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Letter

Enantioselective Direct *anti*-Selective Mannich-type Reactions Catalyzed by 3-Pyrrolidinecarboxylic Acid in the Presence of Potassium Carbonate: Addition of Potassium Carbonate Improves Enantioselectivities

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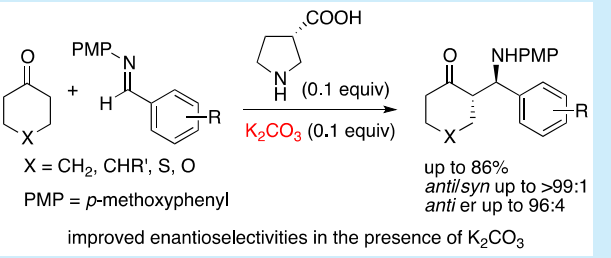
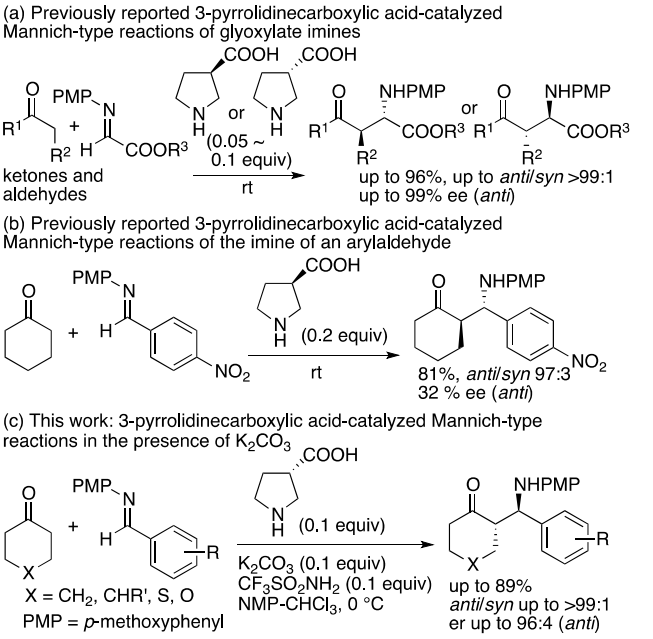
ABSTRACT: Mannich-type reactions of cyclohexanone and related six-membered-ring ketones with *N*-*p*-methoxyphenyl-protected imines of arylaldehydes catalyzed by 3-pyrrolidinecarboxylic acid in the presence of K_2CO_3 that afford *anti*-isomers of the Mannich products with high diastereo- and enantioselectivities are reported. Addition of K_2CO_3 improved the enantioselectivities of the reactions catalyzed by 3-pyrrolidinecarboxylic acid while retaining the *anti*-selectivity of the reaction. Thus, the use of K_2CO_3 expands the scope of these organocatalytic reactions for providing the products with high enantioselectivities.



Asymmetric Mannich and Mannich-type reactions of ketones with imines are important transformations to synthesize enantiomerically enriched amino ketones, amino alcohols, and their related derivatives, which are used for the development of bioactive molecules and related research.[1−4] Various types of catalysts, including metal-based catalysts and organocatalysts, have been used for providing the Mannich products with high diastereo- and enantioselectivities.[1−4] However, each catalyst system has a certain scope. To expand or alter the scope, different catalysts are usually required. The design and the synthesis of new catalysts are important for the development of reaction methods, but we sought an alternative way to expand the scope and improve stereoselectivities of the reactions catalyzed by certain catalysts. We hypothesized that the use of additives, such as alkali metal salts,[5,6] in the reactions catalyzed by organocatalysts would tune the transition states of the reactions to expand or alter the scope of the catalyzed reactions for leading to the products with high enantioselectivities.

Homochiral 3-pyrrolidinecarboxylic acid (or *β*-proline) has been used for catalyzing direct Mannich-type reactions of ketones or aldehydes with *N*-*p*-methoxyphenyl (PMP)-protected imine of glyoxylates to afford *anti*-isomers of Mannich products with high diastereo- and enantioselectivities (Scheme 1a).[4] However, the 3-pyrrolidinecarboxylic acid-catalyzed reactions of cyclohexanone with PMP-protected imines of arylaldehydes previously provided the *anti*-isomers of the Mannich products with low or moderate enantioselectivities (Scheme 1b).[4a] Whereas highly enantioselective Mannich and Mannich-type reactions of cyclohexanone with arylimines to afford the *syn*-isomers of the Mannich products with high

Scheme 1. Mannich-type Reactions Catalyzed by 3-Pyrrolidinecarboxylic Acid



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enantioselectivities have been reported using various catalysts,[2] few examples of the reactions that afford the corresponding *anti*-isomers of the Mannich products with high diastereo- and enantioselectivities have been reported.[3] Here, we report *anti*-selective Mannich-type reactions of cyclohexanone and related ketones with PMP-protected imines of arylaldehydes catalyzed by 3-pyrrolidinecarboxylic acid in the presence of K_2CO_3 (Scheme 1c). We report that the use of K_2CO_3 as additive improves the enantioselectivities of the reactions catalyzed by 3-pyrrolidinecarboxylic acid with retaining the *anti*-selectivities.

In the previously reported 3-pyrrolidinecarboxylic acid-catalyzed reactions of ketones or aldehydes with the imine of ethyl glyoxylate, the hydrogen bonds between the carboxylic acid of the catalyst and the imine or the hydrogen transfer from the carboxylic acid to the imine can locate the glyoxylate imines at the position suitable for the C−C bond formation and control the stereochemistries of the products, leading to the formation of the *anti*-Mannich products (Figure 1a).[4a] In

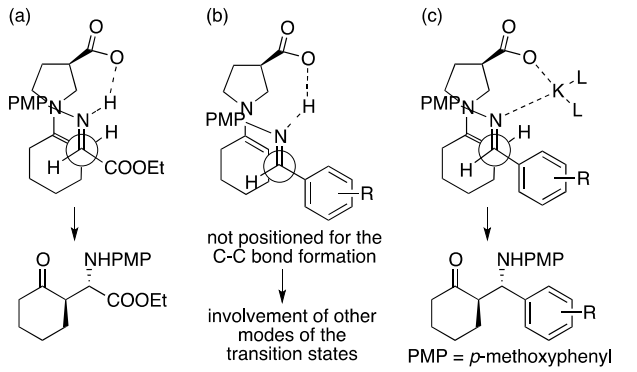
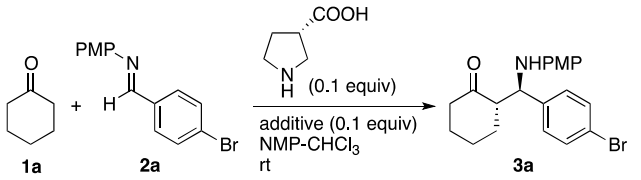


Figure 1. A schematic representation of the transition states. (a) The transition state of the Mannich-type reaction of cyclohexanone with the ethyl glyoxylate imine catalyzed by (*R*)-3-pyrrolidinecarboxylic acid, drawn based on previous reports.[4] (b) (*R*)-3-Pyrrolidinecarboxylic acid alone as catalyst may not lead the transition state that results in the formation of the *anti*-Mannich products with high enantioselectivities in the reactions of the imines of arylaldehydes. (c) Proposed transition state of the Mannich-type reactions of cyclohexanone with the imines of arylaldehydes catalyzed by (*R*)-3-pyrrolidinecarboxylic acid in the presence K_2CO_3, which affords the *anti*-Mannich products with high enantioselectivities.

contrast, in the same catalyst-catalyzed reactions of ketones with the imines of arylaldehydes, the hydrogen bonds or the hydrogen transfer between the carboxylic acid and the imines may not locate the imines at the positions suitable for the C−C bond formation or may locate the imines at the position a little far from that suited for the C−C bond formation (Figure 1b). Accordingly, the C−C bond formation may occur without the involvement of the hydrogen bonds or the hydrogen transfer, resulting the formation of the products with moderate to low enantioselectivities. The differences between the reactions of the ethyl glyoxylate imine and of the arylaldehydes imines may originate from the electron-withdrawing feature and/or the structure of the ester group of the glyoxylate imine. The electron-withdrawing group may affect the length of the hydrogen bonds in the transition state.[7] We hypothesized that addition of alkali metal salts, alkaline earth metal salts, and other additives (such as nontransition metals and ammonium salts) would tune the positioning of the imines in the transition state for the C−C bond formation, leading to the product formation with high enantioselectivities while retaining the *anti*-selectivity (Figure 1c). The O−K and the N−K bonds are longer than the O−H and the N−H bonds in the O−H−N hydrogen bond;[8] the longer bonds would allow the positioning of the reactants in the transition state for the C−C bond formation to form the product in a stereocontrolled way.

First, we evaluated various alkali metal salts, alkaline earth metal salts, and tetraalkylammonium salts as additives in the (*S*)-3-pyrrolidinecarboxylic acid-catalyzed Mannich-type reaction of cyclohexanone (**1a**) with PMP-protected imine **2a** to afford *anti*-**3a** with high diastereo- and enantioselectivities (Table 1, see also Supporting Information). Of additives tested

Table 1. Evaluation of Additives for the (*S*)-3-Pyrrolidinecarboxylic Acid-Catalyzed Mannich-type Reaction of 1a with 2a to Afford 3a[a]



entry	additive	time (h)	yield[b] (%)	*anti*/*syn*[b]	er[c]
1	none	20	40	>20:1	71:29
2	Li_2CO_3	20	70	>20:1	68:32
3	Na_2CO_3	20	44	>20:1	81:19
4	K_2CO_3	20	55	9:1	90:10
5	K_2CO_3	48	90	9:1	90:10
6	Rb_2CO_3	20	12	ND	ND
7[d]	Rb_2CO_3	20	43	8:1	87:13
8[d]	Cs_2CO_3	20	57	5:1	87:13
9	$MgCO_3$	20	59	9:1	89:11
10	$CaCO_3$	20	68	>20:1	70:30
11	$SrCO_3$	20	62	>20:1	70:30
12	$BaCO_3$	20	83	>20:1	68:32
13	Bu_4NOH	20	77	4:1	76:24
14[e]	none	192	92	>20:1	75:25
15[e]	K_2CO_3	168	82	12:1	94:6
16[e,f]	none	168	98	>20:1	76:24
17[e,f]	**K_2CO_3**	**192**	**91 (81)[g]**	**18:1**	**95:5**

[a]Conditions: A mixture of (*S*)-3-pyrrolidinecarboxylic acid (0.1 mmol) and additive (0.1 mmol) in *N*-methylpyrrolidone (NMP) (0.3 mL) was stirred at rt (25 °C) for 1 h. To the mixture, $CHCl_3$ (0.7 mL) and **1a** (10 mmol) were added at the same temperature, followed by **2a** (1.0 mmol). [b]Determined by ^1H NMR analysis before purification. ND = not determined. [c]The er of *anti*-**3a**; determined by HPLC analysis after purification. [d]Additive (0.05 mmol, 0.05 equiv). [e]The reaction at 0 °C. [f]$CF_3SO_2NH_2$ (0.1 mmol) was added before addition of $CHCl_3$. [g]Isolated yield of *anti*-**3a** in parentheses.

in the reaction at room temperature (rt, 25 °C), K_2CO_3 most improved the enantioselectivity (Table 1, entries 4 and 5). The reaction in the presence of K_2CO_3 at 0 °C gave the product with enantiomer ratio (er) 94:6 (Table 1, entry 15). The (*S*)-3-pyrrolidinecarboxylic acid-catalyzed reaction in the presence of K_2CO_3 with further addition of $CF_3SO_2NH_2$ afforded *anti*-**3a** in a high yield with high dr (*anti*/*syn* = 18:1) with high enantioselectivity (er 95:5) (Table 1, entry 17). We expected $CF_3SO_2NH_2$ acts to maintain the neutral environment[9] for the reaction in the presence of K_2CO_3, suppressing potential side reactions and background reactions caused by basic conditions.

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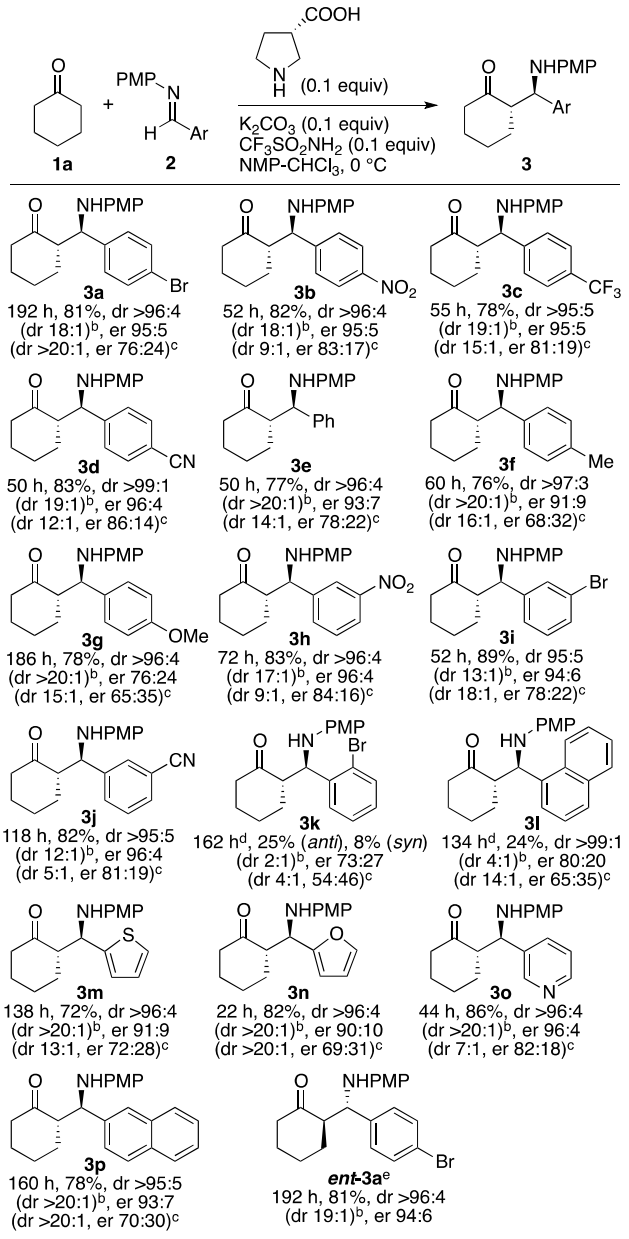
Next, the best conditions identified (i.e., conditions of Table 1, entry 17) were used for the synthesis of various Mannich products **3** (Scheme 2). The reactions catalyzed by (*S*)-3-pyrrolidinecarboxylic acid in the presence of K_2CO_3 afforded the *anti*-products in good to high yields with high diastereo- and enantioselectivities in most cases. The *anti*-Mannich products synthesized from the imines of benzaldehydes bearing electron-withdrawing groups at *p*- or *m*-positions and of the imine of 3-pyridinecarboxyaldehyde were obtained with high enantioselectivities (er 96:4−94:6 for **3a**, **3b**, **3c**, **3d**, **3h**, **3i**, **3j**, and **3o**). In the absence of K_2CO_3, the same products were obtained with moderate enantioselectivities (er 86:14−76:24). The products derived from imines of benzaldehyde, 4-methylbenzaldehyde, 2-naphthaldehyde, and heteroarylaldehydes were obtained with er 93:7−90:10 (**3e**, **3f**, **3m**, **3n**, and **3p**); for these cases, the same products were obtained with er 78:22−68:32 in the absence of K_2CO_3. For the reactions with the imines bearing *p*-methoxy group or an *o*-substituent on the phenyl group and with the imine of 1-naphthylaldehyde, the products were obtained with moderate enantioselectivities (er 80:20−73:27 for **3g**, **3k**, and **3l**); for these reactions, the enantioselectivities in the presence of K_2CO_3 were also higher than those observed in the reactions performed in the absence of K_2CO_3.

The (*S*)-3-pyrrolidinecarboxylic acid−K_2CO_3 catalyst system was also useful for affording *anti*-Mannich products **4** from the reactions of cyclohexanone derivatives and of heteroatom-containing cyclic ketones (Scheme 3). Addition of K_2CO_3 also improved the enantioselectivities of the 3-pyrrolidinecarboxylic acid-catalyzed reactions.

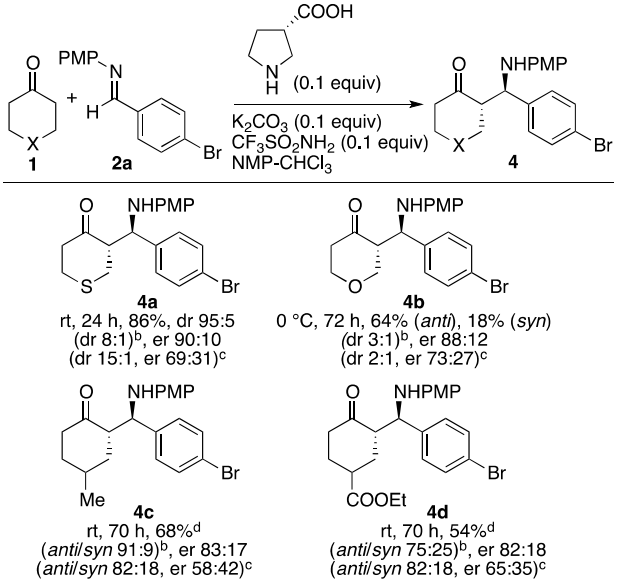
The reaction catalyzed by the (*S*)-3-pyrrolidinecarboxylic acid−K_2CO_3 catalyst system was readily scaled up. From a 3 mmol reaction, product **3c** (*anti*-isomer, 960 mg, 85%) was obtained with er 95:5.

Scheme 2. Scope of the Mannich-type Reactions Catalyzed by the (*S*)-3-Pyrrolidinecarboxylic Acid−K_2CO_3 System[a]



[a]Conditions: **1a** (10 mmol), **2** (1.0 mmol), (*S*)-3-pyrrolidinecarboxylic acid (0.1 mmol), K_2CO_3 (0.1 mmol), and $CF_3SO_2NH_2$ (0.1 mmol) in NMP (0.3 mL)−$CHCl_3$ (0.7 mL) at 0 °C. See Supporting Information. Reaction time, isolated yield containing *anti*- and *syn*-isomers except where noted, dr = *anti*/*syn* determined by ^{1}H NMR analysis of the isolated product, and er of the *anti*-isomer determined by HPLC analysis are shown. Results of **3a** are from Table 1. [b]Data before purification. [c]Data of the reaction performed in the absence of K_2CO_3. [d]Reaction was not completed at the indicated time. [e]Obtained from the reaction using (*R*)-3-pyrrolidinecarboxylic acid instead of the (*S*)-3-pyrrolidinecarboxylic acid.

Scheme 3. Ketone Variations in the Mannich-type Reactions Catalyzed by the (*S*)-3-Pyrrolidinecarboxylic Acid−K_2CO_3 System[a]



[a]Conditions: **1** (10 mmol), **2** (1.0 mmol), (*S*)-3-pyrrolidinecarboxylic acid (0.1 mmol), K_2CO_3 (0.1 mmol), and $CF_3SO_2NH_2$ (0.1 mmol) in NMP (0.3 mL)−$CHCl_3$ (0.7 mL). See Supporting Information. Reaction time, isolated yield containing *anti*- and *syn*-isomers, dr = *anti*/*syn* determined by ^{1}H NMR analysis of the isolated product, and er of the *anti*-isomer determined by HPLC analysis, except where noted, are shown. [b]Data before purification. [c]Data of the reaction performed in the absence of K_2CO_3. [d]Isolated yield of the most major isomer (the major isomer of the *anti*-isomers).

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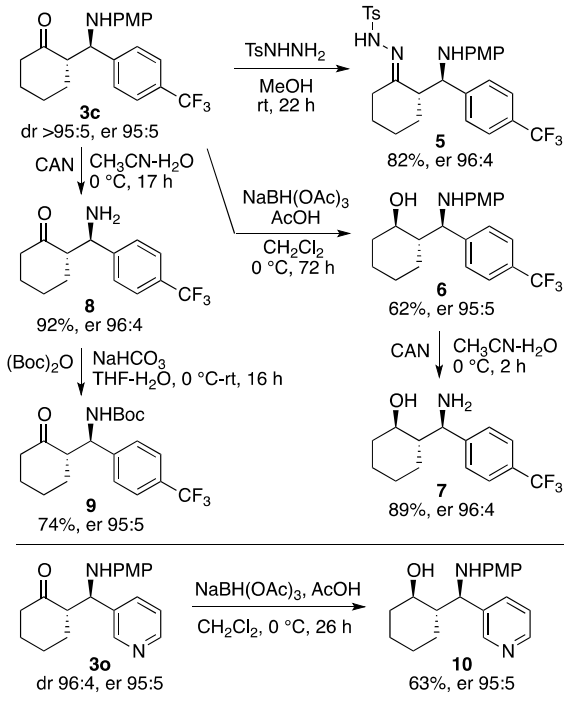
To understand the mechanism of the reactions catalyzed by the (*S*)-3-pyrrolidinecarboxylic acid−K_2CO_3 catalyst system, in the reaction to afford **3a**, the product er was analyzed at various time points. From the initial stage of the reaction (such as at the 15% conversion) to the stage at more than 90% conversion, the dr (*anti*/*syn*) of **3a** was >18:1 and the er of the *anti*-isomer of **3a** was 95:5. No changes in the dr and the er values were observed during the reaction, indicating that the Mannich product is kinetically formed.

The utility of the (*S*)-3-pyrrolidinecarboxylic acid−K_2CO_3 catalyst system was further demonstrated by transformations of the Mannich products (Scheme 4). Mannich product **3c** was

Scheme 4. Transformations of the Mannich Products



transformed to tosylhydrazone derivative **5**. Reduction of the ketone of **3c** by $NaBH(OAc)_3$ afforded **6**. Deprotection of the PMP group of **6** using ceric ammonium nitrate (CAN) afforded amino alcohol **7**. The CAN treatment of **3c** also gave amino ketone **8**, and this was transformed to Boc protected amino ketone derivative **9**. Reduction of Mannich product **3o** also gave amino alcohol derivative **10**. In these transformations, the enantiopurities of the Mannich products were retained, and the products were isolated as single diastereomers.

In summary, addition of K_2CO_3 significantly improved the enantioselectivities of the *anti*-selective Mannich reactions of 6-membered ketones with imines of arylaldehydes catalyzed by homochiral 3-pyrrolidinecarboxylic acid. Detailed mechanisms of the function of K_2CO_3 in the 3-pyrrolidinecarboxylic acid-catalyzed reactions are under investigation. We proposed that K_2CO_3 is involved in positioning of the imine in the transition state for the C−C bond formation to lead to the *anti*-Mannich product with high enantioselectivity. We demonstrated that the use of an additive can expand the scope of the organocatalytic reactions, affording the products with high enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01561.

Experimental procedures, additional information of the results, characterization data of compounds, NMR spectra, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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