Highly diastereoselective and enantioselective direct organocatalytic *anti*-selective Mannich reactions employing *N*-tosylimines†

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Organocatalytic direct *anti*-selective Mannich reactions of *O*-TBS-hydroxyacetone with various *N*-tosylimines derived from aromatic aldehydes in the presence of L-threonine-derived catalyst afforded 1,2-amino alcohols in good yields and with enantioselectivities of 99% in almost all cases.

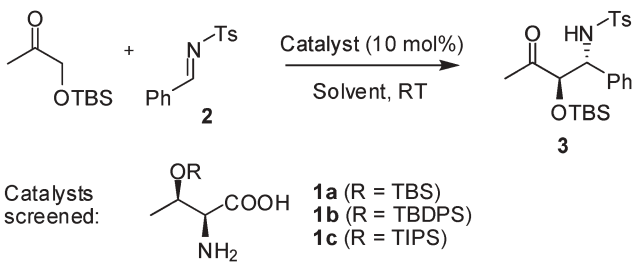
The asymmetric Mannich reaction[1] is one of the most powerful carbon–carbon bond-forming reactions for the construction of nitrogen-containing compounds. The utilization of this reaction allows for the preparation of optically enriched β-amino carbonyl compounds and their derivatives.[2] The direct Mannich reactions employing ketones and preformed imines were recently reported by Trost,[3] Shibasaki[4] and Jorgensen.[5] Because of the synthetic versatility of amino carbonyl compounds, it is of great interest to generate Mannich products with either *syn*- or *anti*-selectivity. The *syn*-Mannich reactions are quite well-established, and have been accomplished by using Cu-,[5a,6] In-,[4b] La-,[7] Zr-[8] or Zn-derived[3a,9] organometallic catalysts. With the recent exciting development of organocatalysis,[10] a number of organocatalysts have also been found to catalyze *syn*-selective Mannich reactions. These catalysts include Brønsted acids,[11] cinchona alkaloids,[12] phase-transfer catalysts,[13] and proline and its derivatives.[14] On the other hand, *anti*-selective Mannich reactions are more challenging.[3b,4a,15] We recently disclosed primary amino acid-promoted direct asymmetric aldol reactions and Mannich reactions in the presence of water.[16] Herein, we wish to report highly enantioselective and *anti*-selective Mannich reactions between an unmodified hydroxy ketone and *N*-tosylimines that can be promoted by a threonine-derived organocatalyst.

Hydroxyacetone is a very useful donor, and its Mannich reaction could yield synthetically versatile 1,2-amino alcohols. In our earlier report,[16c] we described the successful development of direct asymmetric three-component *anti*-Mannich reactions employing an aldehyde, 4-methoxyaniline (*p*-anisidine), and *O*-benzyl hydroxyacetone with threonine-derived **1b** as the organocatalyst. To further develop more efficient *anti*-Mannich reactions, we reasoned that the combination of properly designed preformed imine and threonine-based catalyst might be a feasible approach. *N*-Tosylimines[5a,17] have been widely used, and might be good substrates in our reactions. The two oxygen atoms from sulfone functionality are expected to form hydrogen bonds with hydrogen bond donors in the threonine-derived catalysts. If the above interactions are optimized to yield a well-defined transition state, high enantioselectivity could be achieved.

We performed our initial screenings with *O*-TBS-hydroxyacetone and *N*-tosylimine, in the presence of various siloxy containing organocatalysts (Table 1). To our delight, *anti*-Mannich products with excellent enantiomeric excess were obtained when the reactions were carried out in the presence of water (entries 1–3). A solvent screening (entries 4–11) was then performed to identify the best reaction conditions. Among the various organic solvents tested, toluene was found to be the best solvent. When the reaction was carried out in toluene in the presence of catalyst **1a**, the desired product was obtained in good yield with 27 : 1 *anti* to *syn* selectivity and with 99% ee (entry 6).

Organocatalyst **1a** proved to be remarkably effective (Table 2). The reactions between *O*-TBS-hydroxyacetone and various *N*-tosylimines afforded the *anti*-selective Mannich products in

Table 1 Screening of the asymmetric Mannich reactions between *O*-TBS-hydroxyacetone and *N*-tosylimine[a]



Entry	Catalyst	Solvent	Time/h	Yield[b] (%)	*anti* : *syn*[c]	ee[d] (%)
1	**1a**	H_2O	36	51	10 : 1	99
2	**1b**	H_2O	42	38	6 : 1	98
3	**1c**	H_2O	42	45	11 : 1	99
4	**1a**	DMSO	42	—[e]	—	—
5	**1a**	toluene	42	67	21 : 1	99
6	**1a**	toluene	37	76	27 : 1	99
7	**1a**	THF	37	43	4 : 1	91
8	**1a**	CH_2Cl_2	37	54	13 : 1	98
9	**1a**	DMF	37	<5	—	—
10	**1a**	dioxane	37	20	4 : 1	92
11	**1a**	$CHCl_3$	37	54	14 : 1	99

[a] The reactions were performed with *O*-TBS-hydroxyacetone (either at 0.5 mmol (entries 1–5) or 0.11 mmol (entries 6–11)), *N*-tosylimine (0.1 mmol) and catalyst (0.01 mmol) in solvent (0.2 ml) at room temperature; [b] Isolated yield. [c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis. [e] Not determined.

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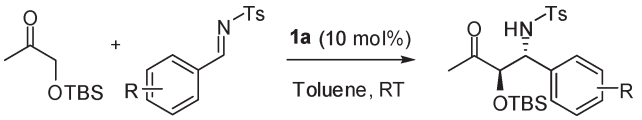
† Electronic supplementary information (ESI) available: Experimental, characterisation of products and Cartesian coordinates of the optimized (HF/3-21G) *anti*-transition state. See DOI: 10.1039/b706793c

Table 2 Organocatalyst **1a**-promoted direct Mannich reactions with various *N*-tosylimines derived from aromatic aldehydes[a]



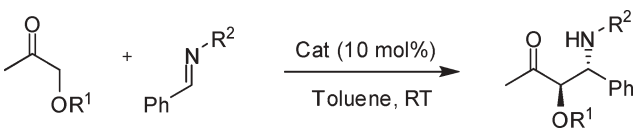
Entry	Product	Time/h	Yield[b] (%)	*anti* : *syn*[c]	ee[d] (%)
1	**4** (R = *p*-Br)	40	70	23 : 1	99
2	**5** (R = *p*-Cl)	28	76	23 : 1	99
3	**6** (R = *p*-F)	40	79	12 : 1	99
4	**7** (R = *o*-CF_3)	24	76	34 : 1	99
5	**8** (R = *p*-CH_3)	44	87	20 : 1	99
6	**9** (R = *o*-CH_3)	45	75	102 : 1	99
7	**10** (R = *p*-OCH_3)	44	67	18 : 1	99
8	**11** (R = 1-naphthyl)	44	61	70 : 1	99
9	**12** (R = 2-naphthyl)	44	75	40 : 1	99
10	**13** (R = *p*-CN)	63	74	40 : 1	99
11	**14** (R = *p*-NO_2)	72	87	17 : 1	97

[a] The reactions were performed with *O*-TBS-hydroxyacetone (0.11 mmol), *N*-tosylimine (0.1 mmol) and catalyst (0.01 mmol) in toluene (0.2 ml) at room temperature. [b] Isolated yield. [c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis.

good yields with excellent diastereoselectivity and enantioselectivity. The method is applicable to virtually any aromatic aldehydes, regardless the electronic nature of the aryl aldehyde. An extension to Mannich reactions involving aliphatic aldehydes was unsuccessful. The Mannich reactions employing *N*-tosylimines derived from aliphatic aldehydes lead to complex product mixtures.

The absolute configuration of the Mannich product was determined to be (3*R*, 4*R*)-**3**. The reaction mechanism is unclear at the moment. We have carried out some preliminary experiments to explore the importance of various groups in this highly enantioselective *anti*-Mannich reaction (Table 3). Sulfonamide functionality appears to be important, and methanesulfonamide

Table 3 Sulfonamide functionality is important in promoting reactions with high stereoselectivities[a]



Entry	R^1	R^2	Cat	Time/h	Yield[b] (%)	*anti* : *syn*[c]	ee[d] (%)
1	TBS	Ts	L-Trp	44	<10	—[e]	—
2	TBS	Ts	L-Thr	72	—	—	—
3	TBS	PMP	**1a**	25	80	1 : 3	51
4	TBS	Bn	**1a**	20	93	1 : 1	17
5	TBS	Boc	**1a**	48	<20	—	—
6	H	Ts	**1a**	40	<20	—	—
7	TBS	SO_2Me	**1a**	48	75	14 : 1	98
8	Bn	Ts	**1a**	40	47	20 : 1	98
9	TBS	Ts	*O*-*t*Bu-Thr	44	<30	50 : 1	99

[a] The reactions were performed with hydroxyacetone (0.11 mmol), imine (0.1 mmol) and catalyst (0.01 mmol) in toluene (0.2 ml) at room temperature. [b] Isolated yield. [c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee value of the *anti*-isomer was determined by chiral HPLC analysis. [e] Not determined.

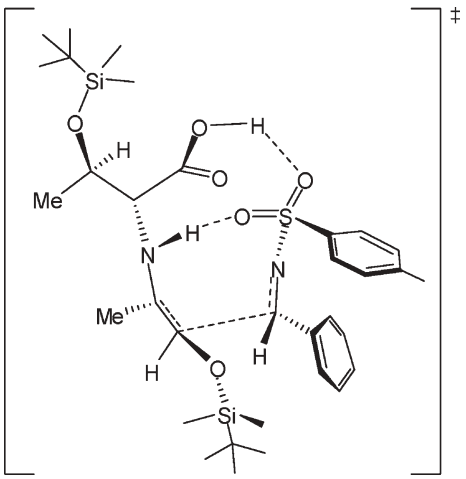


Fig. 1 Calculated transition state for the *anti*- Mannich product formation: the important role of the sulfone group in stabilizing the transition state is reflected in the hydrogen bonds (dotted lines).

also gave excellent results (entry 7). However, reactions employing preformed PMP-, Bn- or Boc-[18] imines only afforded low enantioselectivities (entries 3–5). While natural tryptophan or threonine was completely ineffective (entries 1 and 2), threonine derivative with sterically hindered group at the hydroxy position was effective (entry 9). Preliminary calculations† have supported the key experimental findings, and the calculated transition state for the major *anti*- product is depicted in Fig. 1. Both sulfone oxygen atoms are involved in hydrogen bondings in the calculated transition state for the major stereoisomer, and the formation of *Z*-enamine is facilitated by hydrogen bonding. Furthermore, our calculations suggest that the enantioselectivity is independent of the electronic nature of the tosyl aromatic group. The predominant isomer can be formed *via* the attack of *N*-tosylimine by the enamine from the *Si* face.

In summary, we discovered that employment of *N*-tosylimines can result in remarkably efficient enantioselective *anti*-Mannich reactions. The involvement of both oxygen atoms of sulfone in hydrogen bonding network to stablize the transition state is unprecedented, and may have implications for the design of novel organocatalytic systems. Computational studies to fully understand the observed high stereoselectivities and mechanistic investigations are in progress in our laboratory, and will be reported in due course.

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