N-Methylprolinol Catalysed Asymmetric Baylis–Hillman Reaction

Palakodety Radha Krishna,* V. Kannan, P. V. Narasimha Reddy

D-206/B, Discovery Laboratory, Organic Chemistry Division – III, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax: (+91)-40-2716-0387, (+91)-40-2716-0757, e-mail: prkgenius@iict.res.in

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Abstract: *N*-methylprolinol is used as a chiral base catalyst for the Baylis–Hillman reaction to obtain the adducts in good yields with moderate to good enantioselectivities in 1,4-dioxane:water (1:1, v/v) under ambient conditions.

Keywords: activated alkenes; aromatic aldehydes; asymmetric Baylis-Hillman reaction; chiral base catalyst; 1,4-dioxane:water; *N*-methylprolinol

Recently, small organic molecules have effectively been utilized as catalysts for a variety of organic transformations, at times with the enantioselectivities matching those of enzymes. Some of the advantages of such catalysts over enzymes are high yields and generality to many substrates. Proline[1] is the simplest "enzyme" that catalyses asymmetric aldol, Mannich and Michael reactions. Likewise, chiral amino alcohols derived from proline also catalyse Michael addition reactions,[2] besides enantioselective addition reactions of dialkylzinc,[3] alkyllithium and dialkylmagnesium[4] to aldehydes.

The Baylis–Hillman reaction[5a–d] provides versatile molecules containing various functional groups with a newly created stereogenic centre and the asymmetric version[6] of this reaction has attracted much attention in recent years. The use of chiral substituted DABCOs[7] (high pressure) and chiral pyrrolizidine[8] (normal pressure) afforded the Baylis–Hillman adducts with 11–72% ee. Hatakeyama[9a, b] has developed chiral amine catalysts, 4-(3-ethyl-4-oxa-1-azatricyclo[4.4.0.0]dec-5-yl)quinolin-6-ol (**QD-4**) and β-isocupreidine (**β-ICD**) to achieve high enantioselectivity in Baylis–Hillman reactions (91–99% ee). However, the utility (**QD-4**) was limited to 1,1,1,3,3,3-hexafluoroisopropyl acrylate. Later on, Shi[10a, b] et al. utilized the catalysts **QD-4** and chiral phosphine for the aza-Baylis–Hillman reaction to obtain moderate to good enantioselectivities (7–92% ee). They also performed the Baylis–Hillman reaction using polymer-supported[10c] bases to obtain products in good yields. Recently, a chiral BINOL[11] derived Brønsted acid was used as a catalyst for the Baylis–Hillman reaction between cyclohexenone and aldehyde to achieve high enantioselectivities (67–96%). However, there still remains a need for developing newer chiral bases that are universally applicable to all types of aldehydes and alkenes in the Baylis–Hillman reaction to obtain good selectivity. In continuation of our work on the Baylis–Hillman reaction,[12a–e] we now describe the use of *N*-methylprolinol (**1**) as a chiral base catalyst to obtain adducts in good yields with moderate to good enantioselectivities.

Since the free hydroxy group of **QD-4**[9] played an important role for high enantioselectivities in the Baylis–Hillman reaction, *N*-methylprolinol[3] (**1**) and diphenyl-(1-methylpyrrolidin-2-yl)methanol (DPMPM)[3] (**2**) were screened as they have pendant hydroxy groups, as chiral base catalysts for the study. To assess the feasibility of using **1** and **2** in the Baylis–Hillman reaction, initially a reaction was tried between *p*-nitrobenzaldehyde (**3**) and ethyl acrylate (**9**) in THF at room temperature. Indeed, the catalyst **1** afforded the desired product **3a** in 57% yield after 36 h, whereas the catalyst **2** failed to give any product. Subsequent studies on change of solvents to optimise yield and selectivity established 1,4-dioxane:water (1:1) as the better solvent (Table 1). Since **1** promoted Baylis–Hillman reaction afforded **3a** in good yield in 1,4-dioxane:water (1:1, v/v) with only 22% ee at room temperature, it was decided to carry out the same reaction at 0 °C and indeed a moderate enantioselectivity (52% ee) was obtained for **3a**. However, the same reaction when conducted at −20 °C in DMF was sluggish with little improvement in the stereoselectivity. Hence, for further study, dioxane:water was chosen as the standard solvent system.

This methodology was then extended to other aldehydes such as 2-nitrobenzaldehyde (**4**), phenylacetylenic aldehyde (**5**), 4-chlorobenzaldehyde (**6**) and 4-bromobenzaldehyde (**7**) to afford the corresponding adducts **4a**, **5a**, **6a** and **7a** in good yield with low to moderate enantioselectivities (15–52% ee, Table 2). To demon-

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Table 1. Baylis-Hillman reaction of **3** with **9** catalysed by **1** in different solvents.

Entry	Solvent	Time [h]	Temperature [°C]	Yield [%][a]	ee [%][b]
1	THF	36	25	57	15
2	DMF	24	25	64	12
3	DMSO	20	25	69	10
4	Dioxane : water	12	25	82	22
5	MeCN	24	25	66	15
6	DMF	60	−20	28	56
7	Dioxane:water	15	0	87	52
8	Dioxane:water	20	−10	84	64[c]

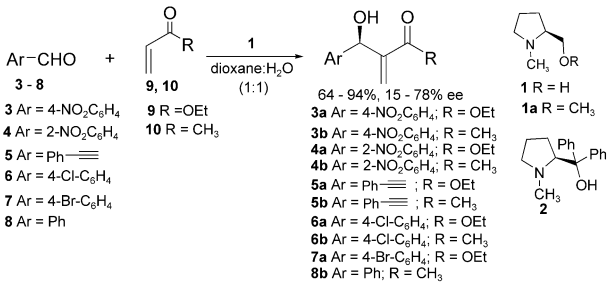
[a] Yields of isolated products.
[b] Determined by comparison of $[\alpha]_D$ values.[12a]
[c] In the presence of ethylene glycol.

strate the versatility of this catalyst, the Baylis–Hillman reaction of aldehydes with methyl vinyl ketone (MVK; **10**) was also carried out under the same set of reaction conditions to obtain **3b**, **4b**, **5b**, **6b** and **8b** in good yields with similar enantioselectivities (Table 2). When the reaction between **3** and **9** was conducted at −10 °C using ethylene glycol as an anti-freezing agent, the ee of the adduct **3a** slightly increased from 52 to 64% (entry 8, Table 1). The *N*-methyprolinol catalysed reaction between cyclohexanecarbaldehyde and MVK was reported earlier[13] under high pressure (10–11 kbar) with 11% ee. Catalyst **1** in CH_2Cl_2 was found to be ineffective under normal atmospheric pressure for the same reaction. Thus, the modified reaction conditions reported herein facilitated the reaction under ambient conditions. Aliphatic aldehydes such as hexanecarbaldehyde and heptanecarbaldehyde did not undergo the Baylis–Hillman reaction with ethyl acrylate under the present reaction conditions or in alternate solvents.[12e] It is pertinent to mention that when a combination of catalysts (**1**:DABCO, 1:0.1**)** was used in order to facilitate the Baylis–Hillman reaction between hexanecarbaldehyde and ethyl acrylate in sulpholane as solvent at room temperature, the reaction resulted in the adduct (52%) albeit with no selectivity.

Having successfully utilised *N*-methylprolinol (**1**) as a chiral base for the Baylis–Hillman reaction, we next aimed at the determination of enantiomeric purity and absolute configuration at the newly created stereogenic centre. The ee of the product was determined by HPLC analysis using a chiral OD column and the absolute configuration was ascertained by comparing the sign of specific rotation values of known compounds with those of products. For instance, the $[\alpha]_D$ value[10a] for the pure *R* isomer of **3a** is +16.5. Since the $[\alpha]_D$ of the compound **3a** in the present study bears the same sign, the absolute stereochemistry of major isomer of **3a** could be assigned as *R*. Likewise, the absolute stereochemistry of major isomer of **3b** was assigned as *R* based on the comparable sign of $[\alpha]_D$ with that of reported (*R*)-**3b**.[7] The absolute configuration of major isomers in all other compounds was assigned as *R* by analogy.

The plausible mechanism is outlined in Figure 1. The Michael addition of **1** to **9** results in enolate **A** which, upon nucleophilic attack on the aldehyde, furnishes two possible intermediates **B** and **C**. Intermediate **B** is more stabilised than **C** due to the favourable formation of intramolecular hydrogen bonding because the OH group and oxy anion are in the same plane. On the other hand, in the intermediate **C**, the groups which are stabilised by hydrogen bonding are in opposite planes. Thus the more favourable intermediate **B** undergoes elimination to produce *R*-**3a** as major product with simultaneous regeneration of catalyst.

Furthermore, to prove that the pendent OH group in *N*-methylprolinol (**1**) has played a major role both in catalysing and inducing the chirality in the Baylis–Hillman reaction, 1-methyl-2-methoxymethylpyrrolinne (**1a**)



Scheme 1.

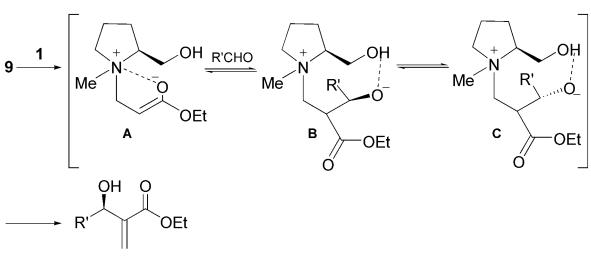


Figure 1. Proposed reaction mechanism.

Table 2. *N*-Methylprolinol catalysed asymmetric Baylis–Hillman reaction between aromatic aldehydes and activated alkenes at 0 °C.

Entry	Aldehyde	Activated Alkene	Time [h]	Yield [%][a, b]	ee [%][c]	Configuration
1	**3**	**9**	15	**3a**, 87	52	*R*[d]
2	**3**	**10**	8	**3b**, 94	46	*R*[d]
3	**4**	**9**	15	**4a**, 79	38	*R*
4	**4**	**10**	10	**4b**, 93	64	*R*
5	**5**	**9**	15	**5a**, 87	45	*R*
6	**5**	**10**	12	**5b**, 92	22	*R*
7	**6**	**9**	24	**6a**, 83	33	*R*
8	**6**	**10**	15	**6b**, 92	20	*R*
9	**7**	**9**	32	**7a**, 64	15	*R*
10	**8**	**10**	40	**8b**, 80	78	*R*

[a] Yields of isolated products.
[b] See Supporting Information for experimental procedure and spectral data.
[c] Determined by HPLC analysis (chiral OD column; flow rate: 1 ml/min, 15% isopropyl alcohol in *n*-hexane).
[d] Determined by comparison of $[\alpha]_D$ values.[7,12a]

was synthesised[14] and the Baylis–Hillman reaction of *p*-nitrobenzaldehyde with ethyl acrylate was conducted in the presence of **1a** (100 mol %) as a Lewis base in dioxane:water (1:1) at room temperature. However, it was found that there was no reaction after 72 h at room temperature or even when the catalyst loading was increased to 1.5 equivalents. Thus, this result conclusively proves that the formation of intramolecular hydrogen bonding between OH and oxyanion (intermediate **B**, Figure 1) not only facilitates the reaction and but also dictates the enantioselectivity.

In conclusion, we have successfully introduced the concept of the catalytic use of the small organic molecule, *N*-methylprolinol, to promote the asymmetric Baylis–Hillman reaction between an aromatic aldehyde and an activated alkene in 1,4-dioxane:water at 0 °C under normal atmospheric pressure to afford the corresponding products in good yields with moderate to good enantioselectivities. The absolute configuration of the products was assigned as *R* based on a correlation with known compounds or by analogy. The asymmetric induction could be partially enhanced when the reaction was conducted at −10 °C in the presence of ethylene glycol. Correspondingly, the (*S*)-Baylis–Hillman adducts could be obtained by using *N*-methylprolinol derived from commercially available (*R*)-proline, thus providing scope for the facile generation of both the enantiomers.

Experimental Section

General Procedure

To a cold (0 °C) solution of aldehyde (1 mmol) in 1,4-dioxane-water (1:1, v/v) were added **1** (0.5 mmol) and activated alkene (3 mmol) and the mixture was stirred for 8–40 h at the same temperature. After completion of the reaction (by TLC), the reaction mixture was partitioned with diethyl ether (2 × 50 mL) and water (1 × 60 mL). The organic phase was washed with brine (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane: EtOAc, 9:1–8.5:1.5) to afford products **3a**, **b**, **4a**, **b**, **5a**, **b**, **6a**, **b**, **7a** and **8b** in good yields (64–94%).

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References and Notes

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