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Unique Steric Effect of Geminal Bis(silane) To Control the High *Exo*-selectivity in Intermolecular Diels–Alder Reaction

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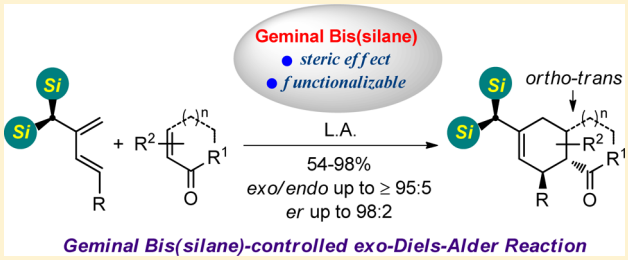
Supporting Information

ABSTRACT: The unique steric effect of geminal bis(silane) [$(R_3Si)_2CH$] allows an *exo*-selective intermolecular Diels–Alder reaction of geminal bis(silyl) dienes with α,β-unsaturated carbonyl compounds. The approach shows good generality to form *ortho–trans* cyclohexenes in good yields with high *exo*-selectivity and high enantioselectivity in some asymmetric cases. The excellent *exo*-stereocontrol aptitude of $(R_3Si)_2CH$ group is highlighted by comparing with R_3SiCH_2 and R_3Si groups, which leads to *endo*-selectivity predominantly. The conformational analysis of dienes suggests that $(R_3Si)_2CH$ group effectively shields both sides of the diene moiety, ensuring the desired *exo*-selectivity. Moreover, the geminal bis(silane) can be further functionalized to transform the resulting *ortho–trans* cycloadducts into useful synthons, which makes the approach hold great potential for organic synthesis.

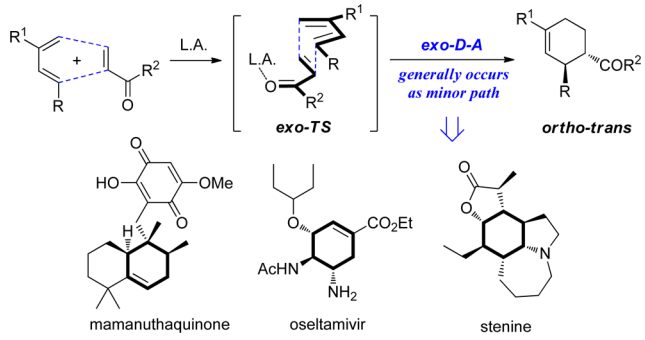


INTRODUCTION

The Diels–Alder (D–A) reaction and its variants are powerful methods for constructing six-membered rings, reflected in their numerous applications in natural product synthesis.[1] Normal-demand intermolecular D–A reaction of diene and α,β-unsaturated carbonyl compounds typically follows the well-known Alder's *endo* rule[2] to give predominantly *ortho–cis* cycloadduct. The *endo*-selectivity can be even dramatically enhanced by the use of Lewis acids.[3] This stereochemical preference is thought to arise from secondary orbital interactions (SOIs) as suggested by Woodward and Hoffman,[4] though a number of other factors such as dipole effect, steric effect, and magnetic properties may play roles as well.[5] The corresponding intermolecular *exo*-D–A reaction, in contrast, usually occurs as a minor path to form *ortho–trans* cycloadduct (Scheme 1). Therefore, a major challenge in this field is the development of general and predictable methods to achieve the highly *exo*-selective intermolecular D–A reaction, which would hold promise for the synthesis of natural products containing the *ortho–trans* cyclohexenes and cyclohexanes (Scheme 1).

When the steric instability increases to overcome the SOIs in the *endo*-transition state, the *exo*-transition state becomes dominant to give the *exo*-selectivity.[6,7] To promote cycloaddition via the *exo*-transition state predominantly, researchers developed several strategies to create the desired steric instability in the *endo*-transition state. For example, conformationally restricted cyclic s-*cis* dienophiles[8] and organometal-substituted bulky dienophiles[9] have been used to achieve a dienophile-controlled *exo*-D–A reaction. The *exo*-selectivity has been also realized by a diene-controlled strategy using highly substituted acyclic dienes[10] or those with one alkene embedded in a congested ring structure.[11] An elegant breakthrough with this approach came when small single-molecule catalyst-

Scheme 1. *Exo*-D–A Reaction Generally Occurs as a Minor Path but Holds Great Potential for Natural Product Synthesis



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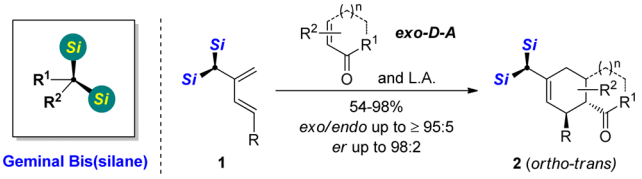
control,[12] supramolecular catalyst-control[13] or monoclonal antibodies-control[14] were utilized to catalyze an asymmetric *exo*-D−A reaction. Despite these advances, the above approaches often suffer from some limitations such as moderate *exo*-selectivity, narrow scope of substrates, and limited applicability to construct the specific ring system. Therefore, it still remains a significant challenge to discover a single species that can not only ensure the generally reliable *exo*-control in an intermolecular D−A reaction, but also meet the requirements of further functionalization.

As part of our continuing efforts to explore geminal bis(silyl) chemistry,[15] we wondered whether this bulky species would provide sufficient steric shielding around diene from the *endo*-attack by dienophile, ensuring the desired *exo*-selectivity in an intermolecular D−A reaction. Here we report an intermolecular *exo*-D−A reaction of geminal bis(silyl) diene **1** with a wide range of α,β-unsaturated carbonyl compounds (Scheme 2). The

Scheme 2. Geminal Bis(silyl) Diene-Controlled *Exo*-D−A Reaction



reaction provides *ortho*−*trans* cyclohexenes **2** with high regio- and *exo*-selectivity as well as high enantioselectivity in some asymmetric cases. The results from control experiments and conformational analysis of dienes suggest that the steric effect of geminal bis(silane) plays a key role in controlling the *exo*-selectivity. Moreover, the geminal bis(silane) can be further transformed into diverse functional groups, which makes the approach hold great potential for organic synthesis.

RESULTS AND DISCUSSION

Screening of Reaction Conditions. The reaction was initially examined in CH_2Cl_2 using bis($SiEt_3$)-substituted diene **1a**[16] as a model scaffold and ethyl vinyl ketone as the dienophile. While $AlCl_3$ led to a complex mixture (Table 1, entry 1), $EtAlCl_2$ gave the desired cycloadduct **2a** in 61% yield with an *exo*/*endo* ratio of 80:20 (entry 2). Use of bulkier Et_2AlCl[17] as the Lewis acid gave an increased yield of 83% and higher diastereoselectivity of 93:7 (entry 3). Decreasing the loading of **1a** from 1.5 to 1.1 equiv lowered both yield (78%) and *dr* (89:11) slightly (entry 4). As expected, the cycloaddition barely occurred when the reaction was refluxed for 72 h without Et_2AlCl (entry 5). The bulkiness of the geminal bis(silyl) group proved crucial for controlling the stereochemical outcome. While reaction of diene **1b** containing a smaller bis($SiMe_3$) group gave a lower *exo*/*endo* ratio of 91:9 (entry 6), reaction of **1c** containing the larger bis($SiMe_2t$-Bu) group gave the higher ratio ≥ 95:5 (entry 7).

Observation of Atropisomerism of the Geminal Bis(*t*-BuMe$_2$Si)-Substituted Cycloadduct. We were surprised to find that the cycloadduct **2c**, particularly its phenyl analogue **2c-Ph**, exists as an approximately 50:50 mixture of two atropisomers at 30 °C[19] (Figure 1). Such atropisomerism[20] usually occurs in bicyclic systems such as BINOL and its derivatives. In our case, the atropisomerism of **2c-Ph** appears to

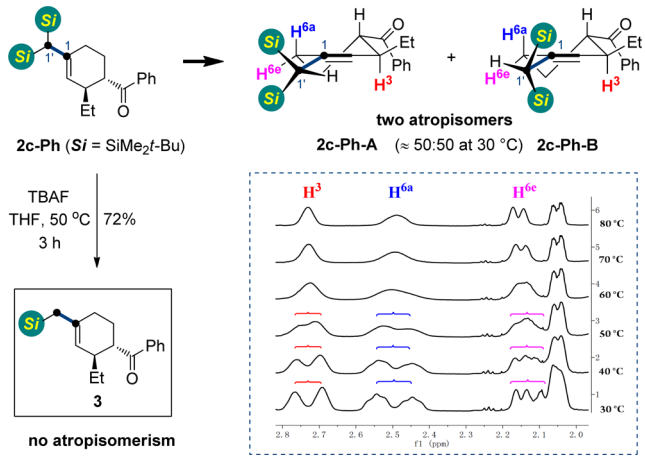
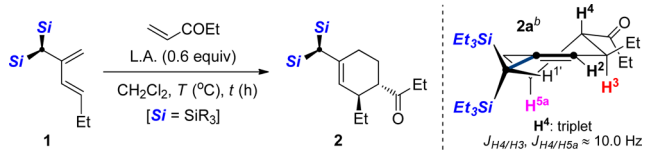


Figure 1. Atropisomers **2c-Ph-A** and **2c-Ph-B** (top). *t*-BuMe_2SiCH_2-substituted cyclohexene 3 (left, bottom). ^{1}H NMR monitoring of **2c-Ph** in DMF-d7 at temperatures ranging from 30−80 °C (right, bottom).

Table 1. Screening of Reaction Conditions[a]



entry	**1** (Si, equiv)	L.A.	*T* (°C)	*t* (h)	**2**: Yield[c]	*exo*/*endo*[d]
1	**1a** ($SiEt_3$, 1.5)	$AlCl_3$	0−25	3	**2a**: N.D.	N.D.
2	**1a** ($SiEt_3$, 1.5)	$EtAlCl_2$	0−25	3	**2a**: 61%	80:20
3	**1a** ($SiEt_3$, 1.5)	Et_2AlCl	0−25	3	**2a**: 83%	93:7
4	**1a** ($SiEt_3$, 1.1)	Et_2AlCl	0−25	3	**2a**: 78%	89:11
5	**1a** ($SiEt_3$, 1.5)		reflux	72	**2a**: N.D.	N.D.
6	**1b** ($SiMe_3$, 1.5)	Et_2AlCl	0−25	3	**2b**: 83%	91:9
7	**1c** ($SiMe_2t$-Bu, 1.5)	Et_2AlCl	0−25	3	**2c**: 81%	≥ 95:5 (50:50[e])

[a]Reaction conditions: geminal bis(silyl) diene **1** and 0.2 mmol of ethyl vinyl ketone and 0.12 mmol of Lewis acid in 2.0 mL of CH_2Cl_2. [b]The *trans*-stereochemistry of **2a** was assigned based on the ^{1}H NMR coupling constants. The signal of H^4 appears as a triplet of ~10 Hz, consistent with vicinal coupling of H^4 to two *trans*-diaxial protons H^3 and H^{5a}.[18] [c]Isolated yields after purification by silica gel column chromatography. [d]*Exo*/*endo* ratios were determined by ^{1}H NMR spectroscopy. [e]The ratio of two atropisomers of **2c**.

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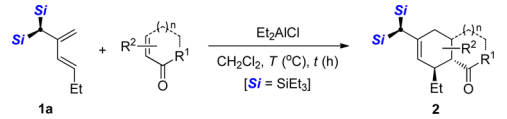
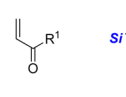
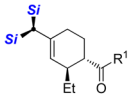
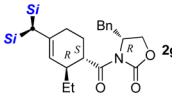
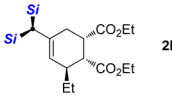
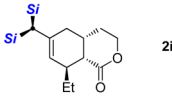
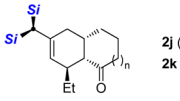
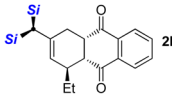
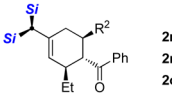
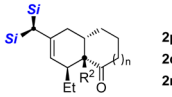
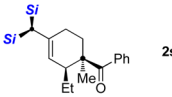
arise from the fact that the extremely bulky geminal bis(*t*-BuMe$_2$Si) group restricts the rotation of the C^1−C$^{1'}$ bond. These two atropisomers probably adopt the most favorable conformations as **2c-Ph-A** and **2c-Ph-B**, respectively, to minimize allylic strain and nonbonded interactions. As expected, removing one of the silyl groups to reduce bulkiness generated **3** with no atropisomerism. Confirming the occurrence of atropisomerism of **2c-Ph** was obtained by measuring its ^{1}H NMR spectrum at temperatures ranging from 30−80 °C. The H^3, H^{6a}, and H^{6e} signals appeared split at 30 °C and increasingly overlapped at higher temperatures. Cooling the solution back down to 30 °C again produced the split signals. These results also rule out the possibility that epimerism, rather than atropisomerism, occurs at the ketone *α*-position.

Scope of *α,β*-Unsaturated Carbonyl Compounds. This approach proved applicable to a range of *α,β*-unsaturated carbonyl compounds, frequently used as dienophiles in the intermolecular *endo*-D−A reaction (Table 2). The extent of *exo*-selectivity appeared to depend on the bulkiness of the R^1 group in monosubstituted dienophiles. As shown in entries 1−4, the *exo*/*endo* ratio was substantially increased by switching R^1 from an Et to Ph group or from OEt to O*t*-Bu. The *ortho*−*trans* stereochemistry of the desired *exo*-cycloadduct was unambiguously confirmed by the X-ray crystallography of **2g**[21] (Figure 2), which was delivered in 65% yield with complete *exo*-selectivity and with facial selectivity of 83:17 (entry 5). The reaction was also suitable for various acyclic and cyclic *Z*-dienophiles to give the predominant *exo*-selectivity (entries 6−10). The thermal condition was applied to cycloaddition with naphthalene-1,4-dione, a highly reactive dienophile, as Et$_2$AlCl only led to a complex mixture (entry 10). The bulkiness of the *β*-substituent in *E*-enones impacted the efficiency of cycloaddition significantly. While cycloaddition of **1a** with *β*-iodo- or *β*-methyl-substituted *E*-enone gave **2m** or **2n** in good yields with excellent *exo*-selectivity (entries 11 and 12), the cycloaddition was totally retarded using *E*-enone containing a bulkier *β*-phenyl group (entry 13). Probably, introducing the phenyl group into the *β*-position of *E*-enone disfavors the desired *exo*-pathway, which might suffer from a severe nonbonded interaction between phenyl and bis(SiEt$_3$) groups. In addition, we found that *α*-bromo cyclopentenone and -cyclohexenone were also suitable dienophiles to give *ortho*−*trans* bicyclic ketones **2p** and **2q**, both of which possess a quaternary carbon center at the ring junction (entries 14 and 15). Unfortunately, introducing a bulkier methyl group into the *α*-position of enones such as *α*-methyl cyclohexenone and -acrylophenone either inhibited the cycloaddition (entry 16) or resulted in **2s** as a normal *endo*-cycloadduct (entry 17).

Scope of Geminal Bis(silyl) Dienes. The *exo*-D−A reaction of geminal bis(SiEt$_3$) dienes **1d**−**1h** with phenyl vinyl ketone gave cycloadducts **2t**−**2x** in good yields as a single *ortho*−*trans* diastereomer (Table 3). The gram-scale reaction showed similarly good efficiency to give **2u** in 63% yield with complete *exo*-selectivity (entry 2). These cyclohexenes contain diverse functional groups at the 3-position, which makes them useful for further applications. The reaction of triene **1h** showed an interesting regioselectivity (entry 5). While no 1,3-*endo* cycloadduct **2xa** was formed as expected, neither **2xb** nor **2xc** was generated from the competing 3,5-diene-involved *endo*- and *exo*-D−A reaction. The reaction provided 1,3-*exo* cycloadduct **2x** in 96% yield as a single regio- and diastereoisomer.

Table 2. Scope of *α,β*-Unsaturated Carbonyl Compounds[a]



Entry	Dienophile	Product		T (°C)	t (h)	Yield[b]	*exo*/*endo*[c]
1			**2a** (R^1 = Et)	0-25	3.0	83%	93:7
2			**2d** (R^1 = Ph)	0-25	3.0	81%	≥ 95:5
3			**2e** (R^1 = OEt)	0-25	3.0	84%	86:14
4			**2f** (R^1 = O*t*-Bu)	0-25	3.0	60%	≥ 95:5
5			**2g**	-40	16	65%	≥ 95:5 [83:17][e]
6			**2h**	0-25	3.0	65%	≥ 95:5
7			**2i**	reflux	12	56%	≥ 95:5
8			**2j** (n = 0)	0-25	3.0	75%	93:7
9			**2k** (n = 1)	0-25	3.0	96%	≥ 95:5
10			**2l**[d]	reflux	72	67%	≥ 95:5
11			**2m** (R^2 = I)	0-25	3.0	60%	≥ 95:5
12			**2n** (R^2 = Me)	0-25	3.0	78%	≥ 95:5
13			**2o** (R^2 = Ph)	0-25	3.0	N.R.	N.D.
14			**2p** (R^2 = Br; n = 0)	-40	16	56%	≥ 95:5
15			**2q** (R^2 = Br; n = 1)	-40	16	83%	≥ 95:5
16			**2r** (R^2 = Me; n = 0)	50	12	N.R.	N.D.
17			**2s**	0-25	3	90%	≤ 5:95[f]

[a]Reaction conditions, unless otherwise specified: 0.3 mmol of **1a**, 0.2 mmol of dienophiles, and 0.12 mmol of Et$_2$AlCl (2.0 M in *n*-hexane) in 2.0 mL of CH$_2$Cl$_2$. [b]Isolated yields after purification by silica gel column chromatography. [c]*Exo*/*endo* ratios were determined by ^{1}H NMR spectroscopy. The *trans*-stereochemistry of *exo*-cycloadducts was confirmed by X-ray crystallography of **2g** and NOE experiments on **2h**.[22] [d]Refluxed in toluene without Et$_2$AlCl. [e]The ratio of facial selectivity for *exo*-cycloaddition. [f]The *ortho*−*cis*-stereochemistry of **2s** was confirmed by the X-ray crystallography of **4** (Figure 2).[23]

Although we cannot rule out the possibility that the hyperconjugation effect[24] between two C−Si bonds and the C^1−C^2 double bond might result in a higher reactivity of the geminal bis(SiEt$_3$)-substituted 1,3-diene than the corresponding 3,5-diene, we more prefer the following rationale based on the steric effect of geminal bis(silane). Because of the severe nonbonded interactions between the benzoyl substituent and the adjacent bulky bis(SiEt$_3$) group that would develop in both *endo*- and *exo*-pathways, cycloaddition to the 3,5-diene in **1h** should be disfavored to give sterically congested cycloadducts **2xb** and **2xc**.

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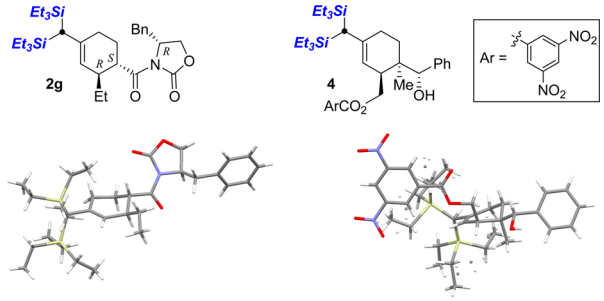
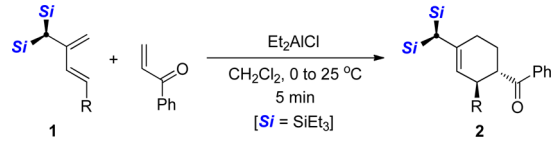


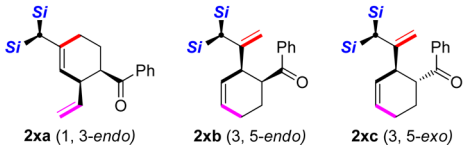
Figure 2. (a) X-ray structures of **2g** and **4**.

Table 3. Scope of Geminal Bis(silyl) Dienes[a]



Entry	1 (R)	Product	Yield[b]	exo/endo[c]
1	**1d** (R = CH_2Cl)	**2t**	66%	≥ 95:5
2	**1e** (R = CH_2OSiEt_3)	**2u**	65% (63%[d])	≥ 95:5
3	**1f** (R = $CH_2Oallyl$)	**2v**	86%	≥ 95:5
4	**1g** (R = CH_2SBn)	**2w**	54%	≥ 95:5
5	**1h**	**2x** (1, 3-*exo*)	96%	≥ 95:5

not observed in entry 5



2xa (1, 3-*endo*) **2xb** (3, 5-*endo*) **2xc** (3, 5-*exo*)

[a]Reaction conditions, unless otherwise specified: 0.3 mmol of diene **1**, 0.2 mmol of phenyl vinyl ketone, and 0.12 mmol of Et_2AlCl (2.0 M in *n*-hexane) in 2.0 mL of CH_2Cl_2, 0–25 °C, 5 min. [b]Isolated yields after purification by silica gel column chromatography. [c]*Exo/endo* ratios were determined by ^1H NMR spectroscopy. [d]The yield was obtained in gram-scale reaction using 5.0 mmol of **1e** and 3.3 mmol of phenyl vinyl ketone.

Asymmetric Geminal Bis(silyl) *Exo*-D–A Reaction. A Lewis acid-catalyzed asymmetric version of the above *exo*-D–A reaction was initially examined using geminal bis(silyl) dienes **1** and acryloxazolidione. While most of Cu(II)/bis(oxazoline) catalysts only provided poor to medium enantioselectivity,[25] the catalyst, prepared from $Cu(NTf_2)_2$ with Ishihara's ligand **6**,[26] showed the optimal catalytic efficiency in CH_3NO_2 at −10 °C. The reaction generally completed within 36 h to give *ortho–trans* cycloadducts **5a–5f** with exclusive *exo*-selectivity and high enantioselectivity (Table 4, entries 1–6). Cycloaddition using bis($SiMe_2t$-Bu)$_2$-substituted **1k** provided an higher *er* of 97:3 than 93:7 obtained using less bulkier bis($SiEt_3$)$_2$-substituted **1i**. The same *er* of 97:3 was obtained in the gram-scale reaction to form **5e** despite the yield deceased slightly from 83% to 76% (entry 5). This asymmetric process was also applicable to trienes **1m** and **1n**, which showed higher reactivity than dienes, giving the 1,3-regioselective cycloadducts **5g** and **5h** as a single *ortho–trans* isomer with high *er* (entries 7 and 8). In addition, similar to previous observation (Table 2, entry 13), introduction of a substituent into the *β*-position of acryloxazolidione inhibited cycloaddition due to the increased steric interaction between bis(silyl) group and *β*-substituent.

Acrolein, the least sterically demanding *α,β*-unsaturated carbonyl compound, is one of the most changeling substrates for asymmetric *exo*-D–A reaction. It has been shown by the previous results that moderate *exo/endo* ratios were generally obtained under either Lewis acid-catalysis or organocatalysis.[12b,d,h,13b] We were delighted to find that geminal bis(silane) was also able to ensure an excellent *exo*-stereocontrol in the asymmetric D–A reaction with acrolein. MacMillan's catalyst **8**[27] showed the superiority over other chiral second amine catalysts[28] for the cycloaddition of dienes **1** and acrolein in benzene at 10 °C. As shown in Table 5, *ortho–trans* cycloadducts **7a–7c** containing varied silyl group were generated with good *exo/endo* ratio (91:9 to 93:7) and high *er* (94:6 to 96:4) for the *exo*-isomer.

Comparing the *Exo*-Stereocontrol Aptitude of $(Et_3Si)_2CH$ with Et_3SiCH_2 and SiR_3 Groups. While the high *exo*-selectivity was achieved using $(Et_3Si)_2CH$-substituted diene **1e**, reaction of the Et_3SiCH_2-substituted diene **9** under otherwise identical conditions led to the cycloadduct **10** in an *endo/exo* ratio of 60:40 (Scheme 3A). In addition, previous studies have shown that reaction of *N*-phenylmaleimide with diene **11a**[29] containing one Et_3Si group at the 2-position or with **11b**[30] containing two Me_3Si groups at the 2- and 3-positions gave cycloadducts **12a** or **12b**, respectively, with a complete *endo*-selectivity (Scheme 3B). These results unambiguously indicate the superiority of $(Et_3Si)_2CH$ over Et_3SiCH_2 and R_3Si groups for the *exo*-stereocontrol.

Conformational Analysis of Dienes 1e and 9. The inversion of diastereoselectivity obtained using dienes **1e** and **9** suggests that the bulkier $(Et_3Si)_2CH$ group provides better shielding around the diene moiety than the Et_3SiCH_2 group, which leads to more reliable *exo*-selectivity. To gain more detailed insights into the different steric effects exerted by $(Et_3Si)_2CH$ and Et_3SiCH_2 groups, we compared the conformational profiles of **1e** and **9**. This approach should provide a reasonable approximation to the true profiles in cycloaddition.[31]

The conformations of **1e** and **9** were analyzed by NOE experiments in $CDCl_3$ at room temperature. Irradiation of $H^{2'}$, H^3, and H^4 significantly enhanced NOEs between $H^{2'}$ and H^3 and between $H^{2'}$ and H^4 (Scheme 4, upper left). However, irradiation of $H^{2'}$ and H^1 did not cause a detectable NOE. These results suggest that the diene moiety in **1e** adopts s-*Z* and s-*E* conformations, which interconvert via C^2–C^3 bond rotation. More importantly, the results also suggest that the geminal bis($SiEt_3$)$_2$ moiety in both **1e-*s*-*Z*** and **1e-*s*-*E*** adopts the same conformation, in which the $C^{2'}$–$H^{2'}$ and C^2–C^3 bonds are *syn*-periplanar. As a result, the two $C^{2'}$–Si bonds are oriented approximately perpendicular to the diene part to minimize allylic strain and nonbonded interactions as well as favor silicon hyperconjugation. This unique conformation of geminal bis($SiEt_3$)$_2$ shields both sides of the *s*-*Z* diene, ensuring the sufficient steric conditions required for the *exo*-cycloaddition (Scheme 4, upper right). The steric argument is consistent with our observation that higher *exo*-selectivity was obtained using a bulkier Lewis acid (Table 1, entries 2 and 3), bulkier geminal bis(silyl) group (Table 1, entries 3, 6, and 7), or dienophiles with bulkier R^1 group (Table 2, entries 1–4).

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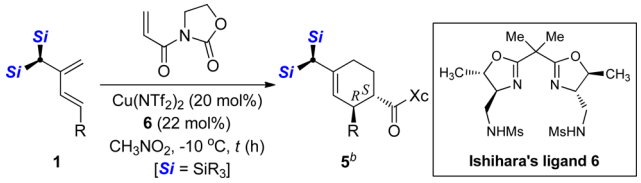
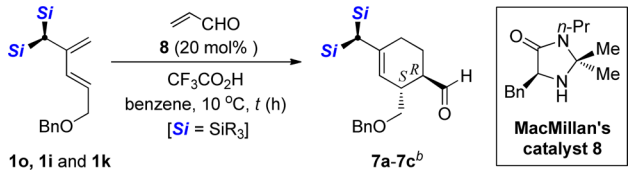
Table 4. Chiral Cu(II)-Catalyzed Asymmetric *Exo*-D−A Reaction with Acryloxazolidione[a]



entry	1 (Si, R)	t (h)	5[c] (Yield[d])	*exo*/*endo*[e]	er[f]
1	**1a** ($SiEt_3$, R = Et)	36	**5a** (61%)	≥ 95:5	91:9
2	**1i** ($SiEt_3$, R = CH_2OBn)	36	**5b** (80%)	≥ 95:5	93:7
3	**1c** ($SiMe_2t$-Bu, R = Et)	36	**5c** (65%)	≥ 95:5	91:9
4	**1j** ($SiMe_2t$-Bu, R = Cl)	36	**5d** (87%)	≥ 95:5	96:4
5	**1k** ($SiMe_2t$-Bu, R = CH_2OBn)	36	**5e** (83% [76%[g]])	≥ 95:5	97:3
6	**1l** ($SiMe_2t$-Bu, R = $CH_2Oallyl$)	36	**5f** (98%)	≥ 95:5	98:2
7	**1m** ($SiMe_2t$-Bu, R = CH=CH_2)	5	**5g** (83%)	≥ 95:5	92:8
8	**1n** ($SiMe_2t$-Bu, R = (*E*)−CH=CH−CH_2OBn)	5	**5h** (90%)	≥ 95:5	93:7

[a]Reaction conditions, unless otherwise specified: 0.1 mmol of diene **1**, 0.15 mmol of acryloxazolidione, $Cu(NTf_2)_2$ (20 mol %), and Ishihara's ligand **6** (22 mol %) in 3 mL of CH_3NO_2 at −10 °C. [b]The absolute configuration of products was determined by reducing **5a** into the corresponding alcohol. Its optical rotation is in accordance with that of the alcohol generated from reducing **2g**. The other products were assigned by analogy. [c]An approximately 50:50 mixture of two atropisomers was observed for geminal bis($SiMe_2t$-Bu)-substituted **5c**−**5h**. [d]Isolated yields after purification by silica gel column chromatography. [e]*Exo*/*endo* ratios were determined by ^{1}H NMR spectroscopy. [f]Determined by HPLC analysis using a chiral stationary phase. [g]The yield was obtained in gram-scale reaction using 3.8 mmol of **1k** and 5.6 mmol of acryloxazolidione.

Table 5. Chiral Amine-Catalyzed Asymmetric *Exo*-D−A Reaction with Acrolein[a]

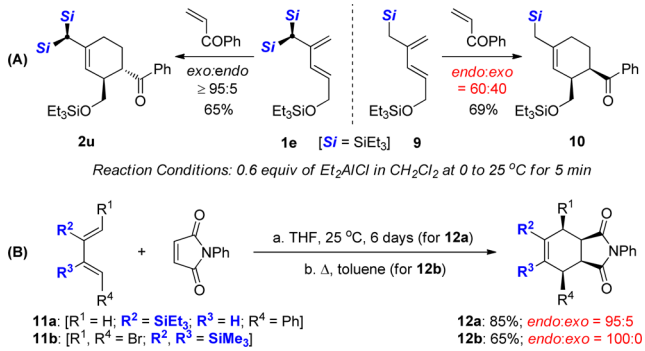


entry	diene (*Si*)	t (h)	product	yield[d]	*exo*/*endo*[e]	er[f]
1	**1o** (*Si* = $SiMe_3$)	12	**7a**	69%	91:9	96:4
2	**1i** (*Si* = $SiEt_3$)	36	**7b**	67%	92:8	94:6
3	**1k** (*Si* = $SiMe_2t$-Bu)	36	**7c**[c]	65%	93:7	95:5

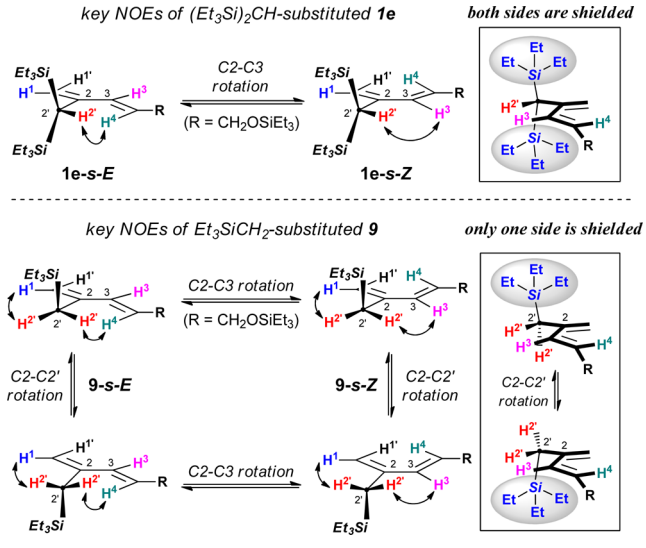
[a]Reaction conditions, unless otherwise specified: 0.1 mmol of diene **1**, 0.5 mmol of acrolein, MacMillan's catalyst **8** (15 mol %), and CF_3COOH (30 mol %) in 2.0 mL of benzene at 10 °C. [b]The absolute configuration of products was determined by reducing **7b** into the corresponding alcohol. Its optical rotation is opposite to that of the alcohol generated from reducing **5b**. The other products were assigned by analogy. [c]An approximately 50:50 mixture of two atropisomers was observed for **7c**. [d]Isolated yields after purification by silica gel column chromatography. [e]*Exo*/*endo* ratios were determined by ^{1}H NMR spectroscopy. [f]Determined by HPLC analysis using a chiral stationary phase.

NOE experiments of Et_3SiCH_2-substituted diene **9** showed enhancement among $H^{2'}$, H^3, and H^4 as well as between $H^{2'}$ and H^1 (Scheme 4, lower left). These results imply the existence of at least four ground-state conformations: two **9**-*s*-*Z* and two **9**-*s*-*E*. In these conformations, the $C^{2'}$−Si bond is oriented approximately perpendicular to the diene moiety to minimize nonbonded interactions. Apparently, one silyl group is sufficient to shield only one side of the diene in either conformation of **9**-*s*-*Z* (Scheme 4, lower right). The other side experiences minimal steric hindrance, probably favoring the normal *endo*-cycloaddition. Consistent with this argument, cycloaddition of **9** with phenyl vinyl ketone provided comparable amounts of *ortho*−*cis*- and −*trans*-**10** in an *endo*/*exo* ratio of 60:40.

Scheme 3. Comparison of the *Exo*-Stereocontrol Aptitude of $(Et_3Si)_2CH$ with Et_3SiCH_2 and R_3Si Groups Using 1e, 9, 11a, and 11b



Scheme 4. Conformational Analysis of Dienes 1e and 9 by Their NOE Experiments



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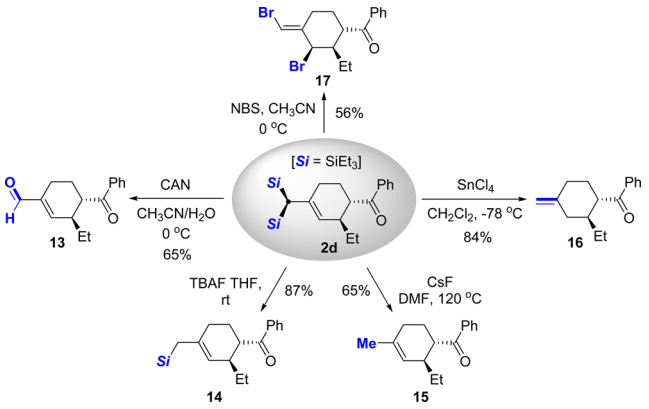
Diverse Functionalization of the Geminal Bis(silyl) Group. In addition to controlling the *exo*-selectivity of the D−A reaction, the geminal bis(silane) also made the reaction a versatile starting point for further transformations (Scheme 5).

Scheme 5. Functionalization of the Geminal Bis($SiEt_3$) Group in 2d



For example, the product **2d** was oxidized by CAN to give enal **13** in 65% yield.[32] TBAF-promoted monodesilylation furnished allylsilane **14** in 87% yield; removal of two silyl groups using CsF generated **15** containing an *endo*-cyclic double bond, while removal of two silyl groups using $SnCl_4$ led to **16** containing an *exo*-cyclic double bond. The reaction of **2d** with 2.0 equiv of NBS led to dibromination, which afforded **17** in 56% yield with excellent 2,3-*cis* diastereo- and *E*-configurational control.

CONCLUSION

In summary, the unique steric effect of geminal bis(silane) has been discovered to achieve an *exo*-selective intermolecular Diels−Alder reaction of geminal bis(silyl) dienes with α,β-unsaturated carbonyl compounds. The approach forms *ortho*−*trans* cyclohexenes in good yields with high regio- and *exo*-selectivity as well as high enantioselectivity in some asymmetric cases. The results from control experiments indicate the superiority of $(R_3Si)_2CH$ over R_3SiCH_2 and R_3Si groups for the *exo*-stereocontrol. The conformational studies of dienes suggest that geminal bis(silane) effectively shields both sides of the diene moiety to ensure the *exo*-selectivity. The products can be transformed into diverse synthons by appropriately functionalizing the geminal bis(silane). Applications of this methodology in the synthesis of natural products containing *ortho*−*trans* cyclohexene and cyclohexane rings are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09689.

Experimental procedures and spectra data for products (PDF)

Detailed information on preparing crystals of **2g** suitable for X-ray diffraction studies has been provided on Page S20. More information on CIF file of **2g** has been provided in Table X-ray/**2g** on page S20-S21 (CIF)

Detailed information on preparing crystals of **4** suitable for X-ray diffraction studies has been provided on Page S34. More information on CIF file of **4** has been provided in Table X-ray/**4** on page S34-S35 (CIF)

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Notes

The authors declare no competing financial interest.

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(16) Diene **1a** was synthesized in 78% yield by a Takai-Utimoto type olefination of 1,1-diidodopropane and geminal bis($SiEt_3$) enal, which was prepared from commercial available propargyl alcohol by four steps on gram-scale in an overall yield of 41%. This process was also used to prepare **1b** and **1c**. Dienes **1d**−**1o** were synthesized from the corresponding geminal bis(sily) enal by Horner−Wadsworth−Emmons reaction and other transformations. For the synthesis of geminal bis(sily) aldehyde and enal, see: (a) Song, Z. L.; Lei, Z.; Gao, L.; Wu, X.; Li, L. J. *Org. Lett.* **2010**, *12*, 5298. (b) Gao, L.; Lin, X. L.; Lei, J.; Song, Z. L.; Lin, Z. *Org. Lett.* **2012**, *14*, 158. For the Takai-Utimoto type olefination, see: (c) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951 See Supporting Information for more details of the preparation of **1a**−**1o**..

(17) Despite that 0.2 equiv of Et_2AlCl was effective to give **2a** in 80% yield, 0.6 equiv appeared to be the optimal loading for reactions with other dienophiles.

(18) Determination of the *trans*-stereochemistry of **2a** by its NOE experiments proved being impractical due to severe overlaps of the signals in the upfield of the ^1H NMR spectra.

(19) We preferred the atropisomerism rather than interconversion between the two half-chair conformers based on the following considerations: (1) One of the half-chair conformers would have both Et and PhCO groups adopting the unfavorable pseudodiaxial orientation. (2) Existence of two groups of similar signals in the ^1H NMR spectra of **2c-Ph** at 30 °C implies that these two mixtures most likely have the same ring conformation.

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(22) The signal of H^2 in the *trans*-isomer generally appears as a singlet, while the signal of the equivalent proton in the *cis*-isomer exists as a doublet of ∼5.0 Hz and is generally 0.2 ppm downfield (see ^1H NMR spectral copies of **2a**, **2b**, **2e**, and **2j** in Supporting Information). One exception was observed in the ^1H NMR spectra of **2h**, in which the signal of H^2 shows as as a doublet of 4.0 Hz. The *trans*-stereochemistry of **2h** was subsequently confirmed by its NOE experiment.

(23) Alcohol **4** was prepared by elaborating the product obtained from the reaction of diene **1e** with α-methyl acrylophenone. See Supporting Information for details. CCDC 1413277 [**4**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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