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Regioselective α-addition of vinylogous α-ketoester enolate in organocatalytic asymmetric Michael reactions: enantioselective synthesis of Rauhut–Currier type products†

Zhibing Weng,‡[ab] Ying Zhou,‡[c] Xin Yue,[c] Feng Jiang[c] and Wengang Guo *[c]

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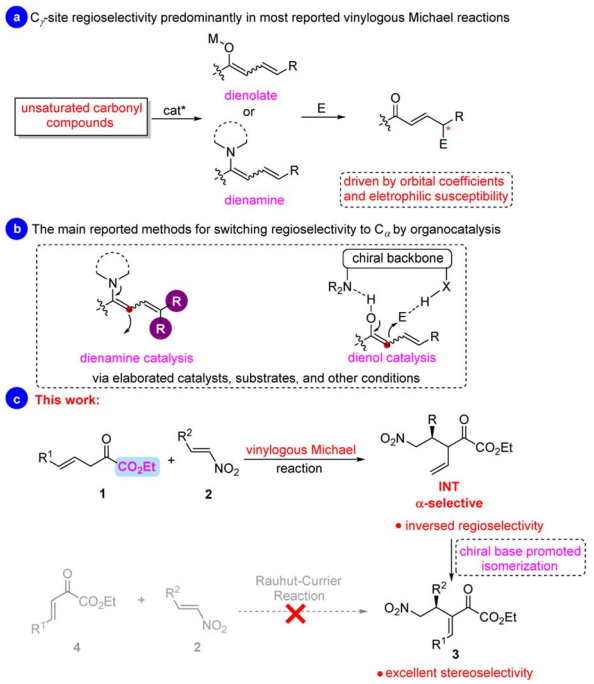
Catalytic asymmetric α-regioselective Michael additions of vinylogous α-ketoester enolate are described herein. With 0.1–1.0 mol% loadings of a chiral bifunctional organocatalyst, the addition of a deconjugated α-keto ester to a series of nitroolefins, including the challenging β-alkylnitroalkenes, efficiently proceed, providing the Rauhut–Currier type products after isomerization of the terminal double bond in good yields (60–88%) with excellent regio- and enantioselectivities (94–99% ee, TON up to 160 with 0.5 mol% of the catalyst).

Introduction

The enolate-based Michael reaction is fundamentally important in synthetic chemistry and could provide highly functionalized valuable products for natural and non-natural product synthesis. Its synthetic power has been dramatically improved by combing with the principle of vinylogy, thus increasing product complexity.[1] Since the landmark report of vinylogous Mukaiya–Michael reaction of 2-silyloxyfurans and enals on use of iminium activation,[2] tremendous asymmetric vinylogous Michael additions, employing 5-member ring heterocycles, such as 2-silyloxyfurans,[3] lactone,[4] and lactam,[5] cyclic,[6] or acyclic carbonyl derivatives[7] as the nucleophiles,[8] have been developed (Scheme 1a), furnishing valuable enantioenriched products with γ-site regioselectivity predominantly as a result of orbital coefficients and electrophilic susceptibility.[9]

Alternatively, Shibasaki and co-workers disclosed a chiral barium complex catalyzed Mannich reaction of a β,γ-unsaturated ester, providing aza-Morita–Baylis–Hillman-type products after base-promoted isomerization of the terminal C=C bond of products.[10a] C–C bond formation at the α-position of "dienolates" or their equivalent "dienamine" intermediate has also been achieved.[10] In this context, several methods were established for taming the issue of regioselectivity in synthetic chemistry, especially in asymmetric organocatalysis. For example, steric shielding of C_γ-position of unsaturated aldehydes is one of the used strategies for achieving α-regioselectivity of vinylogous Michael reaction through dienamine catalysis (Scheme 1b, left).[10b–g] On the other hand, bifunctional Lewis base/hydrogen bonding catalysis is also found to be competent. The attack site of the *in situ* generated dienolate



Scheme 1 Introduction to asymmetric vinylogous Michael addition reactions with dienolates and its equivalent dienamines.

[a]*School of Chemical and Pharmaceutical Engineering, Changzhou Vocational Institute of Engineering, Changzhou, China*

[b]*School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing, China*

[c]*School of Petrochemical Engineering, Changzhou University, Changzhou, China. E-mail: wgguo@cczu.edu.cn*

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‡ Z. Weng and Y. Zhou contributed equally to this work.

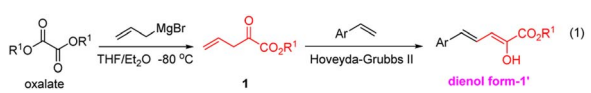
could be controlled *via* the carefully selected organocatalysts through "anchoring effect" (Scheme 1b, right).[10h–o] However, after extensive literature research, it can be found that the elaborated catalyst, substrate, and other reaction conditions are often required for switching the regioselectivity. Inspired by the elegant works of Barbas,[10g] Palomo,[10h,i] and Alemán[10o] in catalytic asymmetric vinylogous Michael additions for the synthesis of RC (Rauhut–Currier)-type products, we questioned whether vinylogous α-keto esters could be employed in vinylogous asymmetric Michael reaction in the control of regioselectivity under low catalyst loading[11] and mild reaction conditions.

α-Dicarbonyl compounds have rarely been used as nucleophiles in Brønsted base catalyzed asymmetric reactions due to their intrinsic potential for self-condensation.[12] α-Ketoamides with a higher pK_a value of α-C–H Bond were usually employed to tame the reactivity in catalytic asymmetric Michael reactions.[13] To this end, Sodeoka and coworkers developed the first example of asymmetric conjugate addition of α-ketoesters to nitroalkenes by elaborating a strategy of "endogenous and exogenous bases effect".[14] Rodriguez and co-workers developed the highly stereoselective 1,4-addition of α-keto esters to nitroolefins by using Takemoto's thiourea organocatalyst.[15] Our continuous interest in developing new organocatalytic asymmetric reactions,[16] and inspiration from the work of Rodriguez and others prompted our investigation into the vinylogous Michael addition reaction of deconjugated α-keto esters. Herein, we report the successful realization of this, affording valuable enantioenriched Rauhut–Currier type products with high enantioselectivities (94–99%) upon *in situ* isomerization of the terminal C=C double bond, which could not be accessed by direct Rauhut–Currier reaction (Scheme 1c).

Results and discussion

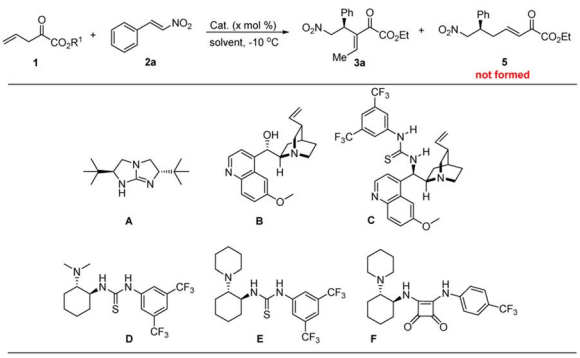
Firstly, our investigations focused on the synthesis of vinylogous α-keto esters. It was reported that vinylogous α-keto esters could exist as stable dienol forms, depending on the properties of substituents on the terminal double bond.[17] Thus, it persuaded us to prepare two types of vinylogous α-ketoesters to investigate their reactivities (Scheme 2, compounds **1** and **1′**, eqn (1).

Secondly, with the desired α-ketoester derivatives in hand, we proceeded to screen chiral organic base catalysts for achieving the asymmetric version of this cascade reaction. Guanidine **A**, which was reported as an excellent organocatalyst for isomerization of 3-alkanoates,[18] was found to be effective in promoting the cascade reaction between **1** and **2a**. However, the corresponding Rauhut–Currier type product **3a** is obtained with moderate enantioselectivity (Table 1, entry 1). Similar enantioselectivities were achieved when evaluating *Cinchona* alkaloid



Scheme 2 Synthesis of vinylogous α-keto esters.

Table 1 Evaluation of reaction conditions[a]



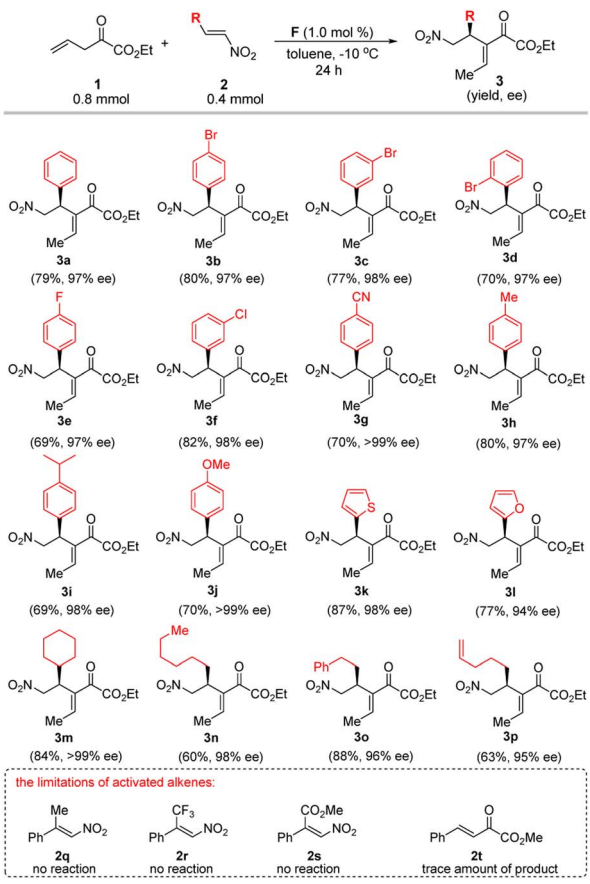
Entry	Cat.	R^1	x	Solvent	Yield[b] (%)	ee[c] (%)
1	**A**	Et	10	Toluene	64	32
2	**B**	Et	10	Toluene	83	−25
3	**C**	Et	10	Toluene	91	38
4	**D**	Et	10	Toluene	70	74
5	**E**	Et	10	Toluene	62	86
6	**F**	Et	10	Toluene	80	97
7	**F**	Et	10	$PhCF_3$	80	95
8	**F**	Et	10	DCM	79	90
9	**F**	Et	10	EtOAc	75	91
10	**F**	Et	5	Toluene	84	98
11	**F**	Et	2.5	Toluene	79	97
12	**F**	Et	1.0	Toluene	77	97
13	**F**	Me	1.0	Toluene	70	95
14	**F**	*t*Bu	1.0	Toluene	50	85
15[d]	**F**	Et	1.0	Toluene	74	97
16[e]	**F**	Et	1.0	Toluene	69	97

[a] Unless otherwise specified, all reactions were performed by employing 0.2 mmol **2a** with 0.4 mmol 1, and the amount of corresponding catalyst in solvent (1.0 mL, 0.2 M) for 24 h. [b] Isolated yield of **3a**. [c] Determined by chiral HPLC analysis of **3a**. [d] Reaction at −5 °C. [e] Reaction at 0 °C.

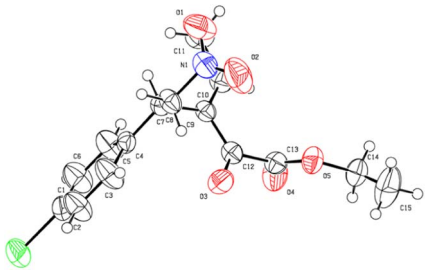
derived organocatalysts (Table 1, entries 2–3). We thus shifted our attentation to Takemoto's thioureas and Rawal's squaraines. General information shows that steric hindrance of tertiary amino moiety exerts a significant effect on the enantioselectivity. In this context, the enantioselectivity of product **3a** was greatly improved to 86%, albeit in somewhat lower yield (Table 1, entry 5 *versus* entry 4) when using catalyst **E**. In view of the structural differences between thiourea and squaramide, and particularly the pK_a and distance between the two donor N–H atoms,[19] Rawal's squaramide catalyst **F** was investigated. As was expected, the reactivity and enantioselectivity were significantly increased (97% ee, Table 1, entry 6).[20] A survey of solvent shows that toluene is the best solvent for this reaction (Table 1, entry 6 *versus* entries 7–9). It is should be noted that α-selectivity of vinylogous Michael reaction is predominant in all of the reactions, the corresponding isomer **5** could not be observed by TLC or crude ^{1}H NMR. The efficiency of this catalytic asymmetric reaction is demonstrated by reducing the catalyst loading to 1.0 mol% without any negative effect in yield and enantioselectivity (Table 1, entries 10–12). Changing the ethyl group in R^1 to methyl shows a negligible effect on the

enantioselectivity (Table 1, entry 13). However, an inferior result was obtained when further increasing the steric bulk of the ester group (Table 1, entry 14). Finally, we found the reaction temperature has a pronounced influence on the isolated yield of the product (Table 1, entries 15–16), a better yield was obtained when the reaction was conducted at −10 °C.[21]

With the optimized reaction conditions in hand (Table 1, entry 12), we examined the substrate scope of this vinylogous Michael addition/isomerization cascade reactions (Scheme 3). Firstly, we investigated β-aryl-substituted nitroalkenes **2a–l** with diverse electronic and steric properties. It was found that nitroalkenes with both electron-donating and electron-withdrawing substituents at different positions on the phenyl ring give the corresponding products **3a–j** with excellent enantioselectivities (97–99% ee). Notably, substrates **2k–l** bearing 2-thienyl and 2-furan rings were also tolerated. β-Alkyl-substituted nitroalkenes **2m–2p** are also tested. To our delight, this type of substrates was also amenable to the reaction protocol, giving rise to the desired products with 95–99% ee. However, β-disubstitutednitroolefins, such as **2q–2s**, are still inactive under the current reaction conditions. Besides, we also tried β,γ-unsaturated α-ketoester as the activated alkene partner



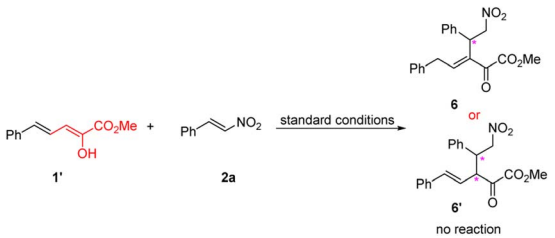
Scheme 3 Substrate scope. Reaction conditions: 0.4 mmol **2a** with 0.8 mmol **1** (2.0 equiv.), and 1.0 mol% **F** (0.004 mmol) in toluene (2.0 mL, 0.2 M) at −10 °C for 24 h. Yields are for the isolated products based on **2** after purification by silica gel flash column chromatography. The ee values were determined by chiral HPLC analysis.



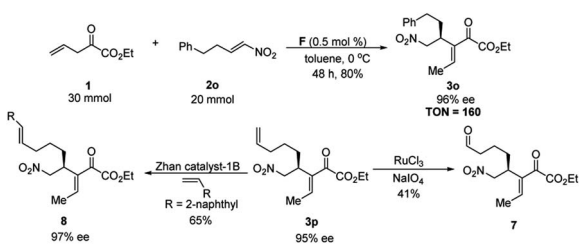
Scheme 4 X-ray structure of **3b**.

(for example **2t**), however, unfruitful results were obtained. The absolute configuration of the product **3b** were unambiguously determined to be (*E*, *S*) by X-ray crystallography (Scheme 4). It needs to be emphasized that only *E*-isomer of RC-type product **3** could be detected. The other products were presumed to have the same absolute configuration as that of **3b**, considering a uniformly stereocontrol mode was maintained during the reactions.

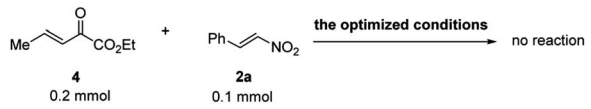
Finally, we study the reactivity of a known stable dienolate of vinylogous α-ketoester **1′**,[17c] conceiving that the scope of vinylogous α-ketoester could be further expanded if it's workable for the current reaction (eqn (3)). However, after many trials, we found this kind of substrate is totally inactive in the current reaction conditions, and the enol form **1′** keeps intact.



To prove the practicality of this methodology, gram-scale synthesis of **3o** was carried out by employing 20 mmol **2o** and 1.5 equiv of **1**. To our delight, when the temperature rised to 0 °C, the amount of catalyst loading could be reduced to 0.5 mol% without significantly affecting the catalytic efficiency as well as the ee of the product (Scheme 5, TON = 160 based on the isolated yield, the amount of substrate, and the catalyst loading).[22] The highly functionalized Rauhut–Currier type products in this study could be utilized as useful synthetic intermediates in organic synthesis. For example, the terminal C=C double in **3p**



Scheme 5 Gram-scale synthesis and synthetic applications.



Scheme 6 Control experiment.

can be selectively transformed into aldehyde **7** by using ruthenium-catalyzed oxidative cleavage of alkene or internal alkene **8** by using intermolecular olefin metathesis.

Control experiments were conducted to clarify the reactive intermediate and pathway of this reaction. We performed the reaction of **4** with **2a** under standard reaction conditions and found that there was no product detected. This fact not only indicates that β,γ-unsaturated α-ketoester **4** is not the reactive intermediate for this formal RC-reaction (Scheme 6), but also suggests deprotonation of vinylogous α-ketoester **1** is more feasible under the action of bifunctional catalyst **F**. In addition, the intermediate of α-selective vinylogous Michael addition **INT** (see Scheme 1c) could be detected at an early stage of reaction. On the basis of the above experiments, a sequential of α-vinylogous Michael addition, followed by isomerization of the terminal double bond is involved, and these two steps are all catalyzed by the same bifunctional Lewis base/hydrogen bonding organocatalyst **F**.

Conclusions

In summary, a highly efficient cascade reaction by using vinylogous α-keto esters as the nucleophiles was developed in the presence of the low loading squaramide organocatalyst. Rauhut–Currier type products were obtained with excellent enantioselectivities (94–99% ee). Control experiments prove that the reaction proceeds *via* α-selectivity of vinylogous Michael addition, followed by isomerization of the terminal double bond.

Author contributions

W. Guo: supervision, conceptualization, methodology, investigation, data curation, and writing–review & editing. Z. Weng: methodology, investigation, data curation, and writing–original draft. Y. Zhou: methodology, investigation, data curation, and writing–original draft. X. Yue, and F. Jiang: resources. Z. Weng, and Y. Zhou contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

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