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Asymmetric Catalytic Cycloetherification Mediated by Bifunctional Organocatalysts

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Supporting Information

ABSTRACT: Oxacyclic structures such as tetrahydrofuran (THF) rings are commonly found in many bioactive compounds, and this has led to several efforts toward their stereoselective syntheses. However, the process of catalytic asymmetric cycloetherification for their straightforward synthesis has remained a challenge. In this study, we demonstrate a novel asymmetric synthesis method for THF via the catalytic cycloetherification of ε-hydroxy-α,β-unsaturated ketones mediated by cinchona-alkaloid-thiourea-based bifunctional organocatalysts. This catalytic process represents a highly practical cycloetherification method that provides excellent enantioselectivities, even with low catalyst loadings at ambient temperature.

The prevalence of oxacyclic frameworks such as tetrahydrofuran (THF) rings in a broad array of natural products and biologically active agents has resulted in the development of a number of methods for their stereoselective synthesis.[1,2] Among these methods, cycloetherification offers straightforward ring construction and has been successfully employed in the synthesis of 2-substituted oxacyclic compounds. However, catalytic enantioselective cycloetherification has remained a challenge despite significant advances in asymmetric catalysis.[3] This challenge is due to the difficulty in achieving a suitable chiral environment and the rapidity of the intramolecular processes involved in the catalysis.[4,5]

Over the past decade, the process of asymmetric catalysis based on hydrogen bonding has seen continuous progress in the field of synthetic chemistry,[6,7] and the use of bifunctional organocatalysts that include a thiourea group and a tertiary amino group has made a significant contribution.[7] In this class of catalysts, the thiourea and tertiary amino groups function cooperatively as hydrogen bond donors and acceptors, respectively; this enables the simultaneous activation of a nucleophile and an electrophile in a suitable reaction direction, thereby leading to the desired stereochemical yields.[6,7] The efficiency of bifunctional organocatalysts stimulated us to exploit the concerted catalysis in order to develop a catalytic asymmetric cycloetherification for THF synthesis via an intramolecular oxy-Michael addition reaction (Figure 1).[8] In this study, we present a highly enantioselective catalytic cycloetherification method for the synthesis of 2-substituted THFs from ε-hydroxy-α,β-unsaturated ketones mediated by cinchona-alkaloid-thiourea-based bifunctional organocatalysts.

We initiated our investigations using (*E*)-6-hydroxy-1-phenylhex-2-en-1-one (**1a**) and 3 mol % of quinidine-derived

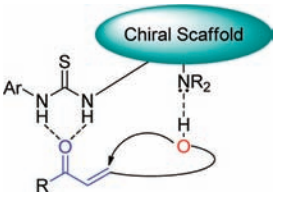
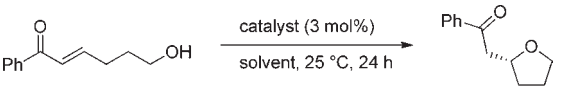


Figure 1. Asymmetric cycloetherification via intramolecular oxy-Michael addition reaction mediated by bifunctional organocatalyst.

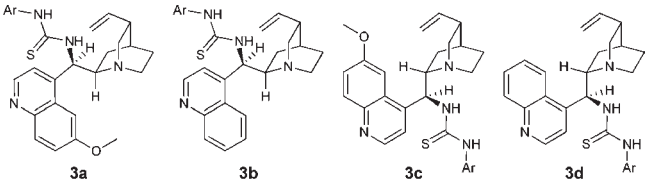
Table 1. Optimization of Conditions[a]



1a **2a**

entry	catalyst	solvent	yield (%)[b]	ee (%)
1	**3a**	CH_2Cl_2	99	92
2	**3a**	benzene	97	94
3	**3a**	THF	73	90
4	**3a**	Et_2O	99	94
5	**3a**	CPME[c]	99	95
6[d]	**3a**	CPME[c]	95	96
7	**3b**	CPME[c]	99	89
8	**3c**	CPME[c]	99	−96
9	**3d**	CPME[c]	99	−94

[a] Reactions were run using **1a** (0.25 mmol) and the catalyst (0.0075 mmol) in the solvent (0.5 mL). [b] Isolated yields. [c] CPME = cyclopentyl methyl ether. [d] Reaction was run using 1 mol % of **3a** (0.0025 mmol).



bifunctional catalyst **3a** in CH_2Cl_2 at 25 °C. As expected, the THF product **2a** was obtained quantitatively and enantioselectively

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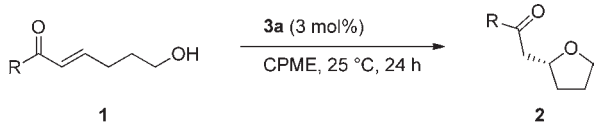
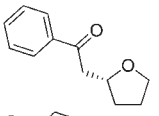
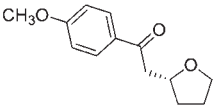
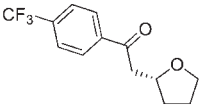
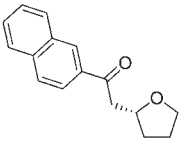
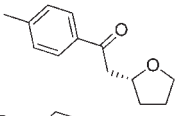
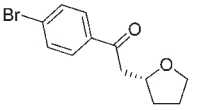
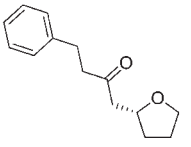
Table 2. Substrate Scope with 3a as Catalyst[a,b]



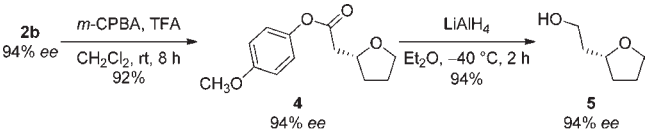
entry	product (2)		yield (%)[c]	*ee* (%)
1		**2a**	99	95
2		**2b**	99	94
3[d]		**2c**	93	85
4		**2d**	98	91
5		**2e**	99	93
6		**2f**	99	92
7[e]		**2g**	97	90

[a] Reactions were run using **1** (0.25 mmol) and **3a** (0.0075 mmol) in CPME (0.5 mL). [b] CPME = cyclopentyl methyl ether. [c] Isolated yields. [d] Reaction was run on a smaller scale (see Supporting Information for details). [e] Reaction was run for 120 h.

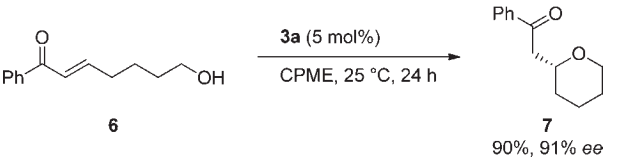
(Table 1, entry 1). The solvent optimization process identified cyclopentyl methyl ether (CPME) as the most suitable solvent for enantioselectivity (Table 1, entries 1−5). Moreover, the catalytic loading could even be lowered to 1 mol % at ambient temperature while still giving excellent yield and enantioselectivity (Table 1, entry 6), thereby showing that this reaction mode allows a highly practical cycloetherification. The screening of catalysts further showed that **3c** is an efficient catalyst for obtaining the opposite enantiomer of **2a** in excellent yield and enantioselectivity (Table 1, entries 7−9).

Subsequently, we explored the substrate scope using 3 mol % of **3a** as a catalyst. Good to excellent yields and enantioselectivities were obtained with both electron-rich and electron-poor enones (Table 2, entries 2 and 3). In addition, substrates bearing naphthyl, *p*-tolyl, or *p*-bromophenyl groups afforded THF products in excellent yields with high enantioselectivities (Table 2, entries 4−6). An enone substituted by an alkyl group also underwent this reaction and yielded a THF product (Table 2, entry 7). In addition, the obtained THF product **2b** could be further transformed into the corresponding ester **4** by means of Baeyer−Villiger oxidation with *m*-CPBA and TFA in 92% yield without any loss of optical purity (Scheme 1). This transformation allows further transformations, such as the subsequent reduction of **4** with lithium aluminum hydride that yielded (*R*)-2-(tetrahydrofuran-2-yl)ethanol (**5**); the product **5** is a valuable synthetic intermediate (Scheme 1).[9] The absolute configuration of **2b** was determined by comparing the optical rotation of **5** derived from **2b** with the literature value[9a] (see Supporting Information for details), and the configurations for all other examples were assigned analogously.

Scheme 1. Transformation of 2b



Scheme 2. Asymmetric Synthesis of 2-Substituted Tetrahydropyran 7



Furthermore, this protocol can also be applied to the asymmetric synthesis of 2-substituted tetrahydropyran (THP) (Scheme 2). Preliminary studies showed that the reaction of ζ-hydroxy-α,β-unsaturated ketone **6** using **3a** as a catalyst afforded the THP product **7** in good yield and high enantioselectivity.

In summary, we have demonstrated a novel asymmetric cycloetherification for the synthesis of 2-substituted THFs by utilizing synergistic activations due to bifunctional organocatalysts. This reaction is highly practical in the sense that the products were obtained in excellent enantioselectivities at ambient temperature, even under low catalyst loading conditions. Furthermore, this approach opens a new avenue for heterocycle synthesis with asymmetric catalysis based on hydrogen bonding. Investigations into the full scope of this reaction and further studies on the application of this methodology to other heterocycle syntheses are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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