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Asymmetric [4+2] cycloadditions employing 1,3-dienes derived from (*R*)-4-*t*-butyldimethyl-silyloxy-2-cyclohexen-1-one

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ABSTRACT

1,3-Dienes derived from (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclohexen-1-one react with activated dienophiles to form predominately (or sometimes exclusively) *syn*/*endo* products. These controlled [4+2] cycloadditions increase the asymmetric complexity from one asymmetric center in the starting material to five asymmetric centers in the products in a single step, and provide a powerful approach for the asymmetric synthesis of compounds containing the bicyclo[2.2.2]octanone carbon skeleton.

(*R*)-4-*t*-Butyldimethylsilyloxy-2-cyclohexen-1-one **1** and its (*S*)-isomer are very useful chiral building blocks and have been widely used in organic synthesis.[1] The advantage of using this compound as a starting material is due to its excellent diastereoselectivity in conjugate additions since all stereochemistry is introduced by communication from the stereogenic center at the C-4 position of **1**.

Recently, we reported for the first time that the cross-conjugated dienolate **2** derived from **1** can be employed in the double Michael reaction for the asymmetric synthesis of a highly functionalized bicyclo[2.2.2]octanone **4** (Scheme 1).[2] The reaction was exclusively *endo* selective and occurred at the face *anti* to the bulky TBSO group to afford only one of the eight possible diastereomers. We have also shown that the combination of the double Michael reaction and an anionic Oxy-cope rearrangement is a powerful approach for the synthesis of the *cis*-decalin portion of the antitumor natural product superstolide A.[2]

The successful double Michael reaction prompted investigation of [4+2] cycloadditions. Although the (*S*)-isomer of **1** was used as a dienophile in Diels–Alder reactions,[1q,s] [4+2] cycloadditions using 1,3-dienes derived from **1** or its (*S*)-isomer have never been reported.

Compound **1** was converted to 1,3-diene **5** in 87% yield (Scheme 2). To our surprise, [4+2] cycloaddition between **5** and various α,β-unsaturated compounds proved to be very difficult because **5** was quite unreactive. In addition, **5** was prone to decomposition and aromatization in the presence of a Lewis acid. Therefore, the desired [4+2] adducts were never detected. To accelerate the reaction, more reactive dienophiles were needed.

We were delighted to observe that the [4+2] cycloaddition between 1,3-diene **5** and *N*-benzyl maleimide **7** gave compounds **8**-*syn* (51%) and **8**-*anti* (43%), which were confirmed by 1D and 2D NMR analysis (Scheme 3). The reaction was exclusively *endo* selective, but the facial selectivity was poor. Surprisingly, the major product **8**-*syn* was formed when *N*-benzyl maleimide **7** approached 1,3-diene **5** from the same face of TBSO substituent on the diene plane, which was opposite to what was observed in the double Michael reaction.[2]

The stereochemical outcome of this reaction is similar to various [4+2] cycloadditions involving 1,3-dienes bearing an OR group at the allylic stereogenic center,[3] and is proposed to be controlled by the Cieplak effect.[4] The preferential *syn* facial selectivity seen in our system was also observed by others when compound **1** was employed as a dienophile.[1q,1s] However, the *syn* versus *anti* pi-facial selectivity seen during cycloaddition for such systems appears to depend on many factors including the specific diene and the reactivity of the dienophile.[5]

To improve the facial selectivity the effect of various enol ether substituents was investigated (Scheme 4). It was discovered that the [4+2] cycloaddition between **9** and **7** provided exclusively *endo* products with the facial selectivity being improved to 4.3:1 (*syn*:*anti*), and the combined yield for **10**-*syn* and **10**-*anti* was 95%. To the best of our knowledge, this is the first successful application of a 1,3-diene derived from **1** in a [4+2] cycloaddition.

Eight different solvents were screened to determine the solvent effect on the facial selectivity of the asymmetric [4+2] cycloaddition between 1,3-diene **9** and *N*-benzyl maleimide **7**. The results are summarized in Table 1. It was found that the facial selectivity (*syn*:*anti*) was higher in solvents such as benzene, methylene chloride, and chloroform. Reactions in polar solvents such as acetone, methanol, and acetonitrile gave lower facial selectivity. The preferred choice of solvent is benzene or methylene chloride since chloroform may contain a trace amount of acid that might promote the formation of side products.

Seven reactive dienophiles were chosen to study the scope and limitation of this asymmetric [4+2] cycloaddition, and the results

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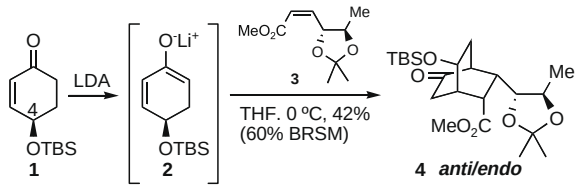
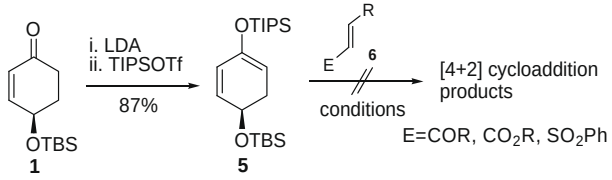
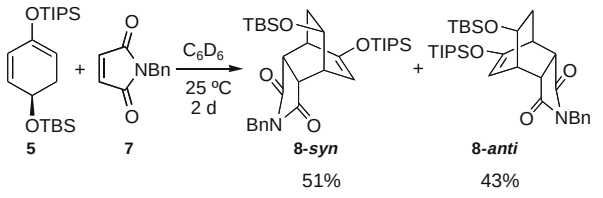


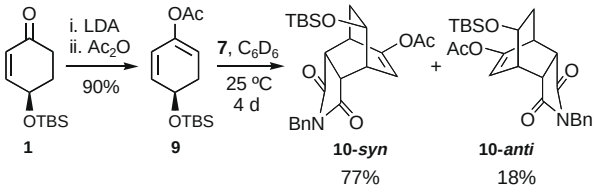
Scheme 1. Asymmetric double Michael reaction.



Scheme 2. Failed [4+2] cycloaddition.



Scheme 3. [4+2] Cycloaddition.



Scheme 4. A facial and stereoselective [4+2] cycloaddition.

Table 1
Solvent effect on the facial selectivity (**10**-*syn*:**10**-*anti*)

Entry	Solvent	**10**-*syn*:**10**-*anti*[a]
1	$CDCl_3$	4.5:1
2	C_6D_6	4.2:1
3	CD_2Cl_2	4.0:1
4	Et_2O	3.3:1
5	Acetone-d_6	2.5:1
6	THF	2.0:1
7	CD_3OD	2.0:1
8	CD_3CN	1.7:1

[a] The *syn*:*anti* ratio was calculated based on the integration of ^{1}H NMR spectra of the mixture of the [4+2] adducts. The reaction was run at 25 °C under argon.

Table 2
Asymmetric [4+2] cycloadditions between 1,3-diene **9** and various reactive dienophiles

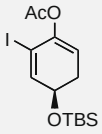
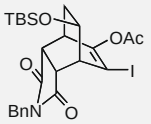
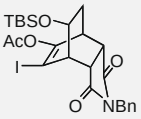
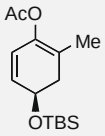
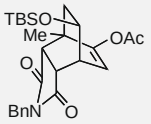
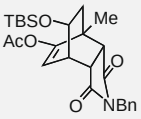
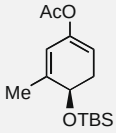
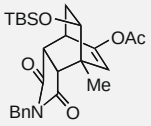
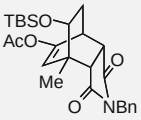
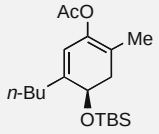
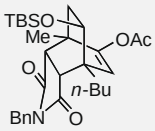
Entry	Diene	Dienophile	Products[a,b]	
1	**9**	**11**	**12-*syn*** 81%	**12-*anti*** 14%
2	**9**	**13**	**14-*syn*** 77%	**14-*anti*** 17%
3	**9**	**15**	**16-*syn*** 87%[c]	**16-*anti*** 13%[c]
4	**9**	**17**	**18-*syn*** 98%	
5	**9**	**19**	No reaction	
6	**9**	**20**	**21-*syn*** 73%	**21-*anti*** 16%
7	**9**	**22**	**23-*syn*** 66%	**23-*anti*** 18%

[a] All reactions were run in either CH_2Cl_2 or C_6H_6 at 25 °C for 3–4 days under argon unless otherwise stated.
[b] All yields were isolated yields unless otherwise stated. All compounds were fully characterized.
[c] The yields were calculated based on the integration of ^{1}H NMR spectrum of the crude mixture of two [4+2] adducts.

are summarized in Table 2. All reactions provided exclusive *endo* products with the facial selectivity favoring the *syn* product, and the yields for the *syn*/*endo* products were very good. The reaction between **9** and **15** had to be carried out in the presence of 0.1 equiv of 2,6-lutidine (Table 2, entry 3), otherwise traces of maleic acid promoted formation of the aromatized side product, phenyl acetate. The yields for **16**-*syn* and **16**-*anti* were not isolated yields. This was because both products contain the anhydride moiety, which decomposed on silica gel during flash column chromatography, resulting in lower yields. Since the reaction was very clean, and only these two products were detected in its unpurified ^{1}H NMR spectrum, and therefore spectral integration of the respective products was used to reflect the real ratio of **16**-*syn* and **16**-*anti*.

Compound **17** was a much more reactive dienophile, and the reaction was complete in 15 min at −20 °C to afford exclusively **18**-*syn* with nearly quantitative yield (Table 2, entry 4). On the other hand, no desired [4+2] cycloaddition product was isolated

Table 3
Asymmetric [4+2] cycloadditions between *N*-benzyl maleimide **7** and various 1,3-dienes derived from compound **1**

Entry	Diene	Dienophile	Products[a,b]	
1	 **24**	**7**	 **25-*syn*** 79%	 **25-*anti*** 17%
2	 **26**	**7**	 **27-*syn*** 81%	 **27-*anti*** 14%
3	 **28**	**7**	 **29-*syn*** 83%	 **29-*anti*** 13%
4	 **30**	**7**	 **31-*syn*** 87%	

[a] All reactions were run in either CH_2Cl_2 or C_6H_6 at 25 °C for 3–4 days under argon.
[b] All yields were isolated yields. All compounds were fully characterized.

after **9** and the relatively less reactive **19**[6] were heated in a sealed tube at 120 °C (Table 2, entry 5). The reaction between **9** and **20** was carried out at 60 °C in a sealed tube whereas the reaction between **9** and **22** had to be heated to 100 °C in a sealed tube. These experiments have shown that various active dienophiles are suitable substrates for this asymmetric [4+2] cycloaddition.

We then turned our attention to the scope of chiral 1,3-dienes. Four chiral 1,3-dienes **24**,[7] **26**,[8] **28**,[9] and **30**[10] were prepared from compound **1** and investigated in the asymmetric [4+2] cycloaddition with *N*-benzyl maleimide **7** (Table 3).

Entry 1 indicates that an iodo group at the 3 position of the 1,3-diene had no effect on the facial selectivity (Table 3, entry 1). However, introducing a methyl group at either the 1 or 4 position of the 1,3-diene slightly improved the facial selectivity, and the yields of the major *syn* adducts were also improved to over 80% (Table 3, entries 2 and 3). These results were consistent with the reaction between 1,3-diene **30** and **7** (Table 3, entry 4). The [4+2] adduct **31**-*syn* was isolated in 87%, and the *anti* product was not detected. It should be noted that among four newly created stereogenic centers in **31**-*syn* two of them are bridgehead quaternary carbons, which are difficult to construct.

In summary, a facial- and stereoselective [4+2] cycloaddition employing 1,3-dienes derived from (*R*)-4-*t*-butyldimethyl-silyloxy-2-cyclohexen-1-one **1** has been developed. We have demonstrated for the first time that these 1,3-dienes can react with activated dienophiles to form predominately (or sometimes exclusively) *syn*/*endo* products. These highly controlled [4+2] cycloadditions can increase the asymmetric complexity from one asymmetric center in the starting material to five asymmetric centers in the products in a single step, and provide a powerful approach for the asymmetric synthesis of compounds containing the bicyclo[2.2.2]octanone carbon skeleton. Application of this new method to total synthesis of natural products is underway, and will be reported in due course.

Acknowledgments

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References and notes

1. (a) Nicolaou, K. C.; Li, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6579; (b) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1935; (c) Nicolaou, K. C.; Li, H.; Nold, A. L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356; (d) Barfoot, C. W.; Burns, A. R.; Edwards, M. G.; Kenworthy, M. N.; Ahmed, M.; Shanahan, S. E.; Taylor, R. J. K. *Org. Lett.* **2008**, *10*, 353; (e) Xia, J.; Brown, L. E.; Konopelski, J. P. *J. Org. Chem.* **2007**, *72*, 6885; (f) Wilson, E. M.; Trauner, D. *Org. Lett.* **2007**, *9*, 1327; (g) Dirat, O.; Elliott, J. M.; Jelley, R. A.; Jones, A. B.; Reader, M. *Tetrahedron Lett.* **2006**, *47*, 1295; (h) Matsuzawa, M.; Kakeya, H.; Yamaguchi, J.; Shoji, M.; Onose, R.; Osada, H.; Hayashi, Y. *Chem. Asian J.* **2006**, *1*, 845; (i) Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6931; (j) Williams, D. R.; Kammler, D. C.; Donnell, A. F.; Goundry, W. R. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 6715; (k) Rodeschini, V.; Van de Weghe, P.; Salomon, E.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2005**, *70*, 2409; (l) Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773; (m) Evarts, J. B.; Fuchs, P. L. *Tetrahedron Lett.* **2001**, *42*, 3673; (n) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166; (o) Lopez-Pelegrin, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, *6*, 1917; (p) Rucker, M.; Bruckner, R. *Tetrahedron Lett.* **1997**, *38*, 7353; (q) Sas, B.; De Clercq, P.; Vandewalle, M. *Synlett* **1997**, 1167; (r) Witschel, M. C.; Bestmann, H. J. *Tetrahedron Lett.* **1995**, *36*, 3325; (s) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 387; (t) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599; (u) Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17; (v) Kitahara, T. *Tetrahedron* **2003**, *59*, 1773.
2. Hua, Z.; Yu, W.; Su, M.; Jin, Z. *Org. Lett.* **2005**, *7*, 1939.
3. (a) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510; (b) Holmberg, K.; Kirudd, H.; Westin, G. *Acta Chem. Scand., Ser. B.* **1974**, *28*, 913; (c) Gillard, J. R.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1439; (d) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1988**, *110*, 4074; (e) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663.
4. Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265. and references cited therein.
5. Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.
6. (a) DePuy, C. B.; Zaweski, E. F. *J. Am. Chem. Soc.* **1959**, *81*, 4920; (b) Ramesh, N. G.; Bakkeren, F. J. A. D.; Groot, D.; Passamonti, U.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **2001**, *57*, 9877.
7. *Synthesis of compound* **24**: compound **1** reacted with I_2 in the presence of pyridine to provide (*R*)-4-(*t*-butyldimethylsilyloxy)-2-iodo-2-cyclohexen-1-one in 63% yield, which was transformed to **24** in 71% yield via the same procedure used in the preparation of **9**.
8. *Synthesis of compound* **26**: compound **1** reacted with LDA followed by the addition of MeI to give (4*R*)-4-(*t*-butyldimethylsilyloxy)-6-methyl-2-cyclohexen-1-one in 66% yield, which was transformed to **26** in 92% yield via the same procedure used in the preparation of **9**.
9. *Synthesis of compound* **28**: conjugate addition of lithium cyano methyl cuprate to compound **1** in the presence of TMSCl provided silyl enol ether that underwent Saegusa oxidation to give (4*R*)-3-methyl-4-(*t*-butyldi- methylsilyloxy)-2-cyclohexen-1-one in 68% yield, which was transformed to **28** in 84% yield via the same procedure used in the preparation of **9**.
10. *Synthesis of compound* **30**: conjugate addition of lithium cyano *n*-butyl cuprate to compound **1** in the presence of TMSCl provided silyl enol ether that underwent Saegusa oxidation to give (4*R*)-3-*n*-butyl-4-(*t*-butyldimethyl-silyloxy)-2-cyclohexen-1-one in 70% yield. Treatment with LDA followed by the addition of MeI afforded (4*R*)-3-*n*-butyl-4-(*t*-butyldimethylsilyloxy)-6-methyl-2-cyclohexen-1-one in 82% yield, which was transformed to **30** in 70% yield via the same procedure used in the preparation of **9**.