Chiral Amine-Catalyzed Asymmetric Baylis−Hillman Reaction: A Reliable Route to Highly Enantiomerically Enriched (α-Methylene-β-hydroxy)esters

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The tertiary amine-catalyzed C−C bond-forming reaction of aldehydes with activated alkenes such as acrylates is widely referred to as the Baylis−Hillman reaction.[1] Both the synthetic utility of the densely functionalized products[1,2] and the exquisite tandem Michael−aldol reaction process under nucleophilic amine catalysis[3] have spurred much research on an asymmetric version of this reaction. However, the reported methods are far from ideal because of low chemical yield and low optical purity of the adducts.[4] Except for one recent report by Leahy and co-workers[5] describing the highly diastereoselective Baylis−Hillman reaction of the acrylamide of Oppolzer's sultam, albeit with the stipulation that a large excess of the aldehyde must be employed, no other method is currently available for this purpose. We report here the first practical catalytic asymmetric Baylis−Hillman reaction which allows conversion of a wide variety of aldehydes to the corresponding (α-methylene-β-hydroxy)esters with high enantiomeric excess in reasonable yields.

To realize an efficient catalytic asymmetric Baylis−Hillman reaction, wherein a high level of asymmetric induction as well as desired rate acceleration[6] is obtained, the appropriate combination of chiral amine catalyst and suitably activated alkene is required. Drewes[6a] and Markó[4a,7] independently reported that an OH group suitably disposed on an amine catalyst exerts a marked effect on rate acceleration as well as asymmetric induction. They suggest that the OH group stabilizes the oxy anion intermediate through hydrogen bonding, which accelerates the aldol addition reaction and also creates an asymmetric environment in some cases. These reports prompted us to survey a series of hydroxylated amines derived from *cinchona* alkaloids. Regarding the activated alkene, we decided to employ 1,1,1,3,3,3-hexafluoroisopropyl acrylate[8] (**2**) because this acrylate turned out to show remarkable rate acceleration.

To assay the ability of various hydroxylated amine catalysts, we surveyed four quinidine derivatives,[10] **QD-1**, **QD-2**, **QD-3**, and **QD-4**, as well as quinidine itself in the reaction of **1a** and **2** (Table 1). Although quinidine, **QD-1**, and **QD-2** did not give satisfactory results (entries1−3), the cyclic ether derivative **QD-3** displayed remarkable catalytic activity, even at −55 °C in DMF,[11] affording **4a** and **6a** in good total yield (entries 4 and 5). In these cases, however, the level of the asymmetric induction was disappointing. We were gratified to find that **QD-4** provided a dramatic increase in the optical purity of **4a** (91% ee, entry 6). This result suggests the crucial role of the phenolic hydroxy group on the enantioselectivity, which is important to highlight. The *large discrepancy* between the optical purity of **4a** (91% ee) and that of **6a** (4% ee) was the key observation which led to our proposed mechanistic explanation (vide infra). The rate enhancement observed for **QD-3** and **QD-4** supposedly results from their increased nucleophilicity due to reduced steric hindrance around the nucleophilic nitrogen of the catalyst by restraining the conformational freedom of the bulky aromatic moiety.[12] The results listed in entries 6 and 7 clearly indicate the temperature dependency on enantioselectivity. In a control experiment using **3** and **QD-4** (entry 8), only poor enantioselectivity (8% ee) was observed, presumably due to the higher reaction temperature employed, highlighting the advantage of **2**.

Having demonstrated the superiority of the combination of **QD-4** and **2** in the reaction of **1a**, we turned our efforts to investigate its applicability (Table 2). It can be seen that aromatic aldehydes including cinnamaldehyde (**1c**) preferentially gave ester **4** with very high optical purity (entries 1−3). This reaction system was also found to be applicable to aliphatic aldehydes, giving the corresponding esters **4** in excellent enantioselectivity, although the yields were moderate. Interestingly, the accompanying dioxanones **6** showed the reverse chirality and irregular ee values (entries 4−7). It should be stressed that even sterically demanding isobutyraldehyde (**1f**) and cyclohexanecarboxaldehyde (**1g**) produced optically pure esters **4f** and **4g** in moderate yields, respectively (entries 6 and 7). Pivalaldehyde (**1h**), however, resulted in quantitative dimerization of acrylate **2**,[13] thus defining the steric limitation of the reaction. The intriguing switch of enantioselectivity between **4** and **6** provided an important mechanistic insight when we found that **QD-4** does not promote acetalization[14] of racemic ester **4a** with aldehyde **1a** to dioxanone **6a**. This observation suggests that highly enantiomerically

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(1) For an eminent review, see: Ciganek, E. *Org. React*. **1997**, *51*, 201−350.

(2) For leading references, see: (a) Markó, I. E. *Organometallic Reagents in Organic Synthesis*; Academic Press: London, 1994. (b) Piber, M.; Leahy, J. W. *Tetrahedron Lett*. **1998**, *39*, 2043−2046. (c) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *J. Chem. Soc., Chem. Commun*. **1998**, 2563−2564.

(3) For mechanistic studies, see: (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem*. **1983**, *95*, 795−796. (b) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem*. **1990**, *3*, 285−293. (c) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett*. **1991**, *32*, 5611−5614. (d) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371−6384. (e) Rosendaal, E. M. L.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *31*, 6931−6936.

(4) (a) Markó, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015−1024. (b) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun*. **1998**, 1271−1272. (c) Barret, A. G. M.; Cook, A. S.; Kamimura, A. *J. Chem. Soc., Chem. Commun*. **1998**, 2533−2534. (d) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Kanematsu, K.; Iwamura, T.; Watanabe, S. *Chem. Lett*. **1999**, 257−258. See also ref 1.

(5) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc*. **1997**, *119*, 4317−4318.

(6) The Baylis−Hillman reaction is notorious for slow reaction rates, and a number of attempts have been made to circumvent the sluggish nature of this reaction. (a) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun*. **1988**, *18*, 1565. (b) Rafel, S.; Leahy, J. W. *J. Org. Chem*. **1997**, *62*, 1521−1522. (c) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 1539−1542. See also ref 1.

(7) Bailey, M.; Markó, I. E.; Ollis, D.; Rasmussen, P. R. *Tetrahedron Lett*. **1990**, *31*, 4509−4512.

(8) The acrylate was purchased form Tokyo Chemical Industry Co., Ltd., and used without purification. The acrylate displayed the highest productivity in the preliminary study using **1a**. For example, the reaction of *p*-nitrobenzaldehyde (**1a**) with **2** in the presence of DABCO (10 mol %) required only 1.5 h even at 2 °C to give ester **4a** (60%) and dioxanone **6a**[9] (15%), whereas the reaction of **1a** with methyl acrylate (**3**) took 12 days to achieve 94% conversion.

(9) The dioxanones are often produced in the reactions using the reactive acrylates. (a) Drewes, S. E.; Emslie N. D.; Karodia, N.; Khan, A. A. *Chem. Ber*. **1990**, *123*, 1447. (b) Perlmutter, P.; Puniani, E.; Westman, G. *Tetrahedron Lett*. **1996**, *37*, 1715. See also ref 5.

(10) The catalysts **QD-1**−**QD-4** were prepared according to the literature procedures. (a) von Riesen, C.; Hoffmann, H. M. R. *Chem. Eur. J*. **1996**, *2*, 680−684. (b) Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495−3512. We found that a multigram sample of **QD-4** was synthesized (∼60%) in one step from (+)-quinidine by heating with 10 equiv of KBr in 85% phosphoric acid at 100 °C for 5 days.

(11) Solvent effects could not be evaluated due to the low solubility of the catalysts in solvents other than DMF.

(12) This supposition is well supported by their stereostructures deduced from NOE experiments of **QD-3** and **QD-4** as well as X-ray crystallographic analysis of **QD-4**. See Supporting Information.

(13) Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett*. **1987**, *28*, 4591−4592.

(14) Reaction of racemic **4a** with **1a** in the presence of **QD-4** in DMF at −55 °C resulted in no reaction after 1 day. At room temperature, very small production of **6** (<3%) was detected after 1 day.

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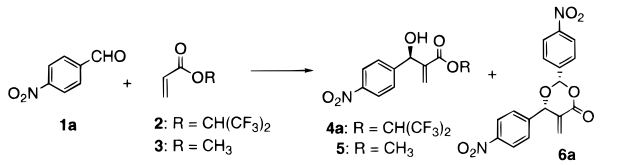
Table 1. Asymmetric Baylis−Hillman Reaction of *p*-Nitrobenzaldehyde (**1a**) with Acrylates Catalyzed by Quinidine Derivatives[a]



entry	acrylate	catalyst	solvent	temp (°C)	time (h)	yield (%),[b] config[c] (% ee[d]) ester	dioxanone[e]
1	**2**	quinidine	THF	2	24	12, nd[f]	22, *R* (33)
2	**2**	**QD-1**[g]	THF	2	72	2, nd	32, *R* (35)
3	**2**	**QD-2**[g]	THF−DMF[h]	2	72	10, nd	26, *R* (10)
4	**2**	**QD-3**	THF	2	1	63, *R* (35)	10, *R* (33)
5	**2**	**QD-3**[i]	DMF	−55	1	74, *R* (10)	7, nd
6	**2**	**QD-4**[i]	DMF	−55	1	58, *R* (91)	11, *R* (4)
7	**2**	**QD-4**[i]	DMF	0	1.5	52, *R* (64)	11, *S* (10)
8	**3**	**QD-4**	DMF	20	14	69, *S* (8)	−

[a] Aldehyde (0.1 mmol) was reacted with acrylate (0.3 mmol) using a 10 mol % of catalyst in 200 μL of the solvent at the indicated temperature, unless otherwise stated. [b] Isolated yield. [c] Configuration determined by comparison of the specific rotation of the corresponding methyl ester **5** with that of the authentic sample obtained by kinetic resolution under Sharpless asymmetric epoxidation conditions. [d] Determined by HPLC analysis using a chiral column. [e] *cis:trans* > 99:1. [f] Not determined. [g] 20 mol % of catalyst was used. [h] 10% DMF was added to dissolve the catalyst. [i] 0.13 mmol of **2** was used.

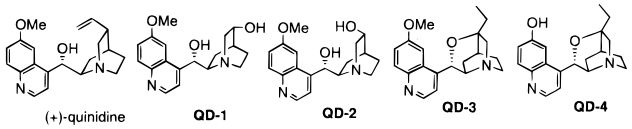
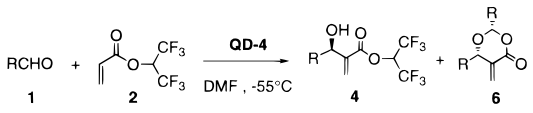


Table 2. **QD-4**-Catalyzed Asymmetric Baylis−Hillman Reaction of Various Aldehydes with **2**[a]



entry	aldehyde	R	time (h)	yield (%),[b] config[c] (% ee[d]) ester **4**	dioxanone **6**[e]
1	**1a**	*p*-NO_2Ph	1	58, *R* (91)	11, *R* (4)
2	**1b**	Ph	48	57, *R* (95)	−
3	**1c**	(*E*)-PhCH=CH	72	50,[f] *R*[g] (92)	−
4	**1d**	CH_3CH_2	4	40, *R* (97)	22, *S* (27)
5[h]	**1e**	$(CH_3)_2CHCH_2$	4	51, *R* (99)	18, *S* (85)
6	**1f**	$(CH_3)_2CH$	16	36, *R* (99)	25, *S* (70)
7	**1g**	*c*-Hex	72	31, *R* (99)	23, *S* (76)
8	**1h**	*t*-Bu	72	−	−

[a] Reactions were carried out at −55 °C in DMF (1.0 M) using **1** (1.0 equiv), **2** (1.3 equiv), and **QD-4** (10 mol %), unless otherwise stated. [b] Isolated yield. [c] Determined by the comparison of the specific rotation of the corresponding methyl esters, unless otherwise stated. [d] Determined by HPLC analysis using a chiral column. [e] *cis:trans* > 95:5 for **6a**,**f**−**h** and 69:31 for **6e**. [f] Yield was calculated on the basis of recovered **1c**. [g] Determined by ^{1}H NMR analysis of the (*R*)- and (*S*)-MTPA derivatives of the corresponding methyl ester. [h] 20 mol % of catalyst was used.

enriched (*R*)-esters **4** are not obtained by virtue of kinetic resolution through preferential acetalization of the antipodal (*S*)-esters with aldehydes **1**. It implies that (*R*)-enriched **4** and (*S*)-enriched **6** are produced via different chemical pathways at the enantio-divergent point.

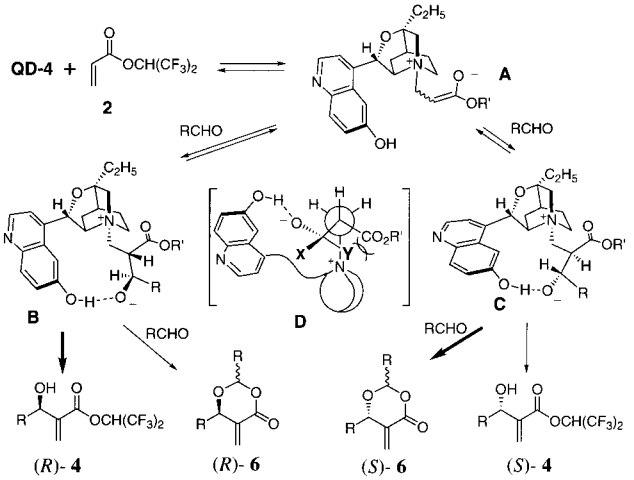


Figure 1. Proposed reaction mechanism.

The following mechanistic consideration would rationalize the absolute stereochemistry of the products and the key role played by the phenolic hydroxy group of **QD-4** (Figure 1). Michael addition of **QD-4** to acrylate **2** forms enolate **A**, which in turn undergoes aldol reaction with an aldehyde to furnish an equilibrium mixture of several diastereomers. Among them, there are two betaine intermediates, **B** and **C**,[15] stabilized by an intramolecular hydrogen bonding between the oxy anion and the phenolic OH, the conformations of which are nearly ideal for the subsequent E2 or E1cb reaction process for stereoelectronic reasons,[3a,16] as depicted in Newman projection **D**. However, intermediate **C** suffers from severe steric interactions between **Y** and the ester and quinuclidine moieties {see **D** (X = H, Y = substituent)}, and thus it undergoes reaction with a second aldehyde molecule rather than elimination to form dioxanone **6**. On the other hand, intermediate **B** undergoes facile elimination to produce (*R*)-ester **4** with regeneration of the catalyst because of less steric hindrance {see **D** (X = substituent, Y = H)}. The irregular ee values observed for dioxanones **6** in Table 2 can be explained on the basis of the reactivity of the starting aldehyde. Thus, as the reactivity of the aldehyde increases, the rate of formation of (*R*)-dioxanone **6** from intermediate **B** also increases in competition with elimination, which gives (*R*)-ester **4**, leading to decrease of the (*S*)-selectivity of **6**.

In summary, we have developed a highly enantioselective Baylis−Hillman reaction based on the discovery of two important reagents, 1,1,1,3,3,3-hexafluoroisopropyl acrylate **(2)** as an activated alkene and (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-hydroxycinchonane **(QD-4)** as a chiral amine catalyst. The novel catalytic behavior of **QD-4** should also inspire new avenues for the design of catalysts for the Baylis−Hillman reaction.

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Supporting Information Available: Experimental details and characterization data for all new compounds, including tables of crystal data for **QD-4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We assumed that intermediates **B** and **C** would be thermodinamically favorable aldol products generated through equilibration. However, based on the mechanistic explanation proposed by Leahy and co-workers,[5] it is also assumed that intermediates **B** and **C** would be produced selectively from the *E*-enolate, stabilized by electrostatic interactions, via an open transition state where an aldehyde approaches to the *re*-face or *si*-face of the *E*-enolate.

(16) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 252−257.