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Oxazaborolidinium Ion-Catalyzed Cyclopropanation of α-Substituted Acroleins: Enantioselective Synthesis of Cyclopropanes Bearing Two Chiral Quaternary Centers

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Supporting Information

ABSTRACT: A catalytic synthetic route to highly functionalized chiral cyclopropane derivatives was developed by Michael-initiated cyclopropanation of α-substituted acroleins with aryl- and alkyl diazoacetates. In the presence of chiral (*S*)-oxazaborolidinium cation **1b** as a catalyst, the reaction proceeded in high yield (up to 93%) with high to excellent diastereoselectivity (up to 98% de) and enantioselectivity (up to 95% ee).

The cyclopropane ring is a common unit in a diverse range of both naturally occurring and artificial compounds. Many biologically active compounds contain complex cyclopropane moieties.[1] Because of their unique combination of a rigid structure with inherent electrophilic reactivity, cyclopropane rings can constitute the key step in complex molecular syntheses.[2] Thus, over the past few decades considerable attention has been devoted to the development of asymmetric methodologies for the synthesis of highly functionalized cyclopropane derivatives.[3,4] Among these methods, catalytic enantioselective Simmons–Smith-type reactions[3] and transition-metal-catalyzed reactions[5] utilizing metal carbenoid intermediates have been studied extensively.

A Michael-initiated ring-closure reaction using ylides[6] is complementary to these variants and proceeds chemoselectively with electron-deficient olefins. Aggarwal[6f] and Gaunt[6l] reported pioneering studies on catalytic enantioselective cyclopropanations via chiral sulfonium and ammonium ylides. Although cyclopropanation of diazo reagents and olefins represents one of the most general methods for constructing cyclopropane derivatives, there are a few reports using diazoacetate as the ylide.[7] Enantioselective cyclopropanation reactions via Michael-initiated ring closure between α,β-unsaturated aldehydes and diazoacetates (eq 1) are highly desirable. This is because the corresponding cyclopropanes contain two or more electron-withdrawing groups that have the potential to be highly valuable synthetic intermediates for various applications.[8] In addition, this asymmetric process with α-substituted acroleins results in the construction of two chiral quaternary stereocenters. This remains a challenging area, and new procedures are necessary.[9] Highly enantioselective catalytic methods have not been reported to date. However, Maruoka and co-workers reported titanium BINOLate-catalyzed asymmetric cyclopropanation with moderate enantioselectivity.[7c]

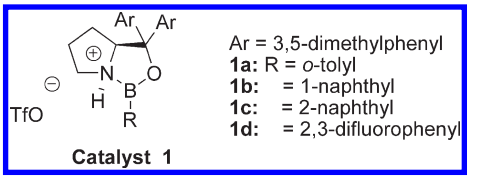
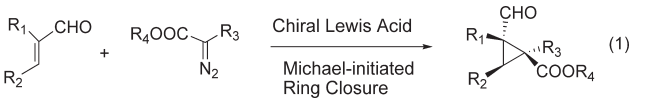


Figure 1. Structures of catalysts **1**.



Catalysts **1** (Figure 1) are generated from the corresponding oxazaborolidines by protonation with trifluoromethanesulfonic acid (triflic acid). They have been proven as effective catalysts for enantioselective Diels–Alder reactions,[10a] cyanosilylations,[10b] three-component coupling reactions,[10c] 1,3-dipolar cycloadditions,[10d] and the Mukaiyama aldol reaction.[10e] In addition, much evidence exists in support of the formation of complexes between **1** and aldehydes.[10a] In view of these powerful catalytic activities, we became interested in evaluating chiral oxazaborolidinium ions **1** as Lewis acid catalysts for asymmetric cyclopropanation. In this communication, we present the first case of highly enantiocontrolled catalytic cyclopropanation of α-substituted acroleins with diazoacetates.

Initially, an asymmetric cyclopropanation reaction between methyl phenyldiazoacetate and methacrolein was examined in the presence of 20 mol % oxazaborolidinium ion **1a** (Figure 1), which was activated by triflic acid. When the reaction was carried out at −45 °C in propionitrile, the desired optically active cyclopropane **2a** was formed in 35% yield with 76% ee and a high level of trans selectivity.[11] At the same time, a 45% yield of 1-pyrazoline **3** (mixture of trans and cis isomers) was isolated. The effect of changing the catalyst boracycle substituent was then investigated, and the best boron aryl substituent was found to be 1-naphthyl (Table 1, entries 2–4). To improve the yield and

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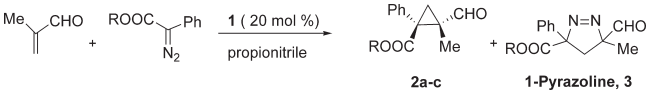
Table 1. Asymmetric Cyclopropanation of Methacrolein with Phenyldiazoacetates Catalyzed by Oxazaborolidinium Ions 1



entry[a]	cat.	R	2	trans:cis[b]	yield (%)[c]	ee (%)[d]
1	**1a**	Me	**2a**	89:11	35	76
2	**1b**	Me	**2a**	91:9	57	84
3	**1c**	Me	**2a**	88:12	35	79
4	**1d**	Me	**2a**	97:3	43	59
5	**1b**	Et	**2b**	95:5	65	87
6	**1b**	*t*-Bu	**2c**	91:9	63	91
7	**1b**	*t*-Bu	**2c**	89:11	71	91

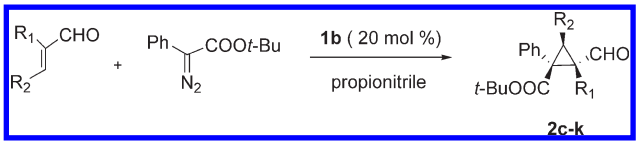
[a] Except for entry 7, the reactions were performed with 1.2 equiv of methacrolein and 1.0 equiv of phenyldiazoacetate at −45 °C for 30 min. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of the trans isomer. [d] The ee of **2** was determined by chiral HPLC.

enantioselectivity further, the methyl group of the diazoacetate was replaced by a more sterically hindered ethyl group. The yield was enhanced to 65% with a diastereomeric ratio of 95:5 and an enantiomeric excess of up to 87% (entry 5). An increase in enantioselectivity was observed in the subsequent reaction when *tert*-butyl phenyldiazoacete was used, although the diastereoselectivity decreased slightly and the yield was still moderate (entry 6). In another experiment under the same conditions and at −45 °C, the diazoacetate was consumed in 30 min, and the reaction mixture was then stirred for 8 h at 0 °C.[12] The desired cyclopropane **2c** was obtained in a higher yield of 71% and with similar diastereo- and enantioselectivties without any pyrazolines (entry 7).

After the optimization of the asymmetric cyclopropanation conditions, the scope of this methodology was investigated using a range of substituted acroleins with **1b** as the catalyst. As summarized in Table 2, the steric properties of the α-substituents had different effects on the acroleins. In spite of this, the results included moderate to good yields, high diastereoselectivities, and excellent enantioselectivities (entries 1−3). Cyclopropanation involving electron-deficient olefins is a more challenging process,[1,3,13] but under our catalytic reaction conditions, electron-deficient olefins bearing electron-withdrawing groups were more favored. For example, cyclopropanations involving α-chloro- and α-bromoacrolein produced corresponding halocyclopropanes[14] **2f** and **2g** in excellent yields and enantioselectivities with nearly complete control of the diastereoselectivity (entries 4, 5). Asymmetric cyclopropanation with the benzyl group also proceeded with good enantiocontrol, although the yield and diastereocontrol were not as high (entry 6). Absolute configurations were assigned on the basis of the structure of **2g**, which was confirmed unambiguously by an X-ray crystallographic study.

The catalytic asymmetric cyclopropanation of α,β-disubstituted acroleins was attempted in order to obtain highly functionalized chiral cyclopropanes containing three stereogenic centers, including two adjacent quaternary centers. Remarkably, good results were obtained with α,β-dimethylacrolein (Table 2, entry 7). The stereochemical relationship of **2i** was unambiguously established by

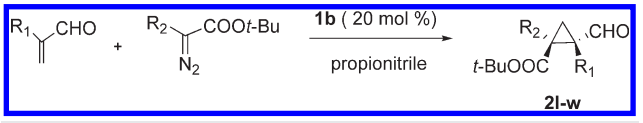
Table 2. Asymmetric Cyclopropanation of *tert*-Butyl Phenyldiazoacetate with α- or α,β-Substituted Acroleins Catalyzed by 1b



entry	R_1, R_2	2	T (°C), t	trans:cis[a]	yield (%)[b]	ee (%)[c]
1	Me, H	**2c**	−45, 0.5 h	89:11	71	91
2[d]	Et, H	**2d**	−45, 0.5 h	88:12	75	93
3[d]	*i*-Pr, H	**2e**	−45, 0.5 h	95:5	52	90
4	Cl, H	**2f**	−45, 0.5 h	99:1	87	92
5	Br, H	**2g**	−45, 0.5 h	93:7	91	95[e]
6	Bn, H	**2h**	−78, 9 h	86:14	64	85
7	Me, Me	**2i**	−20, 20 h	92:8	91	92[f]
8[g]	Me, Et	**2j**	−50, 5 days	91:9	70	82
9[g]	−$(CH_2)_4$−	**2k**	−20, 5 days	90:10	51	94

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of the trans isomer. [c] The ee of the trans isomer was determined by chiral HPLC. [d] For detailed conditions, see the Supporting Information. [e] The (1*S*,2*R*) absolute configuration was determined by X-ray analysis. [f] The (1*R*,2*S*,3*S*) absolute configuration was determined by reduction with $NaBH_4$, *p*-bromobenzoylation, and X-ray analysis. [g] Using 40 mol % catalyst.

Table 3. Asymmetric Cyclopropanation of Various Diazoacetates and α-Substituted Acroleins Catalyzed by 1b



entry	R_1, R_2	2	T (°C), t (h)	trans:cis[a]	yield (%)[b]	ee (%)[c]
1	Me, 4-BrPh	**2l**	−45, 1	80:20	72	89
2	Br, 4-BrPh	**2m**	−25, 5	95:5	93	95
3	Cl, 4-BrPh	**2n**	−25, 5	96:4	93	92
4	Me, 2-MePh	**2o**	−45, 6	92:8	83	90
5	Br, 2-MePh	**2p**	−45, 0.5	90:10	88	94
6	Cl, 2-MePh	**2q**	−45, 0.5	90:10	87[d]	93
7	Cl, 3-MePh	**2r**	−45, 0.5	92:8	88[d]	95
8	Cl, 4-MePh	**2s**	−78, 6	93:7	85	95
9	Cl, 3-MeOPh	**2t**	−45, 1	90:10	87	95
10	Cl, 4-MeOPh	**2u**	−78, 2	55:45	51[e]	95
11	Br, 4-NO_2Ph	**2v**	0, 18	92:8	71[d]	92
12	Cl, H	**2w**	−78, 1	91:9	85[d]	95
13	Br, H	**2x**	−78, 2	91:9	80[d]	95

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of the trans isomer. [c] The ee of the trans isomer was determined by chiral HPLC or GC. [d] Yield of the trans isomer was calculated by ^{1}H NMR analysis of the isolated mixture of isomers. [e] The cis isomer was obtained in 43% yield with 94% ee.

X-ray crystallographic analysis after transformation of the cyclopropane carboxaldehyde to the corresponding *p*-bromobenzoyl ester. Under the optimized conditions, cyclopropanation of 1-cyclohexenecarboxaldehyde afforded electrophilic bicyclic cyclopropane[8c] **2k** with high diastereoselectivity and excellent enantioselectivity, although in moderate yield (entry 9).

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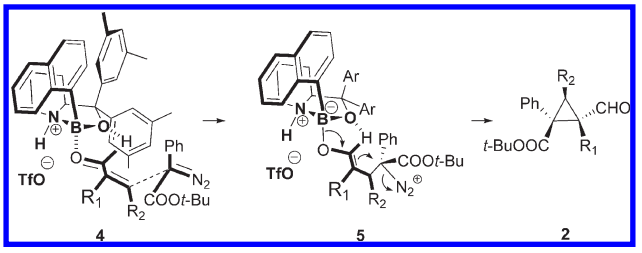

Figure 2. Transition state model for the asymmetric cyclopropanation reaction between *tert*-butyl phenyldiazoacetate and α,β-disubstituted acroleins.

Encouraged by the good results demonstrated in Table 2, we applied this catalytic methodology to the cyclopropanation of α-substituted acroleins using a range of diazoacetates. As summarized in Table 3, although the electronic properties of the aryldiazoacetates[15] varied vastly, the reactions produced the corresponding cyclopropanes in high yields and diastereoselectivities with excellent enantioselectivities (entries 1−9 and 11). It is notable that the substituents at the α-position of the acrolein were also electronically different (entries 1−6). The use of 4-methoxyphenyldiazoacetate dramatically diminished the trans:cis ratio to 55:45,[7c] but high enantiocontrol was still achieved for each isomer (95% ee for trans, 94% ee for cis; entry 10). Although the reaction between *tert*-butyl diazoacetate and methacrolein afforded optically active 2-pyrazoline[10d] in the presence of oxazaborolidinium catalyst **1a**, the reactions of α-haloacroleins provided the corresponding cyclopropanes **2w** and **2x** in high yields with excellent enantioselectivities (entries 12 and 13).

The observed stereochemistry of the asymmetric cyclopropanation using oxazaborolidinium ion catalyst **1b** can be explained by the transition state model shown in Figure 2. The mode of coordination of the α,β-unsaturated aldehyde to **1b** is the same as that previously shown for enantioselective Diels−Alder,[10a] cyanosilylation,[10b] and 1,3-dipolar cycloaddition[10d] reactions. In the pre-transition-state assembly (**4** in Figure 2), the double bond of the acrolein is situated above the 3,5-dimethylphenyl group. This effectively shields the *re* face (back) of the acrolein from attack by the diazoacetate. Because of the dipole−dipole interaction between the two carbonyl groups, when the diazoacetate approaches the β-carbon of acrolein for the 1,4-addition, the *tert*-butyl ester group is situated away from the aldehyde group. Thus, the 1,4-addition of the diazoacetate from the *si* face (front) of the acrolein is facilitated, leading to intermediate **5**, which can then cyclize with the loss of nitrogen to form *trans*-(1*R*,2*S*,3*S*)-cyclopropane as the major enantiomer for **2i** and *trans*-(1*S*,2*R*)-cyclopropane for **2g**.

In summary, the first case of highly enantiocontrolled catalytic cyclopropanation using diazoacetate as an ylide has been developed. This method gives highly functionalized tetrasubstituted cyclopropanes in high yields with excellent enantioselectivities. The absolute configuration of the product is that predicted by the transition state model in Figure 2. We believe that the resulting optically active electrophilic cyclopropane derivatives with densely functionalized groups could be highly valuable for further transformations.

■ ASSOCIATED CONTENT

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

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(11) The trans geometry means the ester and aldehyde groups are directed trans to each other in the cyclopropane.

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