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Oxidant-Resistant Hydrogen-Bond-Donating Organocatalyst for Enantioselective Nucleophilic Epoxidation of α,β -Unsaturated Amides

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Oxidant-Resistant Hydrogen-Bond-Donating Organocatalyst for Enantioselective Nucleophilic Epoxidation of α,β -Unsaturated Amides

Yusuke Kobayashi,^[a] Shanji Li,^[b] and Yoshiji Takemoto*^[a]

Abstract: Bifunctional benzothiadiazine-catalyzed epoxidation of α,β -unsaturated amides proceeded efficiently to give chiral 2-oxiranecarboxamides in excellent yields (89–99%) and with good enantioselectivities (up to 84% *ee*). A synthetic application of the oxiranecarboxamides is also described.

Chiral epoxides are important building blocks, and can be ring opened with a wide range of nucleophiles, with high or often complete stereo- and/or regio-selectivity, to afford two continuous stereogenic centers.^[1] Considerable attention has therefore been paid to, and enormous progress has been made in, the development of chiral epoxide synthesis in the last few decades. Compared with asymmetric electrophilic epoxidations,^[2] including Sharpless–Katsuki epoxidation,^[2a] of electron-rich alkenes, asymmetric nucleophilic epoxidations of electron-deficient alkenes have been less explored,^[3] despite the importance of the produced epoxides. Among these, there has been much interest in 2-oxiranecarboxylic acids^[4] and 2-oxiranecarboxamides^[5] because of their high potential for further derivatization, and because they occur in several naturally occurring products such as cerulenin,^[6] fusarin C,^[7] and cyclophenin,^[8] which exhibit interesting biological activities (Figure 1).

Figure 1. Naturally occurring oxiranecarboxylic acid surrogates.

Metal-catalyzed asymmetric nucleophilic epoxidation of α,β -unsaturated carboxylic acid surrogates has been developed as a

method of accessing this class of oxiranes.^[9] However, the synthesis is difficult to achieve using organocatalysts^[10] because such catalysts are themselves potentially oxidized under the epoxidation conditions. In recent decades, however, great progress has been achieved in organocatalyzed stereoselective epoxidations of electron-poor alkenes such as α,β -unsaturated aldehydes **1** and ketones (Scheme 1, eq. 1).^[11] These substrates can generally be activated by chiral primary and secondary amines via covalent bonds, and the asymmetric epoxidation proceeds highly stereoselectively through the generated chiral iminium cation intermediate.^[11] Although the produced chiral oxiranecarboxaldehydes **2** can be derivatized to give the corresponding amides **4**,^[12] the direct synthesis of these amides by asymmetric epoxidation of α,β -unsaturated amides **3** is highly desirable in terms of redox economy (Scheme 2, eq. 2).^[13] However, only a few examples have been reported to date, and the substrate scopes are also limited, probably because of the relatively poor reactivities of **3** and, again, because of the inherent tendencies of the organocatalysts, particularly sulfur-containing catalysts^[14,15] such as thioureas, to be oxidized in the presence of an oxidant. We envisioned that bifunctional benzothiadiazine catalysts,^[16] which have no reactive sulfur atoms and strong hydrogen-bond (HB)-donating abilities, would promote the asymmetric epoxidation of **3**. Here, we report an oxidant-resistant HB-donating organocatalyst for the enantioselective nucleophilic epoxidation of α,β -unsaturated amides (Scheme 1, eq. 3).

Scheme 1. Organocatalyzed asymmetric nucleophilic epoxidation.

Initially, we used acrylamide **3a** as the starting material, *tert*-butyl hydroperoxide (TBHP) as the oxidant, and dichloromethane as the solvent, at room temperature (Table 1). Notably, thiourea

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catalyst **I** did not afford the desired product **4a**, even after a prolonged reaction time (entry 1), but urea catalyst **II** gave **4a** in moderate yield and selectivity (entry 2). These results strongly indicate that catalyst **I** was deactivated under the reaction conditions. We then examined several HB-donor organocatalysts with different scaffolds, including squaramide (**III**),^[17] benzimidazole (**IV**),^[18] quinazoline (**V**),^[16a] and benzothiadiazine (**VI**)^[16] (entries 3–6). We found that the best catalyst was **VI**, and the reaction was completed within 4 h to furnish **4a** in 90% yield with 70% *ee* (entry 6). In contrast, the reactions did not go to completion with the other catalysts, and the selectivities for **4a** were 40–54% *ee* (entries 3–5). These results suggest that the HB-donating ability is important for substrate recognition and facilitation of the reaction.^[16c] We next examined several oxidants and solvents (entries 7–11), using catalyst **VI**. TBHP as the oxidant and dichloromethane and MeCN solvents were found to be the most suitable conditions for this reaction in terms of chemical yield and enantioselectivity. In all cases, except that with THF as the solvent (entry 10), **4a** was obtained as a single diastereomer. The *ee* value was improved to 84% by steric modification of the substituent on the nitrogen atom (entry 12).

Table 1. Optimization of reaction conditions.

Entry	Catalyst	solvent	Time (h)	Yield (%) ^[a]	Ee (%) ^[b]
1	I	CH ₂ Cl ₂	24	0	n.d.
2	II	CH ₂ Cl ₂	24	43	45
3	III	CH ₂ Cl ₂	24	24	40
4	IV	CH ₂ Cl ₂	24	49	54
5	V	CH ₂ Cl ₂	24	27	44
6	VI	CH ₂ Cl ₂	4	90	70
7 ^[c]	VI	CH ₂ Cl ₂	21	94	20
8 ^[d]	VI	CH ₂ Cl ₂	24	76	24
9	VI	Toluene	2	92	57
10	VI	THF	72	60 ^[e]	55
11	VI	MeCN	72	82	70
12	VII	MeCN	24	98	84

[a] Isolated yield. [b] Determined by chiral HPLC analyses. N.D. = not determined. [c] 30% hydrogen peroxide was used instead of TBHP. [d] Urea hydrogen peroxide was used instead of TBHP. [e] Obtained as an inseparable diastereomer mixture.

With the optimal conditions in hand, we proceeded to investigate the effects of the R¹ and R² substituents on amides **3** (Table 2). When *N,N*-dimethylacrylamide was used as the substrate, the corresponding epoxide **4b** was obtained in 89% yield with 74% *ee* (entry 1), but the enantioselectivities obtained with more electron-deficient amides such as morpholinylamide **4c**, anilides **4d** and **e**, and Weinreb amides **4f** and **g** were lower (42–60% *ee*; entries 2–6). However, it should be noted that almost enantiomerically pure anilides **4d,e** can be obtained after a single recrystallization from EtOH (entries 3 and 4), and the obtained Weinreb amides **4f** and **g** could in principle be converted to a variety of ketones using Grignard and organolithium reagents (vide infra).^[19] Unfortunately, the amide bearing a removable benzyl group resulted in moderate enantioselectivities, albeit in excellent yields (entries 7 and 8). We next investigated the effect of the substituent R³, mainly with respect to substituents on aromatic rings (entries 9–15). The epoxidations of amides bearing both electron-withdrawing and electron-donating groups at the *para* positions of the aromatic rings proceeded efficiently to furnish epoxides **4j–m** in 97–98% yields with 80–84% *ees* (entries 9–12), although the reaction took longer to complete when the substituent was a methoxy group (entry 12). These results suggest that the electronic properties of the amide moiety are more important for the epoxidation stereoselectivities than are those of the substituent R³. In addition, the reaction also proceeded for substrates with *ortho*- and *meta*-substituted aromatic groups, to afford amides **4n** and **4o** (entries 13 and 14).

Table 2. Substrate scope.^[a]

1.	2.	3.

[a] Isolated yields are presented. Enantiomeric ratio was determined by HPLC on a chiral stationary phase. [b] The values after single recrystallization from EtOH.

Scheme 2. Determination of absolute configuration.

Figure 2. Calculated transition state using Gaussian09 at the B3LYP 6-31G* level.

Interestingly, when epoxide **4g** was treated with phenylmagnesium bromide, the Weinreb amide moiety reacted highly chemoselectively to give the corresponding ketone **5** in 62% yield, without any ring opening or addition to the CN group (Scheme 2). The absolute configuration of **5** was determined by comparing its optical rotation value with the literature data,^[11d] and the absolute configuration of **4g** was unambiguously determined to be 2*S*,3*R*. The stereochemistries of the other epoxides in Table 2 were assigned analogously to **4g**, and a plausible transition state, involving the addition of TBHP to the α,β -unsaturated amide **3a** promoted by catalyst **VI**, was calculated using Gaussian09^[20] at the B3LYP 6-31G* level.^[21] If the p*K*_a value of TBHP is taken into consideration, a neutral ternary complex^[10a] would be involved (Figure 2), although an ionic transition state via deprotonation of TBHP cannot be ruled out.^[22]

Scheme 3. Application of epoxide **4e** to synthesis of chiral 2-quinolone **7**.

Finally, the great usefulness of this type of epoxide was further demonstrated by its derivatization to a biologically important scaffold (Scheme 3). The CN group of epoxide **4e** was chemoselectively hydrolyzed to the corresponding amide **6** in 90% yield; **6** was then subjected to sulfuric acid-mediated epoxide–arene cyclization,^[23] without any loss of enantioselectivity, to furnish chiral quinolone^[24] **7** bearing two continuous stereocenters.

In conclusion, we developed a highly oxidant-resistant HB-donor organocatalyst, which effectively promoted the asymmetric epoxidation of α,β -unsaturated amides to give chiral 2-oxiranecarboxamides. These results demonstrated the potential use of benzothiadiazine organocatalysts in a wide range of oxidation reactions. Further refining of the catalyst molecular structure and identification of other applicable reactions are currently underway in our laboratory.

Experimental Section

An *n*-decane solution of TBHP (0.1 mL, 5.5 M) was added to a solution of α,β -unsaturated amide **3** (0.1 mmol) and benzothiadiazine catalyst **VII** (3.5 mg, 0.01 mmol, 10 mol%) in MeCN (1.0 mL, 0.1 M); the resulting mixture was stirred at ambient temperature for the indicated time listed in the tables. The reaction mixture was then evaporated and the resulting crude residue purified by column chromatography on silica gel, with *n*-hexane/ethyl acetate as the eluent, to give the analytically pure compound **4**. The enantiomeric ratios of all of the compounds were determined by HPLC on a chiral stationary phase.

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An unprecedented asymmetric nucleophilic epoxidation of α,β -unsaturated amides has been developed using a bifunctional benzothiadiazine catalyst with a

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