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Catalytic Asymmetric Construction of Spiro(γ-butyrolactam-γ-butyrolactone) Moieties through Sequential Reactions of Cyclic Imino Esters with Morita–Baylis–Hillman Bromides

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Spirocycles containing γ-butyrolactam and γ-butyrolactone moieties are prevalent scaffolds in biologically active molecules and natural products.[1–5] Some representative examples are shown in Figure 1. The privileged cyclic γ-butyrolactam and γ-butyrolactone skeletons have high potential

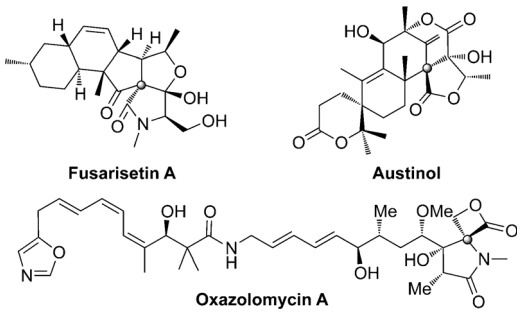

Figure 1. Representative bioactive spiro(γ-butyrolactam)s and spiro(γ-butyrolactone)s containing a quaternary stereogenic center.

as core elements for the development of related compounds that lead to medicinal agents.[5] Therefore, the spiro(γ-butyrolactam-γ-butyrolactone) motif, that is, the combination of the two key units through a spiro quaternary carbon atom,[6] may introduce some unprecedented benefits and is expected to find valuable applications in medicinal chemistry.

In sharp contrast to the well-documented approaches to either γ-butyrolactam- or γ-butyrolactone-containing compounds, an effective method for the construction of the spiro(γ-butyrolactam-γ-butyrolactone) skeleton remains elusive. To our knowledge, there have been no reports on the catalytic asymmetric synthesis of spiro(γ-butyrolactam-γ-butyrolactone) moieties so far.[7] Herein, we report the first asymmetric construction of spiro(γ-butyrolactam-γ-butyrolactone) compounds containing consecutive spiro quaternary and tertiary stereocenters through a Cu^{I}-catalyzed tandem Michael addition–eliminaton of homoserine lactone derived cyclic imino esters with Morita–Baylis–Hillman bromides, followed by a deprotection/lactamization reaction.

The Morita–Baylis–Hillman reaction is one of the most popular atom-economic carbon–carbon bond-forming reactions. This reaction straightforwardly provides densely functionalized molecules, and has recently received considerable attention.[8] Multifunctionalized Morita–Baylis–Hillman adducts have been employed successfully as valuable starting materials for the synthesis of heterocycles and many biologically active molecules.[9] Among these, Morita–Baylis–Hillman carbonates are the most commonly used substrates for a large number of asymmetric transition-metal-catalyzed and organocatalyzed transformations.[10] As part of our continuing interest in the application of Morita–Baylis–Hillman adducts in asymmetric catalysis,[11] we recently reported a catalytic asymmetric method for the rapid construction of pyroglutamate derivatives containing the γ-butyrolactam moiety and a quaternary stereogenic center through Cu^{I}/2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)-catalyzed tandem Michael addition–elimination of α-substituted aldimino esters with Morita–Baylis–Hillman (MBH) carbonates, followed by a simple deprotection/lactamization protocol (Scheme 1a).[11b] Along this research pathway, it occurred to us that with the appropriate Morita–Baylis–Hillman-type adducts as nucleophilic acceptors, such a sequential protocol might be applicable for facile access to enantioenriched spiro(γ-butyrolactam-γ-butyrolactone) skeletons, featuring adjacent spiro quaternary and tertiary stereogenic centers. However, as outlined in Scheme 1b, the expected tandem Michael addition–elimination reaction did not proceed when the less reactive (*Z*)- or (*E*)-trisubstituted MBH-type acetates[12] were initially employed, which was probably caused by the unfavorable steric congestion. Considering that a bromo group at the allylic position of MBH reagents is also a suitable leaving group,[13,14] we envisaged that the sterically less bulky MBH bromides might be employed as an efficient nucleophilic acceptor, and hence facilitate the tandem transformation through regioselective γ-position attack,[14e] leading to the key adduct containing two adjacent stereogenic centers.

To test our hypothesis, we first decided to study the racemic reaction of MBH bromide (*Z*)-2-(bromomethyl)-3-phe-

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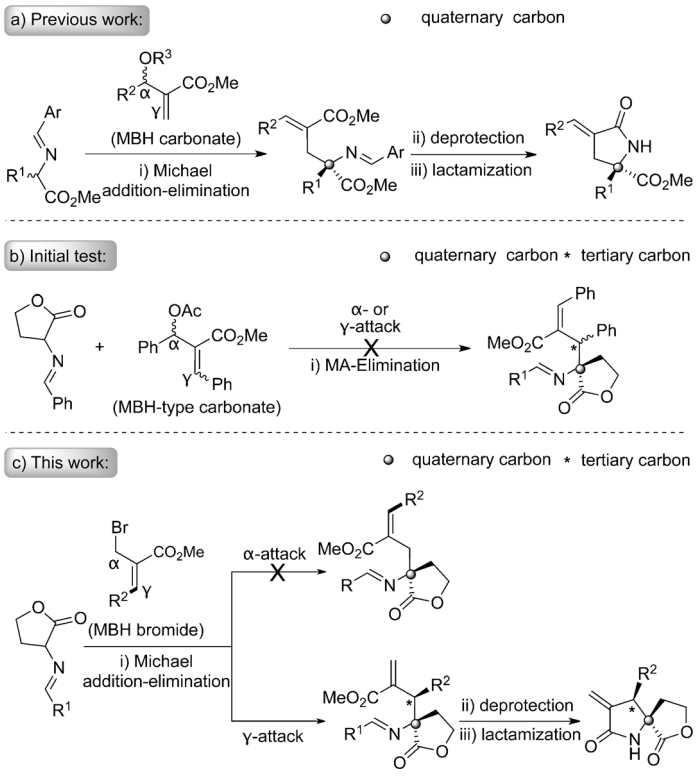
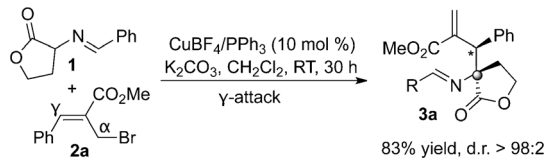


Scheme 1. Asymmetric construction of pyroglutamate (a) and spiro(γ-butyrolactam-γ-butyrolactone) compounds containing one spiro quaternary and one tertiary stereogenic center (b and c).

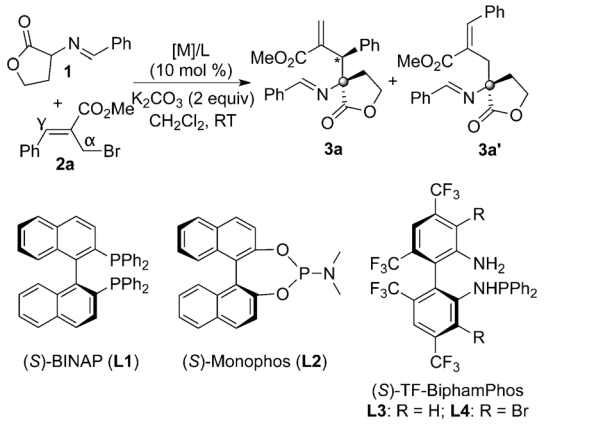
nylprop-2-enoate **2a**[15] with the homoserine lactone derived cyclic imino ester **1** to probe the possible reaction pathway. To our delight, we found that the expected tandem Michael addition–elimination reaction was efficiently promoted by a catalytic amount of the Cu^I/PPh_3 complex, and the expected Michael addition–elimination product **3a** was isolated as a stable compound through exclusively γ-attack,[16] in high yield with excellent diastereoselectivity (d.r. > 20:1; Scheme 2).



Scheme 2. $CuBF_4/PPh_3$-catalyzed tandem Michael addition–elimination reaction of homoserine lactone derived cyclic imino ester **1** with MBH bromide **2a**.

Encouraged by this promising result and inspired by our recent finding that the Cu^I/(*S*)-BINAP complex exhibits excellent results in the catalytic asymmetric tandem Michael addition–elimination of Morita–Baylis–Hillman carbonates, we began chiral-ligand screening with the bisphosphine BINAP. Unfortunately, no reaction occurred between the Morita–Baylis–Hillman bromide **2a** and cyclic imino ester **1** under the previously reported optimal reaction conditions

Table 1. Optimization of the catalytic asymmetric tandem Michael addition–elimination reaction of homoserine lactone derived cyclic imino ester **1** with MBH bromide **2a**.[a]



Entry	L	[M]	Solvent	**3a**/**3a′**[b]	Yield[c] [%]	*ee*[d] [%]
1	**L1**	AgOAc	CH_2Cl_2	2:1	42	15
2	**L1**	$CuBF_4$	CH_2Cl_2	–	–	–
3	**L2**	AgOAc	CH_2Cl_2	–	–	–
4	**L2**	$CuBF_4$	CH_2Cl_2	2:1	30	26
5	**L3**	AgOAc	CH_2Cl_2	>20:1	70	40
6	**L3**	$CuBF_4$	CH_2Cl_2	>20:1	69	54
7	**L4**	AgOAc	CH_2Cl_2	>20:1	74	86
8	**L4**	$CuBF_4$	CH_2Cl_2	>20:1	85	92
9	**L4**	$CuBF_4$	THF	>20:1	25	20
10	**L4**	$CuBF_4$	toluene	>20:1	92	74
11	**L4**	$CuBF_4$	Et_2O	>20:1	60	89
12	**L4**	$CuBF_4$	CH_3CN	>20:1	68	73
13	**L4**	$CuBF_4$	$CHCl_3$	>20:1	47	89
14[e]	**L4**	$CuBF_4$	CH_2Cl_2	>20:1	45	94

[a] All reactions were carried out with **2a** (0.24 mmol) and **1** (0.20 mmol) in a solvent (2 mL) for 36 h. $CuBF_4 = Cu(CH_3CN)_4BF_4$. [b] The ratio of **3a**/**3a′** was determined from the crude ^1H NMR spectrum. [c] Yield of the isolated product. [d] The *ee* was determined by chiral HPLC analysis. [e] Carried at 0 °C for 72 h.

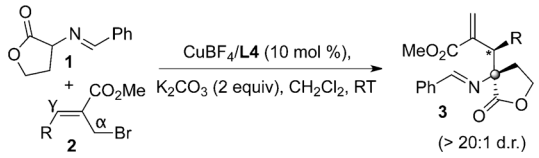
for Morita–Baylis–Hillman carbonates (Table 1, entry 2).[11b] However, with the Ag^I/(*S*)-BINAP complex as the catalyst and K_2CO_3 as the base, the reaction proceeded at room temperature, although α-[16] and γ-attack products were formed in an unsatisfactory ratio with a pretty low *ee* for the major isomer (Table 1, entry 1). If combined with (*S*)-Monophos (**L2**), AgOAc hardly promotes this reaction, whereas the $Cu(CH_3CN)_4BF_4$ salt directs the γ-attack pathway exclusively, albeit with low reactivity and enantioselectivity (Table 1, entries 3 and 4). Next, the chiral ligands TF-BiphamPhos, developed in this laboratory,[17] were screened to identify a more efficient catalyst system. In general, TF-BiphamPhos ligands exhibited the best results in terms of reactivity and regioselectivity, and copper salts gave better enantioselectivity than silver salts (Table 1, entries 5–8). By using the $Cu(CH_3CN)_4BF_4$/TF-BiphamPhos **L3** complex as the catalyst, the γ-attack adduct **3a** was exclusively obtained with good yield, excellent diastereoselectivity and moderate enantioselectivity (54% *ee*; Table 1, entry 6). TF-BiphamPhos **L4**, containing two bromine atoms in the 3,3′-positions of the TF-BIPHAM backbone was revealed to be the most promis-

ing ligand, providing **3a** in 85% yield and 92% *ee* (Table 1, entry 8), which demonstrates the significant role that the *ortho*-substituted biphenyl skeleton (TF-BIPHAM) plays in this process, and similar improvements in enantioselectivity have also been noticed in other asymmetric catalysis reactions.[18] Subsequently, a study of the reaction with Cu^{I}/TF-BiphamPhos **L4** at room temperature in various solvents identified diethyl ether and chloroform to be suitable alternatives to dichloromethane (Table 1, entries 8–13). Reducing the reaction temperature from RT to 0°C led to a small increase in the enantioselectivity, but the reaction rate dropped significantly, providing only a moderate yield even after an extended reaction time (Table 1, entry 14). Thus, the optimized reaction conditions were established to be the $CuBF_4$/**L4** complex (10 mol%) and K_2CO_3 as the base in CH_2Cl_2 at room temperature.

Next, the scope and generality of this novel tandem Michael addition–elimination reaction of the cyclic imino ester **1** with a series of MBH bromides **2** were investigated under the optimized experimental conditions. As shown in Table 2, a wide array of MBH bromides derived from aromatic aldehydes reacted smoothly with cyclic imino ester **1** through the exclusively γ-attack reaction pathway, providing the desired tandem Michael addition–elimination adducts in excellent diastereoselectivities and high enantioselectivities (Table 2, entries 1–11). It appears that the position and electronic properties of the substituents on the aromatic ring have a very limited effect on the stereoselectivity. The consistently excellent diastereo- and enantioselectivities obtained with the sterically hindered *ortho*-methoxyl- and *ortho*-chloro-substituted MBH bromides **2b** and **2f** is noteworthy (Table 2, entries 2 and 6). Additionally, polycyclic aromatic 2-naphthylaldehyde-derived imino ester **2l** was found to be a viable substrate for this process, producing the corresponding product **3l** in 88% yield with >20:1 d.r. and 82% *ee* (Table 2, entry 12). Remarkably, MBH bromide **2m**, derived from an aliphatic aldehyde, also worked well in this tandem reaction, providing the desired γ-attack adduct exclusively with excellent diastereo- and enantioselectivity (Table 2, entry 13).

The regioselective tandem Michael addition–elimination reaction can then be applied for facile access to spiro(γ-butyrolactam-γ-butyrolactone) compounds with high molecular complexity, as exemplified in Scheme 3. Simple treatment of adducts **3a** and **3j** with TsOH (Ts = *para*-toluenesulfonyl) in THF/H_2O (1:1) at room temperature achieved the cleavage

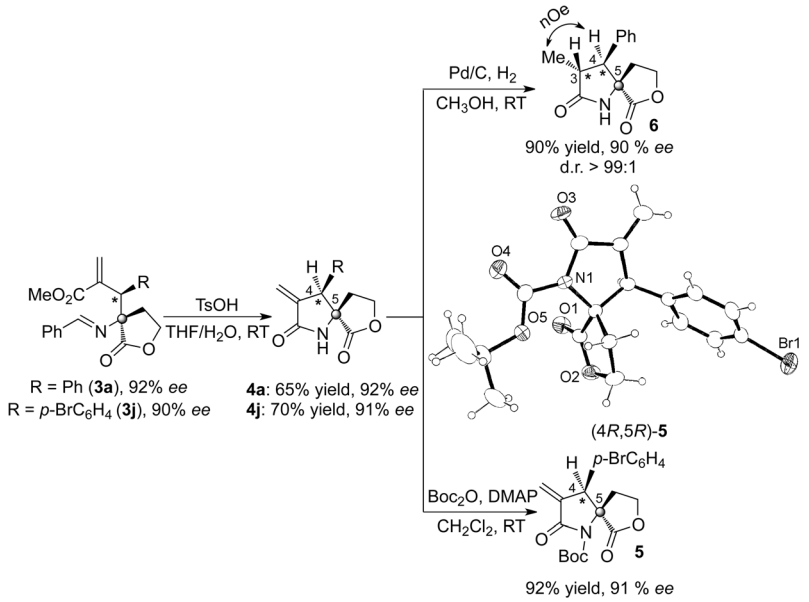
Table 2. Substrate scope of the Cu^{I}-catalyzed asymmetric tandem Michael addition–elimination reaction of homoserine lactone derived cyclic imino ester **1** with MBH bromides **2**.[a]



Entry	R	Product	Yield[b] [%]	*ee*[c] [%]
1	Ph (**2a**)	**3a**	85	92
2	*o*-MeOPh (**2b**)	**3b**	78	92
3	*p*-MeOPh (**2c**)	**3c**	83	93
4	*m*-MeOPh (**2d**)	**3d**	78	94
5	*p*-MeOPh (**2e**)	**3e**	75	92
6	*o*-ClPh (**2f**)	**3f**	75	94
7	*m*-ClPh (**2g**)	**3g**	87	87
8	*p*-ClPh (**2h**)	**3h**	83	89
9	*p*-FPh (**2i**)	**3i**	88	92
10	*p*-BrPh (**2j**)	**3j**	86	90
11	*p*-CF_3Ph(**2k**)	**3k**	75	91
12	2-naphthyl (**2l**)	**3l**	88	82
13	Et (**2m**)	**3m**	68	90

[a] The reactions were carried out with **2** (0.24 mmol) and **1** (0.20 mmol) in CH_2Cl_2 (2 mL) for 36 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis.

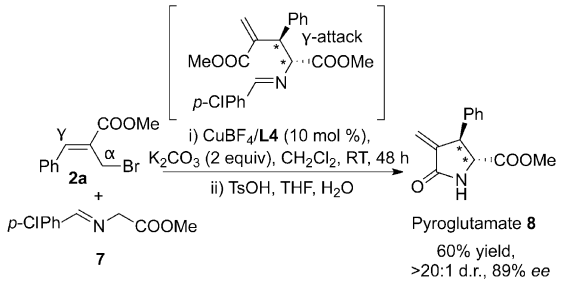
of the imino protecting group and subsequent lactamization, providing the corresponding spiro(γ-butyrolactam-γ-butyrolactone) compounds containing adjacent spiro quaternary and tertiary stereogenic centers without a reduction in diastereomeric ratio or enantiomeric excess. An X-ray crystallographic analysis of a crystal of *tert*-butoxycarbonyl (Boc)-protected compound **5** revealed a (4*R*,5*R*) configuration[19] for the two consecutive stereogenic centers and therefore also for the corresponding moiety in **3j** and **4j**. Direct hy-



Scheme 3. Facile access to spiro(γ-butyrolactam-γ-butyrolactone) compounds with high molecular complexity. Compound (4*R*,5*R*)-**5**: Ellipsoids were drawn at the 30% probability level.

drogenation of the α-methylene group in spirocyclic compound **4a** in the presence of Pd/C delivered compound **6**, containing three consecutive stereogenic centers, and the additional tertiary stereogenic center was efficiently generated in a remarkably diastereoselective manner.

Prompted by these results for the homoserine lactone derived cyclic imino esters, we then investigated the reaction of glycine-derived imino ester **7**, which contains no substitution at the α-position, from which two adjacent tertiary stereogenic centers would be generated in the corresponding adduct (Scheme 4). To our delight, the reaction occurred



Scheme 4. Results of the tandem Michael addition–elimination of an imino ester derived from glycine (**7**) with MBH bromide **2a** and the synthetic transformation.

successfully with the Cu^{I}/TF-BiphamPhos **L4** complex to give pyroglutamate **8** highly diastereo-/enantioselectively through tandem Michael addition–elimination (by γ-attack), followed by the aforementioned deprotection/lactamization protocol.

In conclusion, we have successfully developed the first example of the catalytic asymmetric construction of highly functionalized spiro(γ-butyrolactam-γ-butyrolactone) compounds, a valuable structural motif for drug discovery, through the Cu^{I}-catalyzed tandem Michael addition–elimination reaction of homoserine lactone derived cyclic aldimino esters, followed by a deprotection/lactamization protocol. The success of this methodology relies on the logical design and rational optimization that led to utilizing Morita–Baylis–Hillman bromides as the key nucleophilic acceptors. The highly efficient Cu^{I}/TF-BiphamPhos catalytic system exhibited excellent performance, providing enantioenriched spiro(γ-butyrolactam-γ-butyrolactone) derivatives containing adjacent spiro quaternary and tertiary stereogenic centers in a regioselective manner, with excellent diastereoselectivity (>20:1) and high enantioselectivity (82–94% *ee*). Further investigations into the scope and synthetic applications of this methodology are ongoing, and the results will be reported in due course.

Experimental Section

General procedure: Under an argon atmosphere, $Cu(CH_3CN)_4BF_4$ (6.3 mg, 0.020 mmol) and (*S*)-TF-BiphamPhos **L4** (17.5 mg, 0.022 mmol) were dissolved in CH_2Cl_2 (2 mL), and stirred at room temperature for 1 h. Then, cyclic imino ester **1** (0.20 mmol), K_2CO_3 (0.4 mmol), and MBH bromide **2** (0.24 mmol) were added sequentially. The mixture was stirred at room temperature until full consumption of **1** had occurred (monitored by TLC analysis). Then, the residue was purified by flash column chromatography on silica gel to give the corresponding product **3** as a colorless oil, which was then directly analyzed by chiral HPLC to determine the enantiomeric excess.

Acknowledgements

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Keywords: asymmetric catalysis · bromides · diastereoselectivity · enantioselectivity · imino esters · spiro compounds

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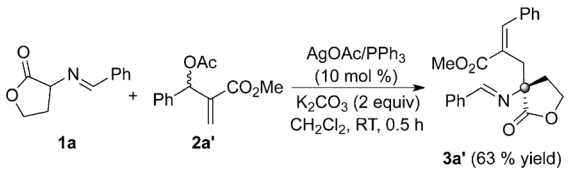
[16] The exclusively α-attack product **3a′** could be formed instead through a $AgOAc/PPh_3$-catalyzed tandem Michael addition–elimination reaction of the homoserine lactone derived cyclic imino ester with the Morita–Baylis–Hillman (MBH) carbonate (ref. [11b]):



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[19] Crystal data for spiro-(4*R*,5*R*)-**5**: $C_{19}H_{20}BrNO_5$, $M_r = 422.27$, $T = 293$ K, monoclinic, space group $P2(1)$, $a = 11.886(3)$, $b = 6.4413(17)$, $c = 12.608(3)$ Å, $V = 953.2(4)$ Å^3, $Z = 2$, 3488 unique reflections, final $R_1 = 0.0340$ and $wR_2 = 0.1210$ for 2555 observed $[I > 2\sigma(I)]$ reflections, Flack $\chi = 0.015(12)$. CCDC-873311 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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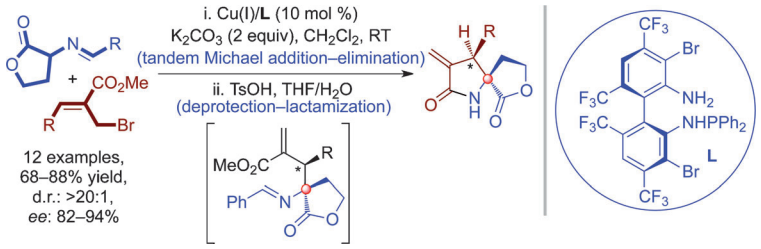

Spiro(γ-butyrolactam-γ-butyrolactone): A route to enantioenriched spiro(γ-butyrolactam-γ-butyrolactone) compounds, a valuable motif for drug discovery, was developed by use of a highly efficient copper(I)/TF-Biphamphos-catalyzed tandem Michael addition–elimination of homoserine lactone derived cyclic imino esters with Morita–Baylis–Hillman (MBH) bromides, followed by treatment with *para*-toluenesulfonic acid (see scheme).

