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Enantioselective Cyclopropanation with α-Alkyl-α-diazoesters Catalyzed by Chiral Oxazaborolidinium Ion: Total Synthesis of (+)-Hamavellone B

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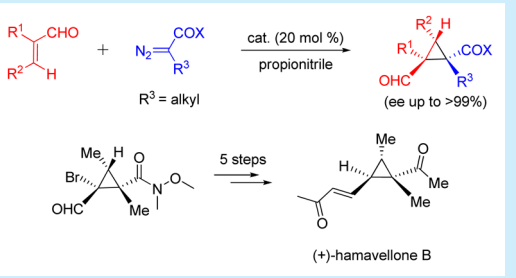
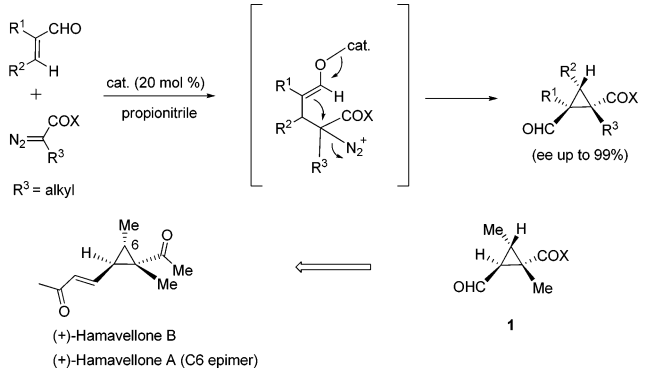
Supporting Information

ABSTRACT: Chiral oxazaborolidinium ion-catalyzed asymmetric cyclopropanation of α- or α,β-substituted acroleins with α-alkyl-α-diazoesters has been developed. With this methodology, chiral functionalized cyclopropanes containing a quaternary stereogenic center were obtained with high to excellent enantioselectivities (up to >99% ee). The synthetic utility of optically enriched functionalized cyclopropane was demonstrated in the first total synthesis of (+)-hamavellone B, which establishes the absolute configuration of natural (+)-hamavellone B.



Substituted cyclopropane is an important structural motif that is essential for biological activity and is found in a wide variety of natural products and medicinal agents.[1] During the past two decades, various catalytic systems have been developed for highly diastereo- and enantioselective cyclopropanation reactions.[2] Among them, catalytic cyclopropanation of diazo reagents and alkenes is a useful method for constructing chiral cyclopropane derivatives. Transition-metal-catalyzed cyclopropanation of alkenes[3] with various types of diazo compounds has been developed to result in stereocontrolled cyclopropane derivatives. In a complementary approach, a Lewis acid catalyzed Michael-initiated ring-closure (MIRC) reaction using diazo compounds as ylides proceeds with electron-deficient olefins, such as α,β-unsaturated carbonyl compounds (Scheme 1).[4] This method provides optically active dicarbonyl cyclopropane compounds, which were found to be important synthetic intermediates for various applications.[5]

Scheme 1. Enantioselective Synthesis of Hamavellone B



Our group reported the first example of highly enantiocontrolled catalytic cyclopropanation using α-aryl-α-diazoester as an ylide (Scheme 1, R^3 = Ar, X = O-*t*-Bu).[4d] The oxazaborolidinium ion catalyzed MIRC reaction provided highly functionalized cyclopropanes in high yields with excellent enantioselectivities. Extension of this methodology to include α-alkyl-α-diazoesters[6] is particularly attractive because this reaction forms cyclopropanes with a quaternary stereogenic carbon center bearing all alkyl groups. We envisaged enantioselective MIRC reactions with α-methyl-α-diazoesters to provide a key intermediate **1**, which has all requisite stereocenters and functional groups for synthesis of natural hamavellone B. In this paper, we report the first case of highly stereoselective catalytic cyclopropanation with α-alkyl-α-diazoester as an ylide. The synthetic utility of optically enriched functionalized cyclopropane was demonstrated in the first total synthesis of (+)-hamavellone B,[7] which also establishes the absolute configuration of natural hamavellone B.

Stereoselective cyclopropanation between α-bromoacrolein and α-benzyl diazoester was first examined in the presence of 20 mol % of oxazaborolidinium ion **2a** activated by triflic imide (Table 1, entry 1). When the reaction was performed at −78 °C in CH_2Cl_2, the desired chiral cyclopropane **3a** was formed in 48% yield, 43% ee, and with a 7:1 of *trans*/*cis* ratio[8] via the MIRC pathway (Table 1, path a). Simultaneously, 40% of diazo carbon-inserted product[9] **4** was formed as a side product via 1,2-hydride shift (path b). Use of the polar solvent propionitrile led to an increased ratio of the desired product in 83% ee with excellent trans selectivity (>20:1) (Table 1, entry 2). With propionitrile as solvent, the effect of changing boracycle catalyst

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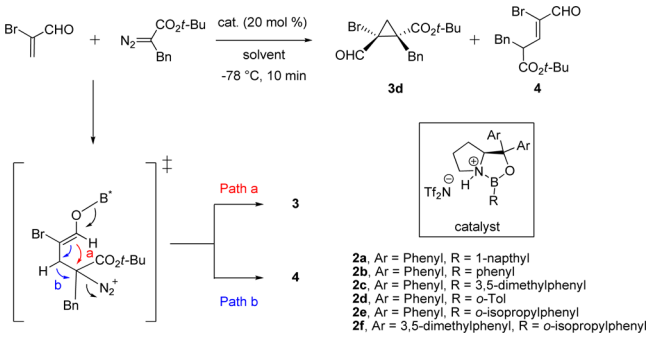
Table 1. Optimization of Asymmetric Cyclopropanation of α-Bromoacrolein with α-Benzyl-α-diazoester[a]



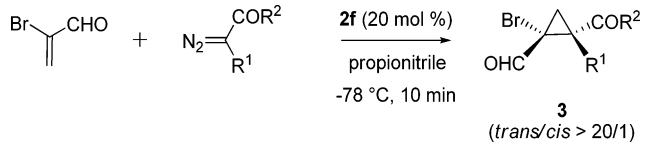
entry	solvent	cat.	3d, yield[b] (%)	3d, ee[c] (%)	*trans*/*cis*[d]
1	CH_2Cl_2	**2a**	48	43	7:1
2	CH_3CH_2CN	**2a**	47	83	>20:1
3	CH_3CH_2CN	**2b**	41	77	>20:1
4	CH_3CH_2CN	**2c**	47	81	16:1
5	CH_3CH_2CN	**2d**	52	85	>20:1
6	CH_3CH_2CN	**2e**	57	98	>20:1
7	CH_3CH_2CN	**2f**	66	99	>20:1

[a]Reaction of α-alkyl-α-diazoester (0.24 mmol) with α-bromoacrolein (0.34 mmol) was performed in the presence of **2** (20 mol %) in 1.0 mL of propionitrile at −78 °C for 10 min. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by ^{1}H NMR analysis of crude product.

substituents was then investigated. The catalyst system with a 3,5-dimethylphenyl Ar substituent and 2-isopropylphenyl R substituent gave the best result (Table 1, entries 3−7). The yield of **2f** improved to 66% in 99% ee with virtually complete *trans*-diastereoselectivity (>20:1) (Table 1, entry 7).

With the optimized reaction conditions for asymmetric cyclopropanation, this synthetic method was evaluated using a range of α-alkyl-α-diazocarbonyl compounds (Table 2).

Table 2. Asymmetric Cyclopropanation of α-Bromoacrolein with α-Alkyl-α-diazocarbonyl Compounds[a]



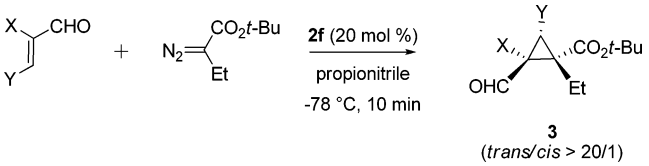
entry	3	R^1	R^2	yield[b] (%)	ee[c] (%)
1	**3a**	Me	O-*t*-Bu	50	99
2	**3b**	Et	O-*t*-Bu	76	>99
3	**3c**	*n*-Hex	O-*t*-Bu	62	>99
4	**3d**	CH_2Ph	O-*t*-Bu	66	99
5	**3e**	Propargyl	O-*t*-Bu	50	91
6	**3f**	allyl	O-*t*-Bu	55	91
7	**3g**	Et	OCH_2Ph	60	92
8	**3h**	Et	OEt	56	99
9	**3i**	Me	NMe(OMe)	51	>99
10	**3j**	CH_2Ph	NMe(OMe)	70	>99

[a]Reaction of α-alkyl-α-diazoester (0.24 mmol) with α-bromoacrolein (0.34 mmol) was performed in the presence of **2f** (20 mol %) in 1.0 mL of propionitrile at −78 °C for 10 min. [b]Isolated yield. About 30% of diazo carbon-inserted product was formed as a major side product. [c]Determined by chiral HPLC analysis.

As shown in Table 2, chiral oxazaborolidinium ion **2f** was applied to a reasonable range of olefinic substrates to provide corresponding cyclopropanes in fairly good yields with excellent enantioselectivities (Table 2, entries 1−6). Considering the other possible reaction pathways, such as 1,2-hydride shift (Table 1, path b),[4c,9] 2-pyrazoline formation,[10] and the Roskamp reaction,[11] the yield of cyclopropanation products is remarkable. Different alkyl α-diazoesters, such as benzyls or ethyls, were good substrates for this catalytic system to provide the corresponding cyclopropanes with lower enantioselectivities (Table 2, entry 7 and 8). Next, α-alkyl-α-diazo *N*-methoxy-*N*-methylamide (Weinreb amide) was applied to these catalytic conditions because the Weinreb amide group has many advantages in terms of facile transformation to ketones or aldehydes. Notably, replacement of the ester group of the diazo compound with the Weinreb amide group afforded optically pure chiral cyclopropanes in moderate to good yields (Table 2, entries 9 and 10).

To further investigate the substrate scope of the present catalytic system, catalytic asymmetric cyclopropanation reaction was performed with a range of α- or α,β-substituted acroleins and α-ethyl-α-diazoester (Table 3). Regardless of the electronic

Table 3. Asymmetric Cyclopropanation of α- or α,β-Substituted Acroleins with α-Ethyl-α-diazoester[a]



entry	3	X	Y	yield[b] (%)	ee[c] (%)
1	**3b**	Br	H	76	>99
2	**3k**	Cl	H	57	>99
3	**3l**	I	H	53	>99
4	**3m**	CH_3	H	45	99
5	**3n**	$(CH_2)_4CH_3$	H	50	86
6	**3o**	CH_2Ph	H	51	95
7	**3p**	Br	Me	75	>99
8[d]	**3q**	Br	Me	52	>99

[a]Reaction of α-ethyl-α-diazoester (0.24 mmol) with α- or α,β-substituted acroleins (0.34 mmol) was performed in the presence of **2f** (20 mol %) in 1.0 mL of propionitrile at −78 °C for 10 min. [b]Isolated yield. About 30% of diazo carbon-inserted product was formed as a major side product. [c]Determined by chiral HPLC analysis. [d]α-Methyl-α-diazo Weinreb amide was used instead of α-diazoester. The reaction time was 1 h.

or steric properties of substituents on the α-position of acroleins, highly optically active cyclopropanes **3** were obtained (Table 3, entries 1−6). Among the α-halogen substituents, α-bromoacrolein was the best substrate to give bromocyclopropanes[12] in good yield with complete control of enantio- and diastereoselectivity (Table 3, entries 1−3).

Encouraged by the good results of α-bromoacrolein, a catalytic asymmetric cyclopropanation of (*Z*)-α-bromo-β-methylacrolein was attempted to obtain highly functionalized chiral cyclopropanes containing three stereogenic centers, including two adjacent quaternary centers. All three chiral centers of controlled cyclopropane were obtained in 66% yield with an optically pure form (Table 3, entry 7). Under the optimized conditions, cyclopropanation with α-methyl-α-diazo Weinreb amide provided corresponding cyclopropane **3q** with

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excellent enantio- and diastereoselectivity, although in moderate yield (Table 3, entry 8). Absolute configurations were assigned on the basis of the structure of **3p**, which was confirmed unambiguously by X-ray crystallographic study after transformation to the corresponding carboxylic acid **3r** with a dimethyl acetal group (Figure 1).

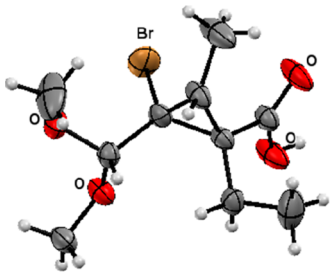
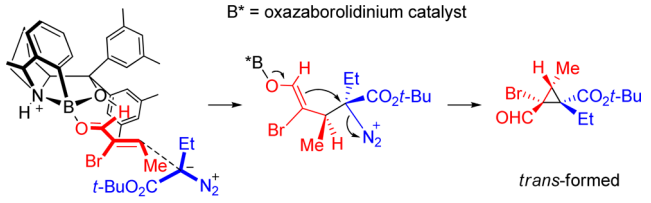


Figure 1. Single-crystal X-ray structure of **3r**.

The observed stereochemistry for the enantioselective cyclopropanation reaction with oxazaborolidinium ion catalyst **2f** is explained by the transition-state model shown in Scheme 2, which is the same as was previously postulated for the enantioselective cyclopropanation reaction with α-aryl-α-diazoester.[4d]

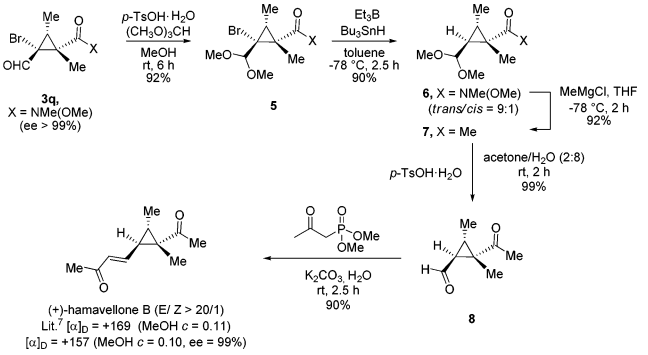
Scheme 2. Proposed Mechanism for Stereoselective Cyclopropanation between (*Z*)-α-Bromo-β-methylacrolein and α-Ethyl-α-diazoester



Having established the scope of the synthetic methodology, we then turned our attention to the first total synthesis of hamavellone B, which was isolated from the soil fungus *Hamigera avellanea* by Isaka and co-workers in 2008.[7] Hamavellone B exhibits antimalarial and anticancer activities. To date, there has been no reported synthesis of hamavellone B, and its absolute structure has not been determined.

Optically pure cyclopropane **3q**, a key intermediate for hamavellone B, was successfully synthesized with catalyst **2f** (Table 3, entry 8) (Scheme 3). After conversion of aldehyde to dimethyl acetal **5** for aldehyde protection, various radical reduction conditions for debromination were attempted. However, most of the attempted reactions resulted in decomposition of starting cyclopropane **5**. Fortunately, the use of Et_3B as a radical initiator at low temperature afforded the desired product **6** in 90% isolated yield of trans isomer. After the Weinreb amide group was converted to methyl ketone **7** with methylmagnesium chloride in 92% yield, deprotection of the dimethyl acetal group under aqueous acidic conditions provided the desired aldehyde **8** in 99% yield. Finally, Horner–Wadsworth–Emmons reaction of **8** with dimethyl 2-oxopropylphosphonate using K_2CO_3 as a base afforded (+)-hamavellone B in 90% yield. The physical data (NMR and optical rotation) of synthetic hamavellone B were in agreement with

Scheme 3. Stereoselective Synthesis of the Natural Product Hamavellone B



the reported data. Its structure determined from spectroscopic analysis indicates that the absolute structure of natural hamavellone B is a (1*S*,2*S*,3*S*)-configuration.[13]

In summary, the first case of highly enantioselective catalytic MIRC cyclopropanation using α-alkyl-α-diazoester has been developed. This method gives highly functionalized cyclopropanes containing quaternary stereogenic centers in which excellent enantioselectivity (up to >99% ee) and virtually complete trans-diastereoselectivity were achieved. Moreover, this methodology was successfully applied to the first total synthesis of (+)-hamavellone B and determination of the absolute structure of natural hamavellone B.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02970.

Experimental procedures and full analytical data (PDF)
X-ray crystallographic data for **3r** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) Conversion of **1** (X = O-*t*-Bu) and **3q** to diol provided same product, and (−)-hamavellone B was synthesized with *ent*-**2f** catalyst; see the Supporting Information.

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