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Catalytic Enantioselective Allenoate−Alkene [2 + 2] Cycloadditions

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Supporting Information

ABSTRACT: Catalytic enantioselective [2 + 2] cycloadditions between allenoates and alkenes is disclosed. The method functions well for a variety of alkenes, and the products are generated with excellent levels of enantioselectivity. One of the most significant aspects of the present method is that unactivated alkenes are suitable substrates for this method, which is distinctly different from nearly all other catalytic enantioselective [2 + 2] cycloaddition methods.

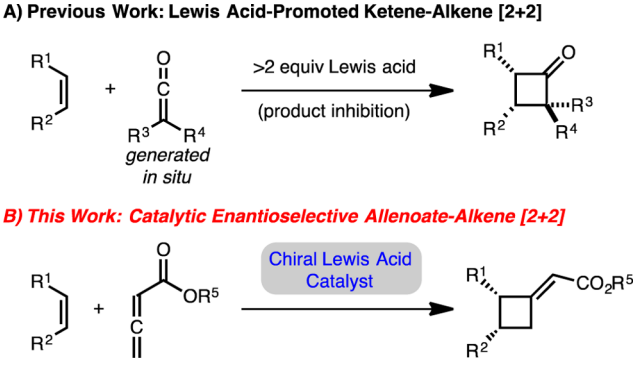
Synthesis of cyclobutanes through [2 + 2] cycloadditions of alkenes has emerged as an indispensible method for chemical synthesis.[1] This is due to the presence of the cyclobutane motif in a variety of important molecules and the ease with which cyclobutanes can be converted readily to a variety of structures.[1] Consequently, catalytic enantioselective [2 + 2] cycloadditions to prepare cyclobutanes have emerged as an attractive target for methods development. The majority of methods for catalytic enantioselective [2 + 2] cycloadditions involve the formal cycloaddition between highly polarized electron-rich and electron-poor alkenes.[2,3] Catalytic enantioselective photochemical [2 + 2] cycloadditions have also recently been reported.[4] Several Au-catalyzed cycloadditions of electron-rich allenes and styrenes have been disclosed.[5] Finally, transition metal-catalyzed cycloaddition of alkynes with bicyclic alkenes are known.[6] Despite these efforts, synthesis of cyclobutanes by catalytic enantioselective [2 + 2] cycloadditions remains extremely limited. In particular, methods that employ weakly activated alkenes are exceptionally rare and are only known for intramolecular photochemical reactions[4a−i,l] and cycloadditions of trisubstituted alkenes.[3a]

Herein, we disclose a new class of catalytic enantioselective [2 + 2] cycloadditions. The process combines readily available allenoates and a variety of alkenes to generate synthetically versatile cyclobutanes. A key feature of this method is that weakly or nonpolarized alkenes can be utilized.

Our lab has initiated a program directed toward developing stereo- and enantioselective [2 + 2] cycloadditions with allenes and heteroallenes. Along these lines, we have previously developed a method for Lewis acid-promoted [2 + 2] cycloadditions between ketenes and alkenes (Scheme 1).[7,8] While this method greatly expands the scope of this venerable reaction, a notable drawback is the requirement for a stoichiometric amount of Lewis acid due to severe product inhibition. Thus, development of catalytic, and hence catalytic enantioselective, variants of this process has been impeded.

To provide a solution to this problem, reactions with allenoates were evaluated as these would generate similar products as reactions with ketenes yet may not suffer from product inhibition. We were encouraged by three seminal reports from Snider and Hoffman who in the early to mid-1980s demonstrated that Al(III)-Lewis acids were capable of promoting [2 + 2] cycloaddition between allenoates and unactivated alkenes (e.g., 1-hexene, cyclopentene, etc.).[9] Furthermore, in several cases, catalytic turnover of the Lewis acid was possible. More recently, Loh and co-workers reported a Lewis acid-catalyzed intramolecular cycloaddition of allenic ketones.[10] These four papers represent the only reported studies in this area over a ∼30-year period.

Scheme 1. [2 + 2] Cycloadditions



We initiated our studies by examining the cycloaddition of benzylallenoate **2** (stable and easily prepared in one step) and allyltrimethylsilane (**1**) in the presence of a variety of chiral Al(III)-Lewis acid catalysts (**4**−**7**).[11] While several classes of chiral Al(III)-Lewis acid catalysts were capable of promoting the cycloaddition, the enantioselectivities of the processes were low (**4**−**5**, **7**). Further evaluation of other highly Lewis-acidic catalysts ultimately led to the discovery that use of oxazaborolidine **9** provided the product in 96:4 enantiomeric ratio (er) but only 20% yield (Scheme 2).[12] Optimization of the catalyst structure revealed that incorporation of a more electron-deficient B−Ar unit led to significantly increased yields at only a small cost in enantioselectivity (Scheme 2, compare catalysts **9** with **10**−**13**). Fine-tuning of this substituent ultimately led to the identification of catalyst **13**, which provided cyclobutane **3** in 92% NMR yield and 92:8 er. Interestingly, related known oxazaborolidine catalyst **8** failed to promote the cycloaddition.[13]

With an optimized set of conditions/catalyst in hand, we explored the scope of this method. As illustrated in Scheme 3 a variety of alkenes undergo cycloaddition with good yields and

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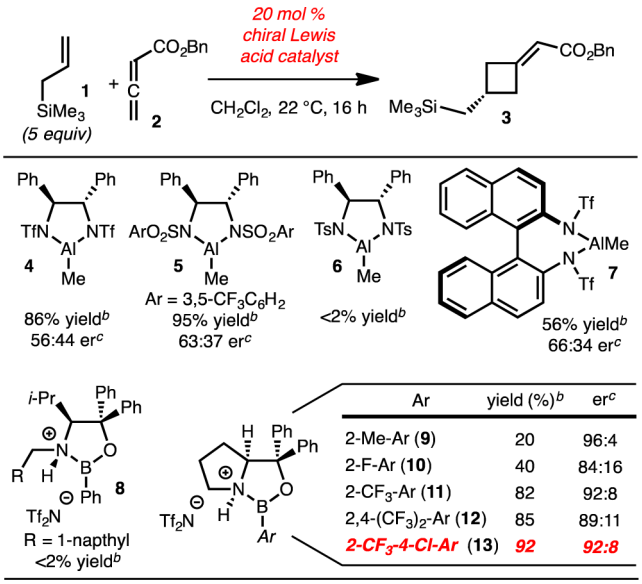
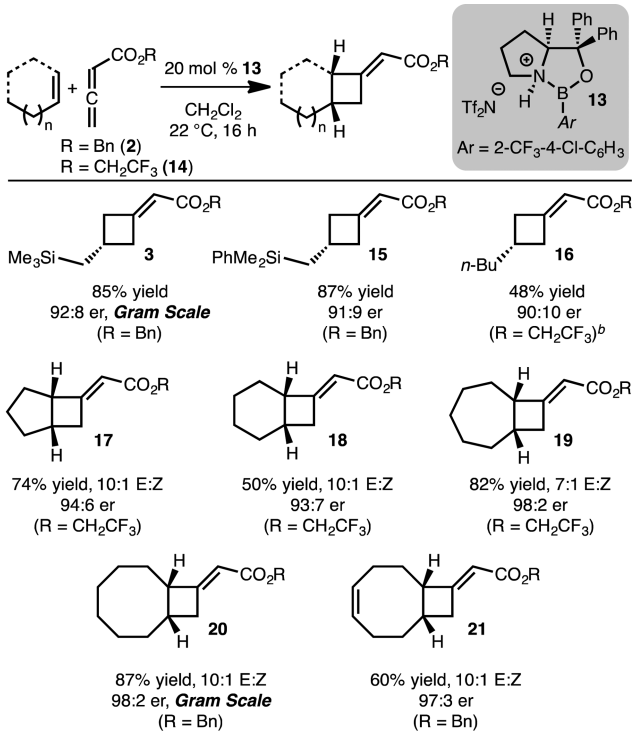
Scheme 2. Initial Evaluation of Chiral Catalysts[a]



[a]See the Supporting Information for experimental details. [b]Determined by ^{1}H NMR analysis with an internal standard. [c]Determined by HPLC analysis with a chiral column.

Scheme 3. Substrate Scope with Cyclic Alkenes[a]

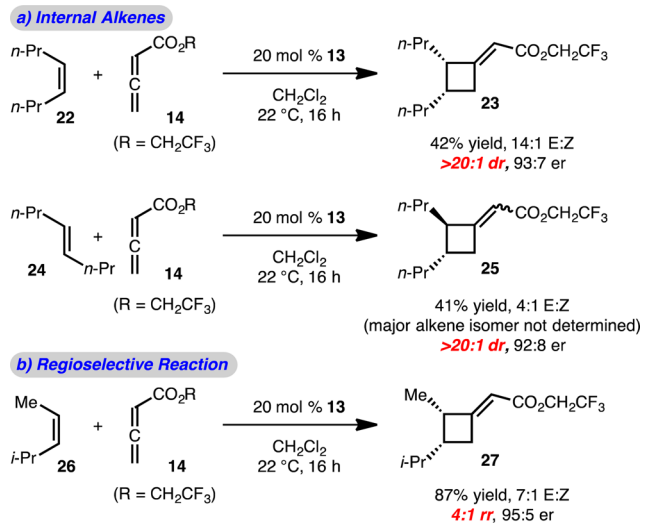


[a]With 5 equiv alkene. See the Supporting Information for experimental details. Yields reported are the average of two experiments. Enantiomeric ratios determined by HPLC analysis with a chiral column. [b]With 50 mol % catalyst and 10 equiv alkene in the absence of CH_2Cl_2.

enantioselectivity.[14] Several points regarding this process are noteworthy: (1) Unactivated alkenes can be used in this process (*e.g.*, cycloheptene, product **19**; 1-hexene, product **16**). This stands in sharp contrast to the vast majority of reported catalytic enantioselective methods (vida supra). (2) In general, higher yields are observed with more strained alkenes. For example, the more strained cyclooctene undergoes cycloaddition with higher yield than a reaction with less strained cyclohexene (compare yields of products **18** and **20**). (3) Cycloaddition with 1-hexene (product **16**) represents a rare example of a catalytic enantioselective reaction with a terminal unactivated alkene.[15] In this example, higher catalyst loading and excess alkene are necessary due to the poor nucleophilicity of 1-hexene. (4) With less reactive alkenes, the more electrophilic trifluoroethylallenoate **14** was employed to obtain higher yields (products **16**–**19**). (5) The catalyst was easily prepared in one step from commercially available starting materials. (6) Current limitations of the method are the use of trisubstituted alkenes and α- or γ-substituted allenes, as low selectivity was observed (not shown).

Internal nonactivated alkenes are also suitable substrates for this process (Scheme 4). Reaction of *cis*-4-octene (**22**) under

Scheme 4. Reactions with Acyclic Internal Alkenes



standard conditions provided **23** in 42% yield, 14:1 *E:Z*, 93:7 er, and >20:1 dr. Likewise reaction of *trans*-4-octene furnished **25** in 41% yield, 4:1 *E:Z*, 92:8 er, and >20:1 diastereomeric ratio (dr). For both isomers of 4-octene the geometry of starting material is completely conserved in the product. These results suggest that the cycloaddition event is concerted or involves an ephemeral intermediate. Furthermore, the processes are likely highly asynchronous as it has been noted for related ketene–alkene [2 + 2] cycloadditions.[7,8] The regioselectivity of the cycloaddition can also be controlled (Scheme 4b). Thus, nonsymmetric alkene **26** undergoes reaction with allenoate **14** to provide the regioisomer in which the *i*-Pr-substituent is distal to the unsaturated carbonyl (4:1 regioisomeric ratio (rr)). The major regioisomer was generated in 7:1 E:Z and 95:5 er.

A rationale that accounts for the observed enantio- and diastereoselectivity is illustrated in Scheme 5 (X-ray of derivative **29** established absolute stereochemistry). On the basis of the above discussion, the reaction is likely concerted and highly asynchronous or involves a short-lived dipolar intermediate.[9,16] In either event, coordination of the allene to the Lewis acidic boron atom likely occurs according to the model illustrated in Scheme 5 (**28**).[12] The orientation of the

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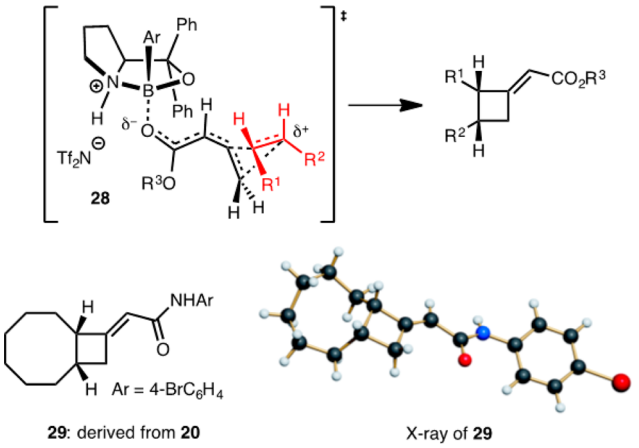
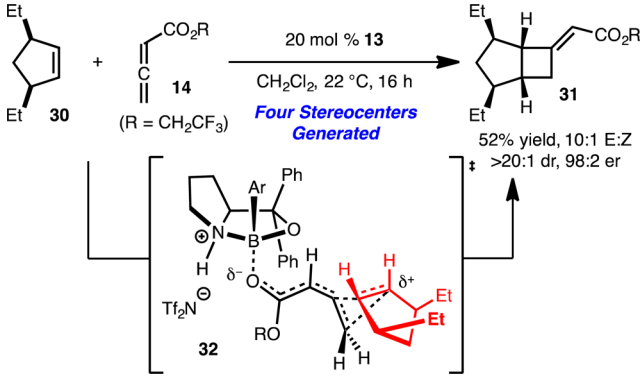
Scheme 5. Proposed Model for Selectivity



allene with respect to the catalyst may be fixed by a putative C–H···O hydrogen bonding interaction as proposed in related Diels–Alder reactions.[12,17] Approach of the alkene can only occur from the front face of allene as the back face is blocked by the Ph-substituent on the convex face of the catalyst. Furthermore, the alkene substituents (R^1 and R^2) are pointed away from the steric bulk of the catalyst.

Cycloadditions with symmetric and nonsymmetric alkenes that have the potential to establish multiple stereocenters have been investigated (Schemes 6 and 7). Thus, cycloaddition of

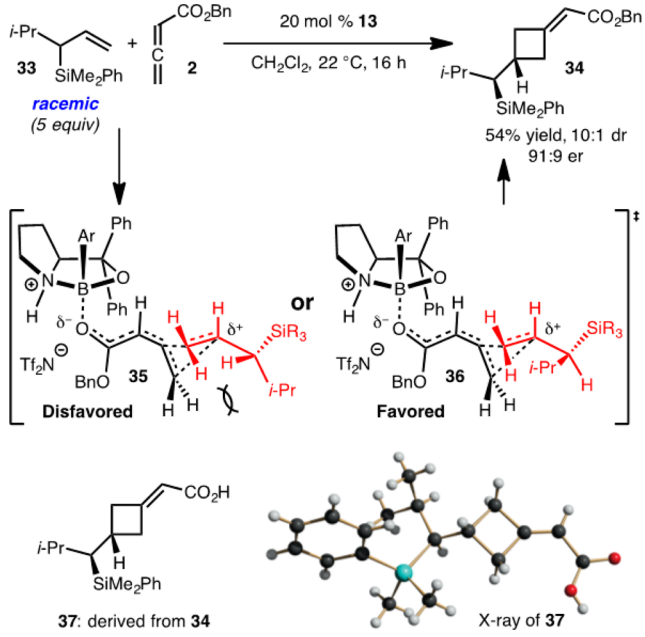
Scheme 6. Desymmetrization by [2 + 2] Cycloaddition



diethyl cyclopentene derivative **30**[7d] and allene **14** promoted by catalyst **13** led to formation of cyclobutane **31** with the generation of four new stereocenters in excellent selectivity (Scheme 6). A model that rationalizes the observed selectivity is shown in Scheme 6 (**32**). It is likely that the alkene approached the allenoate-Lewis acid complex with the large Et-substituents oriented away from the complex to reduce adverse interactions.

Cycloaddition with chiral, racemic allylsilane **33** has also been investigated (Scheme 7).[18] Treatment of allenic ester **2** with an excess of racemic chiral allylsilane **33** in the presence of catalyst **13** led to the formation of the cyclobutane **34** in 54% yield, 91:9 er, and 10:1 dr. In this example, one enantiomer of allylsilane **33** underwent preferential reaction. This reaction likely proceeded through the putative pretransition states **35** and **36** illustrated in Scheme 7. A key component of these models is that the C–Si bond is properly aligned to stabilize the developing positive charge. This alignment positions the *i*-Pr-group either proximal (model **35**) or distal (model **36**) to the

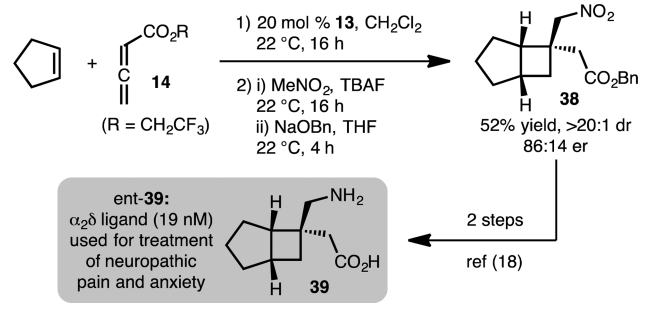
Scheme 7. Kinetic Resolution of Racemic Alkenes



allene. We expect that the rate of reaction in which the *i*-Pr-group is positioned proximal to the allene was reduced due to unfavorable steric interactions (model **35**), thus allowing preferential reaction of the other enantiomer of the allylsilane through pretransition state **36**.

The utility of this method was demonstrated toward the formal synthesis of amino acid **39** (Scheme 8).[19,20] This

Scheme 8. Synthesis of Intermediate 38



molecule was recently identified to be a potent ligand (19 nM) for the $\alpha_2\delta$ subunit of a voltage gated calcium channel and is related to anticonvulsants Lyrica and Neurontin. The reported route to **39** involves nine steps and a resolution to separate enantiomers from a ketene–alkene [2 + 2] cycloaddition.[19] As illustrated in Scheme 8, intermediate **38** could be easily prepared by one-pot catalytic enantioselective [2 + 2] cycloaddition followed by Michael addition and *trans*-esterification in 52% yield > 20:1 dr and 86:14 er.[21] The ethyl ester of **38** has been converted to **39** through a simple two-step sequence.[22]

In summary, a new and highly enantioselective method for catalytic [2 + 2] cycloaddition is disclosed. This method is notable because unactivated alkenes can be utilized. Future directions are aimed at extending the scope to include related classes of electron deficient allenes.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The minor *Z*-isomer is generated in lower enantioselectivity (~70:30 er) than the *E*-isomer (see Scheme 3).

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(16) $[{}_{\pi}2_{s}+{}_{\pi}2_{a}]$, $[({}_{\pi}2_{s}+{}_{\pi}2_{s})+{}_{\pi}2_{s}]$ or a quasi-pericyclic process with carbenoid character have all been proposed for related ketene−alkene [2 + 2] cycloadditions. For a lead reference, see: Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 1754.

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(20) The cycloaddition product **20** can also be converted to the corresponding cyclobutanone by oxidative cleavage in high yield and er; see the Supporting Information for details.

(21) The lower enantiopurity of **36** compared to the direct product of cycloaddition (**17**) is due to simultaneous conversion of the *E*- and *Z*-isomers of **17** to **38** (see ref 14).

(22) The benzyl ester was used only because a chromophore was needed for HPLC analysis with a chiral column.

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