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Catalytic Enantioselective [2+2] Cycloaddition of α-Halo Acroleins: Construction of Cyclobutanes Containing Two Tetrasubstituted Stereocenters

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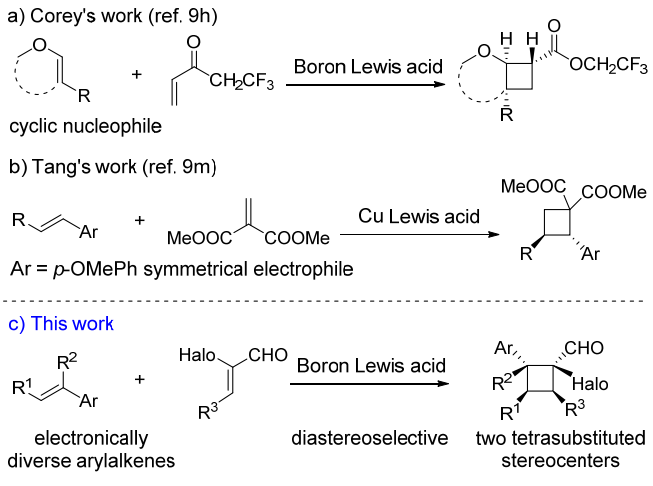
Abstract: A catalytic enantioselective formal [2+2] cycloaddition between α-halo acroleins and electronically diverse arylalkenes is described. In the presence of (*S*)-oxazaborolidinium cation as the catalyst, densely functionalized cyclobutanes containing two vicinal tetrasubstituted stereocenters were produced in high yields and high diastereoselectivities with excellent enantioselectivities. Mechanistic studies revealed that the cis isomer could be transformed into the trans isomer via an enantiocontrolled process. A gram-scale reaction of this catalytic method was used to demonstrate its synthetic potential.

The cyclobutane ring is an important structural motif in natural products and pharmaceutical molecules, and many biologically-active compounds contain a cyclobutane ring.[1] Driven by the relief of inherent ring strain, they can also undergo broad synthetic transformations, which enable the development of new synthetic methods,[2,3] and often act as key intermediates in synthetic routes to obtain structurally complex targets.[4] [2+2] Cycloaddition reactions represent the most straightforward and atom-economical approach for constructing cyclobutanes, and considerable efforts have been devoted to accomplish this transformation.[5,6] Although recent advances have given rise to elegant enantioselective methods, the enantioselective synthesis of cyclobutanes is still challenging.[7-12] Among the established methods, Lewis-acid-catalyzed [2+2] cycloaddition between activated olefins and alkenes is particularly interesting because the resulting donor-acceptor cyclobutanes can behave as 1,4-zwitterionic synthons in chemical transformations.[3] In 1989, the Narasaka group reported the first catalytic enantioselective [2+2] cycloadditions using a Ti-TADDOL complex as the catalyst with 1,1-bis(methylthio)ethylene as the substrate, and the reaction provided excellent enantioselectivity.[9a] Since then, several catalytic asymmetric reactions have been developed.[9b-n] Despite these advances, significant limitations remain. First, due to the formation of dipolar intermediate in transition state, acyclic asymmetrical 1,1-disubstituted olefins or alkenes would generate cyclobutanes with low diastereoselectivities.[9e-g] This is a common challenge in [2+2] cycloadditions, including photochemical [2+2] reactions involving radical intermediates.[5] Thus, in enantioselective [2+2] reactions, alkenes with two same geminal substituents have always been utilized.[7-11] To our knowledge, only one example has reported [2+2] cycloaddition between acyclic asymmetrical 1,1-disubstituted activated olefins and acyclic asymmetrical 1,1-disubstituted alkenes using a photochemical reaction.[7f] To realize Lewis-acid-catalyzed version of such reaction is important, because the resulting cyclobutanes contain two vicinal tetrasubstituted stereocenters. Second, in order to trigger nucleophilic addition, most reactions require the use of highly polarized alkenes with S, O, or N atoms attached to the double bond (Scheme 1a).[9a-j] With exceptions, two examples using highly-activated *p*-methoxyl styrenes were reported.[9k-m] In 2015, Tang et al. reported an impressive Cu-catalyzed reaction by reacting a variety of styrenes with methylidenemalonate in high yield and excellent enantioselectivity.[9m] These reactions are only applicable to *p*-methoxyl styrenes and the reaction of 2-substituted methylidenemalonate gave the product in poor diastero- and enantioselectivity (Scheme 1b). Further, in the realm of [2+2] cycloaddition reactions, the utilization of electron-deficient styrene substrates is challenging.[9k,l,13] In view of the aforementioned challenging questions, to develop a new and efficient catalytic protocol to enlarge the scope of methodologies that can be applied would be highly desirable and valuable. Here, we disclose an oxazaborolidinium-ion-catalyzed formal [2+2] cycloaddition of α-halo acroleins with electronically diverse arylalkenes that can be used to construct cyclobutanes with high diastereoselectivities. The resulting cyclobutanes bearing two



Scheme 1. Chiral Lewis Acid-Catalyzed Asymmetric [2+2] Cycloadditions.

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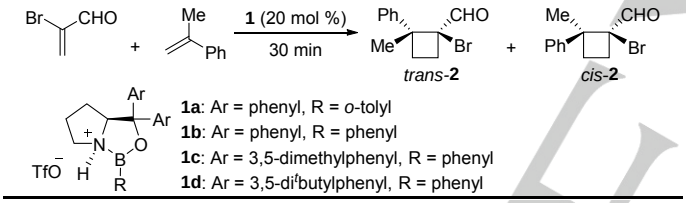
adjacent tetrasubstituted stereocenters[14] and multiple functional groups that facilitate late-stage modifications (Scheme1c).

Initially, the enantioselective [2+2] cycloaddition between α-bromo acrolein and α-methyl styrene was carried out using 20 mol % of catalyst **1a** at −78 °C in toluene. After 30 min, the resulting optically active *trans*-cyclobutane **2**[15] was isolated in 30% yield and 51% ee, with a similar amount of the cis isomer (Table 1, entry 1). Under the same reaction conditions, catalyst **1b** with a phenyl group attached to the boron provided slightly better results (entry 2). To improve the enantioselectivity, sterically hindered 3,5-dimethylphenyl was used as the Ar substituent in **1c**, and the enantiomeric excess substantially increased to 89% (entry 3). The yield and diastereoselectivity dramatically increased with the temperature (entries 4 and 5). When the reaction was carried out at −45 °C, the yield and diastereoselectivity increased to 77% and 15:1, respectively. In another experiment at −25 °C, the yield decreased to 43%, but the dr increased to 20:1 (entry 6). The effect of the solvent was also examined using catalyst **1c**. Dichloromethane provided inverse diastereoselectivity and decreased the ee, while polar butyronitrile afforded a complex mixture (entries 7 and 8). To further investigate the catalytic performance, we performed a reaction using α-methyl styrene as the limiting reactant. Using **1c** as the catalyst in toluene at −45 °C, the desired cyclobutane **2** was produced in 83% yield and 93% ee with a 14:1 diastereoselectivity (entry 9).[16]

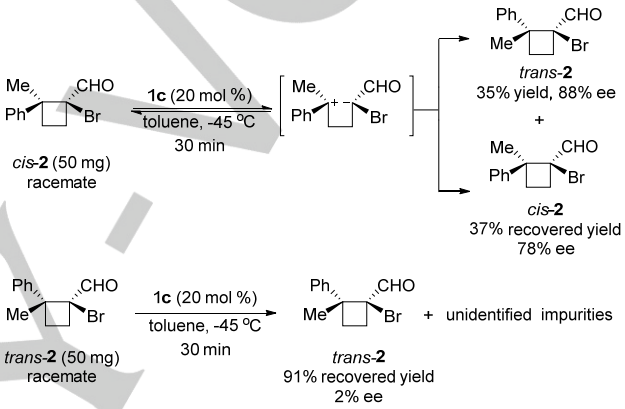
Table 1. Optimization of the Reaction Conditions.[a]



entry	cat.	T (°C)	solvent	trans/cis[b]	yield (%)[c]	ee (%)[d]
1	**1a**	−78	toluene	1.1:1	30/26	51/47
2	**1b**	−78	toluene	1.5:1	33/20	59/41
3	**1c**	−78	toluene	1.4:1	35/26	89/43
4	**1c**	−60	toluene	4:1	52	90/35
5	**1c**	−45	toluene	15:1	77	92
6	**1c**	−25	toluene	20:1	43	88
7	**1c**	−45	CH_2Cl_2	0.5:1	22/43	60/60
8	**1c**	−45	butyronitrile		trace	
9[e]	**1c**	−45	toluene	14:1	83	93

[a] Unless noted, the reaction of α-bromo acrolein (0.27 mmol) with α-methyl styrene (0.41 mmol) was performed with 20 mol % of catalyst **1**, for 30 min in 1.0 mL of solvent. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of the trans/cis isomer. [d] The ee of trans/cis isomer was determined by chiral HPLC. [e] α-Bromo acrolein (0.41 mmol) and α-methyl styrene (0.27 mmol).

Based on the significant effect of reaction temperature on the yield and diastereoselectivity, we envisioned that the cis isomer could be transformed into the trans isomer in the reaction system. To verify this speculation, we carried out experiments with pure *cis*-**2** (Scheme 2). Racemic *cis*-**2** was subjected to the optimized conditions for 30 min, and *trans*-**2** was formed in 35% yield, along with recovered *cis*-**2** and some unidentified decomposition products. Interestingly, this process involved enantioconversion, and the enantiomeric excess of *trans*-**2** and recovered *cis*-**2** were 88% and 78%, respectively. A similar experiment using isolated racemic *trans*-**2** was also carried out. In contrast to the result of *cis*-**2**, *trans*-**2** was recovered in 91% yield and 2% ee, without the formation of *cis*-**2**, according to the crude ^{1}H NMR analysis. These results indicated that neither isomer was stable and both decomposed, but the ring of *cis*-**2** was more easily opened, which allowed some to be converted into *trans*-**2**. Thus, careful control of the reaction temperature and time is crucial to obtain high yields and high diastereoselectivities.



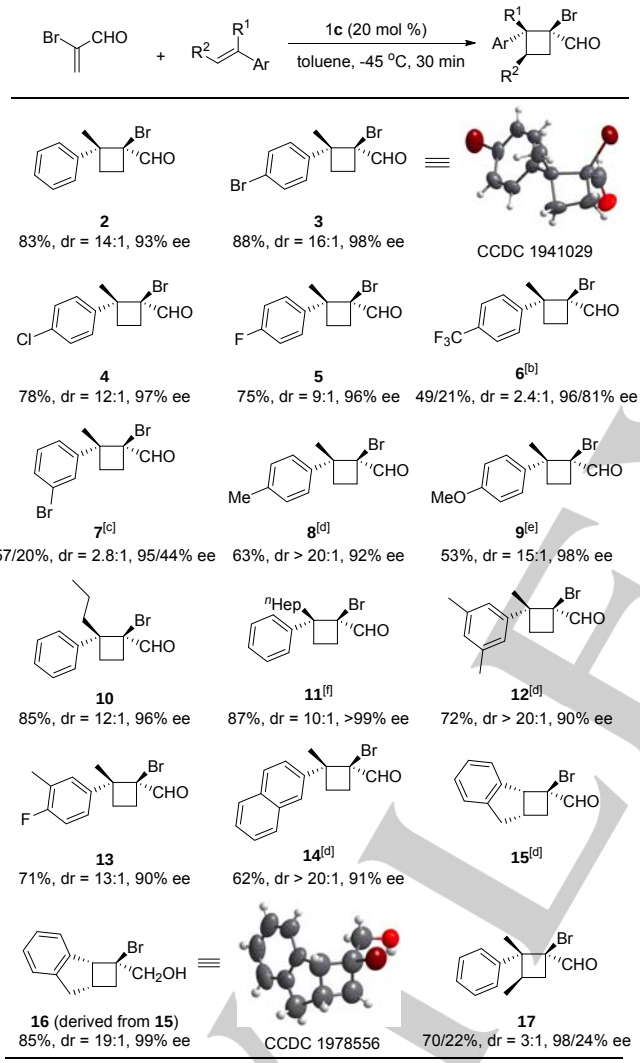
Scheme 2. Mechanistic Considerations.

Based on the preliminary mechanistic investigation and with the optimal reaction conditions determined, we investigated this catalytic system using a broad range of arylalkenes. As depicted in Table 2, various para halogenated styrenes reacted quite well with α-bromo acrolein and generated optically-active cyclobutanes **3**-**5** in high yields with high diastereomeric ratios. The absolute configuration of **3** was determined to be (1*S*,2*R*) based on X-ray crystallographic analysis. Electron-poor styrenes were suitable for this transformation, delivering products **6** and **7** in excellent ee values, albeit moderate yields and diastereoselectivities. Highly reactive *p*-Me and *p*-OMe substituted styrenes furnished **8** and **9** in moderate yields. *n*-Propyl and *n*-heptyl substituted styrene gave higher yields than the corresponding α-methyl styrene (**10** and **11**). Disubstituted phenyl styrene worked well, and products **12** and **13** were obtained in high yields with consistently high enantiomeric excesses. Naphthyl alkene and indene were highly active substrates and provided products **14** and **15** at −65 °C in high yields with excellent diastero- and enantioselectivities. Compound **15** was not sufficiently stable for isolation by silica gel chromatography, thus it was converted to alcohol **16** by adding $NaBH_4$ and menthol to the crude reaction mixture (see SI). The absolute configuration of **16** was confirmed based on X-ray crystallographic analysis. To our delight, (*E*)-2-Phenyl-2-butene could react fast and provided cyclobutane **17** in good diastereoselectivity and excellent enantioselectivity. Application

of 1,1-dialkyl alkenes in this reaction did not provide cyclobutane product.

Given the good results shown in Table 2, the substrate scope with respect to various acroleins was examined. As described in Table 3, α-chloro and α-iodo acroleins reacted well with α-methylstyrene to give highly enantiomerically enriched cyclobutanes **18** and **19** in high yields with high diastereomeric ratios. For α,β-disubstituted (*Z*)-acroleins, however, the optimal catalyst **1c** for monosubstituted acroleins was not suitable for disubstituted (*Z*)-acroleins. The use of a more hindered catalyst **1d** with Ar = 3,5-di^{t}butyl, was found to be more effective for

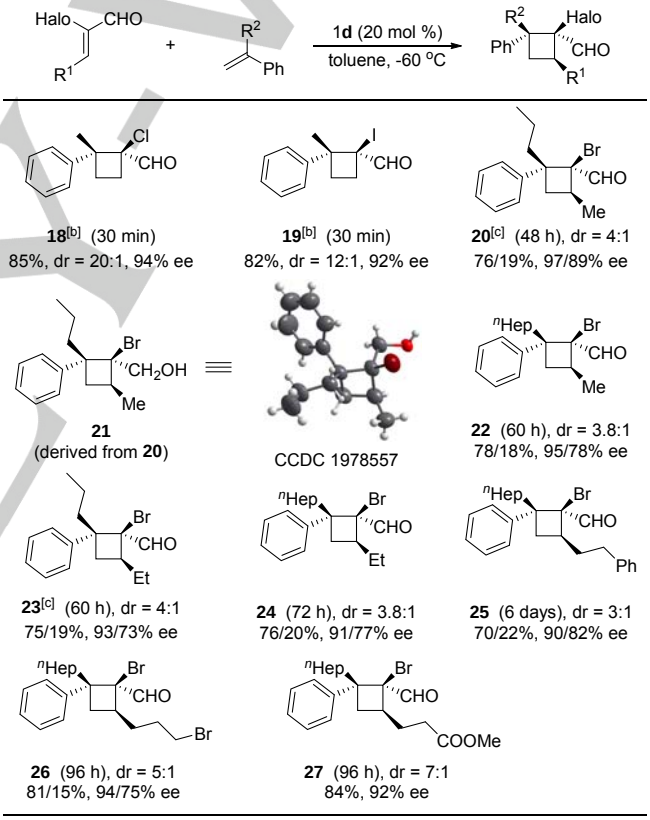
Table 2. Evaluation of the Substrate Scope Using Different Arylalkenes.[a]



[a] Unless otherwise noted, the reaction was performed with α-bromo acrolein (0.41 mmol), arylalkene (0.27 mmol), and catalyst **1c** (20 mol %) in toluene (1.0 mL) for 30 min. The reported yields are of the isolated trans/cis product, the ee was determined by HPLC analysis, and the dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] 30 mol % of catalyst at 0 °C for 15 min. [c] 30 mol % of catalyst for 1 h. [d] 10 mol % of catalyst at −65 °C. [e] 10 mol % of catalyst at −95 °C in 3 mL of toluene for 1 h. [f] The ee was determined after reduction to the corresponding alcohol.

producing a higher enantiomeric excess. Using **1d** as the catalyst, α-bromo-β-methyl, α-bromo-β-ethyl, and α-bromo-β-phenylethyl acroleins reacted effectively with α-propyl and α-heptyl styrenes, affording the corresponding cyclobutanes in good yields and excellent ee (**20**, **22**-**24**). Application of (*E*)-α-bromo-β-methyl acrolein in reaction, result was exactly the same with reaction of (*Z*)-α-bromo-β-methyl acrolein, as the (*E*)-isomer was isomerized into (*Z*)-isomer quickly in the presence of catalyst.To improve the diastereoselectivity, control experiments were performed at higher temperatures. However, in this case, the cis isomers were not converted into trans isomers, and both isomers decomposed into other products. The absolute stereochemistry was determined to be (1*S*,2*R*,4*S*) by the reduction of product **20** and X-ray analysis of the corresponding alcohol **21**. To investigate the functional group tolerance of the reaction, bromo and ester groups were introduced into the substrates. They reacted cleanly and afforded **26** and **27** in high yields with good diastereoselectivities and excellent enantiomeric excess. Unfortunately, α-bromo-β-phenyl acrolein provided the product in low yield under the current reaction conditions.

Table 3. Evaluation of the Substrate Scope Using Different Acroleins.[a]



[a] Unless otherwise noted, the reaction was performed with α-bromo acrolein (0.41 mmol), arylalkene (0.27 mmol), and catalyst **1d** (20 mol %) in toluene (1.0 mL) at −60 °C for the indicated time. Yields are of the isolated trans/cis product, the ee was determined by HPLC analysis, and the dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Reaction was conducted at −45 °C with catalyst **1c**. [c] Yield was calculated from ^{1}H NMR analysis of the isolated isomer mixture, and the ee was determined after reduction to the corresponding alcohol.

The observed stereochemistry of the asymmetric cyclobutanantion reaction using oxazaborolidinium ion catalyst **1c** can be rationalized using the transition state model shown in Figure 1. The coordination mode of acrolein to **1c** was the same as has been previously observed in cyclopropanation reactions.[17] In the pre-transition-state assembly (**28** in Figure 1),

the double bond of the acrolein is situated above the 3,5-dimethylphenyl group, which effectively shields the *re* face (back) of the acrolein from attack by styrene. Because of the steric repulsion between the bromo group and the large phenyl ring of styrene, as well as attractive π−π interactions between the aldehyde group and the phenyl ring of styrene, the styrene likely approached the double bond of acrolein to undergo nucleophilic addition with the phenyl group oriented away from the bromo group. This facilitated the 1,4-addition of styrene from the *si* face (front) of the acrolein, leading to intermediate **29**, which then cyclized to form *trans*-(1*S*,2*R*)-cyclobutane as the major enantiomer for **2** and *trans*-(1*S*,2*R*,4*S*)-cyclobutane for **20**.

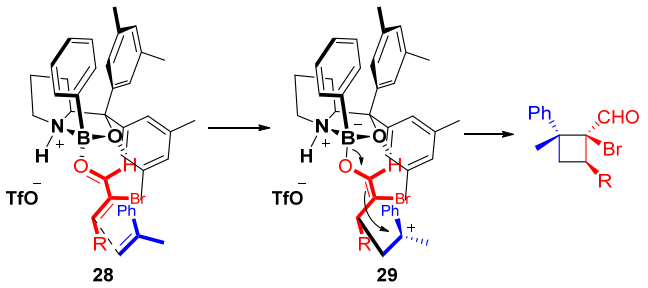
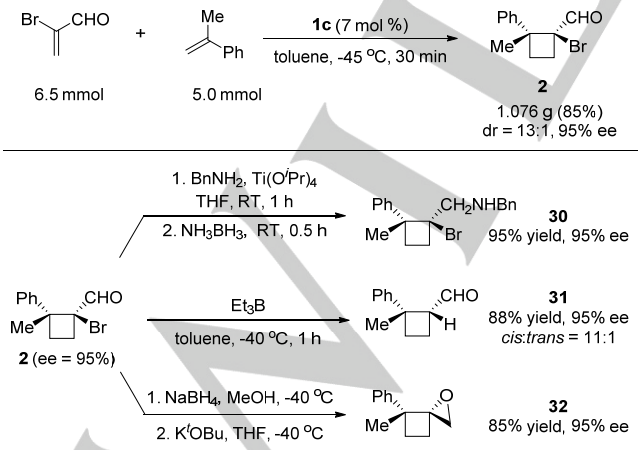


Figure 1. Transition State Model for [2+2] Cycloaddition Reaction.

To demonstrate the scalability and practicality of this catalytic protocol, a 5-mmol-scale reaction was conducted using only 7 mol % of catalyst **1c** to afford isolated cyclobutane **2** in 85% yield and 95% ee. Additional transformations are illustrated in Scheme 3. In the presence of $Ti(O^iPr)_4$, cyclobutane **2** reactedwith benzylamine, followed by reduction with NH_3BH_3 to afford β-benzyl amino cyclobutane **30** in 95% yield.[18] Debromination proceeded effectively using Et_3B as a radical initiator at −40 °C and furnished product **31** in 88% isolated yield of the cis isomer.[19] Reduction of **2** with $NaBH_4$ in MeOH followed by treatment with KO^tBu resulted in an intramolecular SN_2-type substitution that provided the inverted spiro-epoxide **32** in 85% yield with ee retention.[20]



Scheme 3. Scale Up of the Reaction and Derivatizations.

In summary, the first example of a Lewis-acid-catalyzed enantioselectivie [2+2] cycloaddition between acyclic asymmetrical 1,1-disubstituted olefin and acyclic asymmetrical 1,1-disubstituted alkene was accomplished. The reaction produced cyclobutanes with two vicinal tetrasubstituted stereocenters and multiple functional groups in high yields and excellent enantiomeric excess. The absolute stereochemistry of the cyclobutanes predicted by the transition-state model is shown in Figure 1. The cyclobutane products could be prepared at the gram scale, and the densely-functionalized compounds readily underwent late-stage derivatization.

Acknowledgements

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Keywords: Asymmetric synthesis • Chirality • [2+2] Cycloaddition • Cyclobutane • Tetrasubstituted stereocenter

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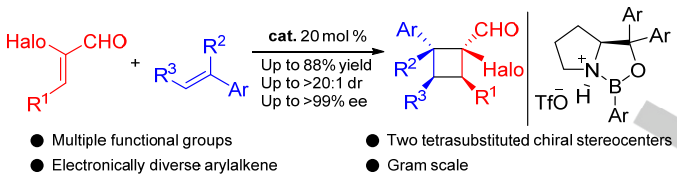

[2+2] Cycloaddition reaction of electronically diverse arylalkenes with α-bromo acroleins provided highly functionalized cyclobutanes bearing two adjacent tetrasubstituted stereocenters. Mechanistic studies revealed *cis*-cyclobutane could be enantioselectively transformed into the trans isomer in reaction system.