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Pyrrolidine-ureas as bifunctional organocatalysts for asymmetric Michael addition of ketone to nitroalkenes: unexpected hydrogen bonding effect

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ABSTRACT

A series of pyrrolidine-urea bifunctional organocatalysts was efficiently synthesized and applied to the asymmetric Michael addition of ketone to nitroolefin. Theoretical study was performed to shed light on the origin of their different activities and revealed that the rigid structure formed between catalyst **1b** with nitroolefin via double hydrogen bonding retarded the approach of nucleophilic enamine intermediate.

1. Introduction

During the last decade, organocatalysis has been developed into one of the most active and attractive research fields in asymmetric organic synthesis.[1,2] In this context, much attention has been paid to the development of efficient organocatalysts by understanding their working mechanism. Of the developed organocatalysts, pyrrolidine scaffold,[1,2] and (thio)ureas[3] moieties have proven to be powerful and applied successfully to asymmetric reactions involving carbonyl and/or nitro groups. Recently, we designed and synthesized pyrrolidine-(thio)urea bifunctional organocatalysts **1a** and **1b** (Fig. 1),[4] which turned out to be efficient for the asymmetric Michael reaction of cyclohexanone with both aryl- and alkylnitroolefins to give the adducts in high yields with high diastereo- and enantio-selectivities.[4a] In our continued efforts toward understanding the catalytic mechanism of them,[5] a series of structural related chiral molecules **1c**–**h** (Scheme 1) were synthesized and subjected to the Michael addition[6] between ketone and nitroolefins.[7] Surprisingly, catalysts **1c**–**e** with only one hydrogen bond proved to be better than **1b**, which can donate two hydrogen bonds. Herein, we wish to report the detailed results.

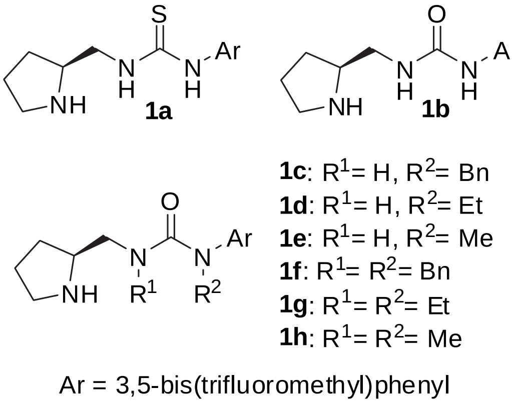

Fig. 1. Pyrrolidine-urea bifunctional organocatalysts **1a**–**h**.

2. Results and discussion

The synthesis of pyrrolidine-urea catalysts **1c**–**h** was commenced with the coupling between known *N*-Boc-protected (*S*)-2-aminomethyl-pyrrolidine **2**[8] and commercially available 3,5-bis(trifluoromethyl)phenyl isocyanate, yielding compound **3** (Scheme 1). Mono- and bis-alkylation at nitrogen atoms of urea moiety in **3** led to

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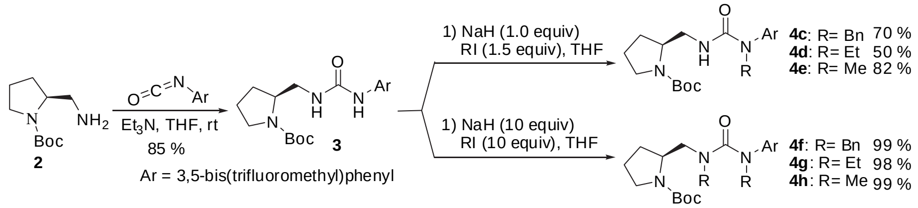
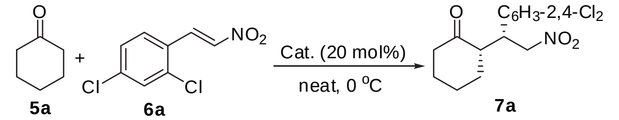


Scheme 1. Synthesis of pyrrolidine-urea catalysts.

N-Boc-protected **4c**–**h**, which were treated with TFA to provide the desired pyrrolidine-urea catalysts **1c**–**h**.[9,10] The exact position of benzyl group in **1c** was determined by X-ray analysis of its precursor *N*-Boc-protected **4c**.[9]

With the above organocatalysts in hand, we then set out to evaluate their performance in asymmetric Michael addition by using cyclohexanone **5a** and nitroolefin **6a** as model substrates under previously optimized conditions.[4a] As shown in Table 1, the addition of acid did not substantially influence the Michael addition (entries 2, 5, 7). Catalysts **1b**–**h** all gave excellent *syn*/*anti* ratio and ees, however, important difference in reaction rate was observed. When catalyst **1b** with two hydrogen bonds was used, 5 days were needed to achieve 100% conversion of **6a** and the *syn*-isomer of adduct was isolated in 76% yield (entry 1). To our surprise, improved efficiency could be obtained without deteriorating diastereo- and enantio-selectivities when catalysts **1c**–**e** (entries 2–4) were employed. Catalyst **1c** proved to be the most efficient one, 93% yield of *syn*-isomer with 94% ee could be achieved in 11 h in the presence of 20 mol % of catalyst **1c** (entry 2).

Table 1
Asymmetric Michael addition of cyclohexanone **5a** and nitroolefin **6a** catalyzed by organocatalysts **1b**–**h**[a].



5a **6a** **7a**

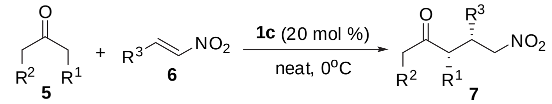
Entry	Catalyst	*t*/h	Yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	**1b**	120	76	>50/1	95
2	**1c**	11 (10)[e]	93 (91)[e]	>50/1 (>50/1)[e]	94 (96)[e]
3	**1d**	21	95	>50/1	94
4	**1e**	23	91	>50/1	94
5	**1f**	96 (96)[e]	96 (93)[e]	>50/1 (>50/1)[e]	95 (96)[e]
6	**1g**	120	80	>50/1	95
7	**1h**	72 (72)[e]	93 (92)[e]	>50/1 (>50/1)[e]	93 (94)[e]
8[f]	**1c**	72	73 (78)[g]	>50/1	96
9[h]	**1c**	9	88	>50/1	94
10[i]	**1c**	20	96	>50/1	96
11[j]	**1c**	49	91	>50/1	95
12[k]	**1c**	9 days	79 (83)[g]	>50/1	89

[a] All reactions were carried out using **5a** (20 equiv) and **6a** (0.25 mmol, 1 equiv) in the presence of 20 mol % of catalyst at 0°C.
[b] Isolated yield of *syn*-isomer.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis for *syn*-isomer.
[e] Data in brackets were results when butyric acid (10 mol %) was added.
[f] −25°C.
[g] Conversion of **6a**.
[h] 25°C.
[i] 15 mol % of **1c**.
[j] 10 mol % of **1c**.
[k] 5 mol % of **1c**.

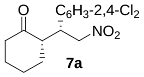
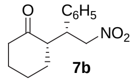
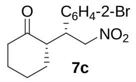
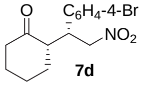
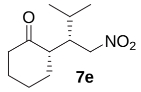
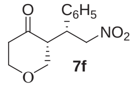
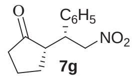
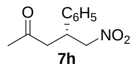
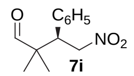
The effect of temperature was then studied. Slightly improved ee could be observed by lowering the temperature from 0 °C to −25 °C (Table 1, entry 8) but the reaction was slowed down significantly. Elevating temperature to 25 °C results in a further short time to complete the reaction and the enantioselectivity was not influenced (entry 9). When the loading of **1c** was reduced to 15 mol % or 10 mol %, the excellent *syn*/*anti* ratio and ee could be maintained although more time was needed to complete the reaction (entries 10 and 11). Further lowering the loading of **1c** to 5 mol % led to a sluggish process with only 83% conversion, even when the reaction time was prolonged to 9 days (entry 12).

Having established optimal conditions, a survey of the scope and limitations of this asymmetric Michael addition was carried out by employing both **1b** and **1c**. As summarized in Table 2, various

Table 2
Asymmetric Michael addition of cyclohexanone **5** and nitroolefin **6** catalyzed by organocatalyst **1c**[a].



5 **6** **7**

Entry	Product (**7**)	*t*	Yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	 **7a**	11 h (5 days)[e]	93 (76)[e]	>50/1 (50/1)[e]	94 (95)[e]
2	 **7b**	13 h (5 days)[e]	91 (73)[e]	>50/1 (50/1)[e]	92 (92)[e]
3	 **7c**	5 h (30 h)[e]	94 (87)[e]	>50/1 (50/1)[e]	96 (96)[e]
4	 **7d**	38 h (7 days)[e]	96 (50)[e]	>50/1 (50/1)[e]	94 (94)[e]
5	 **7e**	5 days (5 days)[e]	94 (21)[e]	>50/1 (50/1)[e]	92 (81)[e]
6	 **7f**	5 days (7 days)[e]	88 (88)[e]	>50/1 (50/1)[e]	87 (81)[e]
7	 **7g**	10 days (22 days)[e]	34 (Trace)[e]	74/26 —	83(73)[f] —
8	 **7h**	5 days (7 days)[e]	41 (23)[e]	—	54 (55)[e]
9	 **7i**	9 days (9 days)[e]	42 (Trace)[e]	—	75

[a] All reactions were carried out using **5** (20 equiv) and **6** (0.25 mmol, 1 equiv) in the presence of 20 mol % of **1c** at 0°C.
[b] Isolated yield of *syn*-isomer.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis for *syn*-isomer.
[e] Data in brackets were the results when **1b** was used.
[f] ee for *anti*-isomer.

nitroolefins reacted smoothly with cyclohexanone with excellent diastereoselectivities and high enantioselectivities in the presence of catalyst **1c** (entries 1–5). Noticeably, alkylnitroolefin (E)-3-methyl-1-nitrobut-1-ene was a suitable substrate in this reaction, furnishing the desired product with high *syn*/*anti* ratio (>50/1) and ee (92%) in 94% yield (entry 5), which gave much better results than the corresponding pyrrolidine-urea catalyst **1b** used (footnote e in Table 2).

The asymmetric addition of other ketones and aldehyde to nitrostyrene **6b** using **1c** as a catalyst was also investigated (Table 2, entries 6–9). It was found that dihydro-2*H*-pyran-4(3*H*)-one also participated in the asymmetric process smoothly, affording the corresponding adduct in 87% ee and 88% yield with *syn*/*anti* ratio as >50/1 (entry 6). The ring size of cyclic ketones strongly affected not only the reaction rate but also the stereoselectivity. For example, the reaction of cyclopentanone gave only 34% yield of *syn*-isomer with 83% ee in 10 days (entry 7). However, no adduct derived from cyclopentanone was observed when using **1b** as a catalyst instead of **1c** (entry 7). For the reaction of acetone and isobutyl aldehyde, moderate yields and ees could be obtained (entries 8–9). In most cases, improved reaction rates could be observed when **1c** was employed instead of **1b**. Thus, mono-Bn substituted pyrrolidine-urea **1c** proved to be more efficient than its precursor **1b** that was reported as a good catalyst for this protocol.[4a]

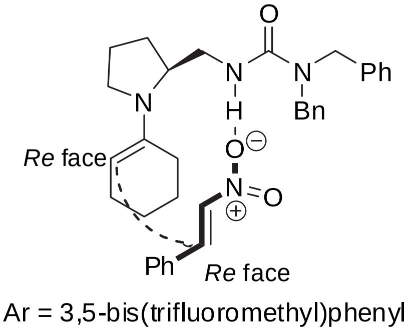


Fig. 2. Proposed transition state model involving catalyst **1c**.

On the basis of the experimental results described above and documented mechanism related with nucleophilic ketone enamines,[1,2] a stereochemical model was proposed. As shown in Fig. 2, pyrrolidine-urea catalyst **1c** worked as a bifunctional catalyst. The pyrrolidine reacted with ketone to form an enamine and the urea moiety activated nitroolefin via hydrogen bonding. Subsequent C–C bond formation occurred between the *Re*-face of enamine and the *Re*-face of *trans*-β-nitroolefin to afford the Michael adduct, which was consistent with the observed stereochemistry.

As demonstrated above, the catalytic activity of **1c** with only one hydrogen bond was much higher than that of **1b**, which has two hydrogen bonds. This is inconsistent with most documented urea catalysts utilizing hydrogen bonding for the asymmetric Michael addition of ketone and aldehyde with nitroolefins, where dual hydrogen bonding was proposed to be preferred in transition state models.[5] In order to understand the difference between organocatalysts **1b** and **1c**, density functional theory (DFT)[11] studies have been performed with the Gaussian 03 program[12] using the B3LYP[13] method and the 6-31G** basis set. Reaction of cyclohexanone **5a** with *trans*-β-nitrostyrene **6b** was studied. For each optimized structure, a harmonic vibrational frequency calculation was carried out and thermal corrections were made. All structures were shown to be either transition states (with one imaginary frequency) or

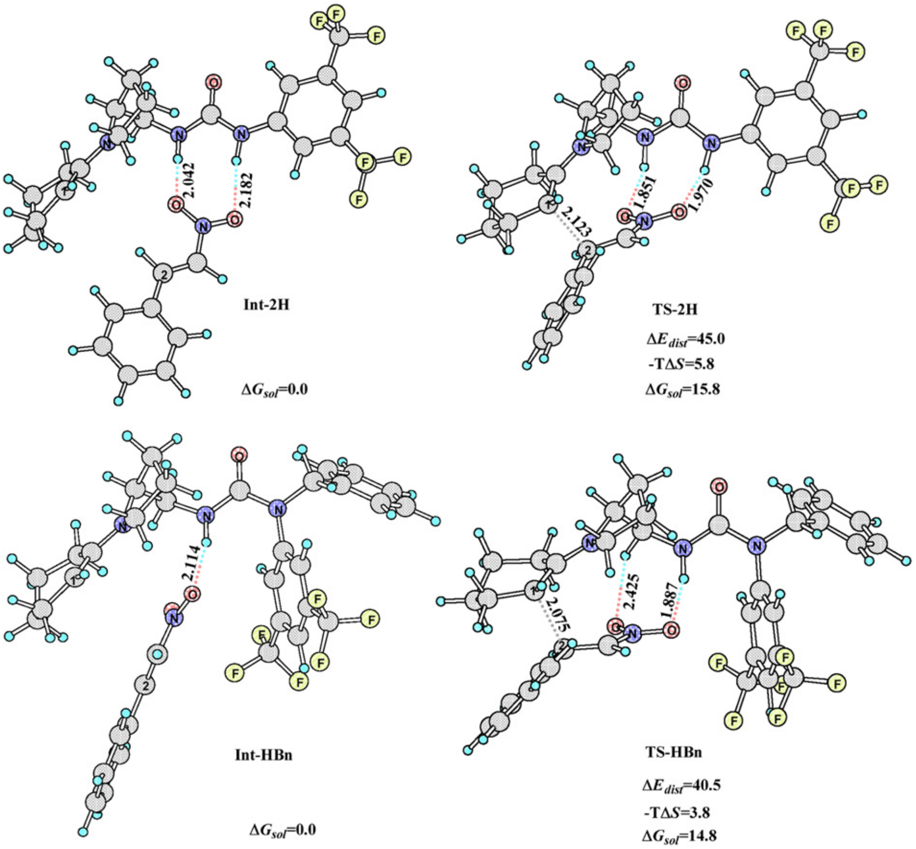


Fig. 3. The optimized intermediates and transition states for **1b** and **1c** systems. The selected bond lengths (in angstroms), and the relative free energies including solvent effect ΔG_{sol}(273.15 K), the distortion energies ΔE_{dist}, and the contribution of ΔS to ΔG ($-T\Delta S$, T=273.15 K) are in kcal/mol. Calculated at B3LYP/6-31G** level.

local minima (with no imaginary frequency). The solvent effect of the cyclohexanone itself was estimated using IEFPCM[14] method (UAHF atomic radii) in acetone (ε=20.7) with the gas-phase optimized structures. The difference of the reaction barrier between **1b** and **1c** systems is expected to be very small (about 1.3 kcal/mol). It is difficult to calculate the absolute reaction barrier accurately and to compare the barriers of two different systems. Nevertheless, the following discussion should be helpful to rationalize the experimental observations.

Models Int-2H/TS-2H, and Int-HBn/TS-HBn are used in the calculation for **1b** and **1c** systems, respectively. The optimized structures are shown in Fig. 3. The distortion energy ΔE_{dist} are defined as the energies required to distort the intermediates into the transition state geometries.[7m,15] The contribution of ΔS to ΔG ($-T\Delta S$, T=273.15 K), and the relative free energies including solvent effect (ΔG_{sol}, 273.15 K) are also given. The structures of Int-2H and TS-2H were constructed based on the former studies.[4] In Int-HBn and TS-HBn, the initial conformation of the Bn group was kept the same as that in *N*-Boc-protected catalyst **4c**, which has been characterized by X-ray crystallography.[9]

Multi hydrogen bonds will benefit the activation of the nitroolefin and will stabilize the negative charges on the oxygen atom of the nitro group in the transition state. These effects will lower the reaction barrier. However, multi hydrogen bonds can also stabilize the intermediate, which causes larger entropy loss and will require larger distortion energy (ΔE_{dist}) to distort their geometries into the transition states. These effects increase the reaction barrier. In Int-HBn, there is only one hydrogen bond between one hydrogen atom of the urea group and one oxygen atom of the nitro group. This structure is flexible and the nitroolefin is parallel to the enamine, indicating that the reaction center C2 approaches C1 easily. Whereas in Int-2H, there are two strong hydrogen bonds and in this rigid structure, the nitroolefin and the enamine are vertical to each other. Therefore, compared with the **1c** system, large distortion and strain energy arosed when the reaction center approaches each other (ΔE_{dist}, 45.0 vs 40.5 kcal/mol). Further more, in the transition state, the structure becomes more rigid and the larger entropy loss leads to energy increasing ($-T\Delta S$, 5.8 vs 3.8 kcal/mol). Thus, the activity of **1c** is relatively higher than **1b**, which could explain the experimental results very well.

3. Conclusion

In conclusion, we have synthesized several pyrrolidine-urea bifunctional organocatalysts and found catalyst **1c** with single hydrogen bond was superior to catalyst **1b**, which contains two hydrogen bonds in the asymmetric Michael addition of ketone with nitroolefin. Theoretical study was performed to shed light on the origin of their difference. The rigid structure formed between catalyst **1b** with nitroolefin via double hydrogen bonding retarded the approach of nucleophilic enamine intermediate. These results provide valuable insight into the function of hydrogen bonding and might be helpful in the development of new and more efficient organocatalysts.

4. Experimental section

4.1. General

Representative procedure for the Michael addition of cyclohexanone **5a** to nitroolefin **6a**. Catalyst **1c** (22.0 mg, 0.05 mmol) in cyclohexanone (0.5 mL, 5.0 mmol) was stirred for 15 min at 0 °C, and then nitroolefin **6a** (55.0 mg, 0.25 mmol) was added. The reaction was stirred at 0 °C until nitroolefin **6a** was consumed (monitored by TLC). The resulting mixture was concentrated under reduced pressure and the residue was then subjected to flash chromatography (petroleum/EtOAc=1/4) to give the product **7a**. Yield: 73 mg (93%), *syn*/*anti*=50/1, 94% ee, determined by HPLC analysis (Chiralcel AS, *i*-PrOH/hexane=10/90, 0.8 mL/min, 238 nm; tr (minor)=12.63 min, tr (major)=18.01 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J=2.4 Hz, 1H), 7.26–7.16 (m, 2H), 4.89–4.87 (m, 2H), 4.25–4.23 (m, 1H), 2.81–2.90 (m, 1H), 2.49–2.37 (m, 2H), 2.13–2.09 (m, 1H), 1.85–1.81 (m, 1H), 1.74–1.70 (m, 2H), 1.67–1.58 (m, 1H), 1.35–1.25 (m, 1H).

Acknowledgements

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Supplementary data

Characterization data for all new compounds, full experimental details, CIF file for **4c**, and chiral HPLC spectra of **7**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.10.038.

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