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Organocatalytic enantioselective Mannich and retro-Mannich reactions and combinations of these reactions to afford tetrasubstituted α-amino acid derivatives†

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Organocatalytic asymmetric Mannich reactions and kinetic resolutions of the products *via* retro-Mannich reactions that afford enantiomerically enriched tetrasubstituted α-amino acid derivatives (α,α-disubstituted-α-amino acid derivatives) were developed. Furthermore, the combination of the Mannich reaction and the retro-Mannich reaction allowed access to products with almost perfect enantiopurities.

α,α-Disubstituted-α-amino acid derivatives or tetrasubstituted α-amino acid derivatives are found in pharmaceuticals and their building blocks[1–4] (Fig. 1). Enantioselective synthesis of these molecules is of interest.[1–4] For example, tetrasubstituted α-amino acid derivatives have been synthesized by Mannich reactions with α-ketimino esters,[1] addition reactions to α-ketimino esters,[2] and α-alkylations and arylations of α-amino acid derivatives.[3] However, there remains a need for methods that provide highly enantiomerically enriched, functionalized tetrasubstituted α-amino acid derivatives.[1–3] For example, Mannich reactions of aldehydes or ketones with ketimines catalyzed by enamine-forming catalysts (or under aminocatalysis) have been reported,[1a,e,5,6] but the ketimines used in these reactions were relatively reactive (Fig. 2) and are not for the syntheses of α-methyl-substituted tetrasubstituted α-amino acid derivatives. Here, we report proline-catalyzed enantioselective Mannich reactions of 1,4-benzoxazinone-derived cyclic ketimino esters **1** and ketones **2** to afford tetrasubstituted α-amino acid derivatives **3** (Scheme 1). We also report kinetic resolutions of (±)-**3** *via* retro-Mannich reactions (Scheme 1). Furthermore, we report a strategy that combines the Mannich reactions with the retro-Mannich reaction to afford highly enantiomerically enriched tetrasubstituted α-amino acid derivatives **3** with er >99 : 1, which are difficult to obtain from either reaction alone (Scheme 1).

The 1,4-benzoxazinone ring structure is often present in bioactive molecules.[7,8] Thus, Mannich reaction products bearing the benzoxazinone moiety could be useful for drug discovery.[7] In addition, benzoxazinone-derived cyclic amino esters can be transformed into other derivatives by reactions on the ester group and the deprotection of the phenol group attached to the amine group.[1a,7a,e,8] The use of cyclic ketimino esters avoids potential hydrolysis of the imine during Mannich reactions. Whereas catalytic enantioselective Mannich reactions involving 1,4-benzoxazinone-derived aldimino esters,[5c,8] other cyclic aldimino esters,[9] or acyclic aldimino esters[10] to afford α-amino acid derivatives have been reported,[5c,8–10] only a small number of examples of Mannich reactions of the corresponding ketimino esters to afford tetrasubstituted α-amino acid derivatives have been reported.[1,5,11] Highly

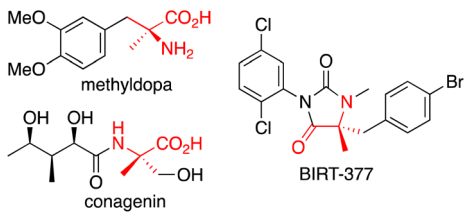

Fig. 1 Examples of bioactive tetrasubstituted-α-amino acid derivatives.

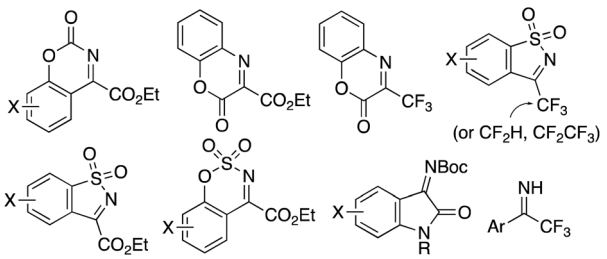

Fig. 2 Ketimines used previously in Mannich reactions under aminocatalysis.

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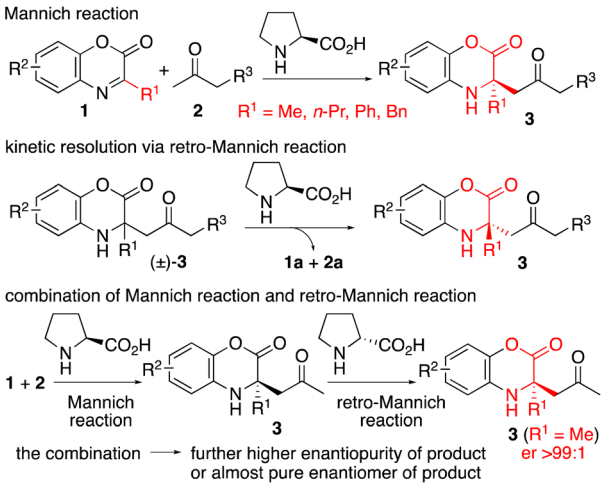


Scheme 1 Catalytic asymmetric Mannich reaction, retro-Mannich reaction, and the combination of these two reactions to afford highly enantiomerically enriched tetrasubstituted α-amino acid derivatives.

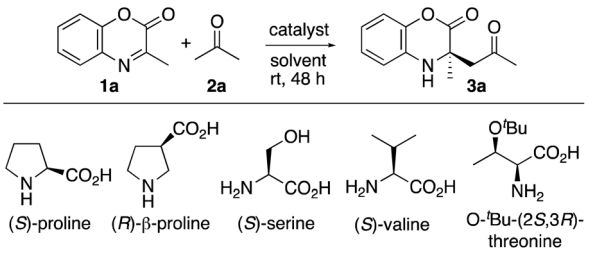
enantioselective Mannich reactions of ketimino esters in which a simple alkyl group (such as a methyl group) is substituted on the imine carbon of the ketimino ester (*i.e.*, the substituent is not an electron-withdrawing substituent) have rarely been reported.[1c] We explored the Mannich reactions of ketones with cyclic ketimino esters bearing alkyl and aryl substituents on the imine carbon.

First, the catalysts and conditions of the Mannich reaction between ketimino ester **1a** and acetone (**2a**) to afford Mannich product **3a** were evaluated (Table 1).

The reaction in the presence of (*S*)-proline (5 to 10 mol%) in DMSO resulted in the formation of **3a** in high yields (>75%) with high enantioselectivities (er 96 : 4 to 97 : 3) in 48 h (Table 1, entries 1 and 12). The reaction in the presence of (*S*)-proline (2.5 mol%) also generated **3a** with high enantioselectivity but was slower (Table 1, entry 14). For the formation of **3a** by the Mannich reaction, the use of (*S*)-proline (5 mol%) as the catalyst in DMSO (Table 1, entries 12 and 15) was optimal for the catalysts and conditions tested. Based on previously reported information,[5c,9a] the stereochemistry of the major enantiomer of Mannich reaction product **3a** obtained by (*S*)-proline catalysis was suggested to be *R*.

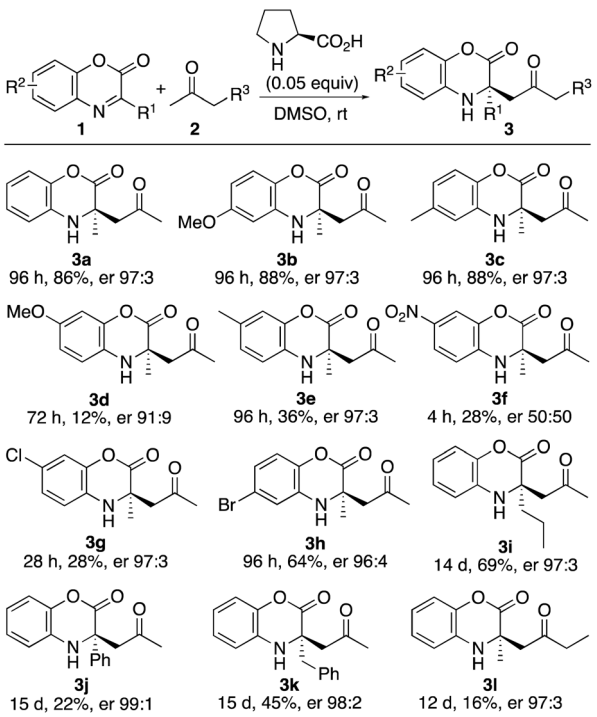
Next, using the optimized conditions identified, the scope of the (*S*)-proline-catalyzed Mannich reactions was examined using various 1,4-benzoxazinone-derived ketimino esters **1** and ketones **2** (Scheme 2). The imines bearing substituents at the *p*-position of the ester oxygen of the benzoxazinone moiety reacted with acetone to afford Mannich products **3b**, **3c**, and **3h** in high yields with high enantioselectivities (er 97 : 3 to 96 : 4). The reactions of the imines bearing the substituents at the *p*-position of the nitrogen of the benzoxazinone moiety were relatively slow (formations of **3d**, **3e**, **3f**, and **3g**). For these reactions, a longer reaction time did not further increase the yield of the product; it seems that the formation of the Mannich product was in equilibrium with the decomposition

Table 1 Evaluation of catalysts and conditions for the reaction of **1a** and **2a** to afford **3a**[a]



Entry	Catalyst (equiv.)	Solvent	Yield[b] (%)	er[c]
1	(*S*)-Proline (0.1)	DMSO	76	96 : 4
2	(*R*)-β-Proline (0.1)	DMSO	15	65 : 35
3	(*S*)-Serine (0.1)	DMSO	0	—
4	(*S*)-Valine (0.1)	DMSO	0	—
5	O-^{t}Bu-(2*S*,3*R*)-threonine (0.1)	DMSO	1	94 : 6
6	(*S*)-Proline (0.1)	2-PrOH	12	97 : 3
7	(*S*)-Proline (0.1)	DMF	14	99 : 1
8	(*S*)-Proline (0.1)	NMP	12	98 : 2
9	(*S*)-Proline (0.1)	CH_3CN	2	98 : 2
10	(*S*)-Proline (0.1)	Toluene	0	—
11	(*S*)-Proline (0.1)	$CHCl_3$	1	94 : 6
12	(*S*)-Proline (0.05)	DMSO	76	96 : 4
13	(*S*)-Proline (0.3)	DMSO	75	96 : 4
14	(*S*)-Proline (0.025)	DMSO	64	98 : 2
15[d]	(*S*)-Proline (0.05)	DMSO	88	97 : 3

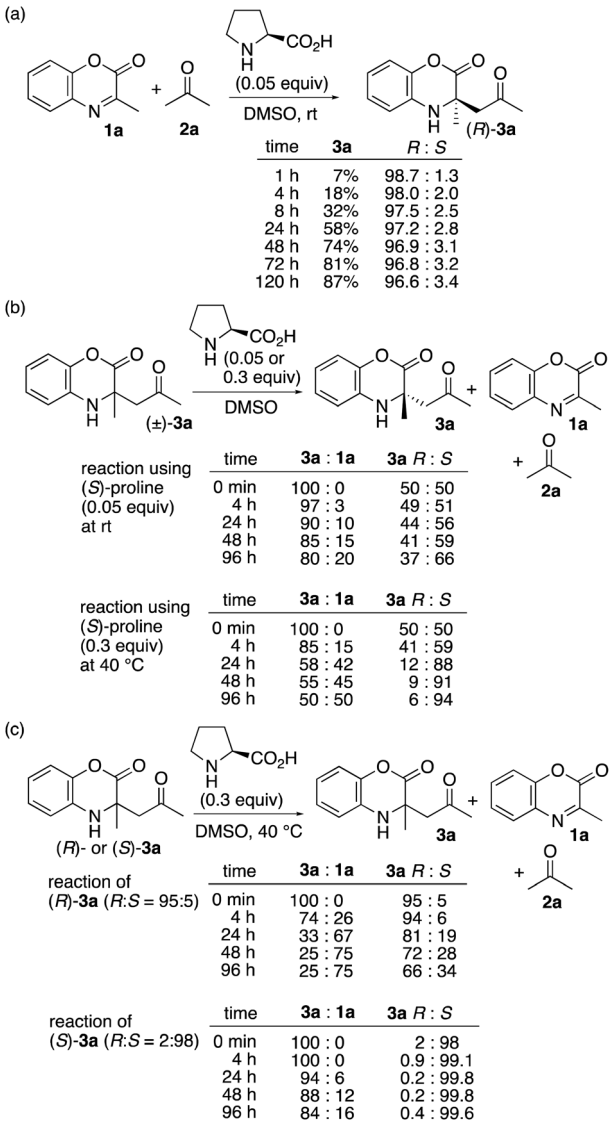
[a] Conditions: **1a** (1.0 mmol, 1.0 equiv.), **2a** (5.0 mmol, 5.0 equiv.), and catalyst in solvent (1.0 mL) at rt (25 °C) for 48 h. [b] Determined by ^{1}H NMR analysis based on the ratio between **1a** and **3a** before purification. [c] Determined by HPLC analysis of purified **3a**. [d] Reaction for 7 days.



Scheme 2 Scope of the Mannich reactions of **1** and **2** to afford **3**. Conditions: **1a** (1.0 mmol), **2a** (5.0 mmol), and (*S*)-proline (0.05 mmol) in DMSO (1.0 mL) at rt (25 °C).

of the Mannich product *via* the retro-Mannich reaction after the Mannich reaction product accumulated to a certain level. Reactions of the imines bearing substituents larger than the methyl groups also afforded the Mannich products **3i**, **3j**, and **3k**. The reaction of 2-butanone with imine **1a** also afforded product **3l**, although the reaction rate was slow. With the exception of **3f**, which has a nitro group substituent, all Mannich products **3** were obtained with high enantioselectivities (er 99 : 1 to 91 : 9).

To investigate the Mannich reactions in more detail and test the possibility of kinetic resolutions of (±)-**3**, the Mannich reaction to afford **3a** and the decomposition of **3a** in the presence of (*S*)-proline were analyzed at various time points (Scheme 3). In the Mannich reaction that forms **3a**, the er ((*R*)-isomer to (*S*)-isomer) of **3a** was 99 : 1 at 7% conversion and was gradually decreased to 97 : 3 at 58% conversion at 24 h, and this er was almost unchanged at 87% conversion at 120 h (Scheme 3a).



Scheme 3 Time-dependent analyses of the Mannich reaction to form **3a** and of the retro-Mannich reaction of **3a**.

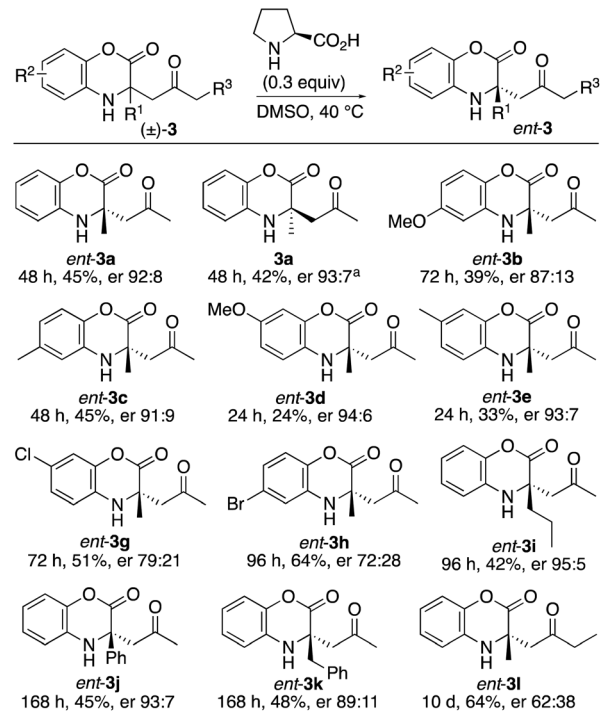
When (±)-**3a** was treated with (*S*)-proline, (*S*)-isomer-enriched **3a** was obtained with the formation of imine **1a** and acetone, indicating that the decomposition of (*R*)-**3a** was more favorable than the decomposition of (*S*)-**3a** in the presence of (*S*)-proline (Scheme 3b). For the kinetic resolution of (±)-**3a**, the use of 0.3 equiv. of proline led to better results than the use of 0.05 equiv. The preferential decomposition of the (*R*)-isomer of **3a** by (*S*)-proline was further confirmed by comparison of the reactions of (*R*)-enriched **3a** and (*S*)-enriched **3a** in the presence of (*S*)-proline (Scheme 3c). The rate of the decomposition of (*R*)-**3a** in the presence of (*S*)-proline was more than 10 times faster than that of (*S*)-**3a** based on the imine formation after 24 h (Scheme 3c). Notably, even when the concentration of (*R*)-**3a** was low or when the ratio of (*R*)-**3a**/(*S*)-**3a** was less than 2 : 98, (*R*)-**3a** was efficiently decomposed in the presence of (*S*)-proline, resulting in (*S*)-**3a** with er >99 : 1 (Scheme 3c, reaction of (*S*)-**3a** (*R* : *S* = 2 : 98)).

These results indicate that (*R*)-**3a** is kinetically formed in the (*S*)-proline-catalyzed Mannich reaction and that (*R*)-**3a**, the major enantiomer formed in the Mannich reaction, is kinetically decomposed by the (*S*)-proline-catalyzed retro-Mannich reaction. This is similar to what was observed in previously reported amine-catalyzed aldol reactions that construct chiral tertiary alcohol centers; in these reactions, stereoselective retro-aldol reactions catalyzed by the catalyst erode the enantiopurity of the aldol product during the aldol reactions.[12]

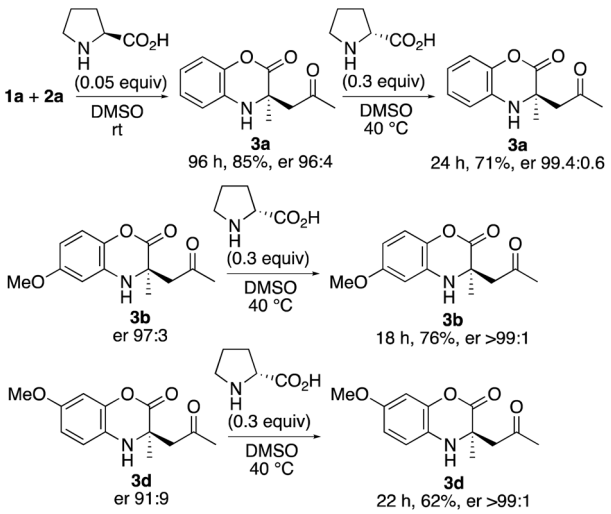
Based on the results of the decomposition of **3a** catalyzed by proline, kinetic resolutions of various (±)-**3** in the presence of (*S*)-proline were performed (Scheme 4). Through the kinetic resolutions catalyzed by (*S*)-proline, the opposite enantiomers of **3a** relative to the (*S*)-proline-catalyzed Mannich reactions were obtained.

Both the Mannich reactions and the kinetic resolutions *via* retro-Mannich reactions afforded enantiomerically enriched **3**, but the enantiopurities of **3** were not perfect. To obtain **3** with er >99 : 1, the (*S*)-proline-catalyzed Mannich reaction and the (*R*)-proline-catalyzed retro-Mannich reaction were combined (Scheme 5). When Mannich products **3** formed by the Mannich reaction in the presence of (*S*)-proline were treated with (*R*)-proline, the minor enantiomers were decomposed, and products **3** with er >99 : 1 were obtained.

In summary, we have developed catalytic enantioselective Mannich reactions of cyclic ketimino esters with ketones that afford highly enantiomerically enriched α-amino acid derivatives bearing tetrasubstituted carbon centers at the α-positions. We have also developed kinetic resolutions *via* retro-Mannich reactions to yield the α-amino acid derivatives. Importantly, we have demonstrated that a combination of catalytic bond formation in the presence of a homochiral catalyst and the decomposition of the minor enantiomer product leads to the formation of highly enantiomerically enriched products (er >99 : 1). The combination of the (*S*)-proline-catalyzed Mannich reaction and the (*R*)-proline-catalyzed retro-Mannich



Scheme 4 Kinetic resolutions of (±)-**3**. Conditions: (±)-**3a** (0.5 mmol) and (*S*)-proline (0.15 mmol) in DMSO (5.0 mL) at 40 °C. [a] (*R*)-Proline was used instead of (*S*)-proline.



Scheme 5 Combination of the (*S*)-proline-catalyzed Mannich reaction and the (*R*)-proline-catalyzed retro-Mannich reaction.

reaction provided tetrasubstituted α-amino acid derivatives with very high enantiopurities.

Conflicts of interest

There are no conflicts to declare.

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