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Asymmetric Mannich Reactions with in Situ Generation of Carbamate-Protected Imines by an Organic Catalyst

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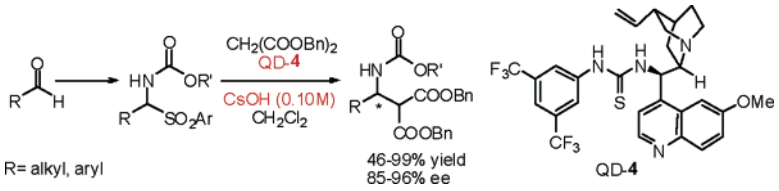
ABSTRACT

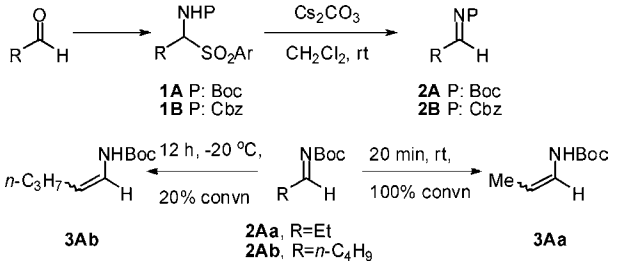


The instability of carbamate-protected alkyl imines has greatly hampered the development of catalytic asymmetric Mannich reactions suitable for the synthesis of optically active carbamate-protected chiral alkyl amines. A highly enantioselective Mannich reaction with in situ generation of carbamate-protected imines from stable α-amido sulfones catalyzed by an organic catalyst was developed. This reaction provides a concise and highly enantioselective route converting aromatic and aliphatic aldehydes into optically active aryl and alkyl *β*-amino acids.

Catalytic enantioselective Mannich reactions provide one of the most versatile and attractive approaches for the generation of optically active chiral amines.[1] While great strides have been made over the last several years with both chiral metal and organic catalysts,[2−4] only a few catalytic asymmetric Mannich reactions include both carbamate-protected aryl and alkyl imines as substrates.[2b,3b] As precursors to carbamate-protected chiral alkyl amines, carbamate-protected alkyl imines constitute a particularly important class of imine substrates. However, their instability renders it extremely challenging for their employment in catalytic asymmetric Mannich reactions. Specifically, spontaneous tautomerization of *N*-Boc alkyl imines, such as **2Aa** and **2Ab,** into the corresponding enamines readily occurs even at −20 °C (Scheme 1). Furthermore, to our knowledge, no procedure has been reported for the preparation of *N*-Cbz alkyl imines (**2B)** in pure form.

Palomo[5a] and the group of Herrera, Bernardi, and Ricci[5b] independently reported highly enantioselective aza-Henry reactions with in situ generation of carbamate-protected aryl and alkyl imines from α-amido sulfones **1A**[6] promoted by a chiral phase-transfer catalyst, thereby establishing asymmetric Mannich reactions tranforming directly the stable α-amido sulfones **1** into the corresponding aza-Henry (Mannich) adducts. Although chiral organic catalysts not based on PTC (phase transfer catalysis) have emerged as versatile catalysts for asymmetric Mannich reactions,[3] to our knowledge, the development of practical asymmetric Mannich reactions with in situ generation of carbamate-protected imines catalyzed by such chiral organic catalysts has not yet been reported.[7]

Scheme 1. Synthesis and Tautomerizaion of *N*-Carbamate Imines



(1) Reviews: (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348. (b) Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089. (c) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (d) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis Supplement I*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Chapter 29.5.

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In this paper, we describe an efficient, general, and practical asymmetric Mannich reaction with in situ generation of carbamate-protected imines **2** from α-amido sulfones **1** catalyzed by a bifunctional organic catalyst not based on PTC.

Recently, the 9-thiourea cinchona alkaloid **4** (Figure 1)[8] was identified independently by us[3b] and Dixon[3c] and co-workers as an efficient catalyst for enantioselective additions of malonates and β-ketoesters to *N*-Boc aryl imines.[3b] We also demonstrated that **4** affords high enantioselectivity for

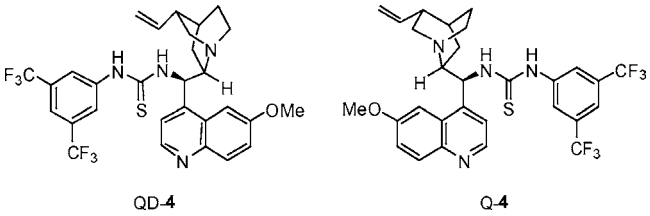
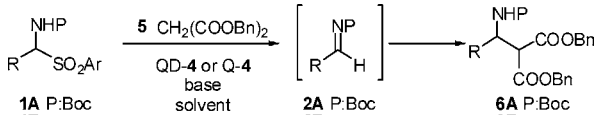


Figure 1. Structure of 9-thiourea cinchona alkaloid

the addition of malonates to *N*-Boc alkyl imines. Due to a background reaction, the Mannich reaction of *N*-Boc phenyl imine **2Ac** (R = Ph) and malonate **5** with 20 mol % of QD-**4** afforded the desired Mannich adduct **6Ac** in only 74% ee at room temperature. Employing a stoichiometric amount of QD-**4**, **6Ac** could be produced in 92% ee at room temperature. Alternatively, highly enantiomerically enriched **6Ac** (97% ee) was obtained by performing the reaction at −60 °C for 36 h with 20 mol % of QD-**4**. The reactions with the less active and unstable *N*-Boc alkyl imines, such as **2Aa** and **2Ab**, afforded the Mannich adduct in useful optical purity and yield only when they were performed with a stoichiometric loading of QD-**4** at 0 °C. Therefore, the synthetic potential of the **4**-catalyzed Mannich reaction is severely diminished by reaction conditions involving a high catalyst loading, the low reaction temperature and the preparation and handling of the unstable carbamate-protected alkyl imines.

The successfully implementation of a **4**-catalyzed Mannich reaction with in situ generation of carbamate-protected imines **2** from the stable α-amido sulfones **1** could overcome these drawbacks (Scheme 2). It would eliminate the separate

Scheme 2. Mannich Reaction of Malonate **5** with in Situ Generated *N*-Carbamate Imines **2**



preparation of the carbamate-protected imines, thereby avoiding the need to handle the highly unstable carbamate-protected alkyl imines **2** (R = alkyl). Moreover, as the Mannich reactions with one equivalent of catalyst **4** were shown to convert both *N*-Boc aryl and alkyl imines **2A** into the corresponding Mannich adducts **6** in high ee at room temperature, by maintaining a higher concentration of catalyst **4** relative to *N*-carbamate imines **2** via the gradual and in situ generation of **2**, a room-temperature Mannich reaction with catalyst **4** in low loading might still furnish the Mannich adduct **6** in high optical purity.

Accordingly, with *N*-Boc amido sulfone **1Ac** and dibenzyl malonate **5**, the **4**-catalyzed Mannich reaction in CH_2Cl_2 with in situ generation of *N*-Boc phenyl imines **2Ac** was examined

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(5) (a) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (b) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975.

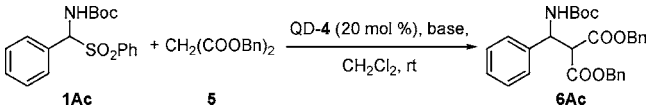
(6) For a comprehnsive review of using α-amido sulfones as stable precursors of *N*-acylimino derivatives, see: Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.

(7) For asymmetric additions of organozinc reagents with in situ generation of *N*-diphenylphosphinoyl imines catalyzed by chiral copper catalysts, see: (a) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405. (b) Côté, A.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 10864.

(8) Catalyst **4**, accessible in two steps from quinine or quinidine, was reported independently by: (a) Li, B.; Jiang, L.; Liu, M.; Chen, Y.; Ding, L.; Wu, Y. *Synlett* **2005**, *4*, 603. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org Lett.* **2005**, *7*, 1967. For asymmetric reactions catalyzed by **4**, see: (c) Wang, J.; Li, H.; Zu, L. Z.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (d) Wang, Y.-Q.; Song, J.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (e) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sagarzabu, V. *Tetrahedron* **2006**, *62*, 375. (f) Mccooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (g) Ye, J.; Dixon, D. J.; Hynes, P. *Chem. Commun.* **2005**, *35*, 4481.

in the presence of various amines and inorganic bases. As summarized in Table 1, especially promising results were

Table 1. Screening of Bases for Asymmetric Mannich Reactions with in Situ Generation of Carbamate-Protected Imines Catalyzed by QD-**4**[a]



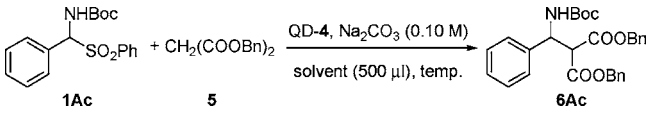
1Ac 5 6Ac

entry	base	time/h	conversion[b]/%	ee[c]/%
1	Proton Sponge	3	14	35
2	2,6-lutidine	3	12	47
3	pempidine	3	38	17
4	K_2CO_3 (solid)	3	33	81
5	Cs_2CO_3 (solid)	3	79	50
6	K_2CO_3 (0.10 M)	3	92	91
7	Cs_2CO_3 (0.10 M)	3	92	90
8	Na_2CO_3 (0.10 M)	3	90	95
9	NaOH (0.10 M)	3	100	83
10	KOH (0.10 M)	3	88	83
11	CsOH (0.10 M)	3	80	82

[a] Unless noted, reactions were run with **1Ac** (0.10 mmol) and dibenzyl malonate **5** (0.15 mmol) in methylene chloride (500 μL) with base (1.0 equiv) in the prescence of QD-**4** (20 mol %) at room temperature. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC.

obtained with several inorganic bases applied in the reaction as either a solid or an aqueous solution (entries 4−11, Table 1). In particular, at room temperature and promoted by 20 mol % of QD-**4**, the biphasic reaction employing a 0.1 M aqueous solution of Na_2CO_3 furnished the desired Mannich adduct **6Ac** in 95% ee. In comparison, with the same loading of QD-**4**, a room-temperature Mannich reaction utilizing the preformed *N*-Boc phenyl imine **2Ac** afforded **6Ac** in only 74% ee. Further optimization studies established that a one-pot transformation of **1Ac** to **6Ac** in 89% yield and 96% ee could be achieved with only 5.0 mol % of QD-**4** at 0 °C (entry 10, Table 2).

Table 2. Reaction Condition Optimization[a]



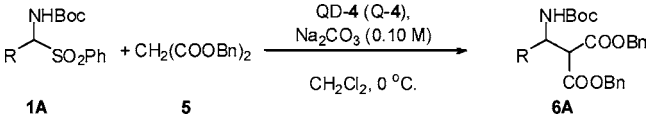
1Ac 5 6Ac

entry	catalyst loading/ %	solvent	*T*/°C	time/ h	conversion[b]/ %	ee[c]/ %
1	20	CH_2Cl_2	rt	3	90	95
2	20	acetone	rt	3	100	74
3	20	THF	rt	3	100	20
4	20	$CHCl_3$	rt	3	82	91
5	20	EtOAc	rt	3	100	76
6	20	toluene	rt	3	47	89
7	10	CH_2Cl_2	rt	5	100	68
8	10	CH_2Cl_2	0	10	100	89
9[d]	10	CH_2Cl_2	0	10	100	96
10[d]	5	CH_2Cl_2	0	20	100	96

[a] Unless noted, reactions were run with **1Ac** (0.10 mmol) and dibenzyl malonate **5** (0.15 mmol) in the solvent (500 μL) with base (1.0 equiv) in the prescence of QD-**4** (20 mol %) at room temperature. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC. [d] Reaction was carried out in methylene chloride (200 μL).

Importantly, the **4**-catalyzed Mannich reactions starting with *N*-Boc α-amido sulfones **1A**, prepared from a broad range of aromatic and heteroaromatic aldehydes, furnished the corresponding Mannich adducts **6** in similarly high ee and yield (Table 3). It is noteworthy that neither the position nor the electronic property of the substituent on the aromatic ring was found to have a significant impact on the enantioselectivity of the reaction.

Table 3. Reactions of Malonate **5** with α-Amido Sulfones Prepared from Aromatic and Heteroaromatic Aldehydes[a]



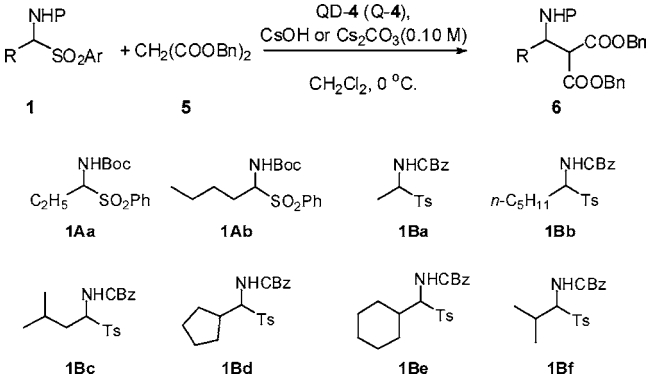
1A 5 6A

entry	1A	R-	yield[b]/%	ee[c]/%
1	**1Ac**	Ph-	89 (92)	96 (92)
2	**1Ad**	2-MePh-	96 (91)	95 (90)
3	**1Ae**	3-MePh-	88 (91[d])	95 (88[d])
4	**1Af**	4-MePh-	97 (88)	95 (89)
5	**1Ag**	4-FPh-	99 (95)	94 (90)
6	**1Ah**	4-OMePh	90 (87)	95 (90)
7	**1Ai**	2-furyl	90 (91)	96 (92)
8	**1Aj**	2-thienyl	91 (87[d])	94 (85[d])

[a] Unless noted, reactions were run with **1A** (0.525 mmol) and dibenzyl malonate **5** (0.50 mmol) in methylene chloride (1.0 mL) with sodium carbonate aqueous solution (0.10 M, 6.0 mL) in the prescence of QD-**4** (5 mol %) at 0 °C for 20 h. The results in parentheses were obtained with Q-**4** (5 mol %) to give the opposite enantiomer. [b] Isolated yield. [c] Determined by HPLC. [d] Reaction was run with Q-**4** (10 mol %).

We next turned our attention to the **4**-catalyzed Mannich reactions with in situ generation of the unstable carbamate-protected alkyl imines **2** (R = alkyl). Since the rates of both the in situ generation of the carbamate-protected alkyl imines and their consumption in the subsequent **4**-catalyzed Mannich reactions differ significantly from those of carbamate-protected aryl imines, optimization studies were necessary for the identification of the optimal base for reactions starting with α-amido sulfones derived from aliphatic aldehydes. For reactions with *N*-Boc α-amido sulfones **1Aa** and **1Ab**, the best results were obtained with aqueous Cs_2CO_3 (0.1 M) solution. With 10 mol % of QD-**4** at room temperature, the one-pot transformations of the α-amido sulfones **1Aa** and **1Ab** into the corresponding Mannich adducts **6Aa**−**6Ab** were accomplished in 88 and 90% ee, respectively (entries 1 and 2, Table 4). However, the optically active Mannich adducts **6Aa-6Ab** were obtained in 44−45% yield, since a significant amount of the in situ generated *N*-Boc alkyl imines was found to undergo spontaneous tautomerization. Interestingly, we found that, with 0.1 M aqueous CsOH, direct transformations of *N*-Cbz α-amido sulfones **1Ba**−**1Bf**,

Table 4. Reactions of Malonate **5** with α-Amido Sulfones Prepared from Aliphatic Aldehydes



entry	**1**	base	time/h	yield[b]/%	ee[c]/%
1[d,e]	**1Aa**	Cs_2CO_3	24	45	88
2[d,e]	**1Ab**	Cs_2CO_3	24	44	90
3	**1Ba**	CsOH	20 (72[f])	64 (70)	91 (93[f])
4	**1Bb**	CsOH	20 (20[d])	78[9] (75)	93 (91[d])
5	**1Bc**	CsOH	20 (72[d,f])	88 (80)	92 (92[d,f])
6	**1Bd**	CsOH	20 (96[f])	70 (67)	85 (82[f])
7[d]	**1Be**	Cs_2CO_3	96 (96)	73 (81)	90 (87)
8[d]	**1Bf**	Cs_2CO_3	96 (96)	67 (70)	85 (82)

[a] Unless noted, reactions were run with **1** (0.40 mmol) and dibenzyl malonate **5** (0.60 mmol) in methylene chloride (0.80 mL) with CsOH (0.10 M, 4.0 mL) or Cs_2CO_3 (0.10 M, 4.8 mL) in the prescence of QD-**4** (10 mol %) at 0 °C. The results in parentheses were obtained with Q-**4** (10 mol %) to give the opposite enantiomer. [b] Isolated yields. [c] Determined by HPLC. [d] Reaction was carried out in methylene chloride (0.40 mL). [e] Reaction was carried out at room temperature. [f] Reaction was carried out in Cs_2CO_3 (1.2 equiv) for 72−96 h.

prepared from aliphatic aldehydes of a significant degree of steric variations, into the corresponding Mannich adducts **6Ba**−**6Bf** could be achieved in good to excellent ee and 64−88% yield (entries 3−8, Table 4). These results represent a significant expansion of the scope of the **4**-catalyzed Mannich reaction of malonates with carbamate-protected imines.

In conclusion, we demonstrated that the thiourea cinchona alkaloid **4** is compatible with strongly basic aqueous solution. This allowed us to develop a highly enantioselective and practical catalytic Mannich reaction to directly convert the readily accessible and stable *N*-carbamate amido sulfones **1** into optically active Mannich adducts **6**. To our knowledge, the current study provides the first highly enantioselective Mannich reaction with in situ generation of carbamate-protected imines promoted by a chiral organic catalyst not based on PTC.[10] This suggests that the strategy of in situ generation of carbamate-protected imines could be explored with other base-compatible chiral organic catalysts for the promotions of various enantioselective additions to imines.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Under identical reaction conditions, the reaction of **5** with the corresponding *N*-Boc-1-aminohexyl-*p*-tolyl sulfone afford the desired Mannch adduct in 55% yield (vs 78% yield for the reaction with **1Bb**).

(10) While this manuscript was in preparation, a chiral phase-transfer catalyst-promoted asymmetric Mannich reaction of malonates with in situ generated of *N*-carbamate imines from α-amido sulfones **1** was reported: Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sagarzabu, V. *Adv. Synth. Catal.* **2006**, *348*, 2043.