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Organocatalytic asymmetric conjugate addition of α-substituted cyanoacetates to maleimides

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ABSTRACT

The asymmetric conjugate addition of α-substituted cyanoacetates to N-substituted maleimides has been developed. A number of cinchona alkaloids and amine thioureas were evaluated as catalysts. Takemoto's catalyst was found to be the most efficient for the transformation. Chiral succinimides with two adjacent quaternary and tertiary stereogenic carbon centers were obtained in good yields, enantioselectivities, and diastereoselectivities. The products were converted to chiral γ-lactams conveniently without a loss in the enantioselectivity.

1. Introduction

The enantioselective conjugate addition reaction with carbon nucleophiles is one of the most efficient for the asymmetric formation of C–C bonds.[1] In recent years, organocatalytic asymmetric conjugate addition has seen great progress.[2,3] α,β-Unsaturated aldehydes, ketones, imides and nitroolefins are mostly used as Michael acceptors. Maleimides are also attractive Michael acceptors, because the resulted enantioenriched succinimides are valuable pharmacophores and synthetic intermediates.[4,5] Organocatalytic conjugate additions of 1,3-dicarbonyl compounds,[6] aldehydes,[7] ketones,[8] 2-mercaptobenzaldehydes,[9] dicyanoolefins,[10] azlactones,[11] 3-substituted benzofuran-2(3*H*)-ones[12], and oxindoles[13] to maleimides have been reported to provide chiral succinimides in good enantioselectivities. On the other hand, the asymmetric construction of quaternary stereocenters has been a challenging area in organic synthesis.[14] α-Substituted cyanoacetates are useful nucleophiles for the construction of stereogenic quaternary carbon centers via the reaction with electrophilic reagents.[15] We speculate that the conjugate addition of α-substituted cyanoacetate to maleimide is an efficient method to prepare chiral succinimides with two adjacent quaternary and tertiary stereogenic carbon centers.[16] Herein we report the enantioselective conjugate addition of α-substituted cyanoacetates to maleimides catalyzed by organocatalysts. The reaction provided functionalized succinimides with high levels of enantioselectivities and diastereoselectivities. Furthermore the products could be converted to chiral γ-lactams without any loss in the enantiomeric purity.

2. Results and discussion

The reaction of α-phenyl cyanoacetate **1a** and *N*-phenyl maleimide **2a** was initially studied. A series of organocatalysts including cinchona alkaloids **4a**–**4d** and amine thioureas **4e**–**4h** were evaluated. The results are summarized in Table 1. The desired product **3a** was obtained in excellent yields with cinchona alkaloids **4a**–**4c**, but the diastereoselectivities and the enantioselectivities were unsatisfactory (Table 1, entries 1–3). 9-Benzyl-6-demethyl-quinine **4d** gave an extremely low yield and almost racemic product (Table 1, entry 4). We then turned our attention to bifunctional amine thioureas **4e**–**4h**. Improved enantioselectivity (77% ee) and moderate diastereoselectivity (83:17) were obtained with Takemoto's catalyst **4e** (Table 1, entry 5).[17] Modified Takemoto's catalyst **4f** provided lower enantioselectivity (Table 1, entry 6). Quinine and cinchonine-derived thioureas **4g**–**4h** also provided inferior enantioselectivities and diastereoselectivities (Table 1, entries 7 and 8).

To determine the optimal reaction conditions with catalyst **4e**, we studied the effects of the reaction solvent, the temperature and the catalyst loading. The results are listed in Table 2. Xylene was found to be the best solvent in terms of enantioselectivity (Table 2, entries 1–7). Decreasing the reaction temperature resulted in a loss of enantioselectivity, although better diastereoselectivities were achieved (Table 2, entries 8 and 9). Both the diastereoselectivity and the enantioselectivity were improved slightly while decreasing the catalyst loading from 10 to 1 mol % (Table 2, entries 6 and 10–12). Good enantioselectivity and yield were kept with 0.5 mol % catalyst loading, but the diastereoselectivity decreased (Table 2, entry 13). Further study indicated that lowering the concentration of the substrates **1a** and **2a** did not provide favorable results (Table 2, entries 14 and 15).

The reaction of a series of α-substituted cyanoacetates **1** and N-substituted maleimides **2** was investigated. The results are summarized in Table 3. The reaction worked very well with *N*-aryl

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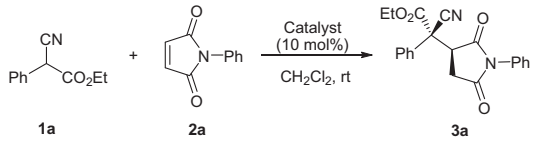
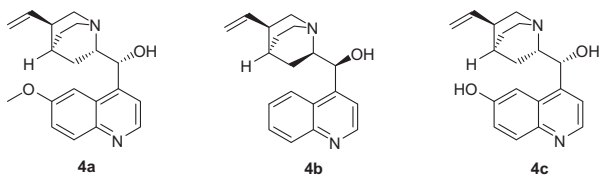
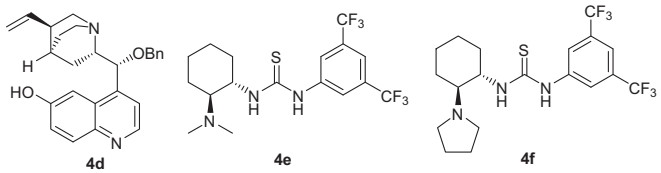
Table 1
Screening of organocatalysts[a]



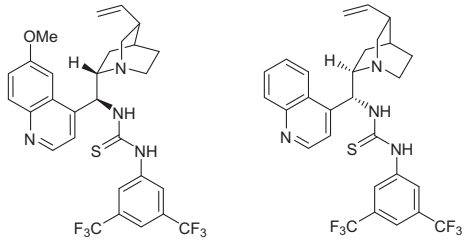
1a 2a 3a



4a 4b 4c



4d 4e 4f



4g 4h

Entry	Catalyst	Time (h)	Conv. [b] (%)	dr[b]	ee[c] (%)
1	**4a**	3	>95	83:17	26
2	**4b**	3	>95	94:16	-27
3	**4c**	3	>95	82:18	30
4	**4d**	12	28	79:21	≈0
5	**4e**	3	>95	83:17	77
6	**4f**	3	>95	81:19	45
7	**4g**	3	>95	72:28	68
8	**4h**	3	>95	77:23	−37

[a] Reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol) and catalyst (0.01 mmol) in CH_2Cl_2 (0.5 mL) at room temperature.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] Ee values of the major diastereomer, determined by HPLC with a chiralpak AD-H column.

Table 2
Optimization of the reaction conditions with catalyst **4e**[a]

Entry	**4e** (mol %)	Solvent	Time (h)	Conv.[b] (%)	dr[b]	ee[c] (%)
1	10	CH_2Cl_2	3	>95	83:17	77
2	10	$CHCl_3$	3	>95	83:17	75
3	10	Ether	3	>95	91:9	75
4	10	THF	3	>95	86:14	34
5	10	Toluene	3	>95	89:11	83
6	10	Xylene	3	>95	90:10	85
7	10	Fluoro-benzene	3	>95	87:13	81
8[d]	10	Xylene	5	>95	90:10	83
9[e]	10	Xylene	8	>95	93:7	81
10	5	Xylene	3	>95 (99%)[f]	90:10	85
11	2	Xylene	4	>95 (99%)[f]	90:10	85
12	1	Xylene	7	>95 (99%)[f]	93:7	87
13	0.5	Xylene	12	>95 (98%)[f]	89:11	86
14[g]	1	Xylene	12	>95 (99%)[f]	91:9	86
15[h]	1	Xylene	36	90 (86%)[f]	90:10	85

[a] Reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol) and the indicated amount of **4e** in the solvent (0.5 mL) at room temperature.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC with a chiralpak AD-H column.
[d] The reaction was conducted at 0 °C.
[e] The reaction was conducted at −40 °C.
[f] The values in parentheses are isolated yields.
[g] 1 mL of xylene was used.
[h] 2 mL of xylene was used.

maleimides **2a**–**2j**. In most cases, the products were obtained in good yields and enantioselectivities. The substitution of electron-withdrawing groups or electron-donating groups at *N*-phenyl did not have a significant effect on the yield or enantioselectivity (Table 3, entries 1–10). Maleimide **2k**, *N*-ethyl maleimide **2l** and *N*-benzyl maleimide **2m** showed significantly lower reactivity than *N*-aryl maleimides. High catalyst loading and extended reaction time were required. Products **3k**–**3m** were obtained in good yields, although with inferior diastereoselectivities and enantioselectivities (Table 3, entries 11–13). This indicates that the electron-donating property of *N*-alkyl groups decreases the electrophilic reactivity of maleimides.[12] With regards to the α-substituted cyanoacetates, α-(4-methyl-phenyl)-cyanoacetate **1b** provided better enantioselectivity than α-(4-MeO-phenyl)-cyanoacetate **1c** and α-(4-bromo-phenyl)-cyanoacetates **1d** (Table 3, entries 14–16). Low yield, enantioselectivity, and diastereoselectivity were obtained for α-ethyl-cyanoacetate **1e** (Table 3, entry 17).

A single crystal of the product **3e** was obtained. Its absolute configuration was determined as (2*R*,3*S*) by X-ray diffraction analysis (Fig. 1).[18] The absolute configurations of the other products were assigned analogously.

A reaction transition state has been proposed to account for the observed enantioselectivity and diastereoselectivity (Scheme 1). Double hydrogen-bonding is generated between the thiourea group of **4e** with the maleimide.[19] This interaction helps to activate the maleimide toward the nucleophilic attack. The tertiary amine group of **4e** removes a proton from α-phenyl-cyanoacetate. The resulting enolate ion forms a hydrogen bond with the ammonium cation. The nucleophilic attack of an enolate ion from the *re*-face of the maleimide gives product **3a**.

Chiral γ-lactams serve as important structural motifs in many biologically active products.[20] The cyano group of product **3a** could be reduced with $NaBH_4/CoCl_2$.[21] The resulting amine underwent a cascade lactamization in situ to give γ-lactam **5** without a decrease in the enantiomeric purity (Scheme 2).

3. Conclusion

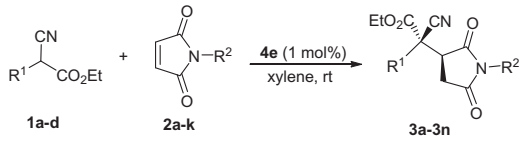
In conclusion, we have developed an organocatalytic asymmetric conjugate addition of α-substituted cyanoacetates to N-substituted maleimides. Takemoto's catalyst was identified as the best. Chiral succinimides with two adjacent quaternary and tertiary stereogenic carbon centers were obtained with good enantioselectivities and diastereoselectivities. The products could be conveniently converted to chiral γ-lactams.

4. Experimental

4.1. General Information

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane ($\delta = 0$). Chemical shifts of carbon are referenced to the central peak of the solvent ($CDCl_3$, $\delta = 77.0$). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were measured on a Perkin–Elmer 341 digital polarimeter. Melting points were

Table 3
Asymmetric conjugate addition of cyanoacetates **1a–e** to maleimides **2a–k**[a]



Entry	R^1	R^2	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph **1a**	Ph **2a**	7	**3a**, 99	93:7	87
2	Ph **1a**	4-MeO-C_6H_4 **2b**	9	**3b**, 93	90:10	84
3	Ph **1a**	4-Me-C_6H_4 **2c**	7	**3c**, 97	93:7	89
4	Ph **1a**	4-Cl-C_6H_4 **2d**	6	**3d**, 97	92:8	91
5	Ph **1a**	4-Br-C_6H_4 **2e**	6	**3e**, 99	91:9	94
6	Ph **1a**	4-F-C_6H_4 **2f**	5	**3f**, 96	90:10	84
7	Ph **1a**	4-NO_2-C_6H_4 **2g**	5	**3g**, 96	84:16	81
8	Ph **1a**	3-Me-C_6H_4 **2h**	8	**3h**, 86	91:9	87
9	Ph **1a**	3-Cl-C_6H_4 **2i**	5	**3i**, 95	96:4	91
10	Ph **1a**	3-Br-C_6H_4 **2j**	7	**3j**, 97	93:7	90
11[e]	Ph **1a**	H **2k**	20	**3k**, 95	75:25	41
12[e]	Ph **1a**	C_2H_5 **2l**	25	**3l**, 87	80:20	33
13[e]	Ph **1a**	$PhCH_2$ **2m**	34	**3m**, 98	79:21	63
14	4-Me-C_6H_4 **1b**	Ph **2a**	9	**3n**, 93	93:7	91
15	4-MeO-C_6H_4 **1c**	Ph **2a**	12	**3o**, 94	88:12	88
16	4-Br-C_6H_4 **1d**	Ph **2a**	6	**3p**, 99	87:13	85
17[e]	C_2H_5 **1e**	Ph **2a**	58	**3q**, 80	56:44	71

[a] Reactions were carried out with **1a–e** (0.12 mmol), **2a–m** (0.1 mmol) and **4e** (0.001 mmol) in xylene (0.5 mL) at room temperature.
[b] Isolated yields.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by HPLC with a chiralpak AD-H or chiralcel OD-H column.
[e] 10 mol % catalyst **4e** was used.

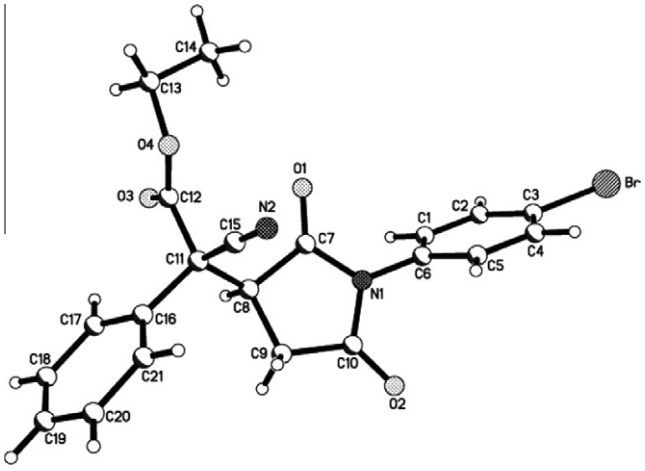
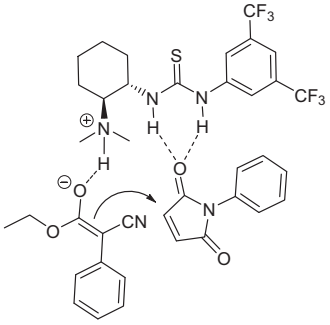
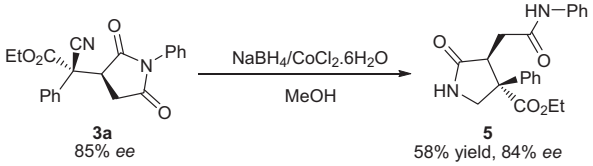


Figure 1. X-ray crystal structure of **3e**.



Scheme 1. Proposed reaction transition state.



Scheme 2. Transformation of product **3a** to γ-lactam **5**.

measured on a WRS-2A melting point apparatus and are uncorrected. The high resolution mass spectroscopic data were obtained with a Shimadzu LC–MS-IT-TOF spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak AD-H or Chiralcel OD-H column and eluting with a hexane/*i*-PrOH solution. Purified products **3a–3q** and **5** were used for the analysis. Flash chromatography was performed over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Xylene was purchased from Tianjin Fuyu Chemical Co., Ltd as a mixture of three isomers. Commercially available reagents and analytical grade solvents were used without further purification. Maleimides were prepared according to reported procedures.[22]

4.2. Typical procedure for asymmetric conjugate addition of cyanoacetates to maleimides

A solution of α-phenyl cyanoacetates **1a** (22.7 mg, 0.12 mmol), maleimide **1b** (17.3 mg, 0.10 mmol), catalyst **4e** (0.42 mg, 0.001 mmol) in xylene (0.5 mL) was stirred at room temperature for 7 h. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc = 3:1) to afford **3a** as a white solid.

4.3. Spectroscopic data of the products

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

White solid, mp 134–135 °C; $[\alpha]_D^{20} = -28.6$ (*c* 0.21, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.64 (m, 2H), 7.50–7.39 (m, 6H), 7.32–7.30 (m, 2H), 4.43–4.35 (m, 2H), 4.29–4.23 (m, 1H), 2.81 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.54 (dd, *J* = 18.4, 6.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 172.8, 166.0, 131.2, 129.9, 129.7, 129.3, 129.2, 129.0, 126.5, 126.5, 115.8, 64.1, 55.4, 46.9, 31.6, 13.7; IR (KBr): 2249 (w), 1792 (w), 1750 (s), 1709 (s), 1597 (w), 1500 (m), 1452 (m); HRMS (ESI) calcd for $C_{21}H_{17}N_2O_4$ $(M-H)^-$: 361.1188, found: 361.1203. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 17.12 min, t_{major} = 24.04 min, 87% ee; minor diastereomer: t_{major} = 9.82 min, t_{minor} = 12.75 min, 13% ee.

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

White solid, mp 136–138 °C; $[\alpha]_D^{20} = -29.1$ (*c* 0.20, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.64 (m, 2H), 7.51–7.46 (m, 3H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.42 -4.23 (m, 3H), 3.82 (s, 3H), 2.79 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.51 (dd, *J* = 18.4, 6.4 Hz, 1H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 173.1, 166.0, 159.8, 131.2, 129.9, 129.7, 127.7, 126.5, 123.8, 115.9, 114.6, 64.1, 55.5, 46.9, 31.5, 13.7; IR (KBr): 2250 (w), 1787 (w), 1749 (s), 1706 (s), 1611 (w), 1514 (m), 1447 (m); HRMS (ESI) calcd for $C_{22}H_{19}N_2O_5$ $(M-H)^-$: 391.1294, found: 391.1298. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 18.52 min, t_{major} = 21.68 min, 84% ee; minor diastereomer: t_{major} = 11.16 min, t_{minor} = 14.98 min, 13% ee.

4.3.3. (*R*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-(*p*-tolyl)pyrrolidin-3-yl)-2-phenylacetate 3c

White solid, mp 184–186 °C; $[\alpha]_D^{20} = -31.0$ (*c* 0.20, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.64 (m, 2H), 7.50–7.46 (m, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.41–4.35 (m, 2H), 4.28–4.24 (m, 1H), 2.79 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.52 (dd, *J* = 18.4, 6.4 Hz, 1H), 2.38 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 173.0, 166.0, 139.2, 131.3, 129.9, 129.9, 129.7, 128.6, 126.5, 126.3, 115.8, 64.1, 55.4, 46.9, 31.6, 21.2, 13.7; IR (KBr): 2252 (w), 1788 (w), 1751 (s), 1706 (s), 1592 (w), 1514 (m), 1452 (m); HRMS (ESI) calcd for $C_{22}H_{19}N_2O_4$ $(M-H)^-$: 375.1345, found: 375.1353. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 14.63 min, t_{major} = 19.98 min, 89% ee; minor diastereomer: t_{major} = 9.30 min, t_{minor} = 11.00 min, 23% ee.

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

White solid, mp 157–158 °C; $[\alpha]_D^{20} = -38.0$ (*c* 0.25, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.50–7.43 (m, 5H), 7.27 (d, *J* = 8.8 Hz, 2H), 4.43–4.23 (m, 3H), 2.81 (dd, *J* = 18.8, 9.6 Hz, 1H), 2.53 (dd, *J* = 18.8, 6.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 172.5, 165.9, 134.9, 131.1, 129.9, 129.7, 129.6, 129.5, 127.7, 126.4, 115.8, 64.2, 55.4, 46.9, 31.6, 13.7; IR (KBr): 2251 (w), 1790 (w), 1749 (s), 1722 (s), 1495 (m), 1451 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4Cl$ $(M-H)^-$: 395.0799, found: 395.0809. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/2-propanol = 80:20, λ = 220 nm, 1.0 mL/min); major diastereomer: t_{major} = 13.43 min, t_{minor} = 24.52 min, 91% ee; minor diastereomer: t_{major} = 21.32 min, t_{minor} = 36.08 min, 26% ee.

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

White solid, mp 157–159 °C; $[\alpha]_D^{20} = -36.1$ (*c* 0.38, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.55 (m, 4H), 7.49–7.49 (m, 3H), 7.21 (d, *J* = 8.8 Hz, 2H), 4.43–4.25 (m, 3H), 2.81 (dd, *J* = 18.8, 9.6 Hz, 1H), 2.52 (dd, *J* = 18.8, 6.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 172.5, 165.9, 132.4, 131.1, 130.2, 129.9, 129.7, 128.0, 126.4, 122.9, 115.8, 64.2, 55.4, 46.9, 31.6, 13.7; IR (KBr): 2250 (w), 1787 (w), 1747 (s), 1711 (s), 1587 (w), 1491 (m), 1447 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4Br$ $(M-H)^-$: 439.0293, found: 439.0299. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/2-propanol = 80:20, λ = 220 nm, 1.0 mL/min); major diastereomer: t_{major} = 14.23 min, t_{minor} = 29.18 min, 94% ee; minor diastereomer: t_{major} = 22.95 min, t_{minor} = 40.68 min, 20% ee.

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

White solid, mp 167–168 °C; $[\alpha]_D^{20} = -27.9$ (*c* 0.28, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.63 (m, 2H), 7.51–7.46 (m, 3H), 7.32–7.28 (m, 2H), 7.18–7.13 (m, 2H), 4.43–4.23 (m, 3H), 2.82 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.53 (dd, *J* = 18.4, 6.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 172.8, 165.9, 162.4 (d, $^1J_{C\text{-}F}$ = 247 Hz), 131.1, 129.9, 129.7, 128.4 (d, $^3J_{C\text{-}F}$ = 8 Hz), 127.1 (d, $^4J_{C\text{-}F}$ = 3 Hz), 126.4, 116.3 (d, $^2J_{C\text{-}F}$ = 22 Hz), 115.8, 64.2, 55.4, 46.8, 31.6, 13.7; IR (KBr): 2252 (w), 1790 (w), 1747 (s), 1710 (s), 1603 (w), 1512 (m), 1450 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4F$ $(M-H)^-$: 379.1094, found: 379.1087. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 19.35 min, t_{major} = 20.68 min, 84% ee; minor diastereomer: t_{major} = 9.62 min, t_{minor} = 13.55 min, 12% ee.

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

White solid, mp 144–145 °C; $[\alpha]_D^{20} = -33.5$ (*c* 0.20, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 9.2 Hz, 2H), 7.65–7.63 (m, 2H), 7.59 (d, *J* = 9.2 Hz, 2H), 7.50–7.48 (m, 3H), 4.549–4.27 (m, 3H), 2.88 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.58 (dd, *J* = 18.4, 6.4 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 172.0, 165.8, 147.3, 136.6, 130.9, 130.0, 129.8, 127.1, 126.4, 124.4, 115.8, 64.3, 55.4, 46.9, 31.6, 13.7; IR (KBr): 2252 (w), 1792 (w), 1752 (s), 1719 (s), 1595 (w), 1496 (s), 1451 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_3O_6$ $(M-H)^-$: 406.1039, found: 406.1045. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{major} = 18.00 min, t_{minor} = 27.49 min, 81% ee; minor diastereomer: t_{major} = 36.20 min, t_{minor} = 41.47 min, 14% ee.

4.3.8. (*R*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-(m-tolyl)pyrrolidin-3-yl)-2-phenylacetate 3h

White solid, mp 92–93 °C, $[\alpha]_D^{20} = -30.5$ (*c* 0.21, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.65 (m, 2H), 7.50–7.46 (m, 3H), 7.37–7.33 (m, 1H), 7.23–7.21 (m, 1H), 7.10–7.04 (m, 2H), 4.42–4.22 (m, 3H), 2.80 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.53 (dd, *J* = 18.4, 6.4 Hz, 1H), 2.38 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 172.9, 165.9, 139.4, 131.2, 131.1, 129.9, 129.9, 129.7, 129.1, 127.1, 126.4, 123.6, 115.8, 64.1, 55.4, 46.9, 31.6, 21.3, 13.7; IR (KBr): 2250 (w), 1792 (w), 1753 (s), 1710 (s), 1611 (w), 1453 (m), 1451 (m); HRMS (ESI) calcd for $C_{22}H_{19}N_2O_4$ $(M-H)^-$: 375.1345, found: 375.1363. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major

diastereomer: t_{minor} = 15.02 min, t_{major} = 22.33 min, 87% ee; minor diastereomer: t_{major} = 9.26 min, t_{minor} = 10.73 min, 16% ee.

4.3.9. (*R*)-Ethyl 2-((*S*)-1-(3-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 3i

White solid, mp 149–150 °C; $[\alpha]_D^{20} = -38.9$ (*c* 0.19, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.49–7.46 (m, 3H), 7.41–7.36 (m, 3H), 7.25–7.23 (m, 1H), 4.43–4.24 (m, 3H), 2.82 (dd, *J* = 18.8, 9.6 Hz, 1H), 2.54 (dd, *J* = 18.8, 6.4 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 172.4, 165.9, 134.8, 132.2, 131.1, 130.2, 129.9, 129.7, 129.2, 126.7, 126.4, 124.7, 115.8, 64.2, 55.4, 46.9, 31.6, 13.7; IR (KBr): 2252 (w), 1792 (w), 1753 (s), 1711 (s), 1591 (w), 1476 (m), 1452 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4Cl$ $(M-H)^-$: 395.0799, found: 395.0809. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 15.77 min, t_{major} = 20.21 min, 91% ee; minor diastereomer: t_{major} = 9.32 min, t_{minor} = 11.24 min, 21% ee.

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

White solid, mp 169–171 °C; $[\alpha]_D^{20} = -34.4$ (*c* 0.25, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.63 (m, 2H), 7.60–7.46 (m, 5H), 7.36–7.27 (m, 2H), 4.43–4.24 (m, 3H), 2.82 (dd, *J* = 18.8, 9.6 Hz, 1H), 2.54 (dd, *J* = 18.8, 6.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 172.4, 165.9, 132.3, 132.1, 131.0, 130.4, 129.9, 129.7, 129.5, 126.4, 125.2, 122.5, 115.8, 64.2, 55.4, 46.9, 31.6, 13.7; IR (KBr): 2254 (w), 1789 (w), 1753 (s), 1710 (s), 1591 (w), 1499 (m), 1451 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4Br$ $(M-H)^-$: 439.0293, found: 439.0299. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 17.15 min, t_{major} = 24.45 min, 90% ee; minor diastereomer: t_{major} = 10.33 min, t_{minor} = 12.62 min, 18% ee.

4.3.11. (*R*)-Ethyl 2-((*S*)-2,5-dioxopyrrolidin-3-yl)- 2-cyano-2-phenylacetate 3k

Colorless oil, $[\alpha]_D^{20} = -2.3$ (*c* 0.56, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.62–7.59 (m, 2H), 7.48–7.44 (m, 3H), 4.42–4.25 (m, 3H), 2.65 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.42 (dd, *J* = 18.4, 6.8 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 173.9, 165.2, 131.2, 129.8, 129.6, 126.3, 115.7, 64.1, 54.9, 48.0, 32.6, 13.7; IR (KBr): 3251 (m), 2249 (w), 1789 (m), 1754 (s), 1704 (s), 1599 (m), 1494 (w), 1451 (m); HRMS (ESI) calcd for $C_{15}H_{13}N_2O_4$ $(M-H)^-$: 285.0875, found: 285.0877. The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 80:20, λ = 215 nm, 0.8 mL/min); major diastereomer t_{major} = 25.43 min, t_{minor} = 28.27 min, 41% ee; minor diastereomer: t_{minor} = 33.02 min, t_{major} = 37.29 min, 21% ee.

4.3.12. (*R*)-Ethyl 2-((*S*)-1-ethyl-2,5-dioxopyrrolidin-3-yl)- 2-cyano-2-phenylacetate 3l

Colorless oil, $[\alpha]_D^{20} = -3.7$ (*c* 0.46, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.44 (m, 5H), 4.44–4.24 (m, 2H), 4.21 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.61 (q, *J* = 7.2 Hz, 2H), 2.63 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.33 (dd, *J* = 18.4, 6.4 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 173.6, 166.0, 131.4, 129.8, 129.6, 126.4, 115.7, 64.0, 55.2, 46.7, 34.2, 31.4, 13.7, 12.9; IR (KBr): 2248 (w), 1780 (m), 1750 (s), 1716 (s), 1599 (m), 1494 (w), 1449 (m); HRMS (ESI) calcd for $C_{17}H_{17}N_2O_4$ $(M-H)^-$: 313.1188, found: 313.1185; The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 70:30, λ = 220 nm, 0.8 mL/min); major diastereomer t_{major} = 9.46 min, t_{minor} = 10.90 min, 33% ee; minor diastereomer: t_{major} = 7.33 min, t_{minor} = 10.12 min, 0% ee.

4.3.13. (*R*)-Ethyl 2-((*S*)-1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-cyano-2-phenylacetate 3m

Sticky oil, $[\alpha]_D^{20} = -0.5$ (*c* 0.21, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.57 (m, 2H), 7.45–7.26 (m, 8H), 4.75–4.59 (m, 2H), 4.43–4.20 (m, 3H), 2.61 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.36 (dd, *J* = 18.4, 6.8 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 173.4, 166.0, 135.0, 131.3, 129.8, 129.6, 128.7, 128.6, 128.1, 126.3, 115.7, 64.0, 55.0, 46.9, 42.8, 31.4, 13.7; IR (KBr): 2248 (w), 1785 (m), 1753 (s), 1718 (s), 1586 (w), 1497 (m), 1453 (m); HRMS (ESI) calcd for $C_{22}H_{19}N_2O_4$ $(M-H)^-$: 375.1345, found: 375.1344. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20, λ = 220 nm, 0.8 mL/min); major diastereomer t_{major} = 16.98 min, t_{minor} = 18.61 min, 63% ee: minor diastereomer: t_{major} = 11.65 min, t_{minor} = 14.20 min, 7% ee.

4.3.14. (*R*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(*p*-tolyl)acetate 3n

White solid, mp 129–131 °C; $[\alpha]_D^{20} = -36.0$ (*c* 0.25, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.38 (m, 5H), 7.32–7.25 (m, 4H), 4.41–4.21 (m, 3H), 2.81 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.53 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.38 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 172.9, 166.1, 140.4, 131.2, 130.3, 129.2, 129.0, 128.2, 126.5, 126.3, 116.0, 64.0, 55.2, 46.9, 31.6, 21.0, 13.7; IR (KBr): 2250 (w), 1783 (w), 1751 (s), 1707 (s), 1594 (w), 1499 (m), 1452 (m); calcd for $C_{22}H_{19}N_2O_4$ $(M-H)^-$: 375.1345, found: 375.1353. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 13.48 min, t_{major} = 17.81 min, 91% ee; minor diastereomer: t_{major} = 9.30 min, t_{minor} = 10.65 min, 14% ee.

4.3.15. (*R*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(4-methoxyphenyl) acetate 3o

White solid, mp 145–146 °C, $[\alpha]_D^{20} = -34.2$ (*c* 0.26, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.53 (m, 2H), 7.49–7.38 (m, 3H), 7.32–7.23 (m, 2H), 6.98–6.94 (m, 2H), 4.39–4.22 (m, 3H), 3.83 (s, 3H), 2.82 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.54 (dd, *J* = 18.6, 6.4 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 172.9, 166.2, 160.5, 131.2, 129.2, 129.0, 127.8, 126.5, 122.9, 116.0, 114.9, 64.0, 55.4, 54.8, 46.9, 31.6, 13.7; IR (KBr): 2250 (w), 1789 (w), 1750 (s), 1710 (s), 1611 (w), 1453 (m); HRMS (ESI) calcd for $C_{22}H_{19}N_2O_5$ $(M-H)^-$: 391.1294, found: 391.1296. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 ml/min); major diastereomer: t_{minor} = 16.24 min, t_{major} = 20.00 min, 88% ee; minor diastereomer: t_{major} = 12.08 min, t_{minor} = 14.20 min, 16% ee.

4.3.16. (*R*)-Ethyl 2-(4-bromophenyl)-2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-acetate 3p

White solid, mp 166–167 °C; $[\alpha]_D^{20} = -22.7$ (*c* 0.63, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.49–7.40 (m, 3H), 7.31–7.24 (m, 2H), 4.40–4.25 (m, 3H), 2.81 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.51 (dd, *J* = 18.4, 6.8 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 172.6, 165.6, 132.8, 131.1, 130.3, 129.3, 129.07, 128.1, 126.4, 124.5, 115.5, 64.4, 55.0, 46.8, 31.5, 13.7; IR (KBr): 2251 (w), 1789 (w), 1753 (s), 1711 (s), 1595 (w), 1498 (m), 1456 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4Br$ $(M-H)^-$: 439.0293, found: 439.0300. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{minor} = 13.78 min, t_{major} = 19.79 min, 85% ee; minor diastereomer: t_{major} = 10.76 min, t_{minor} = 12.41 min, 14% ee.

4.3.17. (*S*)-Ethyl 2-cyano-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)butanoate 3q

Colorless oil, $[\alpha]_D^{20} = -3.3$ (*c* 0.21, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) signals corresponding to the major diastereomer: δ 7.50–7.45 (m, 3H), 7.30–7.29 (m, 2H), 4.39–4.31 (m, 2H), 3.49 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.07 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.81 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.54–2.45 (m, 1H), 2.27–2.20 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); signals corresponding to the minor diastereomer: δ 7.43–7.39 (m, 3H), 7.28–7.27 (m, 2H), 4.39–4.31 (m, 2H), 3.63 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.14 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.83 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.15–2.04 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) signals corresponding to the major diastereomer: δ 173.9, 173.0, 167.0, 131.3, 129.2, 129.0, 126.5, 116.6, 63.7, 51.6, 43.9, 32.4, 28.8, 14.0, 9.6; signals corresponding to the minor diastereomer: δ 173.7, 172.9, 167.2, 131.3, 129.2, 129.0, 126.4, 116.5, 63.6, 52.0, 44.8, 31.9, 29.6, 13.9, 9.5; IR (KBr): 2250 (w), 1784 (w), 1747 (s), 1709 (s), 1596 (w), 1500 (m), 1459 (m). calcd for $C_{17}H_{17}N_2O_4$ $(M-H)^-$: 313.1188, found: 313.1199. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 60:40, λ = 220 nm, 0.8 mL/min); major diastereomer: t_{major} = 10.54 min, t_{minor} = 11.06 min, 71% ee; minor diastereomer: t_{major} = 8.91 min, t_{minor} = 13.43 min, 2% ee.

4.4. Preparation of (3*R*,4*S*)-ethyl 5-oxo-4-(2-oxo-2-(phenyl amino)ethyl)-3-phenylpyrrolidine-3-carboxylate 5

A solution of $CoCl_2{\cdot}6H_2O$ (0.4 mmol) and **3a** (0.1 mmol) in MeOH (3 mL) was stirred under an ice-bath. $NaBH_4$ (6.63 mmol) was added in portions to give a black suspension. Once H_2 evolution ceased, the reaction mixture was warmed to 25 °C and stirred for additional 3 h. After the completion of the reaction, $Na_2SO_4{\cdot}10H_2O$ (3 mmol) was added. The mixture was filtered, and the filtrate was dried over anhydrous Na_2SO_4. After the evaporation of the solvent under vacuum, the crude product was purified by column chromatography over silica gel to afford **5** as a colorless oil. $[\alpha]_D^{20} = -42.3$ (*c* 0.30, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (br s, 1H), 7.52–7.50 (m, 2H), 7.40–7.28 (m, 5H), 7.30–7.21 (m, 2H), 7.08–7.04 (m, 1H), 6.13 (br s, 1H), 4.33–4.25 (m, 2H), 4.07 (d, *J* = 10.4 Hz, 1H), 3.91 (d, *J* = 10.4 Hz, 1H), 3.75 (dd, *J* = 9.2, 3.2 Hz, 1H), 2.35 (dd, *J* = 15.2, 3.2 Hz, 1H), 2.26 (dd, *J* = 15.2, 9.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 172.8, 169.1, 138.4, 137.3, 129.1, 128.8, 128.2, 126.5, 123.8, 119.6, 62.2, 57.8, 49.5, 45.1, 35.9, 14.0; IR (KBr): 1739 (s), 1655 (s), 1598 (m), 1553 (m), 1499 (m), 1444 (m), 759 (m), 696 (m); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_4Br$ $(M-H)^-$: 365.1501, found: 365.1501. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 65:35, λ = 254 nm, 0.8 mL/min); major diastereomer: t_{minor} = 9.40 min, t_{major} = 10.83 - min, 84% ee.

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