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Allenoates in Enantioselective [2+2] Cycloadditions: From a Mechanistic Curiosity to a Stereospecific Transformation

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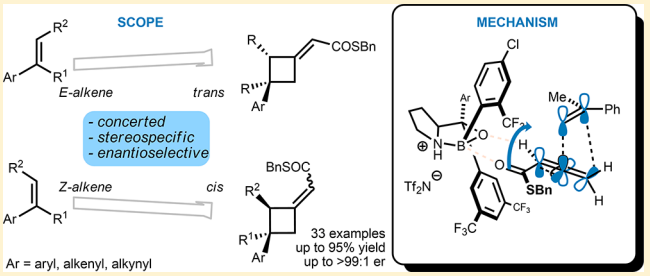
Supporting Information

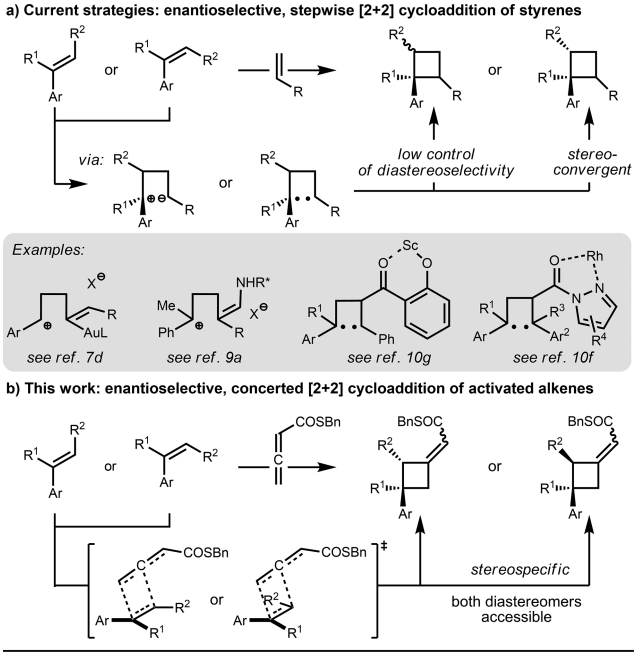
ABSTRACT: Identification of a novel catalyst−allenoate pair allows enantioselective [2+2] cycloaddition of α-methylstyrene. To understand the origin of selectivity, a detailed mechanistic investigation was conducted. Herein, two competing reaction pathways are proposed, which operate simultaneously and funnel the alkenes to the same axially chiral cyclobutanes. In agreement with the Woodward−Hoffmann rules, this mechanistic curiosity can be rationalized through a unique symmetry operation that was elucidated by deuteration experiments. In the case of 1,1-diarylalkenes, distal communication between the catalyst and alkene is achieved through subtle alteration of electronic properties and conformation. In this context, a Hammett study lends further credibility to a concerted mechanism. Thus, extended scope exploration, including β-substitution on the alkene to generate two adjacent stereocenters within the cyclobutane ring, is achieved in a highly stereospecific and enantioselective fashion (33 examples, up to >99:1 er).



INTRODUCTION

Construction of multiple stereocenters in a single event has become an increasingly important strategy to build molecular complexity in an efficient and economical way. Arguably, one of the most powerful methods to achieve such a transformation is the Diels−Alder reaction.[1] It is generally postulated that the aforementioned reaction involves a symmetry-allowed cyclic transition state as predicted by the Woodward−Hoffmann rules.[2] Consequently, the reaction can be performed in a stereospecific fashion, allowing the generation of all possible isomers from the respective *E*- or *Z*-alkenes. Despite significant advances in the realm of enantioselective Diels−Alder reactions,[3] the analogous, concerted [2+2] cycloaddition of alkenes has remained a challenge. Particularly, methods that utilize activated olefins are especially difficult. In contrast to the Diels−Alder reaction, recent methods to construct enantioenriched arylcyclobutanes by [2+2] cycloaddition often proceed through stepwise processes, resulting in decreased reaction selectivity (Scheme 1a).[4,5] With respect to Lewis acid catalyzed examples, gold complexes have been utilized to activate alkynes[6] or allenes[7] to achieve enantioselective cycloaddition with highly activated styrene derivatives. In addition, copper and zinc have been used with electron rich arylalkenes to give cyclobutanes with good control of enantioselectivity.[8] Alternatively, chiral amines can be used to assemble cyclobutanes via ionic intermediates.[9] Photochemical methods[10] often exhibit increased tolerance for electron-poor styrenes, but generally involve excited state biradical intermediates, which lead to either stereoconvergence[10f] or erosion of diastereoselectivity.[10g] Overall, only a few examples,[9a] report good stereospecificity through trapping of reactive intermediates at low temperatures.

Scheme 1. Enantioselective Arylcyclobutane Synthesis



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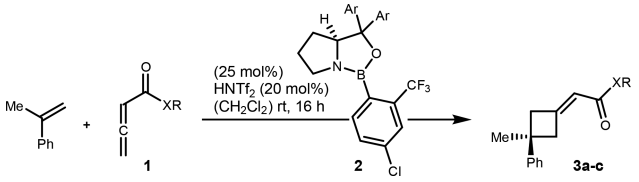
To address this problem, we recently focused our efforts on rendering alkene-allenoate cycloadditions enantioselective.[11] Based on several reports in the literature,[11b,12] alkene-allenoate cycloadditions appear to be concerted and therefore stereospecific in nature, which provides a unique opportunity for an in-depth study (Scheme 1b). Herein, we report the enantioselective [2+2] cycloaddition of α-methylstyrene through identification of a novel alkene-allenoate pair. This method does not only enable catalytic enantioselective formation of quaternary carbon centers[13] but also exemplifies how elucidation of reaction mechanism can go hand in hand with expansion of scope. Ultimately, we propose models that reliably explain the observed selectivity for a range of activated alkenes in this unique [2+2] cycloaddition.

RESULTS AND DISCUSSION

Optimization. We initially envisioned accessing cyclobutanes bearing a quaternary center by using activated 1,1-disubstituted alkenes (e.g., α-methylstyrene). Preliminary data suggested that the identity of the allenoate ester has a significant influence on modulating reactivity as well as selectivity.[12d] As such, investigations of various allenoates **1** were undertaken (Table 1).

Table 1. Reaction Optimization



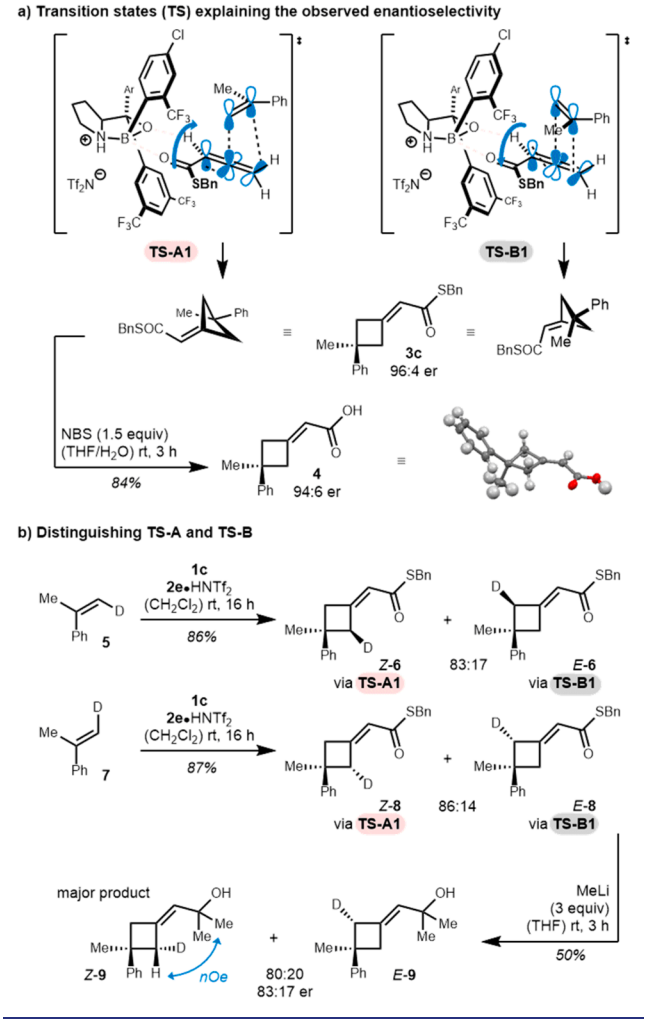
Entry	XR	Ar	Yield[b]	er[c]
1	OBn (**1a**)	Ph (**2a**)	95%	78:22
2	OCH_2CF_3 (**1b**)	Ph (**2a**)	46%	76:24
3	SBn (**1c**)	Ph (**2a**)	72%	81:19
4	SBn (**1c**)	3,5-$(CH_3)_2$-C_6H_3 (**2b**)	71%	90:10
5	SBn (**1c**)	3,5-$(tBu)_2$-C_6H_3(**2c**)	90%	80:20
6	SBn (**1c**)	3,5-$(OMe)_2$-C_6H_3 (**2d**)	56%	87:13
7	SBn (**1c**)	3,5-(CF_3)2-C_6H_3 (**2e**)	96%	96:4
8	OBn (**1a**)	3.5-$(CF_3)_2$-C_6H_3 (**2e**)	87%	86:14

[a]See the Supporting Information for experimental details. [b]Determination by ^{1}H NMR of the crude reaction mixture utilizing a calibrated standard. [c]Determined by HPLC analysis using a chiral column.

Changing from benzyl (**1a**) to the more reactive 2,2,2-trifluoroethyl ester (**1b**) under our previously optimized reaction conditions resulted in decreased yield, due to competitive polymerization of the starting materials under the reaction conditions (Table 1, compare entries 1 and 2). We next examined the use of thiobenzyl allenic ester **1c** in the reaction and were pleased to find a slight increase in reaction selectivity, albeit with decreased overall yield (compare entries 1 and 3). Confident that reaction yield could be improved through catalyst control, we studied modifications of the diarylprolinol scaffold. Whereas increasing the steric size of the aryl groups from phenyl (**2a**) to xylyl (**2b**) provided a significant increase in reaction selectivity, further increase to sterically bulkier 3,5-$(tBu)_2$-C_6H_3 catalyst **2c** resulted in a substantially less selective reaction (compare entries 3–5). Investigation of more electron rich aryl groups (i.e., entry 6, **2d**) resulted in a marked decrease in overall reaction yield while providing higher reaction selectivity. Significant improvements in both reaction yield and enantioselectivity was observed when more electron deficient 3,5-$(CF_3)_2$-C_6H_3 catalyst **2e** was examined in the reaction (entry 7). Interestingly, utilizing the same catalyst with benzyl allenoate resulted in a smaller increase in enantioselectivity (compare entries 1 and 8).

Mechanism. To account for the observed enantiomer obtained in the reaction we propose that upon binding of the Lewis basic carbonyl oxygen to the Lewis acidic boron atom,[14] the orientation of the allenoate may be fixed by a putative C–H···O hydrogen bonding interaction (Scheme 2a).[15] As the bottom face of the allenoate is effectively blocked by the large aryl groups of the catalyst, approach of the alkene may only occur from the top face. Additionally, the sterically large phenyl group of the alkene is oriented distal to the large catalyst–substrate complex. Conveniently, the planar character of the phenyl group thereby also minimizes steric interaction with the protruding C–H bond of the allene, resulting in two plausible transition states (Scheme 2a, **TS-A1** and **TS-B1**) for alkene approach.

Scheme 2. Model for Enantioselectivity



We propose a concerted, asynchronous $[_\pi2_s+(_\pi2_s+_\pi2_s)]$ cycloaddition in which the direction of rotation of the electron deficient allenic π-bond is dictated by the Woodward–Hoffmann rules (indicated by the blue arrows).[2,16] Because

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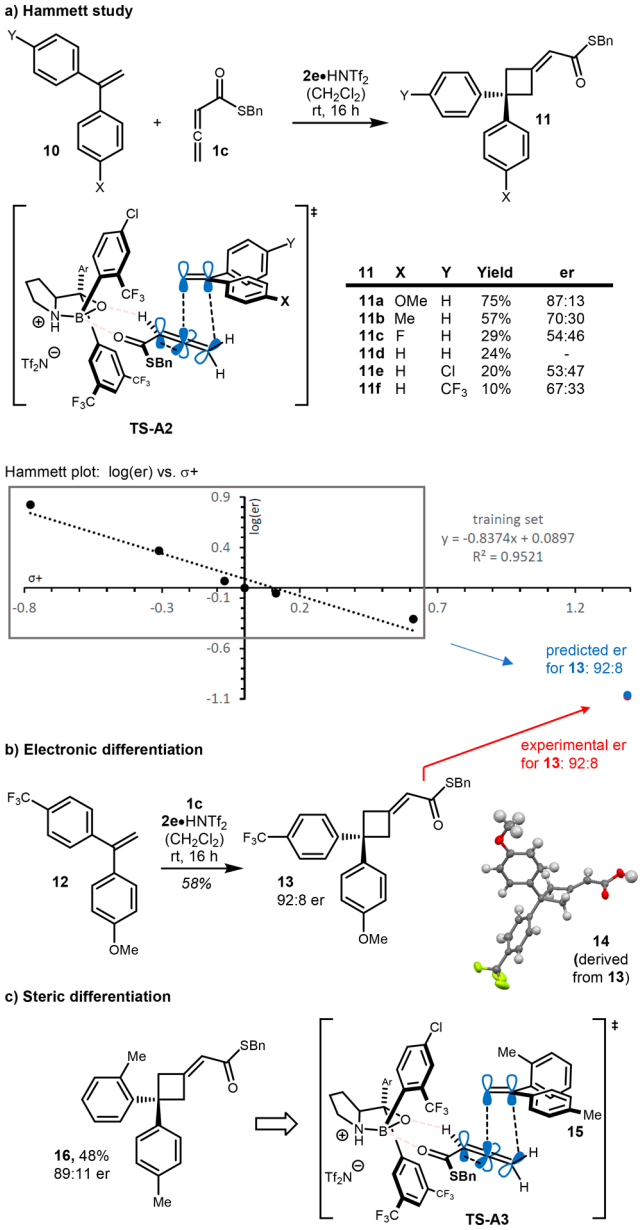
of the unusual symmetry of the system, both transition states lead to the same enantiomer. The absolute configuration of the cycloadduct **3c** was proven through hydrolysis of the thioester and subsequent analysis of the corresponding carboxylic acid **4** via X-ray diffraction.[17] To distinguish **TS-A1** and **TS-B1**, *cis*-β-deutero-α-methylstyrene **5** was subjected to the reaction conditions (Scheme 2b). To our surprise, the cycloadduct **6** was obtained as an 83:17 *Z*:*E* mixture suggesting that both pathways are operating. Accordingly, *trans*-β-deutero-α-methylstyrene **7** furnished cyclobutane **8** as a 86:14 *Z*:*E* mixture. Assignment of the respective *E*- and *Z*-isomers was achieved through derivatization and subsequent NOE analysis of the respective tertiary alcohol **9** (see Supporting Information for details). Thus, we were able to deduce **TS-A1** to be energetically favored, which can be explained by the alkene being distal to the bulky boroaryl group of the catalyst. In addition, the cycloaddition was highly stereospecific, as indicated by the two different pairs of products generated from the respective *cis*- and *trans*-deuteroalkene. This suggests a concerted mechanism, which was not necessarily to be expected considering the stabilization of a potential benzylic carbocation in a stepwise process.

To gain further insight into the reaction mechanism, we became interested in differentiating 1,1-biaryl alkenes based on their steric and/or electronic properties (Scheme 3a). Herein, only one aryl ring is in conjugation with the π-system, resulting in substantial steric differentiation of the two aryl groups (Scheme 3a, **TS-A2**). We propose preferential reaction occurs with the more reactive conformer of alkene (**TS-A2**, X = more electron donating than Y), providing an excellent setting to undertake a more detailed Hammett study. Electronically differentiated biaryl alkenes **10** were evaluated in the reaction. Moderate to good yields were obtained depending on the electronic properties of the biarylalkenes. In agreement with our model, increased disparity between the two aryl groups resulted in improved reaction enantioselectivity (products **11a**–**11f**). We found a good correlation between log(er) and σ^+ with a ρ value <1, suggesting the build-up of positive charge in the transition state in a less sensitive fashion than the parent S_N1 reaction.[18] This correlates with a concerted, highly asynchronous cycloaddition. According to the regression equation obtained from the small training set used for the Hammett study, an enantiomeric ratio of 92:8 was predicted for alkene **12** bearing two electronically altered rings[19] (herein $\Delta\sigma^+$ was obtained from the parent σ^+ values for *para*-CF_3 and *para*-OMe).[18] When **12** was subjected to the reaction conditions, cycloadduct **13** was obtained in 58% yield and 92:8 er highlighting the potential of this type of enantiodiscrimination (Scheme 3b). Proof of absolute stereochemistry was achieved by hydrolysis of product **13** and X-ray analysis of the respective biarylcyclobutanecarboxylic acid **14**.

To further probe our hypothesis, differentially substituted 1,1-biaryl olefin **15** was synthesized and examined in the reaction (Scheme 3c). As the aryl groups of this alkene possess more similar electronic properties, the rotation of one aryl group out of conjugation is primarily driven by adverse intramolecular steric interactions. We hypothesized the *ortho*-tolyl group would preferentially rotate out of plane to minimize 1,3-allylic strain (**TS-A3**, Scheme 3c), thus providing a similar steric environment as proposed in **TS-A2**. Gratifyingly, **16** was obtained in 48% yield and 89:11 er, lending support to our mechanistic hypothesis.

Scheme 3. Distal Differentiation of 1,1-Biarylalkenes



Scope. With a catalyst system that allowed for the cycloaddition of activated alkenes in hand, we examined the substrate scope of the reaction (Scheme 4). α-Methylstyrene underwent [2+2] cycloaddition in 93% yield and 96:4 er (product **3c**) on gram scale (5.26 mmol) with no loss in reaction selectivity. Increasing the steric size of the α-substituent was investigated and proceeds with high enantioselectivity (products **3d** and **3e**). High chemoselectivity for the activated alkene in the presence of an unactivated alkene was observed to provide **3e** in 72% yield and 96:4 er, with no trace of cycloadducts derived from the reaction of the unactivated olefin. Several steric and electronic perturbations of the aromatic ring have been investigated (products **3f**–**3l**). The cycloaddition proceeded in good yield with sterically encumbered (product **3f**), halogenated (products **3h** and **3j**), and electron-poor (products **3i** and **3j**) vinyl arenes. Spirocyclic cyclobutane derivatives can also be accessed from the requisite 1,1-disubstituted olefin in good yield and high

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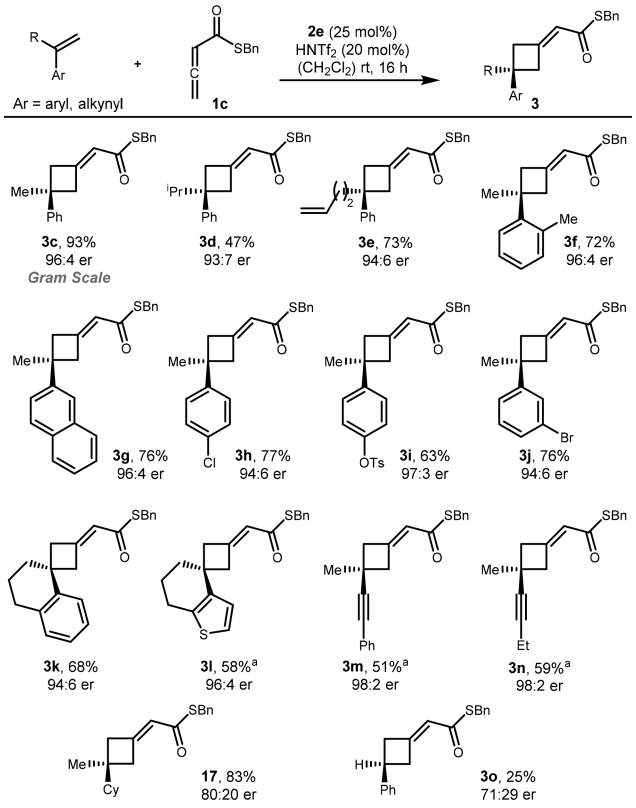
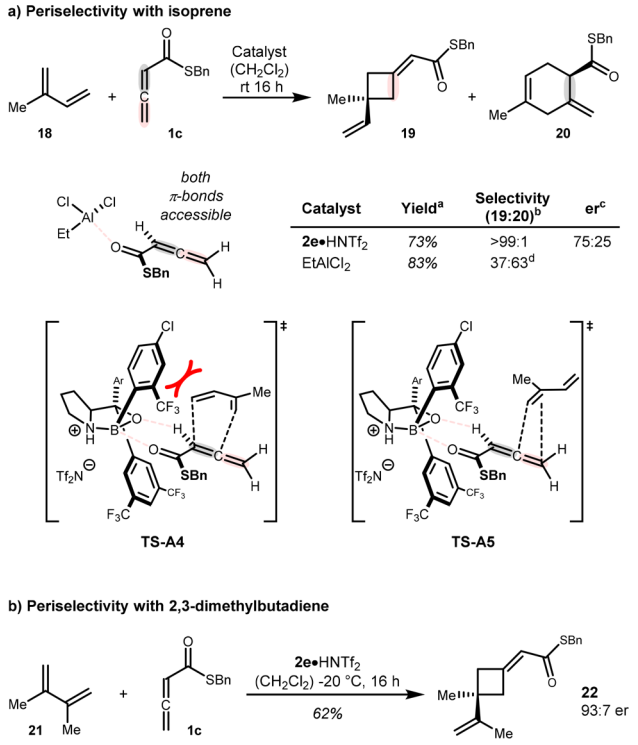
Scheme 4. 1,1-Disubstituted Alkene Substrate Scope*



*All reactions run with 5 equiv of alkene on a 0.25 mmol scale. Yields reported are the average of two experiments. Enantiomeric ratios determined through HPLC analysis with a chiral column Absolute stereochemistry of **17** and **3o** tentatively assigned. [a]Reactions run at −20 °C.

Scheme 5. Catalyst Induced Periselectivity



Catalyst	Yield[a]	Selectivity (19:20)[b]	er[c]
2e•HNTf$_2$	*73%*	>99:1	75:25
EtAlCl$_2$	*83%*	37:63[d]	

[a]Isolated yield of cycloaddition product(s). [b]Determined by 1H NMR analysis of the crude reaction mixture. [c]Enantiomeric ratio determined through HPLC analysis with a chiral column. [d]**20** was obtained as a ∼9:1 mixture of regioisomers. Absolute stereochemistry of **20** tentatively assigned.

enantioselectivity (product **3k** and **3l**). Heterocycles bearing weakly basic heteroatoms, such as thiophene, were also tolerated (product **3l**). In some cases, dropping the temperature improved the yield by decreasing the rate of alkene polymerization. Interestingly, enynes underwent cycloaddition without any interference of the alkyne moiety yielding **3m** and **3n** in moderate yield and excellent enantioselectivity.

Replacement of the aryl group with a cyclohexyl group resulted in substantial decrease in enantioselectivity, demonstrating that the aryl group is necessary to obtain highly enantioenriched products (Scheme 4, compare products **17** and **3c**). Substitution at the α-position was also essential for successful reaction, as styrene itself performed poorly in terms of reactivity and selectivity under several reaction conditions (product **3o**, see Supporting Information for further details). Partial polymerization of styrene presumably accounts for the low yield, whereas low enantioselectivities for **17** and **3o** can be rationalized by lack of steric differentiation with the protruding C−H bond of the allene.

To further expand the reaction scope, we investigated commodity dienes, such as isoprene (**18**), in the cycloaddition reaction (Scheme 5). Initially, when EtAlCl$_2$ was used as a Lewis acid, low periselectivity was observed, favoring Diels−Alder product **20**. In stark contrast to EtAlCl$_2$, catalyst **2e** allowed for >99:1 selectivity favoring [2+2] cycloadduct **19**. The reaction also occurred with high chemoselectivity, as only the more substituted alkene of isoprene underwent cycloaddition; however, the observed enantioselectivity was only moderate for this reaction. We assume that upon binding of allenoate **1c** to catalyst **2e**, the internal π-bond (Scheme 5a, marked in gray in **TS-A4**) is sufficiently blocked by the large boroaryl group of the catalyst, leaving the distal π-bond (marked in red in **TS-A5**) more readily accessible for [2+2] cycloaddition.[20] It should be noted that our system complements previous reports on Diels−Alder reactions between allenoates and cyclic dienes.[14b,21,22] α-Substitution, as imposed by 2,3-dimethylbutadiene (**21**), significantly improved the enantioselectivity while preserving the high level of periselectivity (Scheme 5b, product **22**).

Application to β-Substitution. The potential to generate two adjacent stereocenters piqued our curiosity to further study β-substitution of the alkene starting materials and test our proposed models. We initiated this survey with cyclic alkene **23**. Gratifyingly, the reaction proceeded in good yield, regioselectivity, and with excellent enantioselectivity, but resulted in the formation of both alkene isomers (Scheme 6, *Z*-**24** and *ent-E*-**24**) in a 69:31 ratio. Separation by column chromatography revealed *Z*-isomer *Z*-**24** as the major product. In accordance with the deuteration experiment and as a consequence of β-substitution on the alkene, the two TS do not lead to the same absolute configuration within the cyclobutane ring (see Scheme 6a, **TS-A6** and **TS-B2**). To verify this hypothesis, *Z*-**24** and *ent-E*-**24** were individually transformed to ketone **25** by oxidative cleavage using a modified Lemieux−Johnson oxidation.[23] As expected, **25** revealed opposite absolute configuration indicated by opposite optical rotation.

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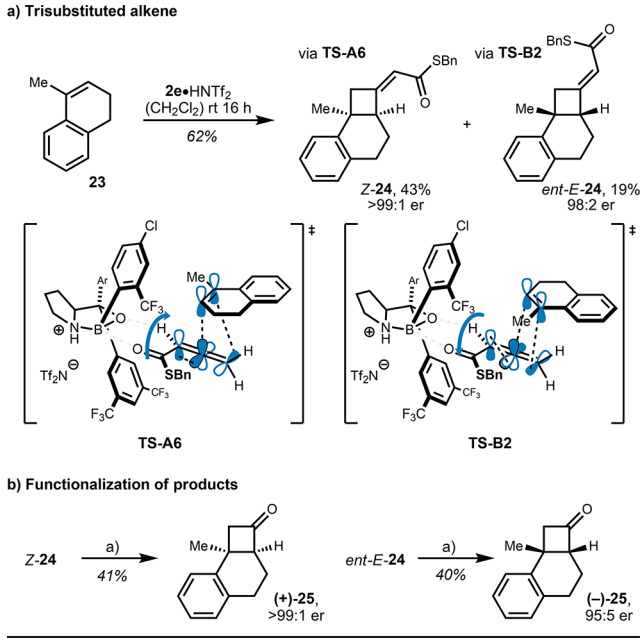
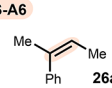
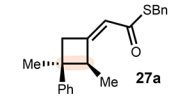
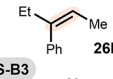
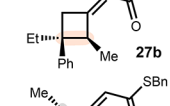
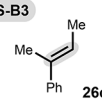
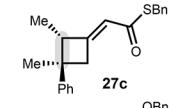
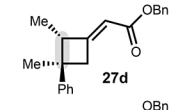
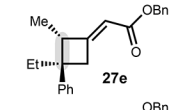
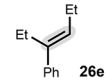
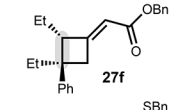
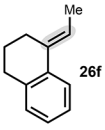
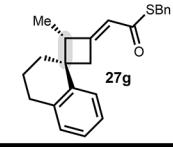
Scheme 6. Initial Study on Trisubstituted Alkenes



[a]$K_2OsO_4 \cdot 2H_2O$, $NaIO_4$, 2,6-lutidine (1,4-dioxane,H_2O) rt, 6 h.

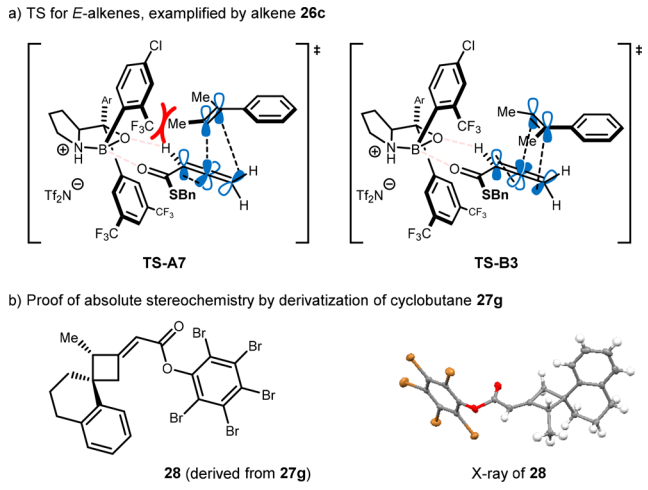
Acyclic trisubstituted alkenes should, based on our mechanistic study, undergo cycloaddition in a concerted, stereospecific fashion. To demonstrate the utility of such an attribute, different pairs of acyclic *E*- and *Z*-alkenes were subjected to the optimized conditions (Table 2). As seen for alkene **23**, modest *E*/*Z* selectivity was observed for *Z*-alkenes; however, the respective cyclobutanes **27a** and **27b** were formed with very high enantioselectivity (entries 1 and 2, the respective **TS-A6** and **TS-B2** from Scheme 6 are likely operating and explain the observed selectivity for alkenes **26a** and **26b**). Gratifyingly, no detectable amounts of the diastereomeric product originating from a nonstereospecific process was observed (compare entry 1 and 3). Interestingly, *E*-alkenes (entries 3–7) performed significantly better in terms of *E*/*Z* selectivity of products. Considering the two transition states **TS-A7** and **TS-B3**, this is not surprising because **TS-A7** encounters a substantial steric interaction between the *E*-*β*-substituent and the boroaryl group, whereas **TS-B3** is less affected by this substituent pointing away from the large boroaryl group (see Scheme 7a for details). Thus, *E*-isomeric cyclobutanes were formed almost exclusively from *E*-alkenes; however, product **27c** (entry 3) was obtained with low enantioselectivity even when the temperature was decreased to −20 °C. A modest improvement was accomplished by exchanging catalyst **2c** with **2a** to provide the desired product in 90:10 er. Interestingly, when benzyl allenoate **1a** was used instead of its thio-analog **1c**, good enantioselectivity was achieved while maintaining the high level of *E*/*Z* selectivity (entry 4). Steric bulk, as imposed by ethyl groups on their respective positions (alkene **26d** and **26e**), was well tolerated giving products **27e** and **27f** in good yield and enantioselectivity. Finally, cyclic alkene **26f** proceeded in 88% yield and 94:6 er with thiobenzyl allenic ester **1c**. Its absolute stereochemistry was unambiguously determined by X-ray diffraction of the respective pentabromophenyl ester **28** and was found to be in agreement with the proposed models (Scheme 7b).

Table 2. Stereospecific [2+2] Cycloadditions

Entry	Alkene	Product	E/Z selectivity[a]	Yield[b]	er[c]
via TS-A6					
1[d]	 **26a**	 **27a**	34:66	40% (60%)[e]	>99:1
2	 **26b**	 **27b**	38:62	32% (52%)[e]	>99:1
via TS-B3					
3[d]	 **26c**	 **27c**	>20:1 with **2a**: > 20:1	68% 65%	84:16 90:10
4	 **26c**	 **27d**	88:12	84%	95:5
5	 **26d**	 **27e**	86:14	78%	96:4
6	 **26e**	 **27f**	95:5	95%	96:4
7[d]	 **26f**	 **27g**	>20:1	91%	94:6

[a]Determination by ^{1}H NMR of the crude reaction mixture utilizing a calibrated standard. Reactions run under optimized conditions using catalyst **2e**. [b]Yields reported of pure major isomer as average of two experiments. [c]Enantiomeric ratio of the major isomer (see Supporting Information for er of minor isomers). [d]Reactions run at −20 °C. [e]Combined yield of both isomers in parentheses.

Scheme 7. TS for *E*-Alkenes



CONCLUSION

In summary, a method for enantioselective [2+2] cycloadditions of activated alkenes with allenoates has been developed. Supported by mechanistic evidence, this reaction resembles a rare example of a concerted, enantioselective [2+2] cycloaddition with activated alkenes. As such, its potential to generate molecular complexity, with precise control of stereochemistry, makes the reaction especially

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attractive toward the synthesis of cyclobutane containing targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b10008.

Crystallographic data for $C_{13}H_{14}O_2$ (CIF)
Crystallographic data for $C_{22}H_{17}Br_5O_2$ (CIF)
Experimental procedures, analytical data for all new compounds (PDF)
Crystallographic data for $C_{20}H_{17}F_3O_3$ (CIF)

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Notes

The authors declare no competing financial interest.

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