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Silver(I)-Catalyzed Enantioselective Desymmetrization of Cyclopentenediones: Access to Highly Functionalized Bicyclic Pyrrolidines

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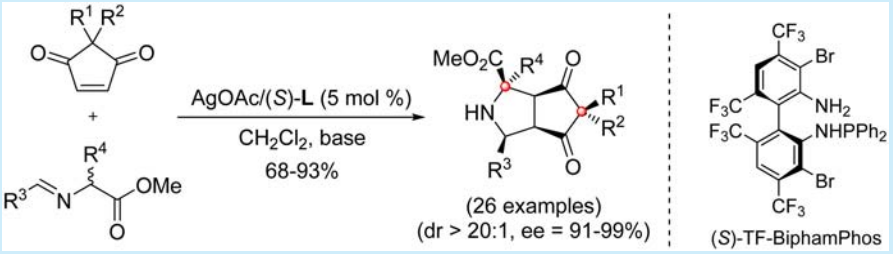
Supporting Information



ABSTRACT: A highly enantioselective desymmetrization of prochiral cyclopentenediones via Ag(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylide has been developed successfully. The methodology performs well over a broad scope of substrates, which provides facile access to a series of highly functionalized bicyclic pyrrolidine/cyclopentane derivatives in good to high yields with excellent stereoselectivities.

Highly functionalized pyrrolidines and cyclopentanes are privileged structural motifs in a large family of bioactive natural products.[1] Bicyclic heterocycles fused by pyrrolidine and cyclopentane moieties play a unique role in numerous bioactive naturally occurring compounds and pharmaceutical ingredients, and typical examples are shown in Figure 1. Telaprevir can covalently and reversibly inhibit hepatitis C virus protease,[2] and DPP-4 protease inhibitor besigliptin tosilate containing SRH-117887 is used for diabetes treatment.[3−5] Therefore, efficiently constructing pyrrolidine and cyclopentane moieties has stimulated considerable interest and achieved significant development.[6] In contrast to well-established methodologies for pyrrolidines[7,8] and cyclopentane scaffolds,[9] expedient and catalytic asymmetric access to the bicyclic pyrrolidine structural skeletons still remains elusive. Recently, we successfully developed facile access to spirolactone−pyrrolidines via Ag(I)/TF-BiphamPhos-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with prochiral spiro-cyclohexadienone lactones[10a] based on the desymmetrization strategy.[11] Encouraged by this achievement and along this research line, we envisaged that readily available prochiral cyclopentenediones[12] could be employed as potential dipolarophiles in the 1,3-dipolar cycloaddition reaction, providing straightforward access to fused bicyclic pyrrolidine/cyclopentane derivatives decorated with one or two quaternary stereogenic centers[13] (Scheme 1). Herein, we report the efficient construction of densely functionalized bicyclic pyrrolidines via Ag(I)-catalyzed asymmetric desymmet-

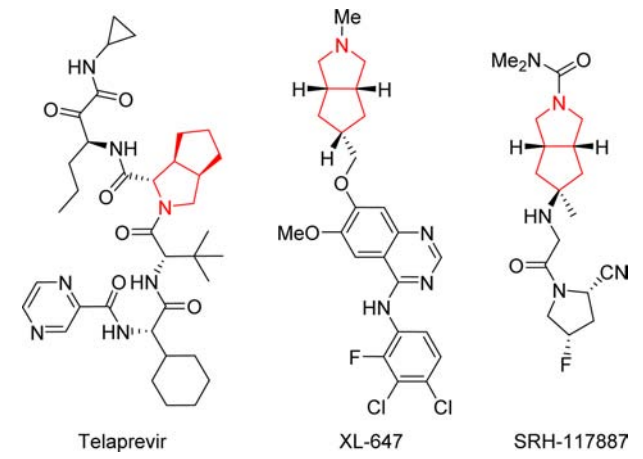


Figure 1. Representative examples of bioactive bicyclic heterocycles fused by pyrrolidine and cyclopentane moieties.

Scheme 1. Asymmetric Desymmetrization of Prochiral Cyclopentenediones via Azomethine Ylide Involved 1,3-Dipolar Cycloaddition Reaction

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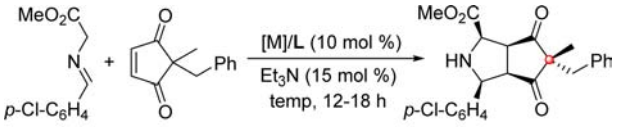
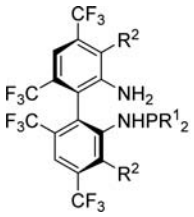
Table 1. Screening Studies of the Catalytic Asymmetric Desymmetrization of Prochiral Cyclopentenedione 2a[a]



entry	L	[M]	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	(*S*)-**L1**	$CuBF_4$	CH_2Cl_2	rt	64	55
2	(*S*)-**L1**	AgOAc	CH_2Cl_2	rt	90	83
3	(*S*)-**L2**	AgOAc	CH_2Cl_2	rt	60	42
4	(*S*)-**L3**	AgOAc	CH_2Cl_2	rt	56	72
5	(*S*)-**L4**	AgOAc	CH_2Cl_2	rt	35	17
6	(*S*)-**L5**	AgOAc	CH_2Cl_2	rt	94	91
7	(*S*)-**L5**	AgOAc	THF	rt	66	2
8	(*S*)-**L5**	AgOAc	EtOAc	rt	68	89
9	(*S*)-**L5**	AgOAc	PhMe	rt	87	86
10[d]	(*S*)-**L5**	AgOAc	MeCN	rt	61	83
11[e]	(*S*)-**L5**	AgOAc	MeOH	rt	trace	
12	(*S*)-**L5**	AgOAc	CH_2Cl_2	0	93	95
13	(*S*)-**L5**	AgOAc	CH_2Cl_2	−20	92	97
14[f]	(*S*)-**L5**	AgOAc	CH_2Cl_2	−20	91	98

[a]All reactions were carried out with 0.30 mmol of **2a** and 0.40 mmol of **1a** (1.2 equiv) in 2 mL of solvent. $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b]Isolated yield. [c]dr >20:1 was determined by crude ^{1}HNMR, and ee was determined by HPLC analysis. [d]In 36 h. [e]In 48 h. [f]5 mol % AgOAc and 6 mol % **L5** were used.



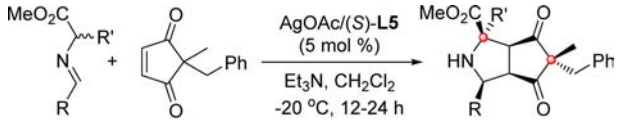
L1, R^1 = Ph, R^2 = H
L2, R^1 = 3,5-bis(methyl)phenyl, R^2 = H
L3, R^1 = 3,5-bis(trifluoromethyl)phenyl, R^2 = H
L4, R^1 = Cy, R^2 = H
L5, R^1 = Ph, R^2 = Br

(*S*)-TF-BiphamPhos

rization of prochiral cyclopentenediones. One additional feature of the current method is that five stereogenic centers could be constructed concurrently with excellent stereoselectivity control along with the formation of two C−C bonds.

Initially, we commenced our investigation using the readily available imino ester **1a** and prochiral 2-benzyl-2-methylcyclopent-4-ene-1,3-dione **2a** as the model substrates for optimization of the reaction conditions (Table 1). To our delight, in the presence of 10 mol % of Cu(I)/*rac*-TF-BiphamPhos (**L1**) complex, the reaction reached completion within 12 h at room temperature and gave the desired cycloadduct **3aa** in moderate yield with excellent diastereoselectivity (dr >20:1). The annulation process did not occur without the catalyst. Switching the metal source to AgOAc had a remarkable improvement in both reactivity and enantioselectivity (Table 1, entries 1 and 2). Encouraged by the promising results exerted by the Ag(I)/(*S*)-**L1** complex, we then examined other chiral TF-BiphamPhos ligands (Table 1, entries 3−6). Compared with (*S*)-**L1**, chiral ligands such as (*S*)-**L2**, (*S*)-**L3**, and (*S*)-**L4** performed poorly, giving unacceptable yields and enantioselectivities for this transformation. To our delight, TF-BiphamPhos (*S*)-**L5** exhibited the most outstanding performance among the tested ligands, delivering the bicyclic pyrrolidine **3aa** in 94% yield with exclusive diastereoselectivity (dr > 20:1) and excellent enantioselectivity (ee = 91%). Subsequently, varying the solvents with Ag(I)/(*S*)-**L5** as catalyst disclosed that CH_2Cl_2 was the

Table 2. Substrate Scope of Azomethine Ylides for Ag-Catalyzed Desymmetrization of Cyclopentenedione 2a[a]



entry	R	R′	1	3	yield[b] (%)	ee[c] (%)
1	*p*-ClC_6H_4	H	**1a**	**3aa**	91	98
2	*m*-ClC_6H_4	H	**1b**	**3ba**	91	95
3	*p*-BrC_6H_4	H	**1c**	**3ca**	90	97
4	*m*-BrC_6H_4	H	**1d**	**3da**	88	92
5	*o*-FC_6H_4	H	**1e**	**3ea**	90	93
6	*p*-$MeOC_6H_4$	H	**1f**	**3fa**	91	>99
7	*m*-$MeOC_6H_4$	H	**1g**	**3ga**	91	95
8	*p*-MeC_6H_4	H	**1h**	**3ha**	90	97
9	Ph	H	**1i**	**3ia**	88	98
10	2-thienyl	H	**1j**	**3ja**	90	96
11	2-naphthyl	H	**1k**	**3ka**	89	96
12	cinnamyl	H	**1l**	**3la**	68	93
13	Bu	H	**1m**	**3ma**	82	91
14[d,e]	*p*-ClC_6H_4	Me	**1n**	**3na**	92	97
15[d,e]	*p*-BrC_6H_4	Me	**1o**	**3oa**	93	94
16[d,e]	*p*-MeC_6H_4	Me	**1p**	**3pa**	89	98
17[d,e]	*p*-$MeOC_6H_4$	Me	**1q**	**3qa**	90	>99
18[d,e]	2-thienyl	Me	**1r**	**3ra**	88	>99
19[d,e]	*p*-ClC_6H_4	Bn	**1s**	**3sa**	90	95

[a]All reactions were carried out with 0.30 mmol of **2a** and 0.40 mmol of **1** in 2 mL of CH_2Cl_2. [b]Isolated yield. [c]dr >20:1 was determined by crude ^{1}HNMR, and ee was determined by HPLC analysis. [d]Inorganic base Cs_2CO_3 was used. [e]The reactions were carried out at rt.

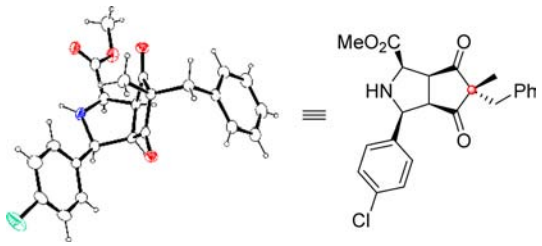


Figure 2. X-ray structure of (1*R*,3*S*,3a*R*,5*R*,6a*S*)-**3aa**.

optimal solvent (Table 1, entries 7−11). Reducing the reaction temperature proved beneficial to enantioselective control, and 97% ee was achieved at −20 °C (Table 1, entry 13). Finally, a lower catalyst loading (5 mol %) had no significant influence on the reaction outcome, which was identified as the optimal reaction conditions, providing the cycloadduct in 91% yield and 98% ee (Table 1, entry 14).

With the optimized reaction conditions in hand, we decided to examine the generality of this process. First, we tested a variety of imino esters, and the results are shown in Table 2. All examined non-α-substituted imino esters (**1a**−**k**) bearing electron-deficient (Table 2, entries 1−5), electron-rich (Table 2, entries 6−8), and electron-neutral (Table 2, entries 9−11) substituents on the phenyl ring reacted smoothly with 2-benzyl-2-methylcyclopent-4-ene-1,3-dione (**2a**), affording the corresponding cycloadducts **3aa**−**ka** exclusively in high yields (89−91%) and excellent optical purity (ee = 92 → 99%). Additionally, imino ester **1l** containing a cinnamyl group was also well tolerated, giving the satisfactory enantioselectivity (ee = 93%),

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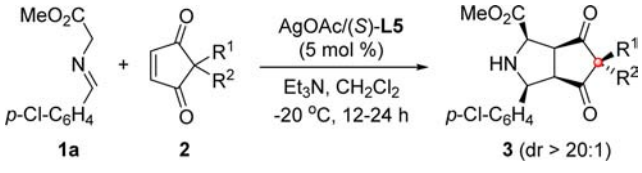
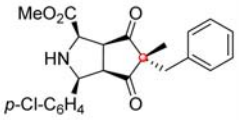
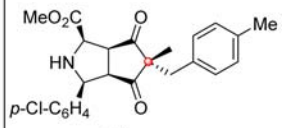
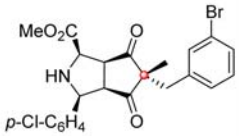
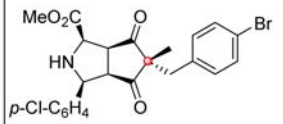
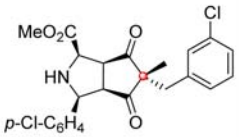
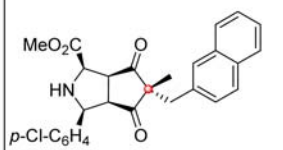
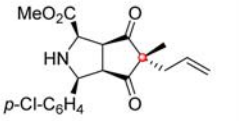
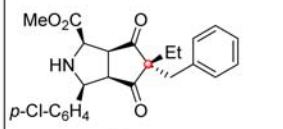
Table 3. Substrate Scope for Ag-Catalyzed Desymmetrization of Various Cyclopentenediones 2[a]



entry	product	entry	product
1	 **3aa** (91%,[b] ee = 98%[c])	5	 **3ab** (87%,[b] ee = 96%[c])
2	 **3ac** (86%,[b] ee = 95%[c])	6	 **3ad** (86%,[b] ee = 95%[c])
3	 **3ae** (85%,[b] ee = 92%[c])	7	 **3af** (84%,[b] ee = 94%[c])
4	 **3ag** (89%,[b] ee = 96%[c])	8	 **3ah** (82%,[b] ee = 94%[c])

[a]All reactions were carried out with 0.30 mmol of **1a** and 0.40 mmol of **2** in 2 mL of CH_2Cl_2. [b]Isolated yield. [c]dr >20:1 was determined by crude ^{1}HNMR, and ee was determined by HPLC analysis.

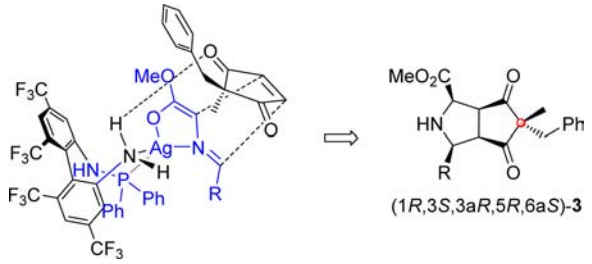
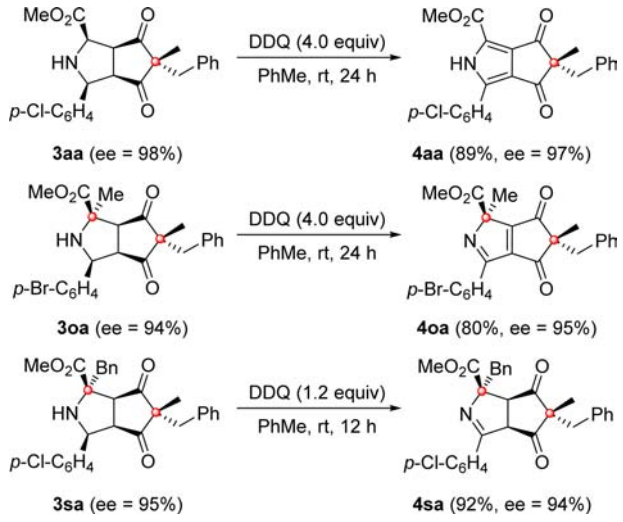


Figure 3. Proposed transition state leading to (1*R*,3*S*,3a*R*,5*R*,6a*S*)-**3**.

despite a relatively lower yield (Table 2, entry 12). It was worth noting that an alkyl imino ester **1m** derived from valeraldehyde could also be applicable to this procedure, resulting in the desired cycloadduct **3ma** in 82% yield with 91% ee (Table 2, entry 13). Then, several α-methyl/benzyl substituted imino esters **1n**−**s** were assayed with the attempts to construct the bicyclic pyrrolidines decorated with two quaternary stereogenic centers. Due to the lower reactivity, we conducted some additional screening of reaction conditions, including the adoption of inorganic base Cs_2CO_3 and the rise of the reaction temperature from −20 °C to rt. The reaction proceeded very well, delivering

Scheme 2. Elaboration of Cycloadducts



the corresponding bicyclic pyrrolidines **3na**−**sa** in high yields (up to 93%) with excellent stereoselectivities (dr >20:1; up to ee = 99%) (Table 2, entries 14−19). The absolute configuration of bicyclic cycloadduct **3aa** was determined as (1*R*,3*S*,3a*R*,5*R*,6a*S*) by X-ray analysis of the single crystal (Figure 2).[14]

Next, various prochiral cyclopentenediones (**2b**−**h**) were further explored in the annulation reaction with imino ester **1a** (Table 3). The divergent substituents in the benzyl group did not display any considerable effect on the catalytic activity and stereochemistry, leading to the desired products **3ab**−**ae** in yields (85−87%) and enantioselectivities (ee = 92−96%) on par with those observed in the model reaction (Table 3, entries 2, 3, 5, and 6). High yield and excellent ee were also obtained when naphthyl-substituted cyclopentenedione underwent this process (Table 3, entry 7). The cyclopentenedione **2g**, combining methyl and allyl groups at the prochiral center, performed well, giving the corresponding annulation product **3ag** in 89% yield and 96% ee (Table 3, entry 4). The protocol for the substrate **2h** bearing an Et group instead of a Me group on the all-carbon quaternary center was also feasible, and high yield (82%) with excellent enantioselectivity (ee = 94%) could be observed (Table 3, entry 8).

Based on the absolute configuration of **3aa** and our previous studies,[15] the stereochemistry observed in this desymmetrization approach can be rationalized by the proposed transition state as illustrated in Figure 3. Under basic conditions, the in situ formed azomethine ylide is coordinated to the silver center of the catalytically active species. The steric congestion imposed by the bulky PPh_2 group in the chiral ligand exclusively forces the prochiral diketone to approach from the *Si* face (C═N) of the azomethine ylide, and the possible hydrogen bond interaction between the oxygen atom of cyclopentenedione and the NH_2 group of the chiral ligand can facilitate stabilizing the transition state, both of which contribute to the stereochemistry of this desymmetrization process.

Finally, to further demonstrate the utility of this method, the bicyclic pyrrolidine **3aa** was treated with DDQ in toluene at room temperature, which could be readily converted into enantiopure bicyclic compound **4aa** in high yields without loss of optical purity (Scheme 2). For the adducts **3oa** and **3sa** bearing two quaternary stereogenic centers, the corresponding 2*H*-pyrrole **4oa** and 3,4-dihydro-2*H*-pyrrole **4sa** could be readily achieved with the different amounts of oxidant.

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In summary, we have developed a concise desymmetrization process for the expedient construction of enantioenriched bicycle pyrrolidine/cyclopentane derivatives possessing up to two quaternary stereocenters through Ag(I)/TF-BiphamPhos-catalyzed asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylide and prochiral cyclopentenedione.[16] This efficient catalytic system showed a broad substrate scope and excellent stereoselectivity control. Further studies to probe the mechanistic details and some applications of this reaction in organic synthesis are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02810.

Experimental details and NMR and HPLC spectra for obtained compounds (PDF)
X-ray data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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