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Asymmetric Mannich Reaction of Imines Derived from Aliphatic and Aromatic Aldehydes Catalyzed by Diarylprolinol Silyl Ether

Tatsuya Urushima, Hayato Ishikawa, and Yujiro Hayashi*^[a]

The Mannich reaction is one of the most useful reactions for the synthesis of nitrogen-containing molecules.^[1,2] Most Mannich reactions are restricted to imines derived from aromatic aldehydes or ethyl glyoxylate, which do not possess a hydrogen atom at the α position of the formyl group. The catalytic asymmetric cross Mannich reaction of imines derived from alkyl aldehydes with α -hydrogen atoms has been regarded as a challenging reaction, because of its isomerization to the corresponding enamines in spite of the recent successful examples.^[3]

Recently, organocatalysts have been applied to the asymmetric, catalytic Mannich reaction with a great success.^[2] As for the organocatalyst-mediated cross Mannich reaction of unmodified aldehyde as a Mannich donor and imines derived from alkyl aldehydes with α -hydrogen atoms as a Mannich acceptor, there are only three reports, with only four examples as far as we know.^[3d,f,h] Thus, even in the field of organocatalysis, there is not a general method of the catalytic asymmetric cross Mannich reaction of unmodified aldehyde and imines derived from alkyl aldehydes with α -hydrogen atoms, even though the generated Mannich product is synthetically important.

Reactions that utilize water as the reaction medium have attracted considerable interest in recent years. Water is considered an environmentally benign medium and exhibits distinct reactivity compared with organic solvents.^[4] Independent discoveries by our group^[5] and the group of Barbas^[6] have led to the development of many enantioselective aldol reactions in aqueous medium. We therefore considered it desirable to develop the Mannich reaction of imines derived from aliphatic aldehydes in the presence of water; the successful realization of which is now described in this communication.

First, we investigated the Mannich reaction of N-Boc imine derived from aliphatic aldehydes, but without success.^[7] We then examined the N-Ts (tosyl) imine because it

[a]	T. Urushima, Dr. H. Ishikawa, Prof. Dr. Y. Hayashi
	Department of Industrial Chemistry
	Faculty of Engineering
	Tokyo University of Science
	Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
	Fax: (+81)3-5261-4631
	E-mail: hayashi@ci.kagu.tus.ac.jp
	Homepage: Home page: http://www.ci.kagu.tus.ac.jp/lab/org-chem1/

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would be more reactive than N-Boc imine, due to the electron withdrawing substituent. Recently, Palomo and coworkers reported the successful Mannich reaction of imines derived from aromatic aldehyde catalyzed by 2-(1-hexyl-1trimethylsiloxy-heptyl)-4-hydroxypyrrolidine, in which the 4hydroxy group is essential for the excellent selectivity.^[8] The N-Ts imine of 3-phenylpropanal was chosen as a model, and the domino reaction of the desulfonylative preparation of N-Ts imine^[9] and the enantioselective Mannich reaction were investigated (Table 1). In the experimental procedure, the organocatalyst and NaHCO3 were added to a mixture of sulfonamidosulfone 5, propanal, and solvent at 0°C and the reaction mixture was stirred. First, trifluoromethyl-substituted diarylprolinol silyl ether $\mathbf{1}^{[10]}$ (Scheme 1) was used as an organocatalyst and the effect of the solvent was investigated. The results are summarized in Table 1.



Scheme 1. Organocatalysts examined in this study.

The domino reaction was found to proceed in CH₂Cl₂, THF, and 1,4-dioxane at room temperature to afford the Mannich product with excellent enantioselectivity. The reaction was also found to proceed in the presence of water, without organic solvent. It should be noted that the N-Ts imine can be successfully used in the presence of water, affording the product in good yield (60%, Table 1, entry 5). When the reaction was performed at 10°C, the yield was increased to 76%, and good diastereoselectivity and excellent enantioselectivity were obtained (Table 1, entry 7). Similar excellent results were obtained when 1,4-dioxane was used at 10°C for a longer reaction time (48 h, Table 1, entry 8). Thus, both water and 1,4-dioxane are suitable solvents. Next, the other organocatalysts 2-4 (Scheme 1) were examined in the presence of water (Table 1, entries 9-11). Diphenylprolinol silyl ether 2 was ineffective and no reaction occurred in the presence of proline (3). The surfactant-proline conjugated catalyst 4, which is a suitable catalyst in the cross aldol reaction in the presence of water,^[5b] was also ineffective.

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Table 1. Effect of solvent and catalyst in the domino desulfonylation/ $Mannich\,reaction^{[a]}$

Pł	HN ^{-Ts} SO	2Ph + H	atalyst (10 NaHCC solvent temperatu 20 h	mol%) 03 t, Ph ure,	HN ^{-Ts}	ю
Entry	Catalyst	Solvent	Т [°С]	Yield [%] ^[b]	anti/syn ^[c]	ее [%] ^[d]
1	1	CH_2Cl_2	0	38	76:24	97
2	1	THF	0	52	95:5	98
3	1	1,4-dioxane	0	62	92:8	98
4	1	H_2O	0	41	93:7	96
5	1	brine	0	60	89:11	96
6	1	brine/CH ₂ Cl ₂	0	49	>95:5	97
7	1	brine	10	76	84:16	94
8 ^[e]	1	1,4-dioxane	10	79	88:12	96
9	2	brine	10	20	n.d.	n.d.
10	3	brine	10	< 5	n.d.	n.d.
11	4	brine	10	10	n.d.	n.d.

[a] Reactions were performed employing α -amidosulfone **5** (0.2 mmol), aldehyde (1.0 mmol), catalyst (0.02 mmol), NaHCO₃ (0.6 mmol), and solvent (0.4 mL) for 20 h. n.d. = not determined. [b] Yield of isolated product. [c] Diastereomer ratio was determined by ¹H NMR spectroscopy after reduction with NaBH₄. [d] Enantiomeric excess of the *anti* isomer was determined by chiral HPLC analysis after reduction with NaBH₄. [e] The reaction time is 48 h.

Next, the reaction was performed using an isolated imine (Scheme 2). Although a good yield and excellent enantioselectivity were obtained when the reaction was carried out in 1,4-dioxane, the product was obtained in only low yield in the presence of water. In the presence of water, low yield was obtained in the reaction of isolated imine, whereas a





good result was obtained in the domino reaction of the desulfonylative preparation of imine and the Mannich reaction. The reason for the successful domino reaction in the presence of water is the gradual generation of imine, which reacts readily with the enamine. Having determined the best reaction conditions, the generality of the domino reaction was investigated using brine and 1,4-dioxane as a solvent (Table 2). The reaction is generally fast in the presence of water and is complete within 20 h because it proceeds under condensed conditions, whereas the reaction in 1,4-dioxane takes 48 h. Excellent enantioselectivity was obtained in both solvents.

As for the imines derived from aliphatic aldehydes, not only 3-phenylpropanal but also isovaleraldehyde, isobutyraldehyde, cyclohexanecarbaldehyde, phenylacetaldehyde, and benzyloxyacetaldehyde were suitable aldehydes for reaction with propanal to afford the Mannich products in good yield with good *anti* selectivity and excellent enantioselectivity (Table 2, entries 1–6). In the reaction of butanal, the yield in the presence of water was not satisfactory; the aldehyde acts not only as a nucleophile but also as a solvent to dissolve the imine, and the dissolving ability of butanal is insufficient for this purpose. The reaction nonetheless proceeds efficiently in 1,4-dioxane to afford the Mannich product in good yield with excellent enantioselectivity (Table 2, entry 7).

The reaction proceeds not only with *N*-Ts imines but also with *N*-Ns (nosyl)^[11] imines. In the reaction of *N*-Ns imines, when the reaction was performed in the presence of water, the desired product was obtained in low yield because *N*-Ns imine is more reactive than *N*-Ts imine and hydrolysis of the imine takes place readily. However, the reaction proceeds well in 1,4-dioxane to afford the Ns-protected Mannich product in good yield with excellent diastereo- and enantioselectivities (Table 2, entries 8 and 9).

The reaction was found to be applicable to imines derived from aromatic aldehydes. Whereas the precursor of the *N*-Ts imine *para*-toluenesulfonamido sulfone, derived from aromatic aldehyde, is rather unstable, the corresponding *N*-Ts imine is more stable and could be isolated. Thus, the isolated *N*-Ts imine was used as starting material. The reaction of propanal and *N*-Ts-imine derived from benzaldehyde in the presence of 10 mol% of catalyst **1** proceeded well to afford the Mannich product in good yield with good diastereo- and enantioselectivities (Table 2, entry 10). The products were isolated as the β -amino aldehyde and also as the γ -amino alcohol by reduction with NaBH₄ (Table 2, entry 11). Imines, not only from benzaldehyde, but also from aromatic aldehydes with electron-rich and electron-deficient substituents were used as suitable substrates (Table 2, entries 12–14).

The absolute configuration was determined after conversion of the Mannich product of propanal and the *N*-Ts imine derived from isovaleraldehyde (Table 2, entry 2) to the amino alcohol by comparing the optical rotation with that reported in the literature.^[12]

In summary, we have developed an asymmetric Mannich reaction catalyzed by diarylprolinol silyl ether to afford the *anti*-Mannich product with excellent enantioselectivity. There are several noteworthy features associated with this reaction: 1) This is one of the rare examples of the successful catalytic asymmetric cross Mannich reaction of unmodified aldehyde as a Mannich donor and an imine derived from an aliphatic aldehyde with α -hydrogen atoms as a Mannich acceptor. 2) The present reaction can be successfully applied not only to imines derived from aliphatic aldehydes. 3) Both *N*-Ts imines and *N*-Ns imines can be used. 4) In the reaction of imines derived from aliphatic solvent) was used as a reaction medium; therefore this offers green reaction conditions.

Previously, only β -alkyloxycarbonyl or β -aryl-substituted β -amino aldehydes could be synthesized by the organocatalyst-mediated Mannich reaction of unmodified aldehyde as

Table 2.	The asymmetric	Mannich	reaction	catalyzed	by	organocatalyst	1[a
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		HN ^{_Ts}	O 1 (10 mol%) NaHCO ₃		HŅ ^{∠Ts}		
	I	R SO ₂ Ph		rine or 1,4-dioxane l0 °C, 20 h or 48 h	RCHO		
Entry	Product	Yield [%] ^[b]	brine anti/syn ^{[c}	^{:]} ee [%] ^[d]	Yield [%] ^[b]	1,4-dioxane anti/syn ^[c]	ee [%] ^[d]
1	Ph CH	10 76	84:16	94	79	88:12	96
2		61	89:11	97	71	>95:5	99
3		67	91:9	98	71	88:12	98
4	ну то	72	>95:5	95	71	>95:5	94
5	Ph CHO	68	>95:5	95	35	86:14	96
6	HN ^{-Ts} BnO CH	D 77	77:23	96	53	78:22	90
7	Ph Et	HO 28	90:10	98	77	93:7	99
8 ^[e]		н 52	>95:5	97	69	>95:5	98
9 ^[e]	HN ^{/Ns} ÖBn	н 9	>95:5	95	74	>95:5	98
10 ^[f]	HN ^{-Ts} CHO	D 88	72:28	92	87	78:22	99
11 ^[e,f]	HN ^{Ts}	H quant	78:22	92	88	78:22	98
12 ^[e,f]	MeO	тs Он 65	71:29	84	quant	77:23	98
13 ^[e,f]	HN ^{-Ts}	^он 73	74:26	96	86	77:23	98
14 ^[e,f]	CF3	s ^_он 84	72:28	86	84	76:24	99

[a] Unless otherwise shown, reactions were performed employing α -amidosulfone (0.2 mmol), aldehyde (1.0 mmol), catalyst 1 (0.02 mmol), NaHCO₃ (0.6 mmol) at 10 °C, and brine (0.4 mL) for 20 h or 1,4-dioxane (0.4 mL) for 48 h. [b] Yield of isolated product. [c] Diastereomer ratio was determined by ¹H NMR spectroscopy after reduction with NaBH₄. [d] Enantiomeric excess of the anti isomer, as determined by chiral HPLC analysis. [e] Mannich product was isolated after reduction with NaBH4. [f] Isolated imine was employed as a starting material, see the Supporting Information for details.

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a Mannich donor. The method described herein widens the reaction scope to include the β alkyl-substituted β-amino aldehydes, which are synthetically useful chiral building blocks and hence this reaction is considered very useful in synthetic organic chemistry.

Keywords: asymmetric synthesis · domino reactions · enantioselectivity · Mannich reaction · organocatalysis

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