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A Facile Cu(I)/BINAP-Catalyzed Asymmetric Approach to Functionalized Pyroglutamate Derivatives Bearing a Unique Quaternary Stereogenic Center

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ABSTRACT

A direct and facile access to enantioenriched pyroglutamate derivatives bearing a unique quaternary stereogenic center has been developed *via* Cu(I)/BINAP-catalyzed tandem Michael addition–elimination of α-substituted aldimino esters with Morita–Baylis–Hillman (MBH) carbonates followed by a deprotection/lactamization protocol, which performs well over a broad scope of substrates and provides biologically active pyroglutamate derivatives in good yields and excellent enantioselectivities.

Optically active nonproteinogenic α,α-disubstituted α-amino acids and derivatives[1] have played a special role in the design of peptides with enhanced properties due to the unique stereochemically stable quaternary carbon center.[2] When incorporated into peptides, α,α-disubstituted α-amino acids confer increased stability under physiological conditions and stabilize secondary structure motifs, which eventually afford useful information for the elucidation of an enzymatic mechanism.[2] Pyroglutamates bearing a unique quaternary stereogenic center, as a particular class of nonproteinogenic α,α-disubstituted α-amino acid derivatives, are prevalent scaffolds that serve as the core structures of natural alkaloids and bioactive molecules.[3] For example, oxazolomycin A and lactacystin were isolated from the fermentation broth of *Streptomyces sp*,[4] and

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salinosporamide A was isolated from a marine actinomycete *Salinispora tropica*[5](Figure 1). These optically active pyroglutamates bearing a quaternary stereogenic center exhibit a broad array of important biological and potentially valuable pharmaceutical properties, which have inspired organic chemists to pursue efficient synthetic methods for those compounds in recent years.[6]

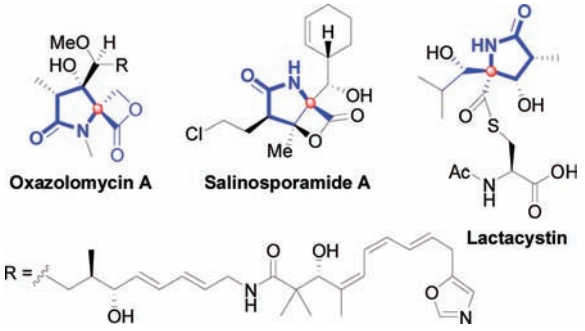
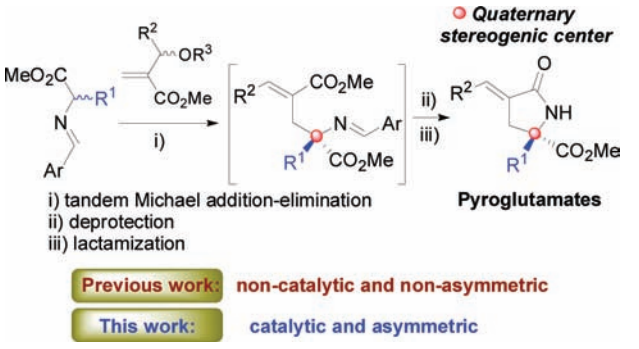


Figure 1. Representatives of biologically active pyroglutamates bearing a quaternary stereogenic center.

Although there are elegant and creative strategies toward the construction of a pyroglutamate architecture,[6] the directly catalytic asymmetric approach to access optically pure pyroglutamate bearing a quaternary stereogenic center has met with little success.[7] To the best of our knowledge, only one noncatalytic and nonasymmetric example has been reported for the synthesis of pyroglutamate derivatives containing a quaternary stereogenic center *via* stoichiometric LiHMDS-mediated tandem Michael addition−elimination of α-substituted aldimino esters with Morita−Baylis−Hillman (MBH) carbonates followed by a deprotection/lactamization protocol[8](Scheme 1). Therefore, the development of a catalytic asymmetric method for the facile synthesis of enantioenriched pyroglutamate derivatives bearing a unique quaternary stereogenic center is in great demand.

Inspired by Maruoka's excellent work on the efficient synthesis of enantioenriched α,α-disubstituted α-amino acids *via* PTC-catalyzed double alkylation of the easily

Scheme 1. Tandem MA-Elimination/Deprotection/Lactamization (3 Steps) for the Construction of Functionalized Pyroglutamates Bearing a Unique Quaternary Stereogenic Center



available and cost-efficient imino ester derived from aldehyde and glycine ester, which demonstrates the α-proton of the *in situ* generated α-substituted aldimino ester is still acidic enough to be deprotonated, enabling the subsequent second alkylation,[9,10] we envisioned that the enantioenriched pyroglutamate derivatives bearing a quaternary stereogenic center[11] could be achieved through employing α-substituted α-amino acids derived aldimino esters as the nucleophile and Morita−Baylis−Hillman carbonates[12] as the Michael acceptors in the presence of an appropriate chiral catalyst and base. Herein, we present the first asymmetric synthesis of pyroglutamates containing a unique quaternary stereogenic center *via* Cu(I)/(*S*)-BINAP-catalyzed tandem Michael addition−elimination of the α-substituted aldimino esters with MBH carbonates followed by deprotection/lactamization.

In view of the above-mentioned literature work and hypothesis, we initially examined the reactivity of MBH carbonate **1a**′ with (±)-phenylalanine-derived aldimino ester **2a** in the presence of 10 mol % of the $AgOAc/PPh_3$ complex as the catalyst and 2 equiv of K_2CO_3 as the base in DCM at rt. To our delight, the tandem Michael addition−elimination reaction proceeded smoothly to afford

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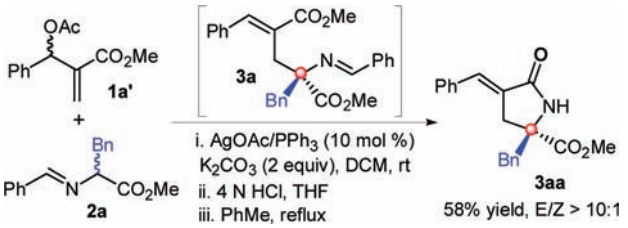
(13) It seems that the first step proceeds by way of tandem Michael addition−elimination due to no reaction occurring when the aldimino ester **2a** reacted with $CH{=}CHCH_2OAc$ under the same reaction conditions.

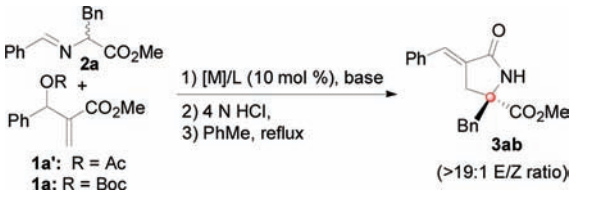
the instable intermediate 4-benzylidene glutamic acid derivative **3a**,[8,13] and no reaction occurred without the $AgOAc/PPh_3$ complex (Scheme 2). Cleavage of the imino-protecting group of **3a** under acidic conditions followed by efficient lactamization delivered (*E*)-4-benzylidene pyroglutamate **3aa** in 58% yield with a >10:1 diastereomeric ratio favoring the *E* diastereomer, which indicated that α-substituted aldimino esters could be applied as efficient nucleophiles for the catalytic asymmetric construction of pyroglutamate derivatives bearing a quaternary stereogenic carbon center.[11]

Scheme 2. $AgOAc/PPh_3$-Catalyzed Tandem MA-Elimination/Deprotection/Lactamization (Overall 3 Steps)



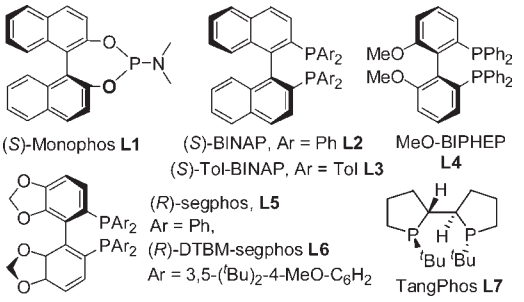
Encouraged by this promising result, different metal salts and commercially available chiral ligands were subsequently examined to establish optimal reaction conditions, and the representative results are summarized in Table 1. Combined with Monophos, both AgOAc and $Cu(CH_3CN)_4BF_4$ salts successfully promote the tandem Michael addition−elimination of **2a** with MBH carbonate **1a**′, and (*E*)-pyroglutamate **3aa** was achieved in 11% and 29% ee, respectively, with an excellent *E*/*Z* ratio through the subsequent deprotection/lactamization protocol (entries 1 and 2). A further survey of ligands revealed that the bisphosphine ligand was more efficient than the monophosphine ligand and the enantioselectivity was greatly affected by the substituted groups on the P-atom and the chiral backbone of the chiral ligands. With $Cu(MeCN)_4BF_4$ as the metal precursor, BINAP gave the best results in terms of the reaction rate and enantioselectivity among the tested bisphosphine ligands (entries 3 and 4). A little lower enantioselectivity was observed when the phenyl group on the P-atom of BINAP was replaced by the bulky *p*-tolyl group (**L3**) (entry 5). The enantioselectivity and catalytic ability decreased remarkably when the axial binaphthyl backbone of bisphosphine ligand was replaced by the axial biphenyl backbone ligand (**L4** and **L5**) (entries 6 and 7). The bulkier and electron-donating biphenyl ligand (*R*)-DTBM-segphos (**L6**) was totally inactive (entry 8). Highly electron-donating *P*-chiral trialkyl phosphine ligand TangPhos (**L7**) was also tested in this transformation affording the desired product with 68% ee (entry 9). The solvent study revealed CH_2Cl_2 was the best in terms of the yield and enantioselectivity. Further examination of the base disclosed that a high yield could be obtained with Cs_2CO_3 while organic bases such as Et_3N or DBU were not suitable for this reaction (entry 10). The effect of the leaving group of carbonate **1** was also investigated. Replacing the acetoxyl group with the bulky *tert*-butoxycarbonyloxyl group gave rise to higher enantioselectivity without loss of reactivity (entries 4 and 11). $Cu(OTf)_2$ could also be used in this transformation albeit with a little lower ee (entry 12). Reducing the reaction temperature from rt to 0 °C led to complete reaction with 96% ee (entry 13). The catalyst loading was successfully reduced to 5 mol %, with comparable results achieved with an extended reaction time (entry 14).

Table 1. Screening Studies for Asymmetric Construction of Funtionalized Pyroglutamate Derivatives Bearing a Quaternary Stereogenic Center[a]



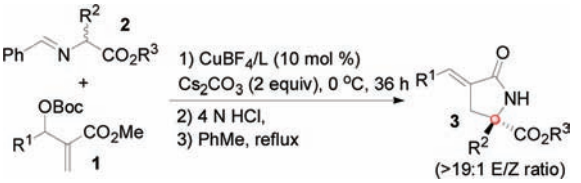
entry	L	[M]	1	base	solvent	*t* (°C)	yield (%)[b]	ee (%)[c]
1	**L1**	AgOAc	**1a**′	K_2CO_3	DCM	rt	43	11
2	**L1**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	58	29
3	**L2**	AgOAc	**1a**′	K_2CO_3	DCM	rt	75	66
4	**L2**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	78	90
5	**L3**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	69	87
6	**L4**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	73	79
7	**L5**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	74	78
8	**L6**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	–	–
9	**L7**	$CuBF_4$	**1a**′	K_2CO_3	DCM	rt	30	68
10	**L2**	$CuBF_4$	**1a**′	Cs_2CO_3	DCM	rt	75	90
11	**L2**	$CuBF_4$	**1a**	Cs_2CO_3	DCM	rt	78	92
12	**L2**	$Cu(OTf)_2$	**1a**	Cs_2CO_3	DCM	rt	75	88
13[d]	**L2**	$CuBF_4$	**1a**	Cs_2CO_3	DCM	0	72	96
14[e]	**L2**	$CuBF_4$	**1a**	Cs_2CO_3	DCM	0	55	94

[a] Tandem Michael addition−elimination reactions (the first step) were carried out with 0.3 mmol of **2a** and 0.36 mmol of **1** in 2 mL of solvent for 20 h. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield of the overall three steps. [c] Determined by chiral HPLC analysis. [d] In 36 h. [e] 5 mol % catalyst loading, 48 h.



The scope and generality of this catalytic system with regard to MBH carbonates and α-substituted aldimino esters were investigated under the optimized experimental conditions. As shown in Table 2, a series of representative MBH carbonates derived from aromatic aldehydes, which

Table 2. Substrates Scope for Asymmetric Construction of Funtionalized Pyroglutamate Derivatives Bearing a Quaternary Stereogenic Center[a]



		2					
entry	R^1	R^2		R^3	prod	yield (%)[b]	ee (%)[c,d]
1	Ph (**1a**)	Bn	**2a**	Me	**3aa**	72	96
2	*p*-MeO-Ph (**1b**)	Bn	**2a**	Me	**3ba**	58	93
3	*m*-MeO-Ph (**1c**)	Bn	**2a**	Me	**3ca**	65	94
4	*o*-Cl-Ph (**1d**)	Bn	**2a**	Me	**3da**	73	94
5	*m*-Cl-Ph (**1e**)	Bn	**2a**	Me	**3ea**	67	93
6	*p*-Cl-Ph (**1f**)	Bn	**2a**	Me	**3fa**	75	94
7	*p*-F-Ph (**1g**)	Bn	**2a**	Me	**3ga**	65	94
8	*p*-Br-Ph (**1h**)	Bn	**2a**	Me	**3ha**	63	94
9	2-Naphthyl (**1i**)	Bn	**2a**	Me	**3ia**	67	91
10	2-thienyl (**1j**)	Bn	**2a**	Me	**3ja**	71	94
11	2-furyl (**1k**)	Bn	**2a**	Me	**3ka**	65	94
12[e]	Cy (**1l**)	Bn	**2a**	Me	**3la**	46	94
13[f]	Et (**1m**)	Bn	**2a**	Me	**3ma**	50	95
14	H (**1n**)	Bn	**2a**	Me	**3na**	62	93
15	Ph (**1a**)	^{i}Bu	**2b**	Me	**3ab**	58	97
16	Ph (**1a**)	Ph	**2c**	Me	**3ac**	40	89
17	Ph (**1a**)	Pr	**2d**	Me	**3ad**	63	77(99)
18	Ph (**1a**)	Bu	**2e**	Me	**3ae**	56	82(99)
19	Ph (**1a**)	^{i}Bu	**2f**	^{t}Bu	**3af**	65	99
20	Ph (**1a**)	Bn	**2g**	Bn	**3ag**	65	95

[a] Tandem MA-elimination reaction (the first step) was carried out with 0.3 mmol of **2** and 0.36 mmol of **1** in 2 mL of DCM. [b] Isolated yield for the overall three steps. [c] Determined by HPLC analysis. The number in bracket is the ee after recrystallization. [d] The configuration of **3ha** was determined to be *S* according to the X-ray analysis (see Supporting Information for more details). [e] 10:1 *E*/*Z* ratio. [f] 6:1 *E*/*Z* ratio.

bear electron-rich (Table 2, entries 2 and 3), -neutral (entries 1 and 9), or -deficient groups (entries 4−8) on the phenyl ring, reacted smoothly with *N*-benzylidene-phenylalanine methyl ester **2a** followed by subsequent deprotection/lactamization to afford the desired *E*-glutamates (**3aa-3ia**) in good yields (58−72% for overall 3 steps) and excellent selectivities (91−96% ee, > 19:1 dr) (entries 1−9). It appears that the position and the electronic property of the substituents on the aromatic rings have very limited effect on the enantioselectivities. Sterically hindered *ortho*-chloro substituted MBH carbonates **1d** work well in this transformation producing **3da** with 73% yield and 94% ee (entry 4). It is noteworthy that MBH carbonates **1j** and **1k** derived from hetero 2-furyl and 2-thienyl aldehyde were tolerated in this transformation leading to (*E*)-**3ja** and (*E*)-**3ka** with 94% ee (entries 10 and 11). Notably, the MBH carbonates **1l**−**1n** from aliphatic cyclohexanecarbaldehyde, propionaldehyde, and paraformaldehyde also worked well in this sequential transformation, and the corresponding products could be obtained in remarkably high enantioselectivity and acceptable yields although a little lower *E*/*Z* ratio[14] was noticed for **3la** and **3ma** (entries 12−14). To further expand the synthetic utility of this transformation for the construction of pyroglutamates bearing a unique quaternary stereogenic center, the aldimino ester derived from other α-substituted amino acids has also been examined. Under the optimal reaction conditions, an acceptable yield and excellent enantioselectivity were uniformly observed for the aldimino esters derived from (±)-phenylalanine and (±)-leucine (Table 2, entries 15 and 19), which bear a branched substituent at the α-position of the corresponding aldimino esters. A lower reactivity by (±)-2-phenylglycine derived aldimino ester **2c** was likely due to the unfavored steric hindrance of the phenyl group at the α-position (entry 16). Yet, ~80% ee was achieved for the aldimino esters derived from (±)-2-aminopentanoic (entry 17) and (±)-2-amino-hexanoic acid (entry 18) bearing a linear substituent at the α-position, indicating that to some extent the steric congestion around the nucleophilic attack position of the aldimino ester was beneficial to the enhancement of asymmetric induction. (±)-Leucine *tert*-butyl ester and phenylalanine benzyl ester derived aldimino ester also worked well in this tandem reaction providing the desired products in 99% and 95% ee, respectively (entries 19 and 20). Fortunately, all the products are solid and enantioenriched compounds can be easily obtained by simple recrystallization of the crude products (entries 17 and 18).

In conclusion, we have successfully developed the first catalytic asymmetric method for the rapid construction of pyroglutamate derivatives bearing a unique quaternary stereogenic center *via* Cu(I)/(*S*)-BINAP-catalyzed tandem Michael addition−elimination of α-substituted aldimino esters with Morita−Baylis−Hillman carbonates followed by a simple deprotection/lactamization protocol. This catalytic system performs well over a broad scope of substrates and provides biologically active pyroglutamates in good yields and excellent enantioselectivities. The ready availability of the starting materials and the great importance of the enantioenriched products make the current methodology particularly interesting in synthetic chemistry. Further investigations of the substrate scope and the limitation of this methodology are ongoing.

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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.

(14) All these compounds could be readily purified by column chromatography to afford the pure (*E*)-pyroglutamates.