A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202104031

Link to VoR: https://doi.org/10.1002/anie.202104031

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10.1002/anie.202104031

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Efficient Asymmetric Biomimetic Aldol Reaction of Glycinates and Trifluoromethyl Ketones by Carbonyl Catalysis

Aolin Cheng,[†] Liangliang Zhang,[†] Qinghai Zhou,[†] Tao Liu, Jing Cao, Guoqing Zhao,* Kun Zhang, Guanshui Song, and Baoguo Zhao*

[a] The Education Ministry Key Lab of Resource Chemistry, Joint International Research Laboratory of Resource Chemistry, Ministry of Education, and Shanghai Key Laboratory of Rare Earth Functional Materials, College of Chemistry and Materials Science, Shanghai Normal University, Shanghai 200234, China. E-mail: gqzhao@shnu.edu.cn; zhaobg2006@shnu.edu.cn

[†] A. Cheng, L. Zhang and Q. Zhou contributed equally

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Abstract: Direct asymmetric aldol reaction of glycinates represents an intriguing and straightforward strategy to make biologically significant chiral β-hydroxy-α-amino acid derivatives. But it is not easy to realize the transformation due to the disruption of the reactive NH_2 group of glycinates. Inspired by enzymatic aldol reaction of glycine, we successfully developed asymmetric aldol reaction of glycinate **5** and trifluoromethyl ketones **4** with 0.1-0.0033 mol% of chiral *N*-methyl pyridoxal **7a** as the catalyst, producing chiral β-trifluoromethyl-β-hydroxy-α-amino acid esters **6** in 55-82% yields (for the *syn*-diastereomers) with up to >20:1 dr and 99% ee under very mild conditions. The reaction proceeds via a catalytic cycle similar to the enzymatic aldol reaction of glycine. Pyridoxal catalyst **7a** activates both of the reactants at the same time and brings them together in a specific spatial orientation, accounting for the high efficiency, excellent diastereo- and enantioselectivities.

Optically active β-hydroxy-α-amino acids have emerged as an important structural motif that can be found in numerous bioactive molecules such as Parkinson drug L-*threo*-DOPS[1a] and drug candidate (2*R*,3*S*)-2-amino-3-hydroxy-3-(pyridin-4-yl)-1-(pyrrolidin-1-yl)propan-1-one[1b,c] (Figure 1).[1,2] Direct asymmetric aldol condensation of glycinates with aldehydes or ketones may provide a straightforward and highly attractive method to construct chiral β-hydroxy-α-amino acid derivatives (Scheme 1a). However, the reaction often suffers from the disruption of the NH_2 group due to its nucleophilicity and N-H acidity. Thus, in order to avoid the disruption, protecting group strategy has been extensively applied for the transformation.[3] The studies include stoichiometric chiral pyridoxal-promoted biomimetic aldol reaction of glycine contributed by Kuzahara and Breslow (Scheme 1b),[4] asymmetric aldol reaction of glycine Schiff base-metal complexes developed by Belokon and Soloshonok (Scheme 1c),[5] and asymmetric aldol reaction of protected glycine derivatives reported by Hayashi, Miller, Maruoka, Dixon, Trost, and others (Scheme 1d).[6-9] Without protecting group

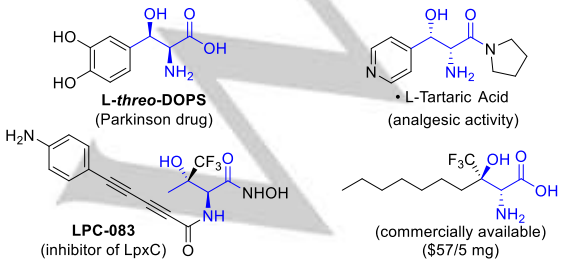
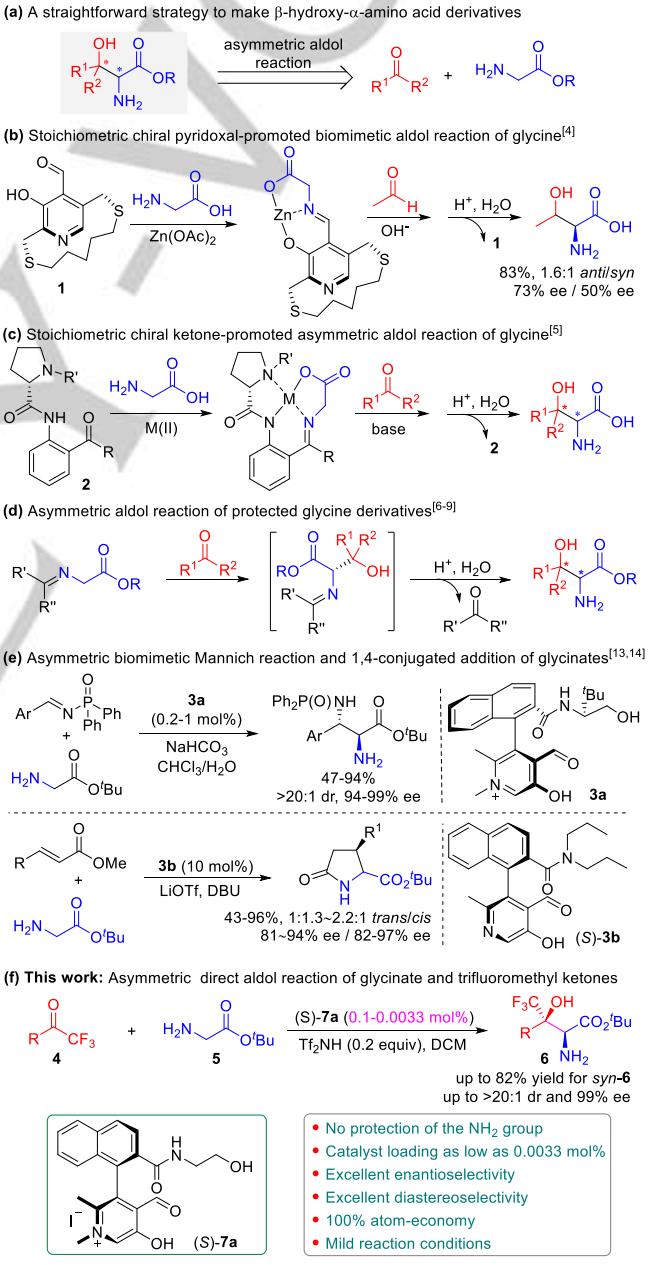


Figure 1. Bioactive β-hydroxy-α-amino acids and derivatives.



Scheme 1. Asymmetric aldol reaction to synthesize chiral β-hydroxy-α-amino acid compounds.

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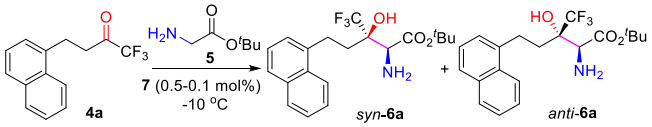
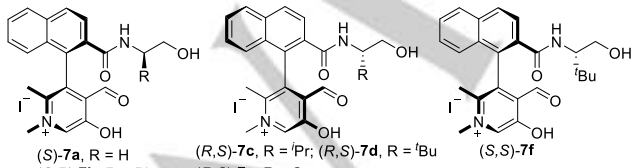
manipulation toward the reactive NH_2 group, pyridoxal-dependent aldolases such as threonine aldolases[10] can promote the asymmetric aldol reaction of glycine to produce chiral β-hydroxy-α-amino acids directly.[11] However, for nonenzymatic systems, direct asymmetric aldol reaction of glycinates still remains a challenge in organic chemistry.

Mimicking the enzymatic process, carbonyl catalysis strategy[12,13] may provide an opportunity to develop chemically catalyzed direct asymmetric aldol reaction of glycinates.[13-16] By using chiral pyridoxals as catalysts, we have successfully developed asymmetric biomimetic Mannich reaction[13] and α-C Michael addition[14] of glycinate, respectively affording chiral α,β-diamino acid esters and pyroglutamic acid esters with excellent enantiopurities (Scheme 1e). Herein, we reported the first catalytic asymmetric aldol reaction of glycinate with trifluoromethyl ketones (Scheme 1f). In the previously developed asymmetric Mannich reaction (Scheme 1e), the *N*-diphenylphosphinyl imine was activated through double hydrogen bonds formed between the phosphinyl O and the imino N of the imine with the side chain of the chiral pyridoxal catalyst,[13] which orients the imine substrate in a specific spatial arrangement and thus results in the excellent diastereoselectivity. For the current aldol reaction, although the trifluoromethyl ketone can also be activated through a hydrogen bond formed between its carbonyl O and the side chain of the pyridoxal catalyst, the ketone still can rotate around the hydrogen bond, leading to a low level of diastereocontrol. Fortunately and to our surprise, introducing a catalytic amount of Brønsted acid additive can greatly improve the diastereoselevity for the reaction with 0.1-0.0033 mol% of *N*-methyl chiral pyridoxal[17] **7a** as the catalyst, producing various chiral β-trifluoromethyl-β-hydroxy-α-amino acid esters **6** with excellent enantiopurities in one step (Scheme 1f). As compared to similar enzymatic transformations,[18] the reaction displayed comparable or even higher stereoselectivity (up to > 20:1 dr and 99% ee) and activity (as low as 0.0033 mol% catalyst loading).[19,20]

Table 1. Optimization of the reaction conditions[a]



entry	catalyst	additive	solvent	yield (%)	*syn*/*anti*	ee (%)
1	(*S*)-**7a**	-	DCE	68	4:1	96
2	none	-	DCE	0	-	-
3	(*S*)-**7a**	AcOH	DCE	85	7:1	96
4	(*S*)-**7a**	$PhCO_2H$	DCE	87	7:1	92
5	(*S*)-**7a**	PhOH	DCE	68	4:1	93
6	(*S*)-**7a**	CF_3CO_2H	DCE	73	7:1	96
7	(*S*)-**7a**	TfOH	DCE	42	7:1	95
8	(*S*)-**7a**	TsOH	DCE	67	9:1	96
9	(*S*)-**7a**	Tf_2NH	DCM	50[b]	9:1	97
10[c]	(*S*)-**7a**	Tf_2NH	DCM	80[b]	9:1	98
11	(*S*)-**7a**	AcOH	DCM	88	7:1	96
12	(*S*)-**7a**	AcOH	dioxane	39	6:1	93
13	(*S*)-**7a**	AcOH	DMF	55	3:1	71
14	(*S*)-**7a**	AcOH	MeCN	63	3:1	92
15	(*S*)-**7a**	AcOH	THF	58	6:1	96
16	(*S*,*R*)-**7b**	AcOH	DCM	56	5:1	98
17	(*R*,*S*)-**7c**	AcOH	DCM	64	4:1	-97
18	(*R*,*S*)-**7d**	AcOH	DCM	93	5:1	-96
19	(*R*,*S*)-**7e**	AcOH	DCM	41	4:1	-97
20	(*S*,*S*)-**7f**	AcOH	DCM	95	5:1	92
21[d]	(*S*)-**7a**	Tf_2NH	DCM	80[b]	9:1	98



[a] All reactions were carried out with **4a** (0.20 mmol), **5** (0.30 mmol), catalyst (0.0010 mmol, 0.5 mol%), and additive (0.10 mmol) in solvent (1.0 mL) at -10 °C for 24 h unless otherwise stated. Isolated yields of **6a** were based on **4a**. The dr (*syn*:*anti*) values were determined by ^1H NMR analysis of the crude reaction mixture. The ee values of *syn*-**6a** were determined by chiral HPLC analysis. The absolute configurations of *syn*-**6a** and *anti*-**6a** were respectively determined as (2*S*,3*R*) and (2*S*,3*S*) based on X-ray analysis. [b] Isolated yield of *syn*-**6a** based on **4a**. [c] Tf_2NH (0.040 mmol). [d] **4a** (1.0 mmol), **5** (1.5 mmol), **7a** (0.0010 mmol, 0.10 mol%), and Tf_2NH (0.20 mmol) in DCM (4.0 mL) at -10 °C for 48 h.

The studies commenced with the reaction of *tert*-butyl glycinate **5** with trifluoromethyl ketone **4a** in the presence of 0.5 mol % *N*-methyl chiral pyridoxal (*S*)-**7a** as the catalyst (Table 1, entry 1). The desired aldol products **6a** were obtained as a pair of diastereomers (4:1 *syn*/*anti*) in 68% yield with 96% ee for *syn*-**6a**. The structures and absolute configurations for *syn*-**6a** and *anti*-**6a** were respectively determined based on X-ray analysis (Figure 2).[21] The pyridoxal catalyst is crucial for the reaction. No desired products were observed without catalyst **7a** (Table 1, entry 2). An acid additive such as AcOH resulted in an improved yield (85% vs. 68%) and an increased diastereoselectivity (7:1 dr) (Table 1, entry 3). Further screening showed that up to 80% yield of the diastereomer *syn*-**6a**, 9:1 dr, and 98% ee were obtained when 0.2 equivalent of Tf_2NH was used (Table 1, entry 10 vs. 3-9). Dichloromethane (DCM) was the choice of solvent (Table 1, entry 11 vs. 3 and 12-15) and catalyst **7a** gave the best performance among the pyridoxals **7a**-**f** examined (Table 1, entry 11 vs. 16-20). To our surprise, the reaction can also proceed smoothly without losing efficiency and selectivity when lowering the catalyst loading to 0.1 mol% (Table 1, entry 21 vs. 10).

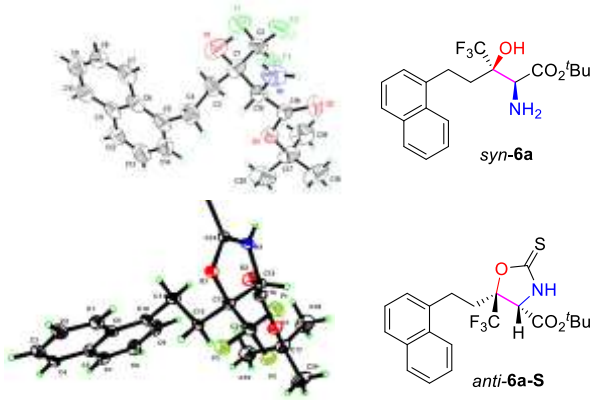


Figure 2. X-ray structures of *syn*-**6a** and *anti*-**6a-S**

Under the optimized reaction conditions, substrate scope was then investigated for the asymmetric biomimetic aldol reaction with 0.1 mol% of (*S*)-**7a** as the catalyst (Table 2). Various alkyl trifluoromethyl ketones **4** underwent the transformation smoothly to give the corresponding chiral β-trifluoromethyl-β-hydroxy-α-amino acid esters **6a**-**aa** in good yields (55-82% for *syn*-**6**) with high diastereoselectivities (up to >20:1) and excellent

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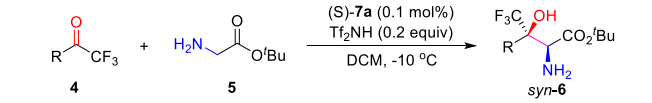
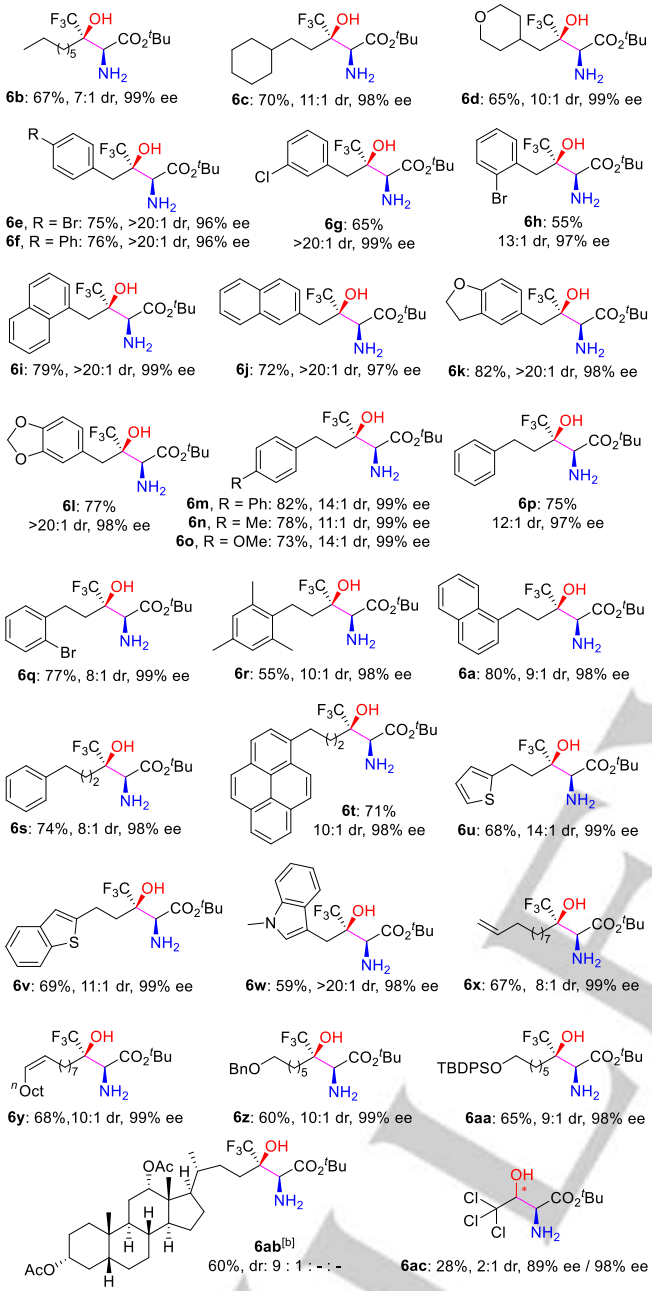
Table 2. Substrate scope investigation[a]





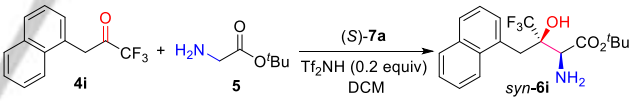
[a] All reactions were carried out with **4** (1.0 mmol), **5** (1.5 mmol), catalyst (*S*)-**7a** (0.0010 mmol, 0.1 mol%), and Tf_2NH (0.20 mmol) in DCM (4.0 mL) at -10 °C for 48 h unless otherwise stated. For **6ac**, reaction was 67 h. For **6a-ab**, isolated yields of *syn*-**6** (major isomer) based on **4** were collected. For **6ac**, isolated yield of *syn*- and *anti*-**6ac** based on **4** was collected. The dr (*syn*:*anti*) values were determined by ^{1}H NMR analysis of the crude reaction mixtures. The ee values were determined by chiral HPLC analysis. The absolute configuration of *syn*-**6a** were determined as (2*S*,3*R*) by X-ray analysis. The absolute configurations of the two newly-generated chiral centers for *syn*-**6b-ab** were tentatively assigned as (2*S*,3*R*) by analogy. [b] The reaction was performed at 0 °C for 72 h.

enantioselectivities (96-99% ee). The substituents on the alkyl chain of the ketones, such as heterocyclic (for **6d**), aromatic (for **6e-t**), heteroaromatic (for **6u-w**), silyl (for **6aa**) groups, and C-C double bond (for **6x-y**) had little impact on the reaction in terms of yield and selectivity. When a chiral alkyl trifluoromethyl ketone such as **4ab** was applied to the reaction, the corresponding chiral β-hydroxy-α-amino acid ester **6ab** was produced with high diastereoselectivity. Trichloroacetaldehyde was also reactive for the transformation, to produce β-hydroxy-α-amino acid ester **6ac** with low diastereoselectivity. Under the standard conditions, aldehydes such as benzaldehyde and dec-9-enal and perfluorinated ketones such as hexafluoroacetone and 1,1,1,3,4,4,4-heptafluoro-3-(trifluoromethyl)butan-2-one are both ineffective for the reaction. Methyl pyruvate can autocatalyze its reaction with glycinate. And the reaction of ethyl glyoxylate with glycinate is very messy.

To further evaluate the efficiency of the biomimetic aldol reaction, a lower catalyst loading such as 0.02 mol% or even 0.0033 mol% was tested with the reaction of glycinate **5** and trifluoromethyl ketone **4i** (Scheme 2a). The aldol product **6i** was obtained in moderate to good yields with comparable diastereo- and enantioselectivities. The reaction became obviously slow during the late stage probably due to the partial deactivation of the catalyst. At -10 °C, almost only product **4i** and unreacted starting materials were observed from the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 2a, entry 1). For the reaction at 10 °C in the presence of 0.0033 mol% of catalyst loading, small amount of unidentified byproducts appeared and product **6i** was obatined in 59% yield along with 18% of **4i** recovered (Scheme 2a, entry 3).

The synthetic transformations of the aldol products have been demonstrated with β-trifluoromethyl-β-hydroxy-α-amino acid ester **6b** (Scheme 2b). Deprotection of the *tert*-butyl group by treatment of **6b** with aqueous HCl gave enantiopure β-hydroxy-α-amino acid **8** in 80% yield. Reduction of **6b** with $LiAlH_4$ formed chiral 2-amino-1,3-diol **9** in 64% yield with 98% ee (Scheme 2b).

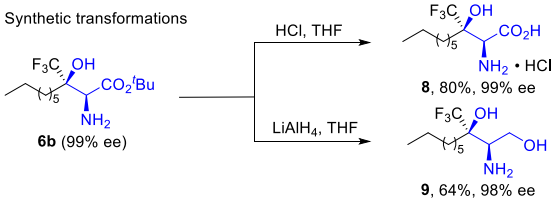
(a) Investigation of catalyst efficiency



entry	4i	7a	conditions	*syn*-6i
1	1.19 g	0.02 mol%	-10 °C, 7 d	72%[a] (1.324 g), 17:1 dr, 98% ee
2	0.952 g	0.01 mol%	10 °C, 8 d	73%[b] (1.082 g), 16:1 dr, 97% ee
3	2.856 g	0.0033 mol%	10 °C, 10 d	59%[b] (2.61 g), 13:1 dr, 97% ee

[a] Isolated yield of *syn*-**6i** based on **4i**. [b] Isolated yield of *syn*- and *anti*-**6i** based on **4i**

(b) Synthetic transformations



Scheme 2. (a) Investigation of catalyst efficiency. (b) Synthetic transformations.

The reaction was proposed to proceed via a mechanistic pathway similar to the biological aldol process[22] (Scheme 3a). Condensation of *N*-methyl pyridoxal catalyst **7a** with glycinate **5** forms imine **10**. Deprotonation of the α–C–H of **10** generates active delocalized carbanion **11**,[23] which then undergoes electrophilic addition to trifluoromethyl ketone **4** and subsequent hydrolysis to produce β-hydroxy-α-amino acid eater **6** and regenerate catalyst **7a**. The main species of the catalytic cycle, including catalyst **7a**, imines **10** and **13**, can be detected according to the HRMS spectroscopy (Scheme 3 and SI).

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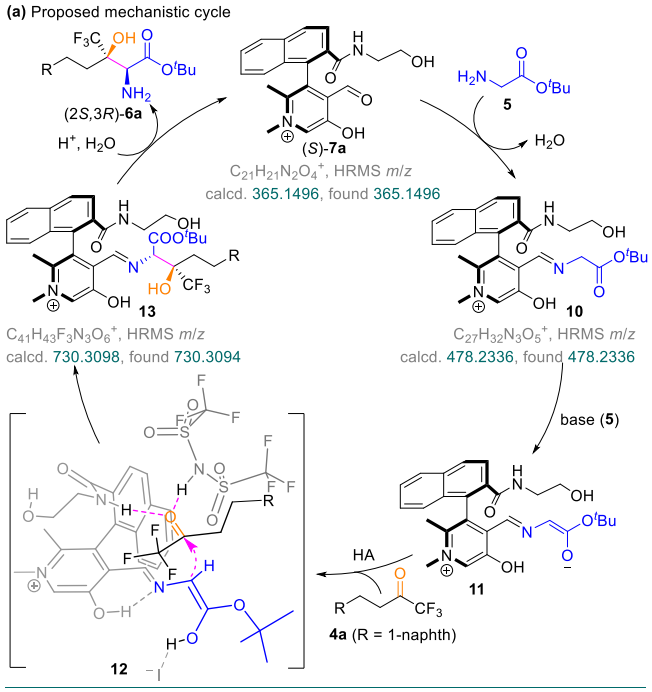
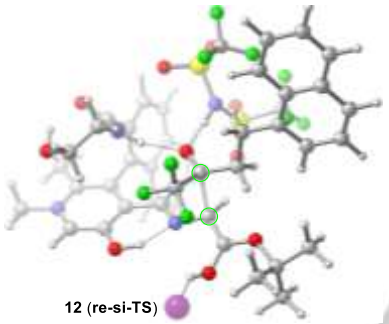
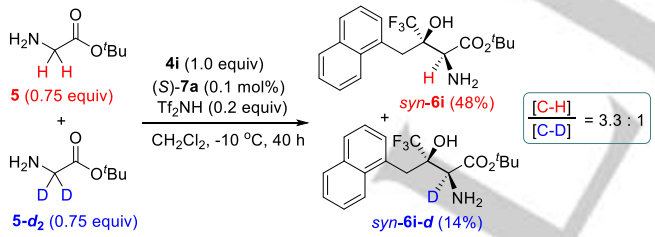


(b) Transition state of the asymmetric addition of **11** to **4a**



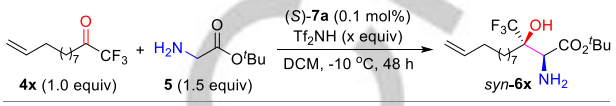
Scheme 3. Proposed mechanism for the reaction.



Scheme 4. Kinetic isotope effect studies.

Kinetic isotope effect studies were carried out with equimolar amounts of **5** and **5-d_2** (Scheme 4). Compound *syn*-**6i** and the deuterated *syn*-**6i-*d*** were obtained with a ratio of 3.3:1. The obvious KIE indicated the deprotonation of imine **10** to form active intermediate **11** is the rate-determining step for the reaction. Considering the very low amount (0.1 mol%) of catalyst **7a** in the reaction and the high tendency of pyridoxals to form imines with amines, the imine **10** should be the resting-state of the catalyst **7a**. Kinetic studies have shown that the reaction was first order in glycinate **5**, zero order in trifluoromethyl ketone **4** and first order in catalyst **7a** (see SI), suggesting that glycinate **5** was involved in the rate-determining step and the addition of intermediate **11** to trifluoromethyl ketone **4** was a quick step. In the rate-determining step from imine **10** to intermediate **11**, glycinate served as a base to deprotonate the α–C–H of **10**.

An acid additive such as AcOH and Tf_2NH led to obviously-increased diastereoselectivity and slightly-improved reaction yield (Table 1, entries 3, 10 and 11 vs. 1). The acid effect was also observed during the investigation of the impact of Tf_2NH amount on the reaction (Scheme 5). Introducing 0.1~0.2 equivalent of Tf_2NH can obviously improve the yield and the dr value of product **6x**. Further increasing the amount of Tf_2NH to 0.4 equivalent led to a slight decrease in yield likely due to low pH conditions disfavoring the deprotonation of **10** to **11**, but with similar diastero- and enantioselectivities.



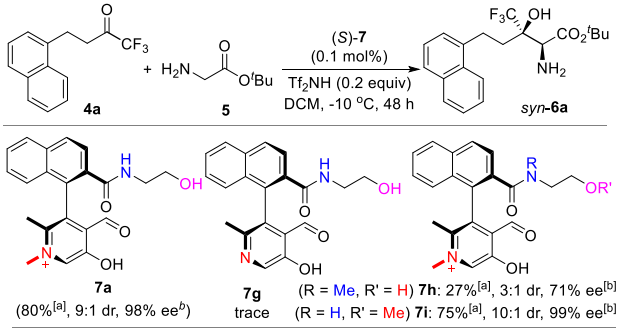
entry	Tf_2NH	yield[a]	dr (*syn*/*anti*)	ee[b]
1	0	64%	4.1:1	98%
2	0.1 equiv	79%	7.1:1	98%
3	0.2 equiv	77%	7.7:1	98%
4	0.4 equiv	65%	8.5:1	98%

[a] Isolated total yield of *syn*-**6x** and *anti*-**6x** based on **4x**. [b] Ee value of *syn*-**6x**

Scheme 5. Impact of Tf_2NH amount.

The impact of an acid additive on diastereoselectivity implied the Brønsted acid likely participated in the asymmetric addition of intermediate **11** toward trifluoromethyl ketone **4** (Scheme 3a). In order to understand the role of Tf_2NH and the origin of the chiral induction, computational studies has been carried out for the step (see SI). As shown in the optimized transition state **12** (Scheme 3b), the ketone **4** was well activated through double hydrogen bonds, respectively, with the N–H group of the amide side chain of **7a** and with Tf_2NH.[24] The CF_3 group of **4** pointed to the direction parallel to the amide side chain of **7a**, which avoided the steric repulsion with the bulky Tf_2N group. The enolated glycinate approached to the trifluoromethyl ketone **4** from beneath, resulting in the formation of chiral β-hydroxy-α-amino acid ester **6** with (2*S*,3*R*) configuration from (*S*)-**7a**.

The proposed transition state got supported from the control experiments on catalyst comparison (Scheme 6). Methylation of the N-H group of the side amide chain of **7a** led to obvious decreases in activity and stereoselectivity (**7a** vs. **7h**), implying the N-H group likely participated in the catalysis via hydrogen bonding with the carbonyl group of ketone **4** as proposed in the transition state **12** (Scheme 3). In addition, the strong electron-withdrawing ability of the N-quaternized pyridine ring of **7a** is also a necessary requirement for its high activity. Pyridoxal **7g** without methylation of the pyridine nitrogen was almost inactive for the reaction (Scheme 6).



[a] Isolated yield of *syn*-**6a** based on **4a**. [b] Ee value of *syn*-**6a**.

Scheme 6. Comparison of catalysts.

In summary, with 0.1-0.0033 mol% of chiral *N*-methyl pyridoxal **7a** as the catalyst, we have developed a highly efficient asymmetric biomimetic aldol reaction of glycinate and trifluoromethyl ketones, producing various chiral β-trifluoromethyl-β-hydroxy-α-amino acid esters **6** in good yields (55-82% for *syn*-**6**) with high distereoselectivities (7:1 – >20:1 dr) and excellent enantioselectivities (96-99% ee) under very mild conditions. The reaction proceeds without any protecting manipulations toward the active NH_2 group, representing a straightforward and atom-economic method for the synthesis of chiral β-trifluoromethyl-β-hydroxy-α-amino acid esters.

Acknowledgements

We are grateful for the generous financial support from the National Natural Science Foundation of China (21871181), the Shanghai Municipal Education Commission (2019-01-07-00-02-E00029), the Shanghai Municipal Committee of Science and Technology (18ZR1447600, 20JC1416800), "111" Innovation and Talent Recruitment Base on Photochemical and Energy Materials (No. D18020), and Shanghai Engineering Research Center of Green Energy Chemical Engineering (No. 18DZ2254200).

Keywords: organocatalysis • biomimetic catalysis • carbonyl catalysis • aldol reaction of glycine • chiral pyridoxal

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[21] CCDC 2068937 and 2068938 respectively contain the supplementary crystallographic data for compounds *syn*-***6a*** and *anti*-***6a***-***S***. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_re-quest@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallo-graphic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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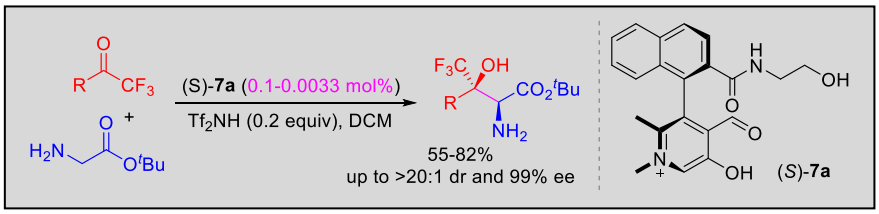

An extremely efficient biomimetic aldol reaction of glycinate and trifluoromethyl ketones was developed with 0.1-0.0033 mol% of chiral pyridoxal **7a** as catalyst, producing β-hydroxy-α-amino acid esters **6** in 55-82% yields with excellent distereo- and enantioselectivities (up to >20:1 dr and 99% ee) without protection to the active NH_2 group. The reaction proceeds via a bifunctional catalysis pathway similar to enzymatic aldol reaction of glycine.