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Organocatalysis

A Theoretical and Experimental Study of the Effects of Silyl Substituents in Enantioselective Reactions Catalyzed by Diphenylprolinol Silyl Ether

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Abstract: The effect of silyl substituents in diphenylprolinol silyl ether catalysts was investigated. Mechanistically, reactions catalyzed by diphenylprolinol silyl ether can be categorized into three types: two that involve an iminium ion intermediate, such as for the Michael-type reaction (type A) and the cycloaddition reaction (type B), and one that proceeds via an enamine intermediate (type C). In the Michael-type reaction via iminium ions (type A), excellent enantioselectivity is realized when the catalyst with a bulky silyl moiety is employed, in which efficient shielding of a diastereotopic face of the iminium ion is directed by the bulky silyl moiety. In the cycloaddition reaction of iminium ions (type B) and reactions via enamines (type C), excellent enantioselectivity is obtained even when the silyl group is less bulky and, in this case, too much bulk reduces the reaction rate. In other cases, the yield increases when diphenylprolinol silyl ethers with bulky substituents are employed, presumably by suppressing side reactions between the nucleophilic catalyst and the reagent. The conformational behaviors of the iminium and enamine species have been determined by theoretical calculations. These data explain the effect of the bulkiness of the silyl substituent on the enantioselectivity and reactivity of the catalysts.

Introduction

The field of organocatalysis is developing rapidly, and many useful organocatalysts with unique properties have been devised and applied to a plethora of asymmetric catalytic reactions.[1] Diarylprolinol silyl ether[2] is one of the privileged organocatalysts, developed concurrently by our group[3] and Jørgensen's group[4] (Figure 1). It is an effective catalyst for reactions involving both enamine[1] and iminium reactive intermediates.[5]

The Michael addition of aldehydes to nitroalkenes is a synthetically useful reaction, in which near perfect enantioselectivity can be achieved by using the diphenylprolinol trimethylsilyl (TMS) ether (**1**) as a catalyst.[3] We used this asymmetric Michael reaction as a key step in the recent one-pot synthesis of (−)-oseltamivir,[6] in a one-pot synthesis of ABT-341,[7] and in a three-pot synthesis of prostaglandin E_1 methyl ester,[8] in which excellent enantioselectivities were realized. On the other hand, in reactions such as the formal aza [3+3] cycloaddition reaction of α,β-unsaturated aldehydes and enecarbamates,[9]

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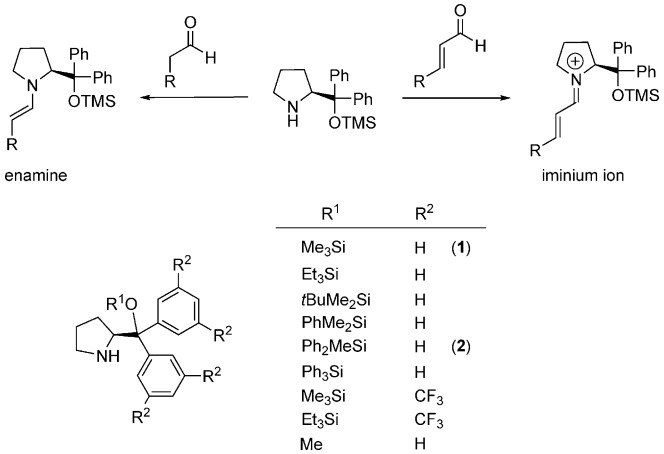


Figure 1. Organocatalysts examined in the present study.

the enantioselectivity is not perfect in the presence of diphenylprolinol TMS ether, and diphenylprolinol *tert*-butyldimethylsilyl (TBS) ether was found to be a superior enantioselective organocatalyst relative to the trimethylsilylated analogue. In these cases, the more bulky silyl group increased the enantioselectivity of the reaction.

Recently, Seebach and co-workers determined the X-ray crystal structures of iminium salts generated from cinnamaldehyde and the diphenylmethyl- and trimethylsilylated diphenylprolinol ethers **2** and **1**, respectively (Figure 1).[10] In the structures of the iminium ions, there could be three conformations around the exocyclic bond, the C=N and the C=C bond could have an *E* or *Z* configuration, and the single bond between C=C and C=N could have an s-*cis* or s-*trans* conformation: in addition, there is puckering of the pyrrolidine ring. The pyrrolidine ring may adopt two distinct conformations, the *down*- and *up*-puckered conformations. These conformations are defined as conformations in which the Cγ atom and the large substituent at the Cα atom are located on the same and opposite sides, respectively, of the plane defined by Cδ, N, and Cα atoms[11] (Figure 2). For both iminium ions derived from **1** and **2**, X-ray crystallographic analysis shows an *E*/*E* configuration, and the conformation around the exocyclic C–C bond in the solid state is found to be (+)-synclinal (*sc-exo*; Figure 2). Additionally, the single bond between the C=C and C=N double bonds adopts an s-*trans* conformation in the solid state. For the pyrrolidine ring, these iminium ions adopt the *down*-puckered conformation in the solid state. Seebach and co-workers also determined the solid-state structure of the enamine derived from diphenylprolinol TMS ether **1** and phenylacetaldehyde.[10a] This enamine adopts an s-*trans* conformation about the C–N single bond, an *E* configuration of the C=C double bond, and the *sc-exo* conformation around the exocyclic C–C bond (Figure 2). The *down* conformation of the pyrrolidine ring is also found for the crystal structure of this enamine. If the *sc-exo* conformer also predominates in solution, the bulkiness of the silyl substituent is likely to affect the enantioselectivity greatly, because of its orientation and proximity to the reacting trigonal center.

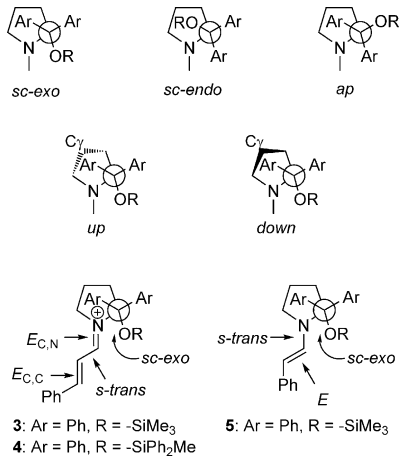


Figure 2. Top: Schematic representations of synclinal-*exo* (*sc-exo*), synclinal-*endo* (*sc-endo*), and antiperiplanar (*ap*) conformations of the exocyclic C–C bond of the iminium ion and the enamine. Middle: The *up*- and *down*-puckered conformations of the pyrrolidine ring. Bottom-left: Schematic representation of the solid-state structure of the iminium ions of diarylprolinol silyl ether. Bottom-right: Schematic representation of the solid-state structure of the enamines of diarylprolinol silyl ether. The stereochemical nomenclature defined here is used throughout the paper.

Although the X-ray crystallographic analyses provided the solid-state structures of the iminium ions **3**, **4** and of the enamine **5**, and taking into account some preliminary calculations and previously published NMR analyses,[10] the detailed overall conformational space and dynamic behaviors of these species still remain unclear. There are a couple of reports with diphenylmethyl silyl ether **2** as a catalyst: Zhang and Liu[12] and Pihko et al.[13] reported moderate enantioselectivity in the Michael reaction of malonate and isatylidene-3-acetaldehyde, and in the Mukaiyama–Michael reaction of methacrolein and 5-methylsiloxyfuran, respectively, whereas Melchiorre and co-workers[14] obtained excellent enantioselectivity in the γ-alkylation of a branched enal. There have been no systematic investigations into the substituent effects of the silyl group upon conformational preference. Herein, we describe in detail our computational and experimental investigations into these conformational and steric effects.

Results

Computational analysis

We carried out conformational analyses of the two iminium ions **3** and **4** derived from diphenylprolinol TMS ether (**1**) and cinnamaldehyde, and diphenylprolinol diphenylmethylsilyl ether (**2**) and cinnamaldehyde, respectively (Figure 2). In addition, the conformations of the enamine **5** derived from diphenylprolinol TMS ether (**1**) and phenylacetaldehyde were investigated (Figure 2). Solid-state structures of the two iminium ions, and of the enamine, have been obtained by X-ray crystal structure analysis.[10] Two structures with very small differences were found in the unit cell of the crystal lattice for the iminium salts **3** (Figure 3a and b) and **4** (Figure 3e and f), and puckered conformers were seen in the crystal structure of the enamine **5** (Figure 3i). Starting from the X-ray crystal structures, we performed conformational searches using CONFLEX 7[15] with the MMFF94s force field[16] and a search limit of 20.0 kcal mol^{-1}. For the structures with relative energies with respect to the lowest-energy structure that were calculated to be less than 3.0 kcal mol^{-1}, we carried out DFT geometry optimizations at the B3LYP/6-31G(d) level.[17] A factor of 0.9806 was used to correct the B3LYP/6-31G(d)-calculated zero-point energies.[18] Furthermore, the energies of the optimized structures were evaluated with single-point calculations at the M06-2X/6-311+G(2df,2p) level.[19] Based on the M06-2X/6-311+G(2df,2p) energies, we estimated the population of each conformer at 298 K. For the isomers of iminium ions **3** and enamine **5**, entropic and solvation contributions were also considered. The calculated values for entropic and solvation contributions are given in the Supporting Information. After taking the entropic and sol-

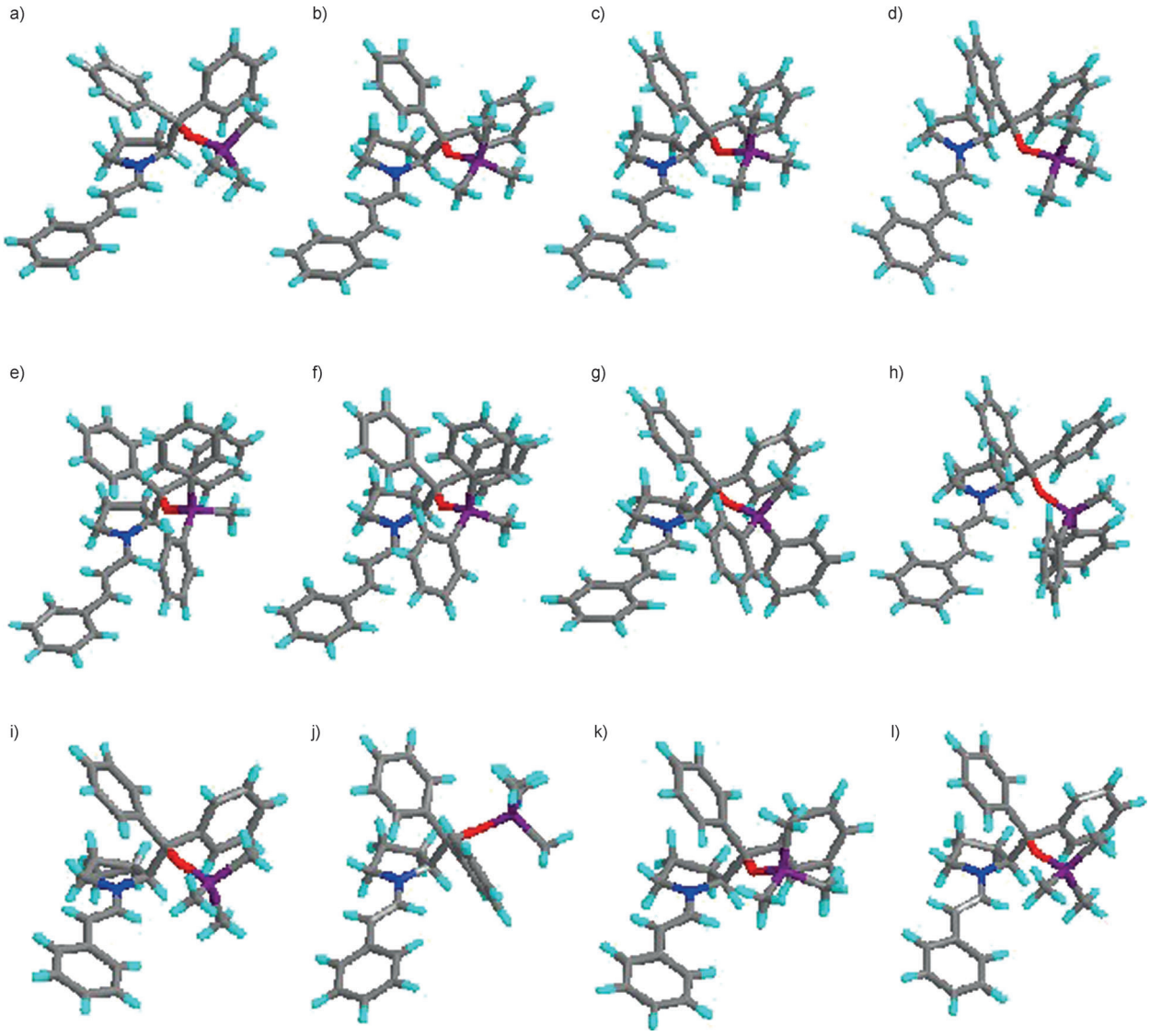


Figure 3. Top: Structures of iminium ion **3**: a, b) crystal structures; c, d) B3LYP-optimized structures (entries 1 and 2 in Table 1). Middle: Structures of iminium ion **4**: e, f) crystal structures; g, h) B3LYP-optimized structures (entries 1 and 2 in Table 2). Bottom: Structures of enamine **5**: i) crystal structure containing puckered isomers; j–l) B3LYP-optimized structures (entries 1, 2, and 4 in Table 3).

vation contributions into account, however, the relative energies of the isomers of iminium ions **3**, as well as those of enamine **5**, did not alter significantly compared with those obtained from the gas-phase electronic energies, and the error bar on the Gibbs free energy predictions is expected to be significantly larger than that of the electronic energies.[13] Accordingly, the relative energies (including the zero-point energies) reported herein are those obtained from gas-phase electronic energies at the B3LYP/6-31G(d) and M06-2X/6-311+G(2df,2p) levels. The DFT calculations were carried out by using the Gaussian 09 program package.[20]

In Table 1 the results of the conformational analysis of the iminium ion **3** are summarized. A conformational search of the lowest-energy structure using the MMFF94s force field suggested twelve conformers in the 3.0 kcal mol^{-1} energy range. All these conformers have an *sc-exo* and an *s-trans* conformation around the exocyclic C–C bond and the C–C single bond between C=C and C=N double bonds, respectively. Some of the twelve conformers converged to the same structure during B3LYP geometry optimizations, and five of the B3LYP-optimized conformers remained unique. The two most stable conformers have ($E_{C,N}$, $E_{C,C}$) configurations for the C=N and C=C double bonds. These are puckered isomers of the pyrrolidine ring conformation: the most stable one adopts a *down* conformation, whereas the second most stable one has an *up* conformation (Figure 3c and d; Figures S1, S2, and S3a and b in the Supporting Information). The population of these two conformers adopting the ($E_{C,N}$, $E_{C,C}$) configuration is estimated to be 98%. The ($Z_{C,N}$, $E_{C,C}$) isomer was found to be the third most stable configuration (Figures S1, S2, and S3c in the Supporting Information). The B3LYP and M06-2X calculations suggest that the ($Z_{C,N}$, $E_{C,C}$) configurational isomer is higher in energy by 3.6 and 2.2 kcal mol^{-1} than the most stable ($E_{C,N}$, $E_{C,C}$) configurational isomer, and the population of the ($Z_{C,N}$, $E_{C,C}$) configura-

Table 1. Results of conformational and configurational analysis of iminium ion **3** using the MMFF94s force field and subsequent DFT calculations.

	Structure			CONFLEX		DFT calculation				
						B3LYP/6-31G(d)		M06-2X/6-311+G(2df,2p)		
				Steric energy [kcal mol^{-1}]	Relative energy [kcal mol^{-1}]	[a.u.][a]	Relative energy [kcal mol^{-1}]	[a.u.][a]	Relative energy [kcal mol^{-1}]	Population [%]
1	*down*	($E_{C,N}$, $E_{C,C}$)	*sc-exo*	121.54	0.44	−1544.341302	0.00	−1544.190411	0.00	77
2	*up*	($E_{C,N}$, $E_{C,C}$)	*sc-exo*	121.10	0.00	−1544.341025	0.17	−1544.189181	0.77	21
3	*up*	($Z_{C,N}$, $E_{C,C}$)	*sc-exo*	123.60	2.50	−1544.335649	3.55	−1544.186914	2.19	2
4	*up*	($E_{C,N}$, $Z_{C,C}$)	*sc-exo*	123.10	2.00	−1544.332982	5.22	−1544.184190	3.90	0.1
5	*down*	($E_{C,N}$, $Z_{C,C}$)	*sc-exo*	123.74	2.64	−1544.332837	5.31	−1544.184104	3.96	0.1

[a] A scaling factor of 0.9806 was used for the B3LYP/6-31G(d) zero-point energies. The zero-point energies are included.

Table 2. Results of conformational and configurational analysis of iminium ion **4** using the MMFF94s force field and subsequent DFT calculations.

	Structure			CONFLEX		DFT calculation				
						B3LYP/6-31G(d)		M06-2X/6-311+G(2df,2p)		
				Steric energy [kcal mol^{-1}]	Relative energy [kcal mol^{-1}]	[a.u.][a]	Relative energy [kcal mol^{-1}]	[a.u.][a]	Relative energy [kcal mol^{-1}]	Population [%]
1	*up*	($E_{C,N}$, $E_{C,C}$)	*sc-exo*	162.71	0.00	−1927.704012	0.00	−1927.523616	0.00	22
2	*down*	($E_{C,N}$, $E_{C,C}$)	*sc-exo*	163.05	0.33	−1927.703936	0.05	−1927.524789	−0.74	76
3	*up*	($E_{C,N}$, $E_{C,C}$)	*sc-exo*	165.61	2.90	−1927.703689	0.20	−1927.521263	1.48	2
4	*up*	($E_{C,N}$, $Z_{C,C}$)	*sc-exo*	165.27	2.56	−1927.692497	7.23	−1927.515647	5.00	–

[a] A scaling factor of 0.9806 was used for the B3LYP/6-31G(d) zero-point energies. The zero-point energies are included.

tional isomer is calculated to be 2%. The calculations indicated that the ($E_{C,N}$, $Z_{C,C}$) and ($Z_{C,N}$, $Z_{C,C}$) configurational isomers are highly energetically disfavored, and contribution to the population by these isomers must be negligible.

Table 2 shows the results of the conformational analysis of the iminium ion **4**. Four conformers with the *sc-exo* and s-*trans* conformations were found in an energy range of 3.0 kcal mol^{-1} of the global minimum of the MMFF94s force field. Two isomers, the energies of which were comparable, were found to be the most stable conformers for the iminium ion **4**. In a slightly higher energy region, one more conformer was found. These three conformers all adopt ($E_{C,N}$, $E_{C,C}$) configurations and *sc-exo* conformations, and their structures are very close to one another (Figures S1, S2, and S3 d–f in the Supporting Information). M06-2X calculations suggest that the isomer adopting a *down* conformation for the pyrrolidine ring is lower in energy than the *up* conformers. The ($E_{C,N}$, $Z_{C,C}$) configurational isomer was calculated to be 7.2 and 5.7 kcal mol^{-1} higher in energy at the B3LYP and M06-2X levels, respectively, relative to the most stable ($E_{C,N}$, $E_{C,C}$) isomer. The ($Z_{C,N}$) configurational isomers were found to be still higher in energy. Consequently, the population of ($E_{C,N}$, $Z_{C,C}$), ($Z_{C,N}$, $E_{C,C}$), and ($Z_{C,N}$, $Z_{C,C}$) configurational isomers was found to be negligible, and the iminium ion **4** will most likely adopt ($E_{C,N}$, $E_{C,C}$) configurations and s-*trans*/*sc-exo* conformations, exclusively.

Table 3 gives the results of the conformational analysis of the enamine **5**. MMFF94s conformational search provided twelve conformers in the energy range 3.0 kcal mol^{-1} from the lowest-energy conformer. All the conformers have an s-*trans* conformation of the C–N single bond and an *E* configuration of the C=C double bond (Figures S1, S2, and S3 g–i in the Supporting Information). Isomers of the s-*trans-Z*, s-*cis-E*, and s-*cis-Z* form were found to be energetically disfavored. The twelve structures converged into nine structures during B3LYP geometry optimizations. Regarding the conformation of the exocyclic C–C bond, the enamine **5** has an *sc-exo* conformation in the crystal structure, but B3LYP and M06-2X calculations, as well as the force field calculations, suggest that the most stable conformer would possess the *ap* conformation. The populations of the *ap* and *sc-exo* conformers were calculated to be almost equal (48 versus 51%). The *sc-endo* conformer was also found in the energy range of 3.0 kcal mol^{-1} by the MMFF94s conformational search, but B3LYP and M06-2X calculations suggest that the energy of the *sc-endo* structure is 3.2–3.4 kcal mol^{-1} higher than that of the lowest-energy *ap* conformer. For the structure of the pyrrolidine ring, DFT calculations, as well as MMFF94s predictions, indicate that the *down* conformation tends to be energetically more preferable than the *up* conformation.

The lowest-energy conformers of the iminium ions **3** and **4** have ($E_{C,N}$, $E_{C,C}$) configurations and s-*trans*/*sc-exo* conformations (Figure 3 c and g). The s-*trans*-(*E*)-*sc-exo* structure is also observed in the second minimum arrangement of the enamine **5** (Figure 3 k). The structures of these conformers are very close to the solid-state structures (Figure 3 a, b, e, f, i). However, the lowest-energy conformer of enamine **5** was found to adopt an *ap* form. These conformational results indicate that the strong conformational *sc-exo* preferences observed in iminium ions **3** and **4** are weakened in the enamine intermediate **5**,[21] that is, the *gauche* effect is stronger with the positively charged imini-

Table 3. Results of conformational and configurational analysis of enamine **5** using the MMFF94s force field and subsequent DFT calculations.

	Conformation			CONFLEX		DFT calculation B3LYP/6-31G(d)		DFT calculation M06-2X/6-311+G(2df,2p)		
				Steric energy [kcal mol^{-1}]	Relative energy [kcal mol^{-1}]	[a.u.][a]	Relative energy [kcal mol^{-1}]	[a.u.][a]	Relative energy [kcal mol^{-1}]	Population [%]
1	*down*	s-*trans*-(*E*)	*ap*	152.65	0.00	−1505.844433	0.00	−1505.715861	0.00	46
2	*down*	s-*trans*-(*E*)	*sc-exo*	153.91	1.26	−1505.844032	0.25	−1505.715282	0.36	25
3	*up*	s-*trans*-(*E*)	*ap*	154.40	1.75	−1505.843394	0.65	−1505.712704	1.98	2
4	*down*	s-*trans*-(*E*)	*sc-exo*	152.82	0.17	−1505.843267	0.73	−1505.714976	0.56	18
5	*up*	s-*trans*-(*E*)	*sc-exo*	153.51	0.86	−1505.843075	0.85	−1505.713217	1.66	3
6	*up*	s-*trans*-(*E*)	*sc-exo*	153.81	1.16	−1505.842023	1.51	−1505.710704	3.24	0.2
7	*up*	s-*trans*-(*E*)	*sc-exo*	153.49	0.84	−1505.841824	1.64	−1505.713334	1.59	3
8	*down*	s-*trans*-(*E*)	*sc-exo*	153.22	0.57	−1505.841145	2.06	−1505.713056	1.76	2
9	*up*	s-*trans*-(*E*)	*sc-endo*	154.60	1.95	−1505.839265	3.24	−1505.710523	3.35	0.2

[a] A scaling factor of 0.9806 was used for the B3LYP/6-31G(d) zero-point energies. The zero-point energies are included.

um nitrogen atom than with the neutral enamine nitrogen atom.[22] It is also apparent from these calculations that there are no electronic interactions (for example, silyl hypervalent interactions) between the silyl atom and the π orbital of the double bond in the iminium ions **3** and **4**, or in the enamine **5**. The effect of the silyl substituent on the enantioselectivity should be steric. However, the distances between the oxygen atom and iminium moiety in iminium ions **3** and **4** are comparable to or somewhat shorter (2.83–2.95 Å) than the sum of the van der Waals radii. Similarly, the distances between the oxygen atom and enamine nitrogen atom are rather short (2.85–2.98 Å) in enamine **5**. Thus, there are possible additional electronic interactions between the oxygen atom and the iminium moiety/enamine nitrogen atom.

Keeping the structural information in the solid phase and gas phase in mind, the effects of the substituents on the silyl group in overall enantioselective catalytic reactions were investigated next.

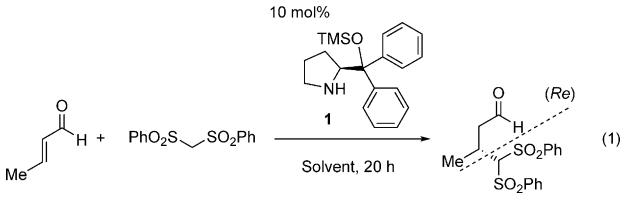
Michael addition of bis(phenylsulfonyl)methane to α,β-unsaturated aldehydes

Preliminary synthetic studies gave moderate enantioselectivity using the diphenylprolinol TMS ether (**1**); therefore, we elected to study the Michael addition of bis(phenylsulfonyl)methane to *trans*-α,β-unsaturated aldehydes. Moreover, this is a synthetically useful reaction because bis(phenylsulfonyl)methane is a synthetic equivalent of the methyl group. At the start of this project, there were no reports of this reaction type being catalyzed by organocatalysts; however, three independent groups subsequently reported similar reactions using the diphenylprolinol silyl ether **1**.[23] Palomo et al. used 1,3-benzodithiole tetraoxide as a nucleophile and diphenylprolinol TMS ether (**1**) as a catalyst. Although excellent enantioselectivity was obtained with cinnamaldehydes, enantioselectivity decreased with aliphatic enals (90.0:10.0 enantiomeric ratio (e.r.) in the reaction of crotonaldehyde).[23c] Aleman and co-workers reported the reaction using diphenylprolinol TMS ether (**1**) in the presence of LiOAc in THF, and excellent enantioselectivities were obtained in most of the reactions except for crotonaldehyde, which afforded the product in 90.0:10.0 e.r.[23a] Rios et al. used 20 mol% diphenylprolinol TMS ether (**1**) in toluene at 4 °C, which provided good yields and excellent enantioselectivities.[23b]

Before investigating changes in the silyl substituents of the catalyst, we first optimized the conditions for the Michael addition of bis(phenylsulfonyl)methane to crotonaldehyde, by using the TMS catalyst **1** [Table 4, Eq. (1)]. The reaction was performed in several solvents at room temperature for 20 h in the presence of catalyst **1**. The best yield and enantioselectivity were observed in toluene. The absolute configuration (*R*) of the product was assigned previously.[23]

Having found suitable reaction conditions, the effect of the substituents on the silyl group of the diphenylprolinol organocatalyst was investigated [Table 5, Eq. (2)]. The enantioselectivi-

Table 4. Solvent effect in the reaction of crotonaldehyde and bis(phenylsulfonyl)methane catalyzed by **1**.[a]



	Solvent	Yield [%][b]	e.r.[c]
1	CH_3CN	35	72.5:27.5
2	MeOH	19	79.0:21.0
3	Et_2O	58	83.0:17.0
4	CH_2Cl_2	60	77.0:23.0
5	toluene	90	85.5:14.5

[a] Reaction conditions: crotonaldehyde (1.5 mmol), bis(phenylsulfonyl)-methane (0.5 mmol), catalyst **1** (0.05 mmol), solvent (1.0 mL), room temperature, reaction time 20 h. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase after reduction to the corresponding alcohol with $NaBH_4$.

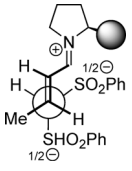
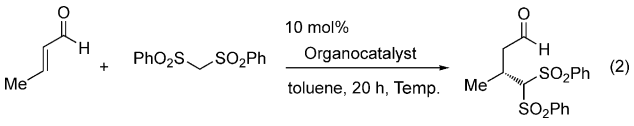


Table 5. The effect of the silyl substituents of the catalyst in the reaction of crotonaldehyde with bis(phenylsulfonyl)methane.[a]



(2)

	R^1	R^2	Temp. [°C]	Yield [%][b]	e.r.[c]
1	Me_3Si	H (**1**)	23	90	85.5:14.5
2	Et_3Si	H	23	83	86.5:13.5
3	*t*BuMe_2Si	H	23	92	89.5:10.5
4	PhMe_2Si	H	23	78	90.5:9.5
5	Ph_2MeSi	H (**2**)	23	88	91.5:8.5
6	Ph_3Si	H	23	90	92.0:8.0
7[d]	Ph_2MeSi	H (**2**)	0	94	95.0:5.0
8	Ph_3Si	H	0	87	94.5:5.5
9	Me_3Si	CF_3	23	15	90.0:10.0
10[d]	Et_3Si	CF_3	23	12	92.5:7.5

[a] Reaction conditions: unless noted otherwise, the reaction was performed using crotonaldehyde (1.5 mmol), bis-sulfone (0.5 mmol), organocatalyst (0.05 mmol), and toluene (1.0 mL) at room temperature for 20 h. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by chiral-phase HPLC analysis after reduction to the corresponding alcohol with $NaBH_4$. [d] The reaction was performed at 0 °C for 48 h.

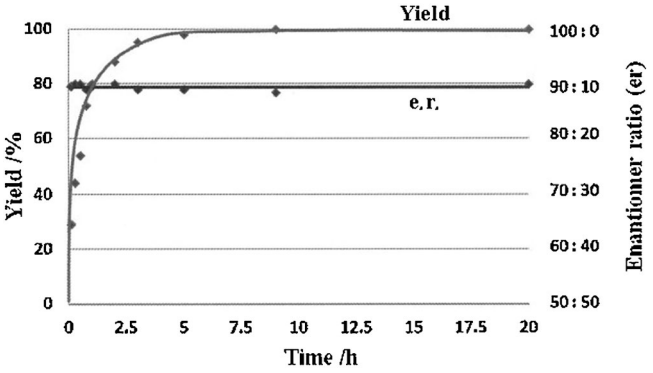


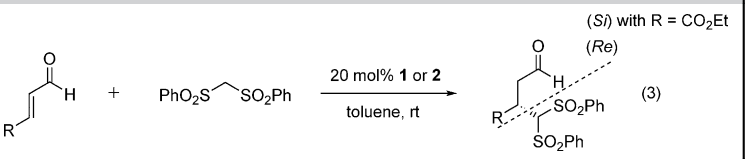
Figure 4. Relationship of yield and enantioselectivity versus time in the Michael reaction of crotonaldehyde with the bis-sulfone catalyzed by **1**. The reaction was performed by using crotonaldehyde (1.8 mmol), bis-sulfone (0.6 mmol), catalyst **1** (0.06 mmol), and toluene (1.2 mL) at 0 °C. Dark gray line: enantiomeric ratio of product. Light gray line: yield of product.

ty obtained with the triethylsilyl (TES) catalyst was found to be the same as that with the TMS version (86.5:13.5 e.r., Table 5, entries 1 and 2). When the substituents on the silyl group became more bulky, such as with the TBS group, the enantioselectivity increased somewhat (89.5:10.5 e.r., Table 5, entry 3). In the case of the dimethylphenylsilyl ether, an e.r. of 90.5:9.5 was obtained. Good enantioselectivity (92.0:8.0 e.r.) was also obtained with the diphenylmethylsilyl (DPMS) ether (**2**; Table 5, entry 5) and the triphenylsilyl[24] ether (Table 5, entry 6). The enantioselectivity increased to 95.0:5.0 e.r. when the reaction was carried out at a lower temperature (0 °C, Table 5, entry 7). Notably in the reaction catalyzed by bis-trifluoromethyl-substituted diarylprolinol silyl ether, the enantioselectivity was high, but the yield dropped (Table 5, entries 9 and 10). Thus, the best catalyst in this reaction was found to be DPMS ether (**2**).

Next, the yield and enantioselectivity versus the reaction time were investigated for this Michael addition catalyzed by diphenylprolinol TMS ether **1**. As shown in Figure 4, the yield was observed to gradually increase, whereas the enantioselectivity remained constant throughout the reaction. These results indicate that no retro Michael reaction occurred in the course of the reaction and the enantioselectivity is determined by kinetic control.

Comparison of the two catalysts, that is, TMS ether (**1**) and DPMS ether (**2**), was further investigated in the Michael addition of the bis(phenylsulfonyl)methane with a selection of β-substituted, *trans*-α,β-unsaturated aldehydes [Eq. (3)], and the results are collected in Table 6. When the β-substituent of the acrolein is *n*Pr, *i*Bu, or 2-phenylethyl, the enantioselectivity with the DPMS catalyst **2** was found to be significantly higher than the corresponding reactions with the TMS ether catalyst **1** (Table 6, entries 1–4). When the β-substituent of the acrolein is an electron-withdrawing group, such as ethoxycarbonyl, a higher enantioselectivity was observed with the DPMS ether catalyst **2** (Table 6, entry 5). From these results, it is concluded that the conjugate addition of bis(phenylsulfonyl)methane to α,β-unsaturated aldehydes under kinetic control proceeds with higher enantioselectivity when a prolinol catalyst with bulkier silyl substituents is used. Experimentally, we found

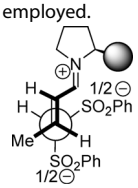
Table 6. Comparison of TMS ether catalyst **1** and DPMS ether catalyst **2** in the Michael reaction of β-substituted α,β-unsaturated aldehydes with bis(phenylsulfonyl)methane.[a]



(3)

	R	Catalyst **1** Time [h]	Yield [%][b]	e.r.[c]	Catalyst **2** Time [h]	Yield [%][b]	e.r.[c]
1[d]	Me	20	94	90.0:10.0	48	87	95.0:5.0
2[e]	*n*Pr	8	82	90.0:10.0	24	87	94.5:5.5
3[e]	*i*Bu	17	77	90.0:10.0	17	82	93.5:6.5
4[e]	CH_2CH_2Ph	12	85	93.0:7.0	28	82	95.5:4.5
5	CO_2Et	10	65	95.0:5.0	12	81	97.5:2.5

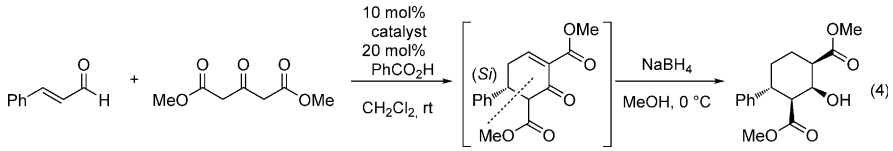
[a] Unless noted otherwise, the reaction was performed using α,β-unsaturated aldehyde (1.5 mmol), bis(phenylsulfonyl)methane (0.5 mmol), organocatalyst (0.05 mmol), and toluene (1.0 mL) at room temperature. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase after reduction to the corresponding alcohol by treatment with $NaBH_4$. [d] The reaction was performed at 0 °C. [e] Catalyst (0.1 mmol) was employed.



the diphenylprolinol DPMS ether (**2**) to be the best organocatalyst.

In general, the reactivity of the DPMS ether **2** is lower than that of the TMS ether **1**, and longer reaction times are required for **2** (Table 6). However, it should be emphasized that the yield was higher when the more bulky catalyst **2** was employed in the case of the more reactive Michael acceptor (see Table 6, entry 5). Such data provide evidence compatible with the assumption that the catalyst **1** might add to the more reactive Michael acceptor to form the adduct **6**, from which the catalyst is released slowly by elimination (see section 2.1.5.1 in ref. [21]). This side reaction might be less pronounced when a more bulky silyl ether is employed.

Table 7. Effect of silyl organocatalyst in the carbo [3+3] cyclization of cinnamaldehyde and dimethyl 3-oxopentanedioate.[a]



	Catalyst	Time [min]	Yield [%][b]	e.r.[c]
1	R^1 = TMS, R^2 = H (**1**)	50	79	95.5:4.5
2	R^1 = TBS, R^2 = H	60	75	97.5:2.5
3	R^1 = Ph_2MeSi, R^2 = H (**2**)	80	76	97.5:2.5

[a] The reaction was performed using cinnamaldehyde (0.5 mmol), dimethyl 3-oxopentanedioate (0.56 mmol), organocatalyst (0.05 mmol), benzoic acid (0.1 mmol), and CH_2Cl_2 (1.0 mL) at room temperature. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase after conversion to the corresponding silyl ether by treatment with TMSCl and imidazole.

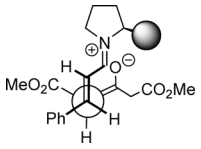
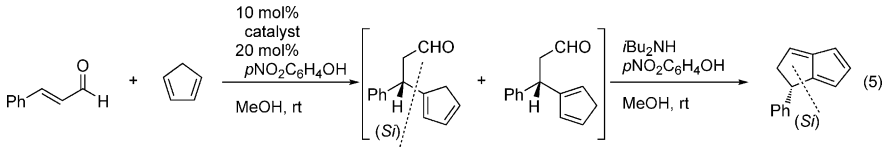
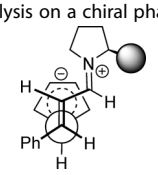


Table 8. Effect of silyl organocatalyst in the one-pot synthesis of a bicyclo[3.3.0]octane derivative.[a]



	Catalyst	Time [h][b]	Yield [%][c]	e.r.[d]
1	R^1 = TMS, R^2 = H (**1**)	25	58	94.0:6.0
2	R^1 = TBS, R^2 = H	20	63	97.5:2.5
3[e]	R^1 = Ph_2MeSi, R^2 = H (**2**)	6.5	52	97.5:2.5

[a] The reaction was performed using cinnamaldehyde (0.5 mmol), cyclopentadiene (1.5 mmol), organocatalyst (0.05 mmol), *p*-nitrophenol (0.1 mmol), and MeOH (1.0 mL) at room temperature. After the first addition, *i*Bu_2NH (0.5 mmol) and *p*-nitrophenol (0.5 mmol) were added and the reaction was further stirred for one day at room temperature. [b] Reaction time for the first Michael reaction. [c] Yield of purified product. [d] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase. [e] Catalyst **2** (0.1 mmol) was employed.



Comparison of the selectivity of catalysts 1 and 2 in some other enantioselective reactions involving iminium ions as reactive intermediates

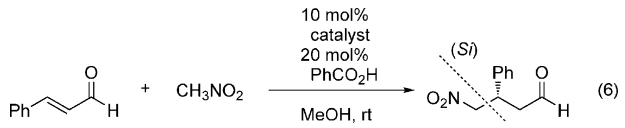
Having determined the superiority of the DPMS ether **2** over the TMS ether **1** in the asymmetric Michael addition of bis(phenylsulfonyl)methane to α,β-unsaturated aldehydes, we investigated the efficiency of **2** in other reactions, in which the organocatalyst **1** had been employed and studied previously. First, the effect of the catalyst was investigated in the carbo [3+3] cyclization of cinnamaldehyde and dimethyl 3-oxopentanedioate through a domino Michael addition/Knoevenagel condensation, in which the key intermediate is an iminium ion [Table 7, Eq. (4)].[25] When TMS ether **1** was employed as the catalyst, an e.r. of 95.5:4.5 was obtained. A higher enantioselectivity (97.5:2.5 e.r.) was indeed obtained with the more bulky TBS catalyst and DPMS ether catalyst **2**.

We then evaluated our previous one-pot synthesis of a bicyclo[3.3.0]octatriene derivative involving Michael addition and intramolecular addition of the cyclopentadiene moiety and dehydration [Table 8, Eq. (5)].[26] Good enantioselectivity (94.0:6.0 e.r.) was obtained when the TMS ether catalyst **1** was employed. Again, the enantioselectivity increased, in this case to 97.5:2.5 e.r., when bulky TBS ether and DPMS ether (**2**) catalysts were used.

Next, the Michael addition of nitromethane to cinnamaldehyde was compared [Table 9, Eq. (6)].[27] Excellent enantioselectivity had already been obtained by the use of the TMS ether catalyst **1** (97.5:2.5 e.r.). The enantioselectivity (98.5:1.5 e.r.) was similar when the DPMS ether **2** was employed. Each reaction was examined three times; the error was found to be within 1%. In this reaction, the bulkiness of the silyl substituent did not affect the enantioselectivity significantly and both TMS ether catalyst **1** and the DPMS ether catalyst **2** gave excellent enantioselectivity.

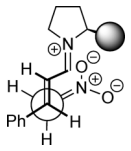
We have now also investigated the Diels–Alder reaction of cinnamaldehyde with cyclopentadiene [Table 10, Eq. (7)].[28]

Table 9. Effect of silyl organocatalyst in the Michael addition of nitromethane to cinnamaldehyde.[a]



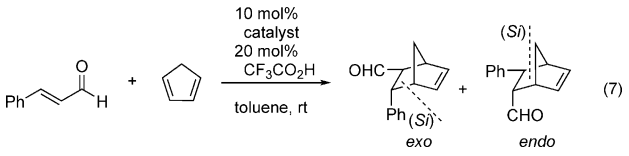
	Catalyst	Time [h]	Yield [%][b]	e.r.[c]
1	R^1 = TMS, R^2 = H (**1**)	16	90	97.5:2.5
2	R^1 = Ph_2MeSi, R^2 = H (**2**)	17	90	98.5:1.5

[a] The reaction was performed using cinnamaldehyde (0.5 mmol), nitromethane (1.5 mmol), organocatalyst (0.05 mmol), benzoic acid (0.1 mmol), and MeOH (1.0 mL) at room temperature. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase.



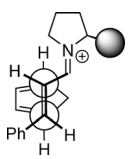
Previously, we had reported the trifluoromethyl-substituted diarylprolinol silyl ether as an effective enantioselective catalyst in this [4+2] cycloaddition; however, the yield was poor in the reaction catalyzed by diphenylprolinol silyl ether. The effect of the silyl substituent on the enantioselectivity with catalysts **1** and **2** is shown in Table 10. Both catalysts gave similar *endo*:*exo* selectivities, and the same enantioselectivity for the major *exo* isomer. This case possibly proceeds through a different reaction mode from the other highly enantioselective reactions (see above) that, likewise, involve iminium ions derived from catalysts **1** and **2**.

Table 10. Effect of silyl organocatalyst in the Diels–Alder reaction of cinnamaldehyde with cyclopentadiene.[a]



	Catalyst	Time [h]	Yield[b] [%]	*exo*:*endo*[c]	e.r.[d] *exo*	e.r.[d] *endo*
1	R^1 = TMS, R^2 = H (**1**)	20	14	80:20	91.5:8.5	76.5:23.5
2	R^1 = Ph_2MeSi, R^2 = H (**2**)	20	16	77:23	91.5:8.5	85.5:14.5
3	R^1 = TMS, R^2 = CF_3	20	86	84:16	97.5:2.5	91.5:8.5
4	R^1 = TES, R^2 = CF_3	20	80	85:15	98.5:1.5	94.0:6.0

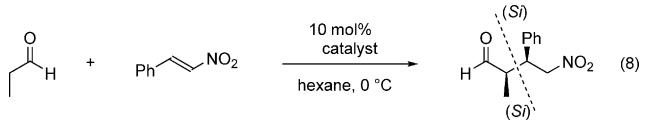
[a] The reaction was performed using cinnamaldehyde (1.0 mmol), cyclopentadiene (3.0 mmol), organocatalyst (0.1 mmol), trifluoroacetic acid (0.2 mmol), and toluene (2.0 mL) at room temperature. [b] Yield of purified product. [c] Diastereomer ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase.



Comparison of catalysts 1 and 2 in some reactions involving enamines as reactive intermediates

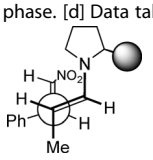
We also studied enantioselective reactions involving enamine intermediates, rather than iminium ions derived from catalysts **1** and **2**. A case in point is the Michael addition of propanal to nitrostyrene [Table 11, Eq. (8)]. Excellent enantioselectivities were reported with the TMS ether catalyst **1**.[3,29] With the

Table 11. Effect of silyl organocatalyst in the Michael addition of propanal to nitrostyrene.[a]



	Catalyst	Time [h]	*syn*:*anti*	Yield [%][b]	e.r.[c]
1[d]	R^1 = TMS, R^2 = H (**1**)	5	16:1	85	99.5:0.5
2	R^1 = Ph_2MeSi, R^2 = H (**2**)	24	>20:1	89	99.5:0.5

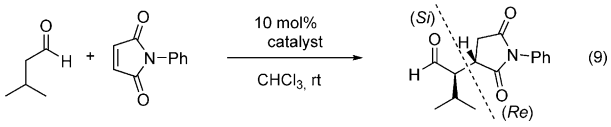
[a] The reaction was performed using nitrostyrene (1.0 mmol), propanal (10 mmol), and organocatalyst (0.1 mmol) in hexane (1.0 mL) at 0 °C. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral phase. [d] Data taken from ref. [3].



DPMS ether catalyst **2**, the enantioselectivity was also excellent, the *syn* selectivity increased, but a longer reaction time was required.

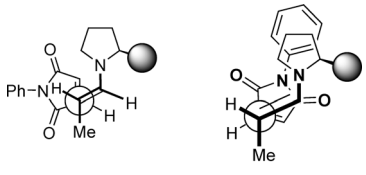
We also studied the enamine-based Michael addition of an aldehyde to *N*-phenylmaleimide [Table 12, Eq. (9)], a reaction

Table 12. Effect of silyl catalyst in the Michael reaction of 3-methylbutanal and *N*-phenylmaleimide.[a]



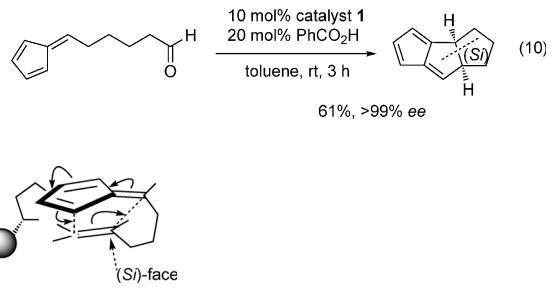
	Catalyst	*anti*:*syn*	Yield [%][b]	e.r.[c]
1[d]	R^1 = TMS, R^2 = H (**1**)	8:1	70	99.5:0.5
2	R^1 = TMS, R^2 = H (**1**)	7:1	65	99.5:0.5
3	R^1 = Ph_2MeSi, R^2 = H (**2**)	5:1	38	99.5:0.5

[a] The reaction was performed using *N*-phenylmaleimide (0.5 mmol), 3-methylbutanal (1.0 mmol), and organocatalyst (0.05 mmol) in $CHCl_3$ (2.0 mL) at 23 °C for 24 h. [b] Yield of purified product. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral column after conversion to α,β-unsaturated ester by treatment with $Ph_3P{=}CHCO_2Et$. [d] Data extracted from ref. [30].



that has been reported by Cordova et al. to give excellent enantioselectivity with the TMS catalyst **1**.[30] We carried out the reaction using both catalyst **1** and **2**, and found that both gave excellent enantioselectivity, but the reactivity of catalyst **2** was lower than that of **1**. Although Cordova and co-workers proposed structure A as the transition-state model,[30] transition-state model B (shown with Table 12) was proposed by one of the present authors (Y.H.) in the Michael reaction of α-alkoxyaldehyde and *N*-(*p*-nitrophenyl)maleimide when the one-pot synthesis of Tamiflu was investigated.[6d]

As a last example of a reaction involving an enamine intermediate, we highlight our previous work on attaining near-perfect enantioselectivity with the diphenylprolinol TMS ether **1** in an intramolecular formal [6+2] cycloaddition [Eq. (10)].[31] Here, there is no need to employ the bulky silyl ether **2**.



Discussion

Enantioselectivity

In general, the organocatalytic reaction of pyrrolidine-based catalysts has previously been categorized by two types of reactions: those involving neutral enamine intermediates and those involving iminium ion intermediates. We propose those reactions involving iminium ions to be subdivided into two types: one involving Michael-type reaction modes and the other involving cycloaddition reaction modes. There are thus three types of reactions, and the effect of the silyl substituent in each type will be discussed according to the following classifications:

Type A: Michael-type reactions involving an iminium ion intermediate. The catalyst with bulkier substituents generally gives better enantioselectivity; for instance, the diphenylprolinol DPMS ether **2** was found to be more selective than the TMS ether **1**. The exception is the Michael reaction of α,β-unsaturated aldehyde with nitromethane, in which excellent enantioselectivity is obtained in both the TMS ether catalyst **1** and the DPMS catalyst **2**.

Type B: Cycloaddition reactions involving an iminium ion intermediate. Excellent enantioselectivity is obtained with the sterically less bulky silyl substituent, for example, with TMS ether **1**.

Type C: Reactions involving an enamine intermediate. Smaller silyl substituents on the catalyst, such as in TMS ether **1**, afford products with excellent enantioselectivities and reasonable yields.

The effect of the silyl substituent on the enantioselectivity in each category will be discussed by considering the structures of the iminium ion and enamine, as revealed by our computational investigation. [Note: we refer to phenyl-substituted reactive intermediates in the following discussions; other substituents, such as CH_3, CH_2-alkyl, $CH(CH_3)_2$, cyclohexyl, and $CH{=}CH_2$, on the iminium ion can lead to a reversal of the stereotopicity descriptor according to CIP rules.]

In the reaction via iminium ions **3** and **4**, which are derived from cinnamaldehyde and the diphenylprolinol TMS ether (**1**) or the diphenylprolinol DPMS ether (**2**) (Figure 2), respectively, nucleophilic attack of the reagents occurs selectively from the *Si* face of the electrophilic β-carbon of the iminium ion (Figure 5). In the reaction via enamine **5**, which is derived from prolinol silyl ether **1** and phenylacetaldehyde, nucleophilic attack occurs selectively from the *Si* face of the nucleophilic α-carbon of the enamine **5** (Figure 5). These diastereo-differentiations stem from two factors: 1) iminium ions **3** and **4** adopt an ($E_{C,N}$, $E_{C,C}$) configuration and an s-*trans* conformation between the C=C and C=N double bonds, and the enamine **5** preferentially adopts an *E* configuration and s-*trans* conformation around the exocyclic N–C bond; and 2) the *syn* face of the pyrrolidine ring is blocked by bulky substituents $-CPh_2(OSiMe_3)$/$-CPh_2(OSiPh_2Me)$. Consequently, an *Re*-face approach of a nucleophile to the iminium ions **3** and **4**, and of an electrophile to the enamine **5**, will be sterically disfavored as compared to an *Si*-face approach. These conclusions are well supported by our conformational structure searches. The iminium ion **4** and enamine **5** were both calculated to exclusively adopt the s-*trans*-($E_{C,N}$, $E_{C,C}$) and (*E*, s-*trans*) structure, respectively (Tables 2 and 3). This conformational preference remains for the iminium ion **3**, of which a small percentile (2% at 298 K, Table 1) was calculated to exist in the ($Z_{C,N}$, $E_{C,C}$) form (Table 1, see below). For the exocyclic C–C bond, our conformational analysis suggested exclusive *sc-exo* conformations for the iminium ions **3** and **4** (Tables 1 and 2), as well as *sc-exo* or *ap* conformations for the neutral enamine **5** (Table 3). In the *sc-exo* and *ap* conformers of **3**, **4** and **5**, one of the phenyl rings on the carbon atom is located above the five-membered pyrrolidine ring (Figures S1 and S2 in the Supporting Information), and hence the top or

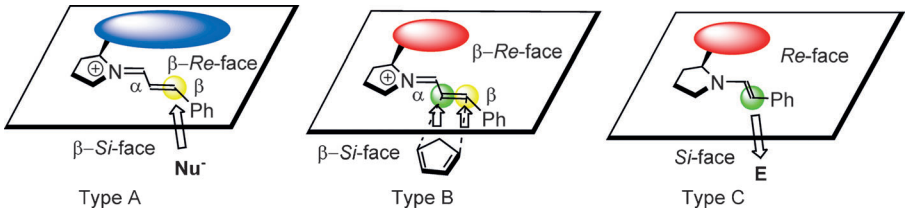


Figure 5. Schematic approach of reactants for type A, type B, and type C processes.

Re faces of these species are all sterically crowded, whereas the bottom or *Si* faces are all relatively accessible (Figure S3 in the Supporting Information).

However, the ability of catalyst **1** to achieve enantiomeric differentiation is slightly lower than that of catalyst **2** in cases of reactions involving iminium intermediates of type A (Tables 5–8). Two factors are considered to marginally lower the enantioselectivity for reactions mediated by catalyst **1**. First, a top-face attack on the electrophilic carbon atom (the Cβ-position) of the iminium ion **3** may not be fully blocked by the silyl substituent $-CPh_2(OSiMe_3)$. For the iminium ion **4**, one of the phenyl groups on the silicon atom is located on the upper side, positioned near the electrophilic center of the iminium portion. In addition to the phenyl ring on the carbon atom, the phenyl ring on the silicon atom can block attack of a reagent from the top face in the iminium ion **4**. Compared with iminium ion **4**, the top face of iminium ion **3** is relatively less hindered due to the lack of phenyl groups on the silicon atom (Figure 3 and Figure S1 in the Supporting Information). Second, contributions of a small population of the ($Z_{C,N}$, $E_{C,C}$) isomers of **3** could be responsible for lowering the overall enantioselectivity, since a bottom facial attack of this diastereomeric iminium ion would result in the opposite (and minor) enantiomeric product.

The Michael reaction of α,β-unsaturated aldehyde and nitromethane is an exception to type A trends, in which both the TMS catalyst **1** and the DPMS catalyst **2** gave excellent enantioselectivity (Table 9). As there would be an ionic interaction between a cationic portion of iminium ion and an anionic moiety of the nitronate ion, nucleophile and Michael acceptor should approach each other as shown in Table 9. Thus, even small TMS-substituted catalyst **1** affords an excellent enantioselectivity. It would be important to consider the trajectory of the reagent to evaluate the effectiveness of the silyl substituent of the catalyst in the Michael reaction.

In reactions of type B, via iminium ion intermediates, both the α- and β-positions of the α,β-unsaturated system participate. As silyl substituents, such as $-CPh_2(OSiMe_3)$, chiefly shield the top face of the α- and β-positions, excellent stereoselectivity is obtained with the TMS catalyst **1**. Bulky substituents such as $-CPh_2(OSiPh_2Me)$ are not necessary for achieving high overall enantioselectivity for this type of catalytic process.

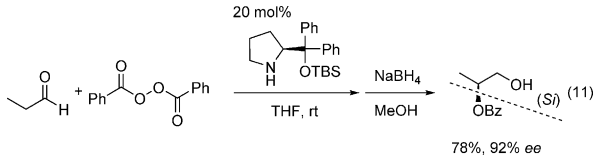
In reactions of type C, the π-selective facial addition of the catalyst-derived chiral (*Z*)-enamine **5** to a nonchiral electrophile is the initial diastereo-differentiating step, irrespective of the next mechanistic steps being put forward. We reason that this initial event, although not necessarily rate-determining, defines the absolute and relative Cα (and Cβ) configurations in all ensuing intermediates. Currently, the exact details of interrelated catalytic cycles, equilibria, and intermediates are still a matter of debate.[29] It is nevertheless reasonable to suggest that this initial addition step installs the necessary stereogenicity in subsequent intermediates so as to influence the resultant Cα enantioselectivity in the product after the chiral prolinol catalyst is released. The intramolecular formal [6+2] cycloaddition reaction of aldehyde and fulvene is a clear case to consider first. Ab initio and DFT calculations thus revealed the cycloaddition to proceed through a transition state whereby the reactive nucleophilic center (the Cα-position) is relatively close to the pyrrolidine ring [Eq. (10)].[31] Accordingly, the less bulky silyl substituent $-CPh_2(OSiMe_3)$ can efficiently block attack from the top π face of the reacting trigonal center of the enamine. Notably, contribution by an (*E*)-s-*cis* form was calculated to be negligible for enamine **5**. A less clear case or process of enantioselection occurs in the Michael addition of aldehyde-derived enamines to nitroalkenes. These reactions have been proposed to proceed via putative zwitterionic, cyclobutane, and dihydrooxazine intermediates both on and off the catalytic cycle (Table 11).[29] Although the rate-determining step is not clear, the enantio-determining step is suggested to be the addition of the enamine to the nitroalkene through the model shown in Table 11. The chirality at both α- and β-positions of the formyl group would arguably be determined in this addition step, even though the α-position might undergo subsequent isomerization.[29a] In this model, a small TMS ether is sufficient to cover the *Re* face efficiently. In the Michael addition of aldehyde-derived enamines to *N*-phenylmaleimide, there is thus the possibility of a [2+2] cycloaddition followed by ring opening of a cyclobutane intermediate.[29f] In this case again, the enantio-determining step would be an addition step [Table 12, Eq. (9)]. For both such cycloaddition and Michael reactions, very high enantioselectivity has been attained by incorporation of a small silyl ether into the prolinol catalyst. In the Michael reaction of aldehyde and nitroalkenes, even the much smaller methyl ether of diphenylprolinol is known to promote the reaction with excellent enantioselectivity.[32] Consequently, the TMS ether catalyst **1** is expected to be sufficient in achieving satisfactory diastereotopic π-facial differentiation for reactions involving catalyst-derived enamines as intermediates (Figure 5; type C).

Reactivity

In general, reactions catalyzed by diphenylprolinol silyl ethers with bulky substituents are slow. As shown in Table 6, the reaction time increased when the DPMS ether catalyst **2** was employed, as compared with reactions catalyzed by the TMS ether **1** (see Tables 7 and 8). The reaction outlined in Table 7 was completed within 50 min with the TMS ether catalyst **1**, whereas a longer reaction time (80 min) was necessary with the DPMS ether catalyst **2**. For the reaction shown in Table 8, 10 mol% of the TMS ether catalyst **1** was found to be sufficient to promote the reaction, whereas a higher catalyst loading of the bulkier DPMS derivative **2** (20 mol%) was required to obtain the product in reasonable yield.

In contrast to the general observations that shorter reaction times result from reactions catalyzed by diphenylprolinol silyl ether with smaller silyl substituents, we found a case in which higher yields were observed when the bulkier catalyst **2** was employed. As shown in entry 5 of Table 6, diphenylprolinol DPMS ether catalyst **2** gave a higher yield of the Michael adduct, which we attributed to the TMS ether **1** "overreacting" with the ester-activated Michael acceptor, thereby forming the unproductive species **6**. In this particular case, the bulky sub-

stituent may suppress this side reaction and thereby increase the yield. In the α-benzoyloxylation of an aldehyde,[33] the catalyst with bulky silyl substituents also gave higher reactivity. In this case, the gradual reaction of the catalyst with benzoyl peroxide was suppressed with the bulkier TBS ether catalyst [Eq. (11)].



(11)

Conclusion

We have investigated the effects of the silyl substituents in diphenylprolinol silyl ether catalysts in several types of enantioselective reactions. We have defined three types of reactions catalyzed by diphenylprolinol silyl ethers. Type A is a Michael-type reaction of α,β-unsaturated aldehydes involving iminium ion intermediates, in which a higher enantioselectivity is realized when the catalyst with a bulkier silyl moiety is employed except for the Michael reaction of an α,β-unsaturated aldehyde with nitromethane. One of the best substituent patterns on the silyl atom in the diphenylprolinol silyl ether catalyst is the diphenylmethyl group. Type B is a cycloaddition reaction via iminium ion intermediates, in which small substituents on the silyl atom, such as the trimethylsilyl (TMS) group, affords excellent enantioselectivity. Type C is a reaction involving enamine intermediates derived from an aldehyde as a nucleophile. In this reaction, small substituents on the silyl group provide excellent enantioselectivity. In general, a bulky silyl group in the diphenylprolinol silyl ether catalyst retards the reaction for steric reasons. In certain cases, however, a better yield results because the bulky silyl substituents suppress unproductive side reactions or destruction of the catalyst molecule that become more prevalent with more nucleophilic diphenylprolinol silyl ether catalysts.

Over all three reaction types, silyl substituent effects on the resultant enantioselectivity are rationalized through conformational analysis of the iminium ions and of the enamine, and the trajectory of the reagents. Theoretical conformational analyses were carried out for the iminium ions **3** and **4**, derived from diphenylprolinol TMS ether (**1**) and cinnamaldehyde, or from diphenylprolinol DPMS ether (**2**) and cinnamaldehyde, as well as for the enamine **5** derived from **1** and phenylacetaldehyde. The most stable structure of the iminium ions **3** and **4** was calculated to be ($E_{C,N}$, $E_{C,C}$)-s-*trans*-*sc*-*exo*, and the most stable structure of the enamine **5** was calculated to be the (*E*)-s-*trans*-*ap* form. For the structure of the pyrrolidine ring, our calculations suggest that the *down* conformation tends to be energetically more favorable than the *up* conformation (Figure 2). The energetic preference for *down* over *up* conformations is also supported in a recent report by Gschwind et al. for prolinol and prolinol ether enamines.[11d] There was no electronic interaction between the silyl atom and the π orbital of the double bond in the iminium ion or in the enamine, and the predominant effects of the silyl substituents were steric. Optimized structures of the most stable geometry of iminium ion **4** indicate that the bulky silyl group $CPh_2(OSiPh_2Me)$ shields the *Re* face of the Cβ-position efficiently, whereas less effective shielding of the Cβ-position results with the smaller silyl group $CPh_2(OSiMe_3)$ on the iminium ion **3**. This is the main reason why a higher enantioselectivity results for type A reactions when a prolinol catalyst with a bulkier silyl moiety is employed. A structural comparison of the iminium ions **3** and **4** leads to the conclusion that the relative bulkiness of the substituent $CPh_2(OSiPh_2Me)$ will reduce the reactivity in some cases, but is, at the same time, able to enhance the enantioselectivity of the catalyst **2**. In addition, the existence of an s-*trans*-($Z_{C,N}$, $E_{C,C}$) diastereoisomer of the iminium ion **3**[10c] could possibly further lower the enantioselectivity with the TMS silyl catalyst **1** in type A reactions.

For type C reactions, the electrophilic reagent attacks the Cα-position of the neutral enamine, whereas for type B reactions, attack of the reagent occurs simultaneously at the Cα- and Cβ-positions of the iminium species (Figure 5). Optimized structures of the most stable forms of the iminium ions **3** and **4**, as well as that of the enamine **5**, indicate that both substituents $CPh_2(OSiMe_3)$ and $CPh_2(OSiPh_2Me)$ can effectively shield the *Re* face of the Cα-position. This finding is in agreement with the fact that even relatively small substituents on the silyl atom in the organocatalyst can infer excellent enantioselectivity for type B and C reactions.

The theoretical and experimental findings described herein should provide valuable information not only for the design of new organocatalytic reactions, but also for the optimization of key asymmetric reactions using diphenylprolinol silyl ether catalysts.

Considering the discussion of stereoelectronic effects[10c] and Jørgensen's recent results about di- and trienamine catalysis,[34] the details of the stereoselectivity of these reactions may be more complex than summarized herein.

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Keywords: asymmetric synthesis · density functional calculations · organocatalysis · reaction mechanisms · substituent effects

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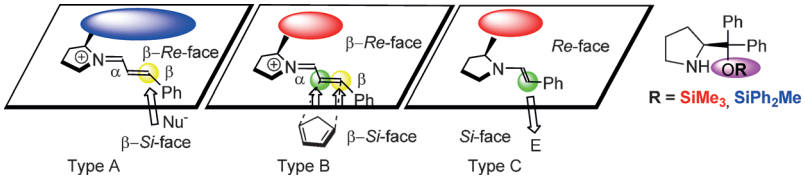

Typecast: Reactions catalyzed by diphenylprolinol silyl ether can be categorized into three types (see figure): two involve an iminium ion intermediate, such as for a Michael-type reaction (type A) and a cycloaddition reaction (type B), and one proceeds via an enamine intermediate (type C). In type A, good enantioselectivity is realized if a catalyst with a bulky silyl moiety is employed. In types B and C, good enantioselectivity is obtained even when the silyl group is less bulky.

Organocatalysis

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A Theoretical and Experimental Study of the Effects of Silyl Substituents in Enantioselective Reactions Catalyzed by Diphenylprolinol Silyl Ether