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Phase-Transfer-Catalyzed Enantioselective Mannich Reaction of Malonates with α-Amido Sulfones

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Abstract: The highly enantioselective reaction between *in situ* generated, Cbz-protected azomethines and malonates in the presence of 150 mol% of potassium carbonate (50% w/w) and 1 mol% of quinine-derived quaternary ammonium bromides as phase-transfer organocatalysts has been developed. This study reports a novel approach for the asymmetric Mannich-type reaction and a wide range of azomethines, including those derived from enolizable aldehydes, is tolerated by the present system. The adducts, obtained in excellent yields with *ee* up to 98%, are suitable precursors of optically pure β-amino acids.

Keywords: α-amido sulfones; asymmetric synthesis; Mannich reaction; nucleophilic addition; phase-transfer catalysis

The Mannich reaction is a fundamental transformation in synthetic organic chemistry.[1] Due to the importance of the products in their enantioenriched form, tremendous efforts have been made in the last years towards the development of an asymmetric version of this reaction.[2] After several chiral auxiliary and reagent-based approaches,[3] the first reports of catalytic asymmetric Mannich reactions involved the use of chiral Lewis acids for the activation of the imine moiety in combination with preformed enolates, such as silylenol ethers.[4] Shortly after, a few direct Mannich reactions were reported, wherein the chiral Lewis acids were also able to trigger the enolization process, thus allowing the use of unmodified carbonyl donors as nucleophiles.[5] More recently several organocatalytic protocols have been developed, especially using as catalysts secondary amines,[6] tertiary nitrogen bases derived from *Cinchona* alkaloids,[7] or chiral Brønsted acids.[8] However, the use of phase-transfer catalysis (PTC) as a tool for the catalytic asymmetric Mannich reaction is still relatively undeveloped,[9] although this approach appears highly attractive considering the mild reaction conditions and the operational simplicity typical of PTC.[10] Furthermore, we and others have recently demonstrated that by exploiting PTC it is possible to generate *N*-carbamoyl (Boc and Cbz) imines *in situ* from the corresponding α-amido sulfones, activating at the same time a nucleophile, namely nitromethane, for the asymmetric addition.[11] This strategy allows the use of enolizable *N*-carbamoylimines derived from aliphatic aldehydes, whose isolation has only seldom been reported as they are unstable and moisture-sensitive and readily tautomerize to the more stable ene-carbamate form.[12] On this basis we decided to explore the direct Mannich reaction of malonates with *N*-carbamoylimines generated *in situ* from α-amido sulfones,[13] using inexpensive and readily available quaternary ammonium salts derived from *Cinchona* alkaloids as phase-transfer catalysts.[14] The products of this transformation are direct precursors of optically active β-amino acids bearing synthetically useful and readily removable *N*-carbamoyl protecting groups such as Boc and Cbz.[15]

The initial screening of several chiral quaternary ammonium salts in the PTC Mannich reaction between dimethyl malonate and α-amido sulfone **1a**, was informative in that only quinine derivatives exhibited a significant though modest enantioselectivity (see Supporting Information). Additional observations gave further insight into the requirements of the catalyst, indicating the crucial importance of the hydroxy function since the catalyst, whose alcohol group has been protected in the form of allyl ether, did not show any significant asymmetric induction. Toluene and potassium carbonate were determined to be the best solvent and base, respectively, and running the reaction under dilute conditions (0.05 M) afforded better enantioselectivities, probably due to a polarity change of the reaction medium.[16] To examine the

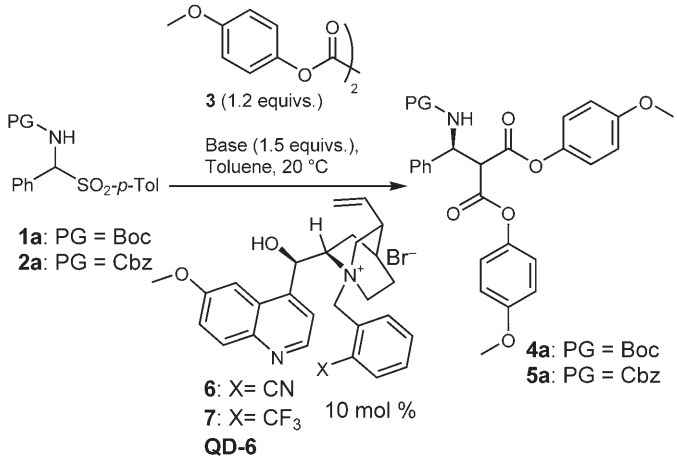
role of the electronic and steric factors present in the quinuclidinic nitrogen substituent, various *N*-benzylquininium derivatives were prepared from quinine and benzyl bromides bearing various functional groups at the *ortho*- and *para*-positions. A significant difference in asymmetric induction was noticed between *para*- and *ortho*-substituted derivatives and notably among the latter were those with electron-withdrawing functional groups, like CN and CF_3, which gave higher enantioselectivity. In general, the size of the ester moiety of the malonates did not affect to a substantial extent the chemical and stereochemical outcomes. Conversely aryl malonates and especially the *p*-methoxyphenyl derivative **3** afforded an increase in stereoselectivity up to 76% *ee* (see Supporting Information).

These observations encouraged us to pursue a study to find the optimized conditions. As shown in Table 1, variously *N*-protected α-amido sulfones were screened using catalysts **6** and **7**, and although excellent conversion yields and fairly good enantioselectivities were uniformly attained, the Cbz protection provided a further beneficial effect (compare entries 1, 3 and entries 2, 4).

Next we attempted the Mannich reaction using 50% (w/w) aqueous K_2CO_3 (entries 5–10). Under these conditions the rate was markedly enhanced and gratifyingly the enantioselectivity was substantially improved with respect to the anhydrous conditions[17] when using the NH-Cbz protected α-amido sulfone **2a** (compare entries 3, 7 and 4, 8 in Table 1), though the enantioinduction in the case of the NH-Boc protected α-amido sulfone **1a** remained unaffected (compare entries 1, 5 and 2, 6). Bearing in mind the possibility to synthesize the opposite enantiomer, we performed the reaction with *N*-(*o*-cyanobenzyl)quinidinium bromide as catalyst and the resulting product was obtained in high yield but with slightly lower enantioselectivity (entry 9, Table 1).[18]

Finally, an enantioselectivity/temperature profile documented that the optimal enantiocontrol was available by lowering the temperature: cooling the reaction had a remarkably positive effect as the enantioselectivity rose to 98% (entry 9) at −20 °C. It is

Table 1. Optimization of the catalyst, base and protecting group at nitrogen in the reaction of *p*-anisyl malonate **3** with α-amido *p*-tolyl sulfones **1a** and **2a**.[a]



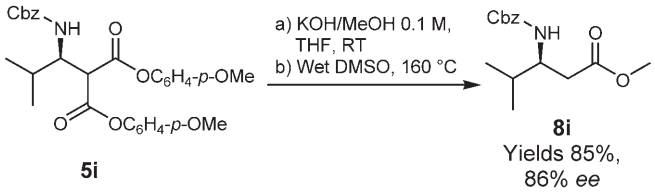
Entry	Catalyst	Base	Protecting Group	Product	Time [h]	Conversion [%][b]	*ee* [%][c]
1	**6**	K_2CO_3 (s)	Boc	**4a**	21	60	76
2	**7**			**4a**		70	67
3	**6**		Cbz	**5a**		85	84
4	**7**			**5a**		80	83
5	**6**	K_2CO_3 (aq)[d]	Boc	**4a**	5	>95	72
6	**7**			**4a**		>95	64
7	**6**		Cbz	**5a**		>95	93
8	**7**			**5a**		>95	93
9	**QD-6**			**5a**	7	>95	87[e]
10	**6**			**5a**	48	>95	98[f]

[a] Reactions conducted on a 0.1 mmol scale.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] Aqueous K_2CO_3 (50% w/w) was used.
[e] The reaction performed with catalyst **QD-6** gave the opposite enantiomer of **5a**
[f] Reaction conducted at −20 °C with 1 mol% catalyst.

noteworthy that this superior level of asymmetric induction and efficiency was maintained even with a catalyst loading reduced to 1 mol% (entry 10). The optimized conditions outlined in Table 1 were selected for exploring the substrate scope of this Mannich reaction (Table 2).

As listed in Table 2 the adducts were generally obtained in very good chemical yields using **6** as the catalyst (1 mol%). With the aryl-substituted α-amido sulfones **1a**, **b** and **2a–e** the reaction proceeded smoothly with excellent enantioselectivity irrespective of the electronic nature of the aromatic ring (entries 1–7). Most remarkably also *alkyl* α-amido sulfones **1c** and **2f–j**, precursors of enolizable azomethines, gave the corresponding adducts **4c** and **5f–j** with enantiomeric excesses in the 76–96% range (entries 8–13).

Finally, a decarboxylation/transesterification sequence (Scheme 1) delineated the synthetic utility of this catalytic process to construct β-amino acid moieties bearing synthetically useful protecting groups at nitrogen such as Cbz, allowing at the same time the determination of the absolute configuration of the adducts.



Scheme 1. Determination of absolute configuration by transesterification/decarboxylation sequence.

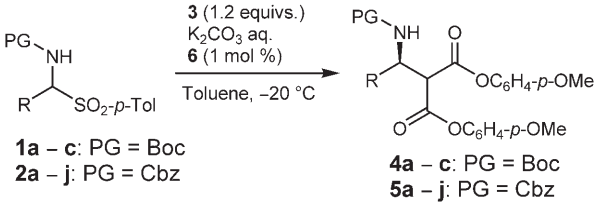
In summary, a novel organocatalytic, highly enantioselective Mannich reaction is described which holds distinct practical advantages and requires only a low catalytic loading. With respect to the direct catalytic, asymmetric reaction,[4–9] our approach displays a considerably broader scope[19] since it also gives a straightforward access to optically active β-alkyl *N*-carbamoyl β-amino acids, starting from readily available and stable α-amido sulfones.

Experimental Section

Preparation of Catalyst 6

A mixture of (−)-quinine (648 mg, 2 mmol) and *o*-cyanobenzyl bromide (431 mg, 2.2 mmol) in a mixture of THF (1.8 mL), ethanol (1.5 mL), and chloroform (0.6 mL), was stirred at 100 °C for 3 h. After cooling to room temperature, the crude material was evaporated under reduced pressure and the product was purified by chromatography on silica gel (CH_2Cl_2/MeOH 90:10) to afford **6** as a pale yellow solid; yield: 925 mg (89%).

Table 2. Scope of the organocatalyzed Mannich reaction of malonate **3** with azomethines generated *in situ* from α-amido sulfones **1** and **2** under PTC.[a]



Entry	α-Amido Sulfone	R	Protecting Group	Product	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	Boc	**4a**	92	90
2	**2a**	Ph	Cbz	**5a**	81	98
3	**1b**	2-Naphthyl	Boc	**4b**	90	84
4	**2b**	1-Naphthyl	Cbz	**5b**	94	95
5	**2c**	*p*-MeO-C_6H_4	Cbz	**5c**	85	98
6	**2d**	*o*-Br-C_6H_4	Cbz	**5d**	95	98
7	**2e**	*p*-Cl-C_6H_4	Cbz	**5e**	90	96
8	**2f**	Me	Cbz	**5f**	93	86
9	**2g**	Et	Cbz	**5g**	90	86
10	**2h**	$PhCH_2CH_2$	Cbz	**5h**	90	96
11	**2i**	*i*-Pr	Cbz	**5i**	80	86[d]
12	**1c**	Cy	Boc	**4c**	50	76
13	**2j**	Cy	Cbz	**5j**	80	95

[a] Reactions conducted on a 0.1 mmol scale at −20 °C for 48 h, using **1** or **2**:**3**:**6**:aqueous K_2CO_3 in a 1:1.2:0.01:1.5 molar ratio.
[b] Isolated yields after column chromatography.
[c] Determined by chiral HPLC analysis.
[d] Determined by chemical correlation with compound **8i**.

General Procedure for the Catalytic Enantioselective Reaction of Malonate 3 with α-Amido Sulfones 1a–c, 2a–j

A solution of *N*-(*o*-cyanobenzyl)quininium bromide **6** in toluene (2 mL, 5.0×10^{-4} M, 1.0 μmol) was added to a test tube containing a mixture of the α-amido sulfone **1a–c**, **2a–j** (0.1 mmol) and malonic acid bis-(4-methoxyphenyl) ester **3** (38 mg, 0.12 mmol). After the resulting solution had been cooled to −20 °C, 50% aqueous K_2CO_3 (w/w, 28 μL, 0.15 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 48 h, the reaction product was directly purified by chromatography on silica gel (CH_2Cl_2).

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[18] Usually the catalyst derived from the *Cinchona* alkaloids that has the opposite absolute configuration at C-9 and C-10 furnishes an inverse catalysis, giving the opposed enantiomer. For more recent example see refs.[7,][11b]

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