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Stereoselective Construction of Spiro(butyrolactonepyrrolidines) by Highly Efficient Copper(I)/TF-BiphamPhos-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition

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Spirocyclic pyrrolidines with multiple contiguous stereogenic centers are core structural elements in a large number of natural alkaloids and synthetic compounds exhibiting important biological activities.[1] Typical examples include cephalotaxine,[2] stemmonamine,[3] and spirotryprostatins A and B[4] (Figure 1).[5] Homoserine lactone derivatives have

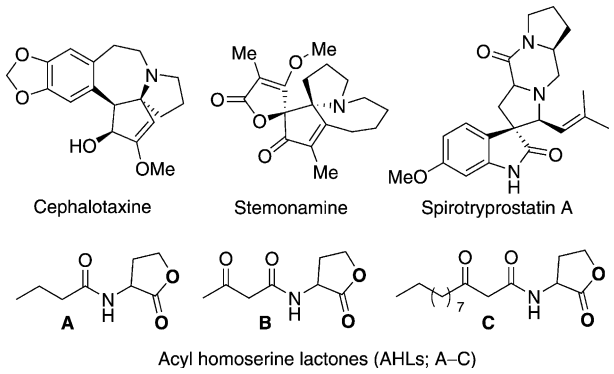

Figure 1. Examples of biologically important molecules containing privileged spiro pyrrolidines and homoserine lactones.

also attracted considerable attention due to their biological activity profile.[6] Typical examples are the acyl homoserine lactones (AHLs), which are important intercellular signaling molecules in many Gram-negative bacteria and are responsible for bacterial quorum sensing (Figure 1).[7] Therefore, combining the two classes of biologically active core structure through a unique spiro-quaternary stereogenic carbon may introduce some unprecedented benefits to drug discovery and is expected to find valuable applications in medicinal chemistry.

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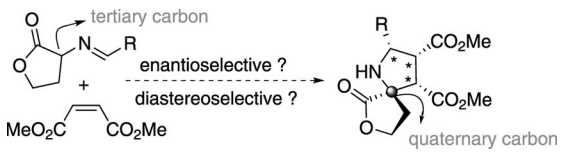
The spirocyclic pyrrolidine skeleton has potential as a key motif for the development of compounds leading to medicinal agents. For this reason, organic chemists have been inspired to pursue efficient methods for the synthesis of these challenging compounds over the past few years.[8] Catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to activated alkenes[9] has been one of the most powerful and most diversity-oriented synthetic (DOS)[10] methods used for the construction of a range of structurally and stereochemically rich pyrrolidines.[11] However, for the synthesis of bioactive spirocyclic pyrrolidines, the direct catalytic asymmetric approach has met with little success. Recently, Gong et al. reported an elegant organocatalyzed asymmetric 1,3-dipolar cycloaddition reaction between *N*-Boc-2-oxoindolin-3-ylidene derivatives and in situ formed azomethine ylides, leading to the first asymmetric synthesis of spiro(oxindolepyrrolidine) derivatives.[12] Subsequently, the use of chiral transition-metal complexes to catalyze asymmetric 1,3-dipolar cycloadditions for the construction of these spiro structures was reported by Waldmann et al.[13] and our research group.[14a] The common feature of these methods is that one of the heterocyclic rings in the generated spirocyclic adducts is contributed by the cyclic dipolarophile.[12–14] For spiro(butyrolactonepyrrolidines), only a few racemic examples have been reported to the best of our knowledge,[15] and quite limited progress towards a direct catalytic asymmetric approach to these spirocyclic compounds has been made. Therefore, the development of a catalytic method for the straightforward synthesis of enantioenriched spiro(butyrolactonepyrrolidines) is in high demand. Herein, we report the first catalytic asymmetric synthesis of spiro(butyrolactonepyrrolidines) containing a unique spiro quaternary stereogenic center[16] by using a Cu^{I}/TF-BiphamPhos catalyzed 1,3-dipolar cycloaddition, and by employing homoserine lactone derived cyclic imino esters as the dipoles (Scheme 1). A key feature of this method is that the lactone



Scheme 1. Asymmetric synthesis of spiro(butyrolactonepyrrolidines) by catalytic asymmetric 1,3-dipolar cycloaddition using homoserine lactone derived cyclic imino esters as the dipoles.

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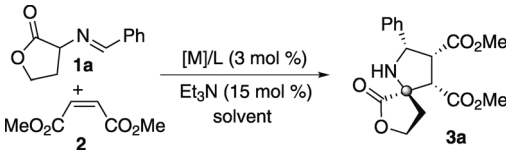
ring in the generated spirocycles is provided by the dipole, rather than by the dipolarophile. Inspired by the seminal work of Grigg et al. on the 1,3-dipolar cycloaddition of homoserine lactone derived aldimino esters with electron-deficient olefins in the presence of a substoichiometric amount of silver salts,[15] our initial studies began with the reaction of the cyclic aldimino ester **1a**, which was readily synthesized from homoserine lactone hydrochloride and benzaldehyde, with dimethyl maleate (**2**). We used the reaction of **1a** as a model reaction to probe the possibility of employing a catalytic amount of metal complex in this transformation. To our delight, 5 mol% of the AgOAc/PPh_3 complex exhibited high catalytic efficiency, and the model reaction was finished in less than 3 h in dichloromethane at room temperature. The expected spiro(butyrolactonepyrrolidine) **3a** was produced in high yield (93%) with excellent diastereoselectivity (diastereomeric ratio (d.r.) > 98:2; Scheme 2).

Scheme 2. Ag^I/PPh_3-catalyzed 1,3-dipolar cycloaddition of homoserine lactone derived cyclic imino ester **1a** with dimethyl maleate **2**.

Table 1. Optimization of the catalytic asymmetric 1,3-dipolar cycloaddition of homoserine lactone derived aldimino ester **1a** with dimethyl maleate **2a**.[a]



Entry	Ligand	[M]	Solvent	T [°C]	Time [min]	Yield[b] [%]	*ee*[c] [%]
1	**L1**	AgOAc	CH_2Cl_2	RT	1440	60	5
2	**L1**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	RT	1440	65	3
3	**L2**	AgOAc	CH_2Cl_2	RT	1440	85	58
4	**L2**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	RT	1440	50	65
5	**L3**	AgOAc	CH_2Cl_2	RT	1440	20	0
6	**L3**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	RT	1440	29	0
7	**L4**	AgOAc	CH_2Cl_2	RT	15	78	40
8	**L4**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	RT	10	80	63
9	**L5**	AgOAc	CH_2Cl_2	RT	10	90	25
10	**L5**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	RT	10	80	88
11	**L5**	$[Cu(MeCN)_4][BF_4]$	PhMe	RT	60	90	73
12	**L5**	$[Cu(MeCN)_4][BF_4]$	ether	RT	40	80	72
13	**L5**	$[Cu(MeCN)_4][BF_4]$	EtOAc	RT	120	85	67
14	**L5**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	0	20	89	97
15	**L5**	$[Cu(MeCN)_4][BF_4]$	CH_2Cl_2	−20	40	88	97

[a] All reactions were carried out by using **1a** (0.26 mmol) and **2** (0.20 mmol) in solvent (2 mL). [b] Isolated yield. [c] The *ee* and > 98:2 diastereomeric ratio were determined by HPLC analysis. The minor diastereomer was not detected by crude ^1H NMR analysis.

Encouraged by this promising result, different metal salts and commercially available chiral ligands (Figure 2) were subsequently examined to establish optimal reaction conditions and representative results are summarized in Table 1. Combined with Monophos (**L1**), both AgOAc and $[Cu(CH_3CN)_4][BF_4]$ salts successfully promoted this model cycloaddition reaction; however, spiroadduct **3a** was formed with a very low enantioselectivity (Table 1, entries 1 and 2) even though Monophos has exhibited excellent asymmetric induction in several Ag^I-catalyzed asymmetric 1,3-dipolar cycloadditions of azomethine ylides.[17] Bisphosphine ligands showed better asymmetric induction than monophosphine ligands. With AgOAc or $[Cu(MeCN)_4][BF_4]$ as the catalyst precursor, BINAP (**L2**) gave the desired adduct with 58 and 65% *ee*, respectively (Table 1, entries 3 and 4). To our surprise, the bulkier and electron-donating biphenyl ligand (*R*)-DTBM-segphos (**L3**) was not suitable for this transformation; only the racemic spiroadduct was achieved, accompanied by a remarkable decrease in catalytic activity (Table 1, entries 5 and 6). The chiral ligands TF-BiphamPhos (**L4**, **L5**),[18] developed in this laboratory, were next screened to identify a more efficient catalyst system. In general, TF-BiphamPhos ligands exhibited the best results in terms of the reaction rate and asymmetric induction, and copper salts gave better enantioselectivity than silver salts (Table 1, entries 7–10). By using a $[Cu(CH_3CN)_4][BF_4]$/**L4** complex as the catalyst, the adduct **3a** was achieved with good yield, excellent diastereoselectivity, and moderate enantioselectivity (63%; Table 1, entry 8). TF-BiphamPhos **L5** with two bromine atoms at the 3,3′ positions of the TF-Bipham backbone was shown to be the most promising ligand when complexed with $[Cu(CH_3CN)_4][BF_4]$, and provided **3a** as the only product in 85% yield and 88% *ee* (Table 1, entry 10). The solvent effects were also investigated, and CH_2Cl_2 was revealed to be the best solvent for the reaction (Table 1, entries 10–13). Reducing the reaction temperature from RT to 0°C resulted in full conversion with 97% *ee* (Table 1, entry 14). Lowering the temperature further did not improve the enantioselectivity, and had a detrimental effect on the reaction rate (Table 1, entry 15).

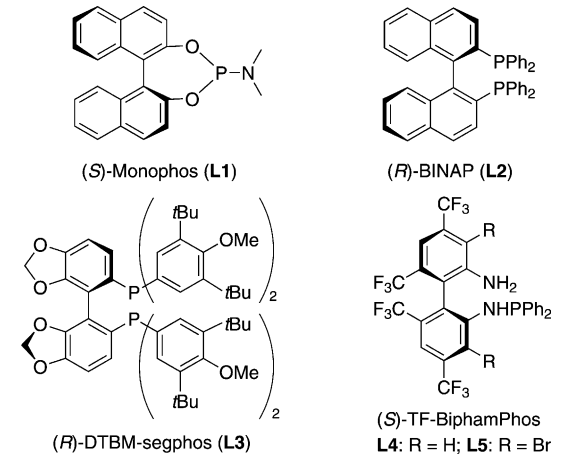


Figure 2. Screened chiral ligands.

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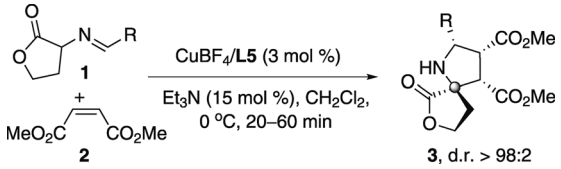
Table 2. Substrate scope of the Cu^{I}-catalyzed asymmetric 1,3-dipolar cycloaddition of various cyclic aldimino esters **1** with dimethyl maleate **2**.[a]

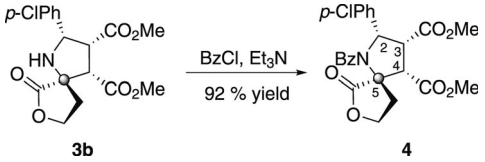


Entry	R	3	Yield[b] [%]	*ee*[c] [%]
1	Ph (**1a**)	**3a**	89	97
2	*p*-ClPh (**1b**)	**3b**	84	96
3	*o*-ClPh (**1c**)	**3c**	86	98
4	*m*-ClPh (**1d**)	**3d**	83	97
5	*p*-BrPh (**1e**)	**3e**	89	99
6	*p*-MePh (**1f**)	**3f**	90	99
7	*o*-MePh (**1g**)	**3g**	89	98
8	*m*-MePh (**1h**)	**3h**	86	99
9	*p*-MeOPh (**1i**)	**3i**	93	99
10	1-naphthyl (**1j**)	**3j**	90	96
11	2-naphthyl (**1k**)	**3k**	90	99
12	2-furyl (**1l**)	**3l**	94	99
13	2-thienyl (**1m**)	**3m**	83	96
14[d]	Cy (**1n**)	**3n**	80	63 (96)[e]

[a] All reactions were carried out by using **2** (0.26 mmol) and **1** (0.20 mmol) in CH_2Cl_2 (2 mL). [b] Isolated yield. [c] The *ee* and >99:1 diastereomeric ratio were determined by HPLC analysis. The minor diastereomer was not detected by crude ^1H NMR analysis. [d] 10 mol % of Ag_2O/**L5** was employed as the metal source. [e] The *ee* value in parentheses was achieved after simple recrystallization.

Having established an optimal reaction protocol, we next explored the scope and the generality of the method. As shown in Table 2, a wide range of aromatic-aldehyde-derived cyclic imino esters were examined, and it was observed that with electron-neutral (Table 2, entries 1, 10, and 11), electron-deficient (Table 2, entries 2–5), or electron-rich groups (Table 2, entries 6–9) on the phenyl ring, the desired spiro(butyrolactonepyrrolidines) (**3a**–**3k**) were obtained in satisfactory yields (83–93%) and excellent selectivities (96–99% *ee*, >98:2 d.r.). It is worth noting that comparable results were achieved for the sterically hindered *ortho*-chloro- and *ortho*-methyl-substituted imino esters **1c** and **1g** in terms of stereoselectivity and reactivity, demonstrating that the substitution pattern of the arene had little effect on the selectivity of the reaction (Table 2, entries 3 and 7). Cyclic imino esters derived from 1- and 2-naphthylaldehyde also worked well in this annulation reaction, providing the spiro adducts **3j** and **3k** with 96% and 99% *ee* respectively (Table 2, entries 10 and 11). Remarkably, heteroaromatic aldehyde-derived cyclic imines **1l** and **1m** were also tolerated in this reaction, and the desired spiro(butyrolactonepyrrolidines) were obtained with excellent enantioselectivity (Table 2, entries 12 and 13). No cycloaddition reaction occurred when the less reactive imino ester **1n**, derived from aliphatic cyclohexanecarbaldehyde, was tested under the optimal reaction conditions. Considering Ag_2O exhibited significant activity for the 1,3-dipolar cycloaddition of some aliphatic aldehyde-derived imino esters,[15] we changed the metal precursor from $Cu(CH_3CN)_4BF_4$ to Ag_2O and found that the reaction took place smoothly and led to the desired adduct **3n** in good yield, albeit with only 63% *ee*. Fortunately, the enantioenriched compound was easily obtained by simple recrystallization of the crude product (Table 2, entry 14).

To determine the relative and absolute configuration of spiro adduct **3b**, the derived compound **4** was synthesized by a highly efficient and simple amidation protocol (Scheme 3). An X-ray analysis of the crystal of **4** revealed a (2*S*,3*R*,4*S*,5*R*) configuration for the spiro quaternary center and the three adjacent tertiary stereogenic centers, and therefore also for the corresponding moiety in **3b** (Figure 3).[19] The absolute configuration of all other products was assigned by analogy.



Scheme 3. Amidation of the spiro adduct **3b**.

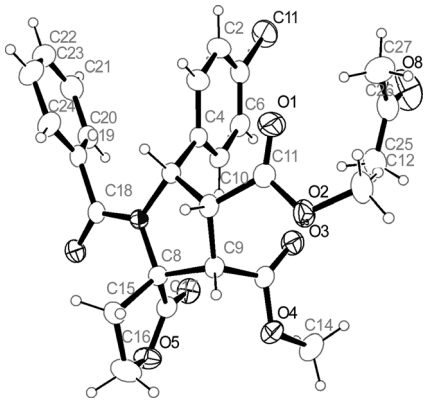


Figure 3. ORTEP representation of the cocrystal of (2*S*,3*R*,4*S*,5*R*)-**4** and acetone (1:1) with thermal ellipsoids at 30% probability level.

To further expand the synthetic utility of this transformation for the construction of spiro(butyrolactonepyrrolidines) containing a unique quaternary stereogenic center, other dipolarophiles were also examined under the optimized reaction conditions. As shown in Figure 4, *tert*-butyl acrylate and (*E*)-4-phenylbut-3-en-2-one proved to be excellent dipolaro-

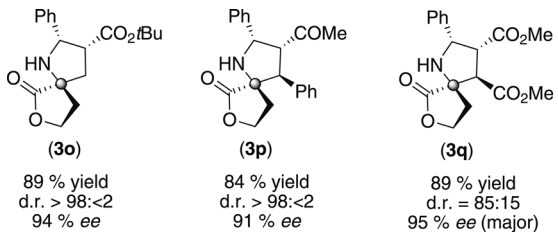


Figure 4. The results of the 1,3-dipolar cycloaddition of cyclic aldimino ester **1a** with other dipolarophiles catalyzed by Cu^{I}/**L5**.

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philes, affording the desired spiroadducts **3o** and **3p** with high yields and excellent diastereo- and enantioselectivity. Moreover, dimethyl fumarate was also investigated; although the diastereoselectivity (85:15) was lower than that of dimethyl maleate (>98:2), the expected spirocyclic adduct **3q** was still obtained in satisfactory yield and 95% *ee* (major diastereomer).

Based on the relative and absolute configuration of (2*S*,3*R*,4*S*,5*R*)-**3a**, the high stereoselectivity observed in the Cu^{I}/(*S*)-TF-BiphamPhos-catalyzed 1,3-dipolar cycloaddition of cyclic aldimino esters with dimethyl maleate can be rationalized by using the proposed tetracoordinated complex shown in Figure 5. The in situ-formed azomethine ylide is

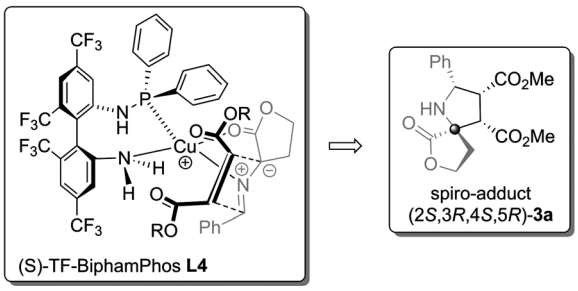

Figure 5. Proposed transition states leading to (2*S*,3*R*,4*S*,5*R*)-**3a**.

coordinated to the metallic center and is oriented in this specific way because of the steric repulsion between the phenyl group in the ylide and the phenyl ring on the phosphorus atom of the chiral ligand. The high steric congestion imposed by the P-phenyl group effectively blocks the approach of the dipolarophile, dimethyl maleate, from the *Re* (C=N) face of the azomethine ylide. Instead, the (2*S*,3*R*,4*S*,5*R*)-spiro(butyrolactonepyrrolidine) **3a** is formed by a *Si* face attack, which is compatible with the experimental results. The carbonyl group of dimethyl maleate could coordinate with the Cu^{I} center, stabilizing the negatively charged oxygen atom in the proposed transition states. However, this does not rule out the possible hydrogen-bonding interaction between the carbonyl group of the dipolarophile and the NH_2 group of the chiral (*S*)-TF-BiphamPhos ligand, which might also facilitate stabilization of the proposed transition states.[20]

In conclusion, we have successfully developed the first catalytic asymmetric method for the construction of spiro(butyrolactonepyrrolidines) containing a unique spiro quaternary stereogenic center by Cu^{I}-catalyzed asymmetric 1,3-dipolar cycloaddition of homoserine lactone derived cyclic imino esters. This catalytic system exhibited high reactivity, excellent diastereoselectivity, good enantioselectivity and broad substrate scope. The methodology presented herein enables facile access to biologically active spirocycles containing both a γ-lactone and pyrrolidine moiety. Efforts are currently underway to elucidate the mechanistic details and the scope and limitations of this reaction.

Experimental Section

General Procedure: Under an argon atmosphere, (*S*)-TF-BiphamPhos **L5** (5.8 mg, 0.0072 mmol) and $[Cu(CH_3CN)_4][BF_4]$ (2.0 mg, 0.006 mmol) were dissolved in dichloromethane (2 mL) and stirred at room temperature for approximately 1 h. The cyclic aldimino ester (0.26 mmol), Et_3N (0.03 mmol) and dimethyl maleate (0.2 mmol) were then added sequentially. Once the starting material had been fully consumed (monitored by TLC), the mixture was filtered through Celite and the filtrate was concentrated to dryness. The crude product was analyzed by ^1H NMR spectroscopy to determine the diastereoselectivity, and the residue was purified by column chromatography to give the corresponding cycloadduct as a white solid. This was then directly analyzed by chiral HPLC to determine the enantiomeric excess.

Acknowledgements

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Keywords: asymmetric catalysis · cycloaddition · diastereoselectivity · enantioselectivity · spiro compounds

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