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Achieving Enantioselectivity in Difficult Cyclohexa-1,3-diene Diels−Alder Reactions with Sulfur-Stabilized Silicon Cations as Lewis Acid Catalysts

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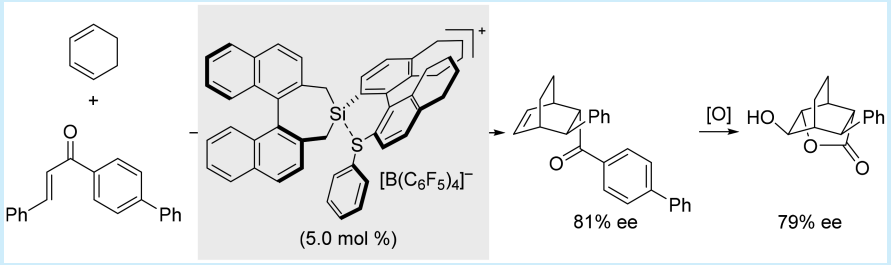
Supporting Information

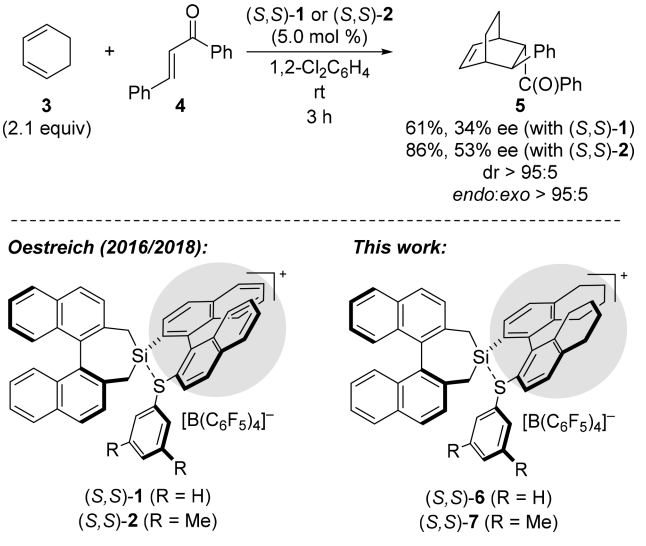


ABSTRACT: A novel cationic silicon−sulfur Lewis pair with a chiral H_8-binaphthyl backbone is reported. It catalyzes otherwise sluggish Diels−Alder reactions of cyclohexa-1,3-diene and chalcone derivatives in good yields and decent enantioselectivities (up to 81% ee). The enantioinduction is highest with a [1,1′-biphenyl]-4-yl substituent at the carbonyl carbon atom. This moiety can be later converted into a carboxyl group by Baeyer−Villiger oxidation. The same oxidant also epoxidizes the double bond in the cycloadduct, and the epoxide engages in a lactonization with the carboxylic acid. Synthetically interesting hexahydro-3,6-methanobenzofuran-2(3*H*)-one skeletons are obtained in one pot.

The ability of cationic silicon Lewis acids to catalyze challenging Diels−Alder reactions of cyclohexa-1,3-diene and unreactive dienophiles[1,2] led to the development of chiral silicon cations to realize asymmetric variants of these difficult transformations.[3−8] Our laboratory currently focuses on the promotion of enantioselective cycloadditions of cyclohexa-1,3-diene and chalcone derivatives[4,7] catalyzed by sulfur-stabilized silicon cations.[4,9] After systematic structural modifications of the catalyst system we eventually arrived at the bis(binaphthyl)-based Lewis acids (*S*,*S*)-**1** and (*S*,*S*)-**2** that induced 34% and 53% ee in the model Diels−Alder reaction of cyclohexa-1,3-diene (**3**) and chalcone (**4**), respectively (**3** + **4** → **5**, Scheme 1, top).[4b,c] With the goal of further improving the enantiomeric excesses of the cycloadducts as well as understanding the influence of the relevant structural elements on the asymmetric induction we replaced the binaphthyl backbone in (*S*,*S*)-**1** and (*S*,*S*)-**2** by the H_8-binaphthyl skeleton, resulting in the new catalysts (*S*,*S*)-**6** and (*S*,*S*)-**7** (Scheme 1, bottom). Here we report the synthesis and spectroscopic characterization of the silicon Lewis acids (*S*,*S*)-**6** and (*S*,*S*)-**7** and their application in Diels−Alder reactions of cyclohexa-1,3-diene (**3**) and various chalcones, leading to substantially improved enantioselectivities.

To investigate the effect of the various structural elements of these catalysts on their enantioselective performance, we synthesized the precursors (*S*)-**8** and (*S*)-**9** with thioether groups of different steric demand (Scheme 2). The new enantiomeric building blocks (*S*)-**10** and (*S*)-**11** were prepared from the literature-known H_8-binaphthyl diiodide according to our previously reported procedure.[4b,c] Reaction of the

Scheme 1. Difficult Cyclohexa-1,3-diene Diels−Alder Reaction (Top) and Chiral Sulfur-Stabilized Silicon Cations as Lewis Acid Catalysts (Bottom)



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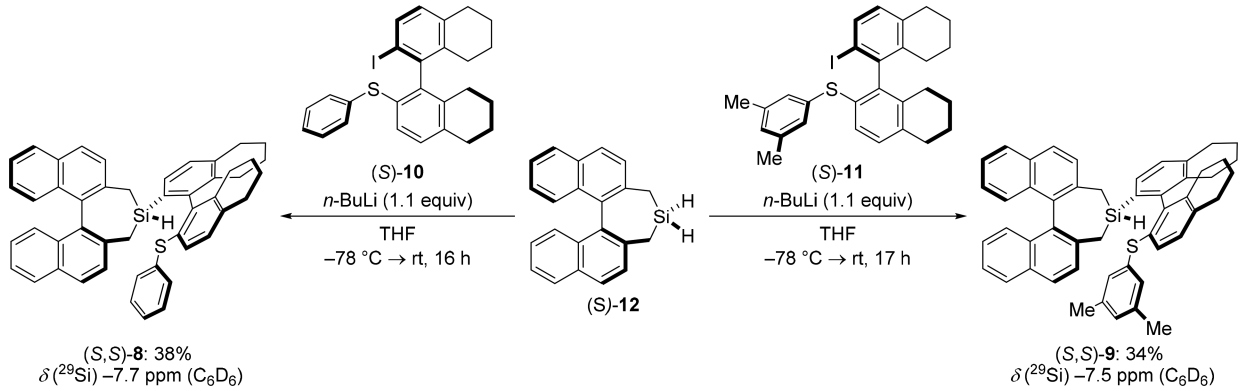
Scheme 2. Preparation of the H_8-Binaphthyl-Based Hydrosilanes (*S*,*S*)-8 and (*S*,*S*)-9



dihydrosilepine (*S*)-**12** with the lithiated thioethers (*S*)-**10** and (*S*)-**11** afforded the hydrosilanes (*S*)-**8** and (*S*)-**9** in moderate yields. Hydride abstraction with trityl tetrakis(pentafluorophenyl)borate[10] $[Ph_3C]^+[B(C_6F_5)_4]^-$ resulted in the formation of the corresponding sulfur-stabilized silicon cations (*S*,*S*)-**6** and (*S*,*S*)-7 (Figure 1). The ^{29}Si HMQC NMR spectra of the

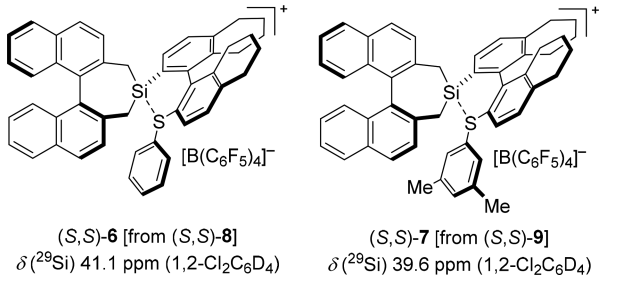


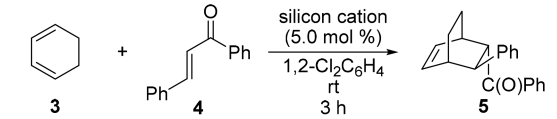
Figure 1. Sulfur-stabilized silicon cations (*S*,*S*)-**6** and (*S*,*S*)-7 and their ^{29}Si NMR chemical shifts.

cationic silicon species (*S*,*S*)-**6** and (*S*,*S*)-7 showed only one resonance signal at δ 41.1 and 39.6 ppm, respectively. These ^{29}Si NMR resonances are in good agreement with those found for our previously reported binaphthyl-based silicon cations (*S*,*S*)-**1** (δ 39.5 ppm) and (*S*,*S*)-**2** (δ 38.3 ppm).

We first tested the H_8-binaphthyl silicon cation (*S*,*S*)-**6** in the model reaction of cyclohexa-1,3-diene (**3**) and chalcone (**4**) (Table 1). The reaction was performed in 1,2-$Cl_2C_6H_4$ at room temperature and was stopped after 3 h.[11] Full conversion of dienophile **3** was achieved, and cycloadduct **5** was isolated in good yield and with an enantiomeric excess of 67%, exhibiting a significant increase in enantioselectivity, compared to 34% ee previously obtained with the parent catalyst (*S*,*S*)-**1** (entry 1 vs entry 2). We assume that the reason for the improved enantioinduction is the increased steric demand of the H_8-binaphthyl system as a result of the larger dihedral angle between the two partially hydrogenated naphthalene rings. We expected even higher ee values with Lewis acid (*S*,*S*)-**7** with the substituted phenyl thioether group. However, the bulky thioether moiety had no influence on the asymmetric induction in this case (entry 3 vs entry 1) but was slightly better than (*S*,*S*)-**2** (entry 4). It is worth mentioning that exactly this structural modification led to improved catalyst performance in our earlier study (entry 2 vs entry 4).[4c]

Although both catalysts (*S*,*S*)-**6** and (*S*,*S*)-7 induced the same level of enantioselection in the model reaction, we decided to explore the dienophile scope with Lewis acid (*S*,*S*)-

Table 1. Testing the Silicon Cations (*S*,*S*)-1, (*S*,*S*)-2, (*S*,*S*)-6, and (*S*,*S*)-7 in the Model Diels–Alder Reaction[a,b]



entry	sulfur-stabilized silicon cation	yield[d] (%)	ee[e] (%)
1[f]	(*S*,*S*)-**6**	74	67
2	(*S*,*S*)-**1**	61	34
3	(*S*,*S*)-7	79	66
4	(*S*,*S*)-**2**	86	53

[a]All reactions were performed according to the general procedure GP6 at a dienophile concentration of 0.5 M. Reactions were conducted on a 0.249 mmol scale. Data are based on multiple runs. [b]Diastereomeric ratios (*trans*:*cis* and *endo*:*exo*) determined by GLC analysis of the crude material prior to purification. [c]Determined by GLC analysis using triphenylmethane as an internal standard. [d]Analytically pure cycloadduct after flash column chromatography on silica gel. [e]Determined by HPLC analysis using a chiral stationary phase. [f]A reaction on a 1.00 mmol scale using 2.5 mol % of (*S*,*S*)-**6** afforded **5** with 64% ee and in 92% isolated yield (see Supporting Information for details).

6 for its easier accessibility. Cyclohexa-1,3-diene (**3**) along with a series of differently substituted chalcones were subjected to the standard reaction conditions, affording the corresponding cycloadducts with excellent *endo*/*exo* selectivities and in good to moderate yields (Scheme 3). In our recent work, we had already shown that an aryl group (R^2) attached to the carbonyl carbon atom is essential for achieving good enantioselectivities. In addition to these findings, the replacement of the aryl group R^1 by a cyclohexyl group also led to markedly diminished enantioselectivity (**4** → **5** vs **13** → **29**). However, additional *para*-substitution of the R^1 phenyl ring had no effect on enantioinduction, giving products **30** and **31** with similar enantiomeric excesses as the parent **5** (**14** → **30** and **15** → **31** vs **4** → **5**). As already found in our previous dienophile screening, chalcones with *para*-substitution of the R^2 aryl group (as in **16**–**18**) as well as chalcone bearing a β-naphthyl group (as in **19**) gave the highest enantioselectivities for the cycloadducts **32**–**35** with ee values up to 81%. We did achieve 91% ee with the chalcone **18**, but this result could not be reliably reproduced. The reported data are generally based on multiple runs. The introduction of bulkier *para*-substituents such as the voluminous triisopropyl silyl group in **20** or linear

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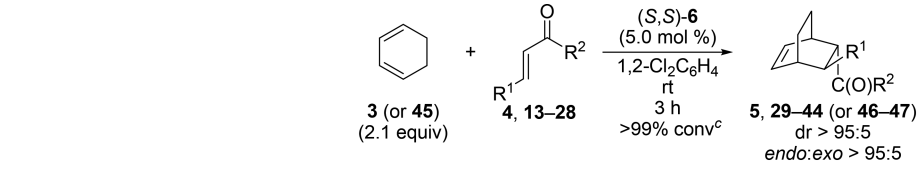
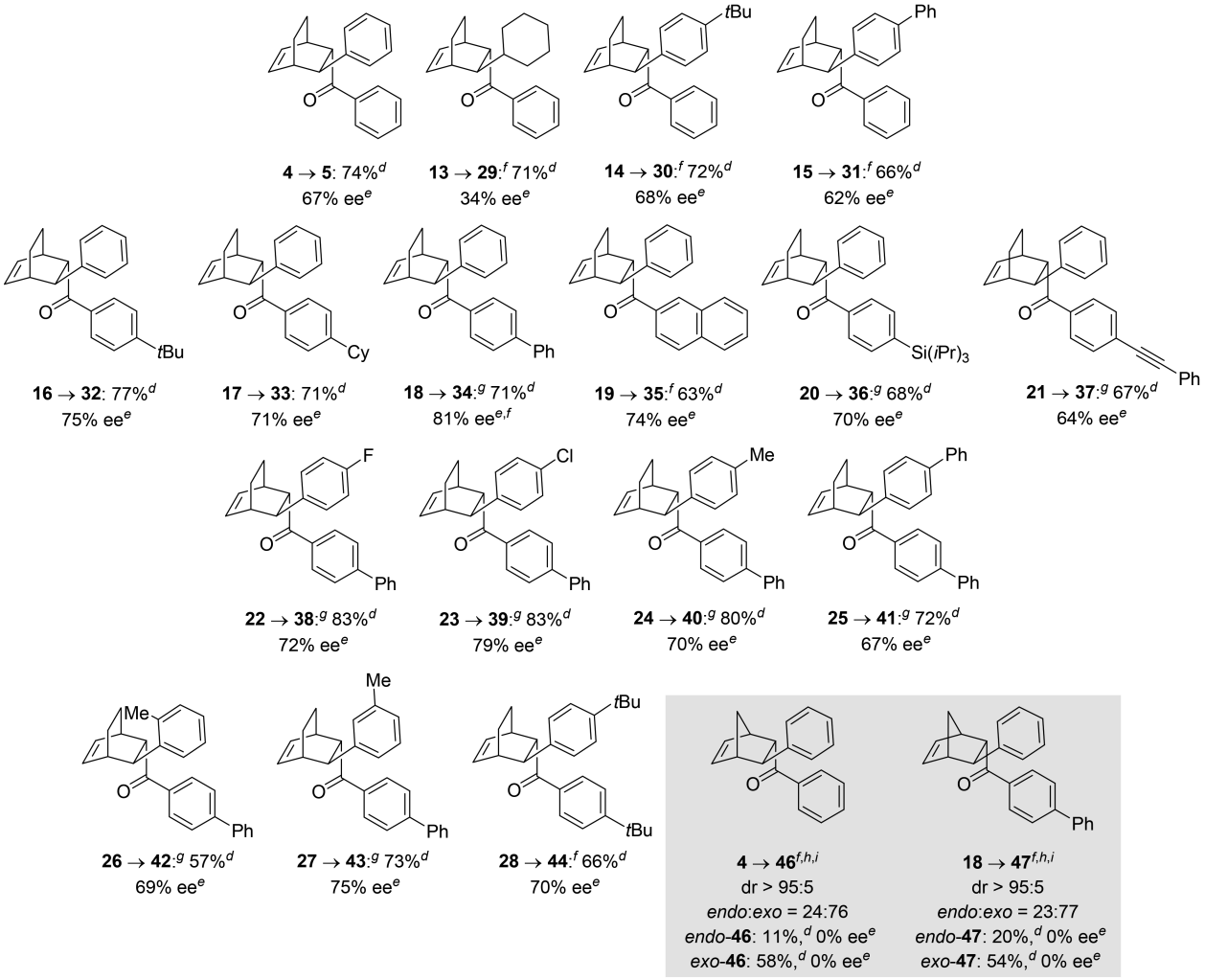
Scheme 3. Enantioselective Diels–Alder Reactions of Cyclohexa-1,3-diene (3) and Chalcones Catalyzed by the Sulfur-Stabilized Silicon Cation (*S*,*S*)-6[a,b]





[a]All reactions were performed according to the general procedure GP6 at a dienophile concentration of 0.5 M. [b]Diastereomeric ratios (*trans*:*cis* and *endo*:*exo*) determined by GLC or ^{1}H NMR analysis of the crude material prior to purification. Data are based on multiple runs. [c]Determined by GLC analysis using triphenylmethane as an internal standard. [d]Analytically pure cycloadduct after flash column chromatography on silica gel. [e]Determined by HPLC analysis using a chiral stationary phase. [f]Dienophile concentration of 0.25 M. [g]Dienophile concentration of 0.13 M. [h]Prepared with cyclopentadiene (**45**). [i]Conversion was not determined.

alkyne in **21** caused a decrease in enantioselectivity compared to the phenyl-substituted case **34** (**20** → **36** and **21** → **37** vs **18** → **34**). After identifying the biphenyl group as the best R^2 substituent to provide good enantioinduction, we focused on variation of R^1. Unfortunately, contrary to a previously described trend, *para*-substitution as in **22**–**25** as well as *ortho*-/*meta*-substitution as in **26**/**27** were detrimental to enantioselection, leading to cycloadducts **38**–**41** and **42**/**43**, respectively, with slightly or considerably diminished enantiomeric excesses. The same outcome was observed in a *tert*-butyl-substituted case (**32** vs **44**).

We also examined the catalysis of selected dienophiles **4** and **18** with cyclopentadiene (**45**). However, in both cases, the *endo*/*exo* selectivity dropped significantly, and the products **46** and **47** were isolated as racemic mixtures (Scheme 3, gray box). These observations had already been made with the catalysts (*S*,*S*)-**1** and (*S*,*S*)-**2** that yielded preferentially *exo*-cycloadducts with no asymmetric induction. Although examples of such anomalous *exo*-selectivity in [4 + 2]-cycloadditions have been reported in the literature,[12,13] the absence of enantioinduction is still not clear.

In our preliminary study of the suitability of various dienophiles for enantioselective Diels–Alder reactions, we found that cycloadditions with cinnamates failed as a result of ester cleavage or simply no conversion. To overcome this limitation, the strategy involving the use of a biphenyl group in

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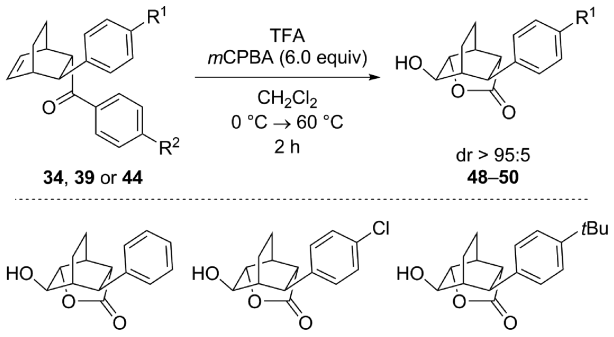
34 as an auxiliary to induce high enantioselectivity followed by removal of this substituent via Baeyer–Villiger oxidation to access the desired esters seemed viable.[14] However, applying the typical Baeyer–Villiger procedure to enantioenriched cycloadducts **34**, **39**, and **44** furnished the corresponding hydroxy lactones **48**–**50** (Scheme 4). Selective Baeyer–

Scheme 4. Hydroxylactonization of the Diels–Alder Adduct by a Baeyer–Villiger/Epoxidation/Epoxide Opening Reaction Sequence[a]



[a]Diastereomeric ratios determined by ^{1}H NMR analysis of the crude material prior to purification. [b]Analytically pure cycloadduct after flash column chromatography on silica gel. [c]Determined by HPLC analysis using a chiral stationary phase.

Villiger oxidation and epoxidation of the C=C double bond with *m*CPBA, followed by intramolecular epoxide opening with the formed carboxylate, finally afforded **48**–**50** in moderate yields and with hardly any erosion of the enantiopurity. This Diels–Alder cycloaddition with subsequent epoxidation–epoxide opening represents a new enantioselective access to bicyclo[2.2.2]octane-derived hydroxy lactones.[15]

In this work, we described the preparation of sulfur-stabilized silicon cations (*S*,*S*)-**6** and (*S*,*S*)-**7** with H_8-binaphthyl thioether backbones. This structural element led to markedly improved enantioselectivities in the Diels–Alder reaction of cyclohexa-1,3-diene (**3**) and chalcone (**4**). With (*S*,*S*)-**6**, enantiomeric excesses of up to 81% were obtained for challenging cyclohexa-1,3-diene/chalcone derivative combinations. We also demonstrated the utility of these enantioenriched cycloadducts by transforming them into the corresponding hydroxy lactones with no loss of enantioselectivity through a one-pot sequential Baeyer–Villiger oxidation, epoxidation, and intramolecular epoxide opening.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02945.

Synthetic procedures and NMR spectra of the compounds synthesized in this paper, as well as analytical data for the unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) The catalysis was examined in different solvents with our previous catalyst system (*S*,*S*)-**2**. The catalyst was stable in all tested solvents (CH_2Cl_2, benzene, toluene, and 1,2-$F_2C_6H_4$), giving cycloadduct **5** in similar yields and enantioselectivities. Also, no improvement of enantioselectivity was observed at lower reaction temperature (0 °C) in our model Diels–Alder reaction with the catalyst (*S*,*S*)-**1**.
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