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Asymmetric Intramolecular Oxa-Michael Reactions to Tetrahydrofurans/2*H*-Pyrans Catalyzed by Primary−Secondary Diamines

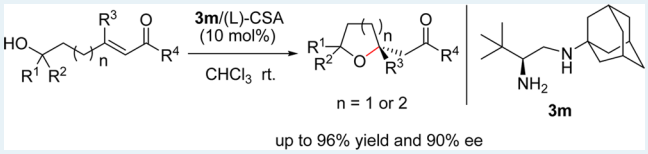
Yingpeng Lu,[†,‡] Gang Zou,*[,†] and Gang Zhao*[,‡]

[†]Laboratory of Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China

[‡]Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: The asymmetric intramolecular oxa-Michael reactions of *α,β*-unsaturated ketones have been achieved by using readily accessible primary−secondary diamines as the organocatalysts, giving the synthetically useful tetrahydrofurans/2*H*-pyrans in good yields and with high enantioselectivities (up to 90% ee).



KEYWORDS: *oxa-Michael reaction, organocatalysis, asymmetric catalysis, diamine catalyst, tetrahydrofurans*

The oxa-Michael reaction has been widely used in organic synthesis as a powerful tool to construct carbon−oxygen bond.[1,2] Compared with the amino group,[3,4] the lower nucleophilicity of the hydroxyl group makes it more challenging as a Michael donor in Michael additions, and a strong base is usually required to promote the reaction, which usually caused difficulty in achieving a compatible chiral environment in catalysis. Solutions to this problem include using more-active phenols,[5−9] oximes[10−13] or hydrogen peroxide[14,15] with improved nucleophilic oxygen atom or using more-reactive conjugate acceptors,[16−21] such as conjugated enals or nitrostyrene, and the design of intramolecular processes.[22−30] Over recent decades, with the rapid development of organocatalysis, organocatalytic enantioselective oxa-Michael additions have also achieved impressive progress, providing efficient access to various oxygen-containing heterocycles[31−33] such as tetrahydrofurans (THF), tetrahydropyrans (THP), chromenes, or xanthones, which could be found in numerous natural products with important biological activities[34−42] (Figure 1).

However, to our knowledge, only a few reports have been focused on the intramolecular oxa-Michael reactions of unsaturated ketones with alcohol nucleophiles which used chiral Brønsted acid[26] or bifunctional chiral thiourea[27] as the catalysts. Very recently, Ye's group has reported that the desymmetrization of cyclohexadienones could be achieved via an asymmetric intramolecular oxa-Michael reaction using primary amine catalysts.[30]

Our group has great interest in the development of amino acid-derived catalysts, and we have first developed from amino acids a variety of primary amine catalysts[43−55] that have showed excellent catalytic reactivity in Michael additions and epoxidation of enones. Inspired by these results, we then became interested in the application of these catalysts to the challenging intramolecular oxa-Michael reactions of enones. Herein, we describe the development of a new primary−secondary diamine catalyst derived from L-*tert*-leucine, which efficiently catalyzed the asymmetric intramolecular oxa-Michael reactions of conjugate enones to give the synthetically useful chiral tetrahydrofurans/2*H*-pyrans.

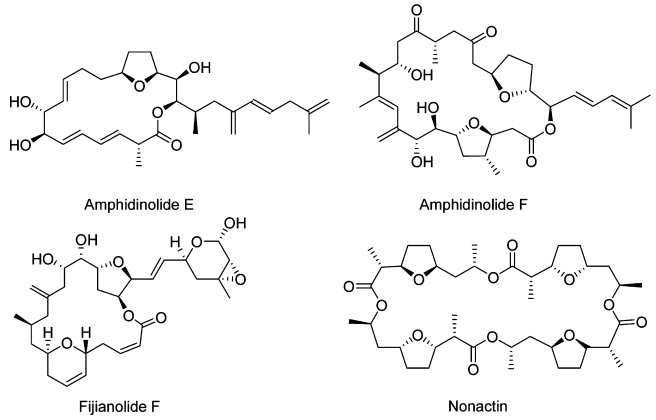


Figure 1. Structures of typical THF/THP containing macrolides.

Initially, (*E*)-8-hydroxy-1-phenyloct-4-en-3-one **1a** was synthesized, and the model reaction with **1a** was carried out in the presence of 10 mol % of catalyst and 10 mol % of TFA as an additive in $CHCl_3$ under room temperature (Table 1). The primary−tertiary diamines, primary−secondary diamines, and primary−primary diamines listed in Figure 2 were prepared and

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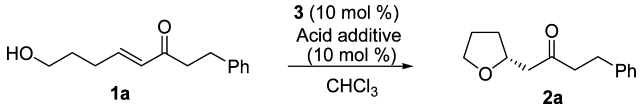
Table 1. Screening the Catalysts and Acid Additives[a]



entry	cat. 3	acid additive	yield (%)[b]	ee (%)[c]
1	**3a**	TFA	85	26
2	**3b**	TFA	80	32
3	**3c**	TFA	85	26
4	**3d**	TFA	92	57
5	**3e**	TFA	90	52
6	**3f**	TFA	86	61
7	**3g**	TFA	90	68
8	**3h**	TFA	76	12
9	**3i**	TFA	80	56
10	**3j**	TFA	74	66
11	**3k**	TFA	72	40
12	**3l**	TFA	76	30
13	**3m**	TFA	88	72
14	**3n**	TFA	91	5
15	**3m**	none	52	7
16	**3m**	PhCOOH	76	45
17	**3m**	*p*-NBA	82	40
18	**3m**	TsOH	89	63
19	**3m**	CCl_3COOH	36	41
20	**3m**	TfOH	88	65
21	**3m**	L-Boc-Ph-OH	77	60
22	**3m**	D-Boc-Ph-OH	80	72
23	**3m**	L-CSA	96	85
24	**3m**	D-CSA	92	51
25	none	L-CSA	96	0

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol), **3** (10 mol %), and acid additive (10 mol %) in $CHCl_3$ (1.0 mL) at room temperature for 48 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. The absolute configuration was determined by comparison of the specific optical rotation value with the literature data.[27]

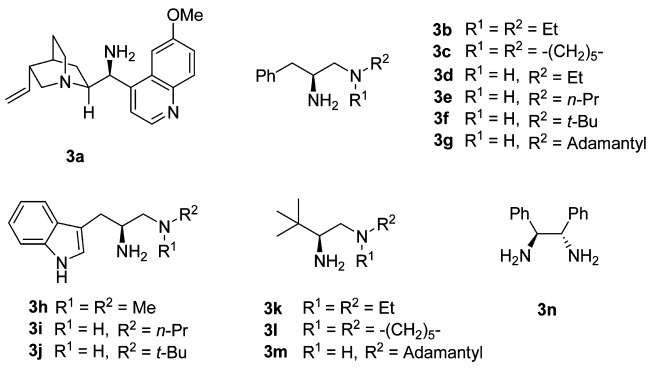


Figure 2. Structures of the catalysts studied.

evaluated in the reaction. *Cinchona* alkaloid-derived primary amine catalyst, which usually worked well in Michael addition and epoxidation, was examined but gave only the product **2a** with 26% ee (Table 1, entry 1). Primary−tertiary diamine catalysts or primary−primary diamine catalyst generally provided inferior stereocontrol in this reaction.

The examination of different amino acids skeletons and substituents of the secondary amine moiety revealed that the catalyst **3m** derived from L-*tert*-leucine bearing a sterically hindered adamantanyl group was the optimal catalyst, affording the ring closure product with 88% yield and 72% ee value (Table 1, entry 13). In our previous and other related works, acid additives have been found to play an important role in the catalytic efficiency of these amino acid-derived diamine catalysts. Similarly, in the absence of an acid, this reaction gave the product with only 50% yield and 7% ee (Table 1, entry 15). A screen of several acids was then performed to improve the enantioselectivity with catalyst **3m**. L-camphorsulfonic acid ((L)-CSA) gave the best result of 96% yield and 85% ee (Table 1, entry 23). Notably, a proper match of the chirality of the diamine catalyst and the chiral acid additive is necessary because the use of (D)-CSA affords only moderate enantioselectivity (Table 1, entry 24). A control experiment with the acid alone gave the racemic product in the same excellent yield (Table 1, entry 25), indicating that cooperative catalysis of the diamine catalyst and the acid additive was crucial to achieve good enantioselectivity in this reaction system.

With the catalyst combination of **3m**/(L)-CSA, other reaction parameters, such as the solvent effect, temperature and the loading of the catalyst, were also examined (for details, see the Supporting Information, Table S1). In general, nonprotic solvents, such as toluene, dichloromethane, and chloroform, bearing no coordinative atoms are superior to protic solvents. Decreasing the temperature or reducing the catalyst/acid loading caused obviously decreases in reactivity and enantioselectivity. Thus, the best reaction conditions are a combination of **3m**/(L)-CSA (1:1) in chloroform at 25 °C, providing the product with 96% yield and 85% ee.

With the optimized reaction conditions in hand, the scope of the oxa-Michael reaction was investigated, and the results are summarized in Table 2. In general, the 2-substituted tetrahydrofuran or tetrahydropyran products were exclusively formed in high yields with good ee values. Substrates with both electron-donating and -withdrawing groups on the phenyl group worked well under the catalysis (Table 2, **2a**−**2c**). Aliphatic enones as well as enones bearing ether or amide functional groups also performed well to give the products with good yields and high stereoselectivity, except for substrate **2d**, the low yield of which might be due in part to the high volatility of the product (Table 2, **2d**−**2f**). Enones with bulky substituents on the side of the ketone moiety gave both significantly lower yield and enantioselectivity (Table 2, **2g**). Secondary alcohol in the substrate also worked well to afford 2,5-substituted tetrahydrofuran with high yields and good enantioselectivities, albeit with a poor diastereoselectivity (Table 2, **2h**). The more sterically demanding tertiary alcohol gave unsatisfactory results, with a sharp drop in the ee value (Table 2, **2i**). Less reactive enones with an additional methyl group on the alkene double bond were also evaluated; however, using (*E*)- or (*Z*)-**1j** as a substrate, both the conversion and the ee value were low, and the absolute configuration of the corresponding product was reversed (Table 2, **2j**). Pleasingly, this catalyst system could also be applied to the synthesis of the six-membered tetrahydropyran products with good to excellent yields, ee values, and similar functional group tolerance (Table 2, **2k**−**2m**).

A bifunctional iminium mechanism similar to those previously proposed for the primary amine catalysts in the iminium catalysis of enone may be invoked to explain the observed stereochemical results (Figure 3). The primary amine moiety of the catalyst **3m** was presumed to activate enone **1** via the formation of an iminium ion, whereas the secondary amine activates the nucleophilic hydroxyl group. The *si*-face of the

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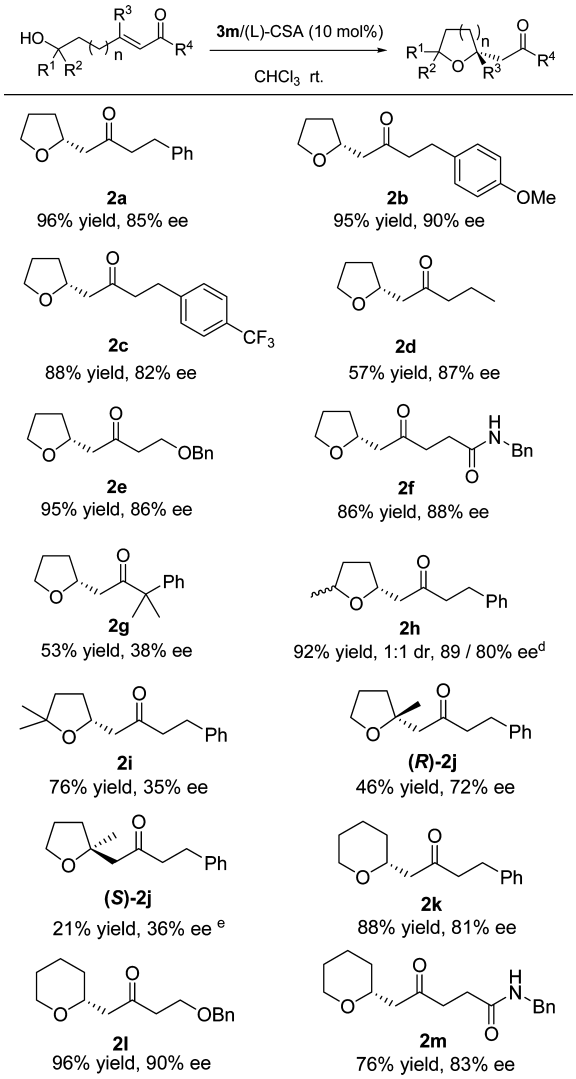
Table 2. Substrate Scope of the Oxa-Michael Reaction[a]



[a]Unless otherwise specified, the reaction was carried out with **1** (0.1 mmol), **3m** (10 mol %), and L-CSA (10 mol %) in chloroform (1.0 mL) at room temperature for 48 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. The absolute configuration was determined by comparison of the specific optical rotation value with the literature data.[27] [d]dr. = 1:1, ee value of the two diastereomer were 89% and 80%, respectively (see the Supporting Information for details). [e](Z)-**1j** was studied under optimized conditions.

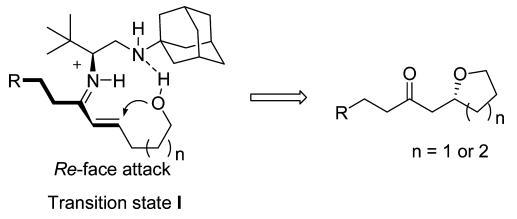


Figure 3. Possible transition state of the reaction.

enone in this transition state assembly **I** is shielded by the bulky groups of both sides of the catalyst, driving the alcohol oxygen atom to attack the *re*-face of the enone **1**. 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 of the catalyst amine.

To gain some insight into the catalytic mechanism of the catalyst system, an ESI-MS analysis was taken for the combination of catalyst and substrate **1b** (Figure 4). A signal matching the key iminium ion could be explicitly observed, which may be supportive of our proposed transition state **I** for the reaction.

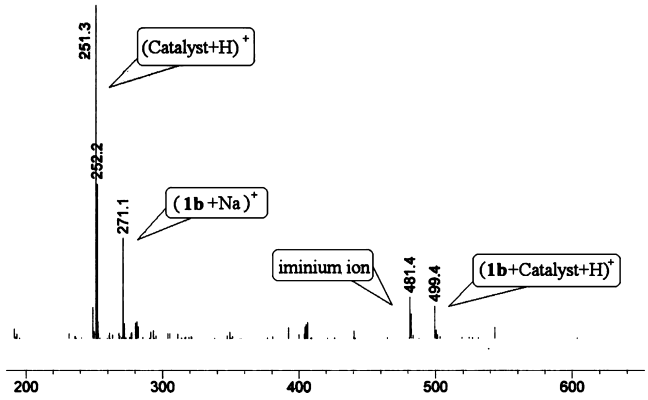


Figure 4. Mass spectrum of the combination of **1b** with catalyst **3m**..

In summary, a novel primary−secondary diamine catalyst has been developed and applied in the intramolecular oxa-Michael addition of α,β-unsaturated ketones. This new system features easily accessible modular catalysts and simple operation, enabling the synthesis of 2-substituded tetrahydrofurans or tetrahydropyrans under mild conditions 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.

■ ASSOCIATED CONTENT

Supporting Information

Details of condition optimization, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org."

■ AUTHOR INFORMATION

Corresponding Author

*(Gang Zou) Fax: (+86)-21-6425-3881. E-mail: zougang@ecust.edu.cn. (Gang Zhao) Fax: (+86)-21-6416-6128; e-mail: zhaog@mail.sioc.ac.cn.

Notes

The authors declare no competing financial interest.

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