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Thiourea-catalyzed asymmetric conjugate addition of α-substituted cyanoacetates to maleimides

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ABSTRACT

Chiral isosteviol-derived tertiary amine-thiourea was proven to be effective in catalyzing the asymmetric conjugate addition between α-substituted cyanoacetate and maleimides. Diverse succinimides bearing vicinal quaternary-tertiary stereocenters were obtained in excellent yields, excellent diastereoselectivities, and with good to high enantioselectivities. This catalytic system can be used efficiently in large-scale reactions with the yields and stereoselectivities being maintained at the same level.

1. Introduction

The chemistry of the construction of vicinal quaternary-tertiary stereocenters has attracted more and more attention in recent years because of their ubiquitous and important role in natural products and pharmaceuticals.[1] To date, numerous strategies have been developed to produce adjacent quaternary and tertiary stereocenters.[2] Among these procedures, the catalytic enantioselective conjugate addition of α-substituted cyanoacetates, prochiral trisubstituted carbon nucleophiles, which contain two useful functional groups of a nitrile and an ester, provides a generally applied and feasible synthetic method.[3]

Substituted succinimides are valuable synthetic targets and important structural scaffolds and precursors of biologically interesting substances.[4] The asymmetric Michael reaction of maleimides using an organocatalyst is one of the most practical synthetic procedures for effectively obtaining chiral α-substituted succinimides. Many asymmetric Michael additions of maleimides with a variety of nucleophiles promoted by organocatalysts have been reported.[5] However, reports using α-substituted cyanoacetates as nucleophiles are rare. To the best of our knowledge, almost at the same time, Yuan and Yan reported the organocatalytic conjugate addition of α-phenyl cyanoacetate onto maleimides.[6] Both used the Takemoto's tertiary amine-thiourea catalyst, but the results were different. Therefore, it is highly desirable to develop new catalytic asymmetric protocols using α-substituted cyanoacetates and maleimides.

Organocatalysis using small organic molecules has been established as a highly selective and efficient method for a wide range of reactions over the last decade and has been developed into an essential third branch of asymmetric catalysis that complements the fields of metal and enzyme catalysis.[7] Over the past few years, a series of thioureas have been designed, synthesized, and emerged as efficient catalysts for various types of asymmetric reactions.[8] Our novel designed chiral bifunctional amine-thioureas are highly efficient and enantioselective in the application of asymmetric Michael additions.[9] Based on our previous work, and the concept of bifunctional catalysis, we envisioned that the addition of α-isocyanoacetates to maleimides could be realized in the presence of our novel chiral tertiary amine thiourea catalysts. As a part of our continuing interests in asymmetric synthesis,[9,10] we herein report the asymmetric Michael addition of α-substituted cyanoacetate to maleimides catalyzed by chiral tertiary amine thioureas.

2. Results and discussion

In our previous study, the novel chiral tertiary amine-thiourea catalyst **1a/b** (Fig. 1) exhibited excellent activity in the asymmetric Michael addition between acetylacetone and nitroolefins.[9c] In order to broaden the scope of the isosteviol-derived organocatalysts and to improve the catalytic activities of the thioureas, we synthesized compounds **1c** and **1d** (Fig. 1).

The catalytic performance of the catalysts was then evaluated in the direct asymmetric Michael addition of α-phenyl cyanoacetate **2a** to *N*-phenylmaleimide **3a** and the results are summarized in Table 1. We found that each catalyst can efficiently catalyze this conjugate addition with high yields and good diastereoselectivities, but only low to moderate enantioselectivites were obtained. As expected, thioureas **1a** and **1b** exhibited a reversed sense of asymmetric induction (Table 1, entries 1 and 2). However, only 20% ee was obtained when **1b** was used as the catalyst. In addition, when the tertiary amine moiety of the thiourea was changed from

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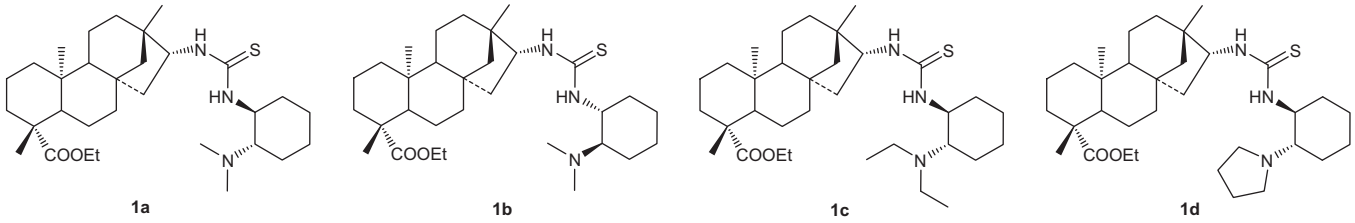
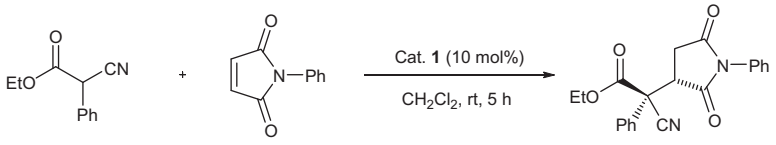


Figure 1. Novel chiral tertiary amine-thiourea catalysts.

Table 1
Comparison of the catalytic activities of thioureas for the model reaction[a]



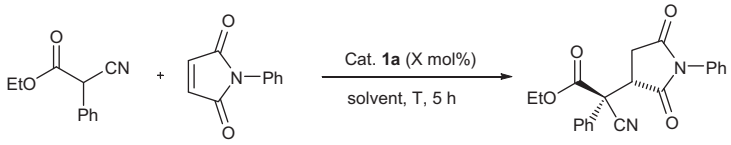
Entry	Catalyst	Yield[b] (%)	dr[c]	ee[c] (%)
1	**1a**	95	82/18	42
2	**1b**	92	80/20	−20
3	**1c**	90	81/19	35
4	**1d**	93	81/19	39

[a] Unless otherwise specified, all reactions were carried out using α-phenyl cyanoacetate **2a** (0.10 mmol), *N*-phenylmaleimide **3a** (0.12 mmol), and 10 mol % of catalyst in 1.0 mL of CH_2Cl_2 at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

a dimethyl group to a diethylamino group or a pyrrolidin-1-yl group, no improvement in the enantioselectivity was obtained. Thus, thiourea **1a** was used for further studies.

A survey of solvents revealed that toluene was the most suitable solvent (Table 2, entries 1–10). The reaction temperature was found to be an essential factor for the diastereoselectivities and

Table 2
Optimization of the reaction conditions[a]



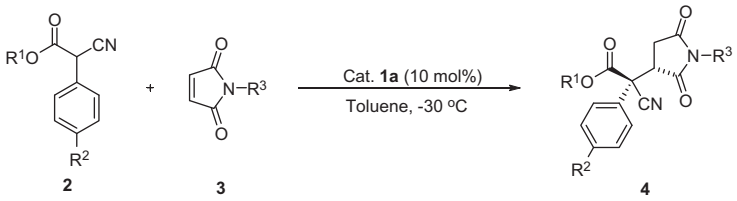
Entry	Solvent	X (mol %)	*T* (°C)	Yield[b] (%)	dr[c]	ee[c] (%)
1	CH_2Cl_2	10	rt	95	82/18	42
2	$CHCl_3$	10	rt	90	84/16	57
4	THF	10	rt	93	82/18	21
5	Ether	10	rt	89	89/11	65
6	Toluene	10	rt	94	92/8	79
7	Xylene	10	rt	90	91/9	77
8	Mesitylene	10	rt	92	90/10	79
9	H_2O	10	rt	Trace	—[d]	—[d]
10[e]	Neat	10	rt	Trace	—[d]	—[d]
11	Toluene	10	0	94	92/8	82
12	Toluene	10	−20	90	94/6	87
13	Toluene	10	−30	97	97/3	93
14	Toluene	10	−40	89	96/4	77
15	Toluene	5	−30	90	96/4	87
16[f]	Toluene	10	−30	88	97/3	92

[a] Unless otherwise specified, all reactions were carried out using α-phenyl cyanoacetate **2a** (0.10 mmol) and *N*-phenylmaleimide **3a** (0.12 mmol) in 1.0 mL of solvent.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Not determined.
[e] 0.40 mmol of ethyl phenylcyanoacetate was used.
[f] 20 mg of 4 Å molecular sieves was used.

enantioselectivities of this reaction. The stereoselectivity gradually increased when decreasing the reaction temperature from room temperature to −30 °C (Table 2, entries 6, 11–13). However, when the temperature was decreased further to −40 °C, both the yield and the stereoselectivities decreased (Table 2, entry 14). In addition, a decrease in the catalyst loading from 10% to 5% did not affect the yield or the diastereoselectivity, but the enantioselectivity was low (Table 2, entries 13 and 15). There was no improvement when 4 Å molecular sieves were used as additive (Table 2, entry 16).

With the optimal reaction conditions in hand, a representative selection of α-substituted cyanoacetates and maleimides was investigated to determine the scope of this Michael addition. As shown in Table 3, *N*-arylmaleimides **3b**–**i** bearing a range of aryl groups of varying electronic properties underwent efficient asymmetric addition with α-phenyl cyanoacetate **2a**, to give structurally diverse succinimides **4b**–**i** bearing vicinal quaternary-tertiary stereocenters in excellent yields, excellent diastereoselectivities, and with good to high enantioselectivities (entries 2–9). In the cases of *N*-arylmaleimides **3f** and **3g** bearing strong electron-withdrawing substituents, the enantioselectivities were slightly poor (entries 6 and 7). In addition, when the reaction was performed with *N*-alkylmaleimides **3k**, the yield and diastereoselectivity were acceptable, but only as low as 20% ee was obtained (entry 11). When using *N*-alkylmaleimides **3l** as the Michael acceptor, the corresponding adduct was observed in only trace amounts (entry 12). This further proved that the *N*-alkylmaleimides had a lower reactivity than the *N*-arylmaleimides in this experimental protocol. To expand upon the scope of this methodology, we subsequently investigated the conjugate addition with various α-aryl cyanoacetates **2b**–**e** to *N*-phenyl maleimide **3a** (entries 13–16). In all cases, the reactions proceeded smoothly to give the desired adducts in excellent yields and with excellent diastereoselectivities and good enantioselectivities. Variation of the ester moiety was then considered. Methyl cyanoacetate **2f** reacted well with *N*-phenylmaleimide **3a** and gave the corresponding adducts with good results (entries 17).

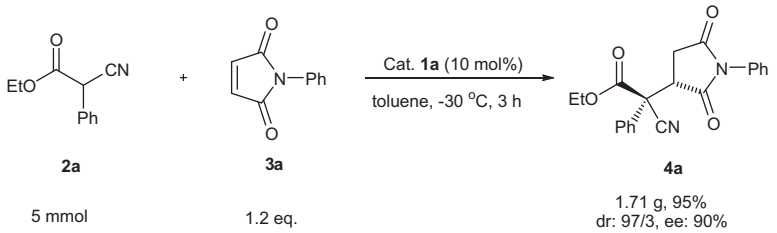
Table 3
Substrate studies of the Michael addition promoted by **1a**[a]



Entry	R^1	R^2	R^3	Time (h)	Product	Yield[b] (%)	dr [c]	ee[c] (%)
1	Et	H **2a**	C_6H_5 **3a**	2	**4a**	97	97/3	93
2	Et	H **2a**	3-Br-C_6H_4 **3b**	2	**4b**	94	96/4	93
3	Et	H **2a**	4-Br-C_6H_4 **3c**	2	**4c**	93	98/2	90
4	Et	H **2a**	3-Cl-C_6H_4 **3d**	2	**4d**	96	98/2	92
5	Et	H **2a**	4-Cl-C_6H_4 **3e**	2	**4e**	96	97/3	90
6	Et	H **2a**	4-F-C_6H_4 **3f**	2	**4f**	92	93/7	75
7	Et	H **2a**	3-NO_2-C_6H_4 **3g**	2	**4g**	95	94/6	73
8	Et	H **2a**	4-CH_3-C_6H_4 **3h**	2	**4h**	96	93/7	91
9	Et	H **2a**	4-OCH_3-C_6H_4 **3i**	10	**4i**	89	96/4	87
10	Et	H **2a**	1-Naphthyl **3j**	10	**4j**	90	95/5	86
11	Et	H **2a**	Bn **3k**	24	**4k**	71	81/19	20
12	Et	H **2a**	*t*-Bu **3l**	24	**4l**	Trace	—[d]	—[d]
13	Et	CH_3 **2b**	C_6H_5 **3a**	2	**4m**	96	95/5	85
14	Et	OCH_3 **2c**	C_6H_5 **3a**	2	**4n**	95	92/8	84
15	Et	Cl **2d**	C_6H_5 **3a**	2	**4o**	96	97/3	77
16	Et	Br **2e**	C_6H_5 **3a**	2	**4p**	93	93/7	80
17	Me	H **2f**	C_6H_5 **3a**	2	**4q**	94	91/9	84

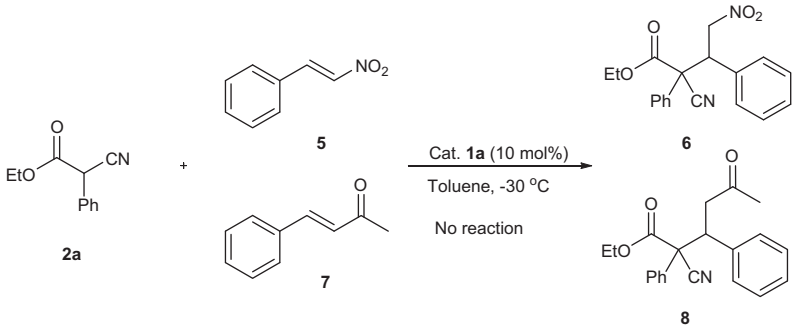
[a] Unless otherwise specified, all reactions were carried out using α-substituted cyanoacetate **2** (0.10 mmol), maleimide **3a**–**l** (0.12 mmol), and Cat. **1a** (10 mol %) in 1.0 mL of toluene at −30 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Not determined.

We further confirmed the synthetic utility of the catalytic approach by a gram-scale experiment. As can be seen from the results summarized in Scheme 1, both the yield and stereoselectivities were maintained at the same level for the large-scale reaction, which offers a great possibility for industrial application.



Scheme 1. Large-scale reaction.

Encouraged by these results, we also examined other electrophiles such as *trans*-β-nitrostyrene **5** and benzylideneacetone **7**. However, no reaction occured and so were not applicable in this asymmetric conjugate addition (Scheme 2).



Scheme 2. Conjugate addition of other electrophiles.

Although the precise reaction mechanism requires further study, a possible transition state has been proposed based on the stereoselectivities observed. In Figure 2, the thiourea moiety of

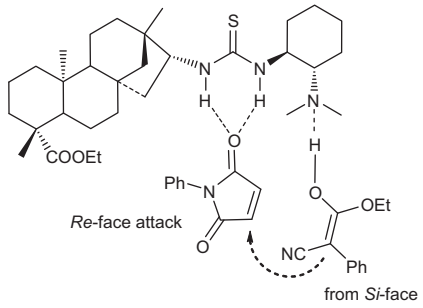


Figure 2. Proposed transition state.

catalyst **1a** interacts through double hydrogen bonding with the maleimide, while the tertiary amine interacts with the OH of the enolate through a single hydrogen bonding interaction. The attack from the *si*-face of the enolate to the *re*-face of the maleimide gives product **4a**. Nevertheless, the precise catalytic mechanism still requires further investigation.

3. Conclusion

In conclusion, we have developed an organocatalytic asymmetric conjugate addition of α-substituted cyanoacetate to maleimides. The thiourea **1a** was efficient for this transformation and furnished structurally diverse succinimides bearing vicinal quaternary-tertiary stereocenters in excellent yields, excellent diastereoselectivities, and with good to high enantioselectivities. This catalytic system can also be used efficiently in large-scale reactions with the yield and stereoselectivity being maintained at the same level, which offers a great possibility for industrial application. Further investigation of these organocatalysts in other asymmetric reactions as well as more detailed mechanistic study is currently ongoing in our laboratory.

4. Experimental

4.1. General

All reagents were obtained from commercial suppliers without further purification. Commercial grade solvent was dried and purified by standard procedures. Chemicals were used as received unless otherwise noted. Reagent grade solvents were redistilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as an internal reference. IR spectra were determined on a Thermo Nicolet IR200 unit. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof Micro™ instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined using an aXT5 Apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Enantiomeric excess was determined by chiral HPLC at room temperature using a Labtech 2006 pump equipped with a Labtech UV600 ultra detector and with Chiral columns (Chiralpak AD-H).

4.2. General procedures for the preparation of catalysts 1

Compounds **1a** and **1b** are known compounds.[9c] Compounds **1c** and **1d** were synthesized according to the similar procedure used for **1a**. [9c,11]

4.2.1. 1-(Ethyl *ent*-beyeran-19-oate-16-yl)-3-((1*S*,2*S*)-2-(diethyl amino)cyclohexyl) thiourea 1c

White solid; mp: 120–121 °C; $[\alpha]_D^{20} = -34.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.70 (s, 3H), 0.85 (dt, *J* = 13.2, 4.0 Hz, 1H), 0.95 (s, 3H), 0.96–1.10 (m, 6H), 1.15 (s, 4H), 1.24 (t, *J* = 7.2 Hz, 5H), 1.34–1.41 (m, 12H), 1.53–1.82 (m, 9H), 1.90 (m, 4H), 2.14 (d, *J* = 13.6 Hz, 1H), 2.62 (m, 4H), 3.29 (s, 2H), 3.97–4.13 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.3, 14.1, 18.8, 21.7, 24.3, 28.9, 33.0, 38.0, 39.9, 41.5, 43.6, 55.7, 59.9, 63.9, 177.5, 182.0; IR (KBr, cm^{-1}): *v* 572, 1028, 1123, 1148, 1235, 1371, 1453, 1542, 1632, 1720, 2849, 2937, 3432; calcd for $C_{33}H_{58}N_3O_2S$ $[M+H]^+$: 560.4250, found 560.4248.

4.2.2. 1-(Ethyl *ent*-beyeran-19-oate-16-yl)-3-((1*S*,2*S*)-2-(pyrrolidin-1-yl)cyclohexyl) thiourea 1d

White solid; mp: 135–136 °C; $[\alpha]_D^{20} = -24.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 0.72 (s, 3H), 0.84 (dt, *J* = 13.2, 4.0 Hz, 1H), 0.95 (s, 3H), 0.97–1.07 (m, 4H), 1.15 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 4H), 1.31–1.47 (m, 9H), 1.58 (t, *J* = 10.8 Hz, 2H), 1.65–1.72 (m, 3H), 1.74–1.84 (m, 3H), 1.92–2.07 (m, 7H), 2.14 (d, *J* = 13.2 Hz, 2H), 2.35 (d, *J* = 12.4 Hz, 1H), 2.97 (s, 1H), 3.14 (s, 1H), 3.41 (t, *J* = 9.6 Hz, 2H), 3.65 (s, 1H), 3.99–4.12 (m, 2H), 4.48–4.58 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR

(100 MHz, $CHCl_3$): δ 13.3, 14.1, 18.9, 21.7, 25.0, 28.9, 32.7, 38.0, 39.9, 41.5, 42.3, 55.0, 56.0, 57.1, 59.9, 62.3, 63.8, 77.3, 177.6, 182.7; IR (KBr, cm^{-1}): ν 753, 973, 1026, 1095, 1151, 1178, 1236, 1368, 1454, 1542, 1719, 2848, 2939, 3058, 3267; calcd for $C_{33}H_{56}N_3O_2S$ $[M+H]^+$: 558.4093, found 558.4091.

4.3. Typical procedure for the Michael addition

The α-phenyl cyanoacetate **2** (0.10 mmol) was added to a mixture of catalyst **1a** (10 mol %) and the corresponding maleimide **3** (0.12 mmol) in toluene (1.0 mL). The reaction mixture was stirred at −30 °C for the required time. After the α-phenyl cyanoacetate was consumed as determined by TLC analysis, the reaction mixture was subjected to thin layer chromatography on silica gel (ethyl acetate/petroleum ether) to afford the pure Michael product.

4.3.1. (*R*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-phenylacetate 4a[6]

$[\alpha]_D^{20} = -51.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.53 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.23–4.31 (m, 1H), 4.34–4.43 (m, 2H), 7.30–7.32 (m, 2H), 7.39–7.50 (m, 5H), 7.64–7.67 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.7, 47.0, 55.5, 64.2, 115.9, 126.5, 126.6, 129.1, 129.3, 129.7, 129.9, 131.3, 166.0, 172.9, 174.0; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 61.6 min, t_{minor} = 38.7 min.

4.3.2. (*R*)-Ethyl 2-((*S*)-1-(3-bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 4b[6]

$[\alpha]_D^{20} = -54.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.53 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.24–4.32 (m, 1H), 4.35–4.43 (m, 2H), 7.26–7.30 (m, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.46–7.51 (m, 4H), 7.54–7.56 (m, 1H), 7.63–7.65 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.7, 47.0, 55.4, 64.3, 115.9, 122.6, 125.2, 126.5, 129.6, 129.8, 130.0, 130.5, 131.1, 132.2, 132.4, 165.9, 172.4, 173.6; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 52.3 min, t_{minor} = 34.0 min.

4.3.3. (*R*)-Ethyl 2-((*S*)-1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 4c[6]

$[\alpha]_D^{20} = -51.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.53 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.25–4.31 (m, 1H), 4.34–4.42 (m, 2H), 7.19–7.23 (m, 2H), 7.45–7.51 (m, 3H), 7.58–7.65 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.7, 47.0, 55.5, 64.2, 115.9, 123.0, 126.5, 128.1, 129.8, 130.0, 130.2, 131.1, 132.5, 165.9, 172.5, 173.7; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 41.6 min, t_{minor} = 37.2 min.

4.3.4. (*R*)-Ethyl 2-((*S*)-1-(3-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 4d[6]

$[\alpha]_D^{20} = -57.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.54 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.82 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.24–4.32 (m, 1H), 4.35–4.43 (m, 2H), 7.23–7.26 (m, 1H), 7.35–7.36 (m, 1H), 7.38–7.43 (m, 2H), 7.44–7.51 (m, 3H), 7.62–7.65 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.7, 47.0, 55.4, 64.3, 115.9, 124.8, 126.5, 126.8, 129.3, 129.8, 130.0, 130.2, 131.1, 132.3, 134.9, 165.9, 172.4, 173.6; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 41.1 min, t_{minor} = 29.3 min.

4.3.5. (*R*)-Ethyl 2-((*S*)-1-(4-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 4e[6]

$[\alpha]_D^{20} = -54.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.53 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.4 Hz, 1H), 4.23–4.31 (m, 1H), 4.34–4.43 (m, 2H), 7.25–7.29 (m, 2H), 7.42–7.51 (m, 5H), 7.62–7.65 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.6, 47.0, 55.5, 64.2, 115.9, 126.5, 127.8, 129.5, 129.8, 134.9, 165.9, 172.6, 173.8; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 43.2 min, t_{minor} = 37.9 min.

4.3.6. (*R*)-Ethyl 2-cyano-2-((*S*)-1-(4-fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate 4f[6]

$[\alpha]_D^{20} = -49.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.53 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.4 Hz, 1H), 4.23–4.43 (m, 3H), 7.13–7.18 (m, 2H), 7.28–7.33 (m, 2H), 7.44–7.51 (m, 3H), 7.63–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.6, 46.9, 55.5, 64.2, 115.9, 116.3, 126.5, 128.4, 129.5, 129.8, 130.0, 131.2, 163.7, 166.0, 172.8, 174.0; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 52.4 min, t_{minor} = 45.9 min.

4.3.7. (*R*)-Ethyl 2-cyano-2-((*S*)-1-(3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate 4g[6]

$[\alpha]_D^{20} = -52.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.60 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.88 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.25–4.44 (m, 3H), 7.45–7.52 (m, 3H), 7.62–7.75 (m, 4H), 8.26–8.30 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.7, 47.0, 55.4, 64.4, 115.9, 121.8, 123.6, 126.5, 129.6, 130.0, 130.1, 132.4, 148.5, 165.8, 172.0, 173.4; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 43.7 min, t_{minor} = 52.7 min.

4.3.8. (*R*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-(p-tolyl)pyrrolidin-3-yl)-2-phenylacetate 4h[6]

$[\alpha]_D^{20} = -54.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.38 (s, 3H), 2.53 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.79 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.23–4.31 (m, 1H), 4.34–4.42 (m, 2H), 7.17–7.28 (m, 4H), 7.43–7.50 (m, 3H), 7.64–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 21.2, 31.6, 47.0, 55.5, 64.2, 115.9, 126.3, 126.5, 126.6, 128.6, 130.0, 139.2, 166.0, 173.0, 174.1; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 38.8 min, t_{minor} = 24.7 min.

4.3.9. (*R*)-Ethyl 2-cyano-2-((*S*)-1-(4-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate 4i[6]

$[\alpha]_D^{20} = -50.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.52 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.80 (dd, *J* = 9.6, 18.4 Hz, 1H), 3.82 (s, 3H), 4.25–4.41 (m, 3H), 6.96–7.00 (m, 2H), 7.20–7.24 (m, 2H), 7.43–7.50 (m, 3H), 7.64–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.6, 46.9, 55.5, 64.2, 114.6, 115.9, 123.8, 126.5, 127.8, 129.7, 129.9, 131.3, 159.8, 166.0, 173.2, 174.2; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 61.9 min, t_{minor} = 46.1 min.

4.3.10. (*R*)-Ethyl 2-cyano-2-((*S*)-1-(naphthalen-1-yl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate 4j

$[\alpha]_D^{20} = -49.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 1.33 (t, *J* = 7.2 Hz, 3H), 2.56 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.84 (dd, *J* = 9.6, 18.8 Hz, 1H), 4.25–4.39 (m, 3H), 7.13–7.20 (m, 2H), 7.24–

7.35 (m, 3H), 7.46–7.53 (m, 5H), 7.65–7.68 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.6, 46.9, 55.5, 64.2, 115.9, 126.5, 126.6, 128.4, 128.5, 129.5, 129.7, 129.8, 130.0, 131.2, 132.0, 166.0, 172.8, 174.0; HRMS (ESI) Calcd for $C_{25}H_{20}N_2NaO_4$ $[M+Na]^+$: 435.1315, found: 435.1316; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 43.6 min, t_{minor} = 38.2 min.

4.3.11. (*R*)-Ethyl 2-((*S*)-1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 4k[6]

$[\alpha]_D^{20} = -11.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.38 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.64 (dd, *J* = 9.2, 18.4 Hz, 1H), 4.22–4.44 (m, 3H), 4.67–4.78 (m, 2H), 7.29–7.48 (m, 8H), 7.60–7.62 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.7, 31.5, 42.8, 46.9, 55.0, 64.1, 115.8, 126.4, 128.6, 128.7, 129.8, 135.1, 166.0, 173.5, 174.5; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 60/40, flow rate = 0.1 mL/min, λ = 254 nm): t_{major} = 69.8 min, t_{minor} = 72.9 min.

4.3.12. (*R*)-Methyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(p-tolyl)acetate 4m[6]

$[\alpha]_D^{20} = -52.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.38 (s, 3H), 2.52 (dd, *J* = 6.4, 18.8 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.4 Hz, 1H), 4.21–4.42 (m, 3H), 7.25–7.31 (m, 4H), 7.38–7.52 (m, 5H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 21.1, 31.7, 46.9, 55.2, 64.1, 116.1, 126.4, 126.6, 128.3, 129.0, 129.3, 130.4, 140.1, 166.2, 173.1, 174.2; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 50.0 min, t_{minor} = 36.6 min.

4.3.13. (*R*)-Methyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(4-methoxyphenyl)acetate 4n[6]

$[\alpha]_D^{20} = -56.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.53 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.82 (dd, *J* = 9.6, 18.4 Hz, 1H), 3.83 (s, 3H), 4.22–4.37 (m, 3H), 6.95–6.98 (m, 2H), 7.25–7.32 (m, 2H), 7.39–7.47 (m, 3H), 7.53–7.57 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.7, 47.0, 54.9, 55.5, 64.1, 114.8, 115.0, 116.1, 123.0, 126.5, 126.6, 127.8, 128.0, 129.1, 129.2, 129.3, 131.3, 160.6, 166.3, 173.0, 174.1; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 61.4 min, t_{minor} = 48.0 min.

4.3.14. (*R*)-Methyl 2-(4-chlorophenyl)-2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)acetate 4o[6]

$[\alpha]_D^{20} = -46.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.32 (t, *J* = 7.2 Hz, 3H), 2.52 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.82 (dd, *J* = 9.2, 18.4 Hz, 1H), 4.24–4.39 (m, 3H), 7.29–7.31 (m, 2H), 7.42–7.50 (m, 5H), 7.58–7.61 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.6, 47.0, 55.0, 64.4, 115.6, 126.5, 128.0, 129.2, 129.3, 136.4, 165.8, 172.6, 173.8; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 51.0 min, t_{minor} = 34.9 min.

4.3.15. (*R*)-Methyl 2-(4-bromophenyl)-2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)acetate 4p[6]

$[\alpha]_D^{20} = -49.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.50 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.80 (dd, *J* = 9.2, 18.4 Hz, 1H), 4.22–4.40 (m, 3H), 7.28–7.30 (m, 2H), 7.38–7.53 (m, 5H), 7.56–7.60 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 13.8, 31.6, 46.8, 55.1, 64.4, 115.6, 124.5, 126.5, 128.2, 129.1, 129.3, 130.4, 131.2, 132.9, 165.7, 172.7, 173.9; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 56.4 min, t_{minor} = 37.4 min.

4.3.16. (*R*)-Methyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-phenylacetate 4q[6]

$[\alpha]_D^{20} = -38.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.54 (dd, *J* = 6.4, 18.4 Hz, 1H), 2.82 (dd, *J* = 9.6, 18.8 Hz, 1H), 3.88 (s, 3H), 4.41 (dd, *J* = 6.4, 9.2 Hz, 1H), 7.03–7.32 (m, 2H), 7.40–7.51 (m, 6H), 7.64–7.67 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 31.6, 47.1, 54.6, 55.3, 115.9, 126.5, 129.1, 129.3, 129.8, 130.0, 131.1, 131.2, 166.6, 172.8, 174.0; HPLC analysis for major diastereomer (Chiralpak AD-H column, *i*-propanol/hexane = 70/30, flow rate = 0.5 mL/min, λ = 254 nm): t_{major} = 95.3 min, t_{minor} = 47.0 min.

4.4. General procedure for large-scale Michael addition

The α-phenyl cyanoacetate **2a** (5.0 mmol) was added to a mixture of catalyst **1a** (10 mol%) and the corresponding *N*-phenylmaleimide **3a** (6.0 mmol) in toluene (50 mL). The reaction mixture was stirred at −30 °C for 3 h. After the maleimide was consumed as determined by TLC analysis, the solvent was removed under reduced pressure and the crude product was purified using column chromatography eluting with ethyl acetate/petroleum ether. The product was obtained as a white solid in 95% yield.

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