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Base-catalyzed three-component direct Mannich reaction of enolizable ketones with high *syn*-selectivities

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ABSTRACT

The three-component direct Mannich reaction between aldehydes, *p*-toluenesulfonamide, and enolizable ketones was achieved for the first time with organic bases as the catalysts. The corresponding N-tosylated β-aminoketones were obtained in high yields and good to excellent diastereoselectivities using TMG as the catalyst. Through reduction of the ketone group, the reaction product may be converted into β-aminol with excellent diastereoselectivity.

Mannich reaction is one of the most useful methods for the construction of carbon–carbon bonds in organic chemistry.[1] The reaction is especially useful for the synthesis of β-amino carbonyl derivatives.[1] Due to the importance of the Mannich products in organic synthesis, various methods for conducting highly diastereoselective and/or enantioselective Mannich reactions have been developed in the past.[1] According to the ways that the reactions are conducted, Mannich reactions may be generally divided into direct Mannich reactions and indirect Mannich reactions.[1] Because direct Mannich reaction do not require the use of preformed enolates or their equivalents as the substrates, it has many advantages over the indirect Mannich reaction, such as better atom economy and operational simplicity.[1]

Since List reported the first example of a proline-catalyzed direct Mannich reaction in 2000,[2] organocatalyzed Mannich reactions have been undergoing vigorous developments in the past decade.[1b,3] Amino acid derivatives, mainly those derived from proline,[4] chiral Brønsted acids,[5] chiral amine thioureas,[6] and cinchona alkaloids[7] have been used as the catalysts in the reported Mannich reactions, and high diastereoselectivities and/or enantioselectivities have been achieved in many cases.[1b,3] Three-component direct Mannich reactions are arguably the most convenient methods for conducting Mannich reactions since the imine substrates are also in situ generated in these reactions. [8] Nonetheless, among those reported organocatalyzed direct Mannich reactions, catalysts that can perform the three-component direct Mannich reactions of enolizable ketones or aldehydes are relatively limited because many of the reported catalysts and/or reaction conditions are not compatible with the in situ generation of the imines. To our knowledge, with the exception of a chiral phosphoric acid reported by Gong and coworker,[9a] all the other catalysts are mainly the amine derivatives[4,9b] that catalyze the reaction through the enamine mechanism.[9]

Although enolate-mediated organocatalyzed direct Mannich reactions of activated methylene compounds are well-known,[6,7] to our knowledge, such an enolate-mediated Mannich reaction of enolizable ketones or aldehydes has not been reported.[9,10] This is most probably due to the low acidity of the α-proton of these ketone compounds, which is difficult to be deprotonated by organic bases to become a suitable enolate nucleophile. Most recently, we have demonstrated that cinchona alkaloid bases are capable of catalyzing enolate-mediated aldol reactions of ketones.[11] The reaction works through the enolate intermediate in a complete noncovalent catalysis and is complementary to the amine-catalyzed aldol reactions in terms of the substrate scope.[11] Because the reaction mechanisms of the aldol and Mannich reactions are very similar, we envisioned that organic Brønsted bases should be also able to catalyze the Mannich reaction of enolizable ketones via the enolate intermediate. Herein we wish to report the first example of a Brønsted base-catalyzed highly *syn*-selective three-component direct Mannich reaction of enolizable ketones.

Using benzaldehyde (**1a**), *p*-toluenesulfonamide, and 3,4-dihydronaphthalen-1(2*H*)-one (**2a**) as the substrates, we initially screened several Brønsted bases for their ability to effect the desired

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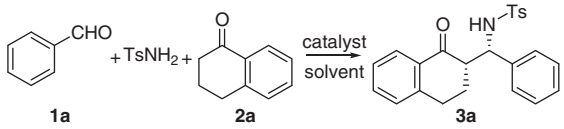
Mannich reaction and to control the diastereoselectivity of this reaction. The results are summarized in Table 1. As the data in Table 1 show, when DBU was used as the catalyst in THF, the expected Mannich product **3a** was obtained in 88% yield with a high dr value of 93:7 after reacting at rt for 15 h (entry 1). A lower yield and a poor dr value were obtained for **3a** when 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was used under similar conditions (entry 2). Moreover, poor conversions were observed when less basic DABCO or quinuclidine was used (entries 3 and 4). Similarly, an inorganic base K_2CO_3 also led to low conversion of the substrate, but the dr value of the obtained product was high (entry 5). In contrast, when 1,1,3,3-tetramethylguanidine (TMG) was used, a high yield of 95% and an excellent dr value of 97:3 were obtained for **3a** (entry 6). Thus, TMG was identified as the best Brønsted base for this reaction. Next we evaluated the solvent effects on this reaction (entries 7–12). Among those common organic solvents, THF (entry 6) and toluene (entry 12) were identified as the best solvents for this reaction. Since in this reaction 1 equiv of water is formed during the formation of the imine intermediate, we intentionally added molecular sieves to the reaction mixture to see whether the reaction can be accelerated with the water removal. As the results show, the reaction indeed became much faster when molecular sieves were added (entries 13 and 14). Under these new conditions, toluene turned out to be a better solvent than THF because a higher product yield was obtained (entry 14). The major product obtained in this reaction was determined to be the *syn*-diastereomer according to the X-ray crystallographic analysis of the product **3a** (Fig. 1).[12]

Once the reaction conditions were optimized, the scope of this reaction was evaluated, and the results are collected in Tables 2 and 3.[13] Firstly, the aldehyde substrates were evaluated using ketones **2a**–**c** and *p*-toluenesulfonamide as the substrates. As the data in Table 2 show, when ketone **2a** was used, benzaldehyde and its derivatives that bear either an electron-withdrawing or an electron-donating group all gave the desired Mannich products **3** in high yields (⩾90%) and excellent dr values (⩾93:7, entries 1–8 and 10), except for 2-bromobenzaldehyde (entry 9), which yielded slightly lower yield and dr, most likely due to steric effects. Aliphatic aldehyde may also be used in this reaction. For example, when cyclohexanecarbaldehyde was used with 1,2-diphenylethanone (**2b**), the corresponding Mannich product **3k** was obtained in 94% yield with a dr of 88:12 (entry 11). Similarly, the reaction of cyclohexanecarbaldehyde with acetophenone (**2c**) also led to the formation of the desired product **3l** in 65% yield (entry 12), although the reaction was more sluggish as compared with the rest of reactions. The formation of the major *syn*-diastereomer was again established by an NOE experiment on compound **3i**.

Next the ketone substrates were studied using benzaldehyde and *p*-toluenesulfonamide as the imine precursors. As the data in Table 3 indicate, besides ketone **2a**, chroman-4-one also led to the formation of **3k** as a single *syn* diastereomer in 95% yield (entry 1). Similar results were also obtained for thiochroman-4-one (entry 2). Cyclohexanone is slightly less reactive, and the product was

Table 1
Brønsted base-catalyzed three-component direct Mannich reaction of benzaldehyde, ***p***-toluenesulfonamide, and ketone **2a**[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c]
1	DBU	THF	15	88	93:7
2	TBD	THF	15	79	64:36
3	DABCO	THF	15	Trace	nd[d]
4	Quinuclidine	THF	15	Trace	nd[d]
5	K_2CO_3	THF	15	35	96:4
6	TMG	THF	15	95	97:3
7	TMG	CH_3OH	15	61	51:49
8	TMG	DMF	15	75	54:46
9	TMG	CH_2Cl_2	15	67	94:6
10	TMG	Et_2O	15	76	91:9
11	TMG	1,4-Dioxane	15	93	95:5
12	TMG	Toluene	15	95	97:3
13	TMG	THF[e]	5	87	97:3
14	TMG	Toluene[e]	5	95	97:3

[a] Unless otherwise specified, all reactions were carried out at with benzaldehyde (**1a**, 0.20 mmol), toluenesulfonamide (0.40 mmol), ketone **2a** (0.40 mmol), and the base catalyst (0.040 mmol, 20 mol %) in the indicated solvent (0.2 mL) at rt.
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction product.
[d] Not determined.
[e] With 4 Å MS (50.0 mg) added.

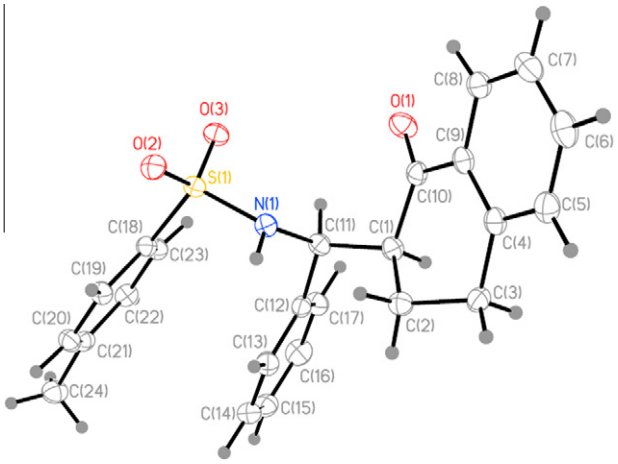
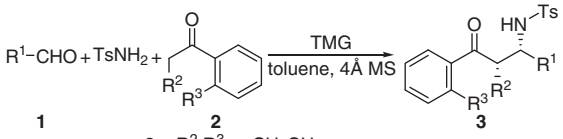


Figure 1. ORTEP drawing of compound **3a**.

Table 2
Substrate study I: the aldehydes[a]

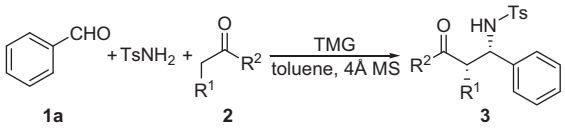


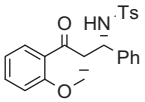
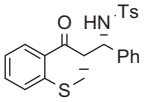
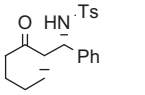
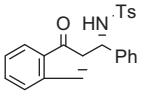
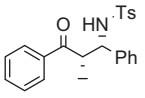
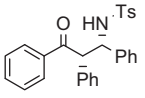
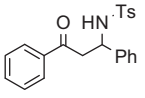
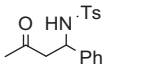
2a: R^2,R^3 = -CH_2CH_2-;
2b: R^2 = Ph, R^3 = H;
2c: R^2 = H, R^3 = H.

Entry	R	2	Time (h)	3	Yield[b] (%)	dr[c]
1	Ph	**2a**	5	**3a**	95	97:3
2	4-FC_6H_4	**2a**	6	**3b**	95	95:5
3	4-ClC_6H_4	**2a**	5	**3c**	95	96:4
4	4-BrC_6H_4	**2a**	5	**3d**	94	>99:1
5	4-CNC_6H_4	**2a**	3	**3e**	97	95:5
6	4-$NO_2C_6H_4$	**2a**	3	**3f**	95	95:5
7	4-MeC_6H_4	**2a**	7	**3g**	90	93:7
8	4-$MeOC_6H_4$	**2a**	8	**3h**	93	93:7
9	2-BrC_6H_4	**2a**	8	**3i**	86	88:12
10	3-BrC_6H_4	**2a**	5	**3j**	97	95:5
11	*c*-C_6H_{11}	**2b**	4	**3k**	94	88:12
12[d]	*c*-C_6H_{11}	**2c**	72	**3l**	65	—

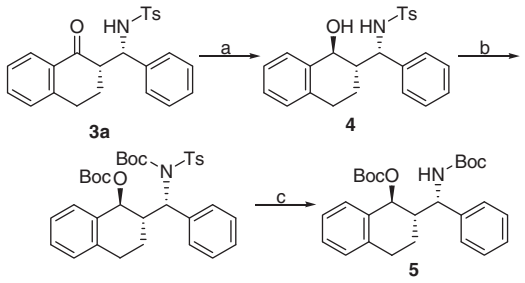
[a] Unless otherwise indicated, all reactions were carried out at with aldehyde **1** (0.20 mmol), *p*-toluenesulfonamide (0.40 mmol), ketone **2** (0.40 mmol), TMG (0.040 mmol, 20 mol %), and 4 Å MS (50.0 mg) in toluene (0.2 mL) at rt.
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction product.
[d] Ketone **2c** (1.0 mmol) was used. Since only one stereogenic center was formed in this case, there was no dr.

Table 3
Substrate study II: the ketones[a]



Entry	Ketone	Time(h)	Product		Yield[b] (%)	dr[c]
1		5		**3m**	95	>99:1
2		5		**3n**	96	>99:1
3		12		**3o**	86	78:22
4		15			Trace	nd[d]
5		7		**3p**	92	88:12
6		1		**3q**	96	>99:1
7		7		**3r**	91	—[e]
8		48		**3s**	65	—[e]

[a] All reactions were carried out at with benzaldehyde (**1a**, 0.20 mmol), toluenesulfonamide (0.40 mmol), ketone **2** (0.40 mmol), TMG (0.040 mmol, 20 mol %), and 4 Å MS (50.0 mg) in toluene (0.2 mL) at rt.
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction product.
[d] Not determined.
[e] Since only one stereogenic center was formed in this case, there was no dr.



Scheme 1. Further elaborations of the reaction product **3a**. Reaction conditions: a: $LiAlH_4$ (3.0 equiv.), THF, 0 °C, 5 h, 95%, dr >99:1; b: Boc_2O (4.0 equiv.), Et_3N (4.0 equiv.), DMAP (10 mol %), THF, rt, 24 h, 98%; c: SmI_2 (12.0 equiv.), HMPA, THF, Ar, reflux, 6 h, 93%.

obtained in a dr of 78:22 (entry 3). Nevertheless, for reasons that are not clear at this stage, 2,3-dihydro-1*H*-inden-1-one failed to give a good conversion under the optimized reaction conditions (entry 4). On the other hand, good results were obtained for acyclic

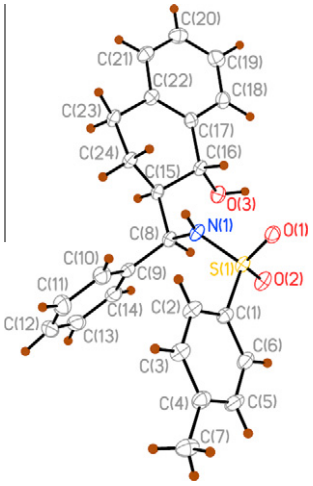


Figure 2. ORTEP drawing of compound **4**.

ketones as well. For example, the Mannich product of propiophenone (**3p**) was obtained in 92% yield with a dr of 88:12 (entry 5), and that of 1,2-diphenylethanone (**3q**) was obtained in 96% yield as a single diastereomer (entry 6). Acetophenone also participates in this reaction, and the corresponding product **3r** was obtained in a high yield of 91% (entry 7). As expected, acetone is less reactive, and the product **3s** was obtained in 65% after 48 h of reaction (entry 8).

The *N*-tosyl-β-aminoketone products obtained in this reaction are very useful in organic synthesis. For example, we demonstrated that product **3a** may be reduced by using $LiAlH_4$ to produce the corresponding *N*-tosyl-β-aminol compound **4** in 95% yield as a single diastereomer (dr > 99:1, Scheme 1).[13] The newly formed hydroxy-substituted stereogenic center was found to be *anti* to the existing stereogenic centers according to the X-ray crystallographic analysis of this compound (Fig. 2).[14] The tosyl group in **4** may be further removed[15] in a two-step sequence to give the Boc-protected *anti*, *syn*-β-aminol **5** in high yield (91% over two steps, Scheme 1)[13]

In summary, we have realized the first example of a base-catalyzed three-component direct Mannich reaction of enolizable ketones using TMG as the catalyst. The corresponding *N*-tosylated β-aminoketones were obtained in high yields and good to excellent *syn* diastereoselectivities. The development of an enantioselective version of this reaction is currently under way and will be reported in due course.

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Supplementary data

Supplementary data (detailed experimental procedures, characterization data of all new compounds, and copy of the NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.140.

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