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Chiral primary amine thiourea promoted highly enantioselective Michael reactions of isobutylaldehyde with maleimides

Jian-Fei Bai [a,b], Lin Peng [a,b], Liang-liang Wang [a,b], Li-Xin Wang [a,*], Xiao-Ying Xu [a,*]

[a] Key Laboratory of Asymmetric Synthesis & Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, PR China
[b] Graduate School of Chinese Academy of Sciences, Beijing 100039, PR China

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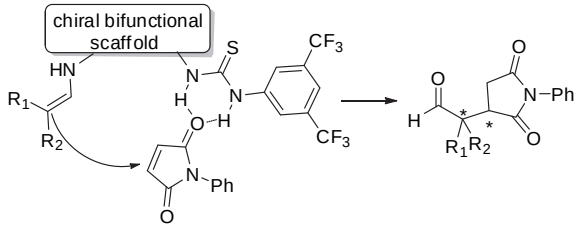
ABSTRACT

Chiral primary amine thiourea catalysts were first successfully applied to promote Michael addition of isobutyraldehyde to maleimides. A variety of *N*-aryl and *N*-aliphatic maleimides provided Michael adducts in excellent yields (up to 98%) and enantioselectivities (up to 99% ee) with 5 mol % catalyst.

1. Introduction

Michael reaction is one of the most efficient carbon–carbon bond formation reactions in organic chemistry and much attention have focused on this organocatalytic reaction.[1] To the best of our knowledge, the acceptors in this powerful type of strategy involved enones,[2] nitroalkenes,[3] and unsaturated imides.[4,5] Asymmetric conjugate addition of nucleophile to maleimides[5] has been studied extensively for it is a straightforward method to access synthetically and biologically interesting building blocks and nature products, such as substituted succinimides and functionalized pyrrolidines.[6] The donors of Michael reaction with maleimides included 1,3-dicarbonyl compounds,[5f–i] 2-mercaptobenzaldehydes,[5j] dicyanoolefins,[5k] azlactones,[5l] ketones,[7] and aldehydes.[8] In 2007, Córdova reported the first highly enantioselective addition of unmodified aldehydes to maleimides employing chiral diphenylprolinol silyl ether.[8] However, the addition of α,α-disubstituted aldehydes to maleimides, such as isobutylaldehyde, was rarely reported. Therefore, catalytic asymmetric Michael addition of isobutylaldehyde to maleimides remains a challenge, and both stereoselectivity and substrate scope are highly desirable to explore.

Bifunctional thiourea catalysts, which were powerful tools to simultaneously activate both donors and acceptors, have been investigated extensively in asymmetric Michael addition.[9] Primary amines-thioureas are proved to be effective in Michael addition[10] because primary amine was suitable for the generation of nucleophilic enamines, which could lead to an efficient addition to electron-deficient alkenes. Inspired by this concept, we envision that chiral primary amine-thioureas should be suitable catalysts for the addition of isobutylaldehyde to maleimides, affording the corresponding optically active desired products via a postulated transition state (TS) as shown in Scheme 1. As a part of our continuing interests in asymmetric synthesis,[11] herein we wish to report the enantioselective conjugate addition of isobutylaldehyde to maleimides promoted by chiral primary amine thiourea in excellent yields (up to 98%) and enantioselectivities (up to 99% ee).[12]



Scheme 1. Proposed transition state.

2. Results and discussion

The direct Michael reaction of isobutyraldehyde (**1a**) with *N*-phenylmaleimide (**2a**) at room temperature was used as a model

* Corresponding authors. Tel./fax: +86 28 85255208; e-mail addresses: wlxioc@cioc.ac.cn (L.-X. Wang), xuxy@cioc.ac.cn (X.-Y. Xu).

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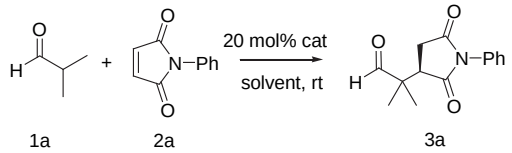
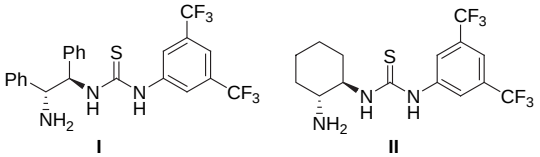
case to determine the asymmetric reaction conditions and the results were summarized in Table 1. To our delight, the model reaction was performed smoothly in CH_2Cl_2 catalyzed by 20 mol % chiral primary amine thiourea catalyst. When the reaction was promoted by catalyst **I** with (1*R*,2*R*)-1,2-diphenyldiamine, moderate yield (84%) and enantioselectivity (87% ee) were obtained (Table 1, entry 1). In contrast, catalyst **II** with (*R*,*R*)-1,2-cyclohexanediamine as chiral scaffold afforded excellent ee value (99% ee) and yield (98%, Table 1, entry 2), and it was selected for further optimization.

Table 1
Organocatalytic enantioselective Michael reaction between isobutylaldehyde (**1a**) and maleimide (**2a**)[a]





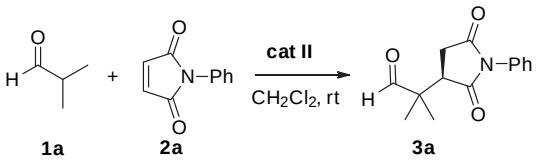
Entry	Catalyst	Solvent	Yield[b] (%)	Ee[c,d] (%)
1	**I**	CH_2Cl_2	84	87
2	**II**	CH_2Cl_2	98	99
3	**II**	$CHCl_3$	95	99
4	**II**	Toluene	96	99
5	**II**	CH_3CN	90	74
6	**II**	THF	96	92
7	**II**	CH_3OH	98	5

[a] Unless otherwise specified, all reactions were carried out with aldehyde (**1a**, 0.40 mmol), *N*-phenylmaleimide (**2a**, 0.20 mmol), and the catalyst (0.04 mmol) in solvent (0.5 mL) at rt for 5 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] The absolute configuration of the product was determined as *R* by comparing with reported data.[8]

Next, the effect of the solvent was investigated with 20 mol % catalyst **II** at room temperature and the results were listed in Table 1. This transformation was carried out well in all solvents and gave excellent yields (90–98%). It was found that solvents have remarkable effects on the enantioselectivities.

Aprotic solvents such as CH_2Cl_2, $CHCl_3$, toluene, CH_3CN, and THF gave good to excellent enantioselectivities (74–99% ee, Table 1, entries 2–6), whereas protic solvent such as CH_3OH gave a low enantioselectivity (5%, Table 1, entry 7). A survey of solvents revealed that CH_2Cl_2 was the best suitable solvent, which gave the highest ee (99%) with good yield (98%) (Table 1, entry 2). The effect of the catalyst loading was also evaluated and the results were summarized in Table 2. Lowering the catalyst loading did not affect the enantioselectivities, whereas slightly sacrificed the yield despite prolonging the reaction time. In the presence of 5 mol % catalyst, the reaction finished nearly in 8 h and gave the corresponding adduct **3a** with nearly the same yield (98%) and enantioselectivity (99% ee) as in the presence of 20 mol % catalyst **II** (Table 2, entry 4 vs entry 1). Notably, the presence of 1 mol % of catalyst **II** is sufficient to afford the reaction in a good yield (85%) and excellent enantioselectivity (99% ee, Table 2, entry 6). Based on all of the above results, a set of acceptable reaction conditions, 2.0 equiv **1a** and 1.0 equiv **2a** in 0.5 mL CH_2Cl_2 with 5 mol % catalyst **II** at room temperature were established. After having established the optimal reaction conditions, we expanded the optimal protocol to this catalytic system with a variety of maleimides and the results were listed in Table 3. The maleimides included those bearing electron-withdrawing and electron-donating substituents on the aryl ring, as well as *N*-aliphatic maleimides. The Michael addition reactions were performed smoothly under the optimal reaction conditions and all the substrates gave excellent yields (up to 98%) and enantioselctivities (up to 99% ee). Various substituted *N*-phenyl maleimides **2a**–**2i** (Table 3, entries 1–9) gave the desired adducts **3a**–**3i** in excellent yields (82–99%) and enantioselectivities (95–99% ee). Notably, the reaction with *N*-aliphatic substituted maleimides as substrate also worked well (Table 3, entries 10 and 11) and afforded excellent results (up to 98% yield, 99% ee). Encouraged by the above results, the scope of aldehyde was investigated by using **2a** as acceptor. The conversion was also underwent well and provided the corresponding product in moderate yield (55%) and excellent

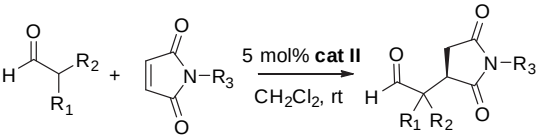
Table 2
Effect of catalyst loading for the Michael reactions of isobutylaldehyde (**1a**) with maleimides (**1b**)[a]



Entry	Catalyst loading (mol %)	Time (h)	Yield[b] (%)	Ee[c] (%)
1[a]	20	5	98	99
2[a]	15	6	98	99
3[a]	10	7	98	99
4[a]	5	8	98	99
5[d]	2	15	91	99
6[d]	1	24	85	99

[a] Unless otherwise specified, all reactions were carried out with aldehyde (**1a**, 0.40 mmol), *N*-phenylmaleimide (**2a**, 0.20 mmol), and the catalyst in CH_2Cl_2 (0.5 mL) at rt.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] Reactions were carried out with *N*-phenylmaleimide in 1 mmol.

Table 3
Scope of organocatalytic conjugates addition of isobutyraldehyde to maleimides[a]

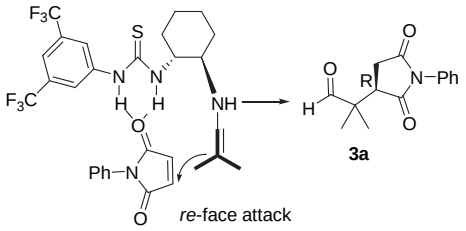


Entry	R_1	R_2	R_3	Product	Yield[b] (%)	dr[c]	Ee[d] (%)
1[e]	CH_3	CH_3 **1a**	C_6H_5 **2a**	**3a**	98	—	99
2	CH_3	CH_3 **1a**	4-$CH_3C_6H_4$ **2b**	**3b**	94	—	99
3	CH_3	CH_3 **1a**	4-$CH_3OC_6H_4$ **2c**	**3c**	82	—	99
4	CH_3	CH_3 **1a**	4-FC_6H_4 **2d**	**3d**	94	—	99
5	CH_3	CH_3 **1a**	4-ClC_6H_4 **2e**	**3e**	93	—	99
6	CH_3	CH_3 **1a**	3-FC_6H_4 **2f**	**3f**	97	—	99
7	CH_3	CH_3 **1a**	3-$NO_2C_6H_4$ **2g**	**3g**	92	—	99
8	CH_3	CH_3 **1a**	3-OHC_6H_4 **2h**	**3h**	98	—	95
9	CH_3	CH_3 **1a**	2-FC_6H_4 **2i**	**3i**	97	—	99
10	CH_3	CH_3 **1a**	CH_3 **2j**	**3j**	94	—	99
11	CH_3	CH_3 **1a**	Bn **2k**	**3k**	98	—	99
12	$-CH_2(CH_2)_3CH_2-$ **1b**		C_6H_5 **2a**	**3l**	55	—	98
13	H	CH_3 **1c**	C_6H_5 **2a**	**3m**	98	1:1.3	96/97
14	Bn	CH_3 **1d**	C_6H_5 **2a**	**3n**	85	1:1	93/94

[a] Unless otherwise specified, all reactions were carried out with aldehyde (0.60 mmol), maleimide (0.30 mmol), and the catalyst **II** (5 mol %) in CH_2Cl_2 (0.5 mL) at rt for 6 h.
[b] Isolated yields.
[c] Determined by HPLC.
[d] Determined by chiral HPLC analysis.
[e] Reaction was carried out with N-phenylmaleimide in 0.2 mmol.

enantioselectivity (98% ee, Table 3, entry 12). Additionally, propanal and 2-methyl-3-phenylpropanal were also investigated, and afforded excellent enantioselectivities and low diastereoselectivities (Table 3, entries 13 and 14).

Based on the configuration of **3a**, a plausible transition state model was proposed. As outlined in Scheme 2, isobutyraldehyde (**1a**) and *N*-phenylmaleimide (**2a**) would be activated by primary amine and thiourea simultaneously. Then Michael addition could take place from *re*-face of **1a**, give the adduct **3a** with (*R*)-configuration.



Scheme 2. Transition state model of Michael addition.

3. Conclusion

In conclusion, chiral primary amine thiourea catalysts were successfully applied to promote Michael addition of isobutyraldehyde to maleimides. It provided Michael adducts in excellent yields (up to 98%) and enantioselectivities (up to 99% ee) with 5 mol% catalyst loading merely.

4. Experimental

4.1. General

All reagents were obtained from commercial supplier without further purification. Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th ed.[13] NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz (Bruker Avance). Chemical shifts (δ) are reported in parts per million downfield from $CDCl_3$ (δ=7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0 ppm) for ^{13}C NMR spectroscopy. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light. Enantiomeric excess was determined by HPLC analysis on Chiralpak OD-H, AD-H, AS-H.

4.2. Representative experimental procedure for Michael addition

In a typical experiment, isobutyraldehyde (0.60 mmol, 2 equiv), maleimides (0.30 mmol, 1 equiv), and the catalyst (0.015 mmol, 0.05 equiv) in CH_2Cl_2 (0.5 mL) were magnetically stirred at room temperature for 6 h (monitored by TLC). The corresponding product was obtained after column chromatography (silica gel, eluent PE/EtOAc=4/1). All products were identified by spectroscopic data (^{1}H, ^{13}C NMR and HRMS).

*4.2.1. 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methyl-propionaldehyde (**3a**).* The product was obtained in 98% yield, white bright solid. $[\alpha]_D^{20}$ +4.1 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (s, 1H), 7.40 (m, 3H), 7.27 (d, *J*=7.2 Hz, 2H), 3.14(dd, *J*=5.5, 9.4 Hz, 1H), 2.95 (dd, *J*=9.5, 18.2 Hz, 1H), 2.60 (dd, *J*=5.4, 18.2 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.6, 176.8, 174.7, 131.8, 129.1, 128.6, 126.5, 48.4, 44.9, 31.7, 20.2, 19.5; HRMS (ESI) calcd for $C_{14}H_{15}NNaO_3$ (M+Na) 268.0944, found 268.0948. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=17.4 min, t_R (major)=21.3 min.

*4.2.2. 2-(2,5-Dioxo-1-p-tolylpyrrolidin-3-yl)-2-methylpropanal (**3b**).* The product was obtained in 94% yield, white bright solid. $[\alpha]_D^{20}$ +6.2 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (s, 1H), 7.25 (d, *J*=7.95 Hz, 2H), 7.13 (d, *J*=8.13 Hz, 2H), 3.12 (dd, *J*=5.4, 9.4 Hz, 1H), 2.93 (dd, *J*=9.51, 18.22 Hz, 1H), 2.57 (dd, *J*=5.37, 18.2 Hz, 1H), 2.36 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 176.9, 174.8, 138.7, 129.7, 129.1, 126.2, 48.3, 44.9, 31.6, 21.1, 20.15, 19.3; HRMS (ESI) calcd for $C_{15}H_{17}NNaO_3$(M+Na) 282.1101, found 282.1103. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=18.2 min, t_R (major)=21.1 min.

*4.2.3. 2-(1-(4-Methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-methyl-propanal (**3c**).* The product was obtained in 82% yield, white bright solid. $[\alpha]_D^{20}$ +6.0 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.50 (s, 1H), 7.17 (d, *J*=8.82 Hz, 2H), 6.95 (d, *J*=8.82 Hz, 2H), 3.80 (s, 3H), 3.11 (dd, *J*=5.4, 9.4 Hz, 1H), 2.93 (dd, *J*=9.48, 18.24 Hz, 1H), 2.57 (dd, *J*=5.37, 18.2 Hz, 1H), 1.30 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 176.1, 174.99, 159.5, 127.7, 124.3, 114.4, 55.4, 48.4, 44.9, 31.7, 20.2, 19.4; HRMS (ESI) calcd for $C_{15}H_{17}NNaO_4$ (M+Na) 298.1050, found 298.1059. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak AS-H column, hexane/2-propanol=80/20, 1 mL/min, 210 nm), t_R (minor)=53.4 min, t_R (major)=58.7 min.

*4.2.4. 2-(1-(4-Fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methyl-propanal (**3d**).* The product was obtained in 94% yield, white bright solid. $[\alpha]_D^{20}$ +2.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.48(s, 1H), 7.25 (m, 2H), 7.15(m, 2H), 3.09 (dd, *J*=5.49, 9.49 Hz, 1H), 2.93 (dd, *J*=9.51, 18.2 Hz, 1H), 2.58 (dd, *J*=5.46, 18.2 Hz, 1H), 1.32 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 176.8, 174.6, 162.1, 128.3, 127.6, 116.1, 48.5, 44.8, 31.6, 20.4, 19.6; HRMS (ESI) calcd for $C_{14}H_{14}FNNaO_3$ (M+Na) 286.0850, found 286.0853. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=17.0 min, t_R (major)=29.8 min.

*4.2.5. 2-(1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methyl-propanal (**3e**).* The product was obtained in 93% yield, white bright solid. $[\alpha]_D^{20}$ +3.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 7.42 (d, *J*=8.67 Hz, 2H), 7.23 (d, *J*=8.7 Hz, 2H), 3.08 (dd, *J*=5.52, 9.48 Hz, 1H), 2.92 (dd, *J*=9.51, 18.18 Hz, 1H), 2.57 (dd, *J*=5.49, 18.18 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 176.6, 174.4, 134.3, 130.3, 129.2, 127.7, 48.5, 44.8, 31.8, 20.4, 19.6; HRMS (ESI) calcd for $C_{14}H_{14}ClNNaO_3$ (M+Na) 302.0554, found 302.0560. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=17.2 min, t_R (major)=29.7 min.

*4.2.6. 2-(1-(3-Fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methyl-propanal (**3f**).* The product was obtained in 97% yield, white bright solid. $[\alpha]_D^{20}$ +5.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 7.41 (m, 1H), 7.06 (m, 3H), 3.08 (dd, *J*=5.52, 9.49 Hz, 1H), 2.93 (dd, *J*=9.54, 18.2 Hz, 1H), 2.57 (dd, *J*=5.52, 18.22 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 176.5, 174.3, 162.5, 133.0, 130.2, 122.1, 115.6, 114.0, 48.5, 44.8, 31.7, 20.3, 19.6; HRMS (ESI) calcd for $C_{14}H_{14}FNNaO_3$ (M+Na) 286.0850, found 286.0858. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=14.1 min, t_R (major)=17.3 min.

*4.2.7. 2-Methyl-2-(1-(3-nitrophenyl)-2,5-dioxopyrrolidin-3-yl) propanal (**3g**).* The product was obtained in 92% yield, white bright solid. $[\alpha]_D^{20}$ −2.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.45 (s,

1H), 8.2 (m, 2H), 7.63 (m, 2H), 3.12 (dd, *J*=5.58, 9.45 Hz, 1H), 2.99 (dd, *J*=9.54, 18.14 Hz, 1H), 2.57 (dd, *J*=5.46, 16.8 Hz, 1H), 1.36 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.6, 176.3, 173.9, 148.5, 132.9, 132.4, 129.8, 123.2, 121.8, 48.9, 44.9, 32.0, 20.7, 20.2; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_5$ 313.0913, found 313.0915. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=26.7 min, t_R (major)=32.1 min.

*4.2.8. 2-(1-(3-Hydroxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (**3h**).* The product was obtained in 98% yield, white bright solid. $[\alpha]_D^{20}$ +2.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.49 (s, 1H), 7.29 (m, 1H), 6.81 (m, 3H), 3.12 (m, 1H), 2.95 (m, 1H), 2.60 (dd, *J*=5.4, 18.23 Hz, 1H), 1.33 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 176.6, 174.6, 157.6, 132.4, 129.5, 117.2, 115.9, 113.8, 48.1, 44.7, 31.3, 20.1, 18.8; HRMS (ESI) calcd for $C_{14}H_{15}NNaO_4$ (M+Na) 284.0893, found 284.0899. Enantiomeric excess: 95%, determined by chiral HPLC analysis (Chiralpak AS-H column, hexane/2-propanol=80/20, 1 mL/min, 210 nm), t_R (minor)=47.5 min, t_R (major)=82.5 min.

*4.2.9. 2-(1-(2-Fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (**3i**).* The product was obtained in 97% yield, white bright solid. $[\alpha]_D^{20}$ +4.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.49 (s, 1H), 7.40 (m, 1H), 7.24 (m, 3H), 3.18 (m, 1H), 2.98 (dd, *J*=9.51, 18.36 Hz, 1H), 2.62 (dd, *J*=4.44, 18.26 Hz, 1H), 1.33 (s, 3H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.6, 173.9, 158.9, 155.6, 130.9, 129.2, 124.6, 116.5, 45.1, 31.7, 20.4, 19.8, 19.3, 18.8; HRMS (ESI) calcd for $C_{14}H_{14}FNNaO_3$ (M+Na) 286.0850, found 286.0863. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=17.5 min, t_R (major)=23.1 min.

*4.2.10. 2-Methyl-2-(1-methyl-2,5-dioxopyrrolidin-3-yl) propanal (**3j**).* The product was obtained in 94% yield, colorless oil. $[\alpha]_D^{20}$ −11.7 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 3.00 (dd, *J*=5.43, 9.24 Hz, 1H), 2.93 (s, 3H), 2.77 (dd, *J*=9.3, 18.2 Hz, 1H), 2.40 (dd, *J*=5.34, 18.2 Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.9, 177.7, 175.8, 49.8, 44.9, 31.3, 24.7, 19.9, 18.9; HRMS (ESI) calcd for $C_9H_{13}NNaO_3$ (M+Na) 206.0788, found 206.0789. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak AS-H column, hexane/2-propanol=80/20, 1 mL/min, 210 nm), t_R (major)=16.5 min, t_R (minor)=19.8 min.

*4.2.11. 2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (**3k**).* The product was obtained in 98% yield, white bright solid. $[\alpha]_D^{20}$ −9.8 (*c* 1.2, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 7.28 (m, 5H), 4.61 (dd, *J*=14.1, 17.9 Hz, 2H), 3.00 (dd, *J*=5.41, 9.30 Hz, 1H), 2.78 (dd, *J*=9.35, 18.2 Hz, 1H), 2.42 (dd, *J*=5.37, 18.25 Hz, 1H), 1.14 (s, 3H), 1.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.6, 177.3, 175.3, 135.6, 128.5, 127.8, 47.9, 44.8, 42.3, 31.3, 19.8, 18.9; HRMS (ESI) calcd for $C_{15}H_{17}NNaO_3$ (M+Na) 282.1101, found 282.1102. Enantiomeric excess: 99%, determined by chiral HPLC analysis (Chiralpak AD-H column, hexane/2-propanol=80/20, 1 mL/min, 220 nm), t_R (minor)=8.2 min, t_R (major)=17.5 min.

*4.2.12. 1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclohexanecarbaldehyde (**3l**).* The product was obtained in 55% yield, white bright solid. $[\alpha]_D^{20}$ +4.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (s, 1H), 7.45 (m, 3H), 7.27 (m, 2H), 3.20 (dd, *J*=5.97, 9.26 Hz, 1H), 2.83 (m, 1H), 2.66 (dd, *J*=5.94, 18.15 Hz, 1H), 1.94 (m, 3H), 1.60 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.5, 177.0, 174.7, 131.9, 129.1, 128.6, 126.6, 52.2, 42.7, 31.5, 28.6, 28.0, 25.1, 21.3, 21.2; HRMS (ESI) calcd for $C_{17}H_{19}NNaO_3$ (M+Na) 308.1257, found 308.1260. Enantiomeric excess: 98%, determined by chiral HPLC analysis (Chiralpak OD-H column, hexane/2-propanol=75/25, 0.9 mL/min, 210 nm), t_R (minor)=19.4 min, t_R (major)=24.5 min.

*4.2.13. 2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-propionaldehyde (**3m**)*[8]. The product was obtained in 98% yield, white bright solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1H), 7.50–7.24 (m, 5H), 3.44–3.36 (m, 1H), 3.18 (dd, *J*=7.6, 3.6 Hz, 1H), 3.03 (dd, *J*=18.4, 9.6 Hz, 1H), 2.52 (dd, *J*=18.4, 5.2 Hz, 1H), 1.33 (d, *J*=7.6 Hz, 3H); The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, hexane/2-propanol=80/20, 0.8 mL/min, 210 nm), major diastereomer: t_R (minor)=14.91 min, t_R (major)=23.5 min; minor diastereomer: t_R (minor)=16.45 min, t_R (major)=18.64 min.

*4.2.14. 2-(2, 5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methyl-3-phenylpropanal (**3n**).* The product was obtained in 85% yield, white bright solid. ^{1}H NMR (30 MHz, $CHCl_3$): δ 9.61(s, 1H), 7.50–7.21 (m, 10H), 3.34 (t, 1H), 3.14 (m, 1H,), 3.07(m, 2H), 2.66 (dd, *J*=4.8 Hz, 17.6 Hz, 1H), 1.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.2, 178.0, 175.0, 136.7, 132.1–126.5 (ArC), 53.5, 38.5, 32.7, 31.2, 29.6; HRMS (ESI) calcd for $C_{20}H_{19}NNaO_3$ (M+Na) 344.1367, found 344.1360. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, hexane/2-propanol=80/20, 0.8 mL/min, 210 nm), major diastereomer: t_R (minor)=13.9 min, t_R (major)=19.82 min; minor diastereomer: t_R (minor)=18.85 min, t_R (major)=24.4 min.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.044. These data include MOL files and InChIKeys of the most important compounds described in this article.

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