

Highly Enantioselective Three-Component Direct Mannich Reactions of Unfunctionalized Ketones Catalyzed by Bifunctional Organocatalysts

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ABSTRACT



A highly stereoselective three-component direct Mannich reaction between aromatic aldehydes, *p*-toluenesulfonamide, and unfunctionalized ketones was achieved through an enolate mechanism for the first time with a bifunctional quinidine thiourea catalyst. The corresponding *N*-tosylated β-aminoketones were obtained in high yields and excellent diastereo- and enantioselectivities (up to >99:1 dr and >99% ee).

The Mannich reaction is a very powerful tool for constructing carbon–carbon bond 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

Since List reported the first example of a proline-catalyzed direct Mannich reaction in 2000,² organocatalyzed Mannich reactions have been undergoing vigorous development 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 alkaloids⁷ have been used as the catalysts in Mannich reactions, and high diastereoselectivities and/or enantioselectivities have been achieved in many cases.^{1b,3} Nonetheless, among those reported organocatalyzed direct Mannich reactions, catalysts

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(3) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P.; Rutjes, F. *Chem. Soc. Rev.* **2008**, *37*, 29. (d) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (e) Bhadury, P. S.; Song, B.-A. *Curr. Org. Chem.* **2010**, *14*, 1989. (f) Benohoud, M.; Hayashi, Y. In *Science of Synthesis, Asymmetric Organocatalysis*; List, B., Maruoka, K., Eds.; Georg Thieme Verlag: Stuttgart, 2012; Vol. 1, pp 73–134. (g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(4) For some leading examples, see: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Córdova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (d) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (e) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058. (f) Ibrahim, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (g) Sunden, H.; Ibrahim, I.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877. (h) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (i) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (j) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609.

(5) For some leading examples, see: (a) Uraguchi, M.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (c) Matsubara, M.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814. (d) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (e) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (f) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631.

that can perform the three-component direct Mannich reactions of unfunctionalized ketones or aldehydes are still very limited because many of the reported catalysts and/or reaction conditions are not compatible with the in situ generation of the imines.^{8,9} To our knowledge, with the exception of a chiral phosphoric acid reported by Gong and co-workers,^{9a} all of the other catalysts are mainly amine derivatives^{4,9b} that catalyze the reaction through the enamine mechanism.⁹

Recently, we demonstrated that Brønsted base catalysts are capable of inducing aldol reactions of unfunctionalized ketones.^{10a} The reaction works through the enolate mechanism¹¹ and is complementary to the amine-catalyzed aldol reactions in terms of the substrate scope.¹⁰ Because the reaction mechanisms of the Mannich and aldol reactions are very similar, we envisioned that Brønsted bases should be also good catalysts for the Mannich reaction of unfunctionalized ketones via the enolate mechanism. With this in mind, we recently realized a TMG-catalyzed high diastereoselective three-component direct Mannich reaction of unfunctionalized ketones.¹² Herein we report a bifunctional Brønsted base-catalyzed highly enantioselective and diastereoselective three-component direct Mannich reaction of unfunctionalized ketones. To our knowledge, although enolate-mediated organocatalyzed enantioselective

direct Mannich reactions of active methylene compounds are known,^{6,7} such a three-component direct Mannich reaction of unfunctionalized ketones has not been reported.^{9,11}

Using benzaldehyde (**1a**), *p*-toluenesulfonamide, and 1,2-diphenylethanone (**3a**) as the model substrates, we initially screened several chiral Brønsted bases (**5–12**, Figure 1) for their ability to effect the desired enolate-mediated three-component Mannich reactions. The results are summarized in Table 1.

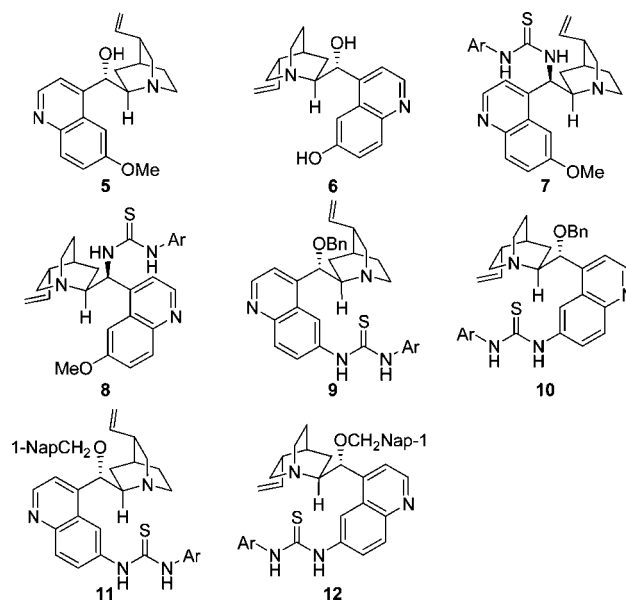


Figure 1. Catalysts screened for the Mannich reaction (Ar = 3,5-(CF₃)₂C₆H₃–; 1-Nap = 1-naphthyl).

(6) For some leading examples, see: (a) Uraguchi, M.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (c) Matsubara, M.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814. (d) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (e) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (f) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631.

(7) For some leading examples, see: (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (b) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606. (c) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B. J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878. (d) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (e) McCooney, S. H.; Cannon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (f) Zhang, H.; Chuan, Y.-M.; Li, Z.-Y.; Peng, Y.-G. *Adv. Synth. Catal.* **2009**, *351*, 2288. (g) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 2664.

(8) For examples of Lewis acid catalyzed three-component direct Mannich reactions of unmodified ketones and aldehydes, see: (a) Xu, L.-W.; Xia, C.-G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482. (b) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533. (c) Das, B.; Majhi, A.; Reddy, K. R.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *274*, 83. (d) Phukan, P.; Katakai, D.; Chakraborty, P. *Tetrahedron Lett.* **2006**, *47*, 5523. (e) Rafiee, E.; Eavani, S.; Nejad, F. K.; Joshaghani, M. *Tetrahedron* **2010**, *66*, 6858. (f) Kureshy, R. I.; Agrawal, S.; Saravanan, S.; Khan, N. H.; Shah, A. K.; Abdi, S. H. R.; Bajaj, H. C.; Suresh, E. *Tetrahedron Lett.* **2010**, *51*, 489.

(9) For examples of enol-mediated Mannich reactions of unmodified ketones, see: (a) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (b) Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6624.

(10) (a) Guo, Q.; Bhanushali, M.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 9460. (b) Guang, J.; Guo, Q.; Zhao, J. C.-G. *Org. Lett.* **2012**, *14*, 3174.

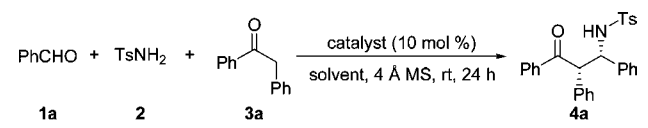
(11) For examples of enolate-mediated Mannich reactions of thioesters, see: (a) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 3376. (b) Utsumi, N.; Kitagaki, S.; Barbas, C. F., III. *Org. Lett.* **2008**, *10*, 3405. For examples of enolate-mediated Mannich reactions of sulfonylimidates, see: (c) Van Nguyen, H.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 5927. (d) Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804.

(12) Guo, Q.; Zhao, J. C.-G.; Arman, H. *Tetrahedron Lett.* **2012**, *53*, 4866.

With toluene as the solvent, the reaction catalyzed by quinidine (**5**) gave a poor yield (10%) and a low ee value (45%) of the desired **4a** (Table 1, entry 1). Similarly, poor results were obtained when cupreine (**6**) was used (Table 1, entry 2). In contrast, quinidine- and quinine-derived thioureas **7** and **8** led to much improved yields and moderate ee values (Table 1, entries 3 and 4). To our pleasure, when quinine- or quinidine-derived thioureas **9**, **10**, **11**, and **12** were applied,¹³ good yields and high diastereoselectivities as well as excellent enantioselectivities were obtained (Table 1, entries 5–8). Catalyst **9** was adopted for further optimizations (Table 1, entries 9–14) since it yields the highest product yield and ee value. Toluene (entry 5) was identified as the best solvent for this reaction since the other tested solvents all led to less satisfactory results. However, it was found that the ee value of **4a** may be improved to 96% when the reaction was carried out at 0 °C (entry 14).

Once the reaction conditions were optimized, the scope of this reaction was evaluated, and the results are collected in Table 2.

(13) Catalysts **9–12** were prepared according to the procedures reported in: (a) Marcelli, T.; van der Haas, R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (b) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418.

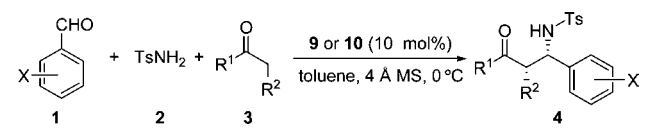
Table 1. Catalyst Screening and Condition Optimizations for the Base-Catalyzed Three-Component Direct Mannich Reaction^a


entry	catalyst	solvent	yield ^b (%)	dr ^c	ee ^d (%)
1	5	toluene	10	>99:1	45
2	6	toluene	trace		
3	7	toluene	44	>99:1	60
4	8	toluene	49	>99:1	78 ^e
5	9	toluene	96	>99:1	94
6	10	toluene	96	>99:1	90 ^e
7	11	toluene	78	>99:1	94
8	12	toluene	68	>99:1	92 ^e
9	9	benzene	96	>99:1	92
10	9	<i>o</i> -xylene	95	>99:1	92
11	9	CH ₂ Cl ₂	95	>99:1	86
12	9	Et ₂ O	87	>99:1	72
13	9	THF	60	>99:1	50
14 ^f	9	toluene	96	>99:1	96

^a Unless otherwise specified, all reactions were carried out at rt with benzaldehyde (**1a**, 0.20 mmol), toluenesulfonamide (**2**, 0.40 mmol), ketone **3a** (0.40 mmol), and the Lewis base catalyst (0.020 mmol, 10 mol %) in the presence of 4 Å MS (50.0 mg) in the indicated solvent (2 mL) for 24 h. ^b Yield of the isolated product after column chromatography. ^c Determined by ¹H NMR analysis of the crude reaction product. ^d Values of ee were determined by chiral HPLC analysis on a ChiralCel AD-H column. ^e The opposite enantiomer was obtained as the major product in this case. ^f The reaction was conducted at 0 °C for 48 h.

First, the aldehyde substrates were evaluated using 1,2-diphenylethanone (**3a**) and *p*-toluenesulfonamide (**2**) as the substrates. As the data in Table 2 show, benzaldehyde (**1a**) and benzaldehyde derivatives that bear either an electron-withdrawing or an electron-donating group (**1b–j**) all produce the desired Mannich products **4** in high yields (≥88%) and excellent ee values (93–97% ee) as a single diastereomer (>99:1 dr, entries 1–10). Next the ketone substrates were studied using benzaldehyde (**1a**) and *p*-toluenesulfonamide (**2**) as the imine precursors. Again, excellent results (>99:1 dr, 96–98% ee) were obtained for 1,2-diphenylethanone derivatives **3b**, **3c**, and **3d** (entries 11–13). The aliphatic 1-phenylbutan-2-one (**3e**) is slightly less reactive, and a lower yield (75%) of **4n** was obtained, but this product was obtained in over 99% ee (entry 14). Excellent results were also obtained for the aliphatic 1,3-diphenylpropan-2-one (**4o**, >99:1 dr, 96% ee, entry 15). Phenacyl *tert*-butyl carbonate (**3g**) was also evaluated as substrate in this reaction, and the corresponding Mannich product **4p** was obtained in 96% yield and >99% ee with a dr of 93:7 (entry 16). Similarly, when 4-bromobenzaldehyde (**1f**) was used with **3g**, the desired product **4q** was obtained in 96% yield and >99% ee with a dr of 92:8 (entry 17). The stereochemistry of the major enantiomer generated with catalyst **9** was determined to be (2*S*,3*S*)

(14) For details, see the Supporting Information.

Table 2. Three-Component Direct Mannich Reaction Catalyzed by Bifunctional Catalysts **9** or **10**^a


entry	X/R ¹ /R ²	1/3/4	time (h)	yield ^b (%)	ee ^c (%)
1	H/Ph/Ph	a/a/a	48	96	96
2	4-Me/Ph/Ph	b/a/b	40	95	96
3	4-MeO/Ph/Ph	c/a/c	48	88	96
4	4-F/Ph/Ph	d/a/d	36	96	95
5	4-Cl/Ph/Ph	e/a/e	24	95	94
6	4-Br/Ph/Ph	f/a/f	24	97	94
7	4-CN/Ph/Ph	g/a/g	40	97	97
8	4-NO ₂ /Ph/Ph	h/a/h	24	93	93
9	2-Br/Ph/Ph	i/a/i	48	96	95
10	3-Br/Ph/Ph	j/a/j	24	96	95
11	H/4-BrC ₆ H ₄ /Ph	a/b/k	30	95	98
12	H/4-ClC ₆ H ₄ /Ph	a/c/l	35	95	96
13	H/4-MeOC ₆ H ₄ /Ph	a/d/m	72	75	96
14	H/Et/Ph	a/e/n	96	75	>99
15	H/PhCH ₂ /Ph	a/f/o	24	95	96
16	H/Ph/OBoc	a/g/p	24	96 ^d	>99
17	4-Br/Ph/OBoc	f/g/q	40	96 ^e	>99
18 ^f	H/4-MeOC ₆ H ₄ /OBoc	a/h/r	48	95 ^e	>99

^a Unless otherwise indicated, all reactions were carried out at 0 °C with aldehyde **1** (0.20 mmol), *p*-toluenesulfonamide (**2**, 0.40 mmol), ketone **3** (0.40 mmol), catalyst **9** (0.020 mmol, 10 mol %), and 4 Å MS (50.0 mg) in toluene (2.0 mL). ^b Yield of the isolated product after column chromatography. Only a single diastereomer was detected by the ¹H NMR analysis of the crude reaction product in all cases (dr >99:1) except for entries 16–18. ^c Determined by HPLC analysis. ^d The dr of this reaction was 93:7. ^e The dr of this reaction was 92:8. ^f Catalyst **10** (10 mol %) was used, and the opposite enantiomer was obtained as the major product. ^g The dr of this reaction was 90:10.

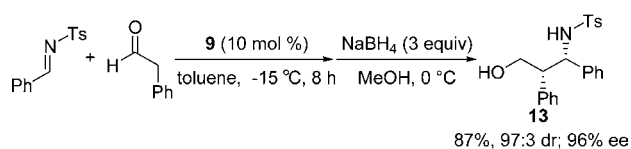
according to the X-ray crystallographic analysis of the reaction product **4k**.¹⁴

When an aldehyde was applied under these optimized conditions, no desired Mannich reaction product was obtained, probably due to the interference of the self-aldol reaction of the aldehyde. However, when phenylacetaldehyde was used with the prepared *N*-tosylimine, the desired Mannich product was obtained in a high yield. To facilitate the purification and ee value determination, the primary Mannich product was in situ reduced to the corresponding alcohol **13**, which was obtained in excellent yield, dr, and ee value (Scheme 1).

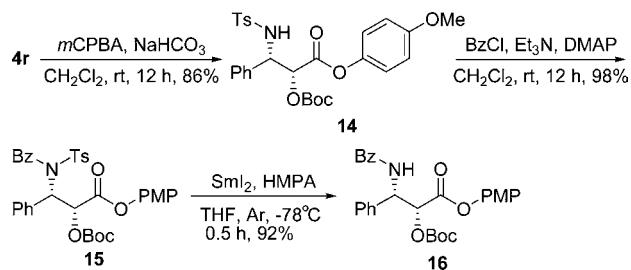
The *N*-tosyl-β-aminoketone products obtained in this reaction are very useful in organic synthesis. For example, when catalyst **10** was used under these optimized conditions, the reaction of **1a**, **2**, and **3h** led to the formation of (2*R*,3*R*)-**4r** with an ee value of >99% and a dr of 90:10 (Table 2, entry 18). This product may be oxidized by using *m*-CPBA to produce the corresponding *N*-tosyl-β-amino ester **14** (Scheme 2), which may be readily benzoylated to

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Scheme 1. Mannich Reaction between *N*-Tosylimine and Phenylacetaldehyde



Scheme 2. Synthesis of Protected Paclitaxel Side Chain



give compound **15**. After removal of the *N*-tosyl group, the *O*-Boc-protected *syn*-β-amino ester **16** was obtained in high yield (78% over three steps). Since the Boc¹⁵ and

(16) Watson, D. A.; Fan, X.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7096.

PMP¹⁶ groups are readily removable during synthesis, compound **16** may be regarded as a protected paclitaxel side chain and should be useful in the synthesis of paclitaxel (Scheme 2).

In summary, we have realized the first enantioselective enolate-mediated three-component direct Mannich reaction of unmodified ketones using bifunctional cinchona alkaloid thioureas as the base catalyst. The corresponding *N*-tosylated β-amino ketones were obtained in high yields, high enantioselectivities, and excellent *syn* diastereoselectivities. We also demonstrated that, with a preformed imine, aldehyde may also be used as the substrate in this reaction.

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Supporting Information Available. Full experimental procedures, compound characterization data, ORTEP drawings, and X-ray data of compound **4k** (CIF) and copies of NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.