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Highly efficient asymmetric synthesis of α,β-epoxy esters *via* one-pot organocatalytic epoxidation and oxidative esterification†

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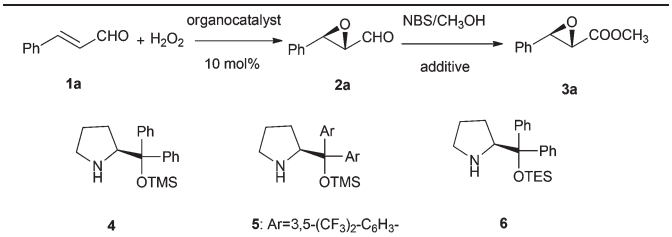
Highly enantioselective synthesis of α,β-epoxy esters was achieved *via* one-pot organocatalytic epoxidation and consequent oxidative esterification. Excellent enantioselectivities (up to 99% ee) and good yields were obtained for a variety of α,β-epoxy esters. The method was readily scaled. Furthermore the product was applied towards the synthesis of (−)-clausenamide with excellent enantioselectivities (>99% ee).

Chiral α,β-epoxy esters are important intermediates for the synthesis of drugs and complex molecules.[1] Many efforts have been devoted to enantioselective synthesis of α,β-epoxy esters.[2–5] Among them, asymmetric epoxidation of prochiral α,β-unsaturated esters presents an attractive strategy. The manganese–salen complexes are effective catalysts for the epoxidation of (*Z*)-cinnamates.[1j,6] Shi *et al.* developed chiral ketone catalysts for the asymmetric epoxidation of α,β-unsaturated esters.[7] However, high catalyst loading (20–30 mol%) and excess oxone (5 equiv.) are necessary for achieving acceptable yields and enantioselectivities. Shibasaki reported highly enantioselective epoxidation of α,β-unsaturated esters catalyzed by an yttrium–biphenyldiol complex,[8] but the diethylene ether-linked biphenyldiol ligands are difficult to synthesize. In addition, highly toxic triphenylarsine is required as an additive. Although other indirect synthetic methods of chiral α,β-epoxy esters were also developed, the development of efficient synthetic methods of α,β-epoxy esters with high enantioselectivity is still highly desirable.

In recent decades asymmetric organocatalysis has emerged as a powerful tool for the synthesis of valuable chiral compounds.[9] Córdova and Jørgensen have independently reported the organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes with good yields and high enantioselectivities.[10] However due to the high strain of the epoxy group, α,β-epoxy aldehydes are susceptible to ring opening reactions. The direct transformation of α,β-epoxy aldehydes to α,β-epoxy esters is still challenging. Here we report an efficient approach for the highly enantioselective synthesis of α,β-epoxy esters by a one-pot organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes and oxidative esterification.[11,12]

We initially explored a model reaction of cinnamaldehyde **1a** with hydrogen peroxide in the presence of organocatalyst **4** in dichloromethane at room temperature (Table 1, entry 1). As expected, the reaction resulted in the desired α,β-epoxy

Table 1 Optimization studies on the one-pot enantioselective synthesis of **3a**[a]



Entry	Catalyst	Time[b] (h)	Additive	Yield[c,d] (%)	ee[e] (%)
1	**4**	16	—	—	—
2	**4**	16	Et_3N	—	—
3	**4**	16	Proton sponge[f]	—	—
4	**4**	12	$NaHCO_3$	44	90
5	**4**	12	Li_2CO_3	53	90
6	**4**	12	NaOAc	52	90
7	**4**	3	Na_2CO_3	61	90
8	**4**	3	K_2CO_3	25	90
9	**5**	3	Na_2CO_3	24	88
10[g]	**6**	3	Na_2CO_3	73	95

[a] Unless otherwise stated, all reactions were performed at room temperature with **1a** (0.5 mmol), H_2O_2 (30 wt% in H_2O) (0.6 mmol), and a catalyst (0.05 mmol) in 0.5 mL of CH_2Cl_2 for 3 h. Then CH_3OH (1 mL), NBS (0.65 mmol) and additive (0.65 mmol) were added. [b] Time for the oxidative esterification step. [c] Overall yield of two steps by GC analysis. [d] Yield of the *trans* product. [e] ee values were determined by chiral HPLC. [f] 1,8-Bis(dimethylamino)naphthalene. [g] Epoxidation was performed with 10 mol% catalyst **6** for 2 h.

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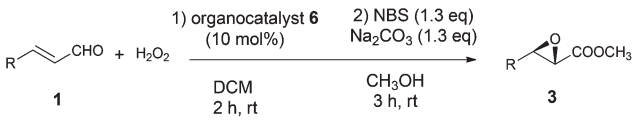
aldehydes **2a**. Due to the chemical instability of **2a**, *in situ* transformation of **2a** to the corresponding ester **3a** *via* oxidative esterification was attempted. After the mixture was diluted with methanol, 1.3 equiv. of *N*-bromosuccinimide (NBS) was added. However, no anticipated α,β-epoxy esters **3a** were found. We doubted that the intermediate α,β-epoxy aldehyde may undergo ring opening reaction with methanol. This side reaction is promoted by HBr produced during the course of the reaction. Therefore basic additives were added. When Et_3N or a proton sponge (1.3 equiv.) is used as the acid scavenger, no desired **3a** was obtained (Table 1, entries 2 and 3). To our delight, when $NaHCO_3$ was used as the additive, the process proceeds smoothly to give α,β-epoxy esters **3a** in 44% yield and 90% ee. Further screening of base additives indicated Na_2CO_3 as the best additive. Full conversion was achieved within 3 hours and α,β-epoxy esters **3a** were obtained with 61% overall yield and excellent enantioselectivity (entry 7).

Two other organocatalysts **5** and **6** were also examined in the reaction. Chiral amine catalyst **6** was found to be more effective than **4** and **5**. The epoxidation step could be completed in 2 hours and epoxy ester **3a** was obtained in 73% yield. In addition, the enantioselectivity was improved further (entry 10).

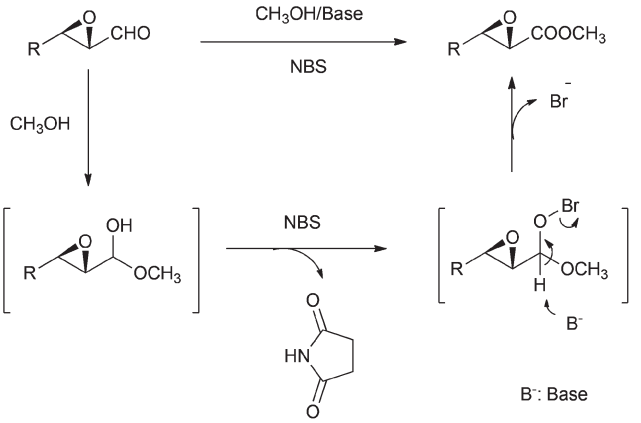
As shown in Table 2, this one-pot epoxidation/oxidative esterification can be extended to a variety of α,β-unsaturated aldehydes. α,β-Epoxy esters were obtained in moderate to good yields and with excellent enantioselectivities (Table 2, entries 1–10). The *ortho*-, *meta*-, and *para*-substitutions on the phenyl ring were tolerated very well. The electronic property of the substituent seemed to have a slight effect on the yield and enantioselectivity. In contrast to direct asymmetric epoxidation

Table 2 Synthesis of chiral α,β-epoxy esters from a variety of α,β-unsaturated aldehydes[a]



Entry	R	Product, yield[b,c] (%)	ee[d] (%)
1	Ph, **1a**	**3a**, 72	95
2	4-Me-C_6H_4, **1b**	**3b**, 54	96
3	2-Cl-C_6H_4, **1c**	**3c**, 55	97
4	3-Cl-C_6H_4, **1d**	**3d**, 71	93
5	4-Cl-C_6H_4, **1e**	**3e**, 62	96
6	4-Br-C_6H_4, **1f**	**3f**, 69	96
7	2-NO_2-C_6H_4, **1g**	**3g**, 67	97
8	4-NO_2-C_6H_4, **1h**	**3h**, 63	99
9	4-NC-C_6H_4, **1i**	**3i**, 73	95
10	4-CF_3-C_6H_4, **1j**	**3j**, 63	96

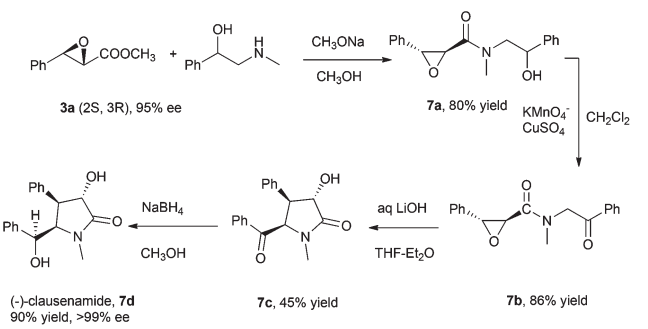
[a] Unless otherwise stated, all reactions were performed at room temperature with **1** (0.5 mmol), H_2O_2 (30 wt% in H_2O) (0.6 mmol), and a catalyst (0.05 mmol) in 0.5 mL of CH_2Cl_2 for 2 h. Then CH_3OH (1 mL), NBS (0.65 mmol) and Na_2CO_3 (0.65 mmol) were added and the mixture was stirred for 3 h. [b] Isolated yield for the overall two steps. [c] Yield for the *trans* product. [d] ee values were determined by chiral HPLC.



Scheme 1 Proposed mechanism for the oxidative esterification of α,β-epoxy aldehyde.

of α,β-unsaturated esters,[7,8,13] this method is very effective for the synthesis of α,β-epoxy esters with a strong electron-withdrawing substituent. Substrates with nitro, nitrile or trifluoromethyl groups on the phenyl ring all proceeded smoothly to afford the α,β-epoxy esters **1g–1j** with good yield and enantioselectivity (Table 2, entries 7–10). β-Alkyl unsaturated aldehydes were also examined. The epoxidation step took place smoothly, but subsequent oxidative esterification gave low yields. The absolute configuration of **3a** was determined to be 2*S*,3*R* by comparing the optical rotation with reported data.[8] By analogy, the other α,β-epoxy esters were proposed to have the same absolute configurations. A proposed mechanism for the oxidative esterification step is depicted in Scheme 1. The α,β-epoxy aldehyde reacted with methanol to give the corresponding hemiacetal. This intermediate underwent S_N2 substitution with NBS to form the hemiacetal hypobromite. Subsequent elimination promoted by a base such as Na_2CO_3 afforded the α,β-epoxy ester product.

The reaction was readily scaled up and performed on a gram scale. A reaction with **1a** (3.96 g, 30 mmol) proceeded efficiently to afford **3a** in a similar yield and enantioselectivity. **3a** could be further applied for the synthesis of (−)-clausenamide **7d**, which is an antiamnaesic agent with potent hepatoprotective activity (Scheme 2).[14,15] **3a** was converted to the amide **7a** in 80% yield using racemic 2-methylamino-1-phenylethanol. Oxidation of **7a** provided **7b** in 86% yield. Base-



Scheme 2 Synthesis of (−)-clausenamide **7d** from **3a**.

catalyzed cyclization of **7b** furnished lactam **7c** in 45% yield. Reduction of **7c** with $NaBH_4$ gave (−)-clausenamide **7d** in 90% yield and excellent enantioselectivity (>99% ee). This method is also potentially applicable for the preparation of clausenamide derivatives.

Conclusions

In summary, we have developed a convenient and efficient method for the asymmetric synthesis of α,β-epoxy esters. The one-pot organocatalytic epoxidation of α,β-unsaturated aldehydes and consequent oxidative esterification provided α,β-epoxy esters in good yields and enantioselectivities. The readily available catalyst, the simple procedure and the scale up potential make the method attractive for the practical synthesis of chiral α,β-epoxy esters.

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