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Catalytic Enantioselective Synthesis of 2,5-Dihydrooxepines

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Abstract: *A Michael addition initiated cyclopropanation/retro-Claisen rearrangement tandem reaction was developed for the enantioselective synthesis of highly functionalized 2,5-dihydrooxepines. In the presence of a chiral oxazaborolidinium ion (COBI) catalyst, the reaction proceeds to give good yields and high enantioselectivity.*

Oxepine and hydrooxepine derivatives form the structural core of numerous naturally occurring biologically active compounds and present interesting challenges as potential synthetic targets (Figure 1).[1] While a variety of synthetic

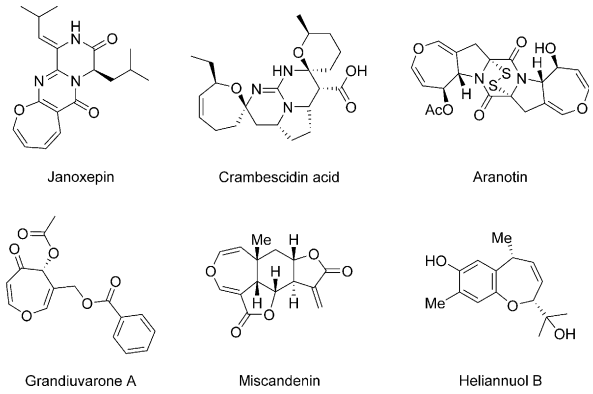
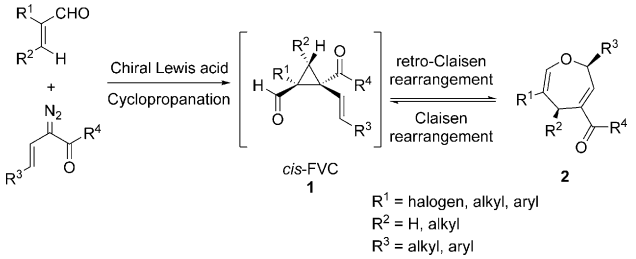


Figure 1. Natural products containing oxepine and hydrooxepine substructures.

methods have been developed through the years for their synthesis,[2–6] few approaches exist for the preparation of enantioenriched hydrooxepines from achiral starting materials.[4] The development of new stereoselective methods to access substituted hydrooxepines from simple, achiral starting materials is thus highly desirable. [3,3]-Sigmatropic rearrangement is an efficient strategy to access dihydrooxepines in a stereospecific manner.[5,6] Cope rearrangement of 1,2-divinyl epoxides provides 4,5-dihydrooxepine derivatives.[5] A similar transformation with cyclopropane derivatives where one of the vinyl groups is replaced with a C=O group, known as the retro-Claisen rearrangement, leads to 2,5-dihydrooxepine derivatives through an analogous mechanism.[6] While retro-Claisen rearrangements of this type are quite common for 2,5-dihydrooxepines, asymmetric examples of this reaction are rare.[4c] Indeed, using this approach for the formation of oxepine derivatives is discouraged due to the multiple steps required to prepare chiral *cis*-1-formyl-2-vinylcyclopropanes (FVCs) for such a rearrangement reactions.[6]

Recently, our group has reported highly enantioselective catalytic Michael addition initiated cyclopropanations[7] using diazoesters as ylides with the chiral oxazaborolidinium ion[8] (COBI) as a Lewis acid catalyst. We envisioned that the reaction of substituted acroleins with vinyldiazoester would generate chiral *cis*-1-formyl-2-vinylcyclopropanes (FVCs; **1**), which are ideally substituted for subsequent retro-Claisen rearrangement to provide highly functionalized 2,5-dihydrooxepines (**2**; Scheme 1).



Scheme 1. Asymmetric tandem cyclopropanation/retro-Claisen rearrangement to provide 2,5-dihydrooxepines.

Although *cis*-FVCs **1** and 2,5-dihydrooxepines **2** are known to be in equilibrium that generally favors **1**, the equilibrium could be controlled to favor **2** by using π-stabilizing substituents such as the COR^4 or R^1 groups (Scheme 1).[4c,6a–b,9] To the best of our knowledge, a catalytic asymmetric synthetic method to prepare dihydrooxepine derivatives has not been reported to date. In this communication, we describe the first example of a catalytic asymmetric formation of 2,5-dihydrooxepines through tandem cyclopropanation/retro-Claisen rearrangement from the simple starting materials acrolein derivatives and vinyldiazo compounds.[10]

Enantioselective formation of 2,5-dihydrooxepine was first examined with α-bromoacrolein and γ-methyl-α-vinyl diazoester in the presence of COBI catalyst **3a**. When the reaction was carried out at −78 °C in propionitrile, chiral 2,5-dihydrooxepine **2a** was formed in 50% yield with 58% *ee* (Table 1, entry 1). At the same time, 48% of *trans*-FVC **1a** was isolated, which was confirmed by 1D NOE experiments as having a *trans* relationship between the aldehyde and olefin (path b). Interestingly, while there are some reports that high temperature is required for retro-Claisen rearrangement,[4c] otherwise mixtures of *cis*-FVC and 2,5-dihydrooxepine form,[6b–c,9b–c] *cis*-FVC **1a** was not observed with these reaction conditions. It appeared that all of the *cis*-FVC **1a** was

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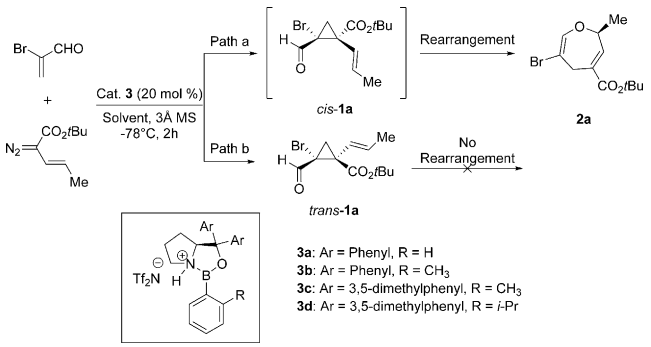
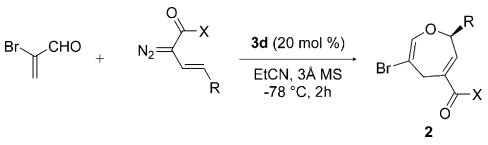
Table 1: Optimization of enantioselective 2,5-dihydrooxepine formation.[a]



Entry	Solvent	Cat.	**2a**/*trans*-**1a**[b]	Yield[c] [%]	*ee*[d] [%]
1	EtCN	**3a**	1:1	50	58
2	EtCN	**3b**	1.6:1	60	86
3	EtCN	**3c**	1.7:1	62	97
4	CH_2Cl_2	**3c**	1.7:1	63	92
5	PhMe	**3c**	1:1	51	85
6	EtCN	**3d**	9:1	82	96

[a] The reactions of γ-methyl-α-vinyldiazoester (0.3 mmol) with α-bromoacrolein (0.2 mmol) were performed in the presence of catalyst **3** (20 mol%) in 1.0 mL of solvent at −78°C for 2 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of isolated product **2a**. [d] *ee* of **2a** determined by chiral HPLC.

Table 2: Enantioselective 2,5-dihydrooxepine formation from α-bromoacrolein and various α-vinyldiazoesters.[a]



Entry	**2**	R	X	Yield[b] [%]	*ee*[c] [%]
1	**2a**	Me	O*t*Bu	82	96
2	**2b**	Me	NMe(OMe)	72	95
3	**2c**	Et	O*t*Bu	84	95
4	**2d**	Bn	O*t*Bu	78	93
5[d]	**2e**	*n*-Hex	O*t*Bu	64	90
6	**2f**	*i*-Pr	O*t*Bu	80	98
7	**2g**	*t*-Bu	O*t*Bu	56	93[e]
8[d]	**2h**	Ph	O*t*Bu	75	97
9[f]	**2i**	3-ClPh	O*t*Bu	80	91
10[f]	**2j**	3-MePh	O*t*Bu	85	90[e]
11[f]	**2k**	4-FPh	O*t*Bu	86	99
12[d]	**2l**	4-BrPh	O*t*Bu	73	98

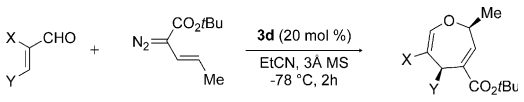
[a] Except for entries 1–3, the reactions of α-vinyldiazoesters (0.2 mmol) with α-bromoacrolein (0.3 mmol) were performed in the presence of catalyst **3d** (20 mol%) in 1.0 mL of solvent at −78°C for 2 h. [b] Yield of isolated 2,5-dihydrooxepine; 5–10% of the *trans*-cyclopropane was also isolated. [c] *ee* determined by chiral HPLC. [d] 0.5 M diazo solution was used. [e] *ee* determined by chiral HPLC after reduction of the ester to the corresponding aldehyde with DIBAL-H. [f] 30 mol% catalyst was used.

immediately transformed into 2,5-dihydrooxepine **2a** through retro-Claisen rearrangement at low temperature (path a). To improve the yield and *ee* of **2a**, we optimized the catalyst structure and solvent. The effect of changing the boracycle catalyst substituents was investigated. Gratifyingly, using catalyst **3b**, which has an *o*-tolyl substituent at the boron center, greatly improved the enantioselectivity to 86% with a small increase in yield (entry 2). When a 3,5-dimethylphenyl Ar substituent was used, the desired product was obtained with 97% *ee* albeit in moderate yield (entry 3). Use of dichloromethane or toluene as the solvent was found to be less effective than using propionitrile (entries 4–5). The sterically hindered catalyst system **3d**, which has a 3,5-dimethylphenyl Ar substituent and an isopropyl R substituent, gave the best result (entry 6). The yield of 2,5-dihydrooxepine **2a** was dramatically improved to 82% with an excellent 96% *ee*.

After optimization of the enantioselective formation of 2,5-dihydrooxepine **2a**, we then evaluated the scope of this reaction using various γ-substituted α-vinyldiazo compounds (Table 2). Various γ-alkyl-α-vinyl diazo compounds were successfully applied, resulting in high yields and excellent enantioselectivity (entries 1–7). Considering other the possible reaction pathways, such as 1,2-hydride shift,[8d,11] 1,3-dipolar cycloaddition[12] and Roskamp reaction,[8a–c,13] the yields obtained for the 2,5-dihydrooxepines are remarkable. This catalytic system was also successfully applied to the reaction of α-vinyl α-diazo Weinreb amide to furnish highly optically active 2,5-dihydrooxepine **2b** in 72% yield and 95% *ee* (entry 2). Notably, diazo compounds with a long alkyl chain or a sterically hindered alkyl group successfully reacted with α-bromoacrolein to provide the corresponding 2,5-dihydrooxepine products in moderate to high yield and excellent *ee* (entries 5–7). While the reactivity of γ-aryl-α-vinyldiazoesters was lower than that of γ-alkyl-α-vinyldiazoesters, enantioselective formation of chiral 2,5-dihydrooxepines with aryl substituents proceeded with high yields and excellent enantioselectivity up to 99% (entries 8–12).

Encouraged by the good results illustrated in Table 2, we next investigated the scope with respect to α- or α,β-substituted acrolein compounds (Table 3). Regardless of the electronic or steric properties of the α-substituents on the acrolein, highly optically active 2,5-dihydrooxepines **2** were obtained in moderate to good yields (entries 1–7). Among the α-halogen-substituted compounds, α-bromoacrolein was the best substrate, providing 2,5-dihydrooxepine **2a** in 82% yield with 96% *ee* (Table 3, entries 1–4). Asymmetric 2,5-dihydrooxepine formation with alkyl or phenyl groups also proceeded with good enantiocontrol, although the yields were not as high (entries 5–8).[7a] Interestingly, some α-alkylacroleins required higher temperature for the retro-Claisen rearrangement of the *cis*-FVC **1** to the 2,5-dihydrooxepine **2** (entries 5–6). The catalytic asymmetric reaction with α,β-disubstituted acroleins was attempted in order to obtain highly functionalized chiral 2,5-dihydrooxepines containing two stereogenic centers. Remarkably, the reaction with α-bromo-β-methylacrolein proceeded well to give 6-bromo-2,5-dimethyl-2,5-dihydrooxepine (**2t**) in good yield with complete control of the enantio- and diastereoselectivity (Table 3, entry 9). The relative and absolute configurations of **2t** were unambiguously established by X-ray crystallographic analysis (Figure 2), and the configurations for all other products are based on this assignment by analogy. Under the optimized

Table 3: Enantioselective 2,5-dihydrooxepine formation from γ-methyl-α-vinyldiazoester and various substituted acroleins.[a]



2

Entry	**2**	X	Y	Yield[b] [%]	*ee*[c] [%]
1	**2a**	Br	H	82	96
2	**2m**	Cl	H	67	97
3[d]	**2n**	Cl	H	71	>99
4	**2o**	I	H	74	93
5[e]	**2p**	Me	H	60	95
6[f]	**2q**	Bn	H	52	87
7	**2r**	n-Pen	H	63	94
8	**2s**	Ph	H	58	76
9[g]	**2t**	Br	Me	82	>99
10[g]	**2u**	Br	Et	65	96

[a] The reactions of γ-methyl-α-vinyldiazoester (0.3 mmol) with acroleins (0.2 mmol) were performed in the presence of catalyst **3d** (20 mol%) in 1.0 mL of solvent at −78°C for 2 h. [b] Yield of isolated 2,5-dihydrooxepine; 5–10% of the *trans*-cyclopropane was also isolated. [c] *ee* determined by chiral HPLC. [d] γ-phenyl-α-vinyldiazoester was used. [e] Reaction temperature was allowed to warm to 0°C over 4 h and kept for another 1 h. [f] Reaction temperature was allowed to warm to room temperature over 4 h and kept for another 1 h. [g] d.r. determined by ^{1}H NMR analysis of the crude reaction mixture; a single diastereomer was obtained.

conditions, the reaction with α-bromo-β-ethylacrolein provided the corresponding 2,5-dihydrooxepine **2u** with excellent enantio- and diastereoselectivity, although in moderate yield (Table 3, entry 10).

The observed stereochemistry for the enantioselective formation of 2,5-dihydrooxepine with COBI catalyst **3d** can be rationalized on the basis of the transition-state model shown in Figure 3. The coordination mode of the acrolein to catalyst **3d** is the same as that previously observed for enantioselective cyclopropanation reactions.[7] After asymmetric cyclopropanation between the α-bromoacrolein and α-vinyldiazo compound, the resulting cyclopropane **1** shows *cis* geometry between the aldehyde and olefin groups. The intermediate cyclopropane *cis*-FVC **1** is immediately converted into *cis*-(2*S*,5*R*)-2,5-dihydrooxepine as the major enantiomer for **2t**. The absolute configuration of *cis*-(2*S*,5*R*)-6-bromo-2,5-dimethyl-2,5-dihydrooxepine (**2t**; Table 3, entry 9) supports the rearrangement proceeding in a concerted manner via boat-like transition state **4**, as several DFT calculations have reported.[6c,14]

Further chemical transformations of the resulting optically active 6-bromo-2,5-dihydrooxepine are illustrated in

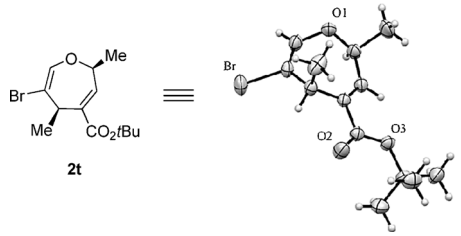


Figure 2. X-ray structure of **2t**.

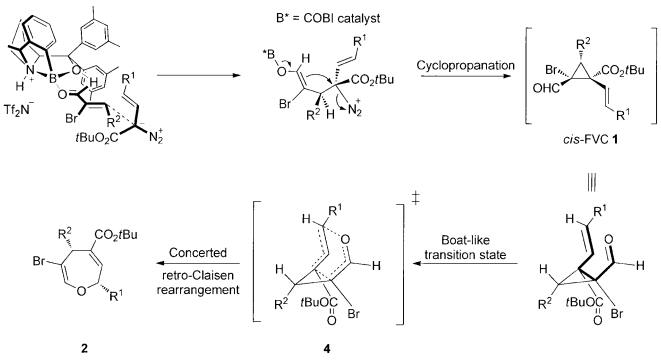
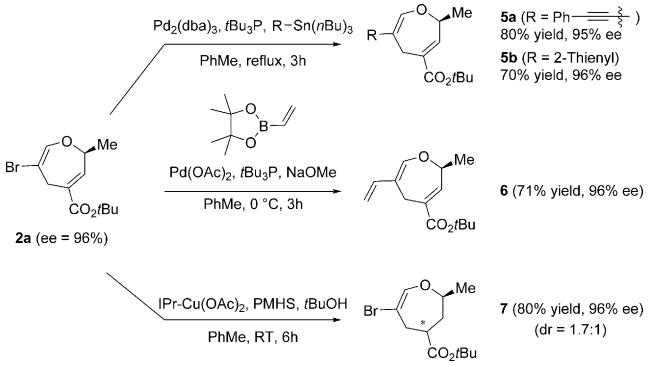


Figure 3. Transition-state model for the enantioselective formation of 2,5-dihydrooxepines as catalyzed by **3d**.



Scheme 2. Derivatization of 2,5-dihydrooxepines.

Scheme 2. Stille coupling reaction of **2a** with the corresponding tin reagents successfully introduced alkynyl (**5a**) and heteroaromatic (**5b**) groups in high yields without an obvious loss of enantiopurity. Suzuki coupling with vinylboronic acid pinacol ester and $Pd(OAc)_2$ produced **6** in 71% yield. In addition, chemoselective conjugate reduction with a carbene-copper complex[15] provided tetrahydrooxepine **7** with one additional chiral center as a 1.7:1 mixture of diastereomers in high yield.

In summary, the first example of a highly enantiocontrolled catalytic formation of 2,5-dihydrooxepine has been developed. This tandem cyclopropanation/retro-Claisen rearrangement reaction gives highly functionalized 2,5-dihydrooxepines in a single step with excellent enantioselectivity. The resulting 6-bromo-2,5-dihydrooxepines can easily be converted into various hydrooxepine derivatives with alkyne, heteroaromatic, and vinyl functional groups without loss of optical purity. We believe that the resulting chiral 2,5-dihydrooxepines could be highly valuable intermediates for the synthesis of useful complex molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enantioselectivity · heterocycles · hydrooxepines · Lewis acids · rearrangement reactions

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Communications

Heterocycles

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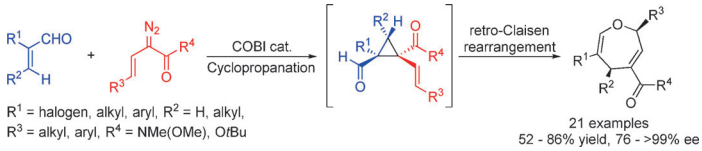
Catalytic Enantioselective Synthesis of 2,5-Dihydrooxepines



I get a round: A Michael addition initiated cyclopropanation/retro-Claisen rearrangement tandem reaction was developed for the enantioselective synthesis of highly functionalized 2,5-dihydrooxepines. In the presence of a chiral oxazaborolidinium ion (COBI) catalyst, the reaction proceeds to give good yields and high enantioselectivity.