligands.[19,20,26]

The electronic properties of the ligands in Table 1 modestly influenced the yield. The reaction with 3,4,7,8-tetramethyl-1,10-phenanthroline (**L1**) as the ancillary ligand gave a low yield of oxasilolane **2** (14%). The reaction with the more electron-poor 1,10-phenanthroline (**L2**) gave a lower yield (7%). The reaction with the most electron-donating 4,7-dimethylamino-1,10-phenanthroline (**L4**) afforded a slightly higher yield (27%). However, those with a more hindered phenanthroline (**L5**), a bipyridine (**L7**), an acyclic diimine (**L8**), a bisoxazoline (**L9**), a pyridyl(oxazoline) (**L10**), and a pyridyl(imidazoline) (**L11**) all formed little or none of the desired product.

With the reaction of the most electron-donating ligand providing the highest yield, we tested ligands that would be even more donating than phenanthrolines, with structures not previously used for silylation reactions. To do so, we tested bisamidine ligands **L12–L14**. Indeed, the reaction containing the tricyclic bisamidine **L12** furnished the desired

oxasilolane product in 69% yield and 10:1 diastereoselectivity for the *anti*-product **2**. Increasing the catalyst loading to 3.0 mol % led to a high yield of 77%. For reasons we do not currently understand, **L13** and **L14** do not form iridium complexes that are active for this transformation. Further experiments were conducted with the combination of $[Ir(cod)OMe]_2$ and L12 with nbe as the hydrogen acceptor.

Table 2 shows examples of 1,3-diols formed by the silylation of secondary alcohols or ketones and the oxidation at the C–Si bond. The starting secondary alcohols or ketones were first converted to the corresponding (hydrido)silyl ethers by dehydrogenative silylation or hydrosilylation with diethylsilane catalyzed by $[Ir(cod)OMe]_2$. The resulting (hydrido)silyl ether undergoes C–H silylation to form an oxasilolane, which was then subjected to Tamao–Fleming oxidation to afford the 1,3-diol. The observed diastereomeric ratio for 1,3-diol products reported in Table 2 is 10:1 unless otherwise specified.

Symmetric secondary alcohols with *n*-butyl and *n*-propyl chains underwent silylation of the secondary C–H bond in high yields (**6a, 6b**). Unsymmetrical secondary alcohols reacted at the less hindered secondary C–H bond, also in high yields, for example, at the methylene C–H bond in an *n*-propyl chain over that in an *n*-pentyl chain (**6c**). In this case, the catalyst selects for the C–H bond α to a methyl group over the C–H bond α to a propyl group. The observed selectivity could result from a selective C–H activation step, an unselective reversible C–H activation and selective reductive elimination step, or a combination of reversible C–H activation and reductive elimination that both favor the less hindered C–H bond.[27] Unsymmetrical secondary alcohols also underwent silylation at the methylene C–H bond in the linear side chain over the branched isopropyl (**6d**), *tert*-butyl (**6e**), cyclohexyl (**6f**), or 1-ethylpropyl (**6g**) group.

Cyclic secondary C–H bonds in alcohols underwent silylation to form 1,3-diols containing one cyclic alcohol and one acyclic alcohol after oxidation. Alcohols containing cyclopropyl (**6h**) and cyclobutyl (**6i**) side chains reacted at the secondary C–H bond in the carbocycle over the secondary C–H bonds in the *n*-propyl side chain. The alcohol containing a cyclopentyl group reacted with 2.4:1 selectivity for the carbocyclic side chain over the *n*-propyl side chain (**6j**). Alcohols containing a larger carbocyclic side chain, such as a six-membered (**6k**), seven-membered (**6l**), or eight-membered (**6m**) ring, led to silylation of the *n*-propyl side chain over the cyclic side chain. However, steric bulk on the acyclic chain redirected the silylation to a C–H bond in the ring, such as a cyclohexyl or tetrahydropyranyl ring (**6n, 6o**), showing that these C–H bonds can undergo reaction when other positions are sterically inaccessible.

Substrates with the silyl ether in a carbocycle also underwent C–H silylation. For example, spiro[4,4]nonan-1-one and bicyclic *exo*-norborneol underwent silylation at a secondary C–H bond to afford cyclic 1,3-diols **6p** and **6q** after oxidation. In addition, a macrocyclic ketone, cyclopentadecanone, underwent hydrosilylation, followed by C–H silylation and oxidation to form 1,3-diol **6r** with 3.3:1 diastereoselectivity for the *anti*-isomer.

We also evaluated the reactions of alcohols and ketones containing aryl C–H bonds. The reaction of 1-phenylpentan-2-one (**3s′**) was selective for the $C(sp^2)$–H bond δ to oxygen

over the C(sp^3)–H bond γ to oxygen in the silyl ether derived from 1-phenylpentan-2-one to form the hydroxyalkyl phenol **6s**. The silylation of 1-phenyloctan-4-one (**3t′**) occurred at the secondary C(sp^3)–H bond over the C(sp^2)–H bond to form diol **6t**, likely because silylation of the C(sp^2)–H bond would result in the formation of an eight-memebred oxasilolane product.

Reactions were also conducted with a set of substrates in which substituents were present on the aryl ring. A chloride (**6u**), fluoride (**6v**), and aryl ether (**6w**) were tolerated. Amide, ester, and carbamate functional groups were investigated but are not tolerant of the highly basic conditions required for the oxidation. This result is consistent with previously published C–H silylation methods.[21]

We also showed that the silylation occurred at secondary C–H bonds in a small terpene (Scheme 2). The sequence of dehydrogenative silylation, C–H silylation, and oxidation with the natural product borneol afforded platydiol with high regioselectivity and moderate yield. The observation of a single product, platydiol, from this three-step sequence indicates that the sequence occurs without epimerization at the carbon α to oxygen. Epimerization at this carbon in [1*S*-*endo*]-(−)-borneol would generate two constitutional isomers of the diol because the silyl ether derived from *exo*-borneol undergoes C–H silylation at the C10 methyl group, not the secondary C–H bond.[19] The absence of epimerization through the three-step sequence is consistent with analogous C–H silylation sequences performed on complex molecules.[14–17]

The functional group compatibility of Ir-catalyzed hydrosilylation of ketones, Ir-catalyzed dehydrogenative silylation of alcohols, and Tamao−Fleming oxidation has been investigated during previous studies on the silylation of C−H bonds.[19–21,24] To assess the functional-group compatibility of the C−H silylation process with the new bisamidine ligand, a robustness test described by Glorius was conducted.[28] The reaction of silyl ether **1** was conducted with 30 additives individually. While many of these groups would not tolerate the Tamao− Fleming oxidation, they do reveal the ability of the silylation process to occur in the presence of a wide range of potentially reactive groups. The stability of the additive and its effect on the yield of oxasilolane **2** were measured (Table 3). Without any additive, the reaction of **1** to form **2** occurred in 85% yield. Twenty-three of these functional groups (alkyl and aryl halides, a tertiary and secondary alkyl amine, aryl amines, a tertiary amide, phthalimide, urea, thiourea, carbamate, sulfonamide, tertiary and secondary alcohol, acetal, ketone, ester, carbonate, 1,1- and 1,2-disubstituted alkene, and a trisubstituted alkene) had little effect on the formation of **2** and were unchanged by the reaction.

Seven of the additives inhibited the silylation process. A secondary amide led to no yield of **2** but was unchanged by the reaction (**7j**). A primary amide led to no yield of **2** and was consumed during the reaction (**7k**). The alkyl and aromatic nitriles significantly reduced the yield of product but were unchanged (**7q, 7r**). Two oxygen-containing functional groups, a primary alcohol and an aldehyde, were incompatible with these conditions, fully interfering with the formation of the product and being fully consumed (**7u, 7x**). Finally, a monosubstituted alkene led to a significantly reduced yield of the product and was consumed (**7ab**). Although this test showed that some functional groups

are not compatible with the silylation reaction, this robustness test showed that many common groups are tolerated. Indeed, the silylation of C−H bonds is more compatible with carbon−carbon multiple bonds and electron-rich, polar functional groups than the subsequent Tamao−Fleming oxidation.

Several experiments were conducted to understand the mechanism of the C−H silylation reaction. First, the initial rates were measured for the separate reactions of nondeuterated and deuterated silyl ether **8** and **8**-d_4 (Scheme 3). These rates revealed a small, primary kinetic isotope effect of 2.2, implying that C−H bond cleavage is turnover-limiting. This value is similar to that for the silylation of secondary C−H bonds in silyl ethers derived from tertiary alcohols.[24]

To assess the origin of the difference in yields from reactions catalyzed by the system with 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen) and that with the bisamidine **L12** on iridium, the electronic properties of the two ligands were compared. $Mo(CO)_4$(**L12**) was synthesized from $Mo(CO)_6$, and the νCO A_{1ax} stretching frequency was measured to be 2001 cm^{-1} (Supporting Information). For comparison, the reported νCO A_{1ax} stretching frequency of $Mo(CO)_4$(tmphen) is 2013 cm^{-1}. These data indicate that **L12** is much more electron-donating than tmphen.[29]

To determine the origin of the difference in ligand on the reaction outcome, we measured the time course of the C−H silylation of **9** with tmphen and with **L12** as ligand. The initial rates of the two reactions were similar, but the reaction with tmphen formed little additional product after 5 h, while the reaction with **L12** continued to form a product for 16 h (Figure 1). This comparison suggests that the ability to form oxasilolanes from secondary alcohols and ketones with the iridium catalyst containing **L12** results, at least in large part, from a longer lifetime of the catalyst for C−H silylation rather than an increased rate of the reaction.

We considered that the longer lifetime of the catalyst generated from L12 could result from a greater binding affinity of **L12**, than of tmphen, to the iridium center, due to the increased electron-donating property of **L12**. To test this hypothesis, a competition experiment was performed that would assess the binding of **L12** and tmphen to an Ir(III) complex. The ratio of the formation of $[Ir(ppy)_2$(**L12**)]Cl and $[Ir(ppy)_2$(tmphen)]Cl, by reaction of $[Ir(ppy)_2Cl]_2$ with an 8-fold excess of the two ligands, was conducted. The ratio of the two products was >99:1, favoring the formation of the Ir complex from reaction with **L12** (Scheme 4). These data imply that the binding affinity of **L12** is greater than that of tmphen for Ir(III) metal centers. This phenomenon may lead to the longer lifetime of the catalyst generated from **L12** compared to the catalyst generated from tmphen.

In summary, we have identified a simple, yet rarely used, bisamidine ligand, **L12**, that forms an iridium catalyst for the silylation of secondary C(sp^3)−H bonds γ to oxygen in secondary alcohols or ketones. The reaction occurs with high stereoselectivity and site-selectivity for the *anti*-isomer of a 1,3-diol after oxidation. A wide variety of acyclic and cyclic substrates underwent the silylation and oxidation sequence in good yield, and the reaction was shown to tolerate a wide range of functional groups. Initial mechanistic data suggest that cleavage of the C−H bond is turnover-limiting and that the high yields achieved with the iridium

catalyst containing **L12** result from a longer lifetime of this catalyst than that of the catalyst containing tmphen. This longer lifetime may result from a greater binding affinity of the bisamidine ligand than of tmphen for iridium. Further studies to elucidate the reaction mechanism are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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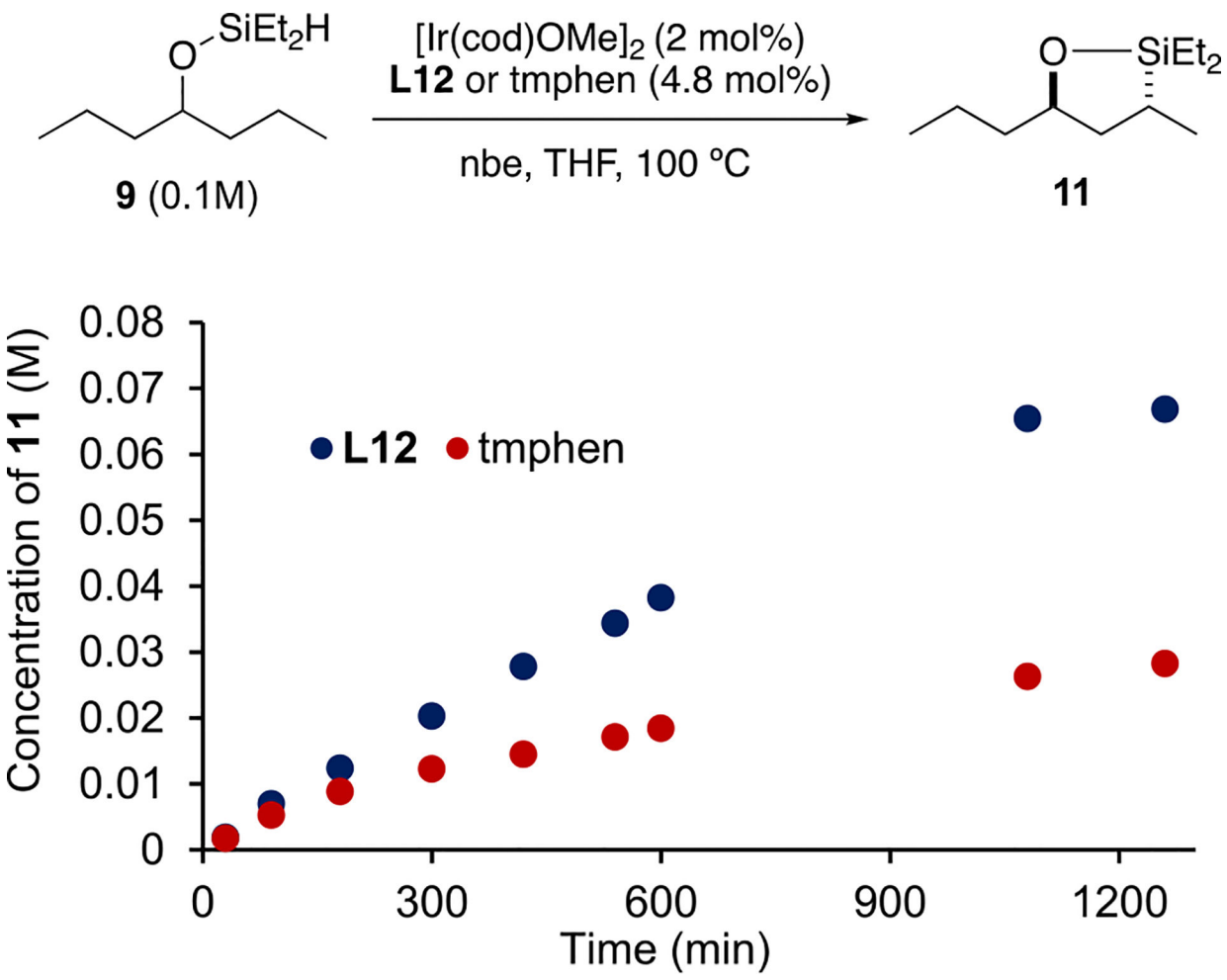
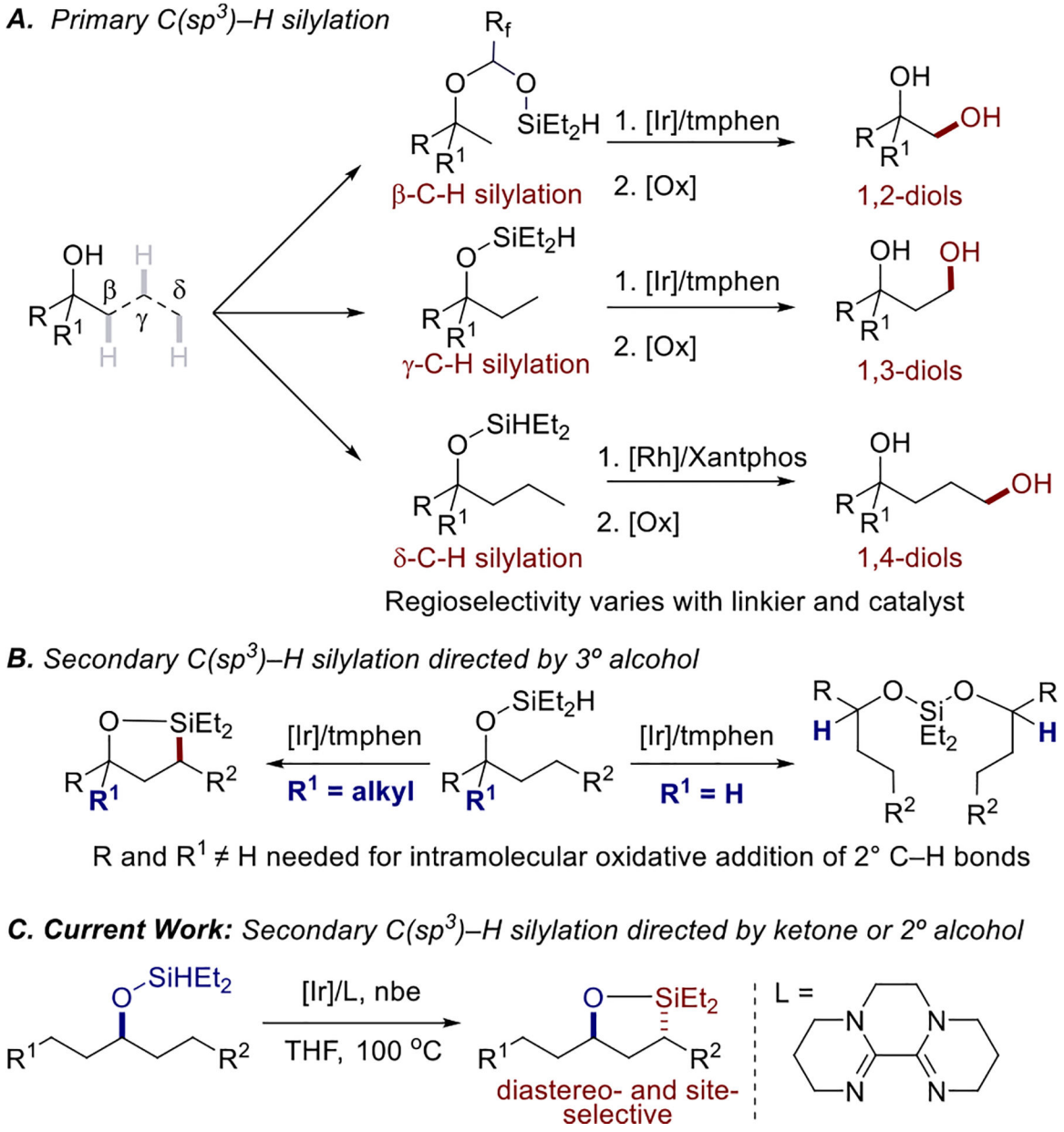
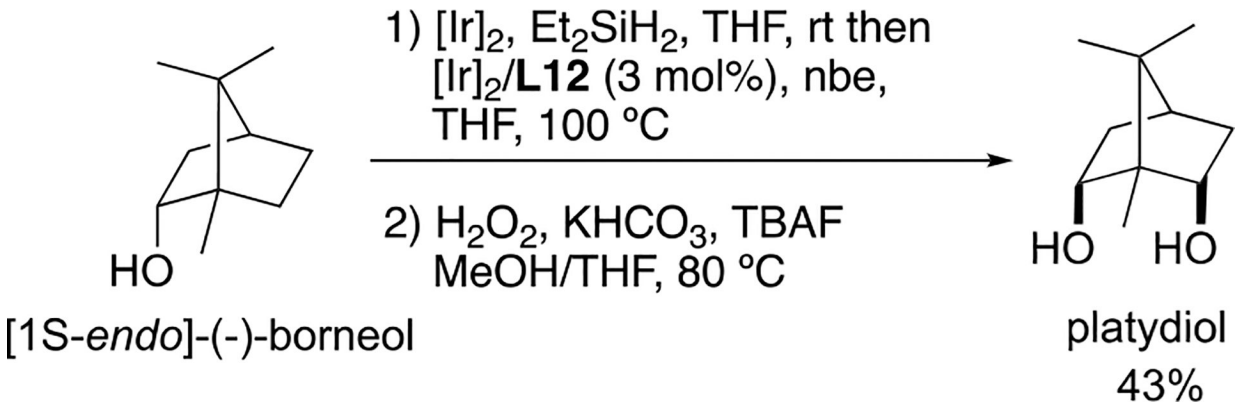


Figure 1.

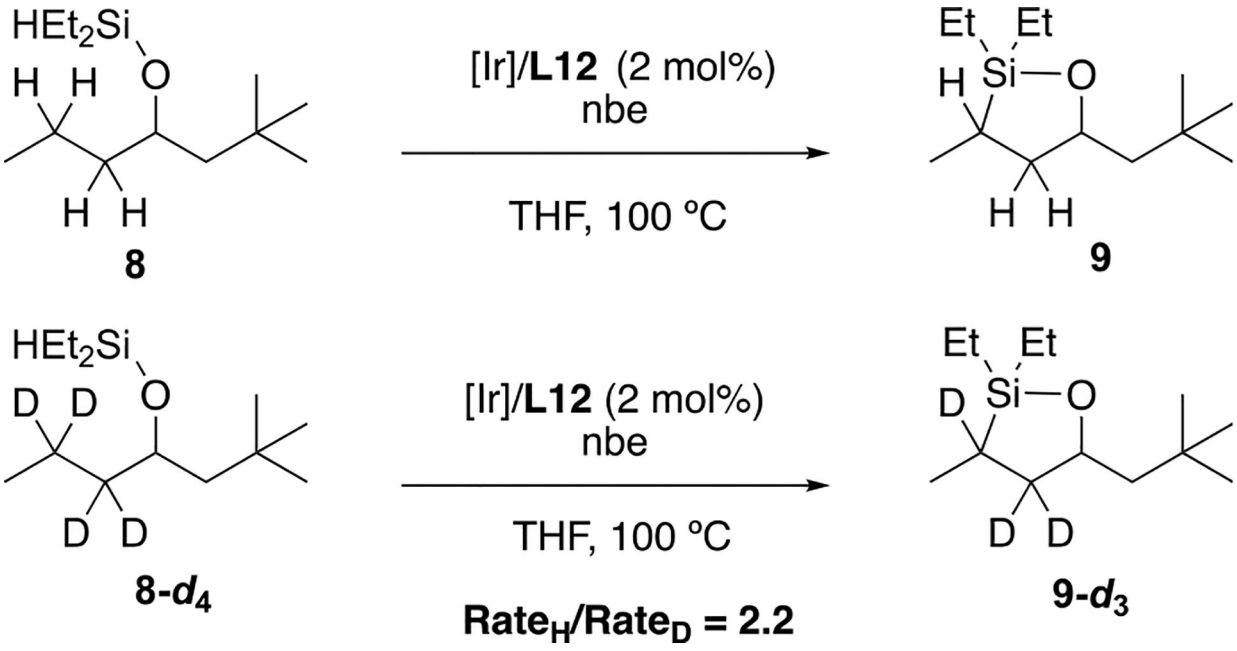
Reaction time courses for C−H silylation catalyzed by complexes with **L12** and tmphen as ligand.



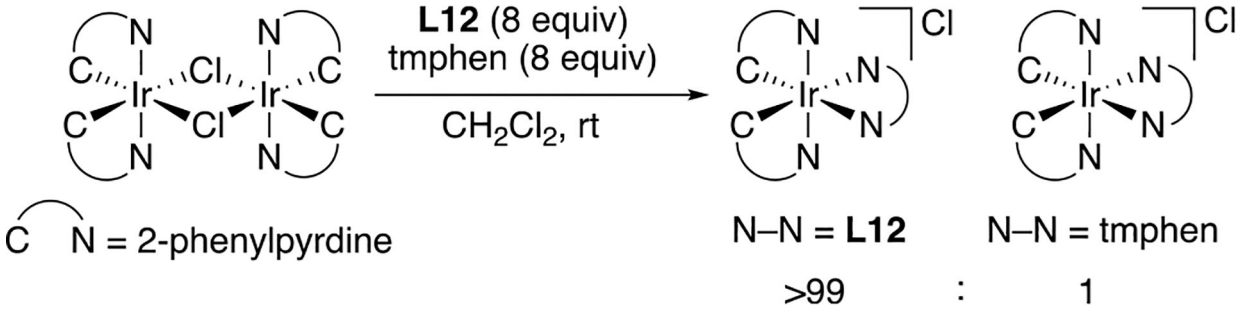
Scheme 1.
Site-Selective Silylation of C(sp^3)–H Bonds in Alcohols and Ketones



Scheme 2.
C–H Silylation and Oxidation of Borneol



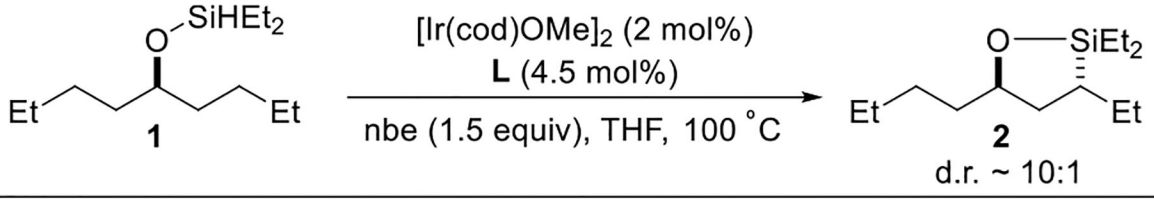
Scheme 3.
Kinetic Isotope Effect on the Silylation Reaction

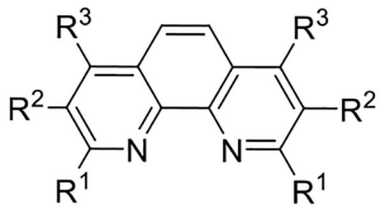


Scheme 4.
Competition Experiment for the Binding of Ancillary Ligands

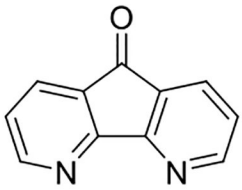
Table 1.

Evaluation of Ligands for the Silylation of Secondary C–H Bonds[a]

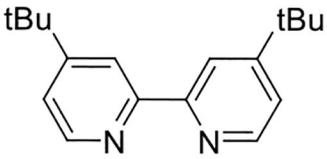




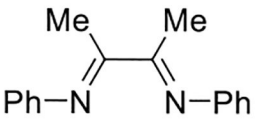
R^1 = H, R^2 = R^3 = Me, **L1:** 14%
R^1 = R^2 = R^3 = H **L2:** 7%
R^1 = R^2 = H, R^3 = OMe **L3:** 14%
R^1 = R^2 = H, R^3 = NMe_2 **L4**: 27%
R^1 = Me, R^2 = R^3 = H **L5:** 0%



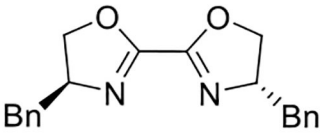
L6: 0%



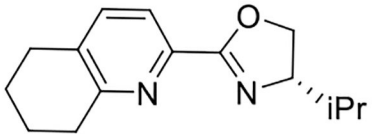
L7: <5%



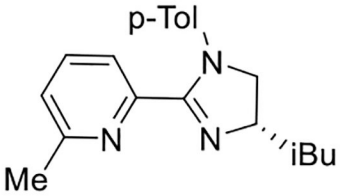
L8: 0%



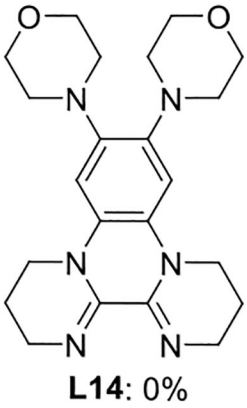
L9: 0%



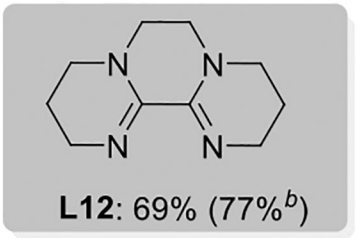
L10: 0%



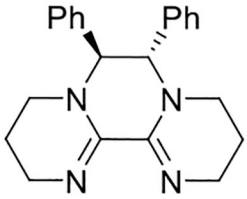
L11: 0%



L14: 0%



L12: 69% (77%[b])



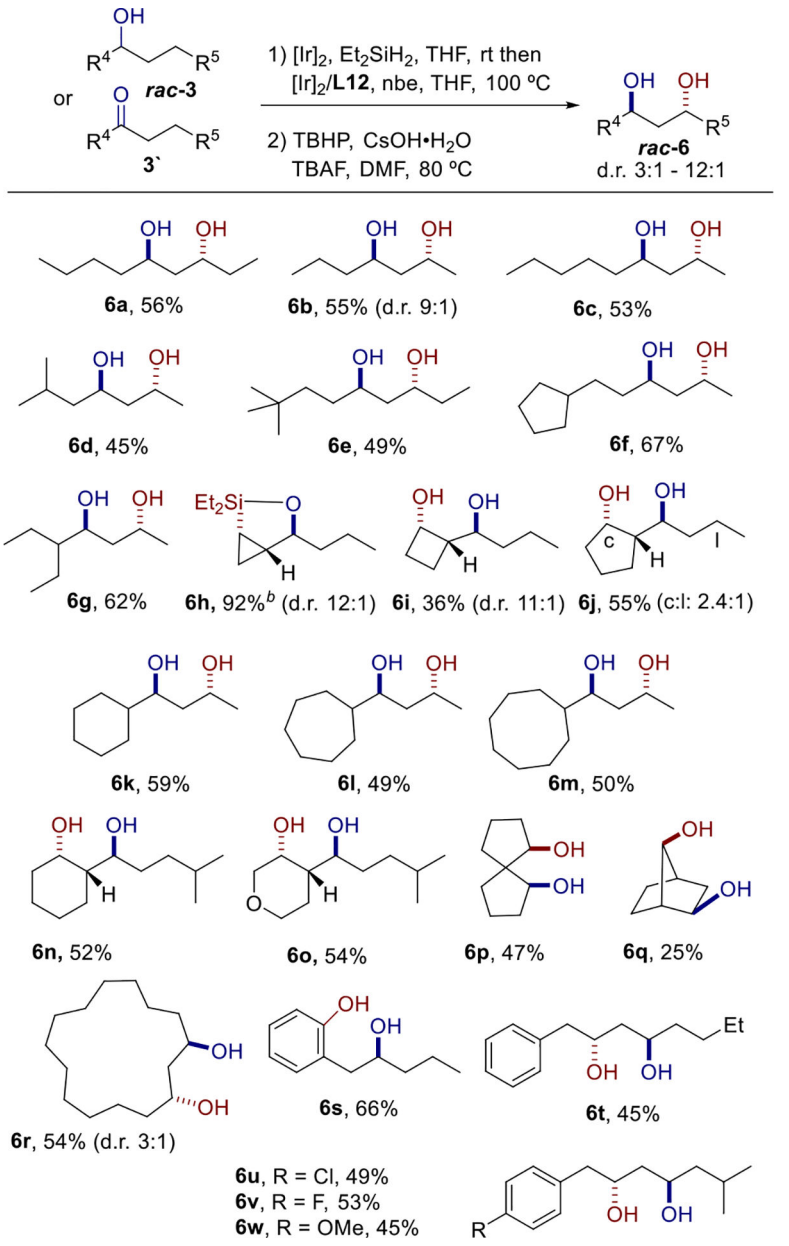
L13: 0%

[a]Conditions: Reactions conducted with 0.10 mmol of **1**. Yields determined by GC using *n*-dodecane as internal standard.

[b]Reaction conducted with 3.0 mol % of $[Ir(cod)OMe]_2$ and 6.5 mol % L.

Table 2.

Examples of the Silylation and Oxidation of Secondary C–H Bonds[a]

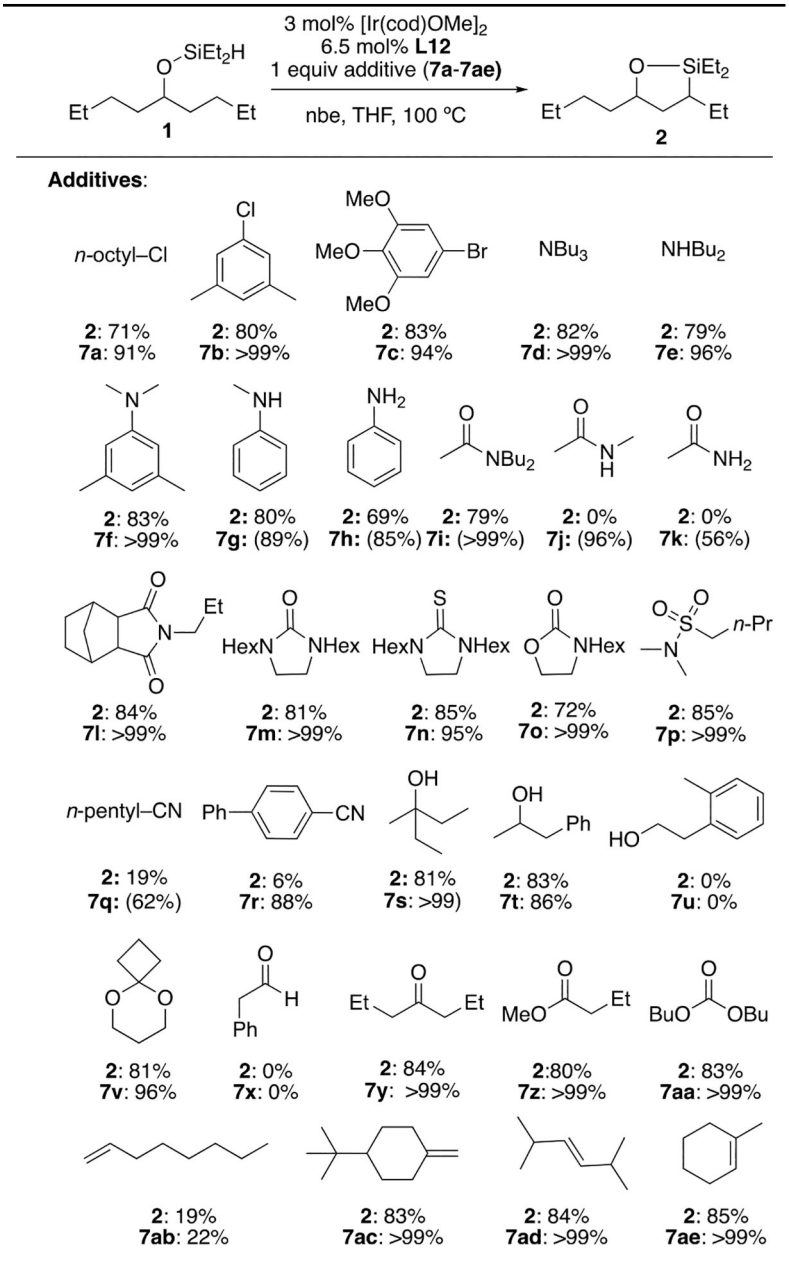


[a]Conditions: 3 or 3′ (1.0 equiv), Et_2SiH_2 (1.5 equiv), $[Ir(cod)OMe]_2$ (0.50 mol %), THF, room temperature; removal of volatiles, then $[Ir(cod)OMe]_2$ (3.0 mol %), **L12** (6.5 mol %), nbe (1.5 equiv), THF, 100 °C. Isolated yields are reported. d.r. determined by GC and is observed as 10:1 unless otherwise specified.

[b]No oxidation was performed and the oxasilolane was isolated after the C–H silylation step.

Table 3.

Evaluation of the Functional-Group Tolerance of the Silylation of Secondary C−H Bonds[a]



[a]Conditions: Reactions conducted with 0.10 mmol of 1. Yield determined by GC using *n*-dodecane as internal standard (IS). Percent recovery of additive determined by GC using *n*-dodecane as IS or ^{1}H NMR using CH_2Br_2 as IS.