Organocatalytic asymmetric Michael addition of α-aryl cyclopentanones to nitroolefins for construction of adjacent quaternary and tertiary stereocenters†

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The first asymmetric Michael addition of α-aryl cyclopentanones to nitroolefins for construction of adjacent quaternary and tertiary stereocenters has been achieved with excellent diastereo-/enantioselectivity.

Catalytic asymmetric construction of quaternary stereocenters, as one of the highly desirable but challenging goals for synthetic chemists, has attracted increasing attention in the past decades, and several methods have been developed to address this issue recently.[1] However, for incorporation of an additional tertiary stereocenter adjacent to the quaternary stereocenter, only limited successful protocols have been reported to achieve high levels of enantio- and diastereoselectivity.[2–4] Although asymmetric Michael addition between trisubstituted carbon nucleophiles and various electron-deficient alkenes offers straightforward access to such compounds, most of the nucleophiles employed in this transformation are limited to carbonyl substrates bearing electron-withdrawing groups such as CO_2R,[2] NO_2,[3] and CN[4] at the α-position. In sharp contrast to the substrates containing two strongly electron-withdrawing groups, α-aryl substituted carbonyl compounds have seldom been applied as nucleophiles in asymmetric Michael addition reaction.[5] To the best of our knowledge, only one racemic version involving α-aryl cyclopentanone as nucleophile and nitroolefin as electrophile has been reported using Et_3N as catalyst in 14–30 days.[6] The required longer reaction time was probably caused by the higher pK_a value of the corresponding α-protons[7] or unfavored steric hindrance. A stereoselective version of this transformation may not only diversify the existing asymmetric Michael addition but also be valuable in the synthesis of chiral building blocks with two adjacent quaternary and tertiary stereogenic centers.

Considering the significant role played by bifunctional catalysts in the tremendous asymmetric catalysis,[8,9] we envisioned that bifunctional amine-thiourea[8] could efficiently activate the α-aryl cyclopentanone and nitroolefin simultaneously through hydrogen bonding interactions and thereby realize this challenging reaction. Herein, we report the first highly stereoselective Michael addition of α-aryl cyclopentanones to nitroolefins catalyzed by bifunctional amine-thiourea bearing multiple hydrogen-bonding donors,[10,11] and subsequent transformation allowed for facile access to enantio-enriched cyclic imine, nitrone and fused pyrrolidines.

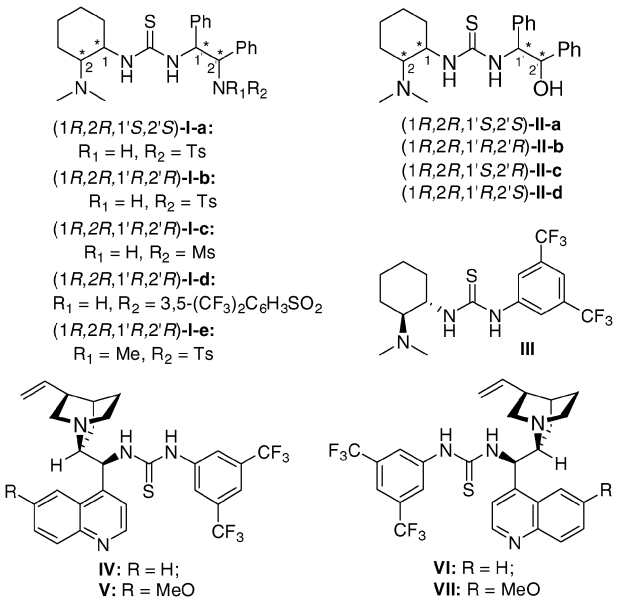

Fig. 1 Structures of the screened bifunctional amine-thiourea organocatalysts (**I–VII**).

We began our studies by evaluating the reaction of α-phenyl cyclopentanone **1a** and nitroolefin **2a** with the fine-tunable organocatalysts **I** and **II** (Fig. 1) developed by our group recently.[10] To our delight, the reaction was finished remarkably in less than 20 h at room temperature with catalyst **I-a**, yielding the desired adduct **3aa** with complete diastereoselectivity (>99 : 1), which preliminarily verifies our hypothesis on accelerating this challenging reaction through the synergistic hydrogen-bonding-activation of both Michael donor and Michael acceptor. Encouraged by the promising results, a series of fine-tunable bifunctional amine-thiourea catalysts **I** and **II** were subsequently screened, and the representative results are summarized in Table 1. In general, both the reaction rate and enantioselectivity were significantly affected by the configuration matching of the two units of the thiourea moiety and the acidity of the third hydrogen bonding donor (Table 1, entries 1–4 *vs.* 6–9). Faster reaction rate and higher enantioselectivity were obtained with organocatalysts **I**, which was ascribed to the additional stronger hydrogen bonding donor rendered by the strong electron-withdrawing sulfonamide group. Among the tested bifunctional amine-thiourea catalysts, (1*R*,2*R*,1′*R*,2′*R*)-**I-d** was revealed as the best catalyst in terms of enantioselectivity and reaction rate (Table 1, entry 4). The reaction

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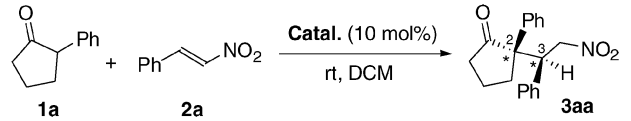
Table 1 Screening studies of asymmetric Michael addition of α-phenyl cyclopentanone **1a** and nitroolefin **2a** catalyzed by bifunctional amine-thiourea catalysts[a]

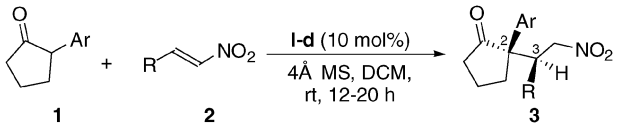


1a **2a** **3aa**

Entry	L	Solvent	t/h	Yield (%)[b]	Ee (%)[c]
1	**I-a**	DCM	17	88	80
2	**I-b**	DCM	15	84	84
3	**I-c**	DCM	15	85	76
4	**I-d**	DCM	12	88	88
5	**I-e**	DCM	72	61	80
6	**II-a**	DCM	48	68	54
7	**II-b**	DCM	48	72	77
8	**II-c**	DCM	48	74	52
9	**II-d**	DCM	48	71	77
10	**III**	DCM	20	86	74
11	**IV**	DCM	18	82	−63
12	**V**	DCM	18	80	−71
13	**VI**	DCM	20	86	65
14	**VII**	DCM	24	87	73
15[d]	**I-d**	DCM	16	87	80
16[e]	**I-d**	DCM	12	90	92
17[e,f]	**I-d**	DCM	19	85	92

[a] All reactions were carried out with 0.2 mmol of **1a**, 0.21 mmol of **2a** in 0.45 mL of DCM. [b] Isolated yield. [c] Enantioselectivity was determined by chiral HPLC analysis, and >99 : 1 diastereomeric ratio was determined by HPLC analysis. Minor diastereomer was not detected on the crude ^{1}H NMR. [d] 5 mol% H_2O was added. [e] 4A MS was added. [f] 5 mol% catalyst.

Table 2 Asymmetric Michael addition of α-substituted cyclopentanones **1** and nitroolefins **2** catalyzed by bifunctional organocatalyst **I-d**[a]



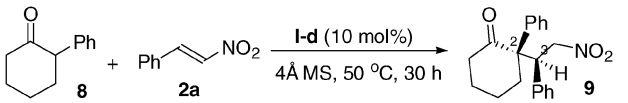
1 **2** **3**

Entry	Ar (**1**)	R (**2**)	**3**	Yield (%)[b]	Ee (%)[c]
1	Ph (**1a**)	Ph (**2a**)	**3aa**	90	92 (99)[d]
2	Ph (**1a**)	*p*-Cl-Ph (**2b**)	**3ab**	88	94
3	Ph (**1a**)	*o*-Cl-Ph (**2c**)	**3ac**	92	94
4	Ph (**1a**)	*p*-Br-Ph (**2d**)	**3ad**	94	94 (99)[d]
5	Ph (**1a**)	*p*-F-Ph (**2e**)	**3ae**	83	95
6[e]	Ph (**1a**)	*p*-Me-Ph (**2f**)	**3af**	90	95
7[e]	Ph (**1a**)	*p*-MeO-Ph (**2g**)	**3ag**	87	95
8[e]	Ph (**1a**)	*m*-MeO-Ph (**2h**)	**3ah**	93	94
9[e]	Ph (**1a**)	*o*-MeO-Ph (**2i**)	**3ai**	85	94
10[e]	Ph (**1a**)	1-Naphthyl (**2j**)	**3aj**	89	96
11	Ph (**1a**)	2-Naphthyl (**2k**)	**3ak**	95	94
12[e,f]	Ph (**1a**)	2-Furyl (**2l**)	**3al**	93	94
13[d]	Ph (**1a**)	Cinnamyl (**2m**)	**3am**	89	96
14[g]	Ph (**1a**)	Propyl (**2n**)	**3an**	50	80
15	*p*-Me-Ph (**1b**)	Ph (**2a**)	**3ba**	88	91
16	*m*-Me-Ph (**1c**)	Ph (**2a**)	**3ca**	91	90
17	*p*-MeO-Ph (**1d**)	Ph (**2a**)	**3da**	93	90
18	*m*-MeO-Ph (**1e**)	Ph (**2a**)	**3ea**	90	91
19	*p*-Cl-Ph (**1f**)	Ph (**2a**)	**3fa**	89	91
20[e]	*m*-Cl-Ph (**1g**)	Ph (**2a**)	**3ga**	95	94
21[e]	*p*-CF_3-Ph (**1h**)	Ph (**2a**)	**3ha**	90	95

[a] See Table 1. [b] See Table 1. [c] See Table 1. [d] Data in parentheses were achieved after recrystallization. [e] Run at −20 °C in 48 h. [f] Diastereomeric ratio was 98 : 2. [g] In 30 h.

became sluggish and the adduct **3aa** was formed in only 61% yield even in 72 h when using methylated **I-e** as the catalyst, which further indicates that synergistic multiple hydrogen bonding activation plays a significant role in this transformation (Table 1, entry 5). Other chiral bifunctional amine-thiourea catalysts derived from 1,2-diaminocyclohexane[12] or cinchona alkaloid[13] were also tested in this transformation, producing the desired adducts with a little lower enantioselectivities (Table 1, entries 10–14). Further improvement of the enantioselectivity could be achieved through the addition of 4A molecular sieves (Table 1, entry 16).[14] A comparable result (>99 : 1 dr, 92% ee) was still achieved even when the catalyst loading was reduced to 5 mol% (Table 1, entry 17).

Next, the scope and generality of this new asymmetric Michael addition with respect to both electrophile and nucleophile were investigated under the optimized experimental conditions. As shown in Table 2, various electron-rich, electron-neutral, or electron-deficient nitroolefins with different substitution patterns on the aromatic ring reacted smoothly with α-phenyl cyclopentanone **1a** to afford the Michael adducts (**3aa–3ai**) with excellent diastereoselectivities (>99 : 1) and high enantioselectivities (92–95%) (Table 2, entries 1–9). Heteroaromatic nitroolefin **2l** was also a viable substrate as condensed-ring nitroolefins **2j** and **2k** (Table 2, entries 10–12). Remarkably, α,β-unsaturated nitroolefin **2m** was well tolerated in this transformation, and the corresponding adduct **3am** could be obtained in 89% yield and 96% ee (Table 2, entry 13). Noticeably, the less reactive alkyl nitroolefin **2n**[15] also works in this reaction to give the desired product with excellent diastereoselectivity and good enantioselectivity (Table 2, entry 14). For nucleophile partners, a wide array of α-aryl cyclopentanones bearing electron-rich and electron-deficient groups on the phenyl ring proved to be excellent donors for this reaction, providing high diastereoselectivity and enantioselectivity (Table 2, entries 15–21).



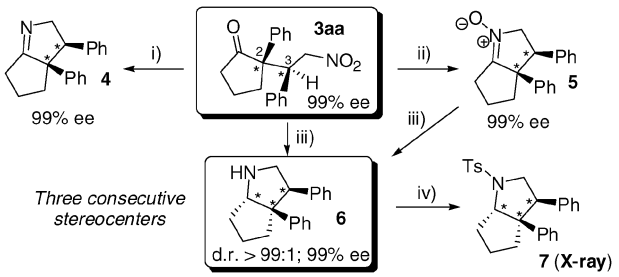
8 **2a** **9**

Our results: **20% yield, dr: > 99:1, ee: 84%**;
Ref. [6]: *no reaction* .

Prompted by the results for α-aryl cyclopentanones, we then investigated the more challenging nucleophile α-phenyl cyclohexanone **8**, for which no racemic Michael addition occurred in the literature:[6] To our delight, the reaction did take place and the desired adduct was achieved in 20% yield and 84% ee when the reaction temperature was improved to 50 °C.

Fortunately, all the products are solid, and enantioenriched compounds can be easily obtained by direct crystallization of the crude products in methanol (Table 2, entries 1 and 4). The absolute configuration of **3ad** was unequivocally determined as (2*S*,3*S*) by X-ray diffraction analysis (See ESI).‡ Those of other adducts were tentatively proposed on the basis of these results.

The optically active conjugate addition products **3aa** containing adjacent quaternary and tertiary stereogenic centers can be readily converted into synthetically useful compounds as exemplified in Scheme 1. The cyclic imine **4** was easily attained by reduction of the nitro moiety with Zn/HCl at 40 °C without loss of diastereo- and enantiomeric excess.[2h] Alternatively, direct hydrogenation of **3aa** in the presence of Pd/C afforded the nitrone **5** in 75% yield;[15,16] further increasing the hydrogen pressure, reaction temperature and extending the reaction time, **3aa** and the above nitrone **5** can be readily converted into fused pyrrolidine **6** with three consecutive



Scheme 1 Synthetic transformation of the Michael adduct **3aa**. *Conditions*: (i) Zn/HCl, 40 °C, 78% yield; (ii) Pd/C, H_2 (20 atm), 50 °C, 10 h, 60% yield; (iii) Pd/C, H_2 (40 atm), 80 °C, 30 h, 63% yield; (iv) TsCl/Et_3N, 91% yield.

stereocenters in a highly diastereo-/enantioselective manner, which comprises a core component of various biological active compounds.[17] An X-ray analysis of a crystal of **7** revealed (2*S*,3*S*,4*S*) configuration for the three consecutive stereocenters therefore also for the corresponding moiety in **6** (See ESI).‡

In conclusion, we have developed the first asymmetric Michael addition reaction of α-aryl cyclopentanones and nitroolefins catalyzed by bifunctional amine-thiourea catalyst bearing multiple hydrogen bonding donors. This catalytic system performs well over a broad scope of substrates and provides the desired adducts containing adjacent quaternary and tertiary stereogenic centers in excellent diastereoselectivity (>98 : 2) and high enantioselectivity (90–96% ee), and subsequent transformations led to expedient preparation of synthetically useful cyclic imine, nitrone and fused pyrrolidines. Further investigations of the scope and synthetic application of this methodology are ongoing, and the results will be reported in due course.

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Notes and references

‡ Crystal data for (2*S*,3*S*)-**3ad**: $C_{19}H_{18}BrNO_3$, M_r = 388.25, T = 293 K, orthorhombic, space group $P2_12_12_1$, a = 8.367(4), b = 13.132(6), c = 16.078(8) Å, V = 1766.6(15) Å^3, Z = 4, 3435 reflections measured, 2914 unique (R_{int} = 0.0201) which were used in all calculations. The final wR_2 = 0.0922 (all data). Flack χ = 0.011(10). For (2*S*,3*S*,4*S*)-**7**: $C_{26}H_{27}NO_2S$, M_r = 417.55, T = 293 K, orthorhombic, space group $P2_12_12_1$, a = 7.4773(6), b = 11.8993(9), c = 25.2455(19) Å, V = 2246.2(3) Å^3, Z = 4, 4657 reflections measured, 3641 unique (R_{int} = 0.0364) which were used in all calculations. The final wR_2 = 0.0787 (all data). Flack χ = 0.05(7). CCDC 768128 (**3ad**), CCDC 768129 (**7**).

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