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A novel Fe(II)/diaryl prolinol catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkenes

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ABSTRACT

A novel Fe(II)/diaryl prolinol catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkenes has been developed. In the presence of $FeCl_2$ (10 mol %) and α,α-bis(3,5-bistrifluoromethylphenyl) prolinol **L1** (10 mol %), [3+2] cycloaddition of azomethine ylides with electronic-deficient olefins underwent smoothly in CH_3CN at room temperature to generate the desired *endo*-adducts in moderate to good yields and enantioselectivities. This is the first example of Fe(II)/N,O-ligand (**L1**) catalyzed 1,3-dipolar enantioselective cycloaddition reaction of azomethine ylides.

1. Introduction

The 1,3-dipolar cycloaddition reaction constitutes one of the most fundamental reactions and efficient strategy for the stereoselective construction of five-membered heterocyclic compounds.[1] Over the past two decades, the development of catalytic asymmetric reactions have been one of the challenging areas within the field of 1,3-dipolar cycloaddition reactions, and this methodology has provided organic chemists with the tools necessary to synthesize a variety of chiral heterocycles in highly enantio-enriched forms.[2] Azomethine ylides reacted with electronic-deficient olefins through a 1,3-dipolar diastereoselective cycloaddition pathway to form optically active pyrrolidines, as one of the important moiety in the structures of many biologically active compounds.[3] Because of their great synthetic potential, a few protocols for the metal-catalyzed enantioselective synthesis of 1,3-dipolar cycloaddition products of azomethine ylides with alkenes have been developed. Grigg and Allway demonstrated that using a stoichiometric amount of chiral Co(II) or Mn(II) complexes with ephedrine derivatives as chiral ligands could give the cycloaddition products of azomethine ylides with up to 96% ee.[4] Zhang et al. reported that efficient catalytic systems, Ag(I) with chiral phosphane ligand, and Ag(I)/P,N-ligand in the presence of *i*-Pr_2NEt, catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides in good yields and stereoselectivities of the desired adducts,[5] and high yields and excellent stereoselectivities of the desired 1,3-dipolar cycloaddition products of azomethine ylides were obtained using AgOAc with chiral N/P- and S/P-ligands derived from ferrocenyloxazolines and PHOX in the absence of amine.[6] In addition, other metals, such as Zn(II),[7] Cu(I) and Cu(II),[8] Ni(II),[9] and Ca(II)[10] in combination with a variety of chiral N/N-, P/P-, P/N-, and P/S-bidentate ligands were also used as effective catalysts for asymmetric 1,3-dipolar cycloadditions of azomethine ylides. Although iron salts as effective, alternative, and promising transition-metal catalysts in organic synthesis have received much more attention because of their cheap, ubiquitous, and environmentally benign properties in the recently years,[11] there is not any report on the Fe-catalyzed enantioselective synthesis of the 1,3-dipolar cycloaddition products of azomethine ylides with alkenes to the best of our knowledge.

Asymmetric organocatalysis[12] has been experiencing a revival since MacMillan et al., independently, disclosed its potential in 2000.[13] For the past decade, L-proline and its derivatives have emerged as one of the most significant and versatile organocatalysts in the enantioselective construction of C–C,[14] C–O,[15] C–N,[16] C–Halogen,[17] C–P,[18] C–S,[19] and C–Se[20] bonds, tandem reaction and Aza-Diels–Alder reaction[21] through covalent activation modes involving enamines,[22] iminium ion,[23] and even SOMO mechanisms.[24] As a result of our ongoing interest in iron-catalyzed organic reaction,[25] we present our investigation herein for the first time on Fe(II)/N,*O*-ligand (**L1**) catalyzed 1,3-dipolar enantioselective cycloaddition reaction. In the

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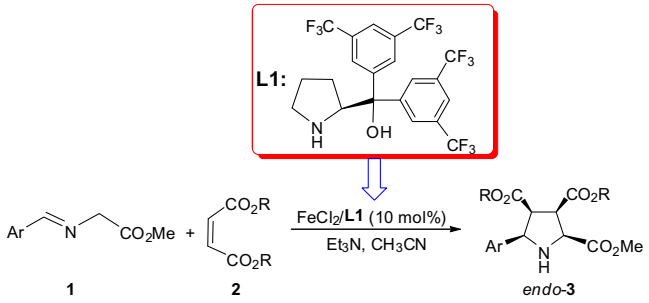
presence of $FeCl_2$ (10 mol %) and α,α-diaryl prolinol **L1** (10 mol %), [3+2] cycloaddition of azomethine ylides with electronic-deficient olefins underwent smoothly to generate the desired *endo*-adducts in moderate to good yields and enantioselectivities (Scheme 1).

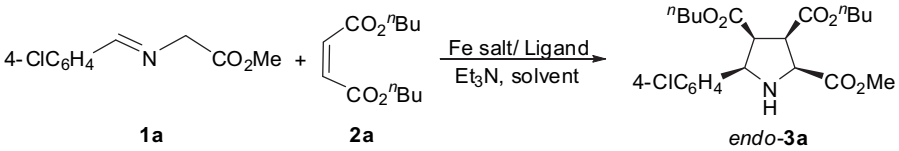


Scheme 1.

2. Results and discussion

Our initial efforts focused on the optimization of 1,3-dipolar enantioselective cycloaddition. [3+2] cycloaddition of *N*-(4-chlorobenzylidene)-glycine methyl ester **1a** with dibutyl maleate **2a** was chosen as a model reaction. As shown in Table 1, when the model addition reaction was carried out in the presence of catalytic amount $FeCl_2$ and **L1** in CH_3CN at room temperature (20 °C), the desired 1,3-dipolar cycloaddition product **3a** in *endo*-form was isolated with 70% yield and 71% ee (Table 1, entry 1). Various chiral ligands were employed in this [3+2] cycloaddition reaction and the experimental results revealed that **L1** exhibited the highest catalytic activity among the ligands **L1**–**L11** in Fig. 1, including various *N*/*N*-, *N*/*O*-, and *O*/*O*-bidentate ones screened in this investigation (Table 1, entries 1–11). Investigations into the diaryl prolinols **L1**–**L5** revealed that the steric and electronic properties of the aromatic ring of the catalyst had a combination impact on its performance (Table 1, entries 1–5). Diaryl prolinols, **L1** and **L2**, bearing an electron-withdrawing group CF_3 on the benzene ring, exhibit the higher reactivity and enantioselectivity than that of its analogue, **L3**, **L4**, and **L5**, respectively (Table 1, entry 1 vs 3 and 4, 2 vs 5). Interestingly, the trimethylsilyl ether **L2** resulted in a sharp drop in both the reactivity and enantioselectivity, comparing to its analogue **L1** (Table 1, entry 2 vs 1). Similar phenomena were also found in **L5** and **L4** (Table 1, entry 5 vs 4). It is suggested that the free OH moiety of the ligand is necessary in this process. It is important to note that more steric hindrance substituted groups are essential in aromatic rings of diaryl prolinol ligand (Table 1, entry 3 vs 4), as well as in prolinol **L6** (Table 1, entry 6 vs 1–5). As expected, in the absence of chiral ligand, no enantioselectivity was observed in the model reaction, and 21% yield of the 1,3-dipolar cycloaddition product was isolated (Table 1, entry 12). In addition, no desired cycloaddition product was observed in the absence of iron salt even in the presence of **L1** (Table 1, entry 13). However, it should be noted that no enantioselectivity was found when **L11**, an O/O-ligand was used as a chiral one (Table 1, entry 11).

Table 1
Screening reaction conditions for Fe-catalyzed [3+2] cycloaddition reaction [a]



Entry	Ligand	Fe salt	Solvent	Temp (°C)	Yield[b](%)	ee[c](%)
1	**L1**	$FeCl_2$	CH_3CN	20	70	71
2	**L2**	$FeCl_2$	CH_3CN	20	51	56
3	**L3**	$FeCl_2$	CH_3CN	20	47	45
4	**L4**	$FeCl_2$	CH_3CN	20	39	15
5	**L5**	$FeCl_2$	CH_3CN	20	31	10
6	**L6**	$FeCl_2$	CH_3CN	20	28	2
7	**L7**	$FeCl_2$	CH_3CN	20	26	6
8	**L8**	$FeCl_2$	CH_3CN	20	35	12
9	**L9**	$FeCl_2$	CH_3CN	20	28	14
10	**L10**	$FeCl_2$	CH_3CN	20	31	7
11	**L11**	$FeCl_2$	CH_3CN	20	30	0
12	—	$FeCl_2$	CH_3CN	20	21	0
13	**L1**	—	CH_3CN	20	0	0
14	**L1**	$FeCl_2$	CH_2Cl_2	0	46	44
15	**L1**	$FeCl_2$	Toluene	0	40	38
16	**L1**	$FeCl_2$	THF	0	38	30
17	**L1**	$FeCl_2$	Hexane	0	42	36
18	**L1**	$FeCl_2$	EtOH	0	26	21
19	**L1**	$FeCl_2$	EtOEt	0	30	28
20	**L1**	$FeCl_2$	CH_3CN	0	51	72
21	**L1**	$FeBr_2$	CH_3CN	0	24	38
22	**L1**	$FeCl_3$	CH_3CN	0	18	6
23	**L1**	$Fe(OTf)_3$	CH_3CN	0	13	7
24	**L1**	$Fe_2(SO_4)_3$	CH_3CN	0	Trace	—
25[d]	**L1**	$FeCl_2$	CH_3CN	0	Trace	—
26	**L1**	$FeCl_2$	CH_3CN	−20	37	73
27	**L1**	$FeCl_2$	CH_3CN	−40	22	75

[a] Reaction conditions: *N*-(4-chlorobenzylidene)-glycine methyl ester **1a** (1.0 mmol), dibutyl maleate **2a** (1.0 mmol), Fe salt (0.1 mmol), ligand (0.1 mmol), Et_3N (1.0 mmol) in solvent (2.0 mL) at the temperature indicated in Table 1, under nitrogen atmosphere, 24 h.
[b] Isolated yields after column chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.
[d] In the absence of Et_3N.

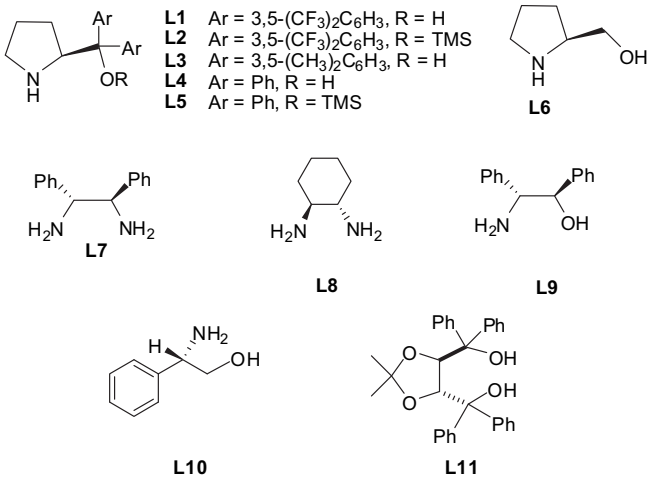


Fig. 1. Screened ligands in Fe(II)-catalyzed asymmetric 1,3-dipolar cycloaddition.

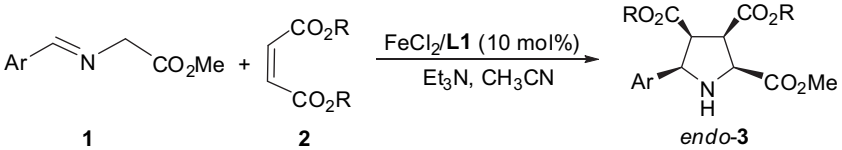
The effect of solvents on the model reaction was also examined. Among the solvents, such as CH_2Cl_2, $C_6H_5CH_3$, THF, hexane, C_2H_5OH, $C_2H_5OC_2H_5$, and CH_3CN tested in the model reaction, CH_3CN was found to be the best of choice. When the model reaction was carried out in CH_3CN, it gave the desired product not only in the highest isolated yield, but also in the best of enantioselectivity (Table 1, entries 14–20). In order to further understand the role of iron salts, a number of iron salts were investigated in the model reaction using Fe/**L1** catalytic system in CH_3CN at 0 °C. It was found that the activity of Fe(II) salts tested in the experiment, such as $FeCl_2$ and $FeBr_2$ is more active than that of Fe(III) salts, such as $FeCl_3$, $Fe(OTf)_3$, and $Fe_2(SO_4)_3$. The use of Fe(III) salts including $FeCl_3$, $Fe(OTf)_3$, and $Fe_2(SO_4)_3$ displayed in low reactivity and poor enantioselectivity (Table 1, entries 20–24).

Only trace amount of desired was obtained when the model reaction was performed in the absence of additional organic amine triethylamine (Table 1, entry 25). In order to find the best reaction conditions for the reaction, the effect of reaction temperature on the cycloaddition reaction was also surveyed. As can be seen from Table 1, at the room temperature (20 °C), the reaction took place smoothly with both good isolated yield and enantioselectivity. A slightly higher ee was obtained along with sacrificing yield when the reaction was performed at 0 to −40 °C (Table 1, entries 26 and 27). It is interesting to note that both of isolated yields and ee were maintained when up 10 mol % of $FeCl_2$ and **L1** was added to the reaction. A lower yield of the product was isolated when less than 10 mol % of $FeCl_2$ and **L1** was used in the reaction. It was found that the reaction was accomplished as the reaction was carried out at room temperature for 24 h.

To explore the scope of $FeCl_2$/**L1**-catalyzed [3+2] cycloaddition of azomethine ylides, a number of imino esters (**1a**–**f**) with dimethyl, di(*n*-butyl) and dibenzyl maleates (**2a**, **2b**, and **2c**) were investigated under the optimized reaction conditions. The results were summarized in Table 2. A variety of imino ester substrates derived from aromatic aldehyde bearing electron-rich, electron-neutral, or electron-deficient group, such as F, Cl, H, CH_3, and CN on the benzene ring were able to undergo [3+2] cycloaddition with electron-deficient olefin **2a**, **2b** or **2c** in the presence of $FeCl_2$/**L1** (10 mol %) in CH_3CN at room temperature (20 °C) for 24 h. The reactions generated the corresponding [3+2] cycloaddition products *endo*-**3a**–**h** in moderate to good yields (47–70%) and enantioselectivities (53–77% ee). Obviously, steric and electronic properties have a certain effect on the enantioselectivity of the model reaction. For imine bearing an electron-withdrawing group on the benzene ring brought about a slight increase in its enantioselectivity, compared with **1b** as substrate (Table 2, entries 1, 2, 3, 5, 7, and 8 vs entry 4). On the other hand, substrate having an electron-donating substituent, such as methyl group on the *ortho*-position of benzene ring, a lower enantioselectivity was observed (Table 2, entry 6). It should be worth noting that **1f** derived from 2-naphthaldehyde and glycine methyl ester reacted with dibutyl maleate **2b** to generate the corresponding [3+2] cycloaddition product **3i** in 46% yield and 60% ee (Table 2, entry 9).

Finally, to extend the more application scope and generality of this iron-catalyzed asymmetric [3+2] cycloaddition protocol, the reactions of imino esters (**1a**–**d** and **1g**) with *N*-methyl and *N*-phenyl maleimides (**4a** and **4b**) were investigated using the optimized reaction conditions. As can be seen in Table 3, imino esters **1a**, **1b**, **1c**, and **1g** reacted with *N*-methyl maleimide **4a** or *N*-phenyl maleimide **4b** to give the corresponding [3+2] cycloaddition products *endo*-**5a**–**5d** and **5f** in moderate to good yields (48–72%) and enantioselectivities (51–78% ee) (Table 3, entries 1–4 and 6). It should be noted that a much low enantioselectivity (ee 20%) was obtained when *N*-(2-methylbenzylidene)-glycine methyl ester **1d** reacted with *N*-phenyl maleimide **4b**, but 57% yield was obtained (Table 3, entry 5).

Table 2
Fe(II)/**L1**-catalyzed enantioselective cycloaddition of azomethine ylides (**1**) with dialkyl maleates (**2**)[a]

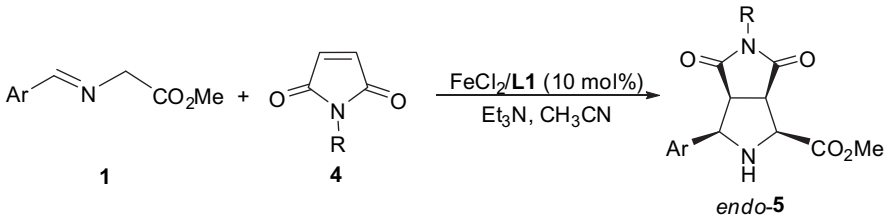


1 **2** *endo*-**3**

Entry	Ar	R	**3**	Yield[b](%)	ee[c](%)
1	4-ClC_6H_4 (**1a**)	*n*-C_4H_9 (**2a**)	**3a**	70	71
2	4-ClC_6H_4 (**1a**)	CH_3 (**2b**)	**3b**	51	77
3	4-ClC_6H_4 (**1a**)	$C_6H_5CH_2$ (**2c**)	**3c**	62	69
4	C_6H_5 (**1b**)	CH_3 (**2b**)	**3d**	47	62
5	4-FC_6H_4 (**1c**)	CH_3 (**2b**)	**3e**	52	70
6	2-$CH_3C_6H_4$ (**1d**)	CH_3 (**2b**)	**3f**	51	53
7	4-CNC_6H_4 (**1e**)	*n*-C_4H_9 (**2a**)	**3g**	68	74
8	4-CNC_6H_4 (**1e**)	CH_3 (**2b**)	**3h**	61	67
9	2-Naphthyl (**1f**)	CH_3 (**2b**)	**3i**	46	60

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), $FeCl_2$ (0.1 mmol), **L1** (0.1 mmol), Et_3N (1.0 mmol) in CH_3CN (2.0 mL) at room temperature (20 °C) under nitrogen atmosphere for 24 h.
[b] Isolated yields after column chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.

Table 3
Fe(II)/**L1**-catalyzed enantioselective cycloaddition of azomethine ylides (**1**) with *N*-substituted maleimides (**4**)[a]

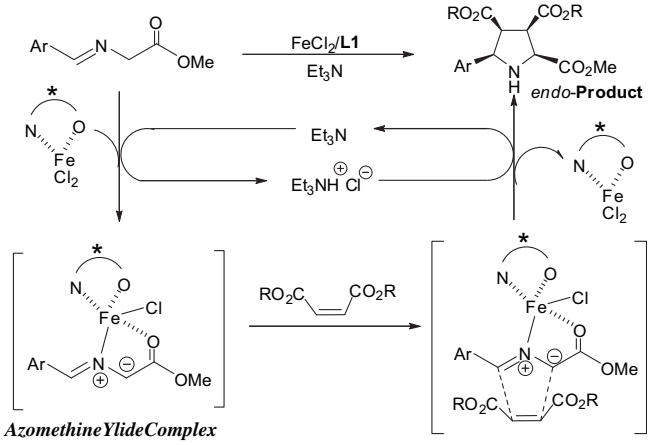


1 4 *endo*-**5**

Entry	Ar	R	**5**	Yield[b](%)	ee[c](%)
1	4-ClC_6H_4 (**1a**)	CH_3 (**4a**)	**5a**	54	51
2	4-ClC_6H_4 (**1a**)	C_6H_5 (**4b**)	**5b**	48	78
3	C_6H_5 (**1b**)	CH_3 (**4a**)	**5c**	60	75
4	4-FC_6H_4 (**1c**)	C_6H_5 (**4b**)	**5d**	49	65
5	2-$CH_3C_6H_4$ (**1d**)	C_6H_5 (**4b**)	**5e**	57	20
6	3-BrC_6H_4 (**1g**)	C_6H_5 (**4b**)	**5f**	72	57

[a] Reaction conditions: **1** (1.0 mmol), **4** (1.0 mmol), $FeCl_2$ (0.1 mmol), **L1** (0.1 mmol), Et_3N (1.0 mmol) in CH_3CN (2.0 mL) at room temperature (20 °C) under nitrogen atmosphere for 24 h.
[b] Isolated yields after column chromatography.
[c] Enantiomeric excesses were measured by chiral HPLC.

A plausible mechanism for the cycloaddition reaction of azomethine ylides is shown in Scheme 2. Coordination of the imino ester to chiral N,O-ligand **L1** and Fe(II) catalyst, followed by deprotonation with base to form the reactive metal-bound azomethine ylide dipole, which reacts with dipolarophiles in a chiral environment, was followed by elimination of cycloadduct to afford the expected *endo*-cycloadduct stereoselectively, and regenerate the chiral catalyst.



Scheme 2. Plausible mechanism of the 1,3-dipolar cycloaddition of azomethine ylides catalyzed by chiral **L1**-Fe(II) complexes.

3. Conclusions

In summary, a novel Fe(II)/diaryl prolinol catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkenes has been developed. In the presence of $FeCl_2$ (10 mol %) and α,α-bis (3,5-bistrifluoromethylphenyl)prolinol **L1** (10 mol %), [3+2] cycloaddition of azomethine ylides with electronic-deficient olefins, including dialkyl maleates and *N*-substituted maleimides underwent smoothly in CH_3CN at room temperature (20 °C) to generate the desired the *endo*-adducts in moderate to good yields and enantioselectivities in the most cases. Efforts to elucidate the mechanistic details of this asymmetric 1,3-dipolar cycloaddition reaction and extension of this protocol to other substrates and reactions are under current investigation in our laboratory.

4. Experimental section

4.1. General remarks

All reactions were carried out under a nitrogen atmosphere. All ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometers. All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. IR spectra were obtained on a Nicolet NEXUS 470 spectrophotometer. Enantiomeric excesses were determined on Agilent 1100 HPLC using Daicel Chiralpak AS-H, AD-H and Chiralcel OD-H columns with racemic compound as standard. Products were purified by flash chromatography on 230–400 mesh silica gel, SiO_2. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Fluka, Fisher Scientific and Novabiochem, USA, or Shanghai Chemical Company, China and were used without purification prior to use.

4.2. General procedure for the $FeCl_2$-catalyzed [3+2] cycloaddtion reaction

Under nitrogen atmosphere, $FeCl_2$ (12.7 mg, 0.1 mmol) and ligand **L1** (52.5 mg, 0.1 mmol) were placed in a dried Schlenk tube and CH_3CN (1.0 mL) was added. The mixture was stirred at room temperature (20 °C) for 1 h. Then imine substrate **1** (1.0 mmol), electronic-deficient olefin **2** or **4** (1.0 mmol) and Et_3N (101 mg, 1.0 mmol) were added as solution in CH_3CN (1.0 mL). The mixture was stirred at room temperature (20 °C) and the progress of the cycloaddition reaction was typically monitored by TLC analysis. After the reaction proceeded for 24 h, the reaction was quenched with saturated ammonium chloride solution and then washed with ethyl acetate (3.0 mL×3), the combined ethyl acetate was concentrated. The obtained residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to provide the desired [3+2] cycloaddtion product.

*4.2.1. (2R,3S,4R,5S)-3,4-Dibutyl,2-methyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (**3a**).* White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 71% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=7.07 min and 8.98 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.30 (s, 4H), 4.43 (d, *J*=6.7 Hz, 1H), 4.11–4.03 (m, 3H), 3.80 (s, 3H), 3.73–3.55 (m, 4H), 1.62–1.56 (m, 2H), 1.39–1.34 (m, 2H), 1.21–1.15 (m, 2H), 1.09–1.03 (m, 2H), 0.92 (t, *J*=7.4 Hz, 3H), 0.78 (t, *J*=7.2 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ=170.9, 170.4, 170.3, 135.8, 133.5, 128.4, 128.3, 65.2, 64.7, 64.5, 62.1, 52.6, 51.2, 30.4, 30.2, 19.1, 18.9, 13.7, 13.5. IR (KBr, cm^{-1}): 3281, 2961, 1737, 1708, 1498, 1460, 1430, 1402, 1381, 1342, 1308, 1293, 1238, 1204, 1178, 1112, 1093, 1078, 1016, 935, 833, 775. Anal. Calcd for $C_{22}H_{30}ClNO_6$: C, 60.06; H, 6.87; N, 3.18. Found: C, 60.33; H, 6.73; N, 3.29.

*4.2.2. (2R,3S,4R,5S)-Trimethyl 5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (**3b**)*[6a]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 77% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=9.22 min and 11.62 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.29 (s, 4H), 4.45 (d, *J*=7.0 Hz, 1H), 4.14 (d, *J*=8.9 Hz, 1H), 3.79 (s, 3H), 3.75–3.70 (m, 1H), 3.68 (s, 3H), 3.60–3.56 (m, 1H), 3.27 (s, 3H), 3.08 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.8, 170.6, 170.5, 135.7, 133.3, 128.3, 128.1, 64.4, 61.9, 52.2, 52.1, 51.9, 51.3, 50.7.

*4.2.3. (2R,3S,4R,5S)-3,4-Dibenzyl-2-methyl-5-(4-chlorophenyl)pyrrolidine-2,3,4-tricarboxylate (**3c**).* White solid; SiO_2 chromatography: *n*-hexane–EtOAc 3:1; 69% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=6.15 min and 13.33 min, 205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.36–7.29 (m, 6H), 7.26–7.13 (m, 8H), 5.22–5.12 (m, 2H), 4.71 (d, *J*=12.1 Hz, 1H), 4.61–4.56 (m, 2H), 4.20–4.16 (m, 1H), 3.73–3.69 (m, 1H), 3.64–3.61 (m, 1H), 3.21(t, *J*=7.2 Hz, 3H), 2.76 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7, 171.3, 170.6, 136.7, 135.3, 134.6, 133.5, 128.9, 128.6, 128.4, 128.2, 127.8, 127.3, 126.7, 126.1, 67.0, 66.8, 64.4, 63.2, 61.5, 53.5, 50.7. IR (KBr, cm^{-1}): 3345, 3032, 2978, 2334, 1954, 1893, 1735, 1721, 1599, 1494, 1455, 1381, 1201, 1014, 908, 751, 698. Anal. Calcd for $C_{28}H_{26}ClNO_6$: C, 66.21; H, 5.16; N, 2.76. Found: C, 66.37; H, 5.09; N, 2.87.

*4.2.4. (2R,3S,4R,5S)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**3d**)*[6a]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 62% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=7.04 and 14.39 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.34–7.26 (m, 5H), 4.49 (d, *J*=7.0 Hz, 1H), 4.17 (d, *J*=9.1 Hz, 1H), 3.81 (s, 3H), 3.80–3.72 (m, 1H), 3.70 (s, 3H), 3.60–3.56 (m, 1H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.0, 170.9, 170.8, 137.0, 128.3, 127.7, 126.7, 65.4, 62.1, 52.5, 52.4, 52.1, 51.3, 50.9.

*4.2.5. (2R,3S,4R,5S)-Trimethyl 5-(4-fluorophenyl)pyrrolidine-2,3,4-tricarboxylate (**3e**)*[6a]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 70% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=7.56 and 11.89 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.35–7.31 (m, 2H), 7.03–6.99 (m, 2H), 4.47 (d, *J*=7.0 Hz, 1H), 4.15 (d, *J*=8.8 Hz, 1H), 3.81 (s, 3H), 3.73–3.71 (m, 1H), 3.69 (s, 3H), 3.58–3.54 (m, 1H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9, 170.8, 170.7, 162.1 (d, *J*=245.8 Hz), 132.9 (d, *J*=3.0 Hz), 128.4 (d, *J*=8.1 Hz), 115.1 (d, *J*=21.2 Hz), 64.6, 62.1, 52.4, 52.1, 52.0, 51.3, 50.8.

*4.2.6. (2R,3S,4R,5S)-Trimethyl 5-(2-methylphenyl)pyrrolidine-2,3,4-tricarboxylate (**3f**)*[5a]. Colorless oil; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 53% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=6.56 and 16.22 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.39–7.36 (m, 1H), 7.18–7.14 (m, 3H), 4.61 (d, *J*=6.6 Hz, 1H), 4.11 (d, *J*=8.7 Hz, 1H), 3.83 (s, 3H), 3.77–3.71 (m, 1H), 3.67 (s, 3H), 3.69–3.64 (m, 1H), 3.12 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.5, 171.0, 135.8, 135.1, 130.4, 127.8, 126.2, 62.2, 61.9, 52.6, 52.3, 51.6, 51.4, 51.0.

*4.2.7. (2R,3S,4R,5S)-3,4-Dibutyl, 2-methyl 5-(4-cyanophenyl)pyrrolidine-2,3,4-tricarboxylate (**3g**).* White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 74% ee. HPLC: Daicel Chiralpak AD-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=12.85 min and 21.28 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.64 (d, *J*=8.4 Hz, 2H), 7.52 (d, *J*=8.4 Hz, 2H), 4,58 (d, *J*=6.2 Hz, 1H), 4.22 (d, *J*=9.1 Hz, 1H), 4.13–4.02 (m, 2H), 3.81 (s, 3H), 3.80–3.58 (m, 4H), 1.63–1.56 (m, 2H), 1.42–1.32 (m, 2H), 1.24–1.15 (m, 2H), 1.11–1.01 (m, 2H), 0.93 (t, *J*=7.4 Hz, 3H), 0.79 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 170.0, 169.8, 142.8, 132.1, 127.8, 118.5, 111.6, 65.3, 64.7, 64.6, 61.8, 52.4, 52.2, 51.0, 30.4, 30.1, 19.0, 18.8, 13.6, 13.5. IR (KBr, cm^{-1}): 3272, 2953, 2924, 2849, 2228, 1743, 1692, 1463, 1431, 1411, 1378, 1369, 1332, 1301, 1284, 1227, 1195, 1164, 1101, 1076, 1052, 1012, 929, 825, 763. Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51. Found: C, 64.29; H, 6.91; N, 6.37.

*4.2.8. (2R,3S,4R,5S)-Trimethyl 5-(4-cyanophenyl)pyrrolidine-2,3,4-tricarboxylate (**3h**)*[8d]. Colorless solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 67% ee. HPLC: Daicel Chiralpak AD-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=8.84 min and 15.40 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.63 (d, *J*=8.1 Hz, 2H), 7.51 (d, *J*=7.8 Hz, 2H), 4.54 (d, *J*=6.3 Hz, 1H), 4.18 (d, *J*=8.7 Hz, 1H), 3.80 (s, 3H), 3.79–3.73 (m, 1H), 3.69 (s, 3H), 3.67–3.61 (m, 1H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.0, 170.8, 170.6, 143.3, 132.2, 128.0, 118.8, 111.7, 64.8, 62.2, 52.7, 52.5, 52.2, 51.8, 51.0.

*4.2.9. (2R,3S,4R,5S)-Trimethyl 5-(2-naphthyl)pyrrolidine-2,3,4-tricarboxylate (**3i**)*[5a]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 60% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=10.19 and 24.29 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.78–7.83 (m, 4H), 7.47–7.41 (m, 3H), 4.63 (d, *J*=6.5 Hz, 1H), 4.23 (d, *J*=9.0 Hz, 1H), 3.83 (s, 3H), 3.81–3.76 (m, 1H), 3.69 (s, 3H), 3.69–3.66 (m, 1H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9, 170.8, 170.6, 134.3, 133.1, 132.8, 128.0, 127.9, 127.5, 126.1, 125.9, 125.5, 124.7, 65.4, 62.0, 52.4, 52.1, 51.3, 51.2, 51.1.

*4.2.10. (1S,3R,3S,6R)-Methyl 5-methyl-4,6-dioxo-3-(4-chlorophenyl)-octahydropyrrole[3,4-c]pyrrole-1-carboxylate (**5a**)*[5f]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 51% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 1.5 mL/min, t_R=6.20 and 25.92 min, λ=205 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.30–7.21 (m, 4H), 4.45 (d, *J*=8.5 Hz, 1H), 4.03 (d, *J*=6.9 Hz, 1H), 3.87 (s, 3H), 3.55 (t, *J*=7.4 Hz, 1H), 3.41 (t, *J*=8.1 Hz, 1H), 2.86 (s, 3H), 2.39 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.7, 174.5, 169.9, 135.2, 133.9, 128.6, 128.4, 63.2, 61.5, 52.3, 49.2, 47.9, 24.9.

*4.2.11. (1S,3R,3S,6R)-Methyl 4,6-dioxo-3-(4-chlorophenyl)-5-phenyl-octahydropyrrole[3,4-c]pyrrole-1-carboxylate (**5b**)*[9]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 78% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 1.5 mL/min, t_R=7.11 and 19.85 min, λ=220 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.36 (m, 4H), 7.33–7.30 (m, 3H), 7.12 (d, *J*=7.1 Hz, 2H), 4.52 (d, *J*=8.7 Hz, 1H), 4.01 (d, *J*=6.6 Hz, 1H), 3.84 (s, 3H), 3.67 (t, *J*=7.2 Hz, 1H), 3.49 (t, *J*=8.2 Hz, 1H), 2.48 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.9, 173.5, 169.9, 135.3, 133.9, 131.4, 129.1, 128.6, 128.5, 128.4, 126.0, 63.3, 61.7, 52.3, 49.0, 47.9.

*4.2.12. (1S,3R,3S,6R)-Methyl 5-methyl-4,6-dioxo-3-phenyl-octahydropyrrole[3,4-c]pyrrole-1-carboxylate (**5c**)*[5f]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 75% ee. HPLC: Daicel Chiralpak AD-H column, *i*-PrOH/hexane 50:50, flow rate 0.7 mL/min, t_R=9.09 and 10.85 min, λ=220 nm; ^1H NMR (400 MHz, $CDCl_3$): δ=7.34 (m, 5H), 4.50 (d, *J*=8.6 Hz, 1H), 4.06 (d, *J*=6.8 Hz, 1H), 3.88 (s, 3H), 3.57 (t, *J*=7.2 Hz, 1H), 3.43 (t, *J*=8.2 Hz, 1H), 2.87 (s, 3H); 2.73(br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.9, 174.6, 170.1, 136.6, 128.4, 128.3, 126.9, 64.0, 61.6, 52.1, 49.5, 48.2, 24.9.

*4.2.13. (1S,3R,3S,6R)-Methyl 4,6-dioxo-3-(4-fluorophenyl)-5-phenyl-octahydropyrrole[3,4-c]pyrrole-1-carboxylate (**5d**)*[9]. White solid;

SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 65% ee. HPLC: Daicel Chiralpak AS-H column, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=5.98 and 11.65 min, λ=220 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45–7.38 (m, 5H), 7.15–7.13 (m, 2H), 7.07–7.03 (m, 2H), 4.60 (d, *J*=8.8 Hz, 1H), 4.14 (d, *J*=6.7 Hz, 1H), 3.87 (s, 3H), 3.73 (t, *J*=7.1 Hz, 1H), 3.55 (t, *J*=8.3 Hz, 1H), 2.49 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.9, 173.5, 169.9, 162.6 (d, *J*=245.5 Hz), 132.4, 131.6, 129.1, 128.8 (d, *J*=8.2 Hz), 128.6, 128.0, 115.5 (d, *J*=21.3 Hz), 63.5, 61.8, 52.3, 49.2, 48.1.

*4.2.14. (1S,3R,3S,6R)-Methyl 4,6-dioxo-3-(2-methylphenyl)-5-phenyl-octahydropyrrole[3,4-c]pyrrole-1-carboxylate (**5e**)*[8i]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 20% ee. HPLC: Daicel Chiralpak AS-H, *i*-PrOH/hexane 50:50, flow rate 0.8 mL/min, t_R=11.21 min and 52.07 min, λ=220 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68–7.64 (m, 1H), 7.37–7.18 (m, 6H), 7.09–7.03 (m, 2H), 4.76–4.73 (m, 1H), 4.17–4.14 (m, 1H), 3.90 (s, 3H), 3.73 (t, *J*=6.2 Hz, 1H), 3.64 (t, *J*=8.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.2, 173.53, 170.2, 135.7, 135.53, 131.3, 130.1, 128.9, 128.5, 128.1, 126.3, 126.2, 125.5, 61.4, 60.5, 52.5, 48.3, 47.1, 19.3.

*4.2.15. (1S,3R,3S,6R)-Methyl 4,6-dioxo-3-(3-bromophenyl)-5-phenyl-octahydropyrrole[3,4-c]pyrrole-1-carboxylate (**5f**)*[9]. White solid; SiO_2 chromatography: *n*-hexane–EtOAc 1:1; 57% ee. HPLC: Daicel Chiralcel OD-H column, *i*-PrOH/hexane 50:50, flow rate 1 mL/min, t_R=19.22 min and 35.37 min, λ=230 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (s, 1H), 7.48–7.35 (m, 5H), 7.25–7.14(m, 3H), 4.57 (dd, *J*=4.5, 9.0 Hz, 1H), 4.14 (dd, *J*=4.5, 6.6 Hz, 1H), 3.88 (s, 3H), 3.75 (t, *J*=6.9 Hz, 1H), 3.57 (t, *J*=8.4 Hz, 1H), 2.52 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.9, 173.7, 169.8, 145.5, 139.4, 131.8, 131.7, 130.3, 129.5, 128.8, 126.4, 126.2, 122.9, 63.6, 61.8, 52.6, 49.2, 47.9.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.091.

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