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Enantioselective epoxidation of α,β-enones promoted by (1*R*,3*S*,4*S*)-2-azanorbornyl-3-methanol as an organocatalyst

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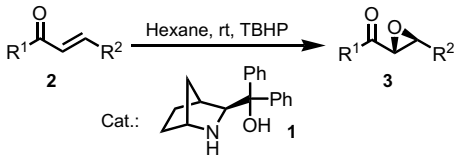
ABSTRACT

(1*R*,3*S*,4*S*)-2-Azanorbornyl-3-methanol was synthesized form (*R*)-1-phenylethylamine and used as a catalyst for the enantioselective epoxidation of α,β-enones to afford the corresponding epoxides in good yields and high enantioselectivities at room temperature.

Chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular, of biologically active compounds.[1] The asymmetric epoxidation of functionalized and unfunctionalized olefins has emerged as a very versatile and important synthetic tool in organic synthesis,[2] and many asymmetric synthetic methods have been developed to meet this purpose.[3] Asymmetric catalysis by small organic molecules is a rapidly growing area, which has led to the development of efficient metal-free methodologies for many asymmetric organic syntheses.[4] Among the most studied organocatalysts, L-proline and its derivatives have shown wide applicability and generally good to high control of asymmetric induction.[5,6]

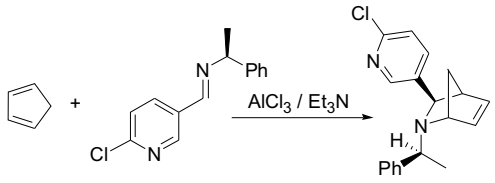
Recently, we have developed methods for the synthesis of azabicyclo[2.2.1]heptene derivatives as analogues of epibatidine (Scheme 1).[7] In connection with our interest in modifying these analogues as organocatalysts for asymmetric epoxidations, a series of chiral azabicyclo[2.2.1] heptane derivatives were prepared and applied in asymmetric reactions.

Herein, we describe a procedure for the synthesis of chiral epoxides by the reaction of α,β-enones with *tert*-butyl hydrogen peroxide (TBHP) catalyzed by chiral 2-azabicyclo[2.2.1]heptane-3-*exo*-bis(phenyl)methanol **1**, which was synthesized with 21% overall yield from (*R*)-1-phenylethylamine (Eq. 1).[8]



(1)

Our initial studies began with the asymmetric organocatalytic epoxidation of *trans*-chalcone with TBHP in different solvents at room temperature. The results are summarized in Table 1. In the presence of 20 mol % of chiral ligand **1**, the best result was obtained when the epoxidation was carried out in hexane (Table 1, entries 1 and 6). The use of toluene and dichloromethane resulted in lower enantioselectivities and yields (Table 1, entries 4 and 5). When the reaction was carried out in THF or MeOH, or using hydrogen peroxide as the oxidant, the reaction failed to afford the corresponding product (Table 1, entries 7–9). Thus, hexane is the solvent of choice. Performing the epoxidation at 4 °C had no effect on the level of selectivity (Table 1, entry 3). Higher catalytic loading of **1** (30 mol %) afforded comparable results in terms of conversion (Table 1, entry 2).



Scheme 1.

Through this screening process, it was established that the epoxidation reaction could be carried out smoothly in the presence of catalyst **1** (20 mol %) in hexane at room temperature, using TBHP as oxidant. To study the scope and potential of this epoxidation method, we extended the catalytic asymmetric epoxidation to a wide variety of α,β-unsaturated ketones. The results obtained are shown in Table 2.

Under the optimal reaction conditions, various α,β-unsaturated ketones in the presence of **1** furnished diastereoisomerically pure *trans*-(2*R*,3*S*)-epoxides in good yields (Table 2, entries 1–12), which indicates that the reaction is a very efficient enantioselective method for epoxidation. Even the more hindered 2-naphthyl derivative could be converted to the corresponding epoxide in moderate yield and comparable ee (Table 2, entry 8). However, when the methyl-substituted enone 2 m was used as the substrate, the epoxide was

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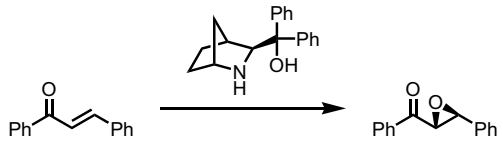
Table 1
Optimization of the reaction conditions for the asymmetric epoxidation of *trans*-chalcone **2a**

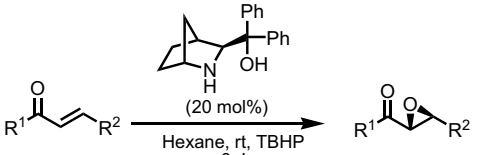


2a **3a**

Entry	Cat. (mol %)	Solvent	Oxidant	*T* (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	20	Hexane	TBHP	rt	60	48	88 (2*R*,3*S*)
2	30	Hexane	TBHP	rt	144	82	88 (2*R*,3*S*)
3	20	Hexane	TBHP	4	144	70	87 (2*R*,3*S*)
4	20	Toluene	TBHP	rt	144	62	80 (2*R*,3*S*)
5	20	DCM	TBHP	rt	144	65	64 (2*R*,3*S*)
6	20	Hexane	TBHP	rt	144	81	88 (2*R*,3*S*)
7	20	THF	TBHP	rt	144	Trace	nd
8	20	MeOH	TBHP	rt	144	Trace	nd
9	20	Hexane	H_2O_2	rt	144	Trace	nd

The reaction was carried out with α,β-enone (1 equiv) and TBHP (1.3 equiv) in the presence of 20 mol %of catalyst **1** at rt.
[a] Yield of isolated product.
[b] Enantiomeric excess was determined by HPLC analysis using a chiral column.

Table 2
Enantioselective epoxidation of α,β-unsaturated ketones catalyzed by chiral ligand **1**



2a-n **3a-n**

Entry	Enone	R^1	R^2	Product	Yield[a] (%)	ee[b] (%)
1	**2a**	C_6H_5	C_6H_5	**3a**	81	88 (2*R*,3*S*)
2	**2b**	C_6H_5	4-BrC_6H_4	**3b**	84	82 (2*R*,3*S*)
3	**2c**	C_6H_5	4-ClC_6H_4	**3c**	84	80 (2*R*,3*S*)
4	**2d**	C_6H_5	4-MeC_6H_4	**3d**	80	86 (2*R*,3*S*)
5	**2e**	C_6H_5	4-$MeOC_6H_4$	**3e**	78	82 (2*R*,3*S*)
6	**2f**	C_6H_5	4-FC_6H_4	**3f**	81	87 (2*R*,3*S*)
7	**2g**	C_6H_5	4-O_2NC6H,	**3g**	76	80 (2*R*,3*S*)
8	**2h**	2-Naphthyl	C_6H_5	**3h**	62	86 (2*R*,3*S*)
9	**2i**	4-ClC_6H_4	C_6H_5	**3i**	88	87 (2*R*,3*S*)
10	**2j**	4-MeC_6H_4	C_6H_5	**3j**	76	84 (2*R*,3*S*)
11	**2k**	4-ClC_6H_4	4-ClC_6H_4	**3k**	80	83 (2*R*,3*S*)
12	**2l**	4-BrC_6H_4	C_6H_5	**3l**	88	84 (2*R*,3*S*)
13	**2m**	Me	C_6H_5	**3m**	25	69 (3*R*,4*S*)
14	**2n**	*t*-Bu	C_6H_5	**3n**	0	—

The reaction was carried out with α,β-enone (1 equiv) and TBHP (1.3 equiv) in the presence of 20 mol % of catalyst **1** at rt in hexane.
[a] Yield of isolated product.
[b] Enantiomeric excess was determined by HPLC analysis using a chiral column, the absolute configuration was determined by comparison of the HPLC retention times or optical rotation with those in the literature.

obtained in poor yield with moderate enantioselectivity (Table 2, entry 13). The reaction failed when the *t*-butyl derivative 2*n* was tested.

In summary, we have disclosed a new catalyst for the asymmetric epoxidation of α,β-enones. The reaction is operationally simple, and could afford the corresponding epoxides in good yields and high enantioselectivities. Although the asymmetric epoxidation catalyzed by this azabicyclo catalyst afforded the products in lower or comparable enantioselectivities as compared to proline derivatives, it opens up a novel avenue for the design of chiral azabicyclo[2.2.1]heptane analogues as organocatalysts. Further work is focused on modifying the chiral 2-azanorbornyl-3-methanol for the epoxidation as well as for other organic transformations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.175.

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