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Highly Enantioselective Epoxidation of α,β-Unsaturated Ketones Catalyzed by Primary-Secondary Diamines

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Abstract: The asymmetric epoxidation of α,β-unsaturated ketones has been achieved by using functional and readily accessible primary-secondary diamines as the catalysts, giving the useful alkyl epoxy products with good yields and high enantioselectivities (up to 99% *ee*).

Keywords: asymmetric catalysis; cumene hydroperoxide; enones; epoxidation; organocatalysis

Chiral epoxy groups are widely used as building blocks in a great number of organic syntheses.[1] Despite the great achievements have been made by Sharpless,[2] Jacobsen,[3] Shi,[4] and Shibasaki[5] in the epoxidation of allylic alcohols, various unactivated alkenes and some examples of α,β-unsaturated carbonyl compounds, methods focused on the non-metal-catalyzed enantioselective epoxidation of α,β-unsaturated ketones were still limited.[6]

Among the organocatalysts employed for the epoxidation of α,β-unsaturated ketones recently,[7–9] there are two types of catalysts with different activation modes that are the most used and valuable (Figure 1). The secondary amine catalysts derived from proline and used for the epoxidation of α,β-unsaturated aryl ketones activate the substrate through hydrogen-bond interaction followed by a nucleophilic pathway (type I),[8] while the primary amine catalysts derived from *Cinchona* alkaloids activate the α,β-unsaturated alkylenones with an iminium transition state (type II).[9]

Due to the significant advantages of the primary amine catalysts in generating congested covalent intermediates to activate the α,β-unsaturated alkyl ketones with both good chemoselectivities and enantioselectivities, many efforts have been made to explore novel and accessible types of this catalysts and their application in asymmetric reactions.[6k,10]

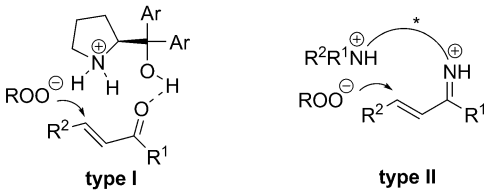


Figure 1. Activation mode of catalysts.

Recently, our group has developed the first novel primary-secondary diamine catalysts, which could be synthesized easily from commercially available natural amino acids, and which provided excellent activities and enantioseletivities in Michael additions.[11] As part of our continuous efforts in developing efficient organocatalysts for asymmetric epoxidation, we postulated that these powerful and readily accessible chiral primary-secondary diamines could also be used for the epoxidation of α,β-unsaturated alkyl ketones, which would provide an alternative way to a series of α,β-epoxy carbonyl compounds with good yields and enantioselectivities.

Preliminary studies were carried out using 6-phenylhex-3-en-2-one as a model substrate with 20 mol% of the primary amine catalysts (Figure 2) and using *tert*-butyl hydroperoxide (TBHP) as an oxidant in toluene (Table 1). The same as we observed in the previous Michael addition, this epoxidation using primary-secondary amine catalyst also proceeded smoothly. All of the catalysts promoted this reaction and most

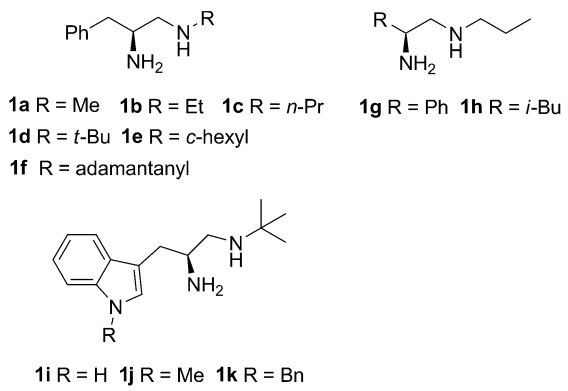
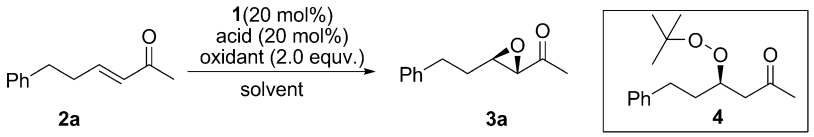


Figure 2. Structures of the catalysts studied.

of them provided the epoxy product with good enantioselectivity. The catalysts derived from L-phenylalanine (**1a**–**1f**) with different protecting groups at the secondary amine gave the product with similar moderate yields and good enantioselectivities, while the presence of a bulky protecting group seems to be more advantageous for the selectivity (Table 1, entries 1–6). L-Phenylglycine-derived catalyst **1g** was inferior in this reaction and showed very low activity and enantioselectivity (Table 1, entry 7). Catalyst derived from L-leucine did not improve the result (Table 1, entry 8). The catalyst derived from L-tryptophan, which showed excellent activity in the Michael addition of malonates to enones,[11a,e] however, afforded the product with no better *ee* value (Table 1, entry 9). Considering that bulky steric hindrance on the indolyl may have a good effect on the enantioselectivity, two N-protected catalysts **1j** and **1k** were prepared and evaluated in the reaction. Unfortunately, rather poor enantioselectivities were obtained

Table 1. Effects of catalyst, oxidant, solvent and additive in the epoxidation reaction.[a]



Entry	Catalyst	Solvent	Acid	Oxidant	Yield [%][b]	*ee* [%][c]
1	**1a**	toluene	TFA	TBHP	68	77
2	**1b**	toluene	TFA	TBHP	73	81
3	**1c**	toluene	TFA	TBHP	74	88
4	**1d**	toluene	TFA	TBHP	74	91
5	**1e**	toluene	TFA	TBHP	77	86
6	**1f**	toluene	TFA	TBHP	77	90
7	**1g**	toluene	TFA	TBHP	46	35
8	**1h**	toluene	TFA	TBHP	61	86
9	**1i**	toluene	TFA	TBHP	74	87
10	**1j**	toluene	TFA	TBHP	86	81
11	**1k**	toluene	TFA	TBHP	76	83
12	**1d**	toluene	TFA	H_2O_2	48	80
13	**1d**	toluene	TFA	UHP	91	64
14	**1d**	toluene	TFA	CHP	87	96
15	**1d**	hexane	TFA	CHP	88	87
16	**1d**	xylene	TFA	CHP	83	95
17	**1d**	$CHCl_3$	TFA	CHP	58	71
18	**1d**	dioxane	TFA	CHP	56	72
19	**1d**	diethyl ether	TFA	CHP	83	71
20	**1d**	CH_3OH	TFA	CHP	26	nd
21	**1d**	toluene	TfOH	CHP	71	87
22	**1d**	toluene	–	CHP	nd	nd
23[d]	**1d**	toluene	TFA	CHP	59	86
24[e]	**1d**	toluene	TFA	CHP	75	93

[a] Unless otherwise specified, The reaction was carried out with **2a** (0.2 mmol), oxidant (2 equiv.), **1** (20 mol%), additive (20 mol%) in solvent (1.0 mL) at 30 °C for 48 h.
[b] Isolated yields of **3a** after chromatography.
[c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparison of the specific optical rotation with that of the literature reported.[9b]
[d] TFA (40 mol%) was used.
[e] 10 mol% of the catalyst was used.

(Table 1, entries 10 and 11). It should be noted that 5–20% of the peroxide product **4** was isolated when TBHP was used as an oxidant, so the yields of the desired product were moderate. This problem could be solved by optimizing the reaction conditions.

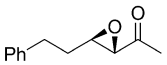
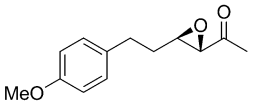
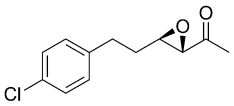
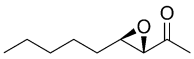
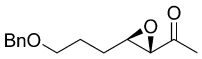
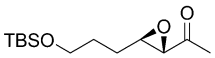
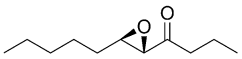
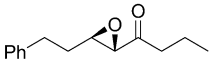
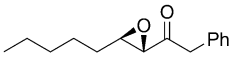
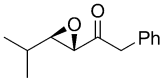
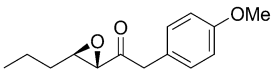
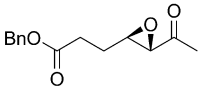
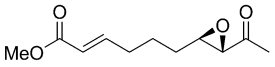
With the best catalyst **1d** that we obtained above, several other oxidants such as hydrogen peroxide (30% w/w in water) (H_2O_2), urea-hydrogen peroxide (UHP) and cumene hydroperoxide (CHP) were evaluated (Table 1, entries 12–14). The by-product **4** was totally suppressed by using UHP or CHP as the oxidant and the yields of the desired product were improved to around 90%, especially an excellent enantioselectivity could also be achieved when CHP was selected as the oxidant. This improvement may be ascribed to the large cumene group, which is beneficial for both enantioselective control and leaving after nucleophilic attack to form the desired product. The H_2O_2 oxidant, which was active in List's epoxidation using *Cinchona* alkaloid-derived primary amine catalysts, however, showed low reactivity in this reaction and some of the starting material was recovered after 48 h. Then, the solvent effect in this reaction was investigated. It seemed that a non-polar solvent such as toluene and hexane is superior to polar solvents and protic solvents. In non-polar solvents such as toluene and hexane, the reaction proceeded smoothly, affording the desired products with high yields and good to excellent enantioselectivities (Table 1, entries 14–16). Other solvents only gave the products with moderate yields or enantioselectivities (Table 1, entries 17–20).

The effect of the additive was also examined. Without trifluoroacetic acid (TFA) as the additive, the reaction could not proceed (Table 1, entry 22). No positive effect was observed when trifluoromethylsulfonic acid (TfOH) was used (Table 1, entry 21). Increasing the loading of TFA led to a sharp decrease in yield due to decomposition of the product (Table 1, entry 23). Reducing the catalyst loading caused an obviously decrease in reactivity and a slight decrease in enantioselectivity (Table 1, entry 24). Thus, the reaction was best performed by using a combination of **1d**/TFA (1:1), CHP as the oxidant in toluene at 30 °C to provide the epoxide with 87% yield and 96% *ee* (Table 1, entry 14).

With the optimized reaction conditions in hand, the scope of the epoxidation was investigated and the results are summarized in Table 2. In most cases, the epoxide products were exclusively formed in good yields and high to excellent *ee* values. α,β-Unsaturated methyl ketones with an aryl group on the side of double bond worked very well to give the products with high yields and above 90% *ee* (Table 2, entries 1–3). Long-chain alkyl-, alkoxy- and siloxy-substituted α,β-unsaturated ketones also performed well to provide good yields of the products. The relatively low yield of **3d** was due to its volatility (Table 2, en-

Table 2. Enantioselective epoxidation of α,β-unsaturated ketones catalyzed by **1d**/TFA.[a]

2 **3**

Entry	Product		Time [h]	Yield [%][b]	*ee* [%][c]
1		**3a**	24	87	96
2		**3b**	24	84	92
3		**3c**	24	86	90
4		**3d**	24	68	91
5		**3e**	24	82	95
6		**3f**	24	80	88[d]
7		**3g**	36	72	99
8		**3h**	24	84	99
9[e]		**3i**	48	74	91
10[e]		**3j**	48	74	92
11[e]		**3k**	48	70	92
12		**3l**	24	79	92
13		**3m**	48	79	83
14		**3n**	24	70	66[f]

[a] Unless otherwise specified, the reaction was carried out with **2** (0.2 mmol), CHP (2 equiv), **1** (20 mol%), TFA (20 mol%) in toluene (1.0 mL) at 30 °C.
[b] Isolated yields after chromatography.
[c] Determined by chiral HPLC/GC analysis.
[d] Determined by chiral HPLC after being transformed.
[e] The reaction was carried out at 40 °C.
[f] Determined by comparison of the optical rotation value with the literature.[9c]

tries 4–7). A long-chain alkyl group on the side of the carbonyl was also found to be favorable in this reaction. Excellent enantioselectivities (99% *ee*) were obtained with these substrates (Table 2, entries 7 and 8). α,β-Unsaturated phenethyl ketones were also reactive in this reaction and high enantioselectivities were obtained although a long reaction time was needed due to the larger aryl groups with low activities (Table 2, entries 9–11). Substrates containing ester groups were also synthesized and subject to the reaction. The epoxidation proceeded selectively on the unsaturated ketones with double bond connected to the ester unchanged (Table 2, entries 12 and 13). Chalcones, and conjugate enones with a trisubstituted or terminal alkene moiety proved to be unreactive under this condition.[12]

A bifunctional iminium mechanism similar to those previously proposed for the primary amine salt catalysts in the iminium catalysis of enone may be invoked to explain the observed stereochemical results (Figure 3).[9a] We presumed that the primary amine

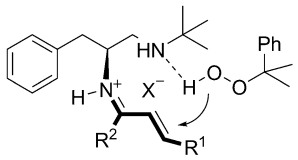


Figure 3. Possible pretransition state **I**.

moiety of the catalyst **1d** activates the enone **2** *via* the formation of an iminium ion **I** while the secondary amine activates the nucleophilic oxidants. The *Re*-face of the enone in this pretransition state assembly **I** is shielded by the bulky benzyl group driving the oxidant to attack the *Si*-face of the enone **2**. The acid additive may facilitate the formation of the iminium ion and promote the intramolecular nucleophilic ring closure by generating a suitable leaving group through protonation.

In summary, we have newly applied the novel primary-secondary diamine catalyst system for the epoxidation of α,β-unsaturated ketones. This easily prepared catalyst and convenient protocol enable the formation of α,β-epoxy carbonyl compounds under mild condition with good yields and high enantioselectivities. Efforts are being focused on further application of this catalyst system to other related reactions as well as a more detailed mechanistic understanding of this reaction.

Experimental Section

General Procedure for the Asymmetric Epoxidation

Catalyst **1d** (8.0 mg, 0.04 mmol) was added to the solution of trifluoroacetic acid (4.6 mg, 0.04 mmol) in toluene (1.0 mL). Then enone **2** (0.2 mmol) was added followed by the addition of cumene hydroperoxide (2.0 equiv., 0.4 mmol, 61 mg) at ambient temperature. The mixture was stirred at 30 °C for 24–48 h. Water (3 mL) was added. The mixture was extracted with ethyl acetate (2×3 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. Crude products were purified by silica gel column chromatography using hexane/ethyl acetate as eluent to afford the pure epoxides **3**.

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