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Organocatalytic and Highly Stereoselective Direct Vinylogous Mannich Reaction

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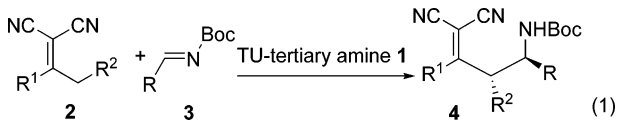
The asymmetric Mannich reaction is one of the most important protocols for the synthesis of optically pure amine compounds, and significant progress has been made catalyzed by chiral metal complexes or small organic molecules over the past years.[1] On the other hand, the vinylogous variant of the Mannich reaction (γ-aminoalkylation of α,β-unsaturated carbonyl compounds) has gained increasing attention because in principle it offers facile access to complicated and highly functionalized δ-amino compounds.[2] Nevertheless, this method is only beginning to be synthetically employed in comparison with the well developed vinylogous aldol reaction.[3] Although diastereoselective vinylogous addition of previously modified dienol ethers to chiral iminium ions is quite fruitful,[4] the exploration on catalytic asymmetric vinylogous Mannich (AVM) process is still in its infancy. Furthermore, the reported few examples in this area are confined to utilize cyclic siloxyfurans or methoxyfuran as the vinylogous equivalents.[5] Therefore, the development of new version of catalytic AVM reaction is in high demand.

Recently we have successfully developed a series of highly asymmetric direct vinylogous Michael reactions of α,α-dicyanoolefins promoted by various amine catalysts.[6] However, their applications as readily available and versatile vinylogous synthons have not been well addressed, especially in asymmetric 1,2-addition C−C bond-forming reactions. In view of the particular importance and challenges of catalytic AVM reaction, we realize the enormous potential of the reaction of α,α-dicyanoolefins and simple imine substrates. Here we would like to describe the first highly regio- and stereoselective direct vinylogous Mannich reaction with a diverse array of α,α-dicyanoolefins and *N*-Boc aldimines.

Chiral hydrogen-bonding donors such as thioureas (TU) have exhibited good activating capacity for imines in a number of enantioselective reactions.[7,8] In combination with the experiences in the facile deprotonation of α,α-dicyanoolefins,[6a,d] we envisaged that *N*-Boc aldimine and α,α-dicyanoolefin might be synergistically activated by a chiral bifunctional thiourea-tertiary amine organocatalyst,[9] hence the direct asymmetric vinylogous Mannich reaction would be facilitated (eq 1).



(1)

In light of such consideration, we first investigated the vinylogous reaction of α,α-dicyanoolefin **2a** and *N*-Boc aldimine **3a** in the presence of thiourea **1a** (Figure 1, 10 mol %) derived from cinchonine.[9a] Gratifyingly, the addition reaction proceeded readily at room temperature (20 °C), and the desired vinylogous Mannich product **4aa** was isolated in high yield after 6 h with complete regio- and diastereoselectivity, while the ee was modest (Table 1, entry 1). Encouraged by the promising results, a range of bifunctional catalysts **1b**−**d** with various chiral scaffolds were screened (entries 2−4). The structurally more rigid catalyst **1d**[9d] exhibited much better enantioselectivity (entry 4, 89% ee). Interestingly, the ee was even elevated with thiourea catalysts **1e** and **1f** bearing less electron-withdrawing groups (entries 5 and 6). Finally we delightfully found that the enantiopure product was directly attained, promoted by Berkessel's catalyst **1g**[9e,f] with a aliphatic cyclohexyl substitution, probably owing to both electronic and steric reasons (entry 7). Moreover, the catalyst loading could be decreased without affecting the enantioselectivity (entries 8 and 9), and *an excellent ee was still achieved in almost quantitative yield employing only 0.1 mol % of* ***1g*** *(entry 10).*[10] To the best of our knowledge, it represents

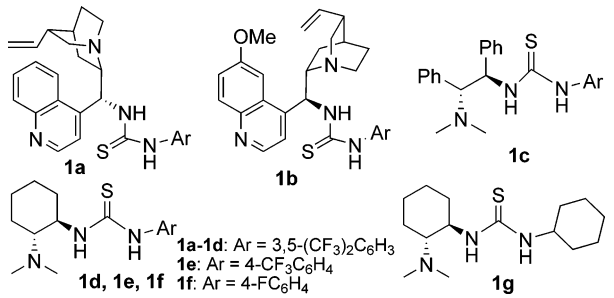
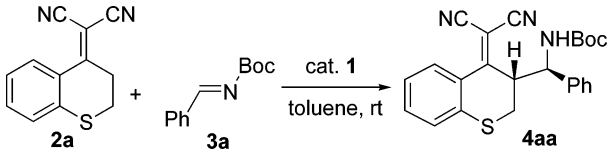


Figure 1. The structures of bifunctional organocatalysts.

Table 1. Screening Studies of Organocatalytic Vinylogous Mannich Reaction of α,α-Dicyanoolefin **2a** and *N*-Boc Benzaldimine **3a**[a]



entry	catalyst (mol %)	*t* (h)	yield[b] (%)	ee[c,d] (%)
1	**1a** (10)	6	89	55
2	**1b** (10)	6	89	61
3	**1c** (10)	6	91	80
4	**1d** (10)	6	99	89
5	**1e** (10)	6	99	93
6	**1f** (10)	6	99	96
7	**1g** (10)	6	99	99
8	**1g** (2)	8	99	99
9	**1g** (0.5)	16	99	99
10	**1g** (0.1)	24	98	98

[a] Reactions performed with 0.1 mmol of **2a**, 0.12 mmol of **3a**, in 1 mL of toluene at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined by X-ray analysis.

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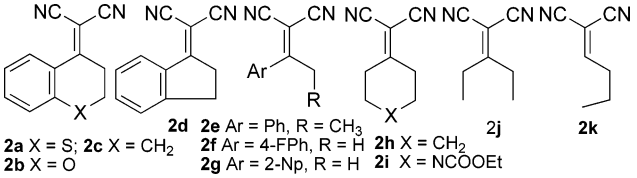


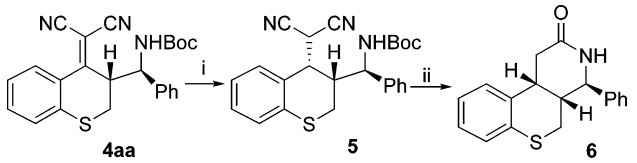
Figure 2. The structures of various α,α-dicyanoolefins.

Table 2. Asymmetric Direct Vinylogous Mannich Reaction of α,α-Dicyanoolefins **2** and *N*-Boc Aldimines **3**[a]

entry	sub. **2**	R (**3**)	product **4**	yield[b] (%)	ee[c] (%)
1	**2a**	Ph (**3a**)	**4aa**	99	99
2	**2b**	Ph (**3a**)	**4ba**	99	98
3	**2c**	Ph (**3a**)	**4ca**	99	97
4	**2d**	Ph (**3a**)	**4da**	99	99
5	**2e**	Ph (**3a**)	**4ea**	99	99
6	**2f**	Ph (**3a**)	**4fa**	99	99
7	**2g**	Ph (**3a**)	**4ga**	94	99
8	**2h**	Ph (**3a**)	**4ha**	99	99
9	**2i**	Ph (**3a**)	**4ia**	99	98
10[d]	**2j**	Ph (**3a**)	**4ja**	67(32)	98(78)
11[d,e]				74(17)	98(78)
12	**2k**	Ph (**3a**)	**4ka**	99	99
13	**2a**	*p*-F-Ph (**3b**)	**4ab**	94	>99
14	**2a**	*p*-MeO-Ph (**3c**)	**4ac**	99	99
15	**2a**	*m*-Cl-Ph (**3d**)	**4ad**	99	98
16	**2a**	*o*-Cl-Ph (**3e**)	**4ae**	99	>99.5
17	**2a**	2-thienyl (**3f**)	**4af**	99	98
18	**2a**	2-furanyl (**3g**)	**4ag**	99	96

[a] Reactions performed with 0.1 mmol of **2**, 0.12 mmol of **3**, 2 mol % of **1g** in 1 mL of toluene at room temperature overnight. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The relative and absolute configuration of products was assigned by analogy to **4aa**. [d] Data in bracket is of the separable minor diastereomer. [e] At 0 °C in xylene for 24 h.

Scheme 1. Synthesis of Chiral δ-Lactam



Conditions: (i) Hantzsch erster, 91%; (ii) concentrated HCl, then $(Boc)_2O$, K_2CO_3, 91%.

the highest substrate/catalyst (*S*/*C*) ratio for this type of bifunctional organocatalysts since the pioneering work of Takemoto.[8d,9d]

The generality of the direct AVM was investigated with a variety of α,α-dicyanoolefins (Figure 2) and *N*-Boc aldimines catalyzed by 2 mol % of **1g** at room temperature overnight (Table 2). The reaction scope proved to be quite broad with respect to both types of substrates. Complete diastereoselectivity (if involved) was detected except the case of **2j**. Excellent stereocontrol was observed in the reactions of *N*-Boc benzaldimine **3a** and α,α-dicyanoolefins derived from cyclic aryl ketones (entries 1−4), acyclic aryl ketones (entries 5−7), and cyclic aliphatic ketones (entries 8 and 9). Acyclic aliphatic **2j** gave two separable disastereomers, and a remarkable ee (98%) was obtained for the major adduct (entry 10). In addition, a better dr value could be attained at 0 °C (entry 11). Notably, a simple α,α-dicyanoolefin **2k** from linear aldehyde also showed high reactivity and enantiomerically pure product was gained in quantitative yield (entry 12). Furthermore, excellent results were achieved in the asymmetric reactions of α,α-dicyanoolefin **2a** and *N*-Boc aryl and heteroaryl aldimines with diverse substitutions (entries 13−18).[11]

As illustrated in Scheme 1, compound **5** with three contiguous chiral centers was stereoselectively produced with Hantzsch ester as the hydride reductant.[6a,b] Then simple hydrolysis in refluxing concentrated HCl gave the desired δ-amino acid, which was easily converted to the δ-lactam **6** in the presence of $(Boc)_2O$.

In conclusion, we have developed the first direct asymmetric vinylogous Mannich reaction promoted by a simple bifunctional thiourea-tertiary amine catalyst. The unprecedented reaction is highly regio- and stereoselective and practical for a broad spectrum of substrates (generally >99% de, 96 to >99.5% ee) at room temperature, and *S*/*C* up to 1000 could be applied without effects on the excellent enantiocontrol. Moreover, a δ-amino acid derivative with multiple chiral centers could be efficiently prepared from the adduct. Further studies are actively underway to expand the scope and application of this valuable reaction.

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Supporting Information Available: Experimental procedures, structural proofs including CIF files for enantiopure **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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