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Prolinate Salt as a Catalyst in the *syn*-Selective, Asymmetric Mannich Reaction of Alkynyl Imine

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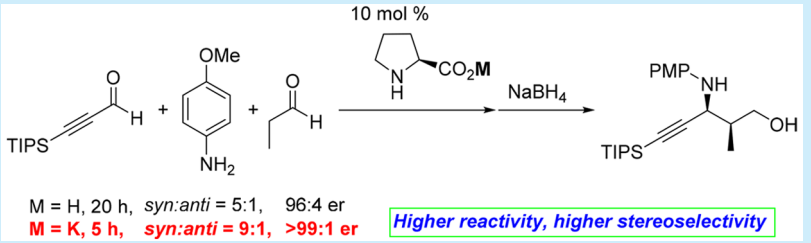
Supporting Information



ABSTRACT: Prolinate salt is an efficient catalyst in the Mannich reaction of alkynyl imine and aldehyde, to afford synthetically useful chiral propargyl amine derivatives with excellent *syn*-selectivity and nearly perfect control of the absolute configuration. The counterion of the prolinate salt does not affect the enantioselectivity. This is a rare example, in which proline alkali metals, alkaline-earth metals, or ammonium salt show higher reactivity and better stereoselectivity than the parent proline.

Since List, Lerner, and Barbas' seminal publication on the proline-mediated intermolecular aldol reaction in 2000,[1] proline has been a central catalyst in asymmetric organocatalytic reactions involving an enamine as a reactive intermediate.[2] There have been tremendous efforts in the development of more reactive, more diastereoselective and enantioselective, and easily prepared organocatalysts.

Instead of the wide applicability of proline as an organocatalyst, the utility of its metal salts or ammonium salts has been rather limited: the additive effect has been intensively investigated in proline-mediated aldol reactions, and marked positive effects of amine additive have not been observed,[3] in which ammonium prolinate would be generated. The only successful aldol reaction is the intramolecular reaction for the formation of bicyclo[3.n.1] alkanones, reported by Iwabuchi, using tetrabutylammonium siloxyprolinate.[4] In the Michael reaction, the proline rubidium salt[5] and proline lithium salt are effective.[6] In the α-amination catalyzed by tetrabutylammonium prolinate, Blackmond observed the reversal of enantioselectivity with a lower enantiomeric excess (ee) value.[7] Recently, we found that potassium and tetrabutylammonium prolinate salts are efficient catalysts in the α-aminoxylation reaction of aldehydes and nitrosobenzene.[8]

On the other hand, the proline-mediated three-component Mannich reaction is one of the powerful methods for the synthesis of chiral nitrogen-containing molecules.[9] Our group reported the three-component cross-Mannich reaction[10] of two different aldehydes catalyzed by proline.[11] Our continuing interest in the asymmetric Mannich reaction[12] prompted us to investigate the Mannich reaction of alkynyl imine because the generated chiral propargyl amine derivative would be a useful chiral synthetic building block. Despite the known *anti*-selective asymmetric Mannich reaction of alkynyl imine,[13] a *syn*-selective asymmetric reaction catalyzed by an organocatalyst is rare. Recently Oiarbide, Palomo, and co-workers reported such a reaction for the first time, using proline and urea derivatives as dual catalysts, in which several hydrogen-bonding interactions were proposed.[14] We happened to find that metal or ammonium prolinate is more reactive and selective than the parent proline in the Mannich reaction, which will be described in this communication.

We chose a three-component Mannich reaction composed of triisopropylsilylpropynal, propanal, and *p*-anisidine as a model reaction (eq 1, Table 1). As we have already reported the proline-mediated Mannich reaction of arylaldehyde,[11a,b] we used similar reaction conditions using L-proline as a catalyst in NMP (*N*-methyl-2-pyrrolidinone). First, we prepared the imine from the alkynyl aldehyde and *p*-anisidine at room temperature for 30 min, then propanal and L-proline were added. The reaction proceeds gradually at −20 °C and affords the desired Mannich product in good yield with moderate diastereoselectivity and excellent enantioselectivity after 20 h (entry 1 in Table 1). In contrast to the slow reaction with the use of L-proline, the reaction was found to be fast in the presence of lithium L-prolinate to afford the product in only 5 h with higher diastereoselectivity and nearly perfect enantioselectivity (entry 2 in Table 1). Next, the other alkali metals and alkaline-earth metals were investigated in detail. When alkali-metal salts of proline were employed, the reaction was

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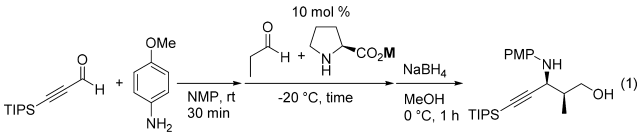
Table 1. Effect of the Cation of the Proline Salt in the Mannich Reaction of Alkynyl Imine[a]



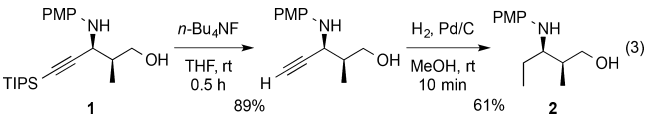
entry	M	time [h]	*syn*:*anti*[b]	yield[c] [%]	er[d] [%]
1	H	20	5:1	74	96:4
2	Li	5	6:1	73	>99:1
3	Na	5	7:1	78	>99:1
4	K	5	9:1	84	>99:1
5	Rb	5	9:1	71	>99:1
6	Cs	5	9:1	74	>99:1
7	Mg	18	12:1	80	95:5
8	Ca	24	9:1	74	>99:1
9	Sr	24	8:1	39	>99:1
10	Ba	24	10:1	79	>99:1
11	Bu_4N	4	7:1	75	>99:1

[a]Unless otherwise shown, the reaction was performed by employing triisopropylsilylpropynal (0.4 mmol), *p*-anisidine (0.4 mmol), propanal (1.2 mmol), and catalyst (0.04 mmol) in NMP (0.8 mL). See the Supporting Information (SI) for details. [b]Determined by ^{1}H NMR. [c]Yield of purified product. [d]Determined by HPLC analysis on a chiral column material.

completed within 5 h to afford the products in good yield with excellent diastereoselectivities and enantioselectivities (entries 3−6 in Table 1). In the case of alkaline-earth metals, except for Mg, excellent diastereoselectivities and enantioselectivities were observed with longer reaction times (24 h) (see entries 8−10 in Table 1). A lower enaniomeric ratio (er) value (95:5) was observed in the case of the Mg salt (entry 7 in Table 1). Note that almost-perfect enantioselectivity is observed, regardless of alkali and alkaline-earth metals, except for Mg. It is also noted that tetrabutylammonium salt is effective, providing the product within 4 h with excellent diastereoselectivity and almost-perfect enantioselectivity (entry 11 in Table 1).

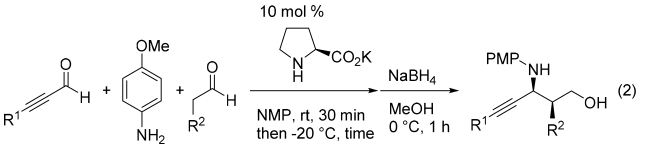
Since excellent results were obtained using metal salts and ammonium salt, the generality of the reaction was investigated using potassium L-prolinate as a catalyst (see Table 2). As a nucleophilic aldehyde, not only propanal, but also butanal, pentanal, isovaleraldehyde, and 3-phenylpropanal can be successfully employed. A functionalized aldehyde, such as 5-octenal, is also a suitable aldehyde. As an alkynyl aldehyde, not only silylpropynal, but also phenylpropynal, non-2-ynal, and 4-siloxy-2-butynal are suitable alkynyl aldehydes. In all cases examined, excellent diastereoselectivity and almost-perfect enantioselectivity have been attained.

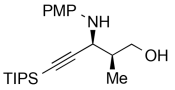
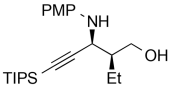
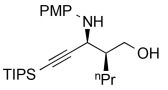
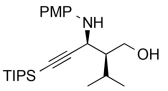
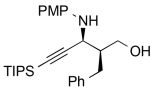
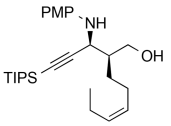
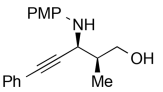
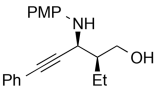
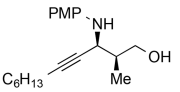
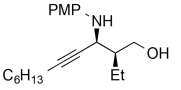
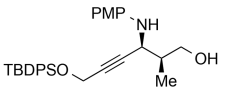
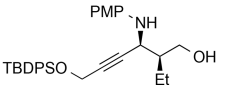
The relative and absolute configurations were determined by the transformation of the Mannich product **1** to the reduction product **2** of the known self-Mannich product of propanal,[11a] as shown in eq 3.



According to the model of Houk and List using proline as a catalyst, the reaction proceeds from an *anti*-enamine via activation of the electrophile through protonation of the carboxy group (see Figure 1A, where M = H).[15] In the present Mannich reaction of

Table 2. Generality of the Asymmetric Three-Component Mannich Reaction of Alkynyl Aldehyde, *p*-Anisidine and Aldehyde Catalyzed by Potassium L-Prolinate[a]



entry	product	time [h]	*syn*:*anti*[b]	yield [%][c]	er [%][d]
1		5	9:1	84	>99:1
2		7	8:1	80	>99:1
3		7	8:1	90	>99:1
4		12	8:1	74	>99:1
5		6	7:1	83	>99:1
6		7	9:1	75	>99:1
7		8	11:1	89	>99:1
8		8	11:1	85	>99:1
9		12	4:1	66	>99:1
10		12	6:1	62	>99:1
11		6	18:1	82	>99:1
12		9	20:1	78	>99:1

[a]Unless otherwise shown, the reaction was performed by employing alkynyl aldehyde (0.4 mmol), *p*-anisidine (0.4 mmol), nucleophilic aldehyde (1.2 mmol), and potassium L-prolinate (0.04 mmol) in NMP (0.8 mL) at −20 °C for the indicated time. See the SI for details. [b]Determined by ^{1}H NMR. [c]Yield of purified product. [d]Determined by HPLC analysis on a chiral column material.

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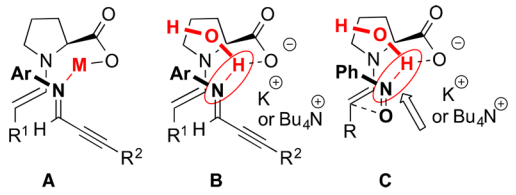

Figure 1. Reaction model of enamine derived from proline and prolinate.

alkynyl imine catalyzed by prolinate, the solvent is the highly polar NMP. Under this condition, the enaminocarboxylate anion intermediate would form a separated ion pair. Moreover, according to the similar transition state of the Houk–List model, the size of the counterion should affect the enantioselectivity (see Figure 1A, where M = metal). However, almost-perfect enantioselectivity is obtained, regardless of the prolinate counterion. Thus, it would be difficult to explain these results using the Houk–List model (Figure 1A).

We reported that potassium and tetrabutylammonium prolinate salts are more reactive and enantioselective catalysts in the α-aminoxylation reaction of aldehydes and nitrosobenzene.[8] We have proposed a transition-state model, as shown in Figure 1C. There are similarities between the α-aminoxylation and the present Mannich reaction: In both reactions, prolinate is more reactive and enantioselective than proline, and proline and prolinate afford the same enantiomers. The basicity of nitrogen of nitrosobenzene and alkynyl imine would be similar. Thus, we would like to propose the following reaction mechanism. Water, generated in the enamine formation, would form a hydrogen bond with the carboxylate anion,[16,17] and this proton would protonate the nitrogen of imine (Figure 1B). This model explains the effect of a countercation on the enantioselectivity and the same absolute configurations of the products using prolinate salt and proline as a catalyst.

The higher reactivity of the prolinate salt, compared to the proline, may be explained as follows:

(1) the enaminocarboxylate is more nucleophilic than enaminocarboxylic acid, because of the anchimeric assistance of the carboxylate group reported by Mayr,[18] and
(2) in the case of proline, stable oxazolidinone **3** (Figure 2) would be generated by the reaction with aldehyde, which reduces the concentration of enamine. Similar oxazolidinone could not be formed in the case of the prolinate salt, leading to a higher concentration of the reactive enaminocarboxylate.

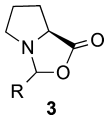

Figure 2. Oxazolidinone intermediate **3**.

In summary, we have found the asymmetric three-component Mannich reaction for metal or ammonium prolinate to act as an effective and reactive catalyst to provide excellent enantioselectivity with superiority over proline. From a synthetic point of view, this is the rare *syn*-selective, asymmetric Mannich reaction of alkynyl imine and aldehyde, which supplements the known *anti*-selective Mannich reaction. Since metal and ammonium prolinate are easily prepared and inexpensive, the present method would be useful for the preparation of chiral propargyl amine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00728.

Experimental procedure, analytical data (^{1}H and ^{13}C NMR, IR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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