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# A Chiral Nitrogen Ligand for Enantioselective, Iridium-Catalyzed Silylation of Aromatic C-H Bonds

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## Abstract

Iridium catalysts containing dative nitrogen ligands are highly active for the borylation and silylation of C-H bonds, but chiral analogs of these catalysts for enantioselective silylation reactions have not been developed. We report a new chiral pyridinyloxazoline ligand for enantioselective, intramolecular silylation of symmetrical diarylmethoxy diethylsilanes. Regioselective and enantioselective silylation of unsymmetrical substrates was also achieved in the presence of this newly developed system. Preliminary mechanistic studies imply that C-H bond cleavage is irreversible, but not the rate-determining step.

## Iridium works now
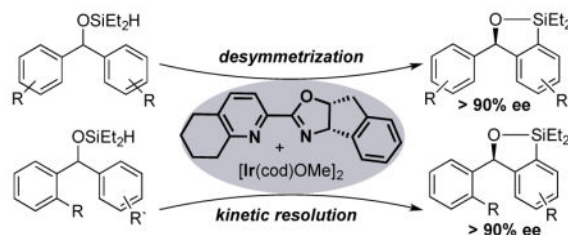


A new chiral pyridinyloxazoline ligand was developed, which enables enantioselective, intramolecular silylation of symmetrical diarylmethoxy diethylsilanes. Regioselective and enantioselective silylation of unsymmetrical substrates was also achieved in the presence of this newly developed system.

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

## Keywords

asymmetric catalysis; C-H activation; chiral dinitrogen ligand; iridium; silylation

Arylsilanes are important in material science[1] and are valuable synthetic intermediates in agroscience,[2] and medicinal chemistry.[3] Among the various reactions that form C-Si bonds,[4] transition metal-catalyzed direct silylation of inert C-H bonds has been a target because of the potential of this reaction to generate organosilanes under mild and neutral conditions from readily available starting materials.[5] The resulting C-Si bond can be transformed to a variety of carbon-carbon and carbon-heteroatom bonds.[5a, 6]

Although various enantioselective, transition metal-catalyzed C-H bond functionalizations have been developed, enantioselective silylations are rare,[7] and all of the current, enantioselective silylations of aromatic C-H bonds have been conducted with rhodium catalysts and a diene or a diphosphine ligand. In 2013, Takai, Kuninubu, and coworkers reported the first enantioselective silylation of aromatic C-H bonds. This reaction produced chiral spirosilabifluorene derivatives, but with an ee of only 81% (Scheme 1a, left).[8] In 2015, Shibata, He, and Takai independently reported enantioselective silylations of C-H bonds in ferrocenes catalyzed by rhodium complexes containing diene or diphosphine ligands (Scheme 1a, middle).[8b, 9] Recently, one of our groups reported enantioselective silylations of aryl C-H bonds with ee values of 72 to 99% catalyzed by rhodium complexes ligated by chiral diphosphines (Scheme 1a, right).[10]

Iridium catalysts containing bipyridine and phenanthroline ligands enable the silylation of C-H bonds with the most favorable combination of rate and functional-group compatibility, but the planar structure of the ligand makes the development of chiral iridium catalysts for enantioselective silylation particularly challenging to develop. To create chiral iridium catalysts for the silylation of C-H bonds, we investigated complexes containing chiral, dative nitrogen ligands. Most chiral bipyridine derivatives are prepared by lengthy sequences,[11] and the reactivity of iridium catalysts ligated by bisoxazoline ligands, which are more accessible and commonly used for asymmetric catalysis, are low for the borylation and silylation of C-H bonds.[10] We report iridium catalysts containing a new ligand containing one tetrahydroquinoline and one oxazoline unit. These systems catalyze the enantioselective desymmetrization of symmetrical diarylmethanol derivatives, as well as kinetic resolution of unsymmetrical diarylmethanols, at low temperatures (30–40 °C) with high enantioselectivities (Scheme 1b). Although quinoline and pyridine oxazoline ligands have been used for enantioselective transformations,[12] the ligands we developed are significantly modified from this basic structure, and the combination of one pyridine and one chiral oxazoline units has been applied previously to just one iridium-catalyzed process.[13]

To identify readily accessible, chiral, dative nitrogen ligands for enantioselective silylation, we first tested iridium complexes of several commercially available, C2-symmetric bidentate and tridentate nitrogen ligands for the intramolecular silylation of **1a** (Table 1. **L1–4**). No conversion was observed from reactions with the classic chiral BOX, PyBOX, and bipyridine ligands. In contrast, reactions with two of the non-C2-symmetric pyridinyl oxazoline ligands (**L5–7**) occurred in good yields. However, enantioselectivities were low

(5% ee and 10% ee, respectively). Replacement of the pyridinyl group in **L5** with a quinolinyl group (**L8**), led to a system that gave the silylated product in a higher, but still modest, ee of 73%, and good yield.

To investigate the steric effects of the substituents on the oxazole ring, ligands **L9–18** were prepared. However, the enantioselectivity was not significantly higher for reactions conducted with any of these quinolyloxazolines. Likewise, the steric and electronic effects of substituents on the quinoline ring were investigated by preparing and testing **L19–L22**. The yield and ee of the reaction with the ligand containing an electron-donating substituent (OMe) at the C-4 position of the quinoline (**L19**) were comparable to those of the reaction with ligand **L8**, and the reaction did not occur with the ligand **L20** containing an electron-withdrawing group ($CF_3$) at the same position. The presence of a methyl group at the C-7 or C-8 position of the quinoline (**L21** and **L22**) to increase steric hindrance on this ring also did not lead to a system that reacts with higher enantioselectivity. Fusion of the oxazoline to an indane skeleton created systems that reacted in good yield or enantioselectivity, but not both. Reaction with quinoline-based **L23** occurred in the highest ee of this set of ligands (87% ee), but in lower yield than that that with ligand **L8**. Reaction with pyridyl-based **L24** led to a catalyst that reacted in high yield, but with no enantioselectivity.

Because the catalyst containing quinoline oxazoline **L23** reacted with the highest ee, and the catalyst containing the more electron-donating ligand **L19** occurred in high yield, we synthesized the partially hydrogenated quinolinyl ligand **L25**. Ligand **L25** should be more electron donating than **L23**, while maintaining the general structural features of **L23**. Indeed, the iridium catalyst generated from this ligand gave the silylation product **2a** in a high 90% yield and a high 92% ee. The reaction with ligand **L26** containing the tetrahydroquinolinyl group but an isopropyl substituent in place of the fused indanyl group on the oxazoline ring occurred with much lower ee, showing the importance of the indanyl moiety in **L25**.

Having established conditions and catalyst to obtain high yield and ee with substrate **1a**, we examined the scope of the reaction (Table 2). In general, the reaction of all of the symmetrical unsubstituted and the *meta*- or *para*-substituted diarylmethanol derivatives (**1a–1l**) gave the desired silylated products (**2a–2l**) in good to excellent yields with high ee values (>90%). Alkyl groups, a phenyl group, oxygen-based functional groups (such as an ester and an ether), and halides were tolerated by the reaction conditions. Substrates containing electron-withdrawing and electron-donating groups at the *meta*- position (**2j–2k**) were also examined, and the reactivity and the enantioselectivity were high in all cases. The reaction of di(2-naphthyl)methanol also produced the silylated product **2l** in 61% yield with 91% ee. In contrast, no reaction was observed, even at 80 °C, with the ortho-substituted **2m**, although one ortho C-H bond on each ortho tolyl group is available for silylation. However, the reaction gave 45% yield (45 °C, 24 h) when less hindered, achiral dtbpy (4,4′-Di-*tert*-butyl-2,2′-dipyridyl) was used as ligands.

This lack of reactivity of the *ortho* aryl group provided an opportunity to determine if the differences in transition states leading to enantioselective silylation would lead to a kinetic resolution of racemic diaryl methanols containing one *ortho*-substituted aryl group. The resulting silylated products can be transformed to enantiopure unsymmetrical

diarylmethanols containing two ortho-substituted aryl groups. Such chiral unsymmetrical diarylmethanols are important precursors for the synthesis of some existing pharmaceuticals, such as neobenodine,[14] an antihistaminic and anticholinergic agent.[15] Although methods are known for the synthesis of chiral unsymmetrical diarylmethanols, such methods are not suitable for the synthesis of the corresponding unsymmetrical diarylmethanols containing one or two ortho-substituted aryl groups.[15–16] Moreover, rhodium catalysts that led to high site selectivity for reaction with enantioenriched, unsymmetrical diarylmethanols[10] did not lead to high selectivity for reaction with one enantiomer over another, even when one of the aryl groups was ortho substituted (see the supporting information for details).

To determine if our newly developed catalyst system (**L25**-**Ir**) would resolve the two enantiomers of such diarylmethanols, *rac*-**3a** was subjected the catalyst system at 50 °C for 12 h. The desired silylation product **4a** and the unreacted product **3a** were obtained with 76% ee and 97% ee respectively, corresponding to a selectivity factor (*s*)[17] of 40 (SI, Table 2, entry 1). The reaction at 40 °C for 12 h occurred with an *s* value of 88, but only 20% of the product was obtained (SI, Table 2, entry 2). When the reaction was conducted for 20 h, product **4a** formed in a higher 46% and 94% ee, corresponding to a selectivity of 72 (SI, Table 2, entry 3).

The yields and ee values of the products obtained from kinetic resolutions of a series of unsymmetrical diaryl methanols are shown in Table 3. These data show the effects of groups on the aryl ring lacking an ortho-substituent. Alkyl, phenyl, electron-donating and electron-withdrawing groups at the *para* position were tolerated. The cyclized product was obtained in these cases in 90% to 95% ee. Substrates containing various substituents at the *meta* position (**4g**–**4i**) also formed the products in good ee. In addition to substrates containing a methyl group at the *ortho* position, those containing an *ortho* CF$_3$ group or 1, 3-dimethyl groups (**4j** and **4k**) reacted with high stereoselectivity. Reactions of **3a** and **3k** lacking any substituent on the reactive aryl group required prolonged reaction times, but acceptable yields of the products were obtained with high ee values. It is well established that the resulting arylsilanes can be converted to diarylmethanols containing two ortho-substituted aryl groups.[10]

A preliminary evaluation of the mechanism was conducted. The reaction under the conditions of the method development occurred with an induction period. During this time two mutually coupled signals due to hydride ligands were observed by $^1$H NMR spectroscopy. These hydride signals decayed as the reaction was initiated, and several hydride signals appeared, complicating a precise identification of the resting state of the catalyst. Moreover, this induction period complicated obtaining quantitative kinetic data. Nevertheless, qualitative data clearly indicated the orders in reaction components. The reaction was faster in the presence of the hydrogen acceptor norbornene than in the absence of norbornene, but the reaction was zeroth order in this component above 0.2 M (1.0 equivalent relative to 1a). The reactions were first order in substrate, as determined by comparing the reaction progress after the induction period with varying concentrations of reagents (for details, see supporting information).

Measurements of the kinetic isotope effect (KIE) gave information on the timing of the C-H bond cleavage step in the catalytic cycle. The kinetic isotope effect (KIE) was measured for separate reactions and for the reaction of a mixture of deuterated and protiated substrates (Scheme 2). An overlay of the kinetic plots for reactions with protiated and deuterated substrates to 90% conversion and the rate constants obtained for these two reactions after the first 50 min (after the induction period) showed clearly that the isotope effect under these conditions was negligible ($k_{\mathrm{obsH}}/k_{\mathrm{obsD}} = 1.2 \pm 0.1$, for details, see supporting information) (Scheme 2, eq 1). In contrast, the KIE measured from reaction of a mixture of the deuterated and protiated substrates (Scheme 2, eq 2) was clearly a primary value ($[P_{H9}]/[P_{D9}]$) of 3.9 $\pm$ 0.7 (26–46% conversion). These two KIE values indicate that cleavage of the C-H bond is irreversible, but occurs after the rate-determining step. We also measured a KIE from side-by-side reactions of the fully protiated substrate and the analogous substrate containing deuterium at the Si-H position. A small KIE of 1.0 was observed for this step (Scheme 2, eq 3). Therefore, the rate-determining step does not involve addition of the Si-H or C-H bond. Our data suggest that the rate-determining step is reductive elimination of norbornane in a catalytic cycle such as that shown in Scheme 3 with the silane adding reversibly prior to elimination of norborane.[18]

In summary, a modular route to chiral dinitrogen ligands led to a new type of pyridinyl-oxazoline ligand, and this ligand enabled the first set of highly enantioselective silylations of C-H bonds catalyzed by iridium. Various symmetrical diarylmethanol derivatives underwent desymmetrization to form cyclic silyl ethers in good to excellent yields with high enantioselectivity. This selectivity also translated to the kinetic resolution of unsymmetrical diarylmethoxydiethylsilanes to form the enantioenriched cyclic silyl ether with high enantioselectivity from racemic diaryl methanols. Mechanistic studies show that the C-H bond cleavage is irreversible and occurs after the rate-limiting step. Further studies on enantioselective silylation and on the mechanism of this process are ongoing.

## Supplementary Material

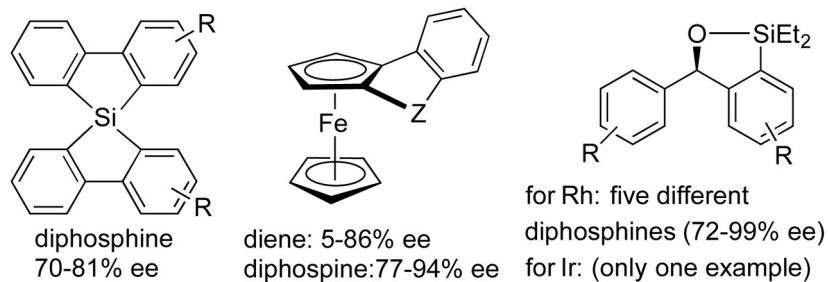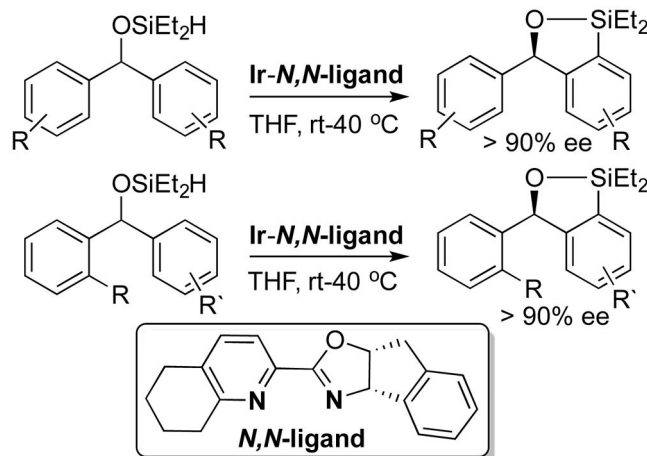Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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17. Kagan HB, Fiaud JC. Top Stereochem. 1998; 18:249–330. Selectivity factors (s) was calculated according to the following equation: s = (rate of fast-reacting enantiomer)/( rate of slow-reacting enantiomer) = ln[(1−C)(1−ee3a)]/ln[(1−C)(1+ee3a)]; Calculated conversion, C = (ee3a)/( ee3a + ee4a).

18. The insertion of norbornene to the Ir-H is reversible, which is supported by the observation of the incorporation of deterium into the norbornene when deterited substrated was used (for details, see SI).

**(a) Rh-catalyzed enantioselective silylation of C-H bonds**



diphosphine
70-81% ee

diene: 5-86% ee
diphospine:77-94% ee

for Rh: five different
diphosphines (72-99% ee)
for Ir: (only one example)

**(b) This work: Ir-catalyzed desymmetrization and kinetic resolution**



**Scheme 1.**
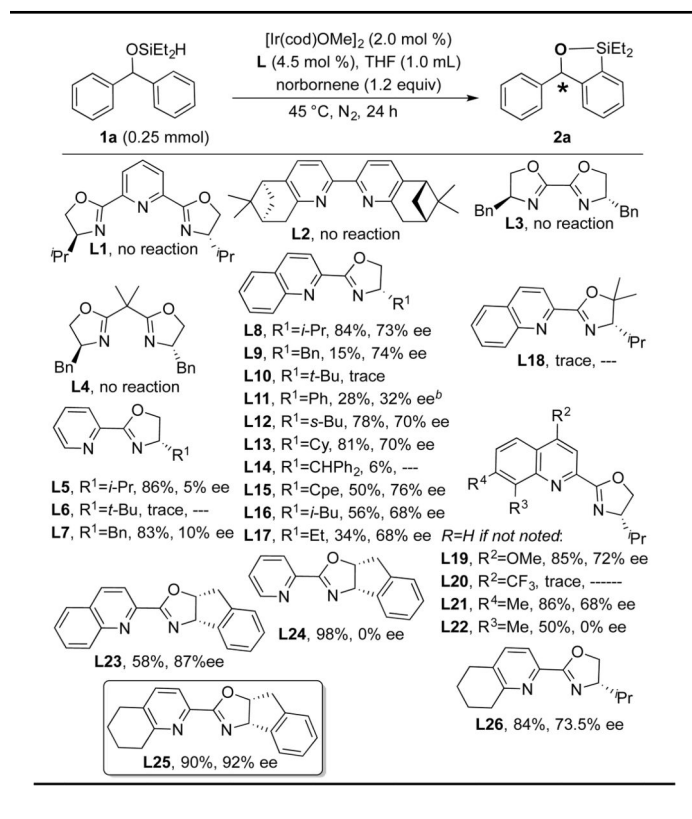Enantioselective aryl C-H silylation.
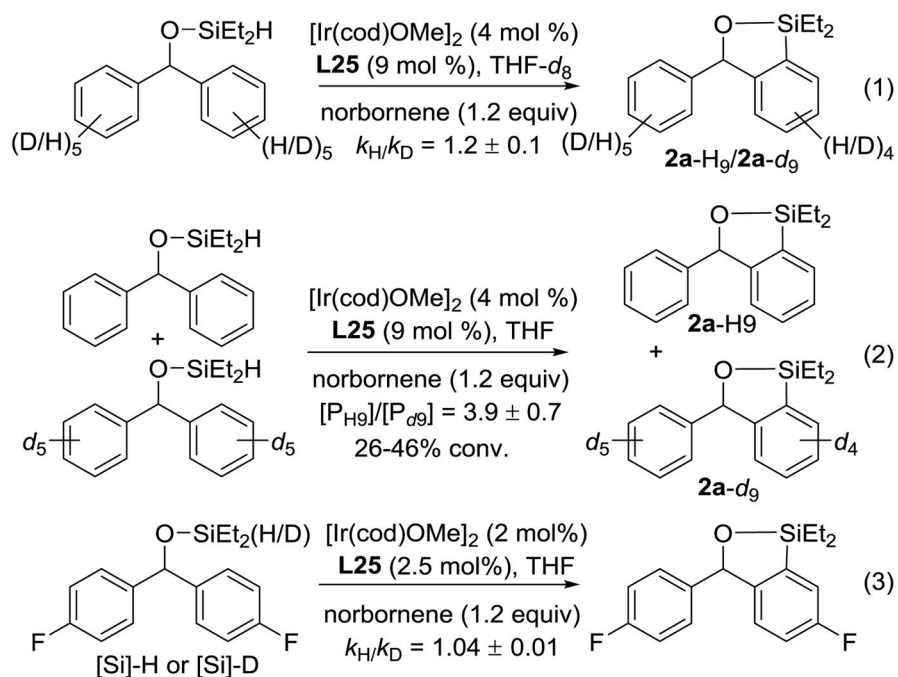
**Scheme 2.**
Results of experiments on the KIE.
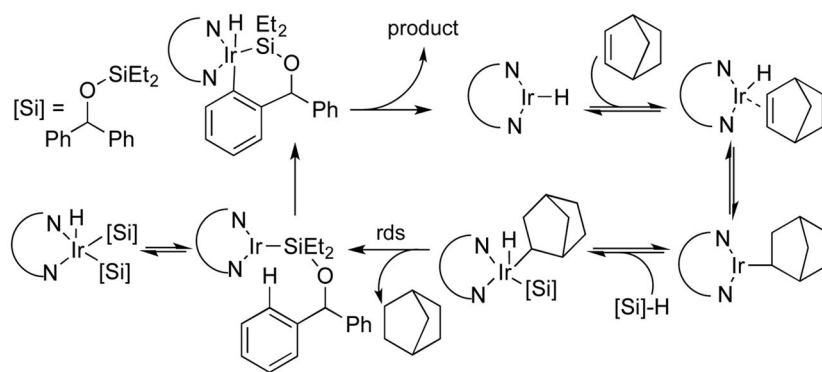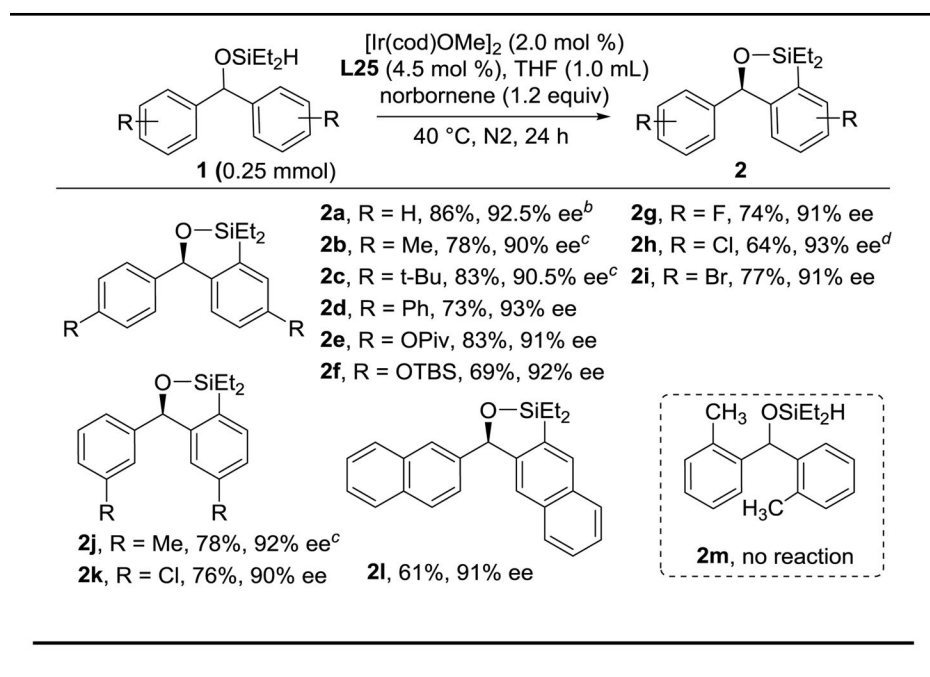
**Scheme 3.**
Proposed catalytic cycle for the silylation.

**Table 1**

Design and modification of ligands.[a]

**Table 2**

Desymmetrization of symmetrical diarylmethyl silanes.[a]



**2a**, R = H, 86%, 92.5% ee[b]      **2g**, R = F, 74%, 91% ee
**2b**, R = Me, 78%, 90% ee[c]       **2h**, R = Cl, 64%, 93% ee[d]
**2c**, R = t-Bu, 83%, 90.5% ee[c]   **2i**, R = Br, 77%, 91% ee
**2d**, R = Ph, 73%, 93% ee
**2e**, R = OPiv, 83%, 91% ee
**2f**, R = OTBS, 69%, 92% ee

**2j**, R = Me, 78%, 92% ee[c]
**2k**, R = Cl, 76%, 90% ee

**2l**, 61%, 91% ee

**2m**, no reaction

[a] The yields refer to isolated yields, and the ee values were analyzed by chiral HPLC. The absolute configuration was assigned by analogy (see SI for details).

[b] The ee was determined after Tamao-Fleming oxidation.

[c] The ee was determined after iodination.

[d] The reaction was conducted using 3 mol % of [Ir(cod)OMe]$_2$ and 6.5 mol % of **L25**.

**Table 3**

Kinetic resolution of unsymmetrical diarylmethyl silanes.[a]



$$\text{3 (0.25 mmol)} \xrightarrow[\text{35 °C, N}_2\text{, 12 h}]{\substack{\text{[Ir(cod)OMe]}_2 \text{ (2.0 mol\%)} \\ \text{L25 (4.5 mol\%), THF (1.0 mL)} \\ \text{norbornene (1.2 equiv)}}} \text{4}$$

**4a,** R[1]=H, 42%, 94% ee[b] (72)
**4b,** R[1]=t-Bu, 35%, 95% ee (57)
**4c,** R[1]=Ph, 35%, 97% ee (104)
**4d,** R[1]=OMe, 35%, 97% ee (119)
**4e,** R[1]=CF$_3$, 38%, 94% ee (69)
**4f,** R[1]=F, 33%, 97% ee[b,c] (114)

**4g,** R[1]=CF$_3$, 38%, 97% ee[d] (120)
**4h,** R[1]=Br, 38%, 95% ee[e] (99)
**4i,** R[1]=Cl, 31%, 96% ee (82)

**4j,** 28%, 94% ee (98)

**4k,** 32%, 97% ee[b] (109)
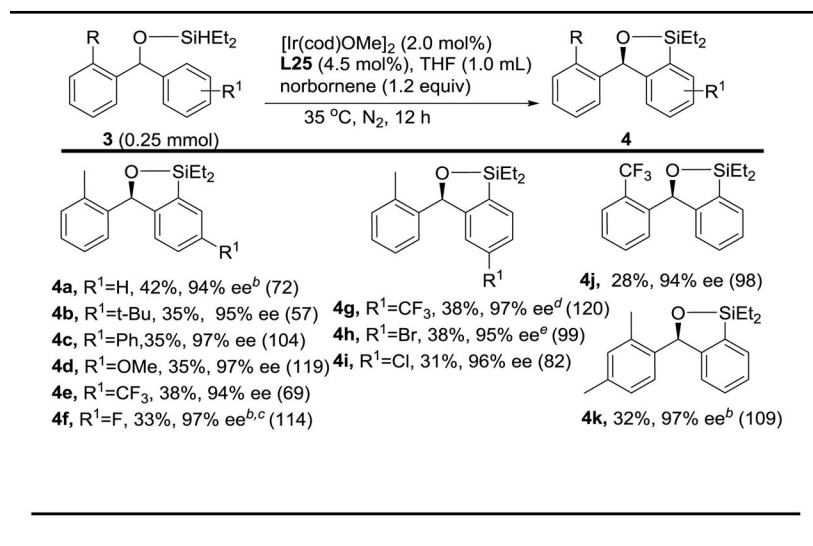
[a] The yields refer to isolated yields, and the ee values were analyzed by chiral HPLC. Numbers in the parentheses refer to selectivity factors, which are averages of two runs.

[b] The reaction was conducted at 40 °C for 20 h.

[c] The reaction was conducted with L23 at 40 °C for 20 h.

[d] The ee was was determined after iodination.

[e] The reaction was conducted for 14 h.