



Published in final edited form as:

Org Lett. 2017 July 21; 19(14): 3703–3706. doi:10.1021/acs.orglett.7b01420.

## Intramolecular Chirality Transfer [2 + 2] Cycloadditions of Allenates and Alkenes

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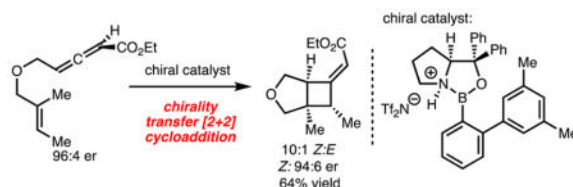
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### Abstract

Intramolecular chirality transfer [2 + 2] cyclo-addition of enantiomerically enriched allenates and alkenes is presented. The use of a chiral catalyst was found to be critical to achieve high levels of diastereoselectivity compared to use of an achiral catalyst. The method developed leads to highly substituted cyclobutanes that would be difficult to prepare by alternative methods.

### Graphical Abstract



### Keywords

Traumatic brain injury; social communication; theory of mind; executive function; speech language pathology

Cyclobutane synthesis by [2 + 2] cycloaddition represents an important class of reaction for chemical synthesis.<sup>1</sup> Despite widespread application of these reactions, enantioselective variants have been slower to develop.<sup>2</sup> Accordingly, our laboratory has taken an interest in

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#### Notes

The authors declare no competing financial interest.

#### ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01420.

Crystallographic data for **S17** (PDB)

Crystallographic data for **S18** (PDB)

Experimental procedures for all compounds and crystallographic data (PDF)

Analytical data for all compounds (PDF)

the development of methods for the enantioselective synthesis of cyclobutanes by [2 + 2] cycloaddition (Scheme 1).

Recently, our laboratory disclosed a method for catalytic enantioselective [2 + 2] cycloaddition of allenates and alkenes.<sup>3</sup> In our efforts to extend the utility of this process, we became interested in developing variants that utilized  $\gamma$ -substituted allenates. This substitution pattern renders the allene chiral and therefore presents the possibility for a chirality-transfer [2 + 2] cycloaddition.<sup>4</sup> This would represent an attractive approach for the synthesis of cyclobutanes, provided the chiral allene can be readily prepared in high enantioselectivity. Several examples of chirality transfer [2 + 2] cycloaddition have been reported.<sup>5</sup> While high chirality transfer has been observed in related chemistry, the use of enantiomerically enriched allenates has not been reported. This would be significant as enantioselective synthesis of allenates is readily achieved by enantioselective isomerization of  $\beta,\gamma$ -unsaturated alkynyl esters.<sup>6,7</sup> Therefore, development of chirality transfer [2 + 2] cycloaddition of allenates and alkenes would be complementary to existing approaches. Herein, we disclose an intramolecular chirality transfer [2 + 2] cycloaddition of allenates and alkenes.<sup>8</sup>

To initiate our studies, the chirality transfer [2 + 2] cycloaddition of allenate **3** was investigated (Scheme 2A). The synthesis of the  $\gamma$ -substituted allenate **3** was accomplished by application of an enantioselective isomerization of non-conjugated alkynyl ketone **2** developed by Tan and coworkers.<sup>6</sup> However, we elected to employ chiral thiourea catalyst **2**<sup>9,10</sup> because it is readily available and delivers allenate **3** in good enantioselectivity (96:4 er). Treatment of chiral allenate **3** with EtAlCl<sub>2</sub> delivered the product in good yield and transfer of chirality, albeit as a 1.4:1 mixture of alkene isomers (Scheme 2A).

Upon determination of the absolute configuration of each alkene isomer, it was revealed that the products were epimeric at the bridgehead positions.<sup>11</sup> The nonselective nature of this reaction can be rationalized by analysis of the putative transition states shown in Scheme 2B. The key difference between the two models is the approach of the tethered alkene on the same face, or opposite face, of the ester unit. Upon coordination of the Lewis acid to the ester group, the steric effects from the ester group are similar in both cases (weak interaction with H or Me), which led to the low diastereoselectivity of the cycloaddition. Computational evaluation (B3LYP/6-31G(d))<sup>11</sup> of the two transition-state structures reveals that they are nearly equal in energy, which is consistent with the experimentally observed low diastereoselectivity.<sup>3,12</sup>

Two strategies were pursued to improve the diastereoselectivity of the cycloaddition. The first was to utilize a *t*-Bu ester (vs Et ester) to increase the steric interaction between the Me and ester unit in **TS-B**, thus favoring **TS-A**. However, use of the analogous *t*-Bu ester of allenate **3** resulted in nearly identical diastereoselectivity (1.4:1 vs 1.2:1 *Z/E*). It is likely that the steric interaction between the *t*-Bu ester and the Me group was still negligible.

The second strategy investigated was to use a Lewis acid catalyst that projects substituents toward the incoming alkene to perturb either **TS-A** or **TS-B**. Along these lines, *N*-activated

oxazaborolidines were investigated due to their success in our prior efforts<sup>3</sup> and for their ability to project substituents toward the allene.

Catalyst **5** was evaluated in the chirality transfer [2 + 2] cycloaddition and afforded **4a,b** in excellent yield and chirality transfer. More importantly, improved and reversed diastereoselectivity was observed (as compared to reactions using EtAlCl<sub>2</sub> illustrated in Scheme 2A). Encouraged by this initial result, a series of *N*-activated oxazaborolidines with different steric and electronic properties were evaluated (Scheme 3, catalysts **6–8**); however, only minimal perturbation in selectivity was observed. Further steric tuning of the catalyst revealed that reaction with catalyst **9**, which incorporates an *o*-PhC<sub>6</sub>H<sub>3</sub> unit, led to improved diastereoselectivity. Additional modification of the B–Ar *o*-aryl group revealed that reaction with catalyst **10** delivered the product in 5.2:1 *E/Z*. Increasing the steric demand on the B–Ar *o*-aryl group (catalyst **11**) led to no improvement in diastereoselectivity but a reduction in yield. Finally, to probe a match/mismatched effect, *ent*-**3** was evaluated with catalyst **10**. In this case, lower diastereoselectivity (*E/Z*) was observed, indicating that proper pairing of the enantiomers of substrate and catalyst is important.

Based on the result shown in Scheme 3 with catalyst **10**, the substrate scope of this method was explored and is illustrated in Table 1. Several points are noteworthy: (1) Reaction with allene **12** bearing an NTs substituent generated **13a,b** with 8:1 *E/Z* selectivity (Table 1, entry 1). (2) With increased substitution of the alkene of starting material, the *Z*-alkene isomer of product was preferentially generated with good chirality transfer (compare Table 1, entry 1 with entries 2 and 3).<sup>13</sup> It is likely that the *Z*-alkene isomer of product was generated because of an unfavorable steric interaction between the  $\beta$ -methyl group of alkene and the ester group in a model analogous to **TS-A** (Scheme 2B).<sup>14</sup> (3) Reaction with *Z*-alkene isomer **18** (Table 1, entry 4) provided **19a,b** in 26% yield. Comparison of the results from reactions of **14** and **18** also served to confirm the stereospecificity of the process and suggests the reaction proceeded via a concerted asynchronous transition state or involves a short-lived intermediate.<sup>3,12</sup> To rationalize the poor reactivity of substrate **18**, inspection of the models **4a** and **4b** in Scheme 2B reveals that if a *Z*- $\beta$ -methyl group is present an unfavorable steric interaction with the tether likely occurs, raising the energy of the TS.<sup>15</sup> (4) Reactions with substrates bearing cyclic alkenes (Table 1, entries 5 and 6) required the use of catalyst **6** to achieve high yield. It appears that use of catalyst **10** is too sterically demanding with substrates bearing increased substitution. (5) Using the terminal dimethyl allenic ester (Table 1, entry 7), a cyclization via an ene reaction pathway was observed, albeit without chirality transfer. (6) With respect to the known limitations of the method, use of either a substrate that lacks the  $\alpha$ -methyl group or a substrate that would lead to a six-membered ring resulted in poor conversion (not shown).<sup>11</sup> The lack of reactivity of these substrates is likely due to reduced nucleophilicity of the alkene and poor cyclization kinetics, respectively.

Reaction with substrate **26** was also attempted as it would lead to synthesis of novel benzofuran structures (Scheme 4). In this case, [2 + 2] cycloaddition occurred under the isomerization reaction conditions to generate **27** and **28** with high enantioselectivity. At this point, it is not clear if the thiourea catalyst also promotes the [2 + 2] cycloaddition.

Finally, [2 + 2] cycloadditions of an allenic phosphonate have also been briefly investigated (Scheme 5). This process is significant due to the ease with which chiral allene **30** can be prepared from secondary alcohol **29** by [2,3]-rearrangement.<sup>16</sup> Chirality transfer could be achieved using EtAlCl<sub>2</sub> at 45 °C and afforded **31** in 13:1 *Z/E* selectivity and 90:10 er. It should be noted that the use of the chiral catalyst was ineffective in these reactions.

In summary, intramolecular chirality-transfer reaction of allenates and alkenes using Lewis acids is disclosed. The use of chiral catalyst led to improved diastereoselectivity of the cycloadditions compared to the use of achiral catalysts. Future investigations aim to extend this method to intermolecular variants.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

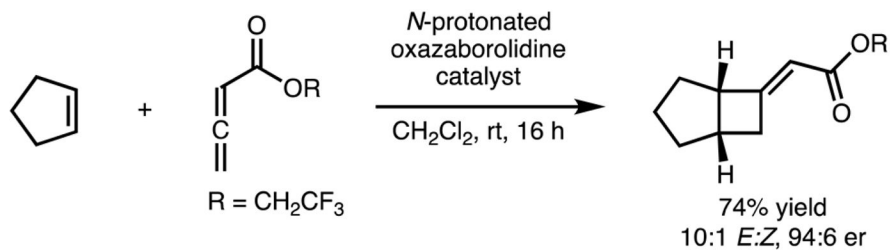
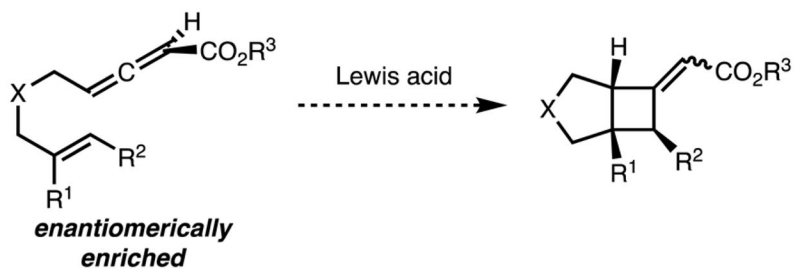
## Acknowledgments

Indiana University and the NIH (R01GM110131) are acknowledged for generous financial support. M.K.B. is a 2017 Novartis Early Career Awardee. We thank Dr. Maren Pink and Dr. Chun-Hsing Chen (IU) for X-ray crystallography. The NSF XSEDE program is acknowledged for computational support.

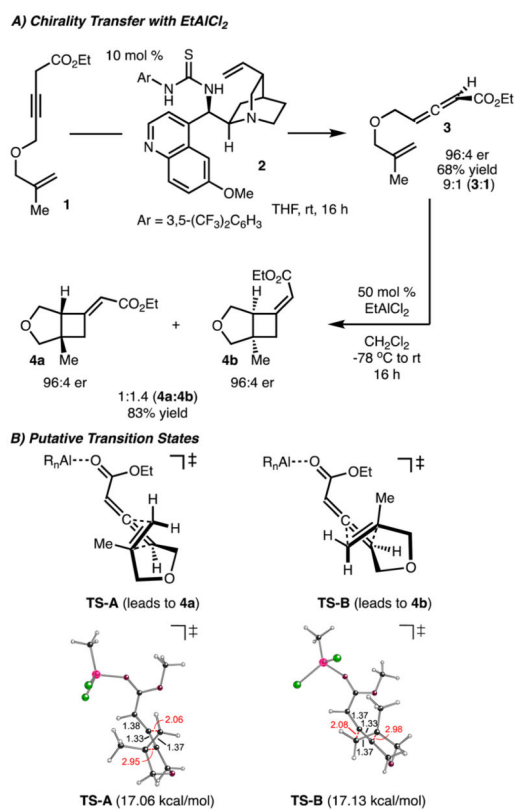
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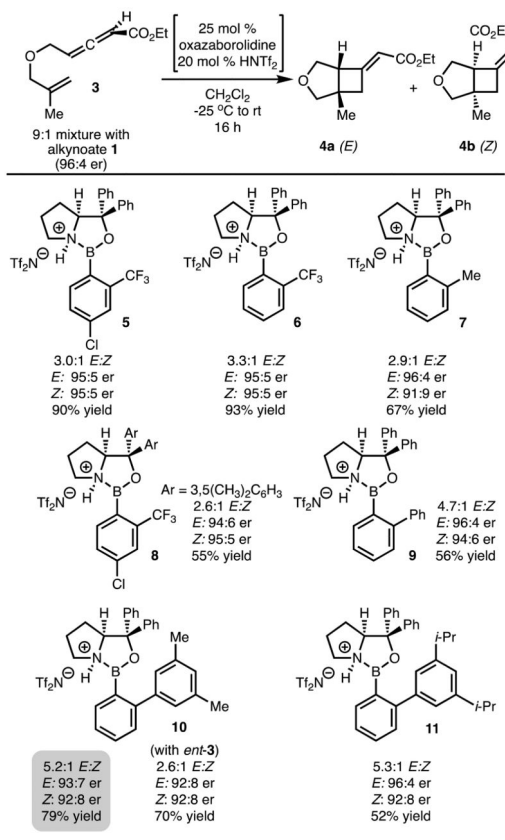
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11. See the Supporting Information for details.
12. [ $\pi^2_s + \pi^2_a$ ], [ $(\pi^2_s + \pi^2_s) + \pi^2_s$ ], or a quasispericyclic process with carbenoid character have all been proposed for related ketene–alkene [2 + 2] cycloadditions. For a lead reference, see: Wang X, Houk KN. J Am Chem Soc. 1990; 112:1754.
13. The reaction to prepare **17a/b** on a 1.0 mmol scale proceeded with similar yield and selectivity to that shown in Table 1, entry 3, on a 0.2 mmol scale. See the Supporting Information for details.
14. Reaction of ( $\pm$ )-**14** with EtAlCl<sub>2</sub> led to formation of ( $\pm$ )-**15a/b** in 1:6 *E/Z*.
15. Using EtAlCl<sub>2</sub> to promote the cycloaddition of ( $\pm$ )-**18** provided ( $\pm$ )-**19a/b** in 76% yield but only 1:1.2 *E/Z* selectivity.
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**A) Enantioselective Allenolate-Alkene [2+2] Cycloadditions****B) This Work: Chirality Transfer Intramolecular [2+2] Cycloadditions**

**Scheme 1.**  
[2 + 2] Cycloadditions



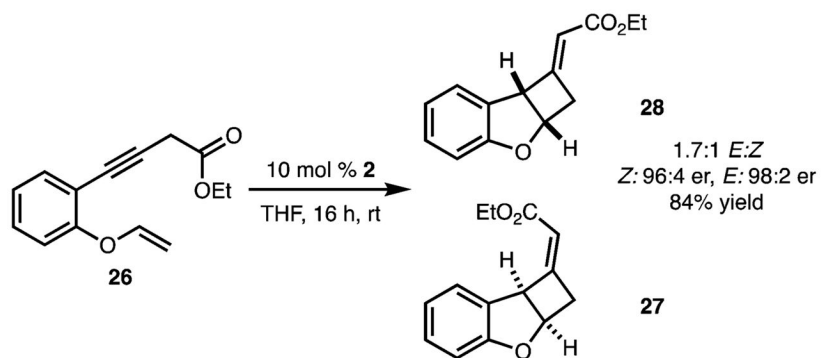
**Scheme 2.**  
Initial Findings



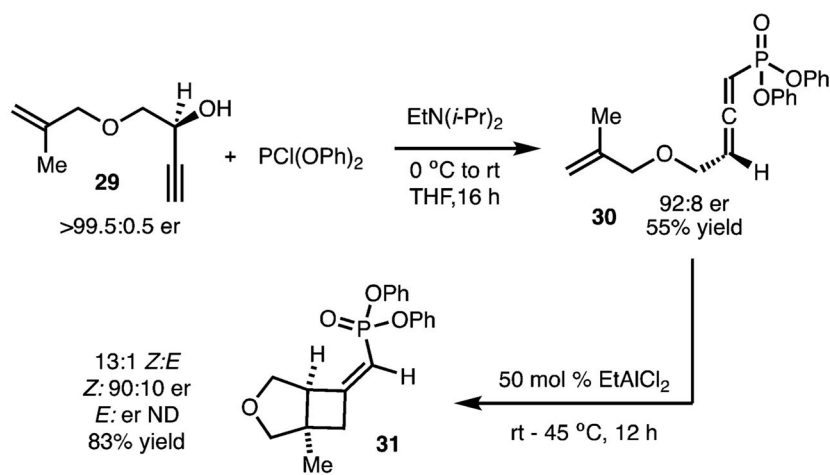
### Scheme 3. Evaluation of Chiral Catalysts<sup>a</sup>

<sup>a</sup>See the Supporting Information for experimental details. Isolated yields and crude *E/Z* selectivity are reported. Enantiomeric ratios determined by HPLC analysis with a chiral column.





**Scheme 4.**  
Cycloaddition To Generate Benzofuran-Derived Cycloadducts



**Scheme 5.**  
Chirality Transfer with Allenic Phosphonate

Table 1

Evaluation of Substrates<sup>a</sup>

entry	starting material	products
1	 12 94:6 er (5.2:1 allene:alkyne)	 13a  13b 8:1 E:Z E: 94:6 er, Z: er ND 53% yield
2	 14 96:4 er (8.4:1 allene:alkyne)	 15a  15b 1:10 E:Z E: er ND, Z: 94:6 er 64% yield
3	 16 95:5 er (8.9:1 allene:alkyne)	 17a  17b 1:20 E:Z E: er ND, Z: 95:5 er 70% yield
4	 18 96:4 er (8.7:1 allene:alkyne)	 19a  19b 10:1 E:Z E: 95:5 er, Z: er ND 26% yield
5	 20 96:4 er (9.0:1 allene:alkyne)	 21a  21b 1:14 E:Z <sup>b</sup> E: er ND, Z: 89:11 er 46% yield
6	 22 95:5 er (8.3:1 allene:alkyne)	 23a  23b 1:2.5 E:Z <sup>b</sup> E: 95:5 er, Z: 86:14 er 62% yield
7	 24 95:5 er (7.2:1 allene:alkyne)	 25 69% yield, 50:50 er <sup>c</sup>

<sup>a</sup>See the Supporting Information for experimental details. Yields reported are the average of two experiments (0.2 mmol scale). Enantiomeric ratios determined by HPLC analysis with a chiral column. The *E/Z* selectivity was determined by analysis of the unpurified reaction mixture by <sup>1</sup>H NMR.

<sup>b</sup>Catalyst **6** was used for the reaction.

<sup>c</sup>50 mol % of EtAlCl<sub>2</sub> was used for the cycloaddition.

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