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Strained silacycle-catalyzed asymmetric Diels–Alder cycloadditions: the first highly enantioselective silicon Lewis acid catalyst

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Abstract—The first highly enantioselective silicon Lewis acid catalyst for an asymmetric organic transformation has been developed. The catalyst derives its activity from the strain induced in the silicon center by virtue of being constrained in a five-membered ring. A simple tridentate ligand has been developed and the derived chlorosilane complex catalyzes the Diels–Alder cycloaddition of methacrolein and cyclopentadiene with 94% ee.
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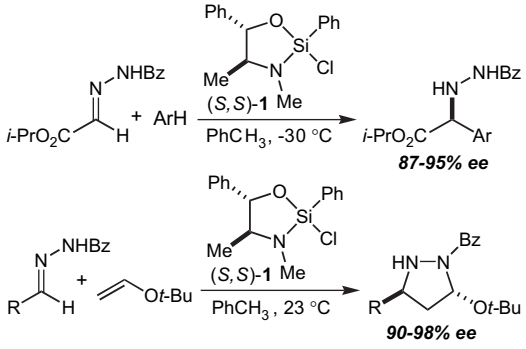
1. Introduction

The possibility that silicon—with all of its inherent practical advantages—might serve as a useful Lewis acid for asymmetric synthesis, has long captured the imagination of organic chemists. Three strategies have emerged for rendering otherwise unreactive silanes Lewis acidic for the promotion/catalysis of organic reactions: (1) attachment of strongly electron-withdrawing groups to the silicon center (e.g., TMSOTf),[1] (2) Lewis base activation of otherwise only weakly Lewis acidic silanes such as $RSiCl_3$ and $SiCl_4$,[2] and (3) constraining the silicon in a small ring (strained silacycles).[3] Despite some creative ideas,[4] the first approach has yielded no highly enantioselective chiral catalysts for asymmetric synthesis. In contrast, the second approach has led to the development of several highly enantioselective reactions.[5] It is typically the Lewis base that serves as the catalyst, however, while the silane component is employed as a stoichiometric reagent. We have recently reported the first examples of highly enantioselective chiral silicon Lewis acid-mediated carbon–carbon bond forming reactions based on the third approach (Scheme 1),[6] and it was natural to wonder whether the same concept might be applied for the discovery of the first highly enantioselective silicon Lewis acid catalyst. Because of its prominent role in the development of chiral Lewis acid catalysis,[7] the Diels–Alder reaction of enals with cyclopentadiene was chosen as the proving ground for this idea.



Scheme 1. Two reactions mediated by silane **1**.

Silane Lewis acid **1** (prepared and employed as a 2:1 mixture of diastereomers) has proven effective both for Friedel–Crafts alkylations of acylhydrazones and [3+2] enol ether–acylhydrazone cycloadditions (Scheme 1).[8] Mechanistic investigations have revealed that these reactions proceed by way of covalent attachment of the hydrazone to the silane Lewis acid with chloride displacement and protonation of the amino group of the pseudoephedrine. Such reactions are therefore mechanistically distinct from the proposed simple Lewis acid activation of methacrolein for a Diels–Alder cycloaddition with cyclopentadiene, and there was no reason a priori to believe that silane **1** would prove effective for this reaction. Indeed, **1** is wholly ineffective as a catalyst for this process, and replacement of the phenyl group

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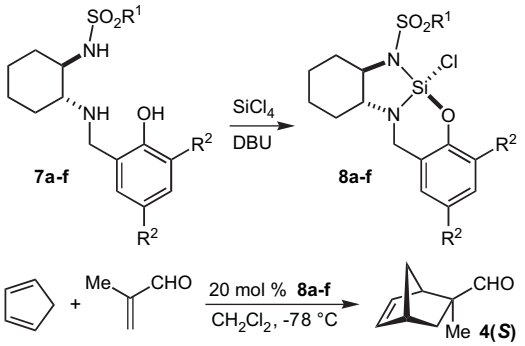
on the silane with various other alkyl, aryl, and heteroatom substituents proved fruitless as well.

2. Results and discussion

A breakthrough was achieved when we examined chiral ligands that carry three functional groups for attachment to the silane. Ephedrine-derived aminophenol **2** was treated with $SiCl_4$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give silane **3** as a single (unassigned) diastereomer (Scheme 2). We were then delighted to discover that **3** is indeed a competent (albeit non-selective) catalyst for the Diels–Alder reaction between cyclopentadiene and methacrolein, producing aldehyde **4**(*R*) in 58% yield and 6% ee. In this and in every case, the *exo* diastereomer was produced highly selectively (>95:5). The diphenylethylenediamine-derived aminophenol **5** was next examined, and the derived silane **6** was also found to be a competent catalyst providing aldehdye **4**(*S*) as the major product in 46% yield and 37% ee. The commonly employed cyclohexanediamine ligand motif was examined in the form of **7a**, which was employed to generate silane **8a** (the illustrated and observed NOE interaction allowed the assignment of relative configuration at the silicon center in **8a**). Gratifyingly, **8a** proved to be a significantly improved catalyst, giving **4**(*S*) in 75% yield and 56% ee, and providing our first true lead catalyst for optimization. Finally, we note that silane **9** is completely inactive under otherwise identical conditions, clearly supporting the hypothesis that the strain induced by the five-membered rings in **3**, **6**, and **8a** is an essential component of their Lewis acidity and catalytic activity.

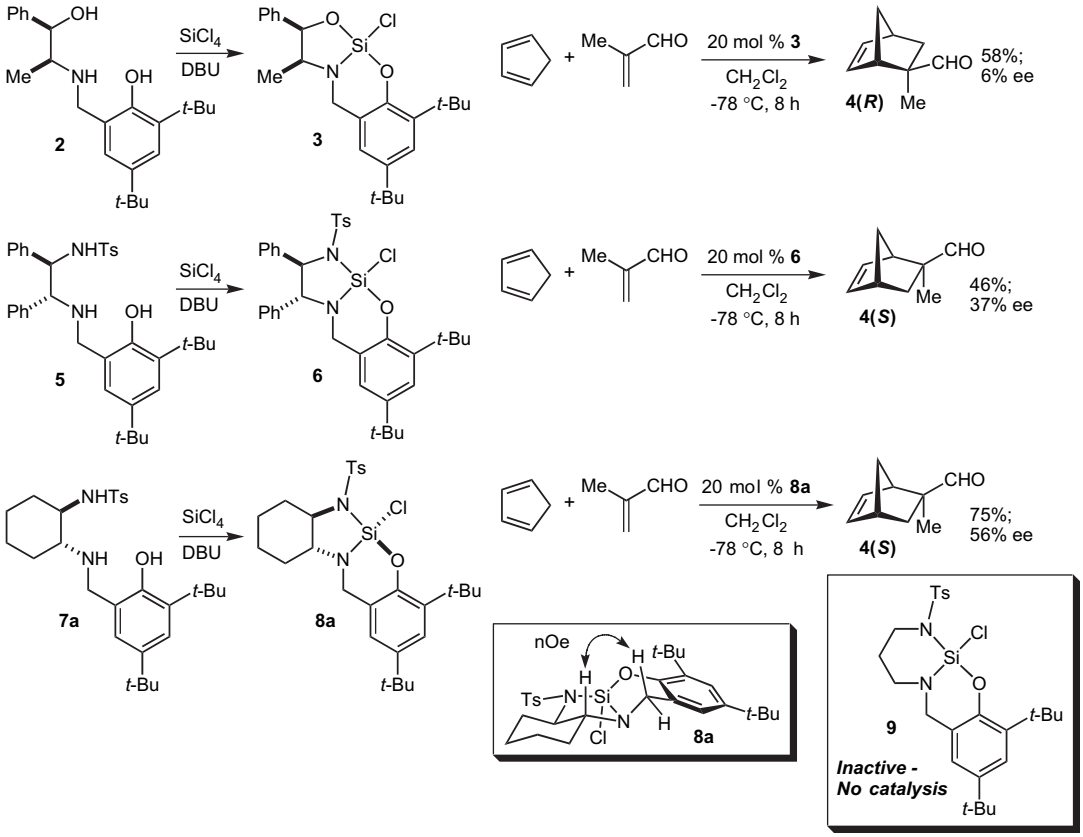
Having recorded a proof of concept with silane **8a**, we turned to a survey of the sulfonamide substituent (R^1) as well as the substituents on the phenol ring (R^2) in an effort to optimize both for efficiency and enantioselectivity (Table 1). Although in some cases the silanes could be isolated in reasonable purity, it was more convenient to employ them in situ. Thus, the precursor sulfonamidoaminophenols **7a–f** were treated with $SiCl_4$ and DBU and the resulting solutions of silanes **8a–f** were simply treated with cyclopentadiene and

Table 1. Optimization of catalyst structure



Entry (cat.)	R^1	R^2	Yield (%)	ee (%)
1 (**8a**)	*p*-Tolyl	*t*-Bu	72	−56[a]
2 (**8b**)	Me	*t*-Bu	75	−75[a]
3 (**8c**)	Mesityl	*t*-Bu	58	−33[a]
4 (**8d**)	*p*-Tolyl	Br	69	57
5 (**8e**)	*p*-F–C_6H_4	H	56	88
6 (**8f**)	*p*-Tolyl	H	78	94

[a] Major enantiomer was **4**(*R*).



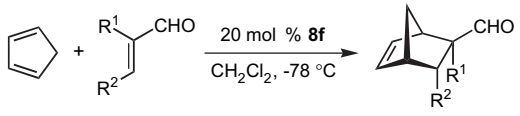
Scheme 2. Initial discovery of competent silane Lewis acid catalysts.

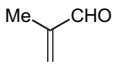
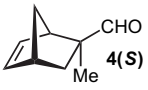
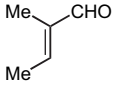
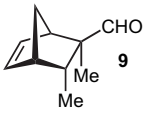
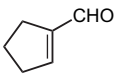
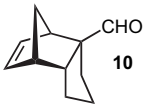
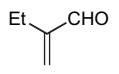
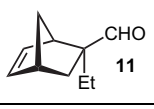
methacrolein. As shown, simple changes to the sulfonamide group and the substituents on the phenol ring produced dramatic changes in the enantioselectivity. Indeed, it was possible to obtain either moderately good enantioselectivity for the *R* enantiomer (entry 2) or excellent enantioselectivity for the *S* enantiomer (entry 6) using the same enantiomer of the cyclohexanediamine core. As shown, the optimal catalyst was the simple tosylamide-unsubstituted phenol **8f**. Using 20 mol % of this catalyst and the in situ procedure, **4**(*S*) was produced in 78% yield and 94% ee. *Silane* **8f** *thus represents the first highly enantioselective silicon Lewis acid catalyst developed for asymmetric synthesis*.

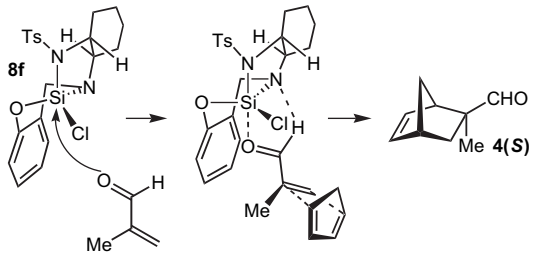
A brief survey of the scope with respect to the enal structure in Diels–Alder reactions with cyclopentadiene catalyzed by **8f** was carried out (Table 2). Whereas β-substitution necessitated extended reaction times, such substrates were nevertheless well tolerated from the standpoint of enantioselectivity (entries 2 and 3). In contrast, and surprisingly, α-substitution beyond a simple methyl group caused a dramatic drop in enantioselectivity (entry 4).

In an attempt to construct a mechanistic model for stereochemical induction, we began with two assumptions: (1) in order for the five-membered diazasilacyclopentane ring to be accommodated in the presumed trigonal bipyramidal (tbp) silane–aldehyde complex, one of the two nitrogens must occupy an apical position, and this will likely be the more electron-poor tosylamide nitrogen, and (2) the aldehyde oxygen will bind to the silane opposite this tosylamide nitrogen so as to occupy the other apical position in the complex (Scheme 3). If a hydrogen bond between the amine and the formyl hydrogen—a type of interaction proposed by Corey to be an essential element in the success of numerous enantioselective chiral Lewis acid catalyzed reactions[9]—is further invoked as depicted, an intriguingly simple model for asymmetric induction emerges as the phenyl ring clearly provides highly effective shielding of the back face of the dienophile. This model can also explain the surprisingly dramatic drop-off in enantioselectivity observed with ethacrolein (Table 2, entry 4). The added methyl group (relative to methacrolein) in this dienophile must swing away from the approaching cyclopentadiene in the transition state, but cannot do so without being forced into a costly steric interaction with the phenyl ring. The likely result is a shift to a greater population of the *s*-cis form of the enal, and in turn eroded levels of enantioselectivity.

Table 2. Survey of enal scope



Entry	Enal	Product	*t* (h)	Yield (%)	ee (%)
1		 **4(*S*)**	8	78	94
2		 **9**	48	87	90
3		 **10**	24	79	86
4		 **11**	16	88	54



Scheme 3. A model for asymmetric induction.

3. Conclusion

We have developed the first highly enantioselective silicon Lewis acid catalyst for asymmetric synthesis. The catalyst is easily and inexpensively prepared and may be employed in situ. Lewis acid catalysts for the Diels–Alder reaction are legion,[7] however, and a powerful new strategy for enal *and* enone activation in Diels–Alder reactions has recently emerged.[10] The significance of this work is therefore not specifically tied to the Diels–Alder reaction, but rather lies in the potential for the development of improved silicon Lewis acid catalyst designs for a broader range of transformations. The present work establishes the validity of this notion and delineates a strategy for achieving such catalysts.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. Flash chromatography was performed on EM silica gel 60 (230–240 mesh). Degassed solvents were obtained from the solvent purification system by passage through a column of activated alumina. ^{1}H NMR spectra were recorded on a Bruker DRX-300 (300 MHz), Bruker DRX-400 (400 MHz), or DMX-500 (500 MHz) spectrometer, and are reported in parts per million from $CDCl_3$ (7.26 ppm), C_6D_6 (7.15 ppm), or DMSO-d_6 (2.50 ppm) as internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad; integration; coupling constant(s) in Hertz; assignment. ^{29}Si NMR spectra were recorded on a Bruker DRX-300 (60 MHz) spectrometer and are reported in parts per million from tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded on a Bruker DRX-300 (338.6 MHz) spectrometer and are reported in parts per million from $CFCl_3$ as internal standard. Proton decoupled ^{13}C NMR spectra were recorded on a Bruker

DRX-300 or Bruker DRX-400 (100 MHz) spectrometer using $CDCl_3$ (77.0 ppm), C_6D_6 (128.0 ppm), or DMSO-d_6 (40.5 ppm) as internal standard. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FTIR spectrometer. Low-resolution mass spectra were obtained on a JEOL HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory. Optical rotations were obtained on a JASCO DIP-1000 polarimeter using a 10 cm path length cell.

4.1.1. Synthesis of ligand 7f. The Schiff base formed by condensation of cyclohexanediamine monotosylamide and salicylaldehyde has been prepared and characterized previously.[11] We prepared the (*R*,*R*)-cyclohexanediamine-derived Schiff base according to this procedure. To a cooled (0 °C) solution of this Schiff base (3.0 mmol) in CH_2Cl_2 (4.0 mL) and MeOH (12.0 mL) was added $NaBH_4$ (337 mg, 9.0 mmol). The reaction mixture was warmed to room temperature after 15 min and stirred for an additional 3 h. The reaction was then quenched by the addition of 1 M NaOH (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with brine (1×5 mL), dried over $MgSO_4$, filtered, and concentrated. The solid residue was then purified by recrystallization (Et_2O/CH_2Cl_2) to afford 1.01 g (90%) of ligand **7f** as a white solid. $[\alpha]_D^{21}$ +9.77 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, 2H, *J*=5.0 Hz, 1.6 Hz, $SO_2C_6(o\text{-}H_2)(m\text{-}H_2)CH_3$), 7.24 (d, 2H, *J*=7.9 Hz, $SO_2C_6(o\text{-}H_2)(m\text{-}H_2)CH_3$), 7.15 (dt, 1H, *J*=1.5 Hz, 7.7 Hz, one of $NCH_2C_6H_4$), 6.91 (dd, 1H, *J*=1.3 Hz, 6.1 Hz, one of $NCH_2C_6H_4$), 6.81–6.73 (m, 2H, two of $NCH_2C_6H_4$), 4.67 (br s, 1H, $NHSO_2Ar$), 3.93 (d, 1H, *J*=13.9 Hz, one of NCH_2Ar), 3.84 (d, 1H, *J*=13.9 Hz, one of NCH_2Ar), 3.02–2.95 (br m, 1H, $CHNHSO_2Ar$), 2.37 (s, 3H, $SO_2C_6H_4CH_3$), 2.31–2.26 (m, 1H, $CHNHCH_2Ar$), 2.14–2.08 (br m, 1H, Cy–*H*), 1.70–1.58 (br m, 3H, Cy–H_3), 1.23–1.12 (m, 4H, Cy–H_4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.7, 137.6, 129.8, 129.8, 128.5, 128.0, 126.9, 126.9, 123.1, 119.0, 116.4, 60.9, 57.1, 50.0, 33.4, 31.1, 24.8, 24.0, 21.5; IR (KBr) 3319, 3237, 3043, 2932, 2857, 1613, 1590, 1478, 1449, 1411, 1322, 1262, 1150, 1091, 934, 912, 748, 666, 547 cm^{-1}; HRMS (FAB+) calculated for $C_{20}H_{27}N_2O_3S$ $[M+H]^+$ 375.1742, found 375.1733.

4.2. General procedure for the Diels–Alder reactions in Table 2

To a cooled (−78 °C) solution of $SiCl_4$ (149 μL, 1.30 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (612 μL, 4.09 mmol) in CH_2Cl_2 (13.0 mL) is added a solution of **7f** (500 mg, 1.33 mmol) in CH_2Cl_2 (13.0 mL). The reaction mixture is slowly warmed to room temperature over the course of 4 h, and after an additional 4 h at room temperature, the resulting solution of the catalyst **8f** in CH_2Cl_2 (0.0500 M) is used directly for the Diels–Alder reactions.

To a cooled (−78 °C) solution of catalyst **8f** (0.05 M in CH_2Cl_2, 4.0 mL, 0.20 mmol) and cyclopentadiene (250 μL, 3.8 mmol) is added the unsaturated aldehyde (1.0 mmol) dropwise. After the indicated reaction time (see Table 2), the mixture is diluted with CH_2Cl_2 (1.0 mL) and quenched with a solution of 4:1 MeOH/H_2O (250 μL). The organic layer is washed with brine (1×1 mL), dried over Na_2SO_4, and concentrated. The residue is purified by flash chromatography (100% pentane → 20% Et_2O/pentane) to afford the pure bicyclic aldehyde products in the yields and enantioselectivities indicated in Table 2.

4.2.1. Diels–Alder reaction products—characterization and determination of enantioselectivity.

4.2.1.1. Table 2, entry 1. The physical and spectral data for this compound matched previously reported data.[12] The diastereoselectivity (*exo*:*endo* ratio = 96:4) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.69 (s, 1H, C*H*O, *exo*), 9.39 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 94%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, 1H, one of CH_2O-(*R*)-MTPA, major), 4.31 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.25 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.22 (d, 1H, one of CH_2O-(*R*)-MTPA, major).

4.2.1.2. Table 2, entry 2. The physical and spectral data for this compound matched previously reported data.[13] The diastereoselectivity (*exo*:*endo* ratio>98:2) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.62 (s, 1H, C*H*O, *exo*), 9.37 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 90%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, 1H, one of CH_2O-(*R*)-MTPA, major), 4.25 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.20 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.14 (d, 1H, one of CH_2O-(*R*)-MTPA, major). The absolute configuration was assigned by analogy to the methacrolein reaction.

4.2.1.3. Table 2, entry 3. The physical and spectral data for this compound matched previously reported data.[14] The diastereoselectivity (*exo*:*endo* ratio>96:4) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.73 (s, 1H, C*H*O, *exo*), 9.45 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 86%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (br s, 1H, =CH–C*H*, major), 2.63 (br s, 1H, =CH–C*H*, minor).

4.2.1.4. Table 2, entry 4. The physical and spectral data for this compound matched previously reported data.[13] The diastereoselectivity (*exo*:*endo* ratio>95:5) was determined by ^{1}H NMR (400 MHz, $CDCl_3$) integration: δ 9.70 (s, 1H, C*H*O, *exo*), 9.42 (s, 1H, C*H*O, *endo*). The enantioselectivity (ee = 54%) was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.37 (d, 1H, one of CH_2O-(*R*)-MTPA, minor), 4.33 (d, 1H, one of CH_2O-(*R*)-MTPA, major), 4.29 (d, 1H, one of CH_2O-(*R*)-MTPA, minor). The absolute configuration was assigned by analogy to the methacrolein reaction.

Acknowledgements

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