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Highly Diastereo- and Enantioselective Organocatalytic Michael Addition of α-Ketoamides to Nitroalkenes

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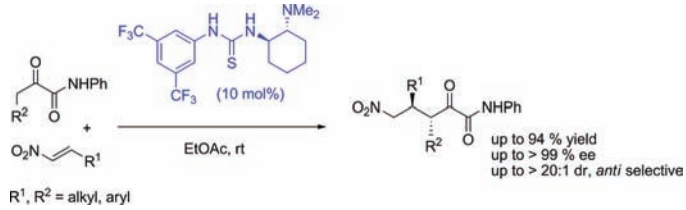
ABSTRACT



The first organocatalytic enantio- and diastereoselective conjugate addition of α-ketoamides to nitroalkenes has been achieved using a bifunctional amino thiourea catalyst. In this new approach, the substrate amide proton plays a critical role in the formation of the Michael *anti*-adducts in high yields and high stereoselectivities. To illustrate the high synthetic potential of this methodology, the diastereo- and enantioselective synthesis of a hexasubstituted cyclohexane via a Michael−Michael−Henry cascade reaction is described.

Modern organic chemistry demands sustainable and selective methods for the construction of carbon−carbon bonds.[1] For this purpose, the organocatalytic Michael addition of carbon-centered nucleophiles to nitroalkenes represents a particularly attractive approach,[2] providing rapid access to versatile building blocks with functional diversity and molecular complexity in an atom-economical manner. In the past decade, the development of small chiral organic molecules mimicking enzyme activation has emerged as an appealing strategy for catalytic asymmetric conjugate addition of malonate derivatives or simple aldehydes and ketones on various activated alkenes.[3] Nevertheless, the search for more elaborated pronucleophiles remains a research area of high interest.[4] In this context, systems of higher complexity and broad synthetic value such as 1,2-dicarbonyl compounds (α-ketoesters or α-ketoamides) were only occasionally explored as pronucleophiles in organocatalysis.[5] Their high electrophilic character[6] combined with their intrinsic potential for

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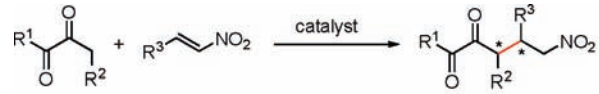
self-condensation[7] and their considered lower acidity compared to 1,3-dicarbonyl compounds,[8] significantly limit their use in intermolecular reactions.

Despite previous achievements,[9,10] asymmetric conjugate addition with 1,2-dicarbonyl compounds remained unsolved until very recent examples from the Sodeoka and Shibasaki groups. In these excellent reports, highly enantioselective 1,4-addition of α-ketoesters or α-ketoamides to nitroalkenes by mono- or dinuclear chiral nickel complexes were independently developed with complementary diastereoselectivities.[11] Our ongoing interest in ketoamide reactivity[12] and organocatalytic conjugated additions to nitroalkenes[13] prompted us to investigate the unexplored and challenging asymmetric Michael reaction of α-ketoamides with nitroalkenes (Scheme 1). Herein we present the first example of diastereo- and enantioselective organocatalytic conjugate addition of 1,2-dicarbonyl compounds as pronucleophiles.

In the past, success in the development of nucleophilic addition of carbonyl compounds has been obtained with chiral organocatalysts through different strategies. Transient enamine formation from aldehydes or ketones provides a widespread method for the catalytic generation of enolate equivalents.[3d] A basic nitrogen center in the catalyst to aid in the deprotonation of the carbonyl substrate and bind to the resulting enolate intermediate represents another important strategy.[14] Concerning the activation of the Michael acceptor, hydrogen bonding promoted by functionalized thioureas largely leads the way with nitroolefins.[15]

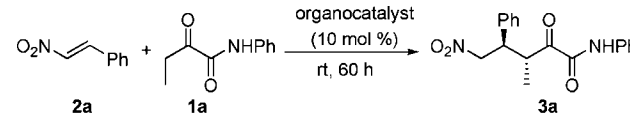
Scheme 1. Asymmetric Conjugate Addition of 1,2-Dicarbonyl Compounds to Nitroalkenes

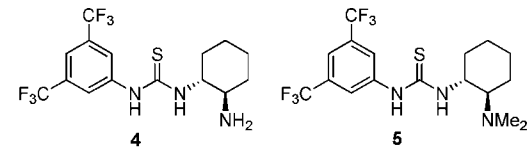


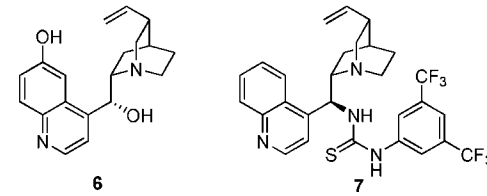
R^1	catalyst	diastereoselectivity	
O^{t}Bu	mono-Nickel complex	anti [11a]	previous work
NHPh	di-Nickel complex	syn [11c]	previous work
NHPh	amino thiourea organocatalyst	anti	this work

Based on previous achievements in organocatalysis, we began our investigation by testing the reaction between α-ketoamide **1a** and nitrostyrene **2a** in the presence of catalytic amounts of a chiral organocatalyst. It is noteworthy that neither proline nor proline derivatives showed any significant activity under standard conditions (see the Supporting Information). Alternatively, bifunctional amine-thiourea **4**−**7** was found to be more appropriate for this transformation (Table 1) indicating that a

Table 1. Optimization of the Reaction Conditions[a]







entry	catalyst	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	**4**	toluene	<10	5:1	nd
2	**5**	toluene	89	>20:1	96
3	**5**	THF	85	>20:1	98
4	**5**	DCM	85	15:1	98
5	**5**	DCE	80	>20:1	99
6	**5**	EtOAc	83	>20:1	>99
7	**5**	2-propanol	82	>20:1	90
8	**6**	EtOAc	40	>20:1	60
9	**7**	EtOAc	44	>20:1	41

[a] Ketoamide **1a** (0.1 mmol), nitrostyrene **2a** (0.11 mmol), solvent (0.2 mL). [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR of the crude reaction product. [d] Determined by chiral HPLC analysis.

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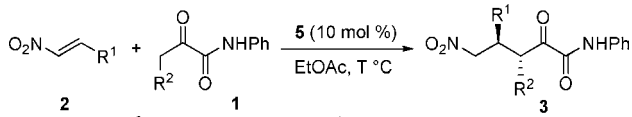
noncovalent hydrogen-bonding catalysis was probably required for this transformation.

While being efficient in the case of simple ketones via enamine formation, the primary-amine thiourea catalyst **4** failed in producing the desired Michael adduct with synthetically useful yield and selectivity after 60 h at room temperature (entry 1).[2g] To our delight, the Takemoto urea catalyst (TUC, **5**) with an appended tertiary amine[15d] efficiently activates both substrates with strictly defined conformation providing the desired product with high diastereomeric ratio and 96% enantiomeric excess in toluene (entry 2). This reaction was greatly product selective, and only a minimal amount of byproduct (5−10%) due to overreaction was isolated (*vide infra*, Scheme 2).

After the reaction solvent was screened, the enantioselectivity was further improved to >99% in ethyl acetate (entry 6). Surprisingly, the catalytic hydrogen-bonding activation appeared to be also efficient in 2-propanol protic solvent, although a lower enantioselectivity was obtained (entry 7). Quinine-derived catalyst **6**,[16] in which either the quinoline phenol or the C-9 alcohol can play the role of the thiourea moiety, was also able to promote the formation of the Michael adduct with the same high diastereoselectivity. However, a moderate yield and a low enantioselectivity resulted in this case (entry 8). Finally, since the more elaborate thiourea-cinchonidine catalyst **7** afforded no advantage (entry 9), we selected the relatively simple and commercially available thiourea **5** as the optimal catalyst.

Under the optimized reaction conditions, both the scope and the generality of this new organocatalytic Michael addition of 1,2-dicarbonyl compounds were explored (Table 2).

Table 2. Thiourea-Catalyzed Conjugate Addition of α-Ketoanilides to Nitroolefins[a]



R^2 = Me: **1a**, Et: **1b**, Ph: **1c**[b]

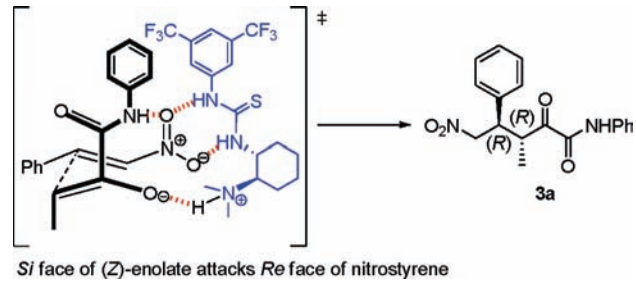
entry	R^1	2	1	product	t (h)	yield[c] (%)	dr[d] *syn*/*anti*	ee[e] (%)
1	Ph	**2a**	**1a**	**3a**	60	83	>20:1	>99
2	4-$MeOC_6H_4$	**2b**	**1a**	**3b**	60	73	>20:1	94
3	4-BrC_6H_4	**2c**	**1a**	**3c**	60	71	14:1	93
4	4-FC_6H_4	**2d**	**1a**	**3d**	48	76	10:1	95
5	2-thienyl	**2e**	**1a**	**3e**	60	67	13:1	98
6	Ph	**2a**	**1b**	**3f**	60	93	>20:1	98
7	4-$MeOC_6H_4$	**2b**	**1b**	**3g**	60	75	>20:1	95
8	2-thienyl	**2e**	**1b**	**3h**	60	73	>20:1	95
9	Ph	**2a**	**1c**	**3i**	16	94	>20:1	91
10	4-$MeOC_6H_4$	**2b**	**1c**	**3j**	16	93	>20:1	85
11	4-FC_6H_4	**2d**	**1c**	**3k**	16	82	>20:1	94
12	4-$NO_2C_6H_4$	**2f**	**1c**	**3l**	16	93	>20:1	90
13	CH_2CH_2Ph	**2g**	**1c**	**3m**	40	92	>20:1	85

[a] Standard conditions: ketoanilide **1** (0.2 mmol), nitroolefin **2** (0.21 mmol) in ethyl acetate (0.4 mL). [b] Ketoanilide **1c** (0.2 mmol), nitroolefin **2** (0.24 mmol) at −35 °C. [c] Isolated yield based on ketoanilides **1**. [d] Determined by ^{1}H NMR of the crude reaction product. [e] Determined by chiral HPLC analysis.

A wide range of aromatic and heteroaromatic nitroalkenes underwent reaction with α-ketoamides in high yield, excellent diastereoselectivities, and very good enantioselectivities (dr >20:1, up to >99% ee). The absolute configuration and the relative *anti*-selectivity were determined by X-ray crystallographic analysis of **3e** (Figure 1).[17] Our findings nicely complement the *syn*-selectivity observed when a dinuclear nickel complex is used as catalyst.[11c]

Figure 1. X-ray structure of product **3e**.

In order to achieve similar results with the highly reactive α-ketoanilide **1c** (Table 2, entries 9−13), reactions were run at lower temperature (−35 °C, see the Supporting Information). Importantly, α-ketoanilide **1c** efficiently reacted with the aliphatic nitroolefin **2g** to afford the adduct **3m** in high yield and stereoselectivity (entry 13). The generally accepted mechanism for Michael adduct formation with bifunctional catalysts such as **5** involves electrophilic activation of the nitroolefin via a bidentate H-bond interaction and concomitant protonation of the tertiary amine basic center.[15] The resulting ion pair would adopt a multiple H-bonded transition state. Therefore, a preferential approach of the *Si* face of (*Z*)-enolate on the *Re* face of the nitroalkene could account for the observed stereochemistry (Figure 2). Moreover, it is



Si face of (*Z*)-enolate attacks *Re* face of nitrostyrene

Figure 2. Proposed transition state for the Michael addition.

important to highlight the critical role of the amide N−H moiety in the described transformation. In fact, only trace

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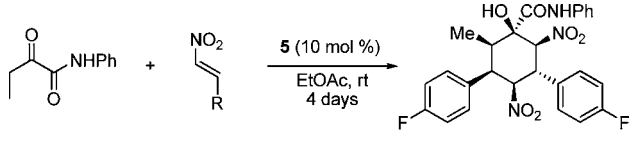
(17) CCDC 790424 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

amounts of the desired product were detected in presence of a tertiary amide substrate preventing an extra potential cooperative H-bonding interaction.[18]

During the course of the reaction scope investigation, we observed the high tendency of the fluorinated nitroalkene **2d** to overreact with the 1,4-adduct and generate the densely functionalized cyclic compound **8** in a Michael−Michael−Henry type of cascade reaction.[19,20] This potential was exploited by reacting α-ketoanilide **1a** with an excess of nitroalkene **2d** for 4 days. Impressively, the hexasubstituted cyclohexane **8** was isolated in a remarkably excellent stereoselectivity of 98% ee (Scheme 2).

Scheme 2. Enantioselective Synthesis of Hexasubstituted Cyclohexane **8** by an Asymmetric Michael−Michael−Henry-Type Cascade Reaction



1a R = 4-F-C_6H_4 **2d** (2 equiv) **8**, 61% yield, dr > 20:1, 98% ee

In conclusion, we developed the first efficient organocatalytic asymmetric conjugate addition of α-ketoamides to nitroalkenes. The commercially available tertiary amine-thiourea catalyst **5** with the cooperative effect of the amide proton provided Michael adducts with broad generality in high yield, excellent *anti*-selectivity and very good enantioselectivity. Such α-keto-δ-nitroamides have potential synthetic usage as intermediates in polysubstituted pyrrolidines preparation.[11] Moreover, the described method nicely complements the *syn*-selective organometallic activation and finds an interesting application in the diastereo- and enantioselective synthesis of a densely functionalized cyclohexane via a Michael−Michael−Henry type of cascade reaction where six stereogenic carbons are created and controlled in one single reaction. The mechanism and synthetic applications of the described organocatalytic transformations are under further investigation.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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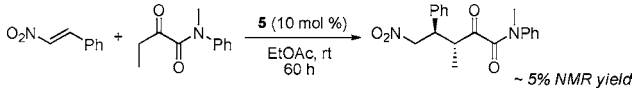
(18) Reaction in the presence of tertiary amide subtrate:



~ 5% NMR yield

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