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Calixarene-based chiral primary amine thiourea promoted highly enantioselective asymmetric Michael reactions of α,α-disubstituted aldehydes with maleimides

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ABSTRACT

Calix[4]arene based chiral bifunctional thiourea-primary amines have been shown to act as effective catalysts for the Michael addition of aldehydes to maleimides for the first time. The corresponding adducts were generally obtained preferentially in (*R*)- or (*S*)-forms with high yields (up to 99%) and with high to excellent enantioselectivities (up to 98% ee).

1. Introduction

Organocatalysis has emerged as an extremely useful method for the synthesis of potentially important optically active compounds. In addition to chiral metal complexes, enzymes, and other biocatalysts, organocatalysts have been employed as chiral tools to promote a variety of asymmetric reactions for many years.[1]

Organocatalysts offer a number of advantages in terms of widespread applicability, operational simplicity, environmental compatibility, reusability, high efficiency, and selectivity.[2] Therefore, the design and synthesis of new effective catalysts is a rapidly growing and competitive research area in synthetic organic chemistry.

The catalytic asymmetric Michael addition is one of the most important approaches to carbon–carbon bond formation in asymmetric synthesis. To date, many asymmetric Michael additions of nucleophiles to a variety of Michael acceptors promoted by chiral organocatalysts have been reported.[3] However, the use of maleimides as Michael acceptors is relatively rare. The Michael addition of carbonyl compounds to maleimides is of particular interest to provide α-substituted succinimides, which play an important role as precursors of biologically active compounds or chiral building blocks in synthetic and medicinal chemistry.

In 2007, the asymmetric Michael reaction of maleimides with aldehydes was first described by Cordova et al. using diphenylprolinol silyl ether as a catalyst and moderate chemical yield and enantioselectivity were observed with sterically hindered α,α-disubstituted aldehydes such as isobutyraldehyde.[4] Since then, a number of research groups[5] have reported highly enantioselective Michael additions of α,α-disubstitued aldehydes to maleimides that were catalyzed by primary amine-thiourea catalysts derived from 1,2-cyclohexanediamine as the chiral source. Recently, Miura et al. have described the asymmetric Michael reactions of maleimides with aldehydes by a recyclable fluorous organocatalyst.[6]

Calixarenes, cyclic oligomers of phenolic units linked through the *ortho*-positions, are an interesting class of macrocycles.[7] The introduction of chiral substituents into the calixarene macrocyclic ring either by attaching chiral units at one of the calix rims, or by synthesizing 'inherently' chiral derivatives could, in turn, lead to chirality of the artificial receptors.[8] Thus, chiral calixarene derivatives obtained in this way might be good candidates as chiral catalysts for the organocatalytic preparation of chiral compounds. Despite the increasing use of chiral calixarenes for the separation,[9] recognition,[10] and discrimination[11] of biologically active compounds, only a few calixarene derivatives have been reported as organocatalysts[12,13] for asymmetric transformations.

To the best of our knowledge, no examples have been reported so far on the organocatalytic Michael reaction of isobutyraldehyde with maleimides catalyzed by calix[4]arenes.

2. Results and discussion

Over the course of our studies on the synthesis of chiral receptors equipped with various functionalities to aid their catalytic activities[14] and enantiomeric recognition properties,[15] we recently synthesized two calix[4]arene-based chiral receptors[16] and used them as catalysts in Michael reactions of aldehydes with β-nitroolefins (Scheme 1). Herein we report the enantioselective Michael addition of isobutyraldehyde to maleimides promoted by chiral calix[4]arene derivatives bearing two primary amine-thiourea units in excellent yields (up to 99%) and enantioselectivities (up to 98% ee).

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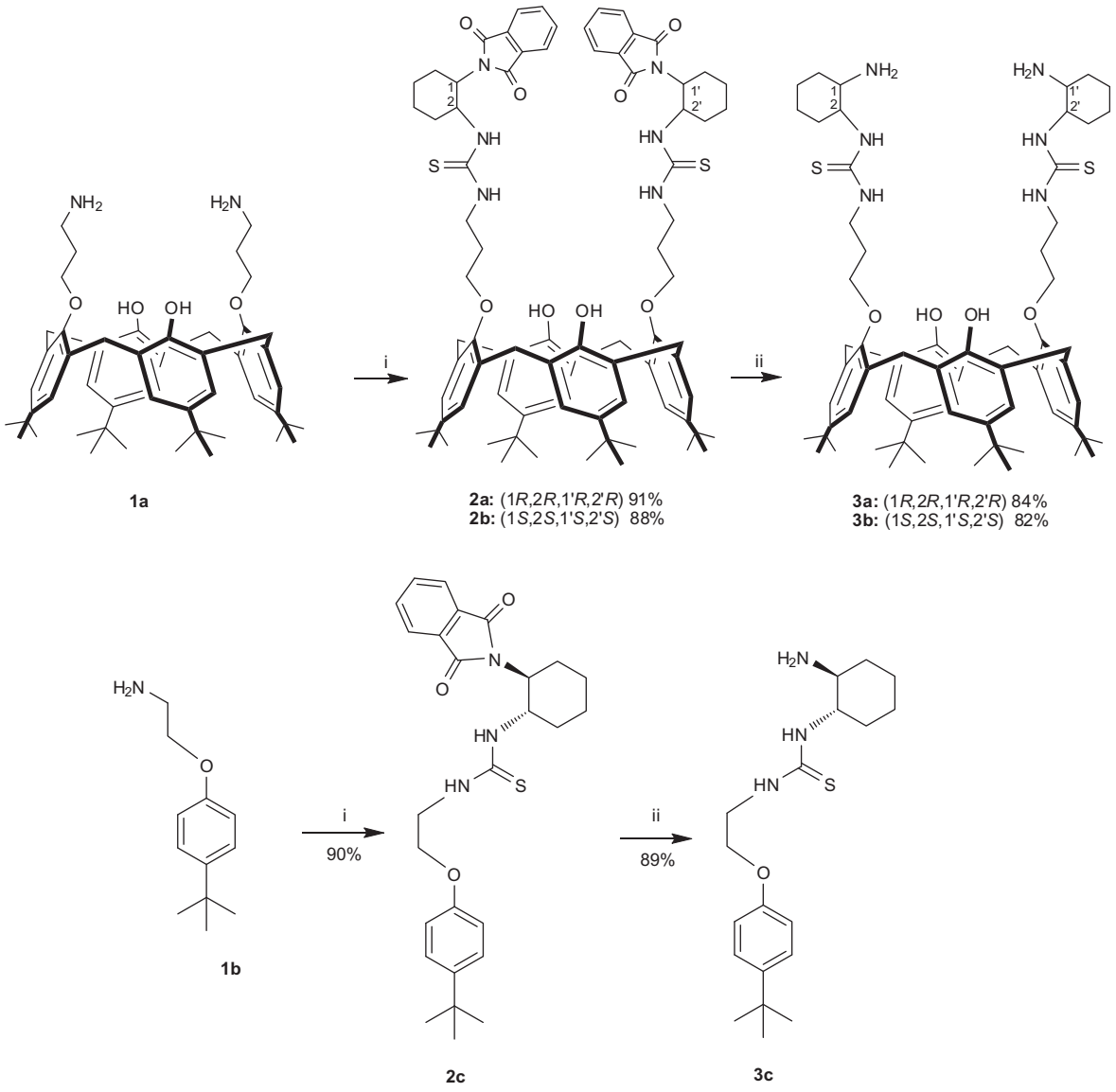


Scheme 1. Synthesis of calix[4]arene-based primary amine thiourea organocatalysts **3a**, **3b** (top), and *p-tert*-butylphenol analogue **3c** (bottom). Reagents and conditions: (i) chiral isothiocyanate, CH_2Cl_2, rt, 24 h; (ii) $N_2H_4{\cdot}H_2O$, EtOH, reflux.

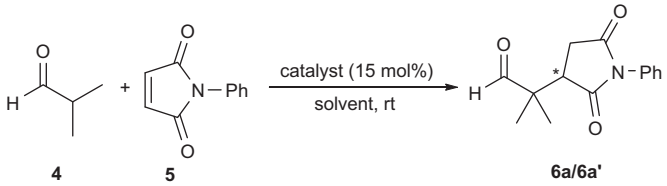
We initially focused on solvent effects in the Michael reactions at ambient temperature; the Michael addition of isobutyraldehyde **4** to *N*-phenylmaleimide **5** was selected as a model reaction in the presence of organocatalysts (15 mol %) **3a**–**3c**. As summarized in Table 1, the Michael addition proceeded smoothly in CH_2Cl_2 to afford the desired products in up to 99% yields and with excellent stereoselectivities (83–95% ee) (Table 1, entries 1–3) at room temperature, whereas using nonpolar solvents, such as CCl_4 and toluene resulted in similar yields and enantioselectivities (Table 1, entries 4 and 5). Furthermore, the use of $CHCl_3$, Et_2O, EtOAc, THF, and 1,2-DCE slightly decreased the reactivity and enantioselectivity (Table 1, entries 6–10), whereas using protic solvents such as *i*PrOH or MeOH afforded the Michael product in lower yields and enantioselectivity (Table 1, entries 14 and 15).

Having identified the best solvent and reaction medium, we next examined the effect of catalyst loading on the reaction. Catalyst loadings, ranging from 10 to 2 mol %, were evaluated. Excellent chemical yields without a compromise to the enantioselectivity of the reaction were obtained when using catalyst loadings of 10 mol % (Table 2, entry 1). However, decreasing the catalyst loading to 5 and 2 mol % reduced the reaction rate along with a loss of the enantiomeric excess (Table 2, entries 2 and 3).

The addition of a catalytic amount of Brønsted acid may promote the formation of the enamine species and subsequently improve reactivity. In order to test this, various organic acids were used as additives (10 mol %) in the reaction mixture. A slight decrease in enantioselectivities and chemical yields were observed when the reaction was carried out in the presence of benzoic acid, acetic acid, phenyl glycine, or (*S*)-1,1′-bi-2-naphthol (Table 2, entries 4, 7, 9, and 10). Adduct **6a**′ was obtained in trace amounts when 10 mol % of TFA or DMAP was used (Table 2, entries 8 and 11).

With the optimal reaction conditions in hand, we next probed the scope of the chiral calix[4]arene **3a** and **3b**-catalyzed reaction with a set of aldehydes and maleimides (Table 3). All reactions were performed in CH_2Cl_2 in the presence of 10 mol % of catalyst **3a** or **3b**. Various aromatic substituted maleimides reacted well with aldehyde donors to give the desired Michael products **6b**/**6b**′–**6r**/**6r**′ in 55–99% yields and with different enantioselectivities (Table 3, entries 1–17). The results in Table 3 also indicate that

Table 1
Optimization of the asymmetric Michael addition of isobutyraldehyde **4** to *N*-phenylmaleimide **5** catalyzed by **3a–3c**[a]

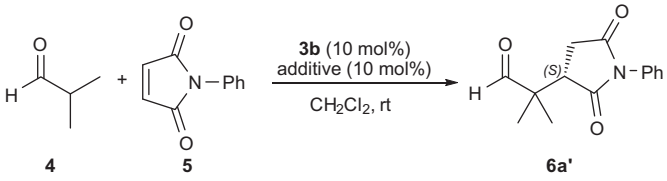


4 **5** **6a/6a'**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**3a**	CH_2Cl_2	0.5	99	92 (*R*)
2	**3b**	CH_2Cl_2	0.5	99	95 (*S*)
3	**3c**	CH_2Cl_2	2.5	76	83 (*S*)
4	**3b**	CCl_4	0.5	99	91 (*S*)
5	**3b**	Toluene	0.5	99	90 (*S*)
6	**3b**	$CHCl_3$	0.5	98	85 (*S*)
7	**3b**	Et_2O	0.5	94	84 (*S*)
8	**3b**	EtOAc	1.5	96	78 (*S*)
9	**3b**	THF	3	85	81 (*S*)
10	**3b**	1,2-DCE	0.5	98	86 (*S*)
11	**3b**	Acetonitrile	2	74	71 (*S*)
12	**3b**	1,4-Dioxane	3	82	73 (*S*)
13	**3b**	MTBE	2	87	70 (*S*)
14	**3b**	*i*-PrOH	6	45	45 (*S*)
15	**3b**	MeOH	6	30	17 (*S*)

[a] All reactions were carried out with isobutyraldehyde **4** (0.40 mmol), *N*-phenylmaleimide **5** (0.20 mmol), and the catalyst (0.03 mmol) in solvents (0.5 mL).
[b] Isolated yields after column chromatography on SiO_2.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] The absolute configuration was determined by comparison with the literature data.

Table 2
Screening of catalyst loading and additives for **3b**-catalyzed addition of isobutyraldehyde **4** to *N*-phenylmaleimide **5**[a]



4 **5** **6a'**

Entry	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	None	0.5	99	94
2[d]	None	1	92	91
3[e]	None	3	90	89
4	Benzoic acid	0.5	97	93
5[f]	Benzoic acid	3	98	93
6	Benzoic acid + H_2O	1	99	91
7	AcOH	1.5	95	87
8	TFA	24	<5	n.d.
9	Phenyl glycine	4.5	95	92
10	(*S*)-1,1′-Bi-2-naphthol	24	75	90
11	DMAP	24	<5	n.d.
12	DABCO	24	73	62

[a] Unless otherwise specified, all reactions were carried out with aldehyde **4** (0.40 mmol), *N*-phenylmaleimide **5** (0.20 mmol), the catalyst (0.02 mmol), and additive (0.02 mmol) in CH_2Cl_2 (0.5 mL).
[b] Isolated yields after column chromatography on SiO_2.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] 5 mol % catalyst used.
[e] 2 mol % catalyst used.
[f] Reaction performed at 4 °C.

the position and the electronic properties of the substituents on the aromatic rings of the maleimides had a limited influence on the stereoselectivity of the conjugate additions.

We next investigated the catalytic efficiency of a simpler primary amine–thiourea **3c** in order to confirm the role of the achiral calixarene platform of **3a** and **3b** in this reaction. The enantioselective Michael addition of isobutyraldehyde **4** to *N*-phenylmaleimide **5** in CH_2Cl_2, for 2.5 h afforded the (*S*)-Michael product in a lower yield and enantioselectivity (Table 1, entry 3) than the calixarene-based chiral primary amine–thiourea derivatives. As reported earlier,[17] these results showed that the presence of the bulky calixarene moiety of the thiourea and the phenolic hydroxy groups on the calixarene scaffold as acidic additives play a crucial role in helping increase the electrophilicity of maleimide and preorganising the reaction substrates.

Although the precise reaction mechanism to explain the high enantioselectivity observed in Michael additions catalyzed by calix[4]arene-based chiral primary amine–thiourea derivatives needs further study, we propose that the reaction proceeds via a dual activation model. The aldehyde is activated by the primary amine group of **3a** or **3b** through the enamine intermediate, while the thiourea moiety of the catalyst directs and activates the maleimide by hydrogen-bonding interactions simultaneously. The attack of this enamine from the *re*- or *si*-face of the maleimide leads to the formation of addition products **6** with an (*R*)- or (*S*)-configuration.

3. Conclusion

In conclusion, new calix[4]arene-based chiral bifunctional primary amine–thiourea catalysts **3a** and **3b** have been developed as efficient organocatalysts for the asymmetric Michael addition of aldehydes to maleimides. The reactions proceeded smoothly in CH_2Cl_2 at ambient temperature to give high yields (up to 99%) and *ee* (up to 98%) with broad substrate scope. Chiral catalyst **3a** preferentially furnished the (*R*)-enantiomer, whereas **3b** selectively produced the (*S*)-enantiomer. Further studies of this catalytic system in other asymmetric C–C bond forming processes are currently underway.

4. Experimental

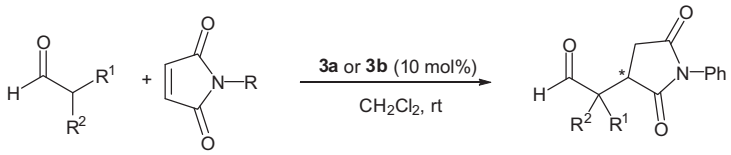
4.1. General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on Varian 400 and Bruker 400 instruments. Chemical shifts are reported in ppm. Data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), and coupling constants (Hz). Infrared (IR) spectra were recorded on a Perkin Elmer spectrum-100 FTIR spectrometer equipped with an ATR unit and are reported in wavenumbers (cm^{-1}). The HPLC measurements were carried out on Agilent 1100 equipment connected with Chiralpak Daicel AD-H, OD-H, and AS-H columns. Optical rotations were measured on an Atago AP-100 digital polarimeter using a 1 dm cell. Elemental analyses were performed using a Leco CHNS-932 analyzer. Analytical TLC was performed using Merck prepared plates (silica gel 60 F254 on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 Mesh). All starting materials and reagents used were of standard analytical grade from Fluka, Merck, Aldrich, Acros, or TCI and used without further purification. Dichloromethane was dried ($CaCl_2$), distilled from CaH_2, and stored over molecular sieves. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

4.2. Synthesis of catalysts

Chiral catalysts **3a–3c** were synthesized by following the literature procedure.[16]

Table 3
Scope of **3a** and **3b** promoted enantioselective conjugate addition reactions of aldehydes with maleimides[a]



Entry	R^1	R^2	R	Product	Yield[b] (%)	ee[c] (%)
1	CH_3	CH_3	4-$NO_2C_6H_4$	**6b/6b′**	96/98	88/90
2	CH_3	CH_3	Bn	**6c/6c′**	99/99	89/92
3	CH_3	CH_3	4-ClC_6H_4	**6d/6d′**	81/84	84/86
4	CH_3	CH_3	4-BrC_6H_4	**6e/6e′**	99/94	88/87
5	$-CH_2(CH_2)_3CH_2-$		C_6H_5	**6f/6f′**	74/72	86/89
6	$-CH_2(CH_2)_3CH_2-$		Bn	**6g/6g′**	79/84	90/92
7	$-CH_2(CH_2)_2CH_2-$		C_6H_5	**6h/6h′**	95/91	91/93
8	$-CH_2(CH_2)_2CH_2-$		Bn	**6i/6i′**	90/94	94/98
9	$-CH_2(CH_2)_2CH_2-$		4-BrC_6H_4	**6j/6j′**	61/64	84/87
10	$-CH_2(CH_2)_2CH_2-$		4-$NO_2C_6H_4$	**6k/6k′**	92/88	83/87
11	$-CH_2(CH_2)_2CH_2-$		4-ClC_6H_4	**6l/6l′**	86/82	88/92
12	C_2H_5	C_2H_5	C_6H_5	**6m/6m′**	88/91	77/87
13	C_2H_5	C_2H_5	4-BrC_6H_4	**6n/6n′**	59/57	84/90
14	C_2H_5	C_2H_5	Bn	**6o/6o′**	85/86	89/93
15	C_2H_5	C_2H_5	4-$NO_2C_6H_4$	**6p/6p′**	90/87	76/81
16	C_2H_5	C_2H_5	4-ClC_6H_4	**6q/6q′**	55/62	81/80
17	CH_3	$CH_3(CH_2)_2$	C_6H_5	**6r/6r′**	61/63	90/94 (1.2:1)[d]

[a] Unless otherwise specified, all reactions were carried out with aldehyde (0.40 mmol), maleimide (0.20 mmol), and the catalyst (0.02 mmol) in CH_2Cl_2 (0.5 mL).
[b] Isolated yields after column chromatography on SiO_2.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H, AD-H or AS-H).
[d] Diastereomeric ratio given in parentheses.

4.3. Representative procedure for the Michael addition

In a typical experiment, α,α-disubstituted aldehyde (0.40 mmol), maleimides (0.20 mmol), and catalyst (0.03 mmol, 15 mol%) in CH_2Cl_2 (0.5 mL) were stirred magnetically at room temperature until the maleimide was consumed (monitored by TLC). The corresponding product was obtained after column chromatography (silica gel, eluent *n*-hexane/EtOAc). The enantiomeric excess of the products was determined by chiral HPLC analysis using chiral columns. All products were identified by spectroscopic data. Racemic samples of the Michael adducts were prepared using racemic catalyst. Compounds **6a′–6i′**, **6m′** and **6r′** are known. The analytical and spectroscopic data are in accordance with those reported.

4.3.1. (*S*)-2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal 6a′[5a,b]

$[\alpha]_D^{25} = -3.2$ (*c* 0.8, $CHCl_3$); Enantiomeric excess: 95%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 75/25, 0.7 mL/min, λ = 210 nm), t_R (major) = 20.2 min, t_R (minor) = 26.3 min.

4.3.2. (*S*)-2-Methyl-2-(1-(4-nitrophenyl)-2,5-dioxopyrrolidin-3-yl)propanal 6b′[5a]

$[\alpha]_D^{25} = -2.9$ (*c* 0.9, $CHCl_3$); Enantiomeric excess: 90%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 80/20, 1.0 mL/min, λ = 254 nm), t_R (major) = 56.6 min, t_R (minor) = 71.7 min.

4.3.3. (*S*)-2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal 6c′[5a,b]

$[\alpha]_D^{25} = +11.6$ (*c* 0.8, $CHCl_3$); Enantiomeric excess: 92%, determined by chiral HPLC analysis (Chiralpak AD-H, hexane/*i*PrOH = 80/20, 0.6 mL/min, λ = 254 nm), t_R (major) = 15.5 min, t_R (minor) = 34.8 min.

4.3.4. (*S*)-2-(1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal 6d′[5b]

$[\alpha]_D^{25} = -2.4$ (*c* 1.0, $CHCl_3$); Enantiomeric excess: 86%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 75/25, 0.6 mL/min, λ = 254 nm), t_R (major) = 30.4 min, t_R (minor) = 56.7 min.

4.3.5. (*S*)-2-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal 6e′[5i]

$[\alpha]_D^{25} = -3.1$ (*c* 0.9, $CHCl_3$); Enantiomeric excess: 87%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 75/25, 0.6 mL/min, λ = 254 nm), t_R (major) = 30.8 min, t_R (minor) = 54.2 min.

4.3.6. (*S*)-1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclohexanecarbaldehyde 6f′[5i]

$[\alpha]_D^{25} = -0.7$ (*c* 0.8, $CHCl_3$); Enantiomeric excess: 89%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 75/25, 0.6 mL/min, λ = 254 nm), t_R (major) = 33.1 min, t_R (minor) = 44.3 min.

4.3.7. (*S*)-1-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)cyclohexanecarbaldehyde 6g′[5e]

$[\alpha]_D^{25} = +1.6$ (*c* 0.9, $CHCl_3$); Enantiomeric excess: 92%, determined by chiral HPLC analysis (Chiralpak AD-H, hexane/*i*PrOH = 80/20, 0.6 mL/min, λ = 254 nm), t_R (major) = 16.9 min, t_R (minor) = 26.6 min.

4.3.8. (*S*)-1-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)cyclopentanecarbaldehyde 6h′[5a]

$[\alpha]_D^{25} = +18.2$ (*c* 1.0, $CHCl_3$); Enantiomeric excess: 93%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 75/25, 0.5 mL/min, λ = 254 nm), t_R (major) = 43.2 min, t_R (minor) = 62.9 min.

4.3.9. (*S*)-1-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde 6i′[5h]

$[\alpha]_D^{25} = -0.7$ (*c* 0.5, $CHCl_3$); Enantiomeric excess: 98%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 92/8, 0.6 mL/min, λ = 254 nm), t_R (major) = 25.0 min, t_R (minor) = 28.6 min.

4.3.10. (*S*)-1-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde 6j′

White solid; $[\alpha]_D^{25} = +1.9$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.74 (m, 1H), 1.77–1.88 (m, 4H), 2.01–2.11 (m, 2H), 2.31–2.38 (m, 1H), 2.50–2.59 (m, 1H), 2.90–3.00 (m, 2H), 7.18–7.22 (m, 2H), 7.56–7.60 (m, 2H), 9.35 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 25.8, 32.4, 32.7, 33.2, 43.2, 60.2,

122.5, 128.3, 131.2, 132.3, 174.6, 177.4, 201.9 ppm; IR (cm^{-1}) : 719, 763, 826, 926, 961, 1014, 1069, 1099, 1180, 1276, 1298, 1383, 1452, 1490, 1703, 1777, 2728, 2870, 2957; Anal. Calcd (%) for $C_{16}H_{16}BrNO_3$ (350.21): C, 54.87; H, 4.61; N, 4.00. Found (%): C, 54.96; H, 4.77; N, 3.91. Enantiomeric excess: 87%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 70/30, 1.0 mL/min, λ = 254 nm), t_R (major) = 16.3 min, t_R (minor) = 36.7 min.

4.3.11. (*S*)-1-(1-(4-Nitrophenyl)-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde 6k′

Light brown solid; $[\alpha]_D^{25} = +2.3$ (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.75 (m, 1H), 1.79–1.89 (m, 4H), 2.03–2.12 (m, 2H), 2.36–2.43 (m, 1H), 2.54–2.62 (m, 1H), 2.94–3.02 (m, 2H), 7.55–7.59 (m, 2H), 8.29–8.33 (m, 2H), 9.33 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 25.7, 32.7, 32.9, 33.4, 43.2, 60.5, 124.4, 127.3, 137.8, 147.1, 174.1, 177.0, 202.0 ppm; IR (cm^{-1}) : 689, 716, 749, 811, 854, 1110, 1175, 1298, 1344, 1378, 1452, 1498, 1597, 1712, 1779, 2727, 2872, 2957; Anal. Calcd (%) for $C_{16}H_{16}N_2O_5$ (316.31): C, 60.75; H, 5.10; N, 8.86. Found (%): C, 60.86; H, 5.24; N, 8.72. Enantiomeric excess: 87%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 65/35, 1.0 mL/min, λ = 254 nm), t_R (major) = 24.5 min, t_R (minor) = 49.9 min.

4.3.12. (*S*)-1-(1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde 6l′

White solid; $[\alpha]_D^{25} = +1.1$ (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.74 (m, 1H), 1.77–1.87 (m, 4H), 2.01–2.11 (m, 2H), 2.30–2.37 (m, 1H), 2.50–2.59 (m, 1H), 2.90–3.00 (m, 2H), 7.24–7.28 (m, 2H), 7.41–7.44 (m, 2H), 9.35 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 25.8, 32.4, 32.8, 33.2, 43.2, 60.2, 128.0, 129.4, 130.6, 134.4, 174.7, 177.5, 201.9 ppm; IR (cm^{-1}) : 730, 770, 812, 830, 927, 1017, 1092, 1181, 1277, 1385, 1451, 1493, 1704, 1777, 2727, 2871, 2957; Anal. Calcd (%) for $C_{16}H_{16}ClNO_3$ (305.76): C, 62.85; H, 5.27; N, 4.58. Found (%): C, 62.63; H, 5.39; N, 4.42. Enantiomeric excess: 92%, determined by chiral HPLC analysis (Chiralpak OD-H, hexane/*i*PrOH = 70/30, 1.0 mL/min, λ = 254 nm), t_R (major) = 16.7 min, t_R (minor) = 39.7 min.

4.3.13. (*S*)-2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-ethylbutanal 6m′[5c,i]

$[\alpha]_D^{25} = -6.3$ (*c* 1.0, $CHCl_3$); Enantiomeric excess: 87%, determined by chiral HPLC analysis (Chiralpak AS-H, hexane/EtOH = 70/30, 0.8 mL/min, λ = 254 nm), t_R (minor) = 13.2 min, t_R (major) = 16.4 min.

4.3.14. (*S*)-2-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-ethylbutanal 6n′

White solid; $[\alpha]_D^{25} = -2.1$ (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (q, *J* = 7.6 Hz, 6H), 1.70 (sextet, *J* = 7.5 Hz, 1H), 1.82–2.05 (m, 3H), 2.63–2.69 (dd, *J* = 5.9, 18.4 Hz, 1H), 2.91–2.98 (dd, *J* = 9.6, 18.4 Hz, 1H), 3.17–3.21 (dd, *J* = 5.9, 9.6 Hz, 1H), 7.16–7.19 (m, 2H), 7.56–7.60 (m, 2H), 9.60 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.1 (d, *J* = 3.0 Hz), 23.3, 24.2, 31.8, 41.8, 54.7, 122.5, 128.1, 130.9, 132.4, 174.6, 177.0, 204.1 ppm; IR (cm^{-1}) : ν 664, 685, 711, 754, 793, 825, 935, 1069, 1174, 1288, 1318, 1381, 1451, 1490, 1584, 1603, 1706, 1779, 2881, 2941, 2969; Anal. Calcd (%) for $C_{16}H_{18}BrNO_3$ (352.22): C, 54.56; H, 5.15; N, 3.98. Found (%): C, 54.18; H, 5.32; N, 3.76%. Enantiomeric excess: 90%, determined by chiral HPLC analysis (Chiralpak AS-H, hexane/EtOH = 70/30, 0.8 mL/min, λ = 254 nm), t_R (minor) = 19.8 min, t_R (major) = 23.4 min.

4.3.15. (*S*)-2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)-2-ethylbutanal 6o′

Colorless oil; $[\alpha]_D^{25} = -2.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (q, *J* = 7.4 Hz, 6H), 1.62 (sextet, *J* = 7.3 Hz, 1H), 1.69–1.86 (m, 3H), 2.48–2.54 (dd, *J* = 5.7, 18.4 Hz, 1H), 2.75–2.82 (dd, *J* = 9.4, 18.4 Hz, 1H), 3.08–3.12 (dd, *J* = 5.8, 9.4 Hz, 1H), 4.59–4.67 (dd, *J* = 14.1, 17.2 Hz, 2H), 7.23–7.31 (m, 3H), 7.34–7.37 (m, 2H), 9.55 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5, 8.7, 24.1, 25.5, 32.3, 42.4, 43.5, 51.5, 127.9, 128.6, 128.9, 135.6, 175.7, 177.7, 179.6, 204.0 ppm; IR (cm^{-1}): ν 705, 759, 796, 931, 1084, 1167, 1293, 1314, 1342, 1397, 1431, 1456, 1497, 1586, 1605, 1694, 1773, 2883, 2942, 2971; Anal. Calcd (%) for $C_{17}H_{21}NO_3$ (287.35): C, 71.06; H, 7.37; N, 4.87. Found (%): C, 70.92; H, 7.20; N, 4.98. Enantiomeric excess: 93%, determined by chiral HPLC analysis (Chiralpak AS-H, hexane/EtOH = 90/10, 0.7 mL/min, λ = 254 nm), t_R (minor) = 20.9 min, t_R (major) = 23.2 min.

4.3.16. (*S*)-2-Ethyl-2-(1-(4-Nitrophenyl)-2,5-dioxopyrrolidin-3-yl)butanal 6p′

White solid; $[\alpha]_D^{25} = -1.7$ (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (q, *J* = 7.7 Hz, 6H), 1.69 (sextet, *J* = 7.5 Hz, 1H), 1.86–1.99 (m, 2H), 2.06 (sextet, *J* = 7.5 Hz, 1H), 2.66–2.73 (dd, *J* = 6.0, 18.5 Hz, 1H), 2.94–3.01 (dd, *J* = 9.6, 18.4 Hz, 1H), 3.16–3.20 (dd, *J* = 6.0, 9.6 Hz, 1H), 7.54–7.57 (m, 2H), 8.29–8.33 (m, 2H), 9.59 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 23.3, 24.1, 32.0, 41.9, 55.0, 124.4, 127.1, 137.5, 147.1, 174.1, 176.6, 204.2 ppm; IR (cm^{-1}): ν 715, 749, 794, 854, 931, 1110, 1172, 1298, 1344, 1378, 1459, 1498, 1524, 1597, 1612, 1714, 1780, 2885, 2941, 2973; Anal. Calcd (%) for $C_{16}H_{18}N_2O_5$ (318.32): C, 60.37; H, 5.70; N, 8.80. Found (%): C, 60.12; H, 5.84; N, 8.68. Enantiomeric excess: 81%, determined by chiral HPLC analysis (Chiralpak AS-H, hexane/EtOH = 75/25, 0.9 mL/min, λ = 254 nm), t_R (minor) = 18.8 min, t_R (major) = 22.5 min.

4.3.17. (*S*)-2-(1-(4-Chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-ethylbutanal 6q′

Light yellow solid; $[\alpha]_D^{25} = -1.9$ (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (q, *J* = 7.6 Hz, 6H), 1.70 (sextet, *J* = 7.4 Hz, 1H), 1.82–2.05 (m, 3H), 2.63–2.70 (dd, *J* = 5.9, 18.4 Hz, 1H), 2.91–2.98 (dd, *J* = 9.6, 18.4 Hz, 1H), 3.18–3.22 (dd, *J* = 5.9, 9.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 9.60 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.1 (d, *J* = 3.1 Hz), 23.3, 24.3, 31.8, 41.8, 54.7, 127.8, 129.4, 130.4, 134.5, 174.6, 177.0, 204.1 ppm; IR (cm^{-1}) : 728, 770, 793, 830, 937, 1017, 1092, 1177, 1277, 1382, 1460, 1493, 1703, 1778, 2883, 2941, 2971; Anal. Calcd (%) for $C_{16}H_{18}ClNO_3$ (307.77): C, 62.44; H, 5.89; N, 4.55. Found (%): C, 62.32; H, 5.74; N, 4.41. Enantiomeric excess: 80%, determined by chiral HPLC analysis (Chiralpak AS-H, hexane/EtOH = 85/15, 0.9 mL/min, λ = 254 nm), t_R (minor) = 16.1 min, t_R (major) = 18.8 min.

4.3.18. (*S*)-2-(2,5-Dioxo-1-phenylpyrrolidin-3-yl)-2-methylpentanal 6r′[5c]

$[\alpha]_D^{25} = -1.3$ (*c* 0.6, $CHCl_3$); Enantiomeric excess: 94%, determined by chiral HPLC analysis (Chiralpak AS-H, hexane/EtOH = 80/20, 0.8 mL/min, λ = 254 nm), t_R (minor1) = 12.1 min, t_R (major1) = 13.5 min, t_R (major2) = 17.3 min, t_R (minor2) = 21.4 min.

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