

Organocatalytic Enantioselective γ -Position-Selective Mannich Reactions of β -Ketocarbonyl Derivatives

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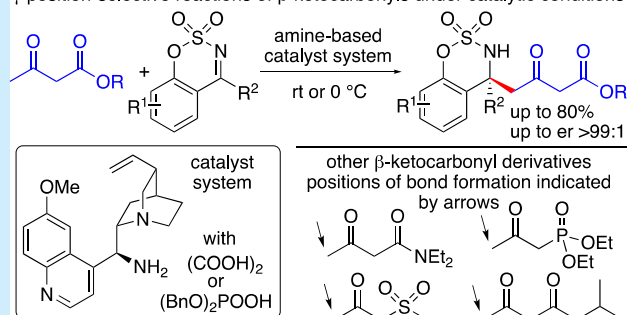
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ABSTRACT: Catalytic asymmetric Mannich reactions of β -ketocarbonyl derivatives (such as β -ketoesters and (2-oxopropyl)-phosphonate), resulting in the formation of a C–C bond at the γ -position of the β -ketocarbonyl derivatives with high enantioselectivities, are reported. The bond formation at the α -position of the β -ketoester was reversible, and the γ -position-reacted product δ -amino β -ketoester derivative was kinetically formed and was stable. The dynamic kinetic process was key for the direct access to the γ -position-reacted products from β -ketocarbonyls under catalytic conditions.

γ -position-selective reactions of β -ketocarbonyls under catalytic conditions



β -Ketocarbonyl derivatives such as acetoacetates (i.e., 3-oxobutanoates) have been used for the synthesis of various molecules.¹ Reactions of these β -ketocarbonyl compounds as nucleophiles (such as enolates) usually occur at the active methylene position (i.e., at the α -position)^{1–3} (Scheme 1a). To perform γ -position-selective reactions of acetoacetates, the formation of dianions, which are generated using two or more equivalents of strong base(s), is usually necessary.⁴ Alternatively, preformed silyl dienol ether and alkyl dienol ether derivatives,⁵ diketene,⁶ and γ -carboxylic-acid-substituted β -

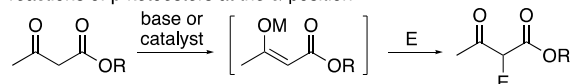
ketoesters⁷ have been used to afford the same type of products.^{5–7} Methods that involve the use of dianions or dienol ether derivatives or decarboxylation usually require severe conditions and/or protection and deprotection steps or are not atom-economical.^{4,5} There have only been a small number of reports of catalytic γ -position-selective reactions of unmodified β -ketocarbonyl derivatives,⁸ including catalytic enantioselective γ -position-selective reactions,^{8d,e} and they are all aldol reactions.⁸ δ -Amino β -ketocarbonyl derivatives are also versatile compounds used for the synthesis of δ -amino β -hydroxy acid derivatives, *N*-heterocycles (such as piperidines, pyrrolidines, and lactams), bioactive natural products, and related molecules.^{4,5b,c,7,9} To provide concise access to highly enantiomerically enriched δ -amino β -ketocarbonyl derivatives and to further enable the γ -position-selective reactions of β -ketocarbonyl derivatives, here we report direct catalytic asymmetric γ -position-selective Mannich reactions of β -ketocarbonyl derivatives that afford δ -amino β -ketocarbonyl derivatives (Scheme 1b).

To catalytically perform γ -position-selective reactions of β -ketocarbonyl derivatives, a carbanion or its equivalent (i.e., enolate or enamine) must be formed at the γ -position of the β -ketocarbonyl derivative under the catalytic conditions. The major enamine or enolate isomer formed in situ is not required to lead to the major product under catalytic conditions.¹⁰ The

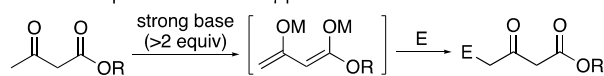
Scheme 1. Mannich Reactions of β -Ketocarbonyls^a

(a) commonly performed reactions:

reactions of β -ketoesters at the α -position

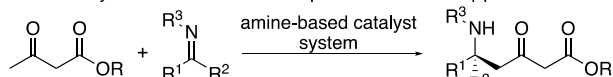


reactions of β -ketoesters at the γ -position via formations of dianions

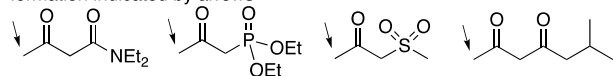


(b) this work:

direct catalytic Mannich reactions of β -ketoesters at the γ -position



other β -ketocarbonyl derivatives used, and the positions of bond formation indicated by arrows

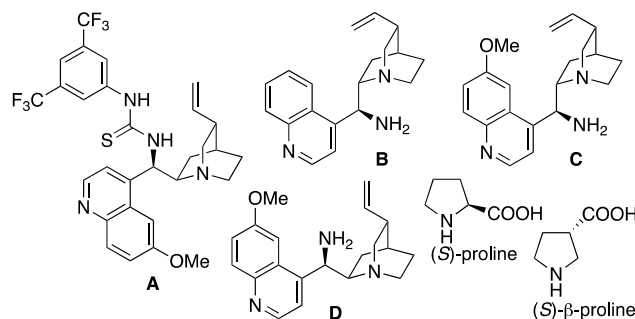
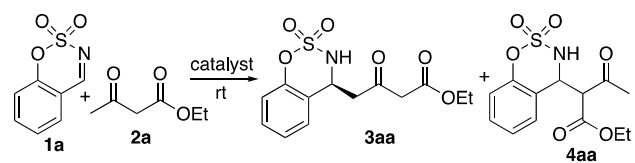


^aE = electrophiles; for simplicity, changes in charge or protonation are not shown.

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Table 1. Evaluations of Catalysts for the Reaction of 1a and 2a to Afford 3aa^a

entry	catalyst (equiv)	time (h)	1a:3aa:4aa ^b	3aa er ^c
1	pyrrolidine (0.2), CH ₃ COOH (0.2)	48	1:92:7	-
2 ^d	pyrrolidine (0.2), CH ₃ COOH (0.2)	12	1:94:5	-
3	(S)-proline (0.2)	72	0.5:98:1.5	51:49
4	(S)-β-proline (0.2)	40	0.5:98:1.5	51:49
5	A (0.2)	95	46:10:44	48:52
6	B (0.2)	83	20:5:75	64:36
7	B (0.2), CH ₃ COOH (0.2)	83	<1:22:68	84:16
8	B (0.2), (COOH) ₂ (0.2)	214	2:39:59	97:3
9	C (0.2), (COOH) ₂ (0.2)	214	2:67:31	98:2
10	C (0.3), (COOH) ₂ (0.3)	190	<1:70:30	99:1
11	C (0.2), (PhCH ₂ O) ₂ POOH (0.2)	190	<1:51:49	98:2
12	D (0.3), (COOH) ₂ (0.3)	190	0:66:34	7:93
13 ^e	C (0.3), (COOH) ₂ (0.3)	58	<1:99:<1	94:6

^aConditions: **1a** (0.25 mmol), **2a** (0.75 mmol), and catalyst in cyclohexane (entries 1–6) or toluene (entries 7–12) (0.5 mL) at room temperature (25 °C). ^bDetermined by ¹H NMR analysis before purification. ^cDetermined by HPLC analysis after purification. ^dReaction at 50 °C. ^eReaction at 40 °C.

minor enamine isomer may result in the formation of the major product when the transition state involving the minor enamine isomer is more favored to lead to the product than the transition state involving the major enamine isomer.¹⁰ Thus, we hypothesized that taking advantage of dynamics in reactions would enable γ -position-selective reactions of β -ketocarbonyl derivatives. That is, when the enamines or enolates are reversibly formed at both α - and γ -positions, the bond-forming reaction would selectively occur at the γ -position under appropriate conditions. Alternatively, when the formation of the α -position reaction product is reversible but that at the γ -position is not, the γ -position reaction product would accumulate, resulting in the formation of the γ -position reaction product as the major product. We expected that appropriate catalysts and conditions would result in such dynamic processes to lead to the formation of γ -position-selective Mannich products from β -ketocarbonyl derivatives.

First, we evaluated catalysts in the reaction of imine **1**¹¹ and ethyl acetoacetate (**2a**) to afford γ -position reaction product **3aa** rather than α -position reaction product **4aa**. Selected

results are shown in Table 1 (see also Supporting Information).

To obtain racemic **3aa** in the reaction, we found that pyrrolidine–acetic acid was a suitable catalyst to afford **3aa** in high yields (Table 1, entries 1 and 2). The reaction at 50 °C was faster than that at 25 °C (Table 1, entry 2).

Catalyst A was previously used for the reactions of **2a** with isatins to afford highly enantiomerically enriched γ -position-reacted aldol products;^{8e} however, this catalyst was not optimal for the enantioselective formation of **3aa** (Table 1, entry 5).

For the asymmetric versions of the reaction, we found that cinchona-derived amines^{11d,12} (such as amines B, C, and D) with certain acids catalyzed the reaction to afford γ -position reaction product **3aa** with high enantioselectivities (Table 1, entries 8–13). The catalyst system composed of quinine-derived amine C and oxalic acid was the best among those tested with respect to the yield of **3aa** and the enantioselectivity (Table 1, entries 9 and 10). During the reactions to form **3aa**, α -position reaction product **4aa** was initially formed, and then γ -position reaction product **3aa** was accumulated. Thus, the reaction time was an important factor to obtain γ -position reaction product **3aa** in high yields. Whereas the formation of γ -position reaction product **3aa** was faster at 40 °C than at 25 °C, the enantioselectivity of the reaction at 25 °C was higher than that at 40 °C (Table 1, entry 10 versus entry 13).

The major enantiomer of **3aa** obtained in the presence of the amine C and oxalic acid was determined to be *S* based on the transformation to a known compound (Supporting Information). The opposite enantiomer was obtained using amine D instead of C in the reaction (Table 1, entry 12).

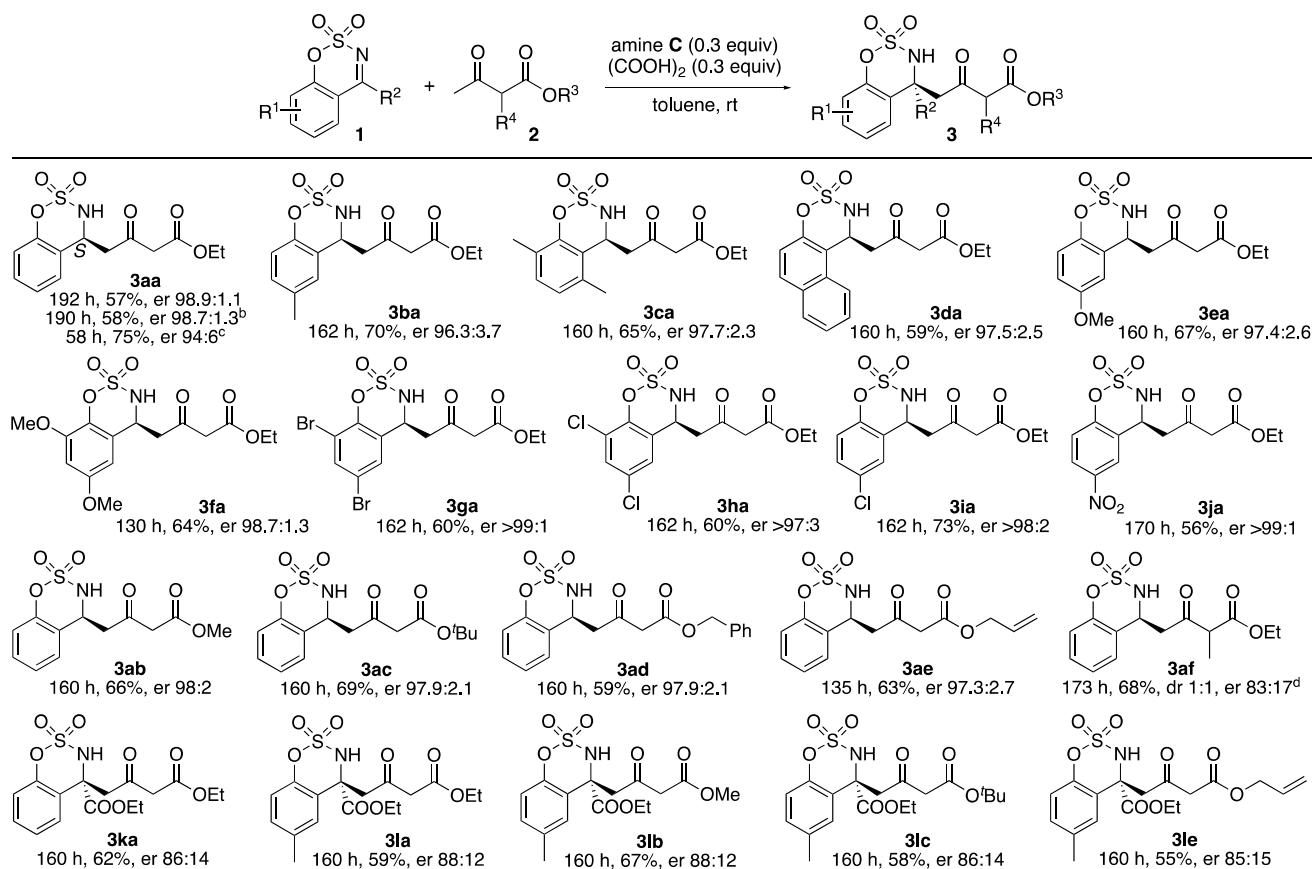
Next, the scope of the enantioselective γ -position-selective Mannich reactions of acetoacetates was examined under the optimized conditions (i.e., conditions of Table 1, entry 10) using amine C with oxalic acid as the catalyst in toluene (Table 2). Various γ -position-reacted Mannich products **3** were obtained in highly enantiomerically enriched forms (up to er >99:1). The constructions of tetrasubstituted carbon centers were also achieved in the γ -position-selective Mannich reactions.

The mechanisms of the formation of **3** were analyzed. When the enantiopurity of the formed **3aa** was analyzed at various time points during the reaction of **1a** and **2a** catalyzed by amine C–oxalic acid, it was essentially the same throughout the time course (Supporting Information).

When α -position reaction product (\pm)-**4aa** was treated under the catalytic conditions with amine C and oxalic acid used for the enantioselective formation of **3aa** from **1a** and **2a**, γ -position reaction product **3aa** was formed with an er of 97:3, and the formation of imine **1a** and acetoacetate **2a** was also observed (Scheme 2).

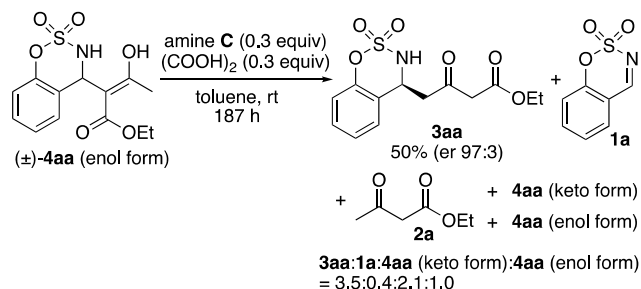
When (\pm)-**4aa** was treated under the catalytic conditions with amine C and oxalic acid in the presence of imine **1c**, which was not the one used for the synthesis of **4aa**, product **3aa** and cross product **3ca** were formed, and both **3aa** and **3ca** obtained were in highly enantiomerically enriched forms (Scheme 3a). Further, when (\pm)-**4aa** was treated under the catalytic conditions in the presence of acetoacetate **2d**, product **3aa** and cross product **3ad** were both obtained with high enantioselectivities (Scheme 3b).

These results indicate that **4aa** was decomposed to the acetoacetate and the imine and that the formed acetoacetate and the formed imine were involved in the formation of the γ -

Table 2. Scope of the Enantioselective γ -Position-Selective Mannich Reactions of Acetoacetates Catalyzed by Amine C and Oxalic Acid^a

^aConditions: **1** (0.5 mmol), **2** (1.5 mmol), amine C (0.15 mmol), and (COOH)₂ (0.15 mmol) in toluene (1.0 mL) at rt (25 °C). ^bA 10 mmol scale reaction. ^cReaction at 40 °C. ^dDetermined after derivatization (see Supporting Information).

Scheme 2. Treatment of 4aa under the Catalytic Conditions with Amine C and Oxalic Acid



position reaction products in the presence of amine C and oxalic acid. The results also indicate that the formation of the γ -position reaction product was not an intramolecular migration from the α -position reaction product.

The stability of the γ -position reaction product **3aa** under the catalytic conditions with amine C and oxalic acid was also analyzed, and **3aa** was unchanged and stable under the catalytic conditions (Supporting Information).

Thus, in the reaction of **1** and **2** in the presence of amine C and oxalic acid, α -position reaction product **4** is reversibly formed, and γ -position reaction product **3** is kinetically and enantioselectively formed. The formation of **3** is likely through the reaction of an enamine formed in situ at the γ -position of the acetoacetate, although the detailed mechanisms have to be

Scheme 3. Reactions of 4aa under the Catalytic Conditions with Amine C and Oxalic Acid

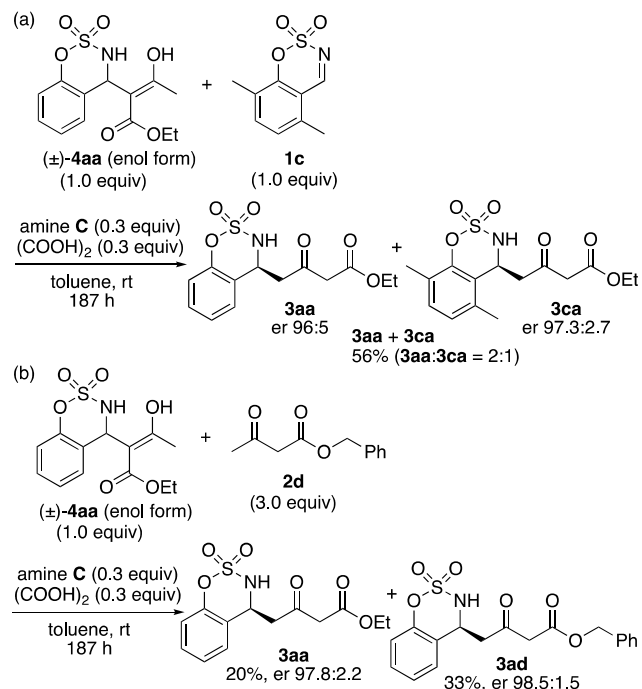
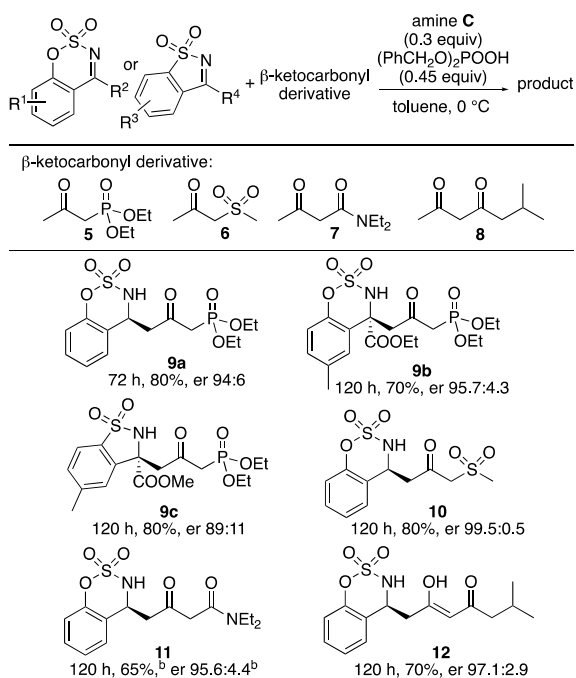
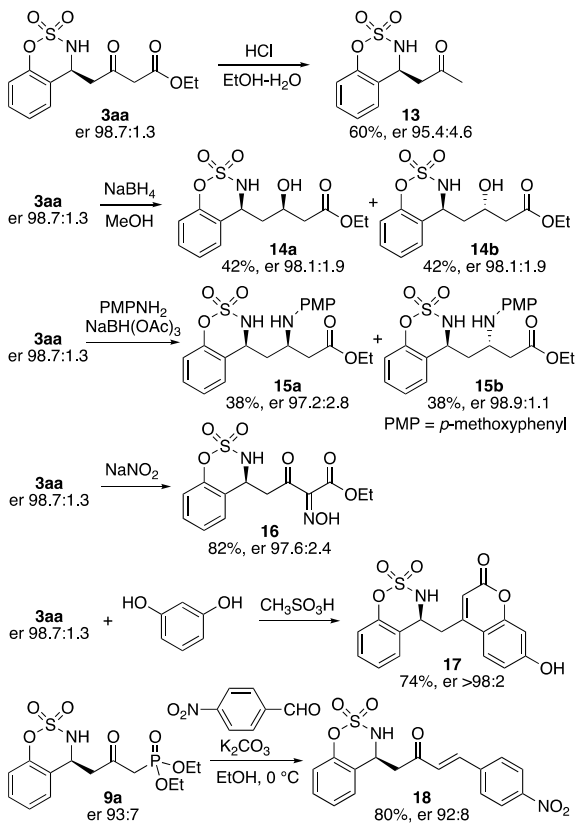


Table 3. Enantioselective γ -Position-Selective Mannich Reactions of Various β -Ketocarbonyl Derivatives^a



^aSee Supporting Information for details. ^bDetermined after derivatization (see Supporting Information).

Scheme 4. Transformations of the γ -Position Reaction Products



determined. The dynamic kinetic process enabled us to afford highly enantiomerically enriched, γ -position reaction product 3

as the main product (see Supporting Information for a plausible pathway).

The γ -position-selective Mannich reactions in the presence of amine C and acids were able to be expanded to perform on various β -ketocarbonyl derivatives 5–8 (Table 3). From the reactions of β -ketophosphonate 5, highly enantiomerically enriched δ -amino β -ketophosphonates 9 were obtained. Similarly, from β -ketosulfone 6, β -ketoamide 7, and 1,3-diketone derivative 8, corresponding Mannich products 10, 11, and 12, respectively, were obtained with high enantioselectivities.

To demonstrate the utility of the developed γ -position-selective Mannich reactions of β -ketocarbonyl derivatives, the products were transformed to further derivatives 13–18 (Scheme 4). For example, δ -amino β -hydroxyacid derivative 14 and β,δ -diamino acid derivative 15 were obtained from 3aa while retaining the enantiopurity. Compound 9a was used in a Horner–Wittig reaction to afford 18, which has a β -amino enone moiety.

In summary, we have developed direct catalytic enantioselective γ -position-selective Mannich reactions of β -ketocarbonyl derivatives that can be performed under mild conditions. A dynamic kinetic process was involved in the formation of the γ -position reaction products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.2c02433>.

Experimental procedures, additional evaluations of catalysts, time course analysis, stability analyses of 3, plausible pathway, NMR spectra, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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