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Asymmetric Baylis-Hillman Reaction between Chiral Activated Alkenes and Aromatic Aldehydes in Me_3N/H_2O/Solvent Medium

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Abstract: Chiral activated alkene, L-menthyl acrylate and (+)-N-α-phenylethyl acrylamide, induced asymmetric Baylis-Hillman reaction of aromatic aldehydes was realized at 25°C for 7 days in Me_3N/H_2O/solvent homogeneous medium. The corresponding Baylis-Hillman adducts were obtained in good chemical yield with moderate to excellent diastereoselectivity (up to 99% de).

Keywords: Chiral activated alkene, asymmetric Baylis-Hillman reaction, aromatic aldehyde, diastereoselectivity.

The Baylis-Hillman reaction has drawn much attention of the organic chemists and become one of the most challenging research areas in modern organic chemistry[1]. This tertiary amine (or phosphine) catalyzed coupling reaction involves the creation of a new chiral center accompanied with the formation of new carbon-carbon bond. Thus there exist rich possibilities for realizing asymmetric transformation through the introduction of a chiral source into any of the three components (activated alkenes[2,3], electrophile[4] and catalysts[5]) of the Baylis-Hillman reaction. The most reported chiral activated alkenes were chiral acrylate esters[2] and acrylamides[3]. Usually, the reaction took place with slow reaction rate. Several days, even weeks were required for completion. Moreover, in most cases low diastereoselectivity was obtained. Actually, the major problem associated with this reaction is its slow reaction rate. Numerous methods have been evaluated to accelerate the reaction. For example, some progress has been made for the application of aqueous medium into the Baylis-Hillman reaction[6].

Recently, we found that addition of low-carbon alcohols or other polar solvents to the reaction system to transform the heterogeneous mixture of aqueous trimethylamine and the substrates into a clear homogeneous solution and the reaction rate could be accelerated drammatically[6d]. Based on this finding, we applied this new homogeneous medium to realize the asymmetric Baylis-Hillman reaction between activated alkenes and aromatic aldehydes.

According to the literature method[7], the reaction of acrylic chloride with L-menthol in the presence of triethylamine in THF led to L-menthyl acrylate **1**. Similarly, the

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coupling of (+)-α-phenylethylamine with acrylic chloride resulted in (+)-N-α-phenylethyl acrylamide **2**.

First of all, a common substrate, 2, 4-dichlorobenzaldehyde was employed to study the effect of polar solvent on the Baylis-Hillman reaction of **1** and aromatic aldehydes. After evaluating a number of aprotic solvents, it was fount that 1, 4-dioxane was the best polar solvent in terms of both the chemical yield and the diastereoselectivity.

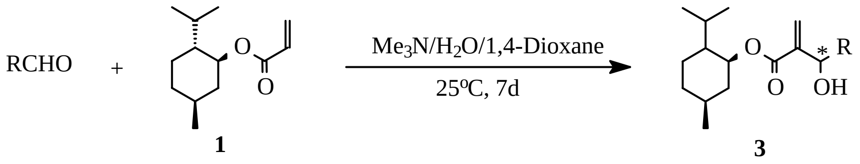
Secondly, by comparison of the reaction carried out at different temperature (0°C, 25°C, 40°C and 60°C, respectively), it was found that the reaction temperature had little influence on the Baylis-Hillman reaction under our conditions. So we chose room temperature as the convenient reaction temperature.

Moreover, we conducted the reaction with a 1:1, 1:2, and 1:3 molar ratio of 3-nitrobenzaldehyde to **1**. The other conditions were the same. The diastereomeric excess value was slightly influenced by this variation. Whereas the product yield was improved remarkably with the increase of the molar ratio (48%, 61%, and 82%, respectively). Hence, the reaction was carried out with 1:3 molar ratio of aldehyde to the activated alkene.

Different aromatic aldehydes were employed to couple with **1** under the aforementioned optimal reaction conditions. The experimental results were listed in **Table 1**.

As shown in **Table 1**, the nature of the aldehyde was found to be an essential factor to the reaction. Better yield was obtained for the aldehyde substituted with strong electron withdrawing group(s), such as nitro, fluoro, trifluoromethyl *etc.* on the benzene ring. While benzaldehyde, *p*-methylbenzaldehyde and aliphatic aldehydes, such as isobutyraldehyde, isovaleraldehyde, failed to produce desired products.

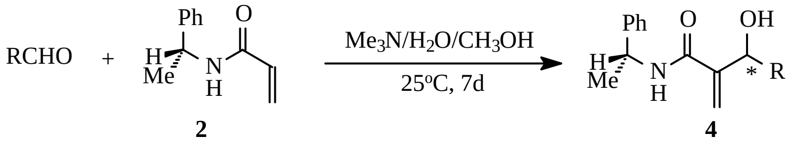
Table 1 Data of adducts **3** prepared from the reaction of aromatic aldehydes with **1**



Product **3**	R	m.p.°C	Yield%[i]	de%[ii]
a	$4\text{-}O_2NC_6H_4$	Viscous liquid	88	83
b	$3\text{-}O_2NC_6H_4$	Viscous liquid	82	99
c	$2,4\text{-}(O_2N)_2C_6H_3$	Viscous liquid	79	78
d	$4\text{-}F_3CC_6H_4$	Viscous liquid	91	67
e	$4\text{-}FC_6H_4$	99-101	72	95
f	$2,4\text{-}Cl_2C_6H_3$	Viscous liquid	86	39
g	$3\text{-}ClC_6H_4$	Viscous liquid	70	98
h	$4\text{-}HOC_6H_4$	87-88	57	71
i	5-Me-2-furan	Viscous liquid	59	12

i. Isolated yield based on aldehyde; ii. De value was determined by HPLC with silica column (250×4.6, dp 5 μm), petroleum ether/2-propanol (95:5) as the eluent.

Table 2 Data of **4** prepared from the reaction between aromatic aldehydes and **2**



Product **4**	R	m.p.°C	Yield%^{i}	de%^{ii}
a	4-$O_2NC_6H_4$	135-137	47	94
b	3-$O_2NC_6H_4$	118-119	54	97

i. Isolated yield based on aldehyde; ii. De value was determined by HPLC.

Since no methanolysis phenomenon was observed upon the treatment of chiral acrylamide **2** with methanol, it is feasible to conduct the asymmetric Baylis-Hillman reaction of **2** with aromatic aldehydes in Me_3N/H_2O/methanol system. The experimental results were listed in the **Table 2**.

As shown in **Table 2**, compared with **1** the chiral acrylamide **2** exhibited much lower reactivity. Only 3-nitrobenzaldehyde and 4-nitrobenzaldehyde could be reacted with **2**, but with rather lower yield (54% and 47%, respectively) in Me_3N/H_2O/methanol system. The other aromatic aldehydes failed to form the Baylis-Hillman adduct under these conditions. However, it was gratifying that both **4a** and **4b** had an excellent diastereoselectivity (97% de and 94% de, respectively).

In conclusion, the asymmetric Baylis-Hillman reaction of two activated alkenes, L-menthyl acrylate and (+)-N-α-phenylethyl acrylamide, with aromatic aldehydes was realized in Me_3N/H_2O homogeneous medium. The corresponding Baylis-Hillman adducts were obtained in good chemical yield with moderate to excellent diastereoselectivity. Compared with other tertiary amine catalytic systems, this medium demonstrated a significant rate acceleration effect on the Baylis-Hillman reaction. Dramatic rate acceleration was observed not only for achiral activated alkenes[6d] but also for chiral alkenes.

Acknowledgments

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References and Notes

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8. The data of ^{1}H NMR and elemental analysis of the prepared compounds are available in the editorial office of CCL.

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