Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c8ob02922a

A new trifluoromethylated sulfonamide phosphine ligand for Ag(I)-catalyzed enantioselective [3 + 2] cycloaddition of azomethine ylides†

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Received 23rd November 2018,
Accepted 18th December 2018

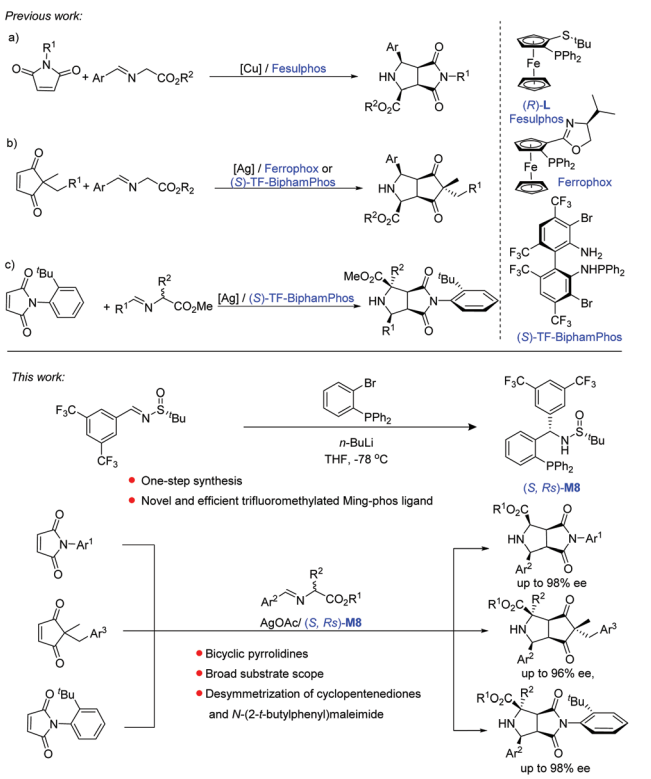
DOI: 10.1039/c8ob02922a

rsc.li/obc

A newly developed Ming-Phos ligand with a 3,5-bis(trifluoromethyl)phenyl substituent was demonstrated to be highly efficient for Ag-catalyzed asymmetric [3 + 2] cycloaddition reactions of azomethine ylides with maleimides, cyclopentene-1,3-diones, and *N*-(2-*t*-butylphenyl)maleimide. Being easily prepared on the gram scale in one step, the ligand in combination with a Ag catalyst enables the synthesis of a variety of highly functionalized bicyclic pyrrolidine derivatives in good yields and excellent enantioselectivities under mild conditions.

Introduction

Highly substituted pyrrolidine derivatives are prevalent in natural products, and biological and pharmaceutical molecules.[1] Furthermore, it is also a privileged architecture in chiral ligands and organocatalysts.[2] Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient alkenes is one of the most powerful and diversity-oriented synthetic methods for the construction of these types of compounds.[3] Various electron-deficient alkenes including dimethyl malenate,[4] *tert*-butyl acrylate,[5] vinylarenes,[6] and nitroalkenes,[7] among others have been utilized in such strategies. Internal C–C double bonds in five-membered cyclic structures are also reactive. In 2005, Carretero *et al.* reported an asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylide with maleimides, using a Cu–Fesulphos complex as the catalyst to produce a series of octahydropyrrolo[3,4-*c*]pyrrole derivatives (Scheme 1a).[8] Recently, Singh[9] and Wang[10] independently reported a Ag(I)-catalyzed desymmetrization of prochiral cyclopentene-1,3-diones *via* [3 + 2] cycloaddition with azomethine ylides using ferrophox and (*S*)-TF-BiphamPhos, respectively (Scheme 1b). Later on, Wang reported a highly efficient Ag(I)-catalyzed atroposelective desymmetrization of *N*-(2-*t*-butylphenyl)maleimide *via* 1,3-dipolar cycloaddition with *in situ* generated azomethine ylides using (*S*)-TF-BiphamPhos as the ligand, affording a range of octahydropyrrolo[3,4-*c*]pyrrole derivatives (Scheme 1c).[11]



Scheme 1 Ag(I)-Catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with maleimides, cyclopentene-1,3-diones, and *N*-(2-*t*-butylphenyl)maleimide.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02922a

Despite the above achievements, it is still highly desirable to develop new catalyst systems, especially the ones with efficient and simple chiral ligands for asymmetric 1,3-dipolar cycloaddition reactions compatible with broad functional groups for the synthesis of multi-substituted pyrrolidine derivatives.

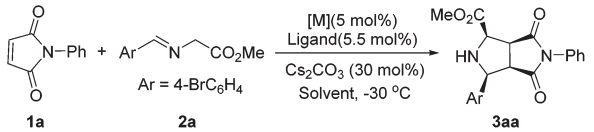
Over the past few years, we have been focusing on the development of new chiral sulfonamide phosphine ligands for transition metal catalysed asymmetric reactions.[12–16] Specifically, Ming-Phoses have been successfully applied to the Au(I)-catalyzed intermolecular asymmetric cyclization of 2-(1-alkynyl)-2-alken-1-ones with nitrones and 3-stylindoles,[13a–c] and Cu(I)-catalyzed asymmetric [3 + 2] cycloaddition reactions of azomethine ylides with β-trifluoromethyl-β,β-disubstituted enones and α-trifluoromethyl-α,β-unsaturated esters with excellent diastereo- and enantioselectivity.[13d–f] Considering the simplicity and modularity in preparation and handling, which leads to a trivial synthesis of a ligand library, we hope to extend its utilization to other kinds of [3 + 2] cycloaddition reactions, especially the ones leading to meaningful cyclic structures. Herein, we describe our results on the application of Ming-Phos in silver catalyzed asymmetric [3 + 2] cycloaddition reactions of azomethine ylides with maleimides, cyclopentene-1,3-diones, and *N*-(2-*t*-butylphenyl)maleimide (Scheme 1, bottom).

Results and discussion

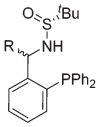
In view of its notable performance in [3 + 2] cycloaddition reactions,[13d–f] Ming-Phos (R,R_s)-**M7** was initially evaluated in combination with the $[Cu(CH_3CN)_4]ClO_4$ catalyst for the reaction maleimide **1a** and azomethine ylide **2a**. However, a racemic cycloadduct **3aa** was obtained (Table 1, entry 1). Delightfully, a dramatically higher yield of 91% was achieved when AgOAc was used, although the enantioselectivity was moderate (Table 1, entry 2). Consequently, while (R,R_s)-**M1** with a phenyl group led to poor enantioselectivity (Table 1, entry 3), the isomeric ligand (S,R_s)-**M1** afforded a much higher ee (Table 1, entry 4), implying that the aryl group might be more effective for the asymmetric transformation. Accordingly, ligands with different aryl substituents were prepared for further investigation. The performances of (S,R_s)-**M3** and **M4**, bearing 4-methoxyphenyl and 1-naphthyl groups, underlined the importance of the aryl moiety: both ligands failed to improve the enantioselectivity (Table 1, entries 5 and 6). To our delight, when (S,R_s)-**M8** with a 3,5-bis(trifluoromethyl)phenyl group was introduced, the reaction proceeded remarkably to give cycloadduct **3aa** in 90% yield and 93% ee (Table 1, entry 7). So we chose (S,R_s)-**M8** as the chiral ligand for further screening. Changing to other silver catalysts such as $AgCO_3$, Ag_2O led to inferior results (Table 1, entries 8 and 9). The reaction was completely shut down with AgBr (Table 1, entry 10). Other solvents were also tested, and xylene was proved to be the best choice (Table 1, entries 11–14).

With the optimized reaction conditions in hand, we first investigated the scope of azomethine ylides **2** with maleimide **1a** (Table 2). Gratifyingly, all of the halogen atoms located at

Table 1 Optimization of the reaction conditions[a]



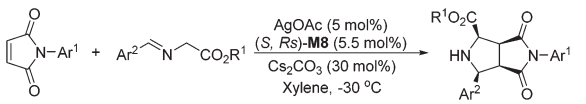
Entry	[M][a]	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	$[Cu(CH_3CN)_4]ClO_4$	(R,R_s)-**M7**	Xylene	29	0
2	AgOAc	(R,R_s)-**M7**	Xylene	91	−50
3	AgOAc	(R,R_s)-**M1**	Xylene	85	20
4	AgOAc	(S,R_s)-**M1**	Xylene	84	75
5	AgOAc	(S,R_s)-**M3**	Xylene	83	66
6	AgOAc	(S,R_s)-**M4**	Xylene	95	29
7	AgOAc	(S,R_s)-**M8**	Xylene	90	93
8	$AgCO_3$	(S,R_s)-**M8**	Xylene	95	90
9	Ag_2O	(S,R_s)-**M8**	Xylene	88	90
10	AgBr	(S,R_s)-**M8**	Xylene	—	—
11	AgOAc	(S,R_s)-**M8**	DCM	82	63
12	AgOAc	(S,R_s)-**M8**	Toluene	88	90
13	AgOAc	(S,R_s)-**M8**	Et_2O	99	86
14	AgOAc	(S,R_s)-**M8**	THF	99	72



(R, R_S)-**M7**: R = ^{t}Bu
(R, R_S)-**M1**: R = Ph
(S, R_S)-**M1**: R = Ph
(S, R_S)-**M3**: R = 4-MeOPh
(S, R_S)-**M4**: R = 1-Napth
(S, R_S)-**M8**: R = 3,5-bis(fluoromethyl)phenyl

[a] All reactions were carried out using 0.1 mmol of **1a**, 0.11 mmol of **2a**, 5 mol% of [M], and 5.5 mol% of ligand in 1.0 mL xylene for 15 h. [b] Yields of **3aa** were determined by ^{1}H NMR analysis with CH_2Br_2 as an internal standard. [c] The ee values of **3aa** were determined by chiral HPLC analysis.

Table 2 The scope of the reaction between aryl maleimide and azomethine ylide[a]



Entry	Ar^1	Ar^2/R^1	3	Yield[b] (%)	ee[c] (%)
1	Ph	4-BrC_6H_4/Me	**3aa**	90	93
2	Ph	4-ClC_6H_4/Me	**3ab**	99	91
3	Ph	4-IC_6H_4/Me	**3ac**	91	90
4	Ph	3-FC_6H_4/Me	**3ad**	85	90
5	Ph	$4\text{-CF}_3C_6H_4$/Me	**3ae**	91	91
6	Ph	4-CNC_6H_4/Me	**3af**	88	98
7	Ph	4-SMeC_6H_4/Me	**3ag**	93	92
8	Ph	4-PhC_6H_4/Me	**3ah**	99	98
9	Ph	2-MeC_6H_4/Me	**3ai**	62	84
10	Ph	2-MeC_6H_4/^{t}Bu	**3aj**	81	94
11	Ph	Ph/Me	**3ak**	98	85
12	Ph	4-BrC_6H_4/Bn	**3al**	83	95
13	4-FC_6H_4	4-BrC_6H_4/Me	**3ba**	95	91
14	4-ClC_6H_4	4-BrC_6H_4/Me	**3ca**	96	83
15	4-ClC_6H_4	4-BrC_6H_4/^{t}Bu	**3cm**	80	96
16	3-ClC_6H_4	4-BrC_6H_4/Me	**3da**	>99	92
17	4-MeC_6H_4	4-BrC_6H_4/Me	**3ea**	93	93

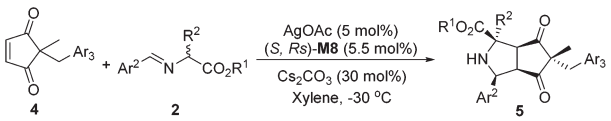
[a] All reactions were carried out with 0.165 mmol of **1**, 0.15 mmol of **2**, 5 mol% of AgOAc, and 5.5 mol% of ligand in 2.0 mL xylene for 12–24 h. [b] Isolated yield. [c] The ees of **3** were determined by HPLC analysis.

both 4- and 3- positions of the phenyl groups were untouched, thus providing opportunities for subsequent manipulation (entries 1–4). Electron-withdrawing trifluoromethyl and nitrile groups were well tolerated (entries 5 and 6). The significantly higher enantioselectivity for the latter might be due to the conjugation effect of the nitrile group. The reaction was not affected by the methylthio group, affording product **3ag** in a high yield and ee value (entry 7). In accordance with the nitrile substrate, azomethine ylide with a conjugated phenyl group showed obviously better results, leading to the desired product **3ah** with 98% ee in quantitative yield (entry 8). The reactivity was impaired for a more sterically hindered substrate with an *ortho*-methyl group (entry 9), which gave a significantly lower yield compared with unsubstituted azomethine imine (entry 11). When sterically hindered *tert*-butyl ester was introduced instead of the methyl substrate, product **3aj** was obtained in notably higher enantioselectivity (entry 10). Glycine ketoimino benzyl ester also showed excellent reactivity, providing chiral bicyclic adduct **3al** in high yield and optical purity (entry 12). As to the scope of maleimide **1**, analogues bearing both fluoride and chlorides were well tolerated, leading to halogenated products efficiently (entries 13–16). Again, the *tert*-butyl ester group led to higher enantioselectivity compared with the methyl substrate (entries 14 and 15). Me-substitution at Ar^1 was also accommodated, as pyrrolidinedione **3ea** was also obtained in excellent yield and enantioselectivity with this strategy (entry 17).

Next, we tried to extend this practical methodology to the synthesis of other types chiral pyrrolidine derivatives. To our delight, cyclopentene-1,3-dione **4** could be applied to the transformation without the necessity to modify the conditions, further demonstrating the power of the new ligand. The broad generality of the reaction is presented in Table 3. Again, various halogens and the methyl group on the phenyl moieties in both cyclopentene-1,3-diones (entries 14–18) and azomethine ylides (entries 1–4, 9–12) were all untouched, leading to the corresponding products in high yields and enantioselectivities. Other types of electron-donating or electron-withdrawing groups such as trifluoromethyl-, nitrile-, methylthio- and phenyl groups were also well tolerated (entries 6–9). Ethyl ester displayed similar reactivity and selectivity (entry 10). Moreover, chiral pyrrolidine products with two quaternary carbon centers could be prepared using more sterically hindered imino esters derived from α-substituted-α-amino acids (entries 11–13). No erosion on the reactivity was detected for all of the substrates tested.

Based on the above work, we envisaged that the Ag(I)/Ming-Phos complex could be employed as an effective catalyst for the atroposelective desymmetrization of prochiral *N*-(2-*t*-butylphenyl)maleimide with azomethine ylides, affording octahydropyrrolo[3,4-*c*]pyrrole derivatives decorated with four adjacent stereogenic centers and one N–C chiral axis through a 1,3-dipolar cycloaddition reaction. Fortunately, the above optimal conditions apply equally well in the cycloaddition of azomethine ylide **2** and prochiral *N*-(2-*t*-butylphenyl)maleimide **6**, affording octahydropyrrolo[3,4-*c*]pyrrole derivatives **7** with

Table 3 The scope of the reaction between cyclopentene-1,3-diones and azomethine ylides[a]



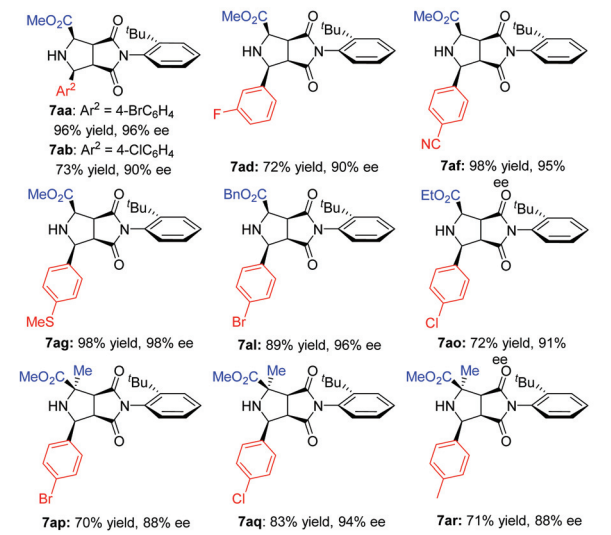
4 2 5

Entry	Ar^3	$Ar^2/R^1/R^2$	5	Yield[b] (%)	ee[c] (%)
1	Ph	4-BrC_6H_4/Me/H	**5aa**	86	96
2	Ph	4-ClC_6H_4/Me/H	**5ab**	95	95
3	Ph	4-IC_6H_4/Me/H	**5ac**	85	94
4	Ph	3-FC_6H_4/Me/H	**5ad**	62	90
5	Ph	4-$CF_3C_6H_4$/Me/H	**5ae**	70	94
6	Ph	4-CNC_6H_4/Me/H	**5af**	83	95
7	Ph	4-$SMeC_6H_4$/Me/H	**5ag**	70	94
8	Ph	4-PhC_6H_4/Me/H	**5ah**	90	95
9	Ph	4-FC_6H_4/Me/H	**5an**	73	92
10	Ph	4-ClC_6H_4/Et/H	**5ao**	82	94
11	Ph	4-BrC_6H_4/Me/Me	**5ap**	89	92
12	Ph	4-ClC_6H_4/Me/Me	**5aq**	91	90
13	Ph	4-MeC_6H_4/Me/Me	**5ar**	80	91
14	4-ClC_6H_4	4-BrC_6H_4/Me/H	**5ba**	84	94
15	4-FC_6H_4	4-BrC_6H_4/Me/H	**5ca**	83	95
16	4-MeC_6H_4	4-BrC_6H_4/Me/H	**5da**	81	95
17	3-ClC_6H_4	4-BrC_6H_4/Me/H	**5ea**	82	95
18	2-ClC_6H_4	4-BrC_6H_4/Me/H	**5fa**	86	85

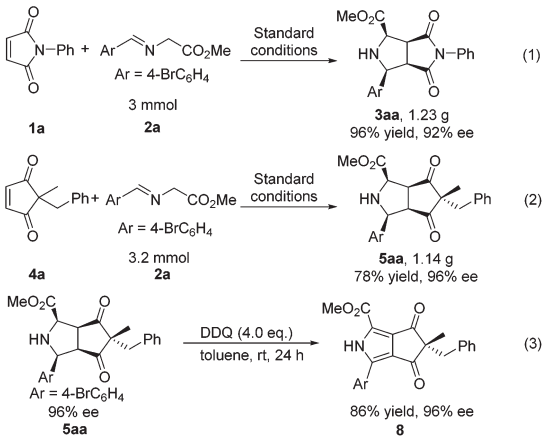
[a] All reactions were carried out with 0.165 mmol of **1**, 0.15 mmol of **2**, 5 mol% of AgOAc, and 5.5 mol% ligand in 2.0 mL xylene for 12–24 h. [b] Isolated yield. [c] The ees of **5** were determined by HPLC analysis.

Table 4 Substrate scope of azomethine ylides for Ag-catalyzed desymmetrization of *N*-(2-*t*-butylphenyl)maleimide[a,b,c]

6 2 7



[a] All reactions were carried out with 0.165 mmol of **1**, 0.15 mmol of **2**, 5 mol% of AgOAc, and 5.5 mol% of ligand in 2.0 mL xylene for 12–24 h. [b] Isolated yield of **7**. [c] The ees of **7** were determined by HPLC analysis.



Scheme 2 Gram-scale experiment and synthetic transformation.

excellent yield and enantioselectivity. Consequently, we examined the scope with respect to the azomethine ylide component **2** by reaction with **6** (Table 4). A series of electron-rich and electron-deficient arylaldehyde-derived benzylideneamino acetates reacted smoothly with **6** delivering the corresponding chiral axis products bearing halogen atoms (**7aa**–**7ad**), nitrile (**7af**) and methylthio groups (**7ag**). Ethyl and benzyl glycine ketoimino esters were also examined, and the desired cycloadducts were generated without any sacrifice of reactivity or selectivity (**7al**, **7ao**). Again, α-methyl substituted azomethine ylides could be applied in the system, affording cycloadducts **7ap**–**7ar** with a quaternary carbon center in high yields and enantioselectivities.

To further explore the practicability of our methodology, gram-scale reactions were conducted. Both the reaction of **1a** and **4a** with **2a** could be efficiently scaled up without any loss of efficiency and selectivity, delivering the cycloadducts **3aa** (Scheme 2, eqn (1)) and **5aa** (Scheme 2, eqn (2)) in high yields and optical purities. Upon oxidation with DDQ, the bicyclic-pyrrolidine cycloadduct **5aa** delivered the enantioenriched bicyclic pyrrole derivative **8** without any loss of enantioselectivity (Scheme 2, eqn (3)).

Conclusions

In conclusion, we have reported the asymmetric [3 + 2] cycloaddition reaction of azomethine ylides with maleimides, cyclopentene-1,3-diones, and *N*-(2-*t*-butylphenyl)maleimide with an easily available Ming-Phos derivative, and firstly realized the silver/Ming-Phos-catalyzed asymmetric reactions. The methodology proceeds well over a broad scope of substrates, providing facile access to a series of highly functionalized bicyclic pyrrolidines in high yields and excellent enantioselectivities. Moreover, prochiral cyclopentenedione and *N*-(2-*t*-butylphenyl) maleimide could also be introduced into the reaction system. The desymmetrization process allowed for the access of the corresponding chiral products efficiently. The investigation of the application of these ligands in other reaction systems is underway in our lab.

Experimental section

Materials and methods

All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. ^{1}H NMR spectra, ^{19}F NMR spectra, ^{31}P NMR spectra, and ^{13}C NMR spectra were recorded on a Bruker 300, 400 and 500 MHz spectrometer in $CDCl_3$. All signals are reported in ppm with the internal TMS signal at 0 ppm as a standard. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift (ppm) relative to a residual solvent peak ($CDCl_3$: 77.0 ppm). Reactions were monitored by thin layer chromatography (TLC) using silica gel plates. Flash column chromatography was performed over silica gel (300–400 mesh). The enantiomeric excesses of the products were determined by chiral stationary phase HPLC using a Chiralpak AS-H, AD-H, IE.

General procedure for the synthesis of ligand (S,R_s)-M8. To a solution of (2-bromophenyl)diphenylphosphane (12 mmol) in dry THF (15 mL) was added *n*-BuLi (12 mmol, 2.4 M in hexane) dropwise under argon at −78 °C. After 2 hours at this temperature, the solution of (*R*,*E*)-*N*-(3,5-bis(trifluoromethyl) benzylidene)-2-methylpropane-2-sulfinamide (10 mmol) in THF (10 ml) was added dropwise, and the reaction mixture was warmed to room temperature overnight. The reaction mixture was quenched by the addition of NH_4Cl (aq.) and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was then purified by flash column chromatography on silica gel (petroleum ether : AcOEt = 15 : 1) to afford (S,R_s)-**M8**.

(S,R_s)-M8. As a white solid (3.5241 g, 58% yield); $[\alpha]_D^{25}$ = −40.9 (c = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 3 H), 7.49–7.44 (m, 2 H), 7.29–7.25 (m, 4 H), 7.23–7.19 (m, 1 H), 7.14 (dd, J = 13.7, 6.0 Hz, 4 H), 7.05 (dd, J = 6.9, 4.0 Hz, 1 H), 6.98 (t, J = 7.4 Hz, 2 H), 6.66 (s, 1 H), 4.13 (s, 1 H), 1.24 (s, 9 H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.78. ^{31}P NMR (162 MHz, $CDCl_3$): δ −18.56; ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.84 (d, J = 24.2 Hz), 144.55, 135.8–135.7 (m), 135.51, 134.70 (d, J = 8.1 Hz), 133.69 (d, J = 12.9 Hz), 133.50 (d, J = 12.3 Hz), 131.53 (q, J = 33.3 Hz), 129.74, 128.81 (d, J = 9.4 Hz), 128.50 (dd, J = 7.0, 4.6 Hz), 128.16 (d, J = 5.6 Hz), 122.98 (q, J_{C-F} = 273.0 Hz), 121.31 (dt, J = 7.3, 3.8 Hz), 60.53, 60.29, 56.41, 22.62. ESI-MS calculated for $C_{31}H_{29}F_6NOPS$: m/z (%): 608.1606 ($M + H^+$), found: 608.1606.

General procedure for the asymmetric silver-catalyzed cycloaddition of azomethine ylides with maleimides. A solution of (S,R_s)-**M8** (5.5 mol%) and AgOAc (5 mol%) in xylene (2 mL) was

stirred at room temperature for 2 h. The reaction mixture was cooled to −30 °C and then the imino ester **2** (0.15 mmol), Cs_2CO_3 (0.045 mmol) and maleimide **1** (0.165 mmol) were added sequentially. Following complete consumption of the imino ester **2**, the solvent was removed under reduced pressure. The crude product was then purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent (2/1–1/1) to afford the desired product.

Methyl (*1R*,*3S*,*3aR*,*6aS*)-3-(4-bromophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (3aa). As a white solid (61.8 mg, 96% yield); mp: 175–176 °C; $[\alpha]_D^{25}$ = −123.8 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.48 (d, *J* = 8.4 Hz, 2 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.34–7.32 (m, 3 H), 7.13 (d, *J* = 7.5 Hz, 2 H), 4.54 (dd, *J* = 8.6, 4.8 Hz, 1 H), 4.12 (dd, *J* = 6.4, 4.7 Hz, 1 H), 3.86 (s, 1 H), 3.71 (t, *J* = 7.2 Hz, 3 H), 3.54 (t, *J* = 8.2 Hz, 1 H), 2.48 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$): *δ* 174.88, 173.43, 169.88, 135.75, 131.59, 131.45, 129.07, 128.79, 128.58, 126.02, 122.27, 63.47, 61.75, 52.34, 49.03, 47.94. ESI-MS calculated for $C_{20}H_{18}BrN_2O_4$: *m*/*z* (%): 429.0444 (M + H^+), found: 429.0449. Enantiomeric excess was determined by HPLC with a Chiralpak ASH column (hexanes : 2-propanol = 50 : 50, 0.8 mL min^{-1}, 210 nm); minor enantiomer tr = 17.9 min, major enantiomer tr = 39.1 min (93% ee).

Methyl (*1R*,*3S*,*3aR*,*6aS*)-3-(4-bromophenyl)-5-(4-fluorophenyl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (3ba). As a white solid (62.7 mg, 93% yield); mp: 231–232 °C; $[\alpha]_D^{25}$ = −119.8 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.47 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.15–7.05 (m, 4 H), 4.55 (d, *J* = 8.4 Hz, 1 H), 4.13 (d, *J* = 6.4 Hz, 1 H), 3.86 (s, 3 H), 3.71 (t, *J* = 7.1 Hz, 1 H), 3.55 (t, *J* = 8.2 Hz, 1 H), 2.33 (s, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): *δ* −112.25−−112.31 (m); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 174.78, 173.32, 169.84, 162.08 (d, *J* = 248.8 Hz), 135.69, 131.61, 128.73, 127.89 (d, *J* = 8.8 Hz), 127.35 (d, *J* = 3.3 Hz), 122.32, 116.09 (d, *J* = 23.0 Hz), 63.45, 61.75, 52.35, 49.01, 47.88. ESI-MS calculated for $C_{20}H_{16}BrF_5NaO$: *m*/*z* (%): 469.0197 (M + H^+), found: 469.0193. Enantiomeric excess was determined by HPLC with a Chiralpak ASH column (hexanes : 2-propanol = 50 : 50, 0.8 mL min^{-1}, 210 nm); minor enantiomer tr = 15.7 min, major enantiomer tr = 28.8 min (93% ee).

General procedure for the asymmetric silver-catalyzed cycloaddition of azomethine ylides with cyclopentene-1,3-diones. A solution of (*S*,R_s)-**M8** (5.5 mol%) and AgOAc (5 mol%) in xylene (2 mL) was stirred at room temperature for 2 h. The reaction mixture was cooled to −30 °C and then the imino ester **2** (0.15 mmol), Cs_2CO_3 (0.045 mmol) and cyclo-pentenedione **4** (0.165 mmol) were added sequentially. Following complete consumption of the imino ester **2**, the solvent was removed under reduced pressure. The crude product was then purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent (2/1–1/1) to afford the desired product. The configuration of **5** was determined by comparison with the literature, see: ref. 9.

Methyl (*1R*,*3S*,*3aR*,*5R*,*6aS*)-5-benzyl-3-(4-bromophenyl)-5-methyl-4,6-dioxooctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5aa). As a white solid (58.8 mg, 86% yield); mp: 153–154 °C; $[\alpha]_D^{25}$ = −9.8 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.46–7.36 (m, 2 H), 7.18 (dd, *J* = 5.4, 2.0 Hz, 5 H), 6.92 (dd, *J* = 6.5, 3.1 Hz, 2 H), 4.29 (d, *J* = 8.0 Hz, 1 H), 3.91–3.88 (m, 1 H), 3.85 (s, 3 H), 2.83 (s, 2 H), 2.75 (dd, *J* = 5.2, 2.6 Hz, 2 H), 2.22 (s, 1 H), 1.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 217.27, 215.43, 170.51, 136.19, 135.63, 131.28, 129.63, 128.63, 128.51, 127.11, 121.73, 65.41, 63.44, 60.22, 55.79, 54.26, 52.09, 43.84, 18.21. ESI-MS calculated for $C_{23}H_{23}BrNO_4$: *m*/*z* (%): 456.0805 (M + H^+), found: 456.0817. Enantiomeric excess was determined by HPLC with a Chiralpak ASH column (hexanes : 2-propanol = 50 : 50, 0.8 mL min^{-1}, 210 nm); minor enantiomer tr = 9.4 min, major enantiomer tr = 13.3 min (96% ee).

Methyl (*1R*,*3S*,*3aR*,*5R*,*6aS*)-3-(4-bromophenyl)-5-(4-chlorobenzyl)-5-methyl-4,6-dioxooctahydrocyclopenta[*c*]pyrrole-1-carboxylate (5ba). As a white solid (62.0 mg, 84% yield); mp: 170–171 °C; $[\alpha]_D^{25}$ = 5.9 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.44 (d, *J* = 8.3 Hz, 2 H), 7.16 (dd, *J* = 11.8, 8.4 Hz, 4 H), 6.84 (d, *J* = 8.3 Hz, 2 H), 4.32 (d, *J* = 7.6 Hz, 1 H), 3.93 (d, *J* = 6.9 Hz, 1 H), 3.84 (s, 3 H), 2.83–2.79 (m, 4 H), 2.25 (s, 1 H), 1.11 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 217.00, 215.17, 170.36, 136.00, 134.22, 133.07, 131.30, 131.07, 128.61, 128.57, 121.77, 65.46, 63.53, 60.06, 55.77, 54.21, 52.10, 42.42, 18.36. ESI-MS calculated for $C_{23}H_{22}BrClNO_4$: *m*/*z* (%): 490.0415 (M + H^+), found: 490.0426. Enantiomeric excess was determined by HPLC with a Chiralpak ASH column (hexanes : 2-propanol = 80 : 20, 0.8 mL min^{-1}, 210 nm); minor enantiomer tr = 15.1 min, major enantiomer tr = 18.1 min (94% ee).

General procedure for the asymmetric silver-catalyzed cycloaddition of azomethine ylides with *N*-(2-*t*-butylphenyl)maleimide. A solution of (*S*,R_s)-**M8** (5.5 mol%) and AgOAc (5 mol%) in xylene (2 mL) was stirred at room temperature for 2 h. The reaction mixture was cooled to −30 °C and then the imino ester **2** (0.15 mmol), Cs_2CO_3 (0.045 mmol) and *N*-(2-*t*-butylphenyl)maleimide **6** (0.165 mmol) were added sequentially. Following complete consumption of the imino ester **2**, the solvent was removed under reduced pressure. The crude product was then purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent (2/1–1/1) to afford the desired product. The configuration of **7** was determined by comparison with the literature, see: ref. 11.

Methyl (*1R*,*3S*,*3aR*,*6aS*)-3-(4-bromophenyl)-5-(2-(*tert*-butyl)phenyl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (7aa). As a white solid (70.2 mg, 96% yield); mp: 196–197 °C; $[\alpha]_D^{25}$ = −102.9 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.49–7.44 (m, 3 H), 7.35–7.30 (m, 3 H), 7.27–7.23 (m, 1 H), 6.85 (d, *J* = 1.5 Hz, 1 H), 4.49 (dd, *J* = 8.2, 4.0 Hz, 1 H), 4.11–4.08 (m, 1 H), 3.83 (s, 3 H), 3.67 (dd, *J* = 14.6, 7.0 Hz, 1 H), 3.52 (t, *J* = 8.1 Hz, 1 H), 2.46 (s, 1 H), 1.21 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 176.03, 174.62, 169.86, 147.65, 135.63, 131.44, 130.80, 129.89, 129.79, 128.75, 128.70, 127.55, 122.05, 63.54, 61.79, 52.29, 48.97, 47.68, 35.58, 31.56. ESI-MS calculated for $C_{24}H_{25}BrN_2NaO_4$: *m*/*z* (%): 507.0890 (M + H^+), found: 507.0901. Enantiomeric excess was determined by HPLC with a Chiralpak ASH column (hexanes : 2-propanol = 50 : 50, 1.0 mL min^{-1}, 220 nm); minor enantiomer tr = 5.8 min, major enantiomer tr = 9.2 min (96% ee).

General procedure for the synthesis of 8. A solution of compound **5aa** (136.9 mg, 0.3 mmol) in toluene (3 mL) was stirred at room temperature in a sealed tube. DDQ (1.2 mmol) was then added. Consumption of the starting material was monitored by TLC analysis. After **5aa** was completely consumed, the reaction mixture was quenched by the addition of $NaHCO_3$ (aq.) and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was analyzed by ^1H NMR and ^{19}F NMR spectroscopy to determine the diastereomeric ratio. The crude product was then purified by flash column chromatography on silica gel (petroleum ether : AcOEt = 3 : 1) to afford the desired product.

Methyl (*R*)-5-benzyl-3-(4-bromophenyl)-5-methyl-4,6-dioxo-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate (8). As a white solid (116.3 mg, 86% yield); mp: 105–106 °C; $[\alpha]_D^{25}$ = 199.0 (*c* = 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 11.16 (s, 1 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 7.54 (d, *J* = 8.6 Hz, 2 H), 7.06–6.99 (m, 5 H), 3.85 (s, 3 H), 3.12 (s, 2 H), 1.40 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.71, 196.29, 160.22, 136.30, 134.16, 132.99, 132.23, 129.82, 129.61, 128.27, 127.97, 126.68, 126.54, 124.67, 116.65, 63.22, 52.87, 41.50, 21.30. ESI-MS calculated for $C_{20}H_{17}ClN_2NaO_4$: *m*/*z* (%): 407.0774 ($M + H^+$), found: 407.0769. Enantiomeric excess was determined by HPLC with a Chiralpak ADH column (hexanes : 2-propanol = 90 : 10, 1.0 mL min^{-1}, 254 nm); major enantiomer tr = 13.4 min, minor enantiomer tr = 17.4 min (96% ee).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the grant from the Science and Technology Development Project of Jilin Province (20170520137JH) and the National Natural Science Foundation of China (Grant No. 21602015).

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