Asymmetric C–H Activation

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Rhodium-Catalyzed Enantioselective Silylation of Cyclopropyl C–H Bonds

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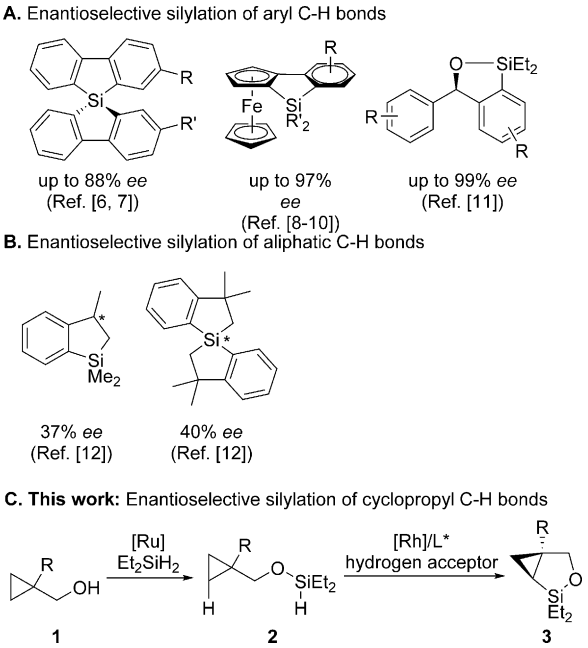
Abstract: *Hydrosilyl ethers, generated in situ by the dehydrogenative silylation of cyclopropylmethanols with diethylsilane, undergo asymmetric, intramolecular silylation of cyclopropyl C–H bonds in high yields and with high enantiomeric excesses in the presence of a rhodium catalyst derived from a rhodium precursor and the bisphosphine (S)-DTBM-SEGPHOS. The resulting enantioenriched oxasilolanes are suitable substrates for the Tamao–Fleming oxidation to form cyclopropanols with conservation of the ee value from the C–H silylation. Preliminary mechanistic data suggest that C–H cleavage is likely to be the turnover-limiting and enantioselectivity-determining step.*

The functionalization of C–H bonds with boranes and silanes has been studied intensively, due to the high regioselectivity of these processes for sterically accessible C–H bonds and the widespread utility of the products.[1,2] However, the development of enantioselective variants of these reactions,[3–5] particularly enantioselective functionalization of alkyl C–H bonds, has been limited (Scheme 1). The group of Kuninobu, Murai, and Takai reported the asymmetric silylation of a C–H bond to generate a stereogenic silicon center with up to 88% enantiomeric excess (*ee*) (Scheme 1 A),[6,7] and the groups of Shibata, He, Murai, and Takai independently reported the synthesis of planar-chiral compounds with moderate to high enantioselectivities by asymmetric C–H silylation of ferrocenes.[8–10] Recently, we reported an enantioselective silylation of aryl C–H bonds to form enantioenriched benzoxasilole products with up to 99% *ee*.[11] Although these reactions can occur with high enantioselectivity, they are limited to the functionalization of aryl C–H bonds. The only published set of enantioselective silylations of alkyl C–H bonds occurs with low *ee* values (37–40% *ee*) and with limited scope (Scheme 1 B).[12]

To create the first silylations of alkyl C–H bonds that occur with high enantioselectivity, we investigated reactions of cyclopropanes. C–H bonds of cyclopropanes are more reactive than C_{sp^3}–H bonds of unstrained rings or alkyl chains,[13] and the rigid conformation of a cyclopropane could allow for high stereoselectivity. Yu and co-workers reported enantioselective, Pd-catalyzed arylation and alkylation reactions of cyclopropanes containing *N*-aryl or triflyl amides as a directing group with organoborane or iodoarene reagents.[14,15] In addition, Cramer and co-workers reported Pd-catalyzed intramolecular arylations and alkylations of cyclopropyl C–H bonds to form tetrahydroquinolines, dihydroquinolones, dihydroisoquinolones, and γ-lactams.[16–18] However, enantioselective functionalization to form products containing a new carbon–heteroatom bond has not been reported. Enantioselective silylation would generate a product containing a new carbon–oxygen bond after oxidation of the C–Si bond in the silylation product.[19] Although two silylations of cyclopropyl C–H bonds have been reported,[20,21] no enantioselective variant of this reaction has been published.



Scheme 1. Enantioselective C–H silylation.

We report a rhodium-catalyzed, enantioselective silylation of cyclopropanes directed by a hydrosilyl group (Scheme 1 C). The reaction is initiated by formation of silyl ether **2** from cyclopropylmethanol **1** and leads to the silylation of a cyclopropyl C–H bond to form the silylcyclopropane product **3** in high yield and with high enantioselectivity. This process is a rare example of the silylation of secondary C–H bonds,[20–24] and the product undergoes oxidation with full conservation of the enantiomeric excess of the silylation product to form a diol containing a secondary carbinol stereocenter that would be difficult to set by more classical hydrogenation of the corresponding ketone.[25]

We began our investigation of the enantioselective silylation of cyclopropanes by examining the reactions of (1-

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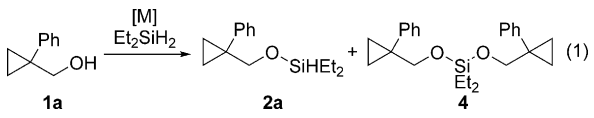
phenylcyclopropyl)methanol (**1a**). The dehydrogenative coupling of **1a** with diethylsilane catalyzed by [{Ir(cod)Cl}$_2$] or [{Ir(cod)OMe}$_2$] under conditions we reported previously for the dehydrogenative silylation of alcohols and amines[24,26–28] led to a mixture of hydrosilyl ether **2a** and dialkoxysilane **4** [Eq. (1)]. In contrast, the same reaction catalyzed by 0.2 mol% [Ru(PPh$_3$)$_3$Cl$_2$] at 50 °C delivered **2a** exclusively.



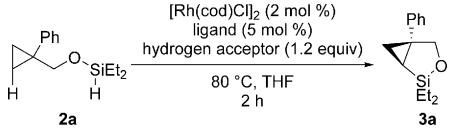
The ruthenium complex did not catalyze the silylation of alcohol **1a** with the silyl ether **2a**.[27,29] Silyl ether **2a** formed by the Ru-catalyzed process was used without further purification for the silylation of a cyclopropyl C–H bond after removal of the solvent and remaining diethylsilane.

Having identified a simple synthesis of **2a**, we sought conditions for this asymmetric, intramolecular silylation (Table 1). Based on previous reports of Rh-catalyzed silylations of C–H bonds,[9–12] we examined the Rh catalyst derived from [{Rh(cod)Cl}$_2$] and (*S*)-DTBM-SEGPHOS (**L1**) with cyclohexene as a hydrogen acceptor[30] at 80 °C (entry 1). The functionalization of the cyclopropyl C–H bond occurred in 2 hours under these conditions, yielding the cyclized product **3a** in 93% yield and 83% *ee*. Other SEGPHOS derivatives, such as (*S*)-SEGPHOS (**L2**), (*R*)-DM-SEGPHOS (**L3**), and (*R*)-DMM-SEGPHOS (**L4**), formed catalysts with lower reactivity and enantioselectivity toward the silylation than did (*S*)-DTBM-SEGPHOS (**L1**) (entries 2–4). These results suggest that bulky substituents on the ligand are important for achieving both high reactivity and high selectivity. Complexes generated from related bisphosphine ligands, such as (*R*)-DTBM-BINAP (**L5**), (*R*)-DTBM-MeOBIPHEP (**L6**), and (*R*)-DTBM-GARPHOS (**L7**) (entries 5–7), were less selective catalysts.

The presence of a hydrogen acceptor in the reaction and the proper identity of this acceptor were critical to achieve high yield and good enantioselectivity, and the temperature substantially affected the enantioselectivity. In the absence of a hydrogen acceptor, competing processes occurred, including the disproportionation of **2a** to form **4** (entry 9), and low yield and *ee* of the silylcyclopropane were observed. The reaction with norbornene instead of cyclohexene as hydrogen acceptor also occurred in lower yield, due to the hydrosilylation and dehydrogenative silylation of norbornene (entry 8). Reactions run at 50 °C occurred with higher enantioselectivity than those run at 80 °C, and high conversion was maintained (entry 10).

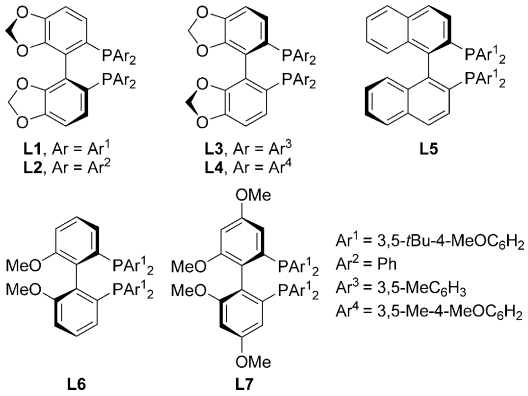
With cyclohexene as hydrogen acceptor, **L1** as ligand, and 50 °C as the reaction temperature (entry 10), the competing processes were suppressed. For example, products from the silylation of aryl C–H bonds were not observed, although the conditions we developed are similar to those used for the silylation of aryl C–H bonds.[11] In addition, ring opening of the cyclopropane by the hydrosilyl group was not observed. Opening of a cyclopropane ring by a hydrosilane in the presence of Rh catalysts has been reported previously.[31–33]

Table 1: Evaluation of reaction conditions.



Entry	Ligand	Hydrogen acceptor	Yield [%][a]	*ee* [%][b]
1	**L1**	cyclohexene	93	83
2[c]	**L2**	cyclohexene	9	nd
3[c]	**L3**	cyclohexene	25	nd
4[c]	**L4**	cyclohexene	35	−11
5[c]	**L5**	cyclohexene	55	−39
6	**L6**	cyclohexene	60	−45
7	**L7**	cyclohexene	48	−36
8	**L1**	norbornene	81	84
9[c]	**L1**	none	54	70
10[d]	**L1**	cyclohexene	90	87

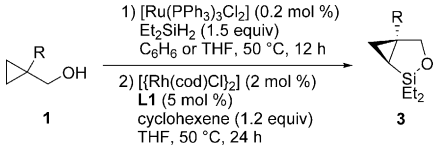
[a] Determined by GC analysis with dodecane as the internal standard. [b] Determined by SFC analysis on a chiral stationary phase. A negative *ee* value indicates *ent*-**3a** was formed as the major enantiomer. nd = not determined. [c] 12 h. [d] 50 °C, 24 h.

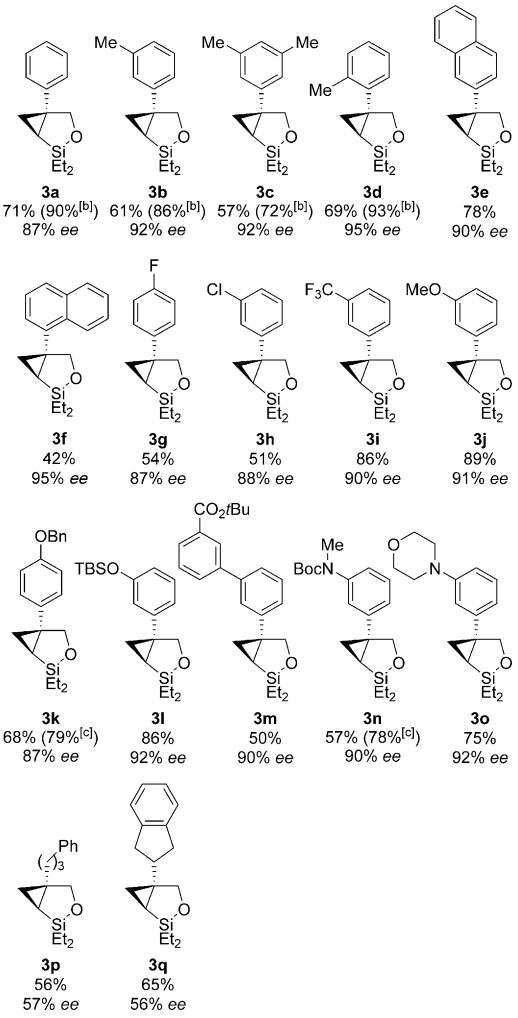


Having established conditions for the enantioselective silylation of cyclopropane **2a**, we investigated the scope of the reaction. Table 2 shows yields of isolated products and representative yields determined by gas chromatography (GC) or ^{1}H NMR spectroscopy.[34] In general, the enantioselectivity of the reaction correlated with the steric properties of the aryl ring in the substrate. The enantioselectivities for reactions of substrates containing *meta* (**1b**,**c**) or *ortho* (**1d**) substituents on the aryl rings were higher than the enantioselectivities for substrates lacking any substituents (**1a**) or those of substrates containing only *para* (**1g**) substituents on the aryl ring. A similar correlation between enantioselectivity and steric properties was observed for the reactions of cyclopropylmethanols substituted with naphthyl groups. For example, the enantioselectivity of the reaction of (1-naphthylcyclopropyl)methanol (**1f**) was higher than that of the reaction of the less sterically demanding (2-naphthylcyclopropyl)methanol (**1e**).

Further reactions probed the functional-group tolerance of the silylation process. Aryl halides (**1g**,**h**) and a trifluoromethylarene (**1i**) were both compatible with the reaction conditions. Oxygen-based functional groups, such as methoxy (**1j**), benzyloxy (**1k**), siloxy (**1l**), and alkoxycarbonyl (**1m**)

Table 2: Scope of the enantioselective C–H silylation.[a]





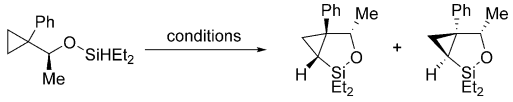
[a] Yields of isolated products for reactions conducted on a 0.25–1.0 mmol scale following purification by bulb-to-bulb distillation or silica gel chromatography. The *ee* values were determined by chiral SFC or HPLC analysis. The absolute configuration was assigned by analogy. [b] Reactions were conducted on a 0.1 mmol scale to determine yields by GC analysis with dodecane as the internal standard. [c] Reactions were conducted on a 0.1 mmol scale to determine yields by ^{1}H NMR analysis with 1,1,2,2-tetrabromoethane as an internal standard added after the reaction.

groups, were also compatible with the silylation process. Whereas nitro groups were not tolerated under the reaction conditions, carbamates (**1n**) and tertiary amino groups (**1o**) were.

The enantioselectivity for reactions of cyclopropanes substituted with alkyl groups (**3p**,**q**) was lower than that for reactions of cyclopropanes substituted with aryl groups. This trend does not correlate with the steric environment imposed by the alkyl groups because the enantioselectivity of the reaction of a cyclopropane bearing a primary alkyl substituent was almost identical to that of the reaction of a cyclopropane bearing a secondary alkyl substituent. The high enantioselectivity for arylcyclopropanes could result from an interaction between the aryl rings of the catalyst and the aryl substituents of the substrate.

In addition to controlling the enantioselectivity, the chiral catalyst could control the diastereoselectivity of the silylation of an enantioenriched cyclopropane, such as substrate **5** in Table 3. To determine the inherent diastereoselectivity controlled by the substrate, we conducted a silylation reaction of **5** with the achiral catalyst generated from [{Ir(cod)OMe}$_2$]

Table 3: Diastereoselective C–H silylation on a chiral substrate.

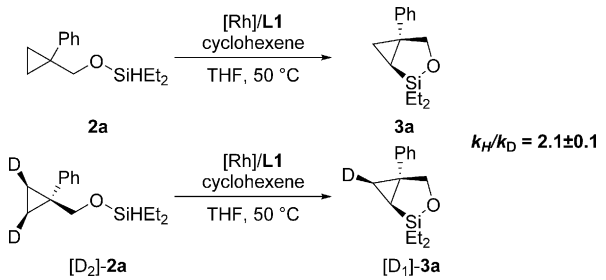


Entry	Conditions	Yield [%][a]	**6a**/**6b**[b]
1	[{Ir(cod)OMe}$_2$]/Me$_4$phen (2 mol%) norbornene, 80°C, 6 h	78	10:1
2	[Rh]/*ent*-**L1** (4 mol%) cyclohexene, 50°C, 24 h	66 >99% *ee*[c]	>20:1
3	[Rh]/**L1** (4 mol%) cyclohexene, 50°C, 24 h	57[d]	1:1.6

[a] Yields of isolated products for reactions conducted on a 0.25 mmol scale following purification by silica gel chromatography. [b] Determined by GC analysis. [c] The *ee* value corresponds to the major isomer **6a** and was determined by chiral HPLC analysis. The absolute configuration was assigned by analogy. [d] The isolated product contained about 5% of inseparable impurities.

and 3,4,7,8-tetramethyl-1,10-phenanthroline (Me$_4$phen) at 80°C (entry 1). This reaction yielded a mixture of **6a** and **6b** in 10:1 ratio. This result suggests that there is a strong preference to form **6a** over **6b**, presumably to avoid the unfavorable steric interaction between the phenyl and methyl groups. In the matched combination of catalyst and substrate, the reaction of **5** catalyzed by the combination of [{Rh(cod)Cl}$_2$] and *ent*-**L1** yielded a mixture of **6a** and **6b** in a ratio over 20:1 (entry 2) and with enantiomeric excess for **6a** exceeding 99%. Thus, this silylation protocol forms an enantiopure compound possessing three consecutive stereogenic centers from a readily accessible enantioenriched secondary alcohol.[35,36] The reaction of **5** conducted with the combination of [{Rh(cod)Cl}$_2$] and **L1** as the catalyst formed a mixture of **6a** and **6b** in a 1:1.6 ratio with **6b** as the major diastereomer (entry 3). Although the diastereoselectivity was low, the catalyst did override the substrate bias and formed the isomer that was strongly disfavored with an achiral catalyst as the major product.

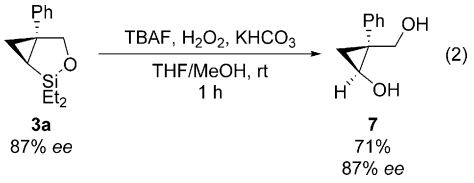
To gain insight into the mechanism of this reaction, we determined the kinetic isotope effect (KIE) by measuring the initial rates of the silylation of non-deuterated and deuterated substrates **2a** and [D$_2$]-**2a** in separate vessels. The KIE from this set of experiments was 2.1 (Scheme 2). This value is similar to that we observed for the Ir-catalyzed silylation of



Scheme 2. KIE on the silylation of cyclopropyl C–H bonds.

secondary C–H bonds[24] and implies that C–H cleavage may be the turnover-limiting step.[37] Assuming this KIE, although modest, implies that the C–H bond is cleaved irreversibly, this value would also imply that the configuration at the C–Si bond in the product is set by the C–H bond cleavage, not by the C–Si bond-forming reductive elimination.

Enantioenriched oxasilolanes are easily converted into cyclopropanols, a useful building block in organic synthesis.[38] For example, the treatment of oxasilolane **3a** with TBAF, aqueous H_2O_2, and $KHCO_3$ formed cyclopropanol **7** without any erosion in the *ee* value [Eq. (2)].[39] The absolute configurations of the stereogenic centers in **7** were unambiguously determined by single-crystal X-ray analysis.[40]



In summary, we have developed an enantioselective silylation of cyclopropanes, which constitutes the first highly enantioselective silylation of an alkyl C–H bond and the first catalytic, enantioselective functionalization of the C–H bond in a cyclopropane to form a carbon–heteroatom bond. The silylation process occurs in high yield and with high enantioselectivity and tolerates a wide range of functional groups when catalyzed by a Rh complex containing a chiral bisphosphine. Tamao–Fleming oxidation of the enantioenriched oxasilolanes yields cyclopropanols with the same *ee* value as the oxasiloles precursors. The observed KIE of 2.1 suggests that the C–H bond cleavage is turnover-limiting and enantioselectivity-determining. Further studies to expand the scope of this enantioselective silylation of C–H bonds are in progress in our laboratory.

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Keywords: asymmetric catalysis · C–H activation · cyclopropanes · rhodium · silylation

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[40] CCDC 1481185 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Communications

Asymmetric C–H Activation

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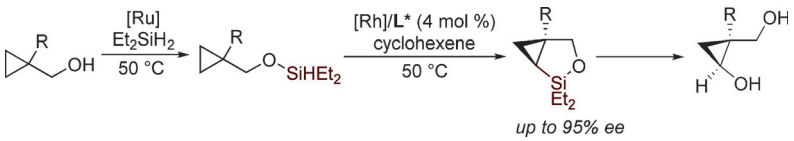

Enantioenriched cyclopropanes: Hydrosilyl ethers, generated in situ by the dehydrogenative silylation of cyclopropylmethanols, undergo asymmetric, intramolecular silylation of cyclopropyl C–H bonds in high yields and with high enantiomeric excesses in the presence of a rhodium catalyst. The silylation products are suitable substrates for Tamao–Fleming oxidation to form cyclopropanols with conservation of the *ee* value from the C–H silylation.