A highly efficient asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by primary amine thiourea salt†

Feng Yu, Zhichao Jin, Huicai Huang, Tingting Ye, Xinmiao Liang* and Jinxing Ye*

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The first highly efficient Michael addition of challenging α,α-disubstituted aldehydes to maleimides catalyzed by a simple bifunctional primary amine thiourea catalyst/benzoic acid system has been successfully developed to generate quaternary carbon centers in high yields (up to 99%) with excellent enantioselectivities (91–99%).

Introduction

Substituted maleimides are considered as important structural scaffolds or precursors of some biologically interesting substances such as functionalized pyrrolidines and α-substituted succinimides.[1] Synthesis of chiral α-substituted succinimides is still a challenging task in organic reactions. Catalytic asymmetric Michael addition has been confirmed as a powerful synthetic strategy for the formation of C–C bonds in the synthesis of valuable chiral compounds.[2,3] It is generally accepted that the asymmetric conjugate addition of different nucleophiles to maleimides will provide a practical method to enrich these structural motifs. Great efforts have been made over the past decade and different kinds of catalysts were introduced to the asymmetric addition of aryl boronic acids,[4] hydrazoic acid,[5] hydroxyketones[6] and 1,3-dicarbonyl compounds[7] to maleimides.

The asymmetric conjugate addition of aldehydes to different kinds of electron-deficient alkenes has become a key transformation in organic synthesis due to the various possible transformations of the aldehyde group.[8] Córdova and co-workers have developed an excellent Michael addition of aldehydes to maleimides employing a kind of chiral secondary amine, diphenylprolinol silyl ether as the enamine catalyst.[9] Highly enantioselective products were obtained for the linear aldehydes. However, when the α,α-disubstituted aldehyde was employed, only a moderate ee value was observed, probably due to steric bulk of the secondary amine in the catalytic conjugate reaction.

In recent years, primary amines have been increasingly considered as complementary catalysts to secondary amines.[10] Furthermore, different chiral primary amines were successfully developed as highly efficient catalysts by activating α,α-disubstituted aldehydes through enamine intermediates in asymmetric Michael reactions of nitroolefins,[11] and vinyl sulfones.[12] In this context, we reported an enantioselective Michael addition of ketones to maleimides catalyzed by bifunctional monosulfonyl DPEN salt based on an enamine mechanism.[13] We envisioned that sterically hindered α,α-disubstituted aldehydes could be activated through an enamine mechanism by a chiral bifunctional primary amine catalyst, and that it could be involved in the asymmetric Michael addition to maleimides, which could generate challenging quaternary carbon centers.[14] In this paper, we describe the asymmetric Michael addition of challenging α,α-disubstituted aldehydes to maleimides catalyzed by a bifunctional primary amine thiourea catalyst/benzoic acid system in excellent yields (up to 99%) and enantioselectivities (91–99%).[15]

Results and discussion

The Michael reaction between isobutyraldehyde **1a** and *N*-phenylmaleimide **2a** was selected as a model and performed in the presence of benzoic acid in DCM at room temperature. Table 1 presents some of the screening results of several readily available primary amine catalysts. (*R*,*R*)-1,2-diphenylethane-1,2-diamine **4a** and (*R*,*R*)-1,2-cyclohexane diamine **4b** lead to good conversions but with unacceptable enantioselectivities (entries 1, 2). To our delight, the simple bifunctional amino *N*-sulfonamide/benzoic acid system **5a** and **5b**, which may provide a weak single hydrogen-bonding interaction, giving Michael addition products with good to excellent enantioselectivities in 72 h and 10 h, respectively (entries 3, 4). Surprisingly, the activities of the catalysts are increased dramatically when the sulfonamide group in **5a** and **5b** is replaced by the thiourea group (entries 5, 6). The catalyst **6b**, derived from 1,2-cyclohexanediamine emerged as the most promising catalyst: the model reaction is complete within 1 h and nearly optically pure adduct is obtained (99% ee). We next screened a series of solvent systems under the same reaction conditions using an arbitrary time of 1 h. Further experiments showed that the reaction activity had a strong dependence upon the solvent systems. In nonpolar solvents such as EtOAc, toluene, MTBE, Et_2O and 1,2-DCE, the reactions proceeded with fairly good conversions along with excellent enantioselectivities (entries 7–11). With increasing solvent polarity, both the catalytic activities and ee values of the reactions decreased (entries 12–14). Significantly, relatively low conversion (15%) is observed in the protic solvent MeOH (entry 15).

It is noteworthy that in the model reaction, the catalyst loading can be reduced to 2 mol% without compromising the enantioselectivity and the yield in prolonged reaction time (entry 16). Furthermore, it should be pointed out that the acidic additive may play an important role in improving the conversion by

Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China. E-mail: yejx@ecust.edu.cn, liangxm@ecust.edu.cn

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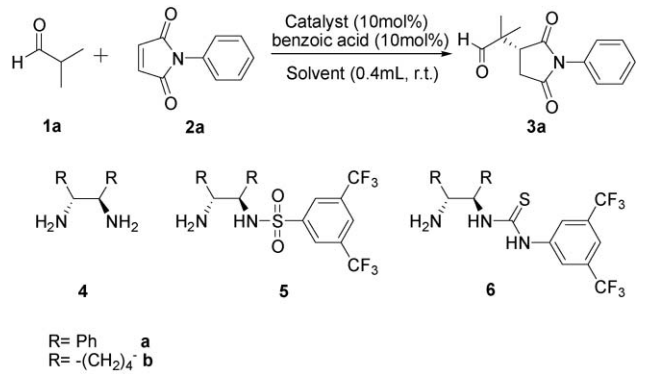
Table 1 Screening of catalysts and solvents



Entry[a]	Catalyst	Time/h	Solvent	Conv. (%)[b]	ee (%)[c]
1	**4a**	72 h	CH_2Cl_2	93	72
2	**4b**	10 h	CH_2Cl_2	99	21
3	**5a**	72 h	CH_2Cl_2	98	98
4	**5b**	10 h	CH_2Cl_2	99	89
5	**6a**	10 h	CH_2Cl_2	full	99
6	**6b**	1 h	CH_2Cl_2	full	99
7	**6b**	1 h	EtOAc	full	96
8	**6b**	1 h	MTBE	full	96
9	**6b**	1 h	Et_2O	full	98
10	**6b**	1 h	Toluene	full	99
11	**6b**	1 h	1,2-DCE	full	99
12	**6b**	1 h	THF	89	91
13	**6b**	1 h	1,4-Dioxane	89	92
14	**6b**	1 h	Acetonitrile	80	83
15	**6b**	1 h	MeOH	<15	nd
16[d]	**6b**	5 h	CH_2Cl_2	full	99
17[e]	**6b**	5 h	CH_2Cl_2	32	99

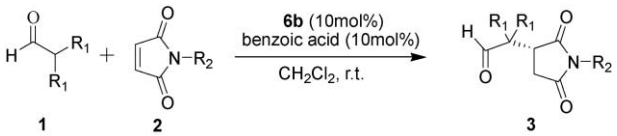
[a] The reaction was carried out with **1a** (0.4 mmol), **2a** (0.2 mmol), catalysts (0.02 mmol) and benzoic acid (0.02 mmol) in solvents (0.40 mL). [b] Detected by ^{1}H NMR analysis of the crude products. [c] Determined by HPLC analysis on chiral AS–H column. [d] 2 mol% **6b** and 2 mol% benzoic acid was used. [e] 2 mol% **6b** was used without benzoic acid.

accelerating the formation of the enamine intermediate (entry 16 *vs.* 17). In the absence of benzoic acid, the reaction gives a diminished conversion (32%) while the ee value is maintained.

With the optimized conditions established, we further explored the scope of the Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by **6b** (10 mol%) in the presence of the benzoic acid additive (10 mol%) in DCM (Table 2). The Michael addition of isobutyraldehyde **1a** to different substituted aromatic maleimides generally proceeds well and the conjugate products are obtained in high yields (93–99%) with excellent enantioselectivities (up to >99%) (entries 1–6). For the *N*-alkyl substituted maleimides, the **6b**-catalyzed conjugate reactions also produce excellent results both in terms of enantioselectivity and yield (entries 8–11). Cyclohexanecarbaldehyde is also shown to be an excellent donor. The reactions with different substituted maleimides provide the anticipated Michael addition products in at least 95% yield with excellent enantioselectivities (>97%) (entries 12–15)).

We next investigated the scope of the reaction employing a variety of α,α-disubstituted aldehydes as donors, two stereogenic carbon centers were formed in these reactions and the results were summarized in Table 3. It appears that the diastereoselectivities of the products are quite dependent on the substituted groups of

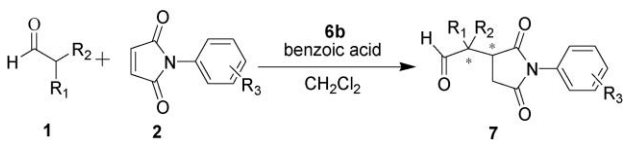
Table 2 Enantioselective Michael addition of aldehydes to maleimides catalyzed by **6b**[a]



Entry	R_1	R_2	Adduct	Yield (%)[b]	ee (%)[c]
1	Me	Ph	**3a**	96	99
2	Me	*p*-MePh	**3b**	93	99
3	Me	*m*-CF_3Ph	**3c**	96	>99
4	Me	*p*-ClPh	**3d**	98	>99
5	Me	*p*-BrPh	**3e**	98	>99
6[d]	Me	*p*-CH_3OPh	**3f**	97	>99
7[e]	Et	Ph	**3g**	95	98
8	Me	Bn	**3h**	97	>99
9	Me	*n*-Pr	**3i**	97	99
10[e]	Me	*i*-Pr	**3j**	96	99
11[e]	Et	*n*-Pr	**3k**	97	99
12[f]	$-(CH_2)_5-$	Ph	**3l**	97	98
13[f]	$-(CH_2)_5-$	*m*-ClPh	**3m**	98	98
14[f]	$-(CH_2)_5-$	*p*-CF_3Ph	**3n**	95	97
15[f]	$-(CH_2)_5-$	*m*-CH_3Ph	**3o**	97	97

[a] Unless otherwise specified, the reaction was carried out with **1** (0.40 mmol), **2** (0.20 mmol), **6b** (10 mol%) and benzoic acid (10 mol%) in CH_2Cl_2 (0.40 mL) at room temperature for 1 h. [b] Isolated yield. [c] Determined by HPLC or GC analysis (see ESI for details).† Reaction time:[d] 2 h, [e] 3 h, [f] 5 h.

Table 3 Diastereoselective and enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by **6b**[a]



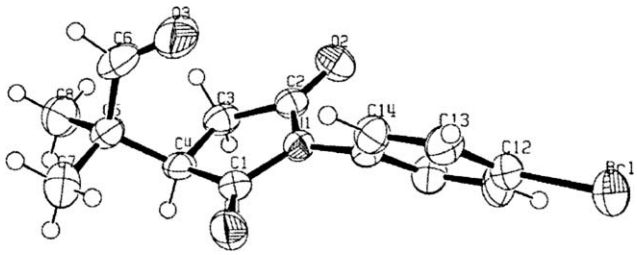
Entry	R_1	R_2	R_3	Adduct	Yield (%)[b]	ee (%)[c]
1	Me	$CH_3(CH_2)_2$	H	**7a**	95 (1/1)	98/96
2[d]	Me	*p*-*t*-BuBn	H	**7b**	96 (2/1)	99/96
3[d]	Me	*p*-*t*-BuBn	*p*-Cl	**7c**	98 (2/1)	99/99
4	Me	$(CH_3)_2CH{=}CH(CH_2)_2$	H	**7d**	99 (2/1)	99/97
5	Me	$(CH_3)_2CH{=}CH(CH_2)_2$	*p*-CH_3O	**7e**	99 (2/1)	99/99
6[h,e]	Me	Ph	H	**7f**	90 (8/1)	91
7[h,e]	Me	Ph	*p*-Br	**7g**	92 (8/1)	95
8[h,f]	Me	Ph	*p*-CH_3O	**7h**	85 (9/1)	93
9[h,g]	Me	Ph	*m*-Cl	**7i**	93 (8/1)	94

[a] Unless otherwise specified, the reaction was carried out with **1** (0.40 mmol), **2** (0.20 mmol), **6b** and benzoic acid in CH_2Cl_2 (0.40 mL) at room temperature for 1 h. [b] Isolated yield after purification. Data in parentheses was dr value of the two diastereomers. [c] Determined by HPLC analysis on chiral column. Reaction time:[d] 4 h, [e] 36 h, [f] 60 h, [g] 24 h. [h] The reaction was carried out using 0.04 mmol of catalyst **6b** (20 mol%) and benzoic acid (20 mol%) at 35 °C.

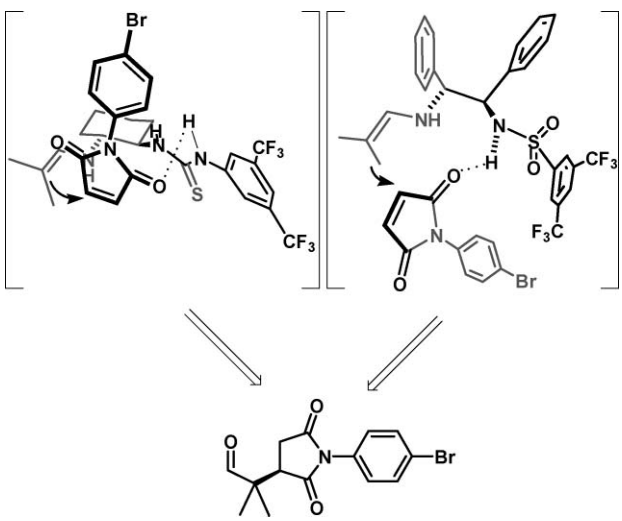
the aldehydes. The reactions of the 2-alkyl-substituted aldehydes that have minimal steric differentiation between the α-substituents provide low diastereoselectivities (approximately 1 : 1–2 : 1, entries 1–5), but both diastereomers are formed in excellent ee values (>96%). The more sterically hindered 2-aryl-substituted aldehyde was also employed as a challenging substrate for this Michael reaction. 20 mol% of catalyst was applied in the presence of 20 mol% benzoic acid and the reactions were performed at 35 °C

(entries 6–9); excellent enantioselectivities of the major diastereomers are obtained. More importantly, the diastereoselectivities are improved to a superior level (up to 9 : 1).

The absolute configuration of the asymmetric Michael product **3e** was unambiguously determined to be (*R*) by X-ray crystallographic analysis (Scheme 1). A synergistic mechanism for this Michael addition has been postulated to illustrate the concomitant activation mode and account for the stereochemical outcome (Scheme 2). As depicted in Scheme 2, the isobutyraldehyde is activated by the primary amine through the enamine intermediate, and the thiourea moiety of the catalyst **6b** directs and activates the maleimide by hydrogen-bonding interactions simultaneously. Considering the plausible steric effect between the substrate of maleimide and the catalyst, a more favored transition state model can be predicated which leads to the *R* product. The catalyst **5a** also gives the *R* adduct with 98% ee but with a much slower reaction rate. For the **5a**-catalyzed Michael addition, we propose that direction of the maleimide substrate is different from that in the **6b**-catalyzed reaction because of the difference in the steric hindrance effect and direction of the thiourea and arylsulfonyl groups.



Scheme 1 X-Ray structure of enantiopure **3e**, thermal ellipsoids are shown at the 50% probability level.



Scheme 2 Plausible transition state models for **6b** and **5a**-catalyzed Michael addition.

Conclusions

In conclusion, the first highly efficient asymmetric Michael addition of α,α-disubstituted aldehydes to maleimides catalyzed by a simple primary amine thiourea/benzoic acid bifunctional system has been successfully developed. The new method provides access to a wide range of α-substituted succinimides in excellent yield and enantioselectivity. Further efforts focusing on the application of this useful synthetic tool in asymmetric synthesis are well under way.

Experimental

General methods

Commercially available starting materials were used without further purification. Column chromatography was carried out with silica gel (200–300 mesh) using mixtures of petroleum ether and dichloromethane as eluent. The NMR was recorded on a Bruker DRX 400 instrument. High resolution mass spectrometry (ESI) was carried out using an ACQUITY™ Ultra Performance Liquid Chromatography system (Waters, Milford MA) coupled with a Q-TOF premier (Waters MS Technologies, Manchester, UK). Low resolution mass spectrometry (ESI) was carried out using a Waters Quatro Macro triple quadrupole mass spectrometer. High resolution mass spectra (EI) were measured on a Waters Micromass GCT spectrometer. Optical rotations were measured on an Autopol III automatic polarimeter (Rudolph Research analytical). Enantiomeric excess was determined by chiral HPLC using Agilent 1200 Series or chiral GC using Agilent GC 7890.

General procedure and characterization data for the synthesis of organocatalysts

Coupling of chiral diamine with benzenesulfonyl chloride. 3,5-Bis(trifluoromethyl)benzene sulfonyl chloride (3.12 g, 10 mmol) in anhydrous THF (25 mL) was added dropwise to a solution of 1,2-diphenylethane-1,2-diamine (2.12 g, 10 mmol) or cyclohexane-1,2-diamine (1.14 g, 10 mmol), triethylamine (2.02 g, 20 mmol) and anhydrous THF (20 mL) with ice-cooling. The reaction mixture was warmed to room temperature and stirred for 12 h. TLC indicated that the reaction was complete. The solvent was removed and the residue was purified by silica gel chromatography to afford the pure product.

N-*((1R,2R)-2-Amino-1,2-diphenylethyl)-3,5-bis (trifluoromethyl)benzenesulfonamide* (***5a***). The product was obtained in 81% yield, white solid. Mp 157–160 °C; $[\alpha]_D^{29} = -10.2°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.87 (s, 2H), 7.80 (s, 1H), 7.17–7.09 (m, 10H), 4.53 (d, J = 4.8 Hz, 1H), 4.18 (d, J = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): (ppm) 143.2, 140.9, 138.1, 132.2, 128.7, 128.5, 127.9, 127.8, 127.1, 126.9, 126.2, 125.5, 125.4, 122.4, 63.4, 60.1. HRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{22}H_{19}F_6N_2O_2S$) requires m/z 489.1071, found m/z 489.1065.

N-*((1R,2R)-2-Aminocyclohexyl)-3,5-bis (trifluoromethyl)-benzenesulfonamide* (***5b***). The product was obtained in 87% yield, yellow foamy solid. $[\alpha]_D^{29} = -35.1°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.39 (s, 2H), 8.06 (s, 1H), 3.12 (br s, 3H), 2.83–2.78 (m, 1H), 2.54–2.49 (m, 1H), 1.98–1.95 (m, 1H), 1.80 (m, 1H), 1.69–1.66 (m, 2H), 1.26–1.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.5, 132.7, 127.3, 125.8, 122.5, 60.4, 54.5, 35.2, 32.6, 24.7, 24.5. HRMS (ESI): exact mass

calculated for $[M+H]^+$ ($C_{14}H_{17}F_6N_2O_2S$) requires m/z 391.0915, found m/z 391.0906.

Coupling of chiral diamine with isothiocyante. Isothiocyanato-3,5-bis(trifluoromethyl)benzene (2.70 g, 10 mmol) was added to a stirred solution of the chiral diamine (10 mmol) in dry THF (25 mL) over a period of 30 min at 0 °C, the reaction was stirred for another 5 h at room temperature. The solvent was removed and the residue was purified by silica gel chromatography to afford the pure product.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-amino-1,2-diphenylethyl)thiourea (**6a**).* The product was obtained in 90% yield, yellow solid. Mp 91–93 °C; $[\alpha]_D^{29} = -12.9°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.4 (br s, 1H), 8.07 (s, 2H), 7.47 (s, 1H), 7.47–6.97 (m, 10H), 5.26 (s, 1H), 4.14 (s, 1H), 2.91 (br s 3H). ^{13}C NMR (100 MHz, DMSO-d_6): (ppm) 180.2, 142.5, 141.9, 140.8, 130.1, 128.5, 128.1, 127.9, 127.1, 127.0, 126.9, 123.2, 121.0, 115.7, 63.1, 59.3. LRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{23}H_{20}F_6N_3S$) requires m/z 484.13, found m/z 484.17.

*1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1R,2R)-2-aminocyclohexyl)thiourea (**6b**).* The product was obtained in 92% yield, yellow solid. Mp 71–73 °C; $[\alpha]_D^{29} = +46.6°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.29 (s, 2H), 7.68 (s, 1H), 3.90 (br s, 1H), 2.59 (br s, 1H), 2.08–1.87 (m, 2H), 1.64 (s, 2H), 1.19–1.17 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): (ppm) 180.7, 142.7, 130.5, 123.8, 122.1, 115.9, 60.3, 54.2, 35.0, 31.2, 24.9, 24.8. LRMS (ESI): exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}F_6N_3S$) requires m/z 386.11, found m/z 386.16.

General Procedure for Asymmetric Michael Addition

To a solution of *N*-phenyl maleimide **2a** (0.2 mmol) in dichloromethane (0.4 mL) was added isobutyraldehyde **1a** (0.4 mmol), catalyst **6b** (0.02 mmol) and benzoic acid (0.02 mmol). The reaction mixture was stirred at room temperature for the time indicated in Table 1 or Table 2. The solvent was removed under vacuum and the residue was purified by silica gel chromatography to yield the Michael addition product.

2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal (3a). The product was obtained in 96% yield, white solid. Mp 104–107 °C; $[\alpha]_D^{24} = -2.7°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.54 (s, 1H), 7.50 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 3.17 (dd, J = 5.6, 9.6 Hz, 1H), 3.00 (dd, J = 5.6, 18.4 Hz, 1H), 2.64 (dd, J = 5.6, 18.0 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 177.0, 174.9, 131.9, 129.2, 128.7, 126.6, 48.5, 45.0, 31.8, 20.4, 19.5. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{14}H_{15}NO_3$) requires m/z 245.1052, found m/z 245.1053. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}]: 17.4 min (major), 19.1 min (minor), ee = 99%.

2-(2,5-Dioxo-1-*p*-tolylpyrrolidin-3-yl)-2-methylpropanal (3b). The product was obtained in 93% yield, white solid. Mp 137–140 °C; $[\alpha]_D^{24} = -1.9°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.54 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.17 (dd, J = 5.6, 9.6 Hz, 1H), 2.99 (dd, J = 5.6, 18.0 Hz, 1H), 2.63 (dd, J = 5.6, 18.0 Hz, 1H), 2.40 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 177.1, 175.0, 138.8, 129.8, 129.2, 126.3, 48.5, 44.9, 31.7, 21.2, 20.3, 19.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{15}H_{17}NO_3$) requires m/z 259.1208, found m/z 259.1207. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–IPA = 4 : 1, 0.8 mL min^{-1}]: 40.0 min (major), 58.7 min (minor), ee = 99%.

2-(2,5-Dioxo-1-(3-(trifluoromethyl)phenyl)pyrrolidin-3-yl)-2-methylpropanal (3c). The product was obtained in 96% yield, white solid. Mp 141–142 °C; $[\alpha]_D^{26} = -0.3°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.51 (s, 1H), 7.70–7.61 (m, 3H), 7.48 (d, J = 8.0 Hz, 1H), 3.15 (dd, J = 5.6, 9.2 Hz, 1H), 3.03 (dd, J = 5.6, 18.4 Hz, 1H), 2.67 (dd, J = 5.2, 18.4 Hz, 1H), 1.41 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 176.6, 174.3, 132.4, 131.6, 129.9, 129.8, 125.4, 123.6, 123.5, 48.8, 45.0, 31.1, 20.6, 19.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{15}H_{14}F_3NO_3$) requires m/z 313.0926, found m/z 313.0921. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4: 1, 0.8 mL min^{-1}]: 10.1 min (major), 13.4 min (minor), ee > 99%.

2-(1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (3d). The product was obtained in 98% yield, white solid. Mp 125–127 °C; $[\alpha]_D^{26} = -1.1°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.51 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 3.13 (dd, J = 5.6, 9.6 Hz, 1H), 3.00 (dd, J = 5.6, 18.4 Hz, 1H), 2.64 (dd, J = 5.6, 12.4 Hz, 1H), 1.38 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 176.7, 174.5, 134.4, 130.3, 129.4, 127.8, 48.7, 44.9, 31.9, 20.5, 19.7. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{14}H_{14}ClNO_3$) requires m/z 279.0662, found m/z 279.0666. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.6 mL min^{-1}]: 20.1 min (major), 21.1 min (minor), ee > 99%.

2-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (3e). The product was obtained in 98% yield, white solid. Mp 126–128 °C; $[\alpha]_D^{25} = +4.4°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.51 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 3.13 (dd, J = 5.6, 9.6 Hz, 1H), 3.00 (dd, J = 5.6, 18.4 Hz, 1H), 2.63 (dd, J = 5.6, 18.4 Hz, 1H), 1.38 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 176.7, 174.5, 132.4, 130.9, 128.1, 122.5, 48.7, 45.0, 31.9, 20.6, 19.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{14}H_{14}BrNO_3$) requires m/z 323.1057, found m/z 323.1059. The enantiomeric excess was determined by HPLC. [IC column, *n*-hexane–IPA = 4 : 1, 0.9 mL min^{-1}]: 23.5 min (major), 25.8 min (minor), ee > 99%.

2-(1-(4-Methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (3f). The product was obtained in 97% yield, white solid. Mp 169–171 °C; $[\alpha]_D^{20} = -1.5°$ (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.54 (s, 1H), 7.21 (d, J = 9.2 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.16 (dd, J = 5.6, 9.6 Hz, 1H), 3.00 (dd, J = 5.6, 18.0 Hz, 1H), 2.62 (dd, J = 5.2, 18.4 Hz, 1H), 1.34 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 177.2, 175.2, 159.6, 127.8, 124.4, 114.5, 55.5, 48.5, 44.9, 31.8, 20.3, 19.6. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{15}H_{17}NO_4$) requires m/z 275.1158, found m/z 275.1159. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.6 mL min^{-1}]: 40.7 min (major), 43.2 min (minor), ee > 99%.

2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-ethylbutanal (3g). The product was obtained in 95% yield, white solid. Mp 100–102 °C; $[\alpha]_D^{26}$ = +8.5° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.65 (s, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 3.27 (dd, *J* = 6.0, 9.6 Hz, 1H), 2.99 (dd, *J* = 9.6, 18.4 Hz, 1H), 2.71 (dd, *J* = 6.0, 18.0 Hz, 1H), 2.05–1.84 (m, 3H), 1.76 (sextet, *J* = 7.6 Hz, 1H), 1.02 (q, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 204.1, 177.3, 175.0, 131.9, 129.2, 128.7, 126.5, 54.6, 41.9, 31.7, 24.4, 23.2, 8.2, 8.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{16}H_{19}NO_3$) requires *m*/*z* 273.1365, found *m*/*z* 273.1369. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 7 : 3, 0.8 mL min^{-1}]: 11.1 min (major), 13.9 min (minor), ee = 98%.

2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (3h). The product was obtained in 97% yield, white solid. Mp 59–62 °C; $[\alpha]_D^{25}$ = –17.5° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.51 (s, 1H), 7.40–7.28 (m, 5H), 4.72–4.63 (m, 2H), 3.06 (dd, *J* = 5.6, 9.6 Hz, 1H), 2.84 (dd, *J* = 5.2, 10.4 Hz, 1H), 2.48 (dd, *J* = 5.6, 18.0 Hz, 1H), 1.19 (d, *J* = 1.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 177.5, 175.4, 135.7, 128.7, 128.0, 48.0, 44.9, 42.4, 31.4, 20.0, 19.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{15}H_{17}NO_3$) requires *m*/*z* 259.1208, found *m*/*z* 259.1212. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.6 mL min^{-1}]: 16.8 min (major), 18.8 min (minor), ee > 99%.

2-(2,5-Dioxo-1-propylpyrrolidin-3-yl)-2-methylpropanal (3i). The product was obtained in 97% yield, colorless oil. $[\alpha]_D^{26}$ = –17.7° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.52 (s, 1H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.03 (dd, *J* = 5.6, 9.6 Hz, 1H), 2.81 (dd, *J* = 9.6, 18.4 Hz, 1H), 2.45 (dd, *J* = 5.2, 18.0 Hz, 1H), 1.58 (septet, *J* = 7.2 Hz, 2H), 1.22 (s, 3H), 1.20 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 177.8, 175.9, 47.9, 44.8, 40.4, 31.3, 20.9, 20.1, 18.9, 11.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{17}NO_3$) requires *m*/*z* 211.1208, found *m*/*z* 211.1209. The enantiomeric excess was determined by HPLC. [AS–H column, 210 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}]: 9.4 min (major), 11.3 min (minor), ee = 99%.

2-(1-Isopropyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (3j). The product was obtained in 96% yield, colorless oil. $[\alpha]_D^{26}$ = –21.1° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.52 (s, 1H), 4.36 (septet, *J* = 6.8 Hz, 1H), 2.98 (dd, *J* = 5.2, 9.6 Hz, 1H), 2.75 (dd, *J* = 5.6, 18.4 Hz, 1H), 2.38 (dd, *J* = 5.6, 18.0 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.17 (dd, *J* = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 177.8, 175.8, 48.0, 44.5, 43.8, 31.2, 20.1, 19.1, 19.0, 18.6. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{17}NO_3$) requires *m*/*z* 211.1208, found *m*/*z* 211.1210. The enantiomeric excess was determined by GC. [Chirasil Dex Cβ column, 1.0 mL min^{-1}, 10 °C min^{-1} from 70 °C to 150 °C then hold for 30 min]: 20.8 min (major), 20.9 min (minor), ee = 99%.

2-(2,5-Dioxo-1-propylpyrrolidin-3-yl)-2-ethylbutanal (3k). The product was obtained in 99% yield, colorless oil. $[\alpha]_D^{26}$ = –7.3° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.61 (s, 1H), 3.46 (t, *J* = 7.2 Hz, 2H), 3.11 (dd, *J* = 5.6, 9.2 Hz, 1H), 2.79 (dd, *J* = 5.6, *J* = 18.4 Hz, 1H), 2.53 (dd, *J* = 5.6, 18.0 Hz, 1H), 1.94–1.75 (m, 3H), 1.69 (qn, 7.2 Hz, 1H), 1.59 (sextet, *J* = 7.6 Hz, 2H), 0.97–0.90 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 204.1, 178.2, 176.0, 53.9, 41.8, 40.4, 31.3, 24.4, 23.1, 20.9, 11.3, 8.1, 8.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{13}H_{21}NO_3$) requires *m*/*z* 239.1521, found *m*/*z* 239.1523. The enantiomeric excess was determined by GC. [Chirasil Dex Cβ column, 1.0 mL min^{-1}, 10 °C min^{-1} from 70 °C to 150 °C then hold for 30 min, then 10 °C min^{-1} from 150 °C to 200 °C then hold for 2 min]: 41.9 min (major), 42.1 min (minor), ee = 99%.

1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclohexane-carbaldehyde (3l). The product was obtained in 97% yield, white solid. Mp 131–134 °C; $[\alpha]_D^{25}$ = +4.5° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.56 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.24 (dd, *J* = 5.6, 8.8 Hz, 1H), 2.93–2.85 (m, 1H), 2.73–2.66 (m, 1H), 1.99–1.86 (m, 3H), 1.65–1.55 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 204.7, 177.1, 174.8, 132.0, 129.2, 128.7, 126.7, 52.2, 42.6, 31.5, 28.6, 28.0, 25.1, 21.4, 21.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{17}H_{19}NO_3$) requires *m*/*z* 285.1365, found *m*/*z* 285.1370. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}]: 22.2 min (major), 35.1 min (minor), ee = 98%.

1-(1-(3-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)cyclohexane-carbaldehyde (3m). The product was obtained in 98% yield, white solid. Mp 155–158 °C; $[\alpha]_D^{25}$ = +2.2° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.52 (s, 1H), 7.44–7.36 (m, 3H), 7.24 (td, *J* = 1.6, 7.2 Hz, 1H), 3.23 (dd, *J* = 6.0, 7.6 Hz, 1H), 2.89 (dd, *J* = 9.6, 18.4 Hz, 1H), 2.68 (dd, *J* = 6.0, 18.4 Hz, 1H), 2.08–2.03 (m, 1H), 1.97–1.91 (m, 1H), 1.87–1.84 (m, 1H), 1.68–1.56 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 204.5, 176.9, 174.4, 134.6, 133.1, 130.1, 128.8, 126.9, 124.9, 52.5, 42.1, 31.6, 28.5, 28.1, 25.1, 21.2, 21.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{17}H_{18}ClNO_3$) requires *m*/*z* 319.0975, found *m*/*z* 319.0978. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 7: 3, 0.8 mL min^{-1}]: 12.4 min (major), 20.1 min (minor), ee = 98%.

1-(2,5-Dioxo-1-(4-(trifluoromethyl)phenyl)pyrrolidin-3-yl) cyclohexanecarbaldehyde (3n). The product was obtained in 95% yield, white solid. Mp 139–140 °C; $[\alpha]_D^{25}$ = +2.7° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.52 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 3.27 (dd, *J* = 6.0, 7.2 Hz, 1H), 2.93 (dd, *J* = 5.6, 18.4 Hz, 1H), 2.71 (dd, *J* = 6.0, 14.0 Hz, 1H), 2.14–2.10 (m, 1H), 1.99–1.92 (m, 1H), 1.90–1.84 (m, 1H), 1.70–1.53 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 204.5, 176.9, 174.3, 135.1, 130.4, 126.9, 126.2, 123.7, 52.6, 41.9, 31.7, 28.4, 28.3, 25.1, 21.1, 21.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{18}H_{18}F_3NO_3$) requires *m*/*z* 353.1239, found *m*/*z* 353.1242. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 7: 3, 0.8 mL min^{-1}]: 8.5 min (major), 10.7 min (minor), ee = 97%.

1-(2,5-Dioxo-1-*m*-tolylpyrrolidin-3-yl)cyclohexane-carbaldehyde (3o). The product was obtained in 97% yield, white solid. Mp 135–137 °C; $[\alpha]_D^{25}$ = +3.6° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.57 (s, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 6.8 Hz, 1H), 7.10–7.08 (m, 2H), 3.23 (dd, *J* = 6.4, 8.8 Hz, 1H), 2.89 (dd, *J* = 9.6, 18.0 Hz, 1H), 2.69 (dd, *J* = 5.6, 18.0 Hz, 1H), 2.41 (s, 3H), 1.98–1.87 (m, 3H), 1.66–1.56 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 204.7, 177.2, 174.9, 139.2, 131.8, 129.6, 129.0, 127.2, 123.7, 52.1, 42.7, 31.6, 28.6, 28.0,

25.1, 21.4, 21.3, 21.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{18}H_{21}NO_3$) requires m/z 299.1521, found m/z 299.1525. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 7 : 3, 0.8 mL min^{-1}]: 11.9 min (major), 19.4 min (minor), ee = 97%.

2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methylpentanal (7a). The product was obtained in 95% yield, white solid. Mp 93–97 °C; $[\alpha]_D^{26}$ = +2.9° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.63 (s, 1Hmaj), 9.46 (s, 1Hmin), 7.51–7.47 (m, 2Hmaj and 2Hmin), 7.43–7.39 (m, 1Hmaj and 1Hmin), 7.29 (d, J = 8.0 Hz, 2Hmaj and 2Hmin), 3.36 (dd, J = 6.0, 9.6 Hz, 1Hmaj), 3.19 (dd, J = 5.2, 9.6 Hz, 1Hmin), 3.00 (dd, J = 9.6, 18.4 Hz, 1Hmin), 2.96 (dd, J = 9.6, 18.0 Hz, 1Hmaj), 2.68 (dd, J = 5.6, 18.4 Hz, 1Hmaj), 2.61 (dd, J = 5.2, 18.4 Hz, 1Hmin), 1.90–1.59 (m, 2Hmaj and 2Hmin), 1.53–1.38 (m, 1Hmaj and 1Hmin), 1.35 (s, 3Hmin), 1.32–1.24 (m, 1Hmaj and 1Hmin), 1.21 (s, 3Hmaj and 3Hmin), 0.99 (t, J = 7.2 Hz, 3Hmin), 0.97 (t, J = 7.2 Hz, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.4 (min), 203.3 (maj), 177.2 (min), 176.9 (maj), 175.0 (min), 174.9 (maj), 131.9 (min), 131.7 (maj), 129.2, 128.7, 126.6 (min), 126.5 (maj), 52.1 (min), 51.3 (maj), 44.1 (maj), 42.7 (min), 38.8 (maj), 36.0 (min), 32.2 (min), 31.1 (maj), 17.0 (min), 16.9 (min), 16.8 (maj), 15.5 (maj), 14.6. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{16}H_{19}NO_3$) requires m/z 273.1365, found m/z 273.1370. The enantiomeric excess was determined by HPLC [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 10.2 min (major 1), 11.6 min (minor 1), ee = 98%; 13.9 min (minor 2), 17.7 min (major 2), ee = 96%.

3-(4-*tert*-Butylphenyl)-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal (7b). The product was obtained in 96% yield, white solid. Mp 125–129 °C; $[\alpha]_D^{26}$ = –31.8° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.62 (s, 1Hmaj), 9.58 (s, 1Hmin), 7.51 (t, J = 7.6 Hz, 2Hmaj), 7.43 (t, J = 7.2 Hz, 2Hmin), 7.38–7.31 (m, 4Hmaj and 4Hmin), 7.19 (dd, J = 8.0, 12.8 Hz, 2Hmaj and 2Hmin), 3.31 (dd, J = 13.6, 19.2 Hz, 1Hmaj and 1Hmin), 3.17 (t, J = 6.4 Hz, 1Hmin), 3.16 (t, J = 6.4 Hz, 1Hmaj), 3.09–2.88 (m, 2Hmaj and 2Hmin), 2.69 (dd, J = 6.0, 18.4 Hz, 1Hmaj), 2.60 (dd, J = 4.8, 18.0 Hz, 1Hmin), 1.39 (s, 3Hmin), 1.34 (s, 9Hmaj), 1.33 (s, 9Hmin), 1.25 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.8 (maj), 203.3 (min), 177.6 (maj), 177.2 (min), 174.9 (min), 174.8 (maj), 150.2 (maj), 150.1 (min), 131.9, 131.8 (min), 131.5 (maj), 130.5 (maj), 130.3 (min), 129.2 (maj), 128.7 (min), 126.6, 125.5, 53.3 (min), 52.6 (maj), 42.6 (maj), 42.1 (min), 39.8 (min), 39.6 (maj), 34.5, 32.6 (min), 31.8 (maj), 31.4, 17.1 (maj), 17.0 (min). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{24}H_{27}NO_3$) requires m/z 377.1991, found m/z 377.1987. The enantiomeric excess was determined by HPLC [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 12.9 min (major 1), 15.4 min (minor 1), ee = 99%; 19.8 min (minor 2), 21.6 min (major 2), ee = 96%.

3-(4-*tert*-Butylphenyl)-2-(1-(4-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (7c). The product was obtained in 98% yield, white solid. Mp 147–149 °C; $[\alpha]_D^{26}$ = –41.1° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.59 (s, 1Hmaj), 9.56 (s, 1Hmin), 7.47 (d, J = 8.4 Hz, 2Hmaj and 2Hmin), 7.37–7.25 (m, 4Hmaj and 4Hmin), 7.20 (d, J = 8.4 Hz, 2Hmaj), 7.15 (d, J = 8.0 Hz, 2Hmin), 3.35 (d, J = 13.2 Hz, 1Hmaj), 3.24 (d, J = 13.6 Hz, 1Hmin), 3.15–3.10 (1Hmaj and 1Hmin), 3.08–2.85 (m, 2Hmaj and 2Hmin), 2.69–2.58 (m, 1Hmaj and 1Hmin), 1.40 (s, 3Hmin), 1.34 (s, 9Hmaj), 1.33 (s, 9Hmin), 1.25 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.7 (maj), 203.2 (min), 177.3 (maj), 176.9 (min), 174.6 (min), 174.4 (maj), 150.3, 134.5, 131.6 (min), 131.3 (maj), 130.5, 130.2, 129.4, 127.9 (maj), 125.6, 53.3 (min), 52.7 (maj), 43.4 (maj), 42.2 (min), 39.8 (min), 39.4 (maj), 34.5, 32.6 (min), 31.9 (maj), 31.4, 17.4 (maj), 17.3 (min). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{24}H_{26}ClNO_3$) requires m/z 411.1601, found m/z 411.1606. The enantiomeric excess was determined by HPLC [IA column, 220 nm, *n*-hexane–EtOH = 4 : 1, 1.0 mL min^{-1}.]: 24.5 min (minor 1), 33.8 min (major 1), ee > 99%; 30.1 min (major 2), 39.3 min (minor 2), ee > 99%.

2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2,6-dimethylhept-5-enal (7d). The product was obtained in 99% yield, white solid. Mp 98–101 °C; $[\alpha]_D^{26}$ = –7.8° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.66 (s, 1Hmaj), 9.46 (s, 1Hmin), 7.52–7.47 (m, 2Hmaj and 2Hmin), 7.43–7.40 (m, 1Hmaj and 1Hmin), 7.31–7.29 (m, 2Hmaj and 2Hmin), 5.10–5.06 (m, 1Hmaj and 1Hmin), 3.40 (dd, J = 6.0, 9.6 Hz, 1Hmaj), 3.22 (dd, J = 5.2, 9.2 Hz, 1Hmin), 3.06–2.94 (m, 1Hmaj and 1Hmin), 2.69 (dd, J = 5.6, 12.8 Hz, 1Hmaj), 2.63 (dd, J = 5.2, 18.4 Hz, 1Hmin), 2.17–2.04 (m, 1Hmaj and 1Hmin), 2.01–1.88 (m, 1Hmaj and 2Hmin), 1.78–1.68 (m, 2Hmaj and 1Hmin), 1.71 (s, 3Hmaj and 3Hmin), 1.63 (s, 3Hmin), 1.62 (s, 3Hmaj), 1.38 (s, 3Hmin), 1.24 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.2 (min), 203.1 (maj), 177.1 (min), 176.8 (maj), 174.9 (min), 174.8 (maj), 133.1 (min), 133.0 (maj), 131.9 (min), 131.7 (maj), 129.2, 128.7, 126.6 (min), 126.5 (maj), 122.9 (maj), 122.8 (min), 51.9 (min), 51.1 (maj), 44.1 (maj), 42.7 (min), 34.7 (maj), 33.8 (min), 32.2 (min), 31.1 (maj), 25.7, 22.3 (min), 22.2 (maj). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{19}H_{23}NO_3$) requires m/z 313.1678, found m/z 313.1682. The enantiomeric excess was determined by HPLC [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 10.8 min (major 1), 14.9 min (minor 1), ee = 99%; 17.1 min (minor 2), 20.3 min (major 2), ee = 97%.

2-(1-(4-Methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2,6-dimethylhept-5-enal (7e). The product was obtained in 99% yield, white solid. Mp 104–109 °C; $[\alpha]_D^{26}$ = –5.8° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.65 (s, 1Hmaj), 9.46 (s, 1Hmin), 7.19 (d, J = 8.8 Hz, 2Hmaj and 2Hmin), 7.00–6.97 (m, 2Hmaj and 2Hmin), 5.09–5.06 (m, 1Hmaj and 1Hmin), 3.83 (s, 3Hmaj and 3Hmin), 3.37 (dd, J = 6.0, 9.6 Hz, 1Hmaj), 3.18 (dd, J = 5.2, 9.6 Hz, 1Hmin), 2.95 (dd, J = 9.6, 17.6 Hz, 1Hmaj and 1Hmin), 2.67 (dd, J = 6.0, 18.4 Hz, 1Hmaj), 2.60 (dd, J = 4.8, 13.6 Hz, 1Hmin), 2.21–2.02 (m, 1Hmaj and 1Hmin), 2.00–1.86 (m, 1Hmaj and 1Hmin), 1.76–1.66 (m, 2Hmaj and 2Hmin), 1.70 (s, 3Hmaj and 3Hmin), 1.62 (s, 3Hmin), 1.61 (s, 3Hmaj), 1.35 (s, 3Hmin), 1.22 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.2 (min), 203.1 (maj), 177.3 (min), 177.0 (maj), 175.3 (min), 175.1(maj), 159.8, 133.13 (min), 133.09 (maj), 127.8 (min), 127.6 (maj), 124.5 (min), 124.3 (maj), 122.9 (maj), 122.8 (min), 114.5, 55.5, 51.9 (min), 51.1 (maj), 44.1 (maj), 42.7 (min), 34.8 (maj), 33.8 (min), 32.2 (min), 31.0 (maj), 25.7, 22.3 (min), 22.2 (maj), 17.7, 16.8 (min), 15.4 (maj). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{25}NO_4$) requires m/z 343.1784, found m/z 343.1782. The enantiomeric excess was determined by HPLC [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 13.9 min (major 1), 17.4 min (minor 1), ee > 99%; 20.5 min (minor 2), 26.7 min (major 2), ee > 99%.

2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-phenylpropanal (7f). The product was obtained in 90% yield, white solid. Mp 163–167 °C; $[\alpha]_D^{26}$ = +77.7° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.80 (s, 1Hmin), 9.70 (s, 1Hmaj), 7.49–7.37 (m, 6Hmaj and 6Hmin), 7.30 (dd, *J* = 7.2 Hz, 2Hmaj and 2Hmin), 7.24 (d, *J* = 7.6 Hz, 2Hmin), 7.08 (d, *J* = 7.6 Hz, 2Hmaj), 3.84 (dd, *J* = 4.8, 9.6 Hz, 1Hmaj), 3.45 (dd, *J* = 5.6, 9.6 Hz, 1Hmin), 2.90 (dd, *J* = 9.6, 18.8 Hz, 1Hmaj), 2.73 (dd, *J* = 9.6, 18.4 Hz, 1Hmin), 2.60 (dd, *J* = 6.0, 18.8 Hz, 1Hmin), 2.54 (dd, *J* = 4.8, 19.2 Hz, 1Hmaj), 1.85 (s, 3Hmin), 1.79 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 201.0 (min), 199.1 (maj), 176.7 (min), 176.6 (maj), 174.7, 135.6, 131.6, 129.5 (maj), 129.4 (min), 129.1, 128.7 (maj), 128.7 (min), 128.6 (maj), 128.4 (min), 127.5 (maj), 127.2 (min), 126.6 (min), 126.4 (maj), 56.4 (min), 56.0 (maj), 46.5 (min), 45.0 (maj), 32.6 (min), 32.1 (maj), 19.4 (min), 16.5 (maj). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{19}H_{17}NO_3$) requires *m*/*z* 307.1208, found *m*/*z* 307.1199. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 19.2 min (major 1), 25.2 min (minor 1), ee = 56%; 23.5 min (minor 2), 34.2 min (major 2), ee = 91%.

2-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylpropanal (7g). The product was obtained in 92% yield, white solid. Mp 157–160 °C; $[\alpha]_D^{26}$ = +74.1° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.78 (s, 1Hmin), 9.68 (s, 1Hmaj), 7.60 (dd, *J* = 8.8 Hz, 2Hmin), 7.56 (dd, *J* = 8.8 Hz, 2Hmaj), 7.47–7.38 (m, 3Hmaj and 3Hmin), 7.28 (d, *J* = 8.8 Hz, 2Hmaj and 2Hmin), 7.15 (d, *J* = 8.4 Hz, 2Hmin), 6.98 (d, *J* = 8.4 Hz, 2Hmaj), 3.81 (q, *J* = 4.8 Hz, 1Hmaj), 3.41 (dd, *J* = 6.0, 9.6 Hz, 1Hmin), 2.90 (dd, *J* = 9.6, 18.8 Hz, 1Hmaj), 2.69 (dd, *J* = 9.6, 18.8 Hz, 1Hmin), 2.54 (dd, *J* = 4.4, 18.8 Hz, 1Hmaj and 1Hmin), 1.79 (s, 3Hmaj), 1.60 (s, 3Hmin). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 201.0 (min), 199.0 (maj), 176.4 (min), 176.3 (maj), 174.2, 135.5, 132.3, 130.5, 129.5, 128.7, 128.2 (min), 127.9 (maj), 127.4 (maj), 127.1 (min), 122.6, 56.5 (min), 56.0 (maj), 46.4 (min), 45.0 (maj), 32.6 (min), 32.1 (maj), 19.6 (min), 19.7 (maj). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{19}H_{16}BrNO_3$) requires *m*/*z* 385.0314, found *m*/*z* 385.0315. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 18.9 min (major 1), 27.0 min (minor 1), ee = 73%; 25.1 min (minor 2), 32.4 min (major 2), ee = 95%.

2-(1-(4-Methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylpropanal (7h). The product was obtained in 85% yield, white solid. Mp 150–153 °C; $[\alpha]_D^{26}$ = +96.5° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.80 (s, 1Hmin), 9.69 (s, 1Hmaj), 7.44 (q, *J* = 7.2 Hz, 3Hmaj), 7.40 (q, *J* = 7.2 Hz, 3Hmin), 7.29 (d, *J* = 8.8 Hz, 2Hmaj), 7.14 (d, *J* = 8.8 Hz, 2Hmin), 6.98 (q, *J* = 9.2 Hz, 4Hmaj and 4Hmin), 3.84–3.80 (m, 1Hmaj), 3.82 (s, 3Hmaj and 3Hmin), 3.44 (dd, *J* = 6.0, 9.6 Hz, 1Hmin), 2.96 (dd, *J* = 9.6, 18.8 Hz, 1Hmaj), 2.71 (dd, *J* = 9.2, 18.4 Hz, 1Hmin), 2.57 (dd, *J* = 5.6, 18.8 Hz, 1Hmin), 2.52 (dd, *J* = 4.8, 19.2 Hz, 1Hmaj), 1.84 (s, 3Hmin), 1.78 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 201.0 (min), 199.0 (maj), 176.4 (min), 176.3 (maj), 174.2, 135.5, 132.3, 130.5, 129.5, 128.7, 128.2 (min), 127.9 (maj), 127.4 (maj), 127.1 (min), 122.6, 56.5 (min), 56.0 (maj), 46.4 (min), 45.0 (maj), 32.6 (min), 32.1 (maj), 19.6 (min), 19.7 (maj). HRMS (EI): exact mass calculated for $[M]^+$($C_{20}H_{19}NO_4$) requires *m*/*z* 337.1314, found *m*/*z* 337.1313. The enantiomeric excess was determined by HPLC. [AS–H column, 240 nm, *n*-hexane–EtOH = 4 : 1, 0.8 mL min^{-1}.]: 28.2 min (major 1), 39.9 min (minor 1), ee = 85%; 46.4 min (major 2), 65.5 min (minor 2), ee = 93%.

2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-phenylpropanal (7i). The product was obtained in 93% yield, white solid. Mp 109–113 °C; $[\alpha]_D^{26}$ = +80.3° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.77 (s, 1Hmin), 9.68 (s, 1Hmaj), 7.48–7.36 (m, 5Hmaj and 5Hmin), 7.28 (d, *J* = 7.2 Hz, 2Hmaj and 2Hmin), 7.19–7.00 (m, 2Hmaj and 2Hmin), 3.81 (dd, *J* = 4.4, 9.6 Hz), 3.42 (dd, *J* = 6.0, 9.2 Hz, 1Hmin), 2.99 (dd, *J* = 9.2, 19.2 Hz), 2.70 (dd, *J* = 9.2, 18.8 Hz, 1Hmin), 2.58 (dd, *J* = 6.0, 19.2 Hz, 1Hmin), 2.55 (dd, *J* = 4.8, 19.2 Hz, 1Hmaj), 1.87 (s, 3Hmin), 1.79 (s, 3Hmaj). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 201.0 (min), 199.0 (maj), 176.2, 174.2, 135.4, 134.6, 133.0 (min), 132.6 (maj), 130.0, 129.5 (maj), 129.4 (min), 128.9 (maj), 128.8 (min), 128.7 (maj), 128.5 (min), 127.4 (maj), 127.1 (min), 126.9 (min), 126.7 (maj), 124.9 (min), 124.6 (maj), 56.5 (min), 55.9 (maj), 46.4 (min), 45.1 (maj), 32.7 (min), 32.1 (maj), 19.5 (min), 16.7 (maj). HRMS (EI): exact mass calculated for $[M]^+$ ($C_{19}H_{16}ClNO_3$) requires *m*/*z* 341.0819, found *m*/*z* 341.0813. The enantiomeric excess was determined by HPLC. [IA column, 220 nm, *n*-hexane–EtOH = 4 : 1, 1.0 mL min^{-1}.]: 25.5 min (minor 1), 33.5 min (major 1), ee = 73%; 36.2 min (major 2), 53.4 min (minor), ee = 94%.

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