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Asymmetric Baylis-Hillman Reactions Using Chiral 2,3-Disubstituted 1,4-Diazabicyclo[2.2.2]octanes Catalysts under High Pressure Conditions

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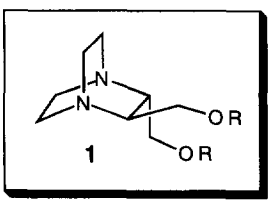
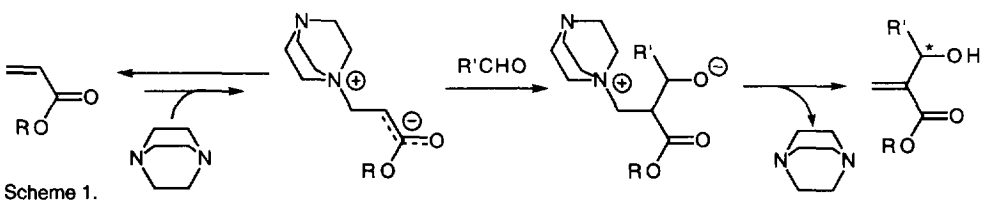
Abstract: Chiral C_2-symmetric 2,3-disubstituted 1,4-diazabicyclo[2.2.2]octanes (DABCOs) (**1**) have been utilized as catalysts for asymmetric Baylis-Hillman reactions. Optically active α-methylene-β-hydroxyalkanone was obtained in up to 47% ee. Under high pressure conditions, a remarkable enhancement of both reaction rate and enantioselectivity has been observed.

Considerable attention has recently been focussed on the asymmetric C-C bond forming reactions.[1] Condensation of acrylates and aldehydes catalyzed by tertiary amines is known as the Baylis-Hillman reaction (Scheme 1).[2,3,4] It is initiated by a conjugate addition of a tertiary amine to an acrylate. Nucleophilic attack of the resulting enolate to an aldehyde followed by β-elimination of the tertiary amine affords α-methylene-β-hydroxyalkanoates. Therefore, this reaction can be regarded as equivalent to a nucleophilic addition of a vinyl carbanion to an aldehyde under mild conditions. In spite of the potential synthetic utility, this reaction had been rarely used for synthesis because of the slow reaction rate. Recently, this problem has been overcome under high pressure conditions.[4b,5] Although the asymmetric reaction using chiral acrylate esters[4b,d,e,6] or chiral amines[3,5b] such as cinchona alkaloid has been explored, only low enantioselectivities have been attained, particularly on the latter catalytic processes. Recent studies on the effects of the amines[3,5a] suggested to us that chiral DABCO derivatives could serve as an effective asymmetric catalyst for this reaction. Preliminary studies of the catalytic asymmetric Baylis-Hillman reaction using C_2-symmetric 2,3-disubstituted DABCOs (**1**) are disclosed herein.



1a ; R=benzyl
1b ; R=t-butyldiphenylsilyl
1c ; R=triisopropylsilyl
1d ; R=phenyl
1e ; R=mesityl
1f ; R=1-naphthyl
1g ; R=1-anthranyl
1h ; R=1-naphthoyl
1i ; R=Cbz-gly



Scheme 1.

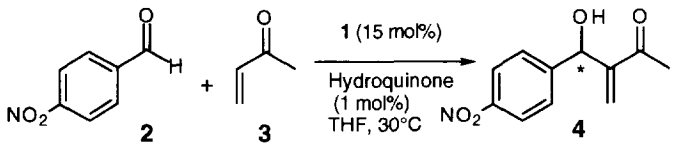


Table 1. Catalytic Asymmetric Baylis-Hillman Reaction of 4-Nitrobenzaldehyde (**2**) and MVK (**3**) Using **1**.

Entry	Ligand	**2** : **3**	Press./Kbar	Time/h	Yield/% (Recovery)[a]	ee/%[b] (Config)[c]
1	**1a**	1 : 3	0.001[d]	504	66[e]	12 (*S*)
2	**1b**	1 : 30	0.001[d]	504	42[e] (41)	15 (*R*)
3	**1a**	1.5 : 1	5	12	45[f]	47 (*S*)
4	**1b**	1.5 : 1	5	12	23[f]	34 (*S*)
5	**1c**	1 : 3	5	28	33[e]	19 (*S*)
6	**1d**	1 : 3	5	16	60[e] (18)	35 (*S*)
7	**1e**	1 : 3	5	28	67[e]	16 (*S*)
8	**1f**	1 : 3	5	16	66[e] (21)	42 (*S*)
9	**1g**	1.5 : 1	5	24	9[f]	11 (*S*)
10	**1h**	1 : 3	10	17	68[e] (18)	15 (*S*)
11	**1i**	1 : 3	10	24	63[e] (10)	21 (*S*)

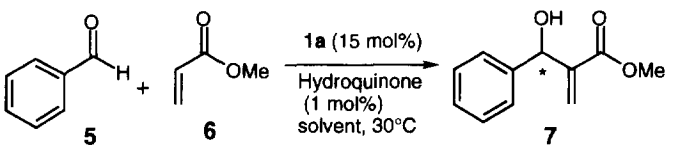
a) Yield of recovered **2**. b) Enantiomeric excess (ee) was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane/2-propanol = 20 : 1). c) Ref 9. d) Atmospheric pressure at room temperature. e) Based on **2**. f) Based on **3**.

Enantiomerically pure (*S,S*)-2,3-disubstituted DABCOs (**1a-i**) were synthesized as previously reported.[7] We first examined the reaction of 4-nitrobenzaldehyde (**2**) with methyl vinyl ketone (**3**) using 15 mol% of **1** as a chiral catalyst in THF. Results are summarized in Table 1. The reaction under atmospheric pressure proceeded very slowly (entries 1 and 2). After 3 weeks the benzyl ether (**1a**)-catalyzed reaction afforded *S*-**2** with 12% ee in 66% yield. Interestingly, when t-butyldiphenylsilyl (TBPS) ether (**1b**) was used, the sense of stereoselectivity was reversed to give *R*-**4** as a major product (15% ee) in 42% yield. Under high pressure conditions (5 Kbar), a remarkable enhancement of both the reaction rate and the enantioselectivity (47% ee) was observed for **1a** (entry 3). The reaction using silyl ethers (**1b** and **1c**) tends to proceed slowly even under high pressure conditions (entries 4 and 5), and the sense of enantioselectivity was reversed for **1b** (entry

4). Phenyl ether derivative (**1d**) (35% ee, entry 6) was superior to the more sterically demanding mesityl ether (**1e**) (16% ee, entry 7), while naphthyl ether (**1f**) increased the selectivity (42% ee, entry 8). However, for larger ligands such as the anthranyl ether (**1g**), the selectivity as well as reactivity was reduced substantially (entry 9). In the case of ester ligands (**1h** and **1i**), the yield became high while the enantiomer excess was relatively low (entries 10 and 11). While these results are still far from satisfactory, the enantioselectivitiy attained by **1a** and **1f** (entries 3 and 8) are much higher than those previously reported.[3,5b]

We then examined the condensation of the less reactive benzaldehyde (**5**) and methyl acrylate (**6**) under the similar high pressure conditions (Table 2). Although no reaction proceeded under 5 Kbar, 14% of coupling product with 10% ee was obtained under 10 Kbar in THF. The reaction was remarkably accelerated to give 72% yield by adding MeOH, while the enantioselectivity remained unchanged (entry 2).[4g,8]

Thus, we have demonstrated that the chiral DABCO derivatives can catalyze the asymmetric Baylis-Hillman reaction. Further exploration of optimal DABCO derivatives are currently under investigation in our laboratory.



5 6 7

Table 2. Catalytic Asymmetric Baylis-Hillman Reaction of Benzaldehyde (**5**) and Methyl Acrylate (**6**) Using **1a**.

Entry	**5** : **6**	Press./Kbar	Solvent	Time/h	Yield/%[a]	ee/%[b]
1	1 : 3	10	THF	23	14	10 (*S*)
2	1 : 3	10	THF / MeOH 5 : 1	23	72	10 (*S*)

a) Based on **5**. b) Determined by optical rotation.[10]

A typical reaction procedure is as follows: A solution of **2** (75.6 mg, 0.5 mmol), **3** (125 μl, 1.5 mmol), hydroquinone (0.8 mg, 1 μmol), and **1f** (31.8 mg, 75 μmol) in THF (ca. 800 μL) in a Teflon® reaction vessel (1 mL) was kept under 5 Kbar for 16 h. The reaction mixture was diluted with ether (80 mL), and washed successively with 0.5 N HCl (5 mL), satd. $NaHCO_3$ (1 mL), and satd. NaCl (1 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by florisil column chromatography (hexane-ethyl acetate) to give **4** (73.5mg, 66%) and recovered aldehyde (15.9 mg, 21%).

Reference and Notes

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2. (a) Baylis, A. B.; Hillman, M. E. D. *German Patent* **1972**, 2155113, *Chem. Abstr.* **1972**, *77*, 34174q
3. For a review of Baylis-Hillman reaction see: Drewes, S. E.; Roos, G. H. P. *Tetrahedron* , **1988**, *44*, 4653.
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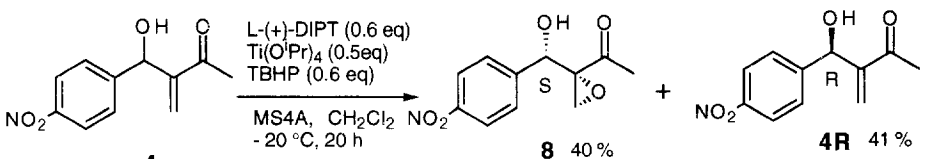
6. (a) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S.; Dharma Rao, P. *Tetrahedron Lett.*, **1990**, *31*, 1621. (b) Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron Asymmetry* **1991**, *2*, 969.
7. Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639. Specific rotations of chiral DABCO derivatives are as follows.
   1a:$[\alpha]_D^{27}$-41.9 (c 1.01, EtOH); **1b**:$[\alpha]_D^{26}$ -7.31 (c 1.04, $CHCl_3$); **1c**:$[\alpha]_D^{26}$ -37.1 (c 1.03, $CHCl_3$); **1d**:$[\alpha]_D^{22}$ -29.0 (c 0.48, EtOH); **1e**:$[\alpha]_D^{22}$ -6.99 (c 0.74, EtOH); **1f**:$[\alpha]_D^{26}$ -68.9 (c 1.02, $CHCl_3$); **1g**:$[\alpha]_D^{23}$ -57.4 (c 1.40, $CHCl_3$); **1h**:$[\alpha]_D^{25}$ -45.3 (c 1.18, $CHCl_3$); **1i**:$[\alpha]_D^{25}$ -15.6 (c 0.84, $CHCl_3$).
8. Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495.
9. Absolute configuration of product **4** was deduced by comparing the sign of the specific rotation of (*R*)-**4** prepared by kinetic resolution of racemic **4** employing Katsuki-Sharpless' asymmetric epoxidation with diisopropyl L-(+)-tartrate which should react with (*S*)-**4** preferencially (see: Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237).



10. Enantiomerically pure (*R*)-**7**:$[\alpha]_D^{27}$ -111.1 (c 1.11, MeOH), see : Drewes, S. E.; Emslie, N. D.; Field, J. S.; Kahn, A. A.; Ramesar, N. *Tetrahedron Asymmetry* **1992**, *3*, 255.

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