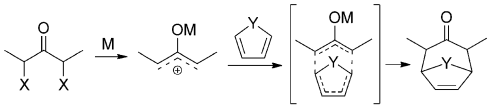
Synthetic Methods

DOI: 10.1002/anie.201207427

# Asymmetric (4+3) Cycloadditions of Enantiomerically Enriched Epoxy Enolsilanes**

*Brian Lo, Sarah Lam, Wing-Tak Wong, and Pauline Chiu**

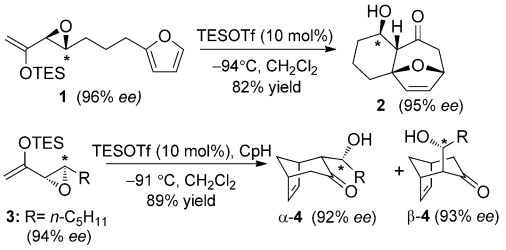
The (4+3) cycloaddition reaction is a direct and efficient method to construct seven-membered carbocycles.[1] Isoelectronic with the Diels–Alder reaction, the classical mechanistic understanding of this reaction is that an allyl cation dienophile, contributing two electrons, undergoes cycloaddition with the diene (Scheme 1). Cyclic dienes are commonly




***Scheme 1.*** Classical mechanism of the (4+3) cycloaddition. M = metal.

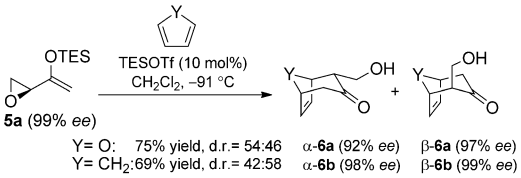
employed, thus resulting in bicyclic adducts which are useful synthetic intermediates.[2] Compared with the (4+2) reaction, however, asymmetric (4+3) cycloadditions remain underdeveloped.[3] Other than two examples of asymmetric catalysis,[4] the majority of asymmetric versions of (4+3) cycloadditions rely on chiral auxiliaries or incorporate chiral elements into the reacting cation or the diene.[5,6]

On the basis of the seminal work by Eguchi et al.,[7] we have developed a silyl-triflate-catalyzed intramolecular (4+3) cycloaddition reaction of furan-tethered epoxy enolsilanes such as **1**, and it affords the cycloadduct **2** in excellent yield and diastereoselectivity (Scheme 2).[8] The corresponding intermolecular (4+3) cycloadditions with epoxy enolsilanes such as **3a** have also been observed to generate *endo* and *exo* cycloadducts with facial selectivity (Scheme 2).[9] In both cases, the reactions with optically active epoxy enolsilanes generate cycloadducts with high conservation of the enantiomeric excess.[8,10] Each of these cycloadducts has inherited one stereocenter (* in Scheme 2) from the epoxide precursor, so the observed selectivity could be understood as a diastereoselective cycloaddition of chiral oxyallyl cations, similar to the previously reported asymmetric (4+3) cycloadditions involving chiral cations.[5]




***Scheme 2.*** Diastereoselective (4+3) cycloadditions. TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

In contrast, for intermolecular (4+3) cycloadditions of simpler enolsilanes such as the optically pure **5a** (Scheme 3), the corresponding oxyallyl cation would be expected to be




***Scheme 3.*** Asymmetric (4+3) cycloaddition of **5a**.

devoid of any stereochemical elements, and should engender racemic cycloadducts. However, we have observed that the enantiomeric purity was, in fact, highly conserved in the cycloaddition. The treatment of **5a**, having a 99% *ee*, with a catalytic amount of TESOTf in the presence of furan and a subsequent $Et_3N{\cdot}3HF$ desilylative workup resulted in *endo* and *exo* diastereomers with 92 and 97% *ee*, respectively.[11] Cycloaddition with the more reactive cyclopentadiene afforded products with even higher enantiomeric excesses, thus showing essentially a complete retention of chirality.

The absolute stereochemistry of the cycloadducts α-**6a** and β-**6a** were determined by X-ray crystallographic analysis of their (−)-camphanoyl and *p*-bromobenzoyl ester derivatives, **7a** and **7b**, respectively (see the Supporting Information for structures).[12] The observed absolute stereochemistry implies that carbon–carbon bond formation occurred with inversion of stereochemistry at the epoxide. The high degree of enantiomeric excess observed in this (4+3) cycloaddition shows that the reaction did not proceed through the putative achiral oxyallyl cation intermediate, which would necessitate that most, if not all, of the chiral information would be lost.[13]

We examined the generality of this phenomenon and the scope of this reaction (Table 1). The epoxy enolsilane **5a**

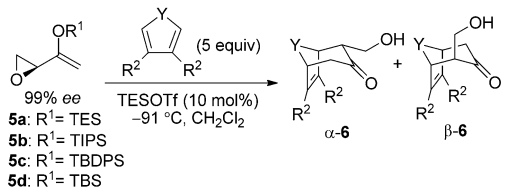
[*] B. Lo, S. Lam, Prof. W.-T. Wong, Prof. P. Chiu
Department of Chemistry, The University of Hong Kong
Pokfulam Road (Hong Kong)
E-mail: pchiu@hku.hk

[**] We thank Dr. S. K. Lam for first suggesting experiments using optically pure epoxy enolsilanes. Support from the Research Grants Council of Hong Kong (GRF HKU 7015/10P) and The University of Hong Kong are gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207427.

underwent cycloaddition with a number of dienes with high to very high degrees of transfer of chirality (Table 1, entries 1–4), and the most reactive diene, cyclopentadiene, afforded the

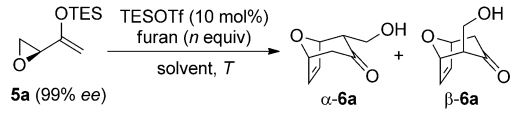
***Table 1:*** Scope of the asymmetric (4+3) cycloaddition.




| Entry | 5 | Diene | | Yield [%][a] | d.r.[b] | *ee* [%][c] | |
|---|---|---|---|---|---|---|---|
| | | Y | $R^2$ | | (α-**6**/β-**6**) | α-**6** | β-**6** |
| 1 | **5a** | O | H | **6a**: 75 | 54:46 | 92 | 97 |
| 2 | **5a** | $CH_2$ | H | **6b**: 69 | 42:58 | 98 | 99 |
| 3[d] | **5a** | O | Me | **6c**: 75 | 66:34 | 94 | 94 |
| 4[d] | **5a** | $(CH_2)_2C$ | H | **6d**: 40 | 73:27 | 99 | 99 |
| 5 | **5b** | O | H | **6a**: 60 | 59:41 | 95 | 97 |
| 6 | **5b** | $CH_2$ | H | **6b**: 60 | 59:41 | 98 | 99 |
| 7[d] | **5c** | O | H | **6a**: 58 | 44:56 | 82 | 97 |
| 8 | **5c** | $CH_2$ | H | **6b**: 55 | 55:45 | 97 | 97 |
| 9 | **5d** | $CH_2$ | H | **6b**: 56 | 52:48 | 98 | 98 |

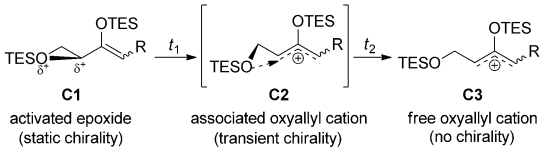
[a] Yield of isolated product. [b] Determined by $^1$H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 20 mol% TESOTf used. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

***Table 2:*** Effect of the reaction conditions on the transfer of chirality.




| Entry | *T* [°C] | Solvent | *n* | Yield [%][a] | d.r.[b] (α-**6a**/β-**6a**) | *ee* [%][c] α-**6a** | β-**6a** |
|---|---|---|---|---|---|---|---|
| 1 | −91 | $CH_2Cl_2$ | 5 | 75 | 54:46 | 92 | 97 |
| 2[d] | −91 | $CH_2Cl_2$ | 5 | 68 | 55:45 | 89 | 97 |
| 3 | −78 | $CH_2Cl_2$ | 5 | 62 | 54:46 | 90 | 96 |
| 4 | −40 | $CH_2Cl_2$ | 5 | 51 | 55:45 | 83 | 90 |
| 5 | −78 | $EtNO_2$ | 5 | 58 | 53:47 | 71 | 85 |
| 6 | −40 | $EtNO_2$ | 5 | 51 | 56:44 | 60 | 76 |
| 7 | −78 | $CH_2Cl_2$ | 1.5 | 15 | 54:46 | 89 | 94 |
| 8 | −78 | $CH_2Cl_2$ | 30 | 69 | 51:49 | 92 | 96 |
| 9 | −78 | furan | >30 | 67 | 40:60 | 93 | 97 |

[a] Yield of isolated products. [b] Determined by $^1$H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase. [d] TfOH used instead of TESOTf.




***Scheme 4.*** Possible electrophilic species in the (4+3) cycloaddition.

highest enantiomeric excesses. The nature of the silyl groups on the enol ethers **5a–d** did not have any significant effect on the enantioselectivity of the reaction, and cycloadducts with excellent *ee* values were uniformly obtained (Table 1, entries 5–9).

We then investigated the effect of the reaction conditions on the conservation of enantiomeric purity in this cycloaddition (Table 2). The use of either TESOTf or TfOH as a catalyst to activate the epoxide resulted in enantioselective reactions (Table 2, entries 1 and 2). Cycloadditions at −91 or −78 °C afforded products with similarly high enantiomeric excesses, but an additional increase in temperature resulted in a decrease in the cycloaddition yield as well as the *ee* value (Table 2, entries 3 and 4). The use of the more polar $EtNO_2$ as a reaction medium resulted in a 10–20 % erosion in enantioselectivity (Table 2, entries 5 and 6). Increasing the amount of the diene improves both the yield and the *ee* value of the products (Table 2, entries 3, 7–9). Generally, the *exo* cycloadducts (β-**6**) were obtained with higher *ee* values than the *endo* cycloadducts (α-**6**).

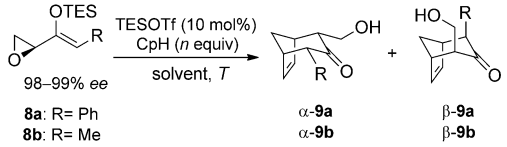
These results imply that a chiral electrophile is undergoing reaction with the diene under these reaction conditions.[14] The possibility of retaining the stereochemical integrity in the oxyallyl cation precursor and utilizing it in the (4+3) cycloaddition has not been reported or exploited previously. At this point, it is unclear which species along the continuum in the evolution of the electrophile is being intercepted by the diene to proceed to the cycloaddition (Scheme 4). It may be an epoxy enolsilane activated by a Lewis acid (**C1**), a species which then reacts with the diene in an $S_N2$-like manner. The electrophilic species could also be the oxyallyl cation **C2**, which possesses planar chirality because of the triethylsiloxy group which remains electrostatically associated with one face of the activated species **C1**. The chiral **C2** would eventually undergo racemization to the dissociated, achiral oxyallyl cation **C3**. This explanation is consistent with our observations that increasing the temperature or polarity of the medium, both of which favor dissociation, indeed resulted in a diminished enantioselectivity in the reaction. The use of a super-stoichiometric amount of the diene was found to increase the *ee* value of the cycloadducts, presumably by increasing the rate of reaction by intercepting either the chiral species **C1** or **C2** before they racemize to **C3**.[15]

For epoxy enolsilanes where $R \neq H$ (Scheme 4), the additional substituent should favor allyl cation formation, and $t_1$ should decrease. Stabilization of the cation should also decrease the electrostatic interactions which maintain the chirality in **C2** and promote the formation of achiral **C3**, therefore also decreasing $t_2$. Hence we should expect to find that when $R \neq H$, the *ee* value of the cycloadducts would decrease. The experiments in Table 3 sought to verify and to examine the extent of the erosion of chirality transfer.

Indeed, the substituted epoxy enolsilanes **8a** and **8b** underwent cycloaddition with greatly diminished enantioselectivities in the range of 18–29 % *ee* (Table 3, entries 1–3). As previously observed, the enantioselectivity could be enhanced by using a large excess of the cyclopentadiene (CpH), and was recovered to 63–72 % *ee* (Table 3, entries 3 and 4). Alternatively, the *ee* value is also significantly improved to 59–64 % by using the same amount of diene, but conducting the reaction in methylcyclohexane, a more nonpolar medium

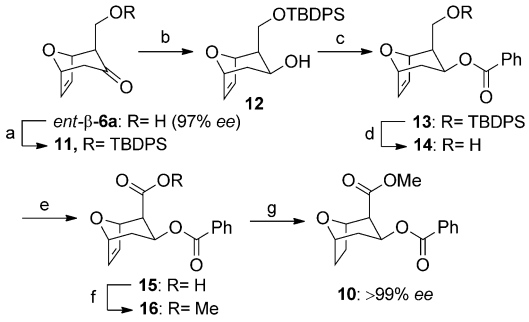
  

***Table 3:*** (4+3) Cycloadditions of substituted epoxy enolsilanes **8**.




| Entry | $T$ [°C] | **8** | Solvent | $n$ | Yield [%][a] | d.r.[b] (α/β) | *ee* [%][c] α | *ee* [%][c] β |
|---|---|---|---|---|---|---|---|---|
| 1 | −91 | **8a** | $CH_2Cl_2$ | 5 | **9a**: 97 | 44:56 | 20 | 18 |
| 2 | −91 | **8b** | $CH_2Cl_2$ | 5 | **9b**: 52 | 53:47 | 25 | 29 |
| 3 | −78 | **8b** | $CH_2Cl_2$ | 5 | **9b**: 51 | 53:47 | 24 | 22 |
| 4 | −78 | **8b** | $CH_2Cl_2$ | 30 | **9b**: 61 | 52:48 | 63 | 72 |
| 5 | −91 | **8b** | MeCy | 5 | **9b**: 47 | 55:45 | 59 | 64 |
| 6 | −78 | **8b** | CpH | >30 | **9b**: 69 | 56:44 | 87 | 90 |

[a] Yield of isolated products. [b] Determined by $^1$H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase.




***Scheme 5.*** Asymmetric synthesis of the DAT inhibitor **10**. Reaction conditions: a) TBDPSCl, imidazole, DMAP, $CH_2Cl_2$, 96%. b) $SmI_2$, *i*PrOH, MeCN, 87%, d.r. = 7:1. c) BzCl, pyridine, DMAP, $CH_2Cl_2$, 94%. d) TBAF, AcOH, THF, 99%. e) $CrO_3/H_5IO_6$, MeCN (containing $H_2O$), 88%. f) MeI, $K_2CO_3$, acetone, 91%. g) $H_2$, 10% Pd/C, MeOH, 98%. Bz = benzoyl, DMAP = 4-(dimethylamino)pyridine, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

(Table 3, entries 2 and 5) in which the electrostatic associations are maximized and the lifetime of either **C1** or **C2** are prolonged. Gratifyingly, by using cyclopentadiene as the solvent, exploiting both the availability of the diene as well as the effect of a nonpolar medium, the enantioselectivity was largely restored from 22–24% to 87–90% *ee* (Table 3, entries 3 and 6).

As a synthetic method, this reaction represents a unique example of an asymmetric (4+3) cycloaddition in which the chiral information of the epoxide has been directly translated to the absolute stereochemistry in the cycloadduct, without the need of any additional chiral elements or external chiral catalysts. The cycloadducts are obtained as a pair of enantiomerically enriched diastereomers, which can be valuable chiral scaffolds for synthesis. To illustrate, the oxatropane **10** is a dopamine transporter (DAT) inhibitor designed by Kozikowski et al. as a possible chemotherapeutic for cocaine addiction.[16] The original synthesis relied on the desymmetrization of a *meso* oxabicyclic ketone by deprotonation using a stoichiometric amount of a chiral lithium amide,[17] which limited the enantiomeric purity of **10** thus obtained (≤85% *ee*). However, using *ent*-β-**6a**, with a 97% *ee* from the cycloaddition of *ent*-**5a**, in stereoselective manipulations as shown in Scheme 5 ultimately yielded **10** in 53% overall yield and with a greater than 99% *ee*.

The optically enriched (4+3) cycloadducts obtained from a $[_\pi4+_\pi2]$ cycloaddition of the transiently chiral oxyallyl cation **C2** (Scheme 4) are indistinguishable from products of sequential C–C bond formations initiated by an $S_N2$-like alkylation of the diene by the activated epoxide **C1**, which has the formal outcome of a (4+3) cycloaddition.[18] The distinguishing characteristic would be whether the reactive intermediate has achieved full trigonalization at the time of the first bond formation with the diene, a result which could only be delineated by computational chemistry. These results merit further examination and will certainly add to our evolving understanding of the mechanism and stereoelectronic forces at play in this cycloaddition.[19]

In summary, we have shown that there is a higher degree of organization and stereochemical integrity in the electrophilic species undergoing (4+3) cycloaddition than previously anticipated. The catalytic (4+3) cycloaddition with optically pure epoxy enolsilanes affords cycloadducts with up to 99% *ee* under mild reaction conditions. Its utility has been highlighted by an application to the asymmetric synthesis of the DAT inhibitor **10** in high optical purity. Our ongoing studies are probing the mechanism of this reaction by experiment and computations, and using the optically pure cycloadducts in various synthetic applications.

Received: September 14, 2012
Published online: October 25, 2012

**Keywords:** allylic compounds · cycloaddition · heterocycles · stereoselectivity · synthetic methods

[1] Selected reviews on the (4+3) cycloaddition: a) H. M. R. Hoffmann, *Angew. Chem.* **1984**, *96*, 29–48; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1–88; b) M. Harmata, *Tetrahedron* **1997**, *53*, 6235–6280; c) J. H. Rigby, F. C. Pigge, *Org. React.* **1997**, *51*, 351–478; d) M. Harmata, *Chem. Commun.* **2010**, *46*, 8886–8903; e) M. Harmata, *Chem. Commun.* **2010**, *46*, 8904–8922; f) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812–3822.

[2] a) P. Chiu, M. Lautens, *Top. Curr. Chem.* **1997**, *190*, 1–85; b) W. Zhao, *Chem. Rev.* **2010**, *110*, 1706–1745.

[3] Reviews on asymmetric (4+3) cycloadditions: a) I. V. Hartung, H. M. R. Hoffmann, *Angew. Chem.* **2004**, *116*, 1968–1984; *Angew. Chem. Int. Ed.* **2004**, *43*, 1934–1949; b) M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297–2306.

[4] Catalytic asymmetric (4+3) cycloadditions: a) J. Huang, R. P. Hsung, *J. Am. Chem. Soc.* **2005**, *127*, 50–51; b) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059.

[5] Selected examples of chiral cations in (4+3) cycloadditions: a) A. S. Kende, H. Huang, *Tetrahedron Lett.* **1997**, *38*, 3353–3356; b) S. Y. Cho, J. C. Lee, J. K. Cha, *J. Org. Chem.* **1999**, *64*, 3394–3395; c) C. B. W. Stark, S. Pierau, R. Wartchow, H. M. R. Hoffmann, *Chem. Eur. J.* **2000**, *6*, 684–691; d) H. Xiong, R. P. Hsung, C. R. Berry, C. Rameshkumar, *J. Am. Chem. Soc.* **2001**, *123*, 7174–7175; e) A. G. Myers, J. K. Barbay, *Org. Lett.* **2001**, *3*, 425–428; f) D. I. MaGee, E. Godineau, P. D. Thornton, M. A. Walters, D. J. Sponholtz, *Eur. J. Org. Chem.* **2006**, 3667–3680.

[6] Selected examples of chiral dienes in (4+3) cycloadditions: a) M. Lautens, R. Aspiotis, J. Colucci, *J. Am. Chem. Soc.* **1996**, *118*,

10930 – 10931; b) A. M. Montaña, P. M. Grima, *Tetrahedron Lett.* **2002**, *43*, 2017 – 2021; c) A. G. Lohse, R. P. Hsung, M. D. Leider, S. K. Ghosh, *J. Org. Chem.* **2011**, *76*, 3246 – 3257.

[7] M. Ohno, K. Mori, T. Hattori, S. Eguchi, *J. Org. Chem.* **1990**, *55*, 6086 – 6091.

[8] W. K. Chung, S. K. Lam, B. Lo, L. L. Liu, W.-T. Wong, P. Chiu, *J. Am. Chem. Soc.* **2009**, *131*, 4556 – 4557.

[9] B. Lo, P. Chiu, *Org. Lett.* **2011**, *13*, 864 – 867.

[10] S. Lam, B. Lo, W.-T. Wong, P. Chiu, *Asian J. Org. Chem.* **2012**, *1*, 30 – 33.

[11] Desilylation with TBAF results in racemization by converting the less stable β-**6a** to *ent*-α-**6a**, and to a lesser extent, α-**6a** to *ent*-β-**6a**.

[12] CCDC 6885848 (**7a**), 885846 (**7b**) contain 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.

[13] In a cross-over experiment, a mixture of (−)-**5a** having a 99% *ee* and (±)-**8b** reacted with CpH to generate **6b** (97% *ee*) and **9b** (0% *ee*), respectively. In another cross-over experiment, a mixture of (±)-**5a** and (−)-**8b** having a 99% *ee* reacted with CpH to generate **6b** (0% *ee*) and **9b** (29–31% *ee*), respectively. These results show that the transfer of chirality is not the result of an aggregation effect.

[14] Chiral intermediates like **C1** or **C2** can also explain the diastereoselectivities observed in Refs. [8,10].

[15] P. R. Carlier, D. C. Hsu, S. A. Bryson in *Topics in Stereochemistry*, *Vol. 26* (Ed.: R. E. Gawley), **2010**, chap. 2, p. 53 – 92.

[16] a) A. P. Kozikowski, D. Simoni, M. Roberti, R. Rondanin, S. Wang, P. Du, K. M. Johnson, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1831 – 1836; b) D. Simoni, M. Roberti, R. Rondanin, A. P. Kozikowski, *Tetrahedron Lett.* **1999**, *40*, 4425 – 4428.

[17] B. J. Bunn, P. J. Cox, N. S. Simpkins, *Tetrahedron* **1993**, *49*, 207 – 218.

[18] Although some (4+3) cycloadditions have long been recognized to be stepwise processes (Ref. [1a]), there has been less emphasis to define what kind of electrophile is undergoing reaction.

[19] Recent computational and mechanistic studies: a) E. H. Krenske, K. N. Houk, A. G. Lohse, J. E. Antoline, R. P. Hsung, *Chem. Sci.* **2010**, *1*, 387 – 392; b) E. H. Krenske, K. N. Houk, M. Harmata, *Org. Lett.* **2010**, *12*, 444 – 447.