Lappaconitine-Catalyzed Asymmetric α-Hydroxylation of β-Keto Esters: A Brønsted Base Organocatalyst Developed from Terpenoid Alkaloids

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Abstract: Discovering organocatalysts with novel framework from terpenoid alkaloids is presented in this paper. Lappaconitine was found to enantioselectively catalyze α-hydroxylation of β-keto esters using *tert*-butyl hydroperoxide as the oxidant in chloroform to afford the corresponding products in high yields and good enantioselectivity (up to 85% ee).

Key words: lappaconitine, asymmetric α-hydroxylation, β-keto esters, organocatalyst, terpenoid alkaloid

Organocatalysis is an efficient synthetic route to promote a considerable number of asymmetric reactions, especially the enantioselective transformation of carbon–hydrogen bonds to carbon–carbon bonds.[1] Effective organocatalysts for asymmetric functionalization of carbon–hydrogen bonds to carbon–oxygen bonds are, however, still limited to several typical organic molecules and their corresponding derivatives, including amino acid derivatives,[2] oligopeptides,[3] cinchona alkaloids,[4] chiral ketones,[5] and iminium salts,[6] etc. Elaborate modification of the present organocatalysts generally achieves desired results in certain transformations, but this is not always the case. Discovering new organocatalysts with novel framework to meet the high standards of synthetic method is now highly imperative and a great challenge to chemists.

During our research on clinical application of alkaloids, we found that most of the alkaloids possess chiral base centers, hydroxyl or carbonyl functional groups and rigid structures, which are essential features of present organocatalysts. In fact, cinchona,[1a,4] tropane alkaloid,[5c] and phenylalkylamines derivatives[7] have been employed as the organocatalysts. We wanted to explore new organocatalysts with novel framework from other alkaloids.

Terpenoid alkaloids are a class of compounds that are normally beneficial for curing feedant, fungal, hypertension, neuralgia as well as rheumatism. A number of terpenoid alkaloids have been developed as the effective drugs in clinical application and are commercially available. For example, lappacontine[8] (Figure 1, c), a diterpenoid alkaloid isolated from *Aconitum sinomontanum Nakai*, is used as hypertensive drug, analgetic, local anesthetic, and for treating arrhythmia (commercially named alapinin).

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In this paper, we chose three commercially available terpenoid alkaloids (Figure 1), possessing a rigid chiral basic center and hydroxyl as well as carbonyl groups, as Brønsted base organocatalysts and tried to demonstrate their catalysis in the asymmetric reactions.

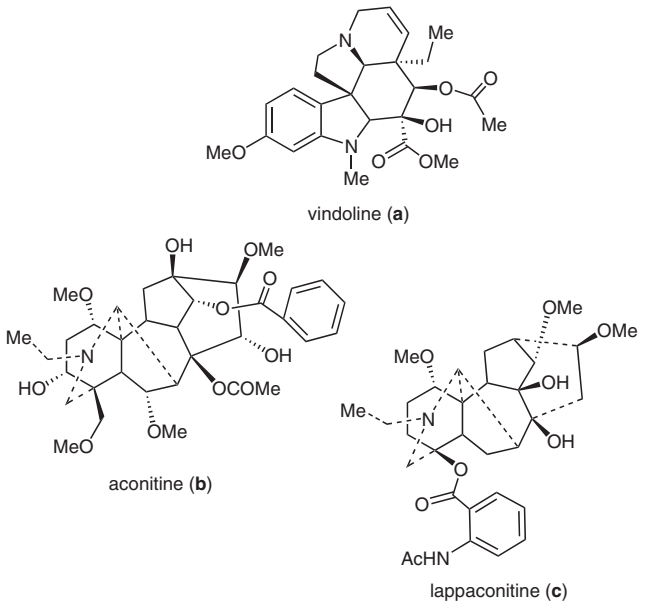
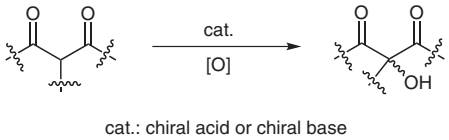


Figure 1 Alkaloids employed as the organocatalysts

The α-hydroxyl-β-keto esters moiety is an important structure in a variety of natural products, pharmaceuticals, and key intermediates.[9] Moreover, these functional units are starting materials for the preparation of optically active *anti*-α,β-diols.[4b] Direct oxidation of β-keto esters catalyzed by ether chiral acid or chiral base is the most convenient approach to obtain the α-hydroxylated products (Scheme 1). Lewis acids[10] were reported as the effective catalysts for α-hydroxylation of some steric β-keto esters, using oxaziridine as the oxidant. Very recently, Zhong et al. used a chiral Brønsted acid[11] derived from chiral BINOL as the catalyst and nitroso compounds as the oxygen source to realize high enantioselective α-hydroxylation of β-dicarbonyl compounds. The asymmetric α-hydroxylation of β-keto esters based on chiral base catalysis achieved satisfactory results (up to 80% ee) only by cinchona alkaloid derivatives as the catalysts as reported by the Dupont group initially[4a] and Jorgensen later.[4b] Herein, we will expand the use of chiral Brønsted bases

developed from terpenoid alkaloids in the α-hydroxylation of β-keto esters.



Scheme 1 α-Hydroxylation of β-dicarbonyl compounds

We initially screened different alkaloids as the organocatalysts under various reaction conditions, and the detail results are summarized in Table 1.

As shown in Table 1, monoterpenoid indole alkaloid vindoline did not promote the α-hydroxylation (entry 1). To our delight, moderate yields of α-hydroxylation products were observed when the diterpenoid alkaloids aconitine as well as lappaconitine (entries 2, 3) were employed as the organocatalysts. Surprisingly, visible enantioselectivity (49% ee) only exhibited in lappaconitine-catalyzed process, instead of aconitine (5% ee), despite of the analogical skeleton of the two alkaloids.

The effects of the solvents were examined next. It was found that the α-hydroxylation could not proceed in polar solvents under the reaction conditions, and trace amount of products were isolated (entries 4–6), while nonpolar and less polar solvents afforded good results, with the best result of 61% yield and 67% ee in chloroform (entries 3, 7, and 8).

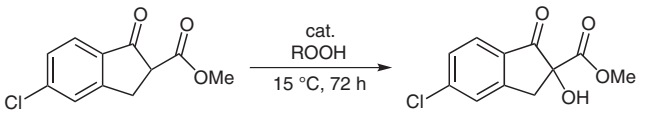
Different peroxides were then introduced as the oxidants for the asymmetric α-hydroxylation reaction (entries 8–11). However, both MCPBA and 30% H_2O_2 failed to oxide β-keto esters under the present conditions, while TBHP gave the better results (61% yield, 67% ee) than CHP (45% yield, 60% ee).

We then decided to decrease the amount of lappaconitine (using 10 mol% and 5 mol%), without obvious influence, and satisfactory enantioselectivity 67% and 64% ee were obtained, respectively (entries 12, 13). Nevertheless, the yield of the reaction remained unsatisfactory for a synthetic method. Alternatively, the amount of TBHP was increased, and it was found that the excessive amount of TBHP distinctly improved the isolated yield from 62% to 92% (entry 14).

Based on the optimized conditions, a series of β-keto esters was investigated to illustrate the general application scope (Table 2).

We initially studied the influence of the ester functionality on the yield and enantioselectivity of the asymmetric α-hydroxylation (entries 1–6, 8–11). The ester functionality with different steric hindrance was well tolerated when the aromatic rings were substituted with halides and the corresponding α-hydroxylation products were obtained in high yields and good ee values (entries 1–6). When the aromatic rings were substituted by methoxy group, the enantioselectivity dropped from 85% to 67% with increasing steric hindrance of the ester functionality (entries 8–11).

Table 1 Effects of Solvents, Catalysts, and Peroxides on the Reaction Outcomes[a]



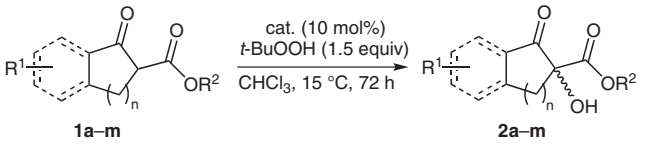
Entry	Cat (mol%)	Solvent	Peroxide[c]	Yield (%)[b]	ee (%)[c]
1	**a**, (20)	CH_2Cl_2	TBHP	<5	–
2	**b**, (20)	CH_2Cl_2	TBHP	57	5
3	**c**, (20)	CH_2Cl_2	TBHP	53	49
4	**c**, (20)	acetone	TBHP	<5	–
5	**c**, (20)	DMF	TBHP	<5	–
6	**c**, (20)	EtOH	TBHP	<5	–
7	**c**, (20)	toluene	TBHP	58	54
8	**c**, (20)	$CHCl_3$	TBHP	61	67
9	**c**, (20)	$CHCl_3$	CHP[d]	45	60
10	**c**, (20)	$CHCl_3$	MCPBA[e]	<5	–
11	**c**, (20)	$CHCl_3$	30% H_2O_2	<5	–
12	**c**, (10)	$CHCl_3$	TBHP	62	67
13	**c**, (5)	$CHCl_3$	TBHP	59	64
14[f]	**c**, (10)	$CHCl_3$	TBHP	92	65

[a] Unless noted, reactions were run with 1 mmol β-keto ester, 1.5 mmol oxidant, certain amount of lappaconitine, 16 mL solvent, 15 °C, 72 h.
[b] Isolated yields after column chromatography.
[c] The ee values were determined by HPLC.
[d] CHP = cumyl hydroperoxide.
[e] MCPBA = *m*-chloroperoxybenzoic acid.
[f] 5 mmol, 5 equiv TBHP was introduced in the reaction.

The substitution on the aromatic rings generally led to different results (entries 1–13). Both halides, substituted and unsubstituted reactants, showed high yields and ee values, for example, 6-bromo-1-oxoindan-2-carboxylic acid methyl ester gave the highest yield of 95% and good enantioselectivity of 78% (entry 5). In addition, the ee value of **2a** was improved to >99% after a single recrystallization in the solvent of ethyl acetate, with the yield of 68%.

The aromatic rings attached with electron-donating groups on position 4 gave the highest ee value of 85% (entry 8), but a bit lower yield of 76%. However, 5,6-dimethoxyl-substituted substrate unexpectedly failed to perform the reaction (entry 12), probably because the key intermediate, the enol form of the β-keto ester, was strongly restrained by the 5,6-electron-donating groups. On the other hand, the six-membered ring substrate **1n** and simple β-keto ester **1o** could not be oxidized when using TBHP as the oxygen source under the reaction conditions (entry 14, 15).[12]

Table 2 Lappacontine-Catalyzed Asymmetric Hydroxylation of β-Keto Esters[a]



Entry	1	n	R^1	R^2	Yield (%)[b]	ee (%)[c]
1	**1a**	1	5-Cl	Me	92 (68)	65 (>99)
2	**1b**	1	5-Cl	Et	88	65
3	**1c**	1	5-Cl	*i*-Pr	85	67
4	**1d**	1	5-Cl	Bn	82	59
5	**1e**	1	6-Br	Me	95	78
6	**1f**	1	6-Br	Et	85	68
7	**1g**	1	5-Cl-6-Br	Me	90	75
8	**1h**	1	4-MeO	Me	78	85
9	**1i**	1	4-MeO	Et	75	73
10	**1j**	1	4-MeO	*i*-Pr	72	74
11	**1k**	1	4-MeO	Bn	53	67
12	**1l**	1	5,6-MeO	Me	Nr	–
13	**1m**	1	H	Me	94	68
14	**1n**	2	H	Me	17[d]	–
15	**1o**	1	without benzene ring	Bn	<5	–

[a] Unless noted, reactions were run with 1 mmol β-keto ester, 5 mmol oxidant, 16 mL solvent, 15 °C, 72 h.
[b] Isolated yields after column chromatography; yield after a single recrystallization is reported in parentheses.
[c] The ee values were determined by HPLC; the ee value after a single recrystallization is reported in parentheses.
[d] Based on the recovered starting material.

In summary, we have developed the diterpenoid alkaloid lappaconitine as a new chiral base organocatalyst for the first time. Using lappacontine as the organocatalyst and *tert*-butyl hydroperoxide as the oxidant in chloroform, the α-hydroxylation of β-keto esters proceeds in high yield, and the products are recovered with up to 85% ee. The ee value was improved to >99% after a single recrystallization. Further investigations on the application of lappaconitine and other alkaloids are under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) Lu, M.; Zhu, D.; Lu, Y. P.; Zeng, X. F.; Tan, B.; Xu, Z. J.; Zhong, G. F. *J. Am. Chem. Soc.* **2009**, *131*, 4562.
(12) **General Procedure for Lappaconitine-Catalyzed Asymmetric α-Hydroxylation of β-Keto Esters**
A mixture of β-keto ester (1 mmol), *tert*-butyl hydroperoxide (5 mmol), lappaconitine (0.1 mmol) in $CHCl_3$ (6 mL) was stirred for 72 h at 15 °C. The reaction was monitored by TLC. After the starting material vanished, the mixture was washed with 10 wt% Na_2SO_3 and extracted with CH_2Cl_2. The organic layer was then dried over anhyd Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (*n*-hexane–EtOAc = 3:1) to give the product. The ee value was determined by chiral HPLC on CHIRALCEL OD-H or AD-H column (hexane–*i*-PrOH = 90:10, flow rate 1.0 mL/min, 254 nm, unless noted). See Supporting Information for data of all compounds.