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Silver-Catalyzed Enantioselective Desymmetrization: Facile Access to Spirolactone-Pyrrolidines Containing a Spiro Quaternary Stereogenic Center

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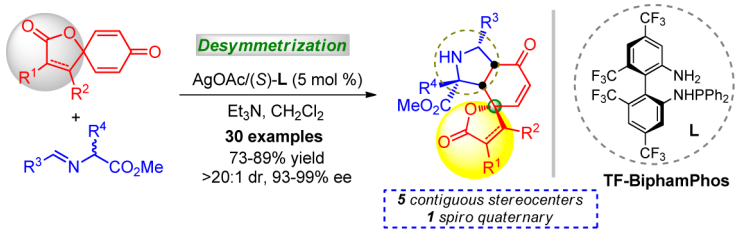
ABSTRACT



An unprecedented Ag(I)-catalyzed asymmetric desymmetrization of spiro cyclohexadienone lactones has been developed successfully, which performs well over a broad scope of substrates and provides a facile access to optically active spirolactone-pyrrolidines in high yields with excellent levels of diastereo-/enantioselectivities.

The application of chirotechnology in fine-chemicals and materials sciences has achieved the goal of efficiently constructing versatile building blocks in enantioenriched forms within recent decades.[1] Spiro heterocycles with multiple contiguous stereogenic centers are prevalent scaffolds in bioactive molecules and natural products and have always been a great challenge for synthetic organic chemists.[2] Elegant and creative strategies toward the construction of spiro quaternary stereogenic centers with excellent stereoselective control are still quite limited due to the intrinsic steric congestion.[3,4] Asymmetric desymmetrization[5] is a versatile and economical protocol for generating enantioenriched products with complex structures and multiple stereogenic centers,[6,7] which is effected by differentiation of two enantiotopic groups on the readily available symmetric or prochiral molecules.

Highly functionalized spirolactones such as spiro γ-butyrolactone and butenolide constitute the core structure

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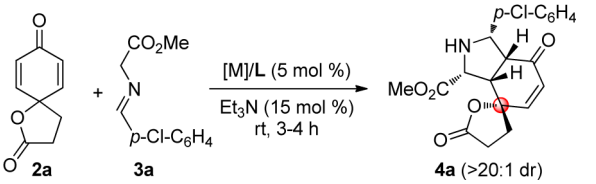
in a number of biologically interesting natural and synthetic products.[8] Furthermore, they also serve as versatile building blocks for organic synthesis.[9] Five-membered nitrogen heterocycles, especially highly substituted pyrrolidines, are observed widely in pharmaceuticals and natural alkaloids.[10] Therefore, a combination of the above two key units may introduce some unprecedented benefits and is expected to find valuable applications in medicinal chemistry. We envisioned that the efficient stereochemical control attained recently in azomethine ylide involved 1,3-dipolar cycloaddition reactions[11] for pyrrolidine synthesis renders them highly suitable in the implementation of the desymmetrization strategy, thereby fulfilling the asymmetric assembly of a structurally diverse spirolactone and pyrrolidine moiety from a readily available cyclohexadienone spirolactone and simultaneous generation of a unique spiro quaternary stereogenic center. Herein, we reported the first asymmetric construction of spirolactone-pyrrolidines through Ag-catalyzed desymmetrization of a prochiral spirolactone *via* asymmetric 1,3-dipolar cycloaddition. The advantage of this method is that various complicated but structurally diverse spiro-lactone-pyrrolidine derivatives containing one spiro quaternary and up to five contiguous stereogenic centers could be efficiently constructed by a single process.

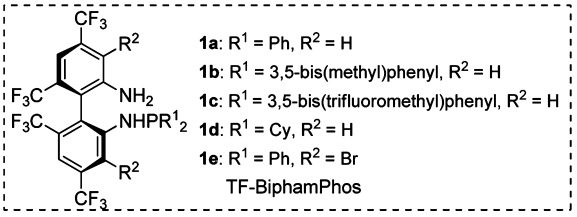
Guided by these considerations and the application of a desymmetrization strategy,[5,7] we began our initial investigation by testing the reaction of prochiral spiro cyclohexadienone butyrolactone **2a** and imino ester **3a** with the Cu(I)/*rac*-TF-BiphamPhos[12] (**1a**) as the catalyst and Et_3N as the base. Gratifyingly, the reaction reached completion in less than 8 h at room temperature and delivered a single isomer **4a** in 85% yield with excellent diastereoselectivity (> 20:1 dr)[13] (Table 1, entry 1). Spirocyclic **4a** is stable, and no further reaction occurred with the remaining C=C double bond. Encouraged by the initial desymmetrization results exerted by the Cu(I)/*rac*-**1a** complex, we then conducted the asymmetric variant of this reaction to evaluate the enantioselectivity with a chiral ligand. Empolying the Cu(I)/(*S*)-**1a** complex as the catalyst, the adduct **4a** was exclusively obtained in good yield with

Table 1. Screening Studies of the Catalytic Asymmetric Desymmetrization of Spiro Cyclohexadienone Butyrolactone **2a**[a]



entry	L	[M]	solvent	t (°C)	yield (%)[b]	*ee* (%)[c]
1	*rac*-**1a**	CuBF4	CH_2Cl_2	rt	85	–
2	(*S*)-**1a**	CuBF4	CH_2Cl_2	rt	83	66
3	(*S*)-**1a**	AgOAc	CH_2Cl_2	rt	85	94
4	(*S*)-**1b**	AgOAc	CH_2Cl_2	rt	81	88
5	(*S*)-**1c**	AgOAc	CH_2Cl_2	rt	68	65
6	(*S*)-**1d**	AgOAc	CH_2Cl_2	rt	74	67
7	(*S*)-**1e**	AgOAc	CH_2Cl_2	rt	50	69
8	(*S*)-**1a**	AgOAc	THF	rt	80	82
9	(*S*)-**1a**	AgOAc	Et_2O	rt	82	88
10	(*S*)-**1a**	AgOAc	PhMe	rt	84	84
11	(*S*)-**1a**	AgOAc	MeCN	rt	84	67
12[d]	(*S*)-**1a**	AgOAc	CH_2Cl_2	0	88	97

[a] All reactions were carried out with 0.30 mmol of **2a** and 0.40 mmol of **3** in 2 mL of solvent. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] > 20:1 dr was determined by crude ^1H NMR, and ee was determined by HPLC analysis. [d] In 10 h.



excellent diastereoselectivity albeit moderate enantioselectivity (66% ee) (entry 2). To our delight, significant enhancement of the enantioselectivity (94% ee) was achieved while maintaining high diastereoselectivity by switching the metal precursor from $Cu(CH_3CN)_4BF_4$ into AgOAc (entry 3). Then, using AgOAc as the metal precursor, we then carried out the reaction with other (*S*)-TF-BiphamPhos ligands (**1b**–**1e**). When the phenyl group on the phosphorus atom of ligand **1a** was replaced by a bulky xylyl, 3,5-bis(trifluoromethyl)phenyl, or cyclohexyl group, the enantioselectivity of the desymmetrization product dropped from 94% to 88%, 65%, and 67%, respectively (entries 4–6). Sterically hindered chiral ligand **1e** afforded almost the same stereoselectivity as the simple ligand **1a** but with much lower reactivity (entry 7). A subsequent survey of the solvent effect indicated that CH_2Cl_2 was the best solvent of choice (entries 8–11). After further optimization of the reaction temperature with ligand **1a**, spirolactone-pyrrolidine **4a** was isolated in 88% yield, with > 20:1 dr and 97% ee after 10 h at 0 °C (entry 12).

Having observed that Ag-catalyzed desymmetrization of a prochiral spiro butyrolactone under the above optimized reaction conditions can be realized with highly

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(10) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W., Eds.; Wiley & Sons: New York, 2002.

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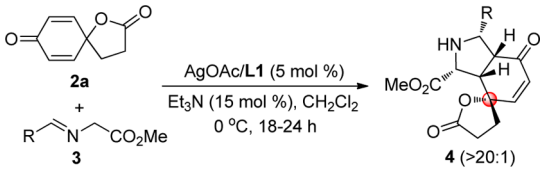
(13) When PPh_3 was employed as the ligand, the desymmetrical cycloadduct was separated in 75% yield along with around 10% of the uncyclized imine adduct *via* a Michael addition reaction.

Table 2. Substrate Scope for Ag-Catalyzed Desymmetrization of Spiro Cyclohexadienone Butyrolactone **2a**[a]



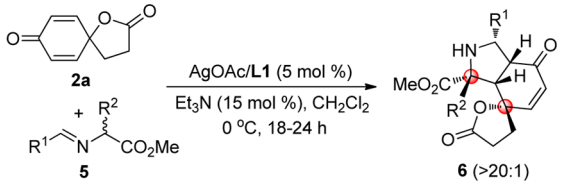
entry	R	4	yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4 (**3a**)	**4a**	88	97
2	*o*-Cl-C_6H_4 (**3b**)	**4b**	80	95
3	*m*-Cl-C_6H_4 (**3C**)	**4c**	84	95
4	*p*-CF_3-C_6H_4 (**3d**)	**4d**	87	95
5	*p*-CO_2Me-C_6H_4 (**3e**)	**4e**	89	95
6	*p*-NO_2-C_6H_4 (**3f**)	**4f**	82	98
7	Ph (**3g**)	**4g**	85	98
8	*p*-Me-C_6H_4 (**3h**)	**4h**	81	99
9	*o*-Me-C_6H_4 (**3i**)	**4i**	88	96
10	2-naphthyl (**3j**)	**4j**	82	95
11	2-furyl (**3k**)	**4k**	88	96
12	2-thienyl (**3l**)	**4l**	83	93
13[d]	Cy (**3m**)	**4m**	73	98
14[d]	^{i}Bu (**3n**)	**4n**	78	99

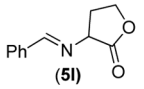
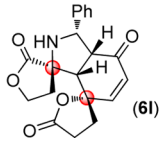
[a] All reactions were carried out with 0.30 mmol of **2a** and 0.40 mmol of **3** in 2 mL of CH_2Cl_2. [b] Isolated yield. [c] >20:1 dr was determined by crude ^{1}H NMR, and ee value was determined by HPLC analysis. [d] Inorganic base Cs_2CO_3 was used.

stereoselective control, we then decided to investigate the substrate scope of this process. We were pleased to find that a wide array of imino esters **3** derived from aromatic aldehydes bearing electron-deficient (Table 2, entries 1−6), electron-neutral (entry 7), and electron-rich substituents (entries 8 and 9) on the aryl rings reacted smoothly with spirolactone **2a**, affording the corresponding spiro heterocyclic products in good to high yields (81−89%), with excellent diastereoselectivities (>20:1 dr) and high enantioselectivities (95−99% ee). The substitution pattern of the arene had little effect on the selectivity of the reaction, and *ortho*-substituted imino ester **3b** and **3i** were readily applicable in this desymmetrization leading exclusively to the desired spirolactone-pyrrolidines **4b** and **4i** with 95% ee and 96% ee, respectively (entries 2 and 9). Additionally, heteroaromatic derived imino ester **3k** and **3l** underwent this transformation as 2-naphthylaldehyde derived imino ester **3j**, affording the corresponding adducts in good yields with excellent diastereo-/enantioselectivity (entries 10−12). It is noteworthy that less reactive alkyl imino esters[11] **3m** and **3n** were also readily applicable in this desymmetrization process with Cs_2CO_3 as the base, delivering the desired adducts in good yield with 98% and 99% ee, respectively (entries 13 and 14).

Encouraged by the desymmetrization results for less sterically hindered imino esters from glycinate, we then investigated this reaction with the challenging imino ester derived from various α-substituted amino acids, from which a nitrogen-substituted quaternary stereogenic center was generated along with one spiro stereogenic center in

Table 3. Use of a Variety of α-Substituted Imino Esters for Ag-Catalyzed Desymmetrization of Spiro Cyclohexadienone Butyrolactone **2a**[a]



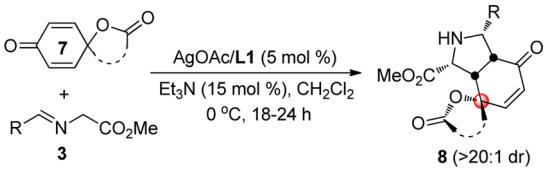
entry	R^1	R^2	6	yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4 (**5a**)	Me	**6a**	85	99
2	*m*-Cl-C_6H_4 (**5b**)	Me	**6b**	88	98
3	*p*-CF_3-C_6H_4 (**5c**)	Me	**6c**	82	98
4	Ph (**5d**)	Me	**6d**	87	97
5	*p*-Me-C_6H_4 (**5e**)	Me	**6e**	83	98
6	*o*-Me-C_6H_4 (**5f**)	Me	**6f**	85	97
7	2-Furyl (**5g**)	Me	**6g**	81	98
8	Ph (**5h**)	Et	**6h**	84	97
9	Ph (**5i**)	Pr	**6i**	88	97
10	Ph (**5j**)	^{i}Bu	**6j**	82	94
11	Ph (**5k**)	Bn	**6k**	89	97
12	 (**5l**)		 (**6l**)	85	98

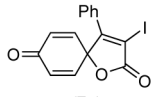
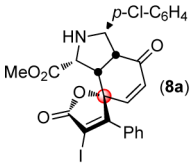
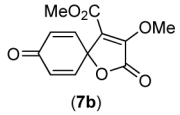
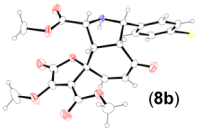
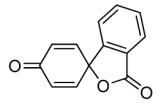
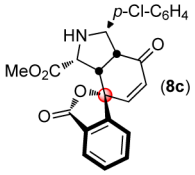
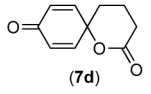
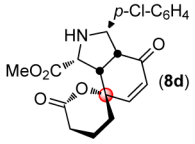
[a] All reactions were carried out with 0.30 mmol of **2a** and 0.40 mmol of **5** in 2 mL of CH_2Cl_2. [b] Isolated yield. [c] >20:1 dr was determined by crude ^{1}H NMR and ee value was determined by HPLC analysis.

the corresponding spirolactone-pyrrolidines. The results are summarized in Table 3. Gratifyingly, (±)-alanine derived imino esters have proved to be excellent substrates affording the desired spiro adducts in good yields with excellent diastereo-/enantioselectivities, regardless of the position and electronic property of the substituents on the aromatic ring (Table 3, entries 1−6). Noticeably, up to 98% ee was still obtained for heteroaromatic 2-furyl derived imino ester **5g** (entry 7). Furthermore, imino esters derived from other α-substituted amino acids have also been examined for this transformation. Under the optimized reaction conditions, a satisfactory yield and an excellent stereoselectivity were uniformly observed for the imino esters derived from (±)-2-aminobutyric acid, (±)-2-aminopentanoic acid, (±)-leucine, and (±)-phenylalanine (entries 8−11). Additionally, (±)-homoserine derived cyclic imino ester **5l** worked well in this reaction (98% ee), giving the desired highly functionalized spirocyclic **6l** containing two spiro γ-butyrolactone moieties (entry 12).

Finally, in order to investigate more deeply the scope and generality of this desymmetrization reaction, other prochiral spirolactones were also examined under the optimized reaction conditions. As shown in Table 4, spiro cyclohexadienone-butenolide **7a** and **7b** bearing different substituents on the lactone ring proved to be excellent substrates for this tranformation affording good yields and excellent diastereo-/enantioselectivities (Table 4,

Table 4. Enantioselective Desymmetrization of Spiro Cyclohexadienone Butenolides and Spiro Cyclohexadienone Pentylolactone[a]



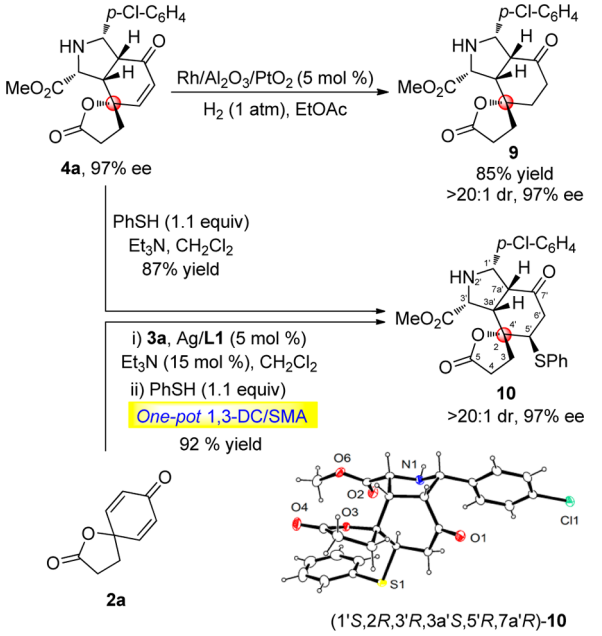
entry	7	8	yield (%)[b]	ee (%)[c]
1	 (7a)	 (8a)	85	96
2	 (7b)	 (8b)	80	95
3	 (7c)	 (8c)	89	96
4	 (7d)	 (8d)	78	95

[a] All reactions were carried out with 0.30 mmol of **7** and 0.40 mmol of **3** in 2 mL of CH_2Cl_2. [b] Isolated yield. [c] > 20:1 dr was determined by crude ^1H NMR and ee value was determined by HPLC analysis.

entries 1 and 2). Spiro cyclohexadienone phthalanone **7c** was tested as a prochiral partner in this reaction, and 96% ee was achieved for the desired adduct **8c** (entry 3). Moreover, desymmetrization of spiro cyclohexadienone pentylolactone **7d** was also tolerated in this catalytic system. The relative and absolute configuration of product **8b** catalyzed by Ag(I)/(*S*)-**1a** was unequivocally determined as (1′*S*,2*S*,3′*R*,3a′*S*,7a′*R*) by X-ray diffraction analysis.

The optically active spirolactone-pyrrolidines can serve as precursors for other stereochemically rich structures (Scheme 1). Chemoselective reduction of the C=C bond of **4a** with Rh/Al_2O_3 and Adams' catalyst afforded **9** in 85% yield. Upon treatment of **4a** with thiophenol in the presence of a catalytic amount of Et_3N, the highly functionalized sulfa-Michael adduct **10** was obtained in an excellent diastereoselective manner, and the generated sixth stereogenic center was determined to possess an *R* configuration

Scheme 1. Synthetic Transformations



according to crystal X-ray analysis of **10**. Remarkably, the desymmetrization and subsequent sulfa-Michael addition reaction could be carried out via a one-pot protocol in higher yield without loss of diastereomeric and enantiomeric excess.

In summary, we have developed the first catalytic asymmetric synthesis of highly functional spirolactone-pyrrolidine derivatives bearing five contiguous stereocenters and one unique spiro quaternary stereocenter through enantioselective desymmetrization of a prochiral spirodienone-lactone *via* silver-catalyzed asymmetric 1,3-dipolar cycloaddition. This catalytic system exhibited excellent diastereoselectivity, enantioselectivity, and a broad substrate scope. Notably, this methodology presented herein could reveal new prospects in the stereoselective construction of spirolactone-pyrrolidine derivatives, a valuable structural motif for drug discovery. Efforts are currently underway to elucidate the mechanistic details as well as scope and limitations of this reaction.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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