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Highly Enantioselective Michael Addition of α-Substituted Cyano Ketones to β,γ-Unsaturated α-Keto Esters using Bifunctional Thiourea-Tertiary Amine Catalysts: An Easy Access to Chiral Dihydropyrans

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Abstract: An asymmetric Michael addition of α-substituted cyano ketones to β,γ-unsaturated α-keto esters to form chiral dihydropyrans catalyzed by a series of α-amino acid-derived thiourea-tertiary amines is presented. A novel tyrosine-derived thiourea catalyst was identified as the optimal catalyst providing the desired product in 91–95% yields and with 90–96% *ee* at a low catalyst loading of 2.0 mol%. The utility of the reaction was exemplified by facile conversion of the dihydropyran product into pharmaceutically useful dihydropyridine.

Keywords: enantioseteroselectivity; Michael addition; organocatalysts; thioureas

The development of carbon-carbon bond formation reactions for asymmetric synthesis has been an important challenge in organic synthesis.[1,2] In this field, organocatalysis as a powerful and environmentally friendly methodology has achieved great advances in the past decade.[3] Particularly, organocatalytic Michael addition of nucleophiles with an activated methylene group to α,β-unsaturated carbonyl compounds has recently been extensively explored because of its offering an extremely effective way to synthesize a variety of useful chiral functionalized organic molecules.[4]

Heterocyclic compounds occupy a very important place in organic chemistry, agrochemistry and medicinal chemistry due to their omnipresence in nature and varied biological properties.[5] The synthesis of this kind of compounds has been one of the focuses in organic synthesis.[6] Our group has been interested in developing asymmetric reactions using β,γ-unsaturated α-keto esters as substrates for conversion to useful chiral molecules.[7] During this process, we found that the asymmetric Michael addition of 3-oxo-3-phenylpropanenitrile (**1a**) to methyl 2-oxo-4-phenylbut-(*E*)-3-enoate (**2a**) could be realized to provide a novel chial dihyropyan product **3a** firstly using the chiral thiourea catalyst **4a**, which has been successfully used in a similar reaction by us.[7d] (Figure 1). The ^{1}H and ^{13}C NMR spectra of **3a** revealed a rapid equilibrium[8] between the cyclic hemiketal **3a** and the Michael-type product **3a′** with a ratio of around 5:1 (**3a**:**3a′**) (Scheme 1). Preliminary solvent screening with this catalyst furnished Et_2O as the optimal solvent, in which the desired product was obtained in 95% yield and 60% *ee* value (Table 1, entry 7). This result promoted us to design and explore new bifunctional thiourea-tertiary amine catalysts for this reaction.

With experience in the successful development of several efficient α-amino acid-derived diamine catalysts for the Michael addition of malonates to enones,[9] we next focused on the utilization of different α-amino acids as the chiral skeletons for catalyst elaboration. Figure 1 lists the bifunctional thiourea-tertiary amine catalysts investigated in this study.

Catalysts **4b**–**4e** were prepared from phenylalanine or tryptophan according to the literature.[10,11] Catalysts **4f**–**4i** were synthesized from the commercially available *N*-Boc (*tert*-butyloxycarbonyl) protected tyrosine **5** with a modified procedure as above (Scheme 2). Specifically, **5** was first easily converted into amide **6** with dimethylamine hydrochloride in the presence of *N*-methylmorpholine (NMM) and ethyl chloroformate, which was then treated with benzyl bromide under basic conditions in acetone to give the product **7**. After deprotection of the Boc group followed by reduction with lithium aluminium hydride, **7** was converted to diamine **9**. Condensation of **9** with different isothiocyanates then gave rise to the target thiourea catalysts **4f, 4h, 4j** and **4k**. With similar pro-

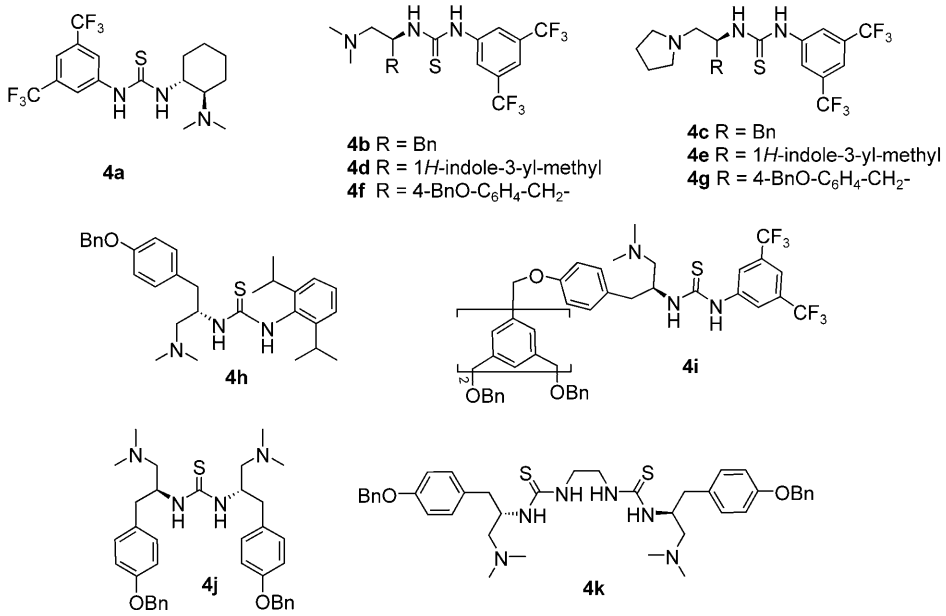
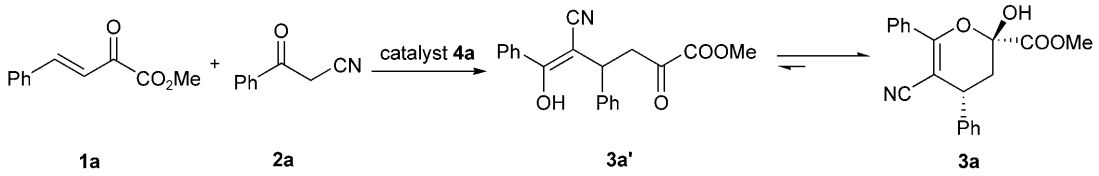
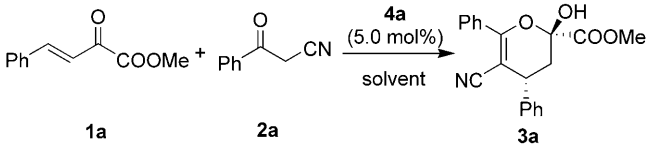


Figure 1. Organocatalysts tested in this study.



Scheme 1. Equilibrium of the product **3a and 3a′**.

Table 1. Screening of solvents using Takemoto's catalyst **4a**.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	Toluene	94	12
2	DCM	95	22
3	CH_3CN	94	31
4	DMF	78	6
5	THF	94	44
6	1,4-Dioxane	92	57
7	Et_2O	95	60

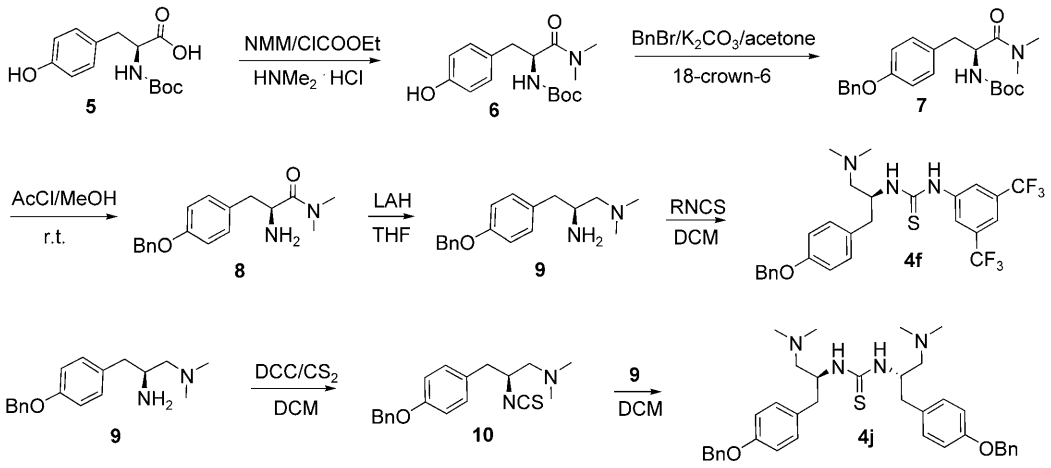
[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **1a** and 0.11 mmol of **2a** in the presence of 5.0 mol% of **4a** in 2.0 mL of solvent at room temperature for 10 h.

[b] Isolated yields.

[c] Determined by chiral HPLC analysis on a chiralcel OD-H column.

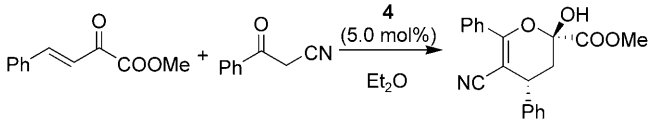
cedures, catalysts **4g** and **4i** could also be obtained in five steps from the starting material **5**.

Subsequently, catalysts **4b–4k** were evaluated with this model reaction of **1a** and **2a** using Et_2O as the solvent (Table 2). In general, better results in terms of enantioselectivity were obtained with similarly high yields from these catalysts than that from Takemoto's catalyst **4a**. The inefficiency of catalyst **4h** may imply that large steric hindrance and electron-donating substituents on the benzene ring of the thiourea moiety are not favored for this reaction. Moreover, changing the tertiary amine moiety from a dimethylamine to a cyclic amine has little influence on this reaction in that rather similar results were observed when catalysts **4b, 4d, 4f** and **4c**, **4e**, **4g** were used, respectively. Especially, both catalysts **4f** and **4g** gave the product with 90% *ee* at ambient temperature (Table 2, entries 5 and 6). However, replacement of benzyl group on the tyrosine structure by a sterically larger group (catalyst **4i**) led to a slight drop in the enantioselectivity (Table 2, entry 8). The C_2-symmetrical catalysts **4j** and **4k** were also examined, but only moderate enantioselectivities were obtained (Table 2, entries 9 and 10). Then, further optimizing efforts were done with the best catalyst **4f**. Pleasingly, reducing the catalyst



Scheme 2. Preparation of the catalysts **4f** and **4j.**

Table 2. Evaluation of catalysts with the model reaction.[a]



1a 2a 3a

Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**4b**	95	73
2	**4c**	94	73
3	**4d**	94	67
4	**4e**	95	68
5	**4f**	95	90
6	**4g**	93	90
7[d]	**4h**	90	42
8	**4i**	94	88
9	**4j**	91	74
10	**4k**	92	78
11[e]	**4f**	90	91
12[f]	**4f**	93	94
13[g]	**4f**	94	87
14[h]	**4f**	95	92
15[i]	**4f**	94	95
16[j]	**4f**	95	90
17[k]	**4f**	94	96

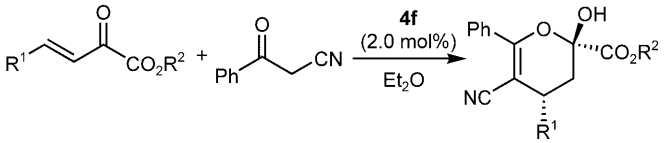
[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **1a** and 0.11 mmol of **2a** in the presence of 5.0 mol% of **4** in 2.0 mL of solvent at room temperature, 10 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiralcel OD-H column.
[d] The reaction time was extended to 48 h.
[e] 1.0 mol% of **4f** was used.
[f] 2.0 mol% of **4f** were used.
[g] 10 mol% of **4f** were used.
[h] 1.0 mL of Et_2O was used.
[i] 3.0 mL of Et_2O were used.
[j] 4.0 mL of Et_2O were used.
[k] The reaction was conducted at 0 °C for 20 h.

loading to 2.0 mol% could increase the *ee* value to 94% while the use of 1 mol% or 10 mol% were not favored, which exemplified the effect of catalyst concentration on the enantioselectivity in the system (Table 2, entries 11–13).[12] Further investigation with different volumes of the solvent also revealed the existence of an optimum concentration for this transformation (Table 2, entries 14–16). Additionally, no apparent improvement in the enantioselectivity was observed when the reaction was conducted at a lower temperature (Table 2, entry 17).

With the optimal reaction conditions achieved above, subsequently we examined the reactions of a range of β,γ-unsaturated α-keto esters **1** with **2a** to explore the generality of this reaction, and the results are summarized in Table 3. Generally, high yields and excellent enantioselectivities were achieved with β,γ-unsaturated α-keto esters bearing various γ-aryl substituents or segments of ester in 12 h. For substrates **1a–1h**, electron-donating or electron-withdrawing substituents on the *meta*, *para*, or *ortho* positions of the benzene ring of R^1 were equally well-tolerated in the reaction (Table 3, entries 1–8). Heterocyclic substrate **1i** also provided an excellent result (Table 3, entry 9). Furthermore, substrates **1j–1o** with different substituents on the ester moiety (R^2) also gave almost the same good results (Table 3, entries 10–15). Particularly, the reaction also proceeded smoothly with chain substrate and 87% *ee* value was obtained.

Next, the scope examination of the reaction was extended to different 3-oxo-3-phenylpropanenitrile derivatives with β,γ-unsaturated α-keto esters **1a** or **1d** (Table 4). When R^3 are aromatic groups (**2b–2e**), the reactions proceeded smoothly with **1a** or **1d** to furnish the desired adducts **3q–3t** with high enantioselectivities and yields (Table 4, entries 1–4). However, when R^3 is an alkyl group (**2f**, $R^3 = t$-Bu) or an alkoxy (**2g**, R^3 = EtO), the reaction failed to proceed and only

Table 3. Reaction of different β,γ-unsaturated α-keto esters **1** with **2a** catalyzed by **4f**.[a]



1 2a 3

Entry	R^1, R^2 (**1**)	Product	Yield [%][b]	*ee* [%][c]
1	Ph, Me (**1a**)	**3a**	94	95
2	4-F-C_6H_4, Me (**1b**)	**3b**	95	94
3	4-Cl-C_6H_4, Me (**1c**)	**3c**	94	94
4	4-Br-C_6H_4, Me (**1d**)	**3d**	94	92
5	2,4-Cl_2-C_6H_3, Me (**1e**)	**3e**	94	94
6	4-NO_2-C_6H_4, Me (**1f**)	**3f**	95	94
7	2,5-$(MeO)_2$-C_6H_3, Me (**1g**)	**3g**	92	90
8	2-Br-C_6H_4, Me (**1h**)	**3h**	93	90
9	2-Furyl, Me (**1i**)	**3i**	93	92
10	Ph, Bn (**1j**)	**3j**	95	92
11	Ph, 4-BrBn (**1k**)	**3k**	95	94
12	Ph, Et (**1l**)	**3l**	93	94
13	Ph, *i*-Pr (**1m**)	**3m**	94	92
14	Ph, allyl (**1n**)	**3n**	95	92
15	Ph, *t*-Bu (**1o**)	**3o**	92	90
16[d]	Phenethyl, Et (**1p**)	**3p**	70	87

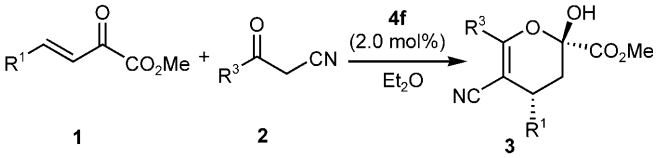
[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **1** and 0.11 mmol of **2a** in the presence of 2.0 mol% of **4f** in 3.0 mL of Et_2O at room temperature for 12 h.
[b] Isolated yields.
[c] Determined by HPLC analysis on a chiral OD-H column.
[d] The reaction time was extended to 48 h.

most of the starting material was recovered after 12 h. (Table 4, entries 5 and 6).

The highly enantiomerically enriched dihyropyrans **3** obtained by this method can be easily converted into dihydropyridines (DHPs),[13] which have been recognized as an important class of organic calcium-channel modulators for the treatment of cardiovascular diseases[14,15] and recent biological assays disclosed that this kind of compounds also have a broad range of other pharmaceutical activities[16]. As an example, **3a** was converted to dihydropyridine **11** in high yield and 92% *ee* by a simple one-step treatment (Scheme 3).[17] The absolute configuration of the product **3k** was determined to be 2*S*,4*R* by X-ray crystallographic analysis (Figure 2)[18] and the rest of the products were assigned by analogy.

In conclusion, we have firstly developed an enantioselective organocatalytic Michael addition of α-substituted cyano ketones to β,γ-unsaturated α-keto esters using novel amino acid-derived thiourea-tertiary amine catalysts. With a low catalyst loading of

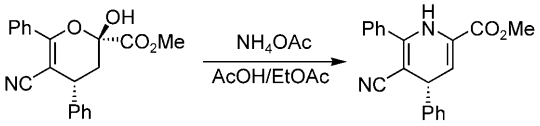
Table 4. Reaction of different α-substituted cyano ketones **2** with **1** catalyzed by **4f**.[a]



1 2 3

Entry	R^1	R^3	Product	Yield [%][b]	*ee* [%][c]
1	Ph (**1a**)	4-FC_6H_4 (**2b**)	**3q**	95	96
2	Ph (**1a**)	4-BrC_6H_4 (**2c**)	**3r**	93	90
3	Ph (**1a**)	4-$MeOC_6H_4$ (**2d**)	**3s**	91	90[d]
4	4-BrC_6H_4 (**1d**)	4-BrC_6H_4 (**2e**)	**3t**	93	94
5	Ph (**1a**)	*t*-Bu (**2f**)	–	–	–
6	Ph (**1a**)	EtO (**2g**)	–	–	–

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **1** and 0.11 mmol of **2** in the presence of 2.0 mol% of **4f** in 3.0 mL of Et_2O at room temperature for 12 h.
[b] Isolated yields.
[c] Determined by HPLC analysis on a chiral OD-H column.
[d] Determined by HPLC analysis on chiral OD-H + AD columns.



3a 92% *ee* **11** 93% yield, 92% *ee*

Scheme 3. Conversion of **3a** to **11**.

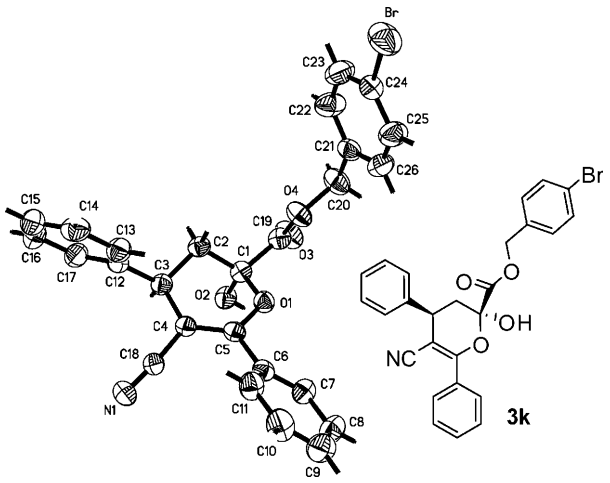


Figure 2. X-ray structure of compound **3k**.

2.0 mol%, a series of synthetically useful chiral dihydropyrans were obtained with high yields and up to 96% *ee*. Further elaboration of the products and application of the novel catalysts to other reactions are now under investigation in our group.

Experimental Section

Typical Procedure for the Michael Reaction using Catalyst 4f in Diethyl Ether at Ambient Temperature

To a solution of β,γ-unsaturated α-keto ester **1a** (0.11 mmol) and 3-oxo-3-phenylpropanenitrile **2a** (0.10 mmol) in 3.0 mL of diethyl ether (Et_2O), **4f** (0.002 mmol, 2.0 mol%) was added. The mixture was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure, the crude product was purified directly by column chromatography on silica gel (hexanes/EtOAc = 6/1) to afford the product **3a** as a colorless oil; yield: 94%; $[\alpha]_D^{22.1}$: −11.3 (*c* 1.70, EtOH); IR (KBr): $\nu = 3342$, 2210, 1750, 1617 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.74$–7.76 (m, 2H), 7.32–7.45 (m, 8H), 5.21 (brs, 1H), 3.95–4.01 (m, 1H), 3.84–3.88 (m, 3H), 2.32–2.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.2$, 162.5, 140.2, 132.6, 131.0, 129.3, 128.8, 128.6, 127.8, 118.6, 95.2, 89.8, 53.9, 36.9, 36.0; HR-MS (EI): $m/z =$ 335.1160; calcd. for $C_{20}H_{17}NO_4$: 335.1158. HPLC (separation conditions: Chiralcel OD-H column, 20 °C, 254 nm, hexane/*i*-PrOH = 80/20, flow rate 0.5 mL min^{-1}): $t_{major} = 18.4$ min, $t_{minor} = 24.8$ min.

Acknowledgements

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[18] CCDC 738625 [for **3k**, formula: $C_{26}H_{20}BrNO_4$, unit cell parameters: $a=13.6827(14)$, $b=10.3113(10)$, $c=16.6297(17)$ Å, space group $P21/n$] 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.

