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Asymmetric Catalysis

Enantioselective Synthesis of Pyroglutamic Acid Esters from Glycinate via Carbonyl Catalysis

*Jiguo Ma, Qinghai Zhou, Guanshui Song, Yongchang Song, Guoqing Zhao, Kuiling Ding, and Baoguo Zhao**

Abstract: *Direct α-functionalization of NH_2-free glycinates with relatively weak electrophiles such as α,β-unsaturated esters still remains a big challenge in organic synthesis. With chiral pyridoxal* ***5d*** *as a carbonyl catalyst, direct asymmetric conjugated addition at the α-C of glycinate* ***1a*** *with α,β-unsaturated esters* ***2*** *has been successfully realized, to produce various chiral pyroglutamic acid esters* ***4*** *in 14–96 % yields with 81–97 % ee's after in situ lactamization. The trans and cis diastereomers can be obtained at the same time by chromatography and both of them can be easily converted into chiral 4-substituted pyrrolidin-2-ones such as Alzheimer's drug Rolipram (****11****) with the same absolute configuration via tert-butyl group removal and subsequent Barton decarboxylation.*

Chiral pyroglutamic acids and their derivatives are a type of important compounds with high bioactivities.[1,2] The pyroglutamic acid moieties are present in many natural products[1] and medicinal molecules.[2] Besides, pyroglutamic acids have also been used as versatile synthons to make various N-containing compounds.[3] Thus the synthesis of pyroglutamic acid derivatives is highly desirable and it has already attracted much attention. Conjugated addition at the α-C of glycinates with α,β-unsaturated esters followed by lactamization is a highly straightforward strategy to access pyroglutamic acid derivatives (Figure 1). However, NH_2 protecting group manipulation is usually needed before and after the α-C conjugated addition since the reaction can be easily interrupted by the nucleophilic NH_2 group. For example, Vialle-font, Kanemasa, Kobayashi, and other groups found that glycinate imines could undergo conjugated addition to α,β-unsaturated esters, followed by deprotection of the carbonyl protecting groups and subsequent in situ lactamization, to afford various pyroglutamic acid esters (Figure 1a).[4,5] Soloshonok and Hruby utilized Ni^{II} complexes of glycine Schiff bases as α-C nucleophiles to react with α,β-unsaturated amides to make substituted pyroglutamic acids in three steps with excellent diastereoselecivity (Figure 1b).[6] Direct reaction of glycinates with α,β-unsaturated esters to synthesize pyroglutamic acid derivatives without protecting group manipulation is highly attractive but it still remains a big challenge in organic synthesis. Carbonyl catalysis uses an appropriate aldehyde or ketone as the catalyst to activate the α C–H of primary amines for direct α functionalization,[7–9] which theoretically provides an opportunity for asymmetric conjugated addition at the α-C of glycinate **1a** with α,β-unsaturated esters **2** without pre-protection of the NH_2 group, to produce the desired chiral pyroglutamic acid esters **4** after in situ lactamization (Figure 1c). Herein, we report our studies on the project.

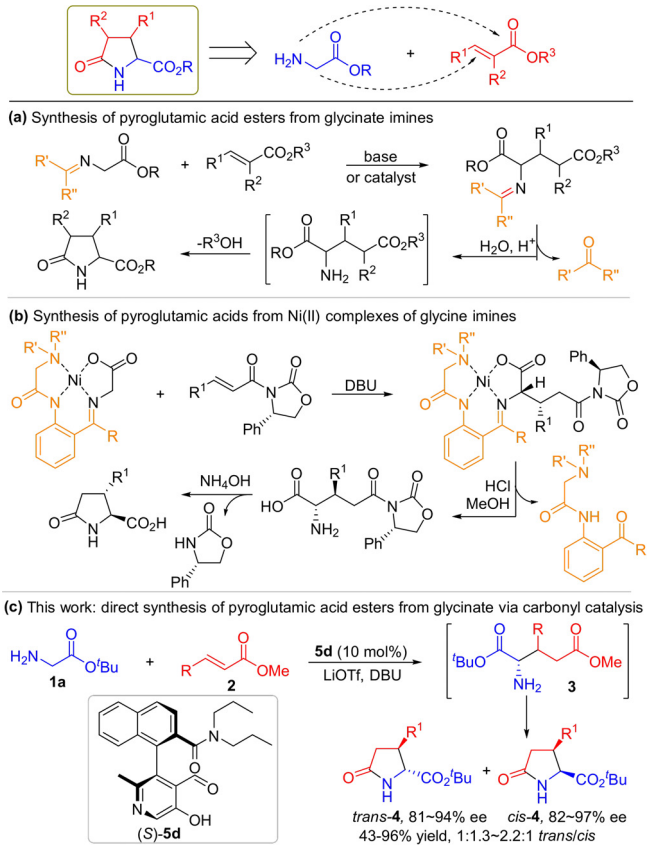

Figure 1. Strategies for the synthesis of pyroglutamic acids and esters from glycine derivatives.

The studies started with the investigation of the reaction of *tert*-butyl glycinate (**1a**) with α,β-unsaturated ester **2a** (Table 1). In the presence of 10 mol % of chiral pyridoxal[8,10] **5b** as the carbonyl catalyst (Scheme 1), the reaction did occur

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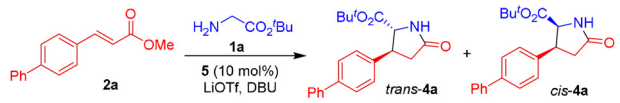
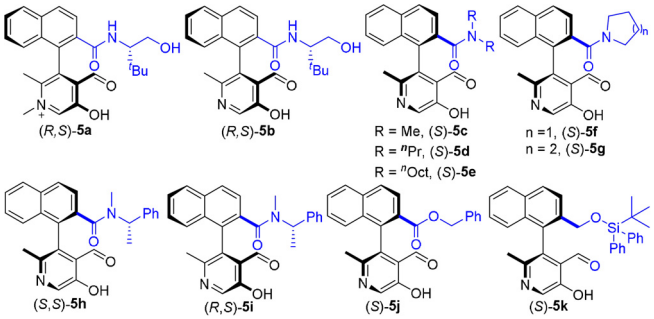
Table 1: Optimization for the synthesis of chiral pyroglutamic acid esters **4**.[a]



Entry	Cat.	Conditions	Yield [%][b]	*trans*:*cis*[c]	*ee* [%][d]
1	–	LiOTf, DBU, THF, 40 °C	0	–	–
2	**5a**	LiOTf, DBU, THF, 40 °C	0	–	–
3	**5b**	LiOTf, DBU, THF, 40 °C	47	1.2:1	−75/−82
4	**5c**	LiOTf, DBU, THF, 40 °C	77	1:1	77/87
5	**5d**	LiOTf, DBU, THF, 40 °C	85	1.5:1	82/85
6	**5f**	LiOTf, DBU, THF, 40 °C	60	1.1:1	74/85
7	**5g**	LiOTf, DBU, THF, 40 °C	88	1.1:1	80/84
8	**5d**	LiOTf, DBU, CH_3CN, 40 °C	90	1.1:1	86/91
9	**5e**	LiOTf, DBU, CH_3CN, 40 °C	58	1.1:1	84/89
10	**5h**	LiOTf, DBU, CH_3CN, 40 °C	70	1.2:1	86/89
11	**5i**	LiOTf, DBU, CH_3CN, 40 °C	89	1.1:1	−87/−90
12	**5j**	LiOTf, DBU, CH_3CN, 40 °C	71	1.2:1	35/41
13	**5k**	LiOTf, DBU, CH_3CN, 40 °C	46	1.3:1	21/−15
14	**5d**	LiOTf, DBU, $CHCl_3$, 40 °C	60	1.2:1	82/85
15	**5d**	LiOTf, DBU, DMF, 40 °C	26	1.2:1	87/91
16	**5d**	DBU, CH_3CN, 40 °C	0	–	–
17	**5d**	$Zn(OTf)_2$, DBU, CH_3CN, 40 °C	0	–	–
18	**5d**	$LiBF_4$, DBU, CH_3CN, 40 °C	59	1:1	86/92
19	**5d**	LiOTf, CH_3CN, 40 °C	0	–	–
20	**5d**	LiOTf, Et_3N, CH_3CN, 40 °C	0	–	–
21	**5d**	LiOTf, LiOH, CH_3CN, 40 °C	trace	–	–
22	**5d**	LiOTf, DBU, CH_3CN, 20 °C	39	1:1	85/91
23	**5d**	LiOTf, DBU, CH_3CN, 50 °C, 48 h	71	1.4:1	87/91
24	**5d**	LiOTf, DBU, CH_3CN, 50 °C, 30 h	58	1.2:1	86/92
25	**5d**	LiOTf, DBU, CH_3CN, 50 °C, 15 h	47	1.1:1	86/92

[a] All reactions were carried out with glycinate **1a** (0.15 mmol), **2a** (0.10 mmol), **5** (0.010 mmol), LiOTf (0.040 mmol) and DBU (0.10 mmol) in solvent (0.30 mL) at 40 °C for 48 h unless otherwise stated. [b] Isolated yields based on **2a**. [c] The *trans*/*cis* ratios were determined by HPLC analysis. [d] The *ee* values were determined by chiral HPLC analysis.



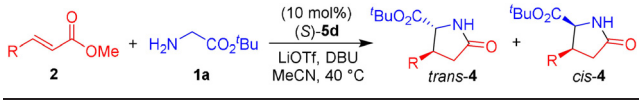
Scheme 1. Chiral pyridoxals **5a–k** examined.

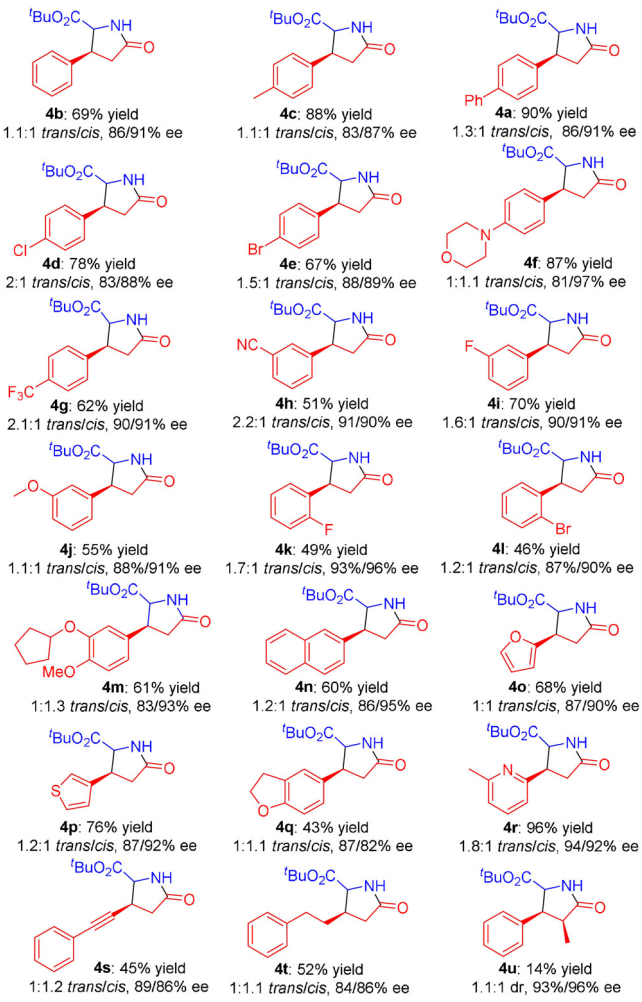
as expected, producing the desired chiral pyroglutamic acid ester **4a** in a 47 % yield with moderate enantioselectivities for both of the diastereomers (Table 1, entry 3). Although the diastereoselectivity was very low (*trans*/*cis* 1.2:1), fortunately the big polarity difference between the two diastereomers makes it easy to get them separated by column chromatography. The pyridoxal catalyst is crucial for the reaction. No desired addition products were observed in the absence of pyridoxals **5** (Table 1, entry 1). To our surprise, *N*-methyl chiral pyridoxal **5a** was totally ineffective for the reaction although it has very strong electron-withdrawing capability and displayed good catalytic activity and excellent selectivity in biomimetic Mannich reaction of glycinate (Table 1, entry 2).[8] This is probably because the too stable α-amino carbanion intermediate promoted by **5a** during the catalysis is not nucleophilic enough for the 1,4-conjugated addition to **2a**. Replacement of the primary amide side chain of the catalyst **5b** with a secondary amide (**5c**) led to an obvious improvement in reaction yield (Table 1, entry 4 vs. 3). Further catalyst screening showed that chiral pyridoxal **5d** was the best choice among the catalysts **5a–k** examined in terms of activity and enantioselectivity (Table 1, entries 5 and 8 vs. 2–4, 6–7 and 9–13). Further condition investigations indicated that acetonitrile was the best solvent (Table 1, entry 8 vs. 5 and 14–15) and DBU was the base of choice (Table 1, entry 8 vs. 19–21). Lewis acid was a necessary additive (Table 1, entry 8 vs. 16) and LiOTf was the most active for the reaction (Table 1, entry 8 vs. 17–18). Interestingly, temperature influenced the activity of the reaction, but displayed little impact on the enantioselectivity of the products **4a** (Table 1, entry 8 vs. 22 and 23). The reaction was chosen to carry out at 40 °C.

Under the optimal conditions, the substrate scope was then investigated for the pyridoxal-catalyzed direct synthesis of chiral pyroglutamic acid esters **4** (Table 2). Phenyl (for **4b**) and various substituted phenyl (for **4a** and **4c–m**) α,β-unsaturated esters all smoothly underwent asymmetric 1,4-conjugated addition and subsequent lactamization to give chiral pyroglutamic acid esters **4a–m** in good yields with low diastereoselectivities but high enantioselectivities for both of the *trans*- and *cis*-diastereomers. The 2-substituted substrates such as methyl (*E*)-3-(2-fluorophenyl)acrylate (for **4k**) and methyl (*E*)-3-(2-bromophenyl)acrylate (for **4l**) gave somewhat lower reaction yields likely due to steric hindrance. The electronic property of the substituted phenyl groups seemed to have little influence on the enantioselectivity. Naphthyl (for **4n**) and heteroaromatic (for **4o–r**) α,β-unsaturated esters both were effective substrates for the transformation, providing the corresponding chiral pyroglutamic acid esters **4n–r** in 43–96 % yields with similar selectivities. Alkynyl and alkyl α,β-unsaturated esters underwent the transformation to produce chiral pyroglutamic acid esters **4s** and **4t** in 45 % and 52 % yields, respectively. Disubstituted α,β-unsaturated ester methyl (*E*)-2-methyl-3-phenylacrylate was less reactive for the reaction likely due to steric hindrance, to give a pair of diastereomers **4u** with the 3-phenyl and 4-methyl groups on the same side of the pyrrolidinone ring in a 14 % yield with excellent enantioselectivities. The *trans*/*cis* configurations of the products **4a–u** were determined by ^{1}H-^{1}H NOESY (see Supporting Information). The absolute configurations for *trans*-**4a** and *cis*-**4p** were, respectively assigned as (2*R*,3*S*) and (2*S*,3*S*) based on X-ray analysis (Figure 2).[11]

While a precise mechanism awaits further studies, a plausible pathway has been proposed for the reaction (Scheme 2a). Chiral pyridoxal **5d** condenses with glycinate **1a** to

Table 2: Substrate scope investigation.[a]





[a] The reactions were carried out with glycinate **1a** (0.45 mmol), **2** (0.30 mmol), (*S*)-**5d** (0.030 mmol), LiOTf (0.12 mmol), DBU (0.30 mmol) in CH_3CN (0.90 mL) at 40 °C for 48 h unless otherwise stated. Reaction time was 96 h for **4t**. Isolated yields based on **2**. The *trans*/*cis* ratios of **4a–t** and the dr value of **4u** were determined by ^{1}H NMR analysis of the crude reaction mixtures. The *ee* values were determined by chiral HPLC analysis. The absolute configurations of *trans*-**4a** and *cis*-**4p** were, respectively determined as (2*R*,3*S*) and (2*S*,3*S*) based on X-ray analysis.[11] The absolute configurations for *trans*-isomers of products **4b–s** were proposed as (2*R*,3*S*), *cis*-isomers of **4a–o** and **4q–s** as (2*S*,3*S*), *trans*-**4t** as (2*R*,3*R*), and *cis*-**4t** as (2*S*,3*R*) by analogy.

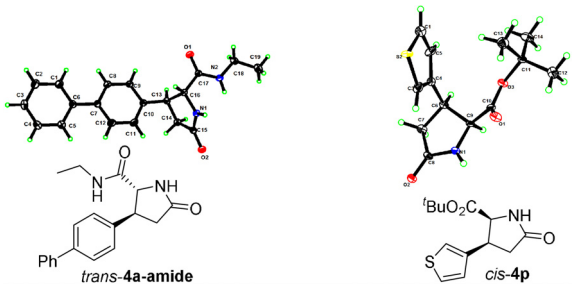
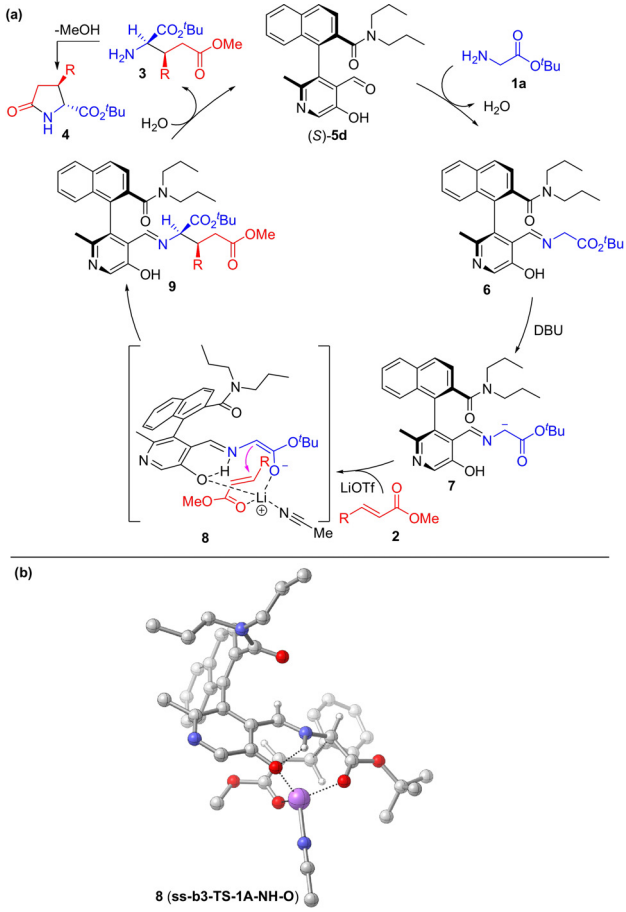


Figure 2. The X-ray structures of *trans*-**4a-amide** and *cis*-**4p**.



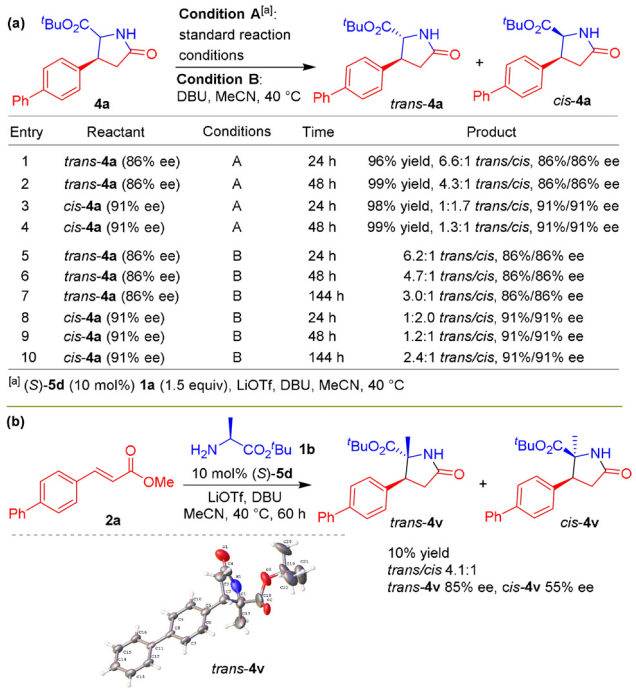
Scheme 2. a) Proposed reaction mechanism. b) Computationally-optimized transition state.

form Schiff base **6**, which is deprotonated[12] at the α position of the ester by the base DBU to generate delocalized carbon anion **7**.[13] The intermediate **7** undergoes asymmetric 1,4-conjugated addition to α,β-unsaturated ester **2** and subsequent hydrolysis to produce γ-amino ester **3** and regenerate the pyridoxal catalyst **5d**. Compound **3** is in situ converted into pyroglutamic acid ester **4** through intramolecular cyclization.

In order to understand the role of LiOTf and the origin of the chiral induction, computational studies has been carried out for the key step, that is, asymmetric addition of carbon anion **7** to α,β-unsaturated ester **2** (see SI). As shown in the optimized transition state **8** (Scheme 2b), LiOTf coordinates with both compound **2** and anion **7**, which not only improves the electrophilicity of the α,β-unsaturated ester but also brings the two reactants together with a specific spatial arrangement, accelerating the conjugated addition. This was supported by the fact that no desired product **4** was obtained without the Lewis acid additive (Table 1, entry 16 vs. 8 and 18). The *N*,*N*-propyl groups of the amide locate above the pyridine ring of **5d**, serving as a rigid and bulky group to block the up side of the pyridine ring. The α,β-unsaturated ester **2** approaches the enolate anion from the below of the pyridine

ring, away from the amide side chain, resulting in the formation of chiral product **4** with (2*R*,3*S*) configuration (if the R in **4** is an aryl group) from (*S*)-**5d**. Pyridoxal **5j** bearing an ester side chain showed good catalytic activity but much lower enantioselectivity as compared to **5d** (Table 1, entry 12 vs. 8), although the ester group has similar ability to coordinate with LiOTf as the amide of **5d**, indicating the amide doesn't coordinate with LiOTf but provides steric shielding for enantioselective control during catalysis.

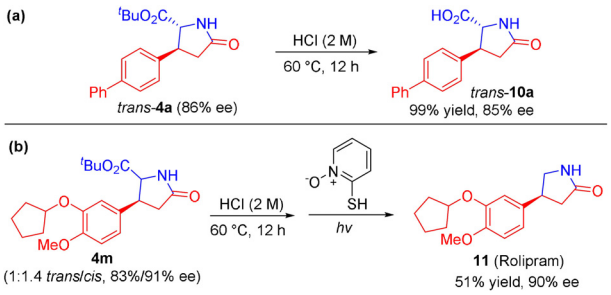
Low *trans*/*cis* ratios were obtained for pyroglutamic acid esters **4a**–**t** in the reaction likely due to the epimerization between the *trans*- and *cis*-isomers under the basic reaction conditions (Table 2). As expected, control experiments revealed that the two isomers *trans*-**4a** and *cis*-**4a** indeed can be interconverted into each other under the standard reaction conditions (Scheme 3a, entries 1–4). The epimerization also occurred when only in presence of the base DBU. And similar *trans*/*cis* ratios (3.0:1 vs. 2.4:1) were obtained in the experiments started from either *trans*-**4a** or *cis*-**4a** after extended reaction time (144 h) (Scheme 3a, entries 5–10). The epimerization during the reaction likely was faster than the pyridoxal-catalyzed conjugated addition, which was supported by the fact that the reactions carried out for different times gave different yields but with similar *trans*/*cis* ratios and *ee* values (Table 1, entries 23–25). For *tert*-butyl alaninate (**1b**) with a α-substituent, the corresponding 2-methyl pyroglutamic acid esters **4v** were obtained in a lower yield (10%) albeit with an obviously higher *trans*/*cis* selectivity (4.1:1) (Scheme 3b),[11] further supporting the proposed transition state for the asymmetric 1,4-addition step (Scheme 2).



Entry	Reactant	Conditions	Time	Product
1	*trans*-**4a** (86% ee)	A	24 h	96% yield, 6.6:1 *trans*/*cis*, 86%/86% ee
2	*trans*-**4a** (86% ee)	A	48 h	99% yield, 4.3:1 *trans*/*cis*, 86%/86% ee
3	*cis*-**4a** (91% ee)	A	24 h	98% yield, 1:1.7 *trans*/*cis*, 91%/91% ee
4	*cis*-**4a** (91% ee)	A	48 h	99% yield, 1.3:1 *trans*/*cis*, 91%/91% ee
5	*trans*-**4a** (86% ee)	B	24 h	6.2:1 *trans*/*cis*, 86%/86% ee
6	*trans*-**4a** (86% ee)	B	48 h	4.7:1 *trans*/*cis*, 86%/86% ee
7	*trans*-**4a** (86% ee)	B	144 h	3.0:1 *trans*/*cis*, 86%/86% ee
8	*cis*-**4a** (91% ee)	B	24 h	1:2.0 *trans*/*cis*, 91%/91% ee
9	*cis*-**4a** (91% ee)	B	48 h	1.2:1 *trans*/*cis*, 91%/91% ee
10	*cis*-**4a** (91% ee)	B	144 h	2.4:1 *trans*/*cis*, 91%/91% ee

[a] (*S*)-**5d** (10 mol%) **1a** (1.5 equiv), LiOTf, DBU, MeCN, 40 °C

Scheme 3. a) Epimerization investigation. b) Reaction of alaninate **1b** with **2a.**



Scheme 4. Synthetic transformations.

As demonstrated in Scheme 4a, treatment of the pyroglutamic acid ester *trans*-**4a** with 2 M HCl may remove the *tert*-butyl group to afford the corresponding pyroglutamic acid *trans*-**10a** in 99% yield without any loss of enantioselectivity. Although a mixture of *trans* and *cis* pyroglutamic acid esters **4** were formed in the reaction (Table 2), both of them can be readily converted into bioactive 4-substituted pyrrolidin-2-ones with the same absolute configuration via *tert*-butyl group removal and subsequent Barton decarboxylation.[14] For example, Alzheimer's drug (*S*)-Rolipram[15] (**11**) can be synthesized with high enantiopurity from a mixture of *trans*-**4m** and *cis*-**4m** via the reaction sequence (Scheme 4b).

In summary, we have successfully realized direct asymmetric α-functionalization of NH_2-unprotected glycinate with relatively weak electrophile α,β-unsaturated esters by using carbonyl catalysis strategy. In the presence of chiral pyridoxal catalyst **5d**, asymmetric 1,4-conjugated addition of glycinate **1a** at the α-position to α,β-unsaturated esters **2** and subsequent in situ lactamization formed chiral pyroglutamic acid esters **4** in 14–96% yields with 81–97% enantioselectivities, providing an interesting and highly efficient way to make chemically and biologically significant pyroglutamic acid compounds. This work has also displayed the magic catalytic power of pyridoxal structure in asymmetric catalysis.[16]

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric Michael addition · carbonyl catalysis · chiral pyridoxal · vitamin B_6 · α-functionalization of amines

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