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Catalytic Asymmetric Construction of Spirocycles Containing Pyrrolidine Motifs and Spiro Quaternary Stereogenic Centers *via* 1,3-Dipolar Cycloaddition of Azomethine Ylides with 2-Alkylidene-Cycloketones

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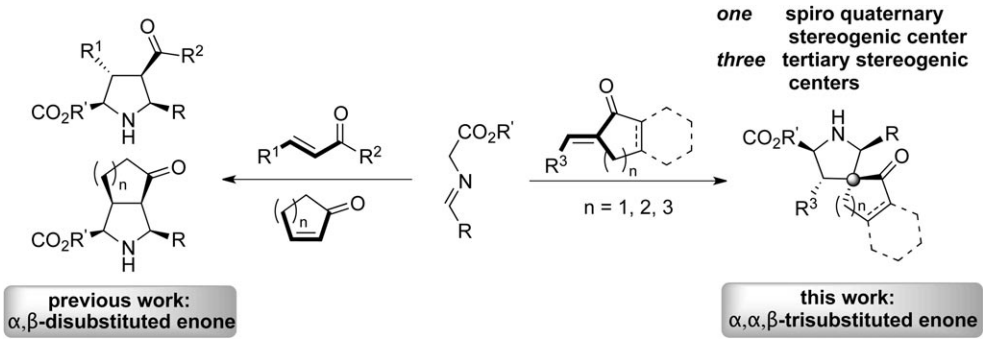
Abstract: The first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with various sterically hindered α,α,β-trisubstituted 2-alkylidene-cycloketones has been developed successfully with silver acetate/TF-BiphamPhos complex for the construction of spiro heterocyclic compounds containing pyrrolidine motifs and a spiro quaternary stereogenic carbon center. The highly efficient catalytic system exhibited high reactivity, excellent diastereoselectivity, good enantioselectivity and broad substrate scope under mild conditions. Subsequent transformations led to the expedient preparation of synthetically useful spiro[pyrrolidine-tetrahydropyranone] and spiro[pyrrolidine-isochroman-1-one] without loss of the diastereo- and enantiomeric excesses.

Keywords: asymmetric catalysis; azomethine ylides; diastereoselectivity; 1,3-dipolar cycloaddition; enantioselectivity; α,α,β-trisubstituted 2-alkylidene-cycloketones

The catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes is a powerful and atom-economical carbon-carbon bond forming reaction that facilitates the synthesis of a range of structurally and stereochemically rich pyrrolidines.[1] Because the resulting highly substituted pyrrolidines are prevalent in many natural alkaloids, compounds of pharmaceutical significance, organocatalysts, and biologically important building blocks in organic synthesis,[2] recent research has focused on the catalytic asymmetric version of the 1,3-dipolar cycloaddition of azomethine ylides. Since the pioneering work of Grigg[3] employing stoichiometric amounts of a chiral metal complex and the first catalytic asymmetric version reported by Zhang[4] using Ag(I)/xylyl-FAP system, various types of chiral metal catalysts[5–9] and organocatalysts[10] have been successfully developed to afford moderate to high enantio-/diastereoselectivities for this reaction over the last few years. Although most of the electron-deficient alkenes applied in these reactions are the derivatives of conjugated unsaturated esters, maleimides, vinyl sulfones, nitroalkenes and cyclopropylideneacetates,[3–10] α,β-disubstituted enones as dipolarophiles have also received attention in the asymmetric 1,3-dipolar cycloaddition due to their high electron-withdrawing carbonyl group and synthetic potential (left side of Scheme 1). Recently, Carretero has developed a general procedure for the first asymmetric 1,3-dipolar cycloaddition of azomethine ylides with α,β-disubstituted enones[11] catalyzed by Cu(I)/Fesulphos affording high diastereoselectivity and enantioselectivity. Chiral silver(I) complex-catalyzed asymmetric 1,3-dipolar cycloadditions with cyclic and acyclic α,β-disubstituted enones have been reported by Nájera using chiral $AgClO_4$/phosphoramidite[5c] and Fukuzawa using AgOAc/ThioClickFerrophos[5d] with excellent performances, respectively. More recently, Zheng and Hu's seminal work[12] showed that the combinations of Cu(I) or Ag(I) salts and newly-designed chiral ferrocenyl P,S-ligands also provided excellent enantioselectivities and diastereoselectivities for the catalytic 1,3-dipolar cycloaddition of azomethine ylides with various cyclic and acyclic α,β-disubstituted enones, such as cyclopent-2-enone, cyclohex-2-enone and chalcones. Never-

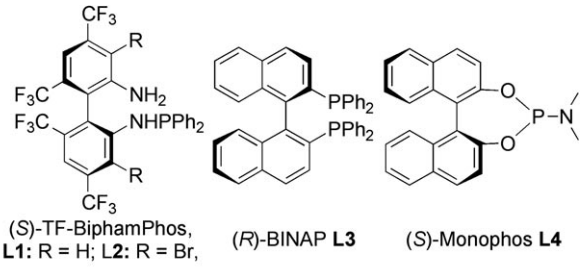


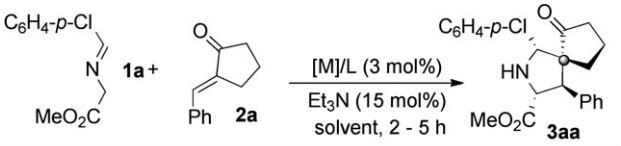
Scheme 1. Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylide with α,β-disubstituted enones (previous work) and α,α,β-trisubstituted enones for the construction of spirocyclic compounds (this work).

theless, in spite of recent advances on the application of enones as dipolarophiles, notable shortcomings still persist in this area, particularly in the context of efficient construction of spiro quaternary stereogenic carbon centers[13] using easily accessible but sterically hindered α,α,β-trisubstituted 2-alkylidene-ketones as dipolarophiles. In view of the simultaneous creation of one unique spiro quaternary and three tertiary stereogenic centers in the five-membered pyrrolidine rings, it is a great challenge to control both high enantioselectivity and diastereoselectivity in the asymmetric 1,3-dipolar cycloaddition reaction involving α,α,β-trisubstituted enones. Herein, we describe the first catalytic asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylide with various α,α,β-trisubstituted 2-alkylidene-ketones for the synthesis of spiro heterocyclic compounds containing pyrrolidine motifs and spiro quaternary stereogenic carbon centers using Ag(I)/TF-BiphamPhos complex[14] with excellent diastereoselectivity and up to 92% enantioselectivity (the right side of Scheme 1). In addition, subsequent transformations allowed for facile access to otherwise inaccessible enantioenriched spiro pyrrolidine-pyranones and pyrrolidine-isochroman- 1-ones *via* direct Baeyer–Villiger oxidation.

We began our investigations by examing the ability of Cu(I) and Ag(I)/TF-BiphamPhos complexes, previously developed in our laboratories, to promote the 1,3-dipolar cycloaddition of *N*-(4-chlorobenzylidene)-glycine methyl ester **1a** with α,α,β-trisubstituted enones. As the main objective of this research is 2-alkylidene-cycloketones, we chose (*E*)-2-benzylidenecyclopentanone **2a** to serve as the model dipolarophile. To our delight, the reaction was finished remarkably in less than 3 h with $Cu(CH_3CN)_4BF_4$/(*S*)-TF-BiphamPhos (**L1**) as the catalyst and Et_3N as base in dichloromethane at room temperature, yielding the expected spiro[cyclopentanone-2,3′-pyrrolidine] **3aa** with exclusive diastereoselectivity and 50% *ee* (Table 1, entry 1), which indicated that α,α,β-trisubstituted cyclic enones could be applied in our catalytic system as dipolarophiles for the efficient construction

Table 1. Optimization of catalytic asymmetric 1,3-dipolar cycloaddition of methyl *N*-(4-chlorobenzylidene)-glycinate **1a** with (*E*)-2-benzylidenecyclopentanone **2a**.[a]





Entry	L	[M]	Solvent	*T* [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	(*S*)-**L1**	$CuBF_4$	CH_2Cl_2	r.t.	3	78	50
2	(*S*)-**L1**	AgOAc	CH_2Cl_2	r.t.	3	80	75
3	(*S*)-**L2**	AgOAc	CH_2Cl_2	r.t.	3	90	84
4	(*S*)-**L2**	AgOAc	CH_2Cl_2	0	3	80	89
5	(*S*)-**L2**	AgOAc	CH_2Cl_2	–20	5	85	91
6	(*R*)-**L3**	AgOAc	CH_2Cl_2	–20	10	NR	-
7	(*S*)-**L4**	AgOAc	CH_2Cl_2	–20	5	60	30
8	(*S*)-**L2**	AgOAc	THF	–20	5	70	90
9	(*S*)-**L2**	AgOAc	Et_2O	–20	5	76	88
10	(*S*)-**L2**	AgOAc	CH_3CN	–20	5	67	80
11	(*S*)-**L2**	AgOAc	PhMe	–20	5	65	91
12	(*S*)-**L2**	AgOAc	$CHCl_3$	–20	5	85	89

[a] All reactions were carried out with 0.40 mmol of **1a** and 0.20 mmol of **2a** in 2 mL solvent. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$.

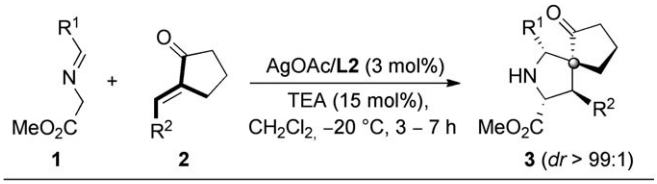
[b] Isolated yield.

[c] Enantioselectivity was determined by chiral HPLC analysis, and a >99:1 diastereomeric ratio was determined by HPLC analysis. Minor diastereomer was not detected in the crudematerial by ^1H NMR.

of chiral spirocyclic compounds. Subsequent studies showed that a silver(I) salt as the metal precursor gave better results than copper(I) salts in terms of the yield and enantioselectivity (Table 1, entry 2). Encouraged by these promising results, AgOAc was selected as the metal source for further ligand, solvent and base screening, and the representative results are presented in Table 1. (*S*)-TF-BiphamPhos (**L2**) bearing two bromines at the 3,3′-positions of the TF-BIPHAM backbone was the chiral ligand of choice and provided **3aa** as the sole product in high yield and 84% *ee* (Table 1, entry 3). The other commercially available chiral phosphine ligands such as BINAP and MonoPhos are either ineffective or provide relatively poor enantiomeric excesses (Table 1, entries 6 and 7). Reducing the temperature to −20 °C in DCM led to full conversion with exclusive diastereoselectivity and 91% *ee* within 5 h (Table 1, entry 5), but further lowering the temperature could not improve the enantioselectivity. Examination of various bases such as DBU, TMG, DMAP, and K_2CO_3 disclosed that Et_3N was the optimal base. A study of reaction with AgOAc/(*S*)-**L2** in various solvents identified PhMe and $CHCl_3$ as suitable alternatives to CH_2Cl_2 (Table 1, entries 5 and 8–12).

In the presence of 3 mol% of AgOAc/(*S*)-TF-BiphamPhos (**L2**), and 15 mol% Et_3N in CH_2Cl_2, 1,3-dipolar cycloadditions of different glycine imino esters with various substituted α,α,β-trisubstituted 2-alkylidene cyclopentanones were carried out to test the generality of the reaction. As shown in Table 2, imino esters bearing electron-rich (Table 2, entries 7 and 8), electron-neutral (Table 2, entries 6, 9 and 10), and electron-deficient groups (Table 2, entries 1–5) on the aryl rings reacted with 2-benzylidenecyclopentanone **2a** smoothly affording the corresponding spiro cycloadducts (**3aa–3ja**) exclusively in good yields (72–90%) and good enantioselectivities (87–92%) at −20 °C within 3–7 h. The substitution pattern and electronic property of the phenyl ring have little effect on the enantioselectivity. It is noteworthy that comparable results were still achieved for the sterically hindered *ortho*-bromo-, *ortho*-methyl- and 1-naphthyl-substituted imino esters **1d**, **1h** and **1i** in terms of diastero/enantioselectivity and reactivity (Table 2, entries 4, 8 and 9). Additionally, the heteroaryl substituted imino ester **1k** derived from 2-furylaldehyde also works in this transformation leading to 80% yield and 78% *ee* (Table 2, entry 11). The potential of this catalytic approach is further demonstrated by the reaction of other trisubstituted 2-arylidenecyclopentanones (**2b–2e**) with imino esters to afford the desired spirocyclic compounds in excellent diastereoselectivities and high enantioselectivities (88–92% *ee*) (Table 2, entries 12–16). Noticeably, alkylidenecyclopentanones with alkyl substitution (**2f–2i**) were also able to undergo the 1,3-dipolar cycloaddition providing the desired products

Table 2. Substrate scope of Ag(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of imino esters **1** with various substituted α,α,β-trisubstituted 2-alkylidenecyclopentanones **2**.[a]

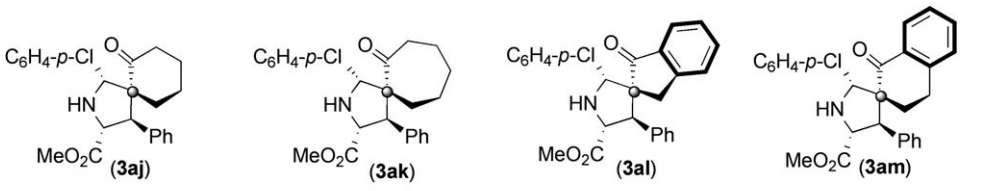


Entry	R^1	R^2	3	Yield [%][b]	*ee* [%][c]
1	*p*-Cl-C_6H_4 (**1a**)	Ph (**2a**)	**3aa**	85	91
2	*m*-Cl-C_6H_4 (**1b**))	Ph (**2a**)	**3ba**	76	87
3	*p*-Br-C_6H_4 (**1c**)	Ph (**2a**)	**3ca**	83	92
4	*o*-Br-C_6H_4 (**1d**)	Ph (**2a**)	**3da**	72	89
5	*p*-F-C_6H_4 (**1e**)	Ph (**2a**)	**3ea**	83	87
6	Ph (**1f**)	Ph (**2a**)	**3fa**	85	87
7	*p*-Me-C_6H_4 (**1g**)	Ph (**2a**)	**3ga**	87	87
8	*o*-Me-C_6H_4 (**1h**)	Ph (**2a**)	**3ha**	74	89
9	1-naphthyl (**1i**)	Ph (**2a**)	**3ia**	88	88
10	2-naphthyl (**1j**)	Ph (**2a**)	**3ja**	90	87
11	2-furyl (**1k**)	Ph (**2a**)	**3ka**	65	78
12	*p*-Cl-C_6H_4 (**1a**)	*p*-Cl-C_6H_4 (**2b**)	**3ab**	83	89
13	*p*-Cl-C_6H_4 (**1a**)	*p*-Br-C_6H_4 (**2c**)	**3ac**	85	90
14	*p*-Br-C_6H_4 (**1c**)	*p*-C_6H_5-C_6H_4 (**2c**)	**3cc**	88	92
15	*p*-Cl-C_6H_4 (**1a**)	*p*-MeO-C_6H_4 (**2d**)	**3ad**	76	90
16	*p*-Cl-C_6H_4 (**1a**)	*p*-Me-C_6H_4 (**2e**)	**3ae**	85	88
17	*p*-Cl-C_6H_4 (**1a**)	Et (**2f**)	**3af**	77	91
18	*p*-Cl-C_6H_4 (**1a**)	Pr (**2g**)	**3ag**	82	90
19	*p*-Cl-C_6H_4 (**1a**)	*i*-Bu (**2h**)	**3ah**	66	77
20	*p*-Cl-C_6H_4 (**1a**)	PhCH=CH- (**2i**)	**3ai**	80	88

[a] All of the reaction was carried out with 0.20 mmol of **2** and 0.40 mmol of **1** in 2 mL of DCM.
[b] Isolated yield.
[c] Enantioselectivity was determined by chiral HPLC analysis, and a >99:1 diastereomeric ratio was determined by HPLC analysis. Minor diastereomer was not detected in the crude matreial by ^{1}H NMR.

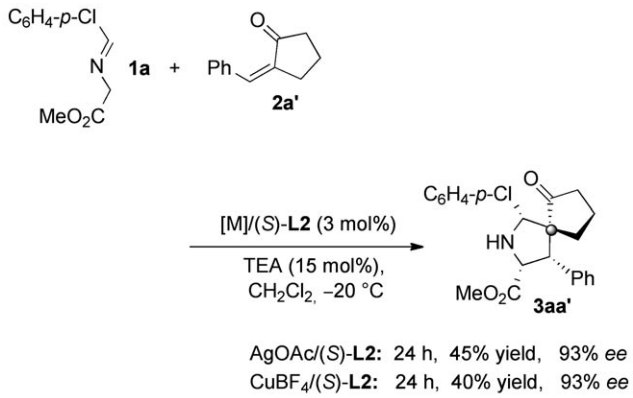
with good yields and 77–91% *ee* (Table 2, entries 17–20). However, no cycloaddition was observed when an alkyl-substituted imino ester was tested under the same reaction conditions.

The asymmetric 1,3-dipolar cycloaddition of imino ester with other α,α,β-trisubstituted 2-benzylidene-cycloketones was also investigated. As shown in Scheme 2, this catalytic system could also affect on the asymmetric cycloaddition of both six-membered cyclohexanone derived **2j** and seven-membered cycloheptanone derived **2k**. Although moderate enantioselectivities were achieved with AgOAc/(*S*)-TF-BiphamPhos (**L2**) complex for the expected cycloadducts spiro[cyclohexanone-2,3′-pyrrolidine] **3aj** and spiro[cyclohepetanone-2,3′-pyrrolidine] **3ak**, the corresponding enantioselectivities could be improved significantly through switching the metal precursor

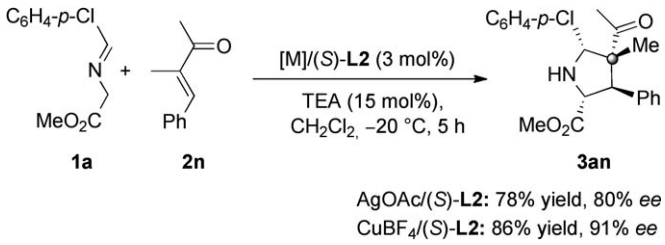


	yield	ee		yield	ee		yield	ee		yield	ee
Ag(I)/**L2**:	80%	67%	Ag(I)/**L2**:	55%	62%	Ag(I)/**L2**:	86%	93%	Ag(I)/**L2**:	78%	83%
Cu(I)/**L2**:	89%	88%	Cu(I)/**L2**:	90%	92%	Cu(I)/**L2**:	84%	80%	Cu(I)/**L2**:	85%	91%

Scheme 2. The results of catalytic asymmetric 1,3-dipolar cycloaddition of other α,α,β-trisubstituted 2-benzylidene-cycloketones and bicyclic 2-benzylidene-cycloketones.



Scheme 3. Catalytic asymmetric 1,3-dipolar cycloaddition of methyl *N*-(4-chlorobenzylidene)-glycinate **1a** with (*Z*)-2-benzylidenecyclopentanone **2a′**.



Scheme 4. The results of catalytic asymmetric 1,3-dipolar cycloaddition of imino ester **1a** with acyclic α,α,β-trisubstituted (*E*)-3-benzylidenebutanone **2n**.

AgOAc into $Cu(CH_3CN)_4BF_4$. Bicyclic 2-benzylidene-cycloketones **2l** and **2m** were also tested in this reaction, and 93% *ee* and 91% *ee* were achieved with Ag(I)/TF-BiphamPhos and Cu(I)/TF-BiphamPhos complex, respectively, for the corresponding cycloadducts spiro[indene-2,3′-pyrrolidin]-1(3*H*)-one **3al** and 3,4-dihydro-1*H*-spiro[naphthalene-2,3′-pyrrolidin]-1-one **3am**. These results indicated that Ag(I)/TF-BiphamPhos complex was more efficient for α,α,β-trisubstituted 2-alkylidene-cycloketones derived from five-membered cyclopentanone, and Cu(I)/TF-BiphamPhos complex exhibited better asymmetric induction capacity for 2-alkylidene-cycloketones derived from six-membered cyclohexanone and seven-membered cycloheptanone.

The asymmetric 1,3-dipolar cycloaddition of methyl *N*-(4-chlorobenzylidene)-glycinate **1a** with (*Z*)-2-benzylidenecyclopentanone **2a′**[15] using (*S*)-TF-BiphamPhos **L2** as chiral ligand was also investigated (Scheme 3). Although the reactivity of the *Z*-**2a′** was lower than that of *trans*-substrate *E*-**2a**, the expected adduct **3aa′** was still obtained in moderate yield and 93% *ee* when employing AgOAc or $Cu(CH_3CN)_4BF_4$ as the metal precursor.

Prompted by these results for the α,α,β-trisubstituted 2-alkylidene-cycloketones, we then investigated acyclic butan-2-one derived trisubstituted (*E*)-3-benzylidenebutanone **2n**, from which a unique quaternary stereogenic center was still generated in the corresponding *non-spiro* cycloadduct. To our delight, the reaction did take place with AgOAc/TF-BiphamPhos or $Cu(CH_3CN)_4BF_4$/TF-BiphamPhos complex as catalyst to give the highly diastereoselective cycloadduct **3an** in 80% *ee* and 91% *ee*, respectively (Scheme 4).

The absolute configuration of the adduct **3al** achieved by AgOAc/(*S*)-**L2** was unequivocally determined as (2*R*,2′*R*,4′*R*,5′*R*) by X-ray crystallographic analysis of a single crystal (Figure 1).[16] Those of other adducts were tentatively proposed on the basis of these results.

The optically active cycloadducts containing one spiro quaternary and three tertiary stereogenic centers can be readily converted into synthetically useful compounds. As shown in Scheme 5, direct Baeyer–Villiger oxidation[17] of the cycloadducts **3aa** and **3al** with *m*-CPBA in DCM at room temperature afforded otherwise inaccessible spiro[pyrrolidine-tetrahydropyranone] and spiro[pyrrolidine-isochroman-1-one] without loss of diastereo- and enantiomeric excesses, and the oxidative transformation selectively occurs on the carbon-carbon single bond between the spiro quaternary carbon and the carbon of carbonyl group in cyclopentanone moiety (**3aa**) and 2,3-dihydro-1*H*-inden-1-one moiety (**3al**).

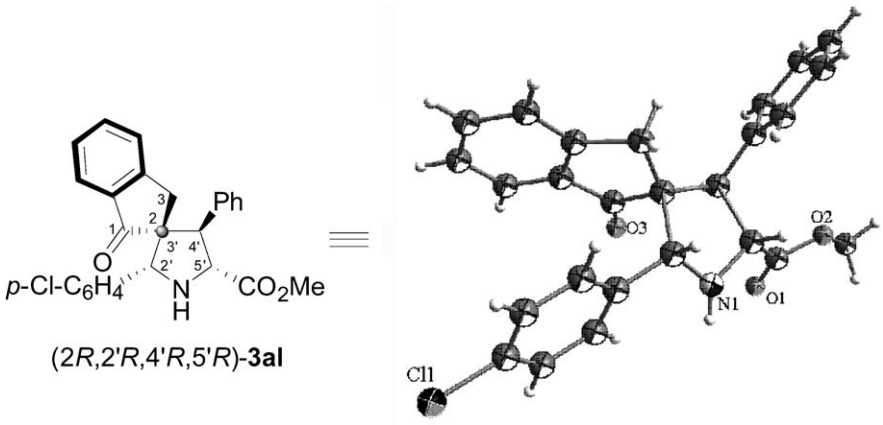
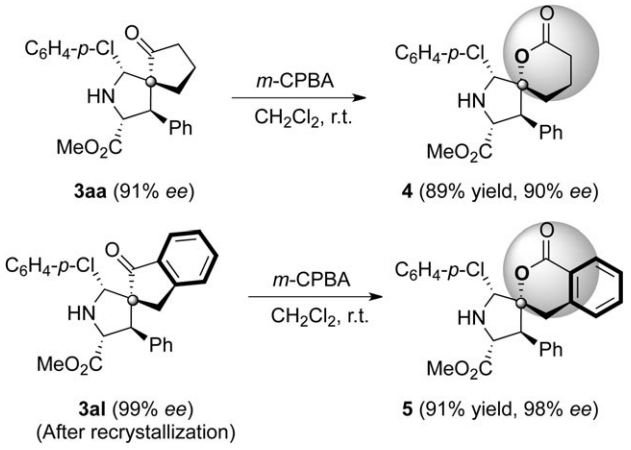


Figure 1. X-ray crystal structure of (2*R*,2′*R*,4′*R*,5′*R*)-**3al**.



Scheme 5. Synthetic transformations of the spiro heterocyclic compounds **3aa** and **3al**.

In conclusion, we have successfully developed the first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with various sterically hindered α,α,β-trisubstituted 2-alkylidene-cycloketones. This catalytic system performances well over a broad scope of substrates and provides the desired spirocyclic compounds containing pyrrolidine motifs and spiro quaternary stereogenic carbon centers in excellent diastereoselectivity and up to 92% *ee*, and subsequent transformations lead to the expedient preparation of synthetically useful spiro[pyrrolidine-tetrahydropyranone] and spiro[pyrrolidine-isochroman-1-one] without loss of diastereo- and enantiomeric excesses. Further investigations on the scope and synthetic application of this methodology are ongoing, and the results will be reported in due course.

Experimental Section

General Procedure for Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with (*E*)-Benzylidene Cyclopentanones Catalyzed by AgOAc/(*S*)-TF-BiphamPhos Complex:

Under an argon atmosphere (*S*)-TF-BiphamPhos **L2** (5.8 mg, 0.0072 mmol) and AgOAc (1.0 mg, 0.006 mmol) were dissolved in 2 mL DCM, and stirred at room temperature for about 1 h. Then, the imine substrate (0.4 mmol), Et_3N (0.03 mmol) and (*E*)-benzylidenecyclopentanone (0.2 mmol) were added sequentially. Once the starting material had been consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The product purified by column chromatography to give the corresponding cycloaddition product, which was then directly analyzed by chiral HPLC to determine the enantiomeric excess.

(1*R*,3*R*,4*R*,5*R*)-Methyl 1-(4-chlorophenyl)-6-oxo-4-phenyl-2-azaspiro[4.4]nonane-3-carboxylate (3aa): The title compound was prepared according to the general procedure as described above in; yield: 85%; $[\alpha]_D^{25}$: +46.5 (*c* 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 7.35–7.22 (m, 9H), 4.32 (s, 1H), 4.23 (d, J = 6.9 Hz, 1H), 3.82 (d, J = 6.3 Hz, 1H), 3.75 (s, 3H), 2.04–1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ = 219.92, 173.04, 139.13, 136.93, 133.72, 129.09, 128.59, 128.43, 127.04, 72.82, 64.99, 55.82, 53.36, 52.09, 57.53,32.20, 18.38; IR (KBr): ν = 3681, 3621, 3021, 2977, 2899, 2428, 2400, 1735, 1521, 1476, 1424, 1215, 1047, 929, 878, 773, 669, 626 cm^{-1}; HR-MS: m/z = 384.1363, calcd. for $C_{22}H_{22}ClNO_3$: 384.1361. The product was analyzed by HPLC to determine the enantiomeric excess: 91% *ee* (Chiralcel AS-H, 2-propanol/hexane = 10/90, flow rate 1.0 mL min^{-1}, λ = 220 nm): t_r = 14.01 and 31.58 min.

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