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Catalytic Enantioselective Baylis-Hillman Reactions. Correlation between Pressure and Enantiomeric Excess¶

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¶ Dedicated to the memory of Professor W. Oppolzer

Abstract: Several chiral amino-alcohols induce asymmetry in the Baylis-Hillman condensation of aldehydes with methyl vinyl ketone. Pressure plays an interesting role in this reaction. A model accounting for the pressure effect and rationalising the observed absolute stereochemistry is discussed.

The Baylis-Hillman condensation is an unusual reaction, affording β'-hydroxy enones (acrylates) such as **7** by a connective process formally equivalent to the addition of the vinyl anion **8** to an aldehyde **4** (Figure 1).[3]

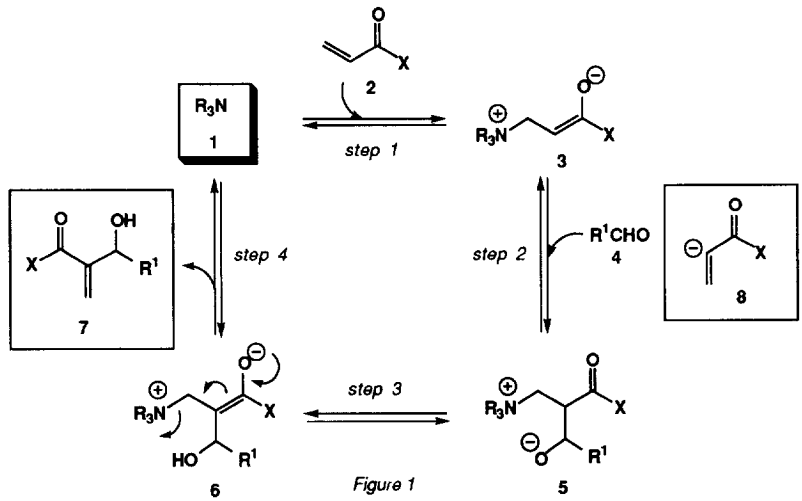

Figure 1

R_3N = DABCO, quinuclidine (QCD), 3-hydroxy-quinuclidine (3-HQ).
X = alkyl, aryl, OR, NR_2. **R^1** = aryl, alkyl.

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This three-component condensation, catalysed by certain nucleophilic tertiary amines (particularly DABCO, quinuclidine (QCD), 3-hydroxyquinuclidine (3-HQ)) and phosphines, is thought to proceed by the initial Michael addition of the amine **1** onto the α,β-unsaturated carbonyl compound **2**, generating the zwitterion **3**. Aldol reaction between **3** and aldehyde **4** then leads to alkoxide **5** which undergoes proton transfer, affording enolate **6**. At this stage, fragmentation of **6** produces the desired β'-hydroxy-α,β-unsaturated ketone (ester) **7** and regenerates the tertiary amine which then re-enters the catalytic cycle (Figure 1).[3a]

Such a mechanistic scheme is an over-simplification and several elegant studies have shown that, depending upon the nature of the aldehyde and the α,β-unsaturated carbonyl component, some, if not all the steps of the catalytic cycle could be reversible.[4] Baylis-Hillman adducts such as **7** are particularly useful intermediates possessing a contiguous assembly of varied functionalities. Their synthetic utility has been considerably investigated, most notably by Hoffmann[3b] and Drewes.[3a]

During the course of the total synthesis of clerocidin **10** and terpenticin **11**, two important bacterial metabolites exhibiting antibiotic and antitumour activities, we required rapid access to the highly oxygenated side-chain **9** (Figure 2). We envisioned a preparation of **9** by a *syn*-directed epoxidation of the β'-hydroxy enone **7** (X = CH_3), followed by subsequent oxidation of the methylketone function into the requisite α-keto aldehyde.

This approach has proven particularly rewarding and we have already reported on the highly *syn*-diasteroselective epoxidation of Baylis-Hillman adducts such as **7** using both Weitz-Scheffer and metal-mediated oxidation procedures.[5] Such methodology has been subsequently applied to the rapid and efficient synthesis of the racemic upper-chain **9** of clerocidin **10** and terpenticin **11** (Figure 2).[6]

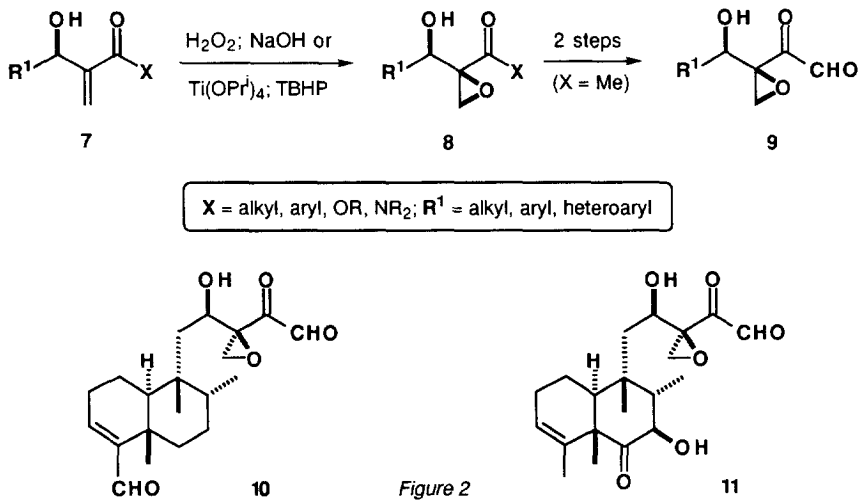


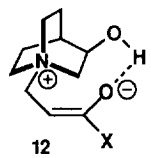
Figure 2

The development of an enantioselective route towards **9** prompted us to investigate the asymmetric epoxidation of β'-hydroxy enones and acrylates. It was rapidly found that kinetic resolution of Baylis-Hillman adducts **7** using the Sharpless titanium-based asymmetric epoxidation protocol afforded a convenient entry into optically active *syn*-epoxyalcohols **8** of good enantiomeric purity.[7] However, this approach suffers from the inevitable

drawback that a maximum of only 50% yield can ever be reached.[8] A better alternative involves the preparation of enantiopure **7** followed by its subsequent diastereoselective transformation into side-chain **9**. Although an enantioselective version of the Baylis-Hillman condensation would clearly prove to be particularly useful, we are aware of only two reports in the literature specifically devoted to this topic.[9]

Whereas Hirama *et al.*[10] employ C_3-symmetric DABCO derivatives to induce asymmetry in the Baylis-Hillman condensation, Barrett and co-workers[11] use a two-step protocol: Michael-like addition of a thiol or selenol derivative followed by an asymmetric aldol reaction catalysed by Yamamoto's acylborane reagent. Oxidative elimination of the sulfide (selenide) then completes the sequence.

In this article, we report the results of our efforts in generating optically active β'-hydroxy enones employing catalytic quantities of chiral β-amino-alcohols. The decision to use β-hydroxy-amines as catalysts stems from early mechanistic investigations of the Baylis-Hillman reaction. Indeed, both Drewes[12a] and ourselves[12b] noticed that 3-HQ was a better catalyst than DABCO and QCD.



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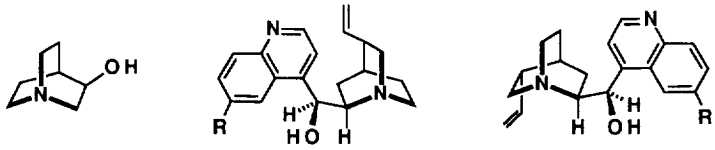
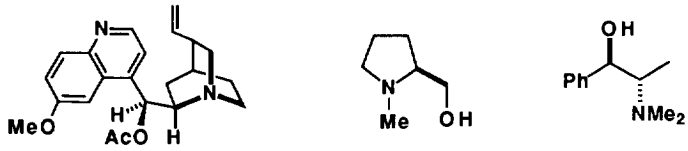
The rate of the Baylis-Hillman reaction using 3-HQ as the catalyst was up to seven times faster than the same process catalysed by QCD.[13] This remarkable effect was explained by Drewes as resulting from an intramolecular hydrogen-bonding interaction between the β-OH substituent of 3-HQ and the enolate oxygen of betaine **12**.[12a]

We noticed that similar rate enhancements could be obtained by simply adding an alcohol (CH_3OH, phenol or naphtol) to QCD.[13] This observation suggests a different role for the hydroxyl function of 3-HQ and we speculated that intermolecular H-bonding in the rate-determining step of the Baylis-Hillman reaction could be responsible for the rate acceleration.



13 **14a** : **R** = OMe; **14b** : **R** = H **15a** : **R** = OMe; **15b** : **R** = H



16 **17** **18**

Figure 3

Besides the addition of the tertiary amine to the α,β-unsaturated carbonyl compound **2**, two steps can be rate-limiting: the aldol reaction between zwitterion **3** and aldehyde **4** (step 2) and the proton transfer from betaine **5** to enolate **6** (step 3). Only in step 2 should this H-bonding effect lead to asymmetric induction.

Based on this hypothesis, various chiral β-hydroxy amines **13-18** were tested in the Baylis-Hillman reaction between methyl vinyl ketone (MVK) and cyclohexyl carboxaldehyde (Figure 3). Some selected results are displayed in Table 1.

Apart from (*R*)-3-HQ, which catalysed the Baylis-Hillman condensation at atmospheric pressure, although with no enantioselectivity, all the other amino-alcohols required high-pressure conditions.[14] Amongst the various β-hydroxy amines employed, the *cinchona* alkaloids displayed the highest level of enantioselection (Entries 2 and 4) followed closely by ephedrine and proline derivatives (Entries 7 and 8). As expected, quinine and cinchonidine gave lower but opposite enantioselectivities to quinidine and cinchonine (compare Entries 2-5).[15] The crucial role played by the β-hydroxyl function is also evident from this Table, as derivatisation of quinidine into its O-Acetyl analogue suppressed enantioselectivity (Entries 2 and 6).

Table 1. Variation of ee's *versus* amino-alcohol structure[(a)]

Entry	Amino-alcohol	No	ee (%)[(b)]
1	(R)-3HQ	**13**	0[(c)]
2	quinidine	**14a**	27[(d)]
3	quinine	**15a**	9[(e)]
4	cinchonine	**14b**	25[(d)]
5	cinchonidine	**15b**	10[(e)]
6	O-acetyl quinidine	**16**	2
7	N-methyl prolinol	**17**	11[(d)]
8	N-methyl ephedrine	**18**	15[(d)]

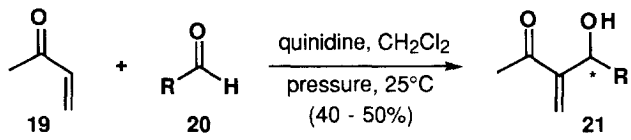
(a) = The reactions were performed in CH_2Cl_2, at 10-11 Kbars; **(b)** = The e.e.'s were measured by ^1H NMR spectroscopy using $Eu(hfc)_3$ and by chiral GC; **(c)** = This reaction was conducted at atmospheric pressure; **(d)** = the *(S)*-enantiomer is the major one formed; **(e)** = the *(R)*-enantiomer is the major one formed.

From this preliminary survey of β-amino alcohols, we selected the *cinchona* alkaloids quinine and quinidine as our lead catalysts and decided to increase the level of enantioselectivity by optimising some of the parameters of this reaction.

For this purpose, four variously substituted aldehydes were condensed with methyl vinyl ketone, at pressures ranging from 3 to 18 Kbars. The concentration of the amine catalyst, the nature of the solvent and the dilution of the reaction medium was systematically varied. In each case, the enantiomeric excess of the β-hydroxy enone **7** was measured on the crude material, either by ^{1}H NMR in the presence of Eu(hfc)$_3$ or by chiral GC. The e.e. values obtained by both methods are in excellent agreement.

We were quite surprised to note that modifying the concentration of the β-amino alcohol catalyst affected the e.e. of the product in a negligible way. For example, the enantiomeric excess of **21** (R = Cy) varied from 30% e.e., using 1 mol% quinidine, to 28% e.e. with 100 mol% quinidine. On the other hand, the variation of e.e. as a function of the concentration of the other reagents reached an optimum value at 0.1 M in aldehyde and MVK.

Table 2. Enantioselective Baylis-Hillman reactions



19 **20** **21**

Entry	R	Pressure	ee[(a)]
1	^{n}C$_3$H$_7$	15 Kbar	10%
2	^{n}C$_3$H$_7$	10 Kbar	15%
3	^{n}C$_3$H$_7$	5 Kbar	17%
4	**^{n}C$_3$H$_7$**	**3 Kbar**	**18%**
5	^{n}C$_9$H$_{19}$	15 Kbar	21%
6	**^{n}C$_9$H$_{19}$**	**10 Kbar**	**31%**
7	^{n}C$_9$H$_{19}$	5 Kbar	22%
8	^{i}C$_3$H$_7$	15 Kbar	6%
9	^{i}C$_3$H$_7$	10 Kbar	10%
10	^{i}C$_3$H$_7$	5 Kbar	21%
11	**^{i}C$_3$H$_7$**	**3 Kbar**	**37%**
12	^{c}C$_6$H$_{11}$	18 Kbar	13%
13	^{c}C$_6$H$_{11}$	10 Kbar	20%
14	^{c}C$_6$H$_{11}$	5 Kbar	42%
15	**^{c}C$_6$H$_{11}$**	**3 Kbar**	**45%**

All yields are for isolated, pure products. **(a)** = the e.e.'s were measured by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ and by chiral GC. The *S*-enantiomer is always the major one in these reactions.

Rather unexpectedly, the nature of the solvent (polar, apolar, protic, aprotic) has virtually no influence on the

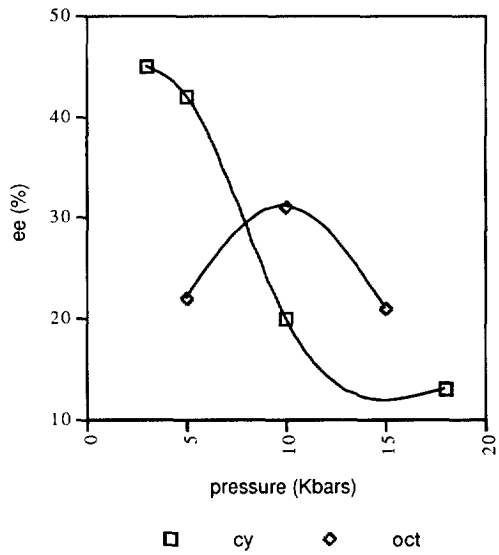
enantioselectivity of the BH reaction (CH_2Cl_2: 25% e.e.; CH_3OH: 24% e.e.; CH_3CN: 28% e.e.). Pressure has proven to be the most important parameter (Table 2).

Reactions under high pressure tend to proceed by minimisation of their volume of activation and therefore, the expectation is to observe enhanced enantioselective discrimination with increased pressure. This results mainly from one transition state being more compact (with less steric repulsions) than the other.[14]

It was thus quite a surprise to observe, that in contrast to what was expected for the condensation of simple aliphatic aldehydes such as butanal, an increase in pressure results in decreased enantiomeric excesses (Entries 1-4). Branching at the α-centre of the aldehyde provides a significant enhancement in the enantioselectivity of the Baylis-Hillman reaction, more than doubling the e.e.'s (Entries 4, 11 and 15). Again, an increase in pressure results in a decrease in selectivity, the best e.e.'s being obtained at 3 Kbars (Entries 8-15).

A remarkable effect of pressure is noticed when decanal is used as the aldehydic partner in the Baylis-Hillman condensation. In this case, working at low (5 Kbars) or high (15 Kbars) pressure leads to low e.e.'s. An intermediate pressure of 10 Kbars is found to provide optimum enantioselectivities. The variation of e.e. with pressure is illustrated in Figure 4.

Figure 4. Variation of ee with pressure



We believe that the following mechanistic model rationalises these observations, including the absolute stereochemistry of the β'-hydroxy enones obtained and the key-role played by the hydroxy function present in the catalyst (Figure 5).

Under pressure, Michael addition of the nucleophilic nitrogen atom of quinidine to methyl vinyl ketone generates

the expected zwitterion. Approach of the aldehyde then leads to the two diastereomeric transition states **22** and **23**. The energy difference between **22** and **23** could result from enhanced steric interactions between the R group of the aldehyde and the two hydrogens located at C_α of the catalyst in transition state **22** as compared to **23**. This implies that the bulkier the R group, the higher the enantioselectivities, a trend which is clearly visible in Table 2. Moreover, this model suggests that the role of the hydroxyl group is not only to lock the conformation of the ternary complex by hydrogen bonding to one of the lone pairs of the aldehyde carbonyl, but also to lower the energy of the transition states by stabilising the incipient negative charge developing on that oxygen atom during the aldol reaction. This latter effect provides an alternative explanation for the rate enhancement observed when using 3-HQ rather than QCD or when employing the mixture QCD/alcohol.[16]

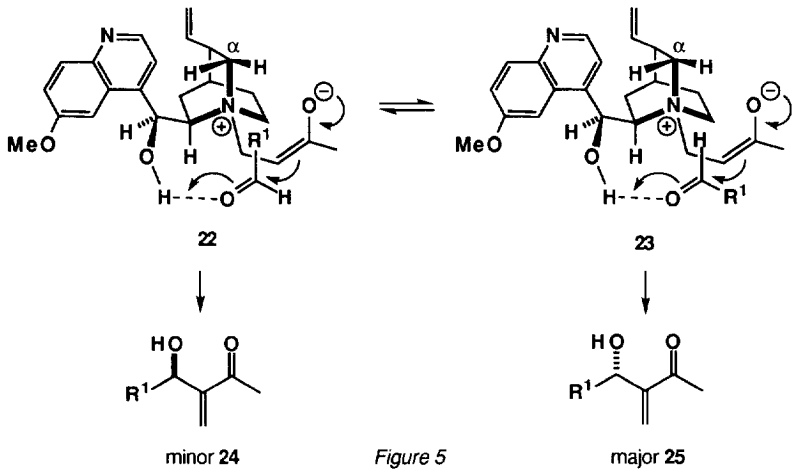


Figure 5

The variation of e.e.'s with pressure can then be explained by a lesser degree of selection between **22** and **23** at high pressure where these subtle interactions will be overridden by the very high pressures employed. Finally, the unusual behaviour of decanal can be attributed to the following competitive events: at low pressure, the lipophilic chain of decanal exists mostly in the preferred zig-zag conformation, conferring to the aldehyde a steric bulk not dissimilar to that of butanal (compare Entries 4 and 5, Table 2). As the pressure is gradually increased, the chain coils over itself, resulting in a greater steric size of the R substituent and thus higher enantioselectivity. At very high pressure, the e.e.'s will decrease according to the explanation discussed above.

In summary, we have shown that chiral amino-alcohols can act as catalysts in the enantioselective version of the Baylis-Hillman reaction.[17] Although the enantiomeric excesses are moderate at present, several important parameters have been delineated and the results of these investigations have provided useful insights into the understanding of this unique reaction. Based on these observations, the construction of catalysts which should afford higher levels of enantioselectivities is currently being investigated in our laboratory. The results of these studies will be communicated in due course.

Acknowledgements

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Experimental Section

General Methods

All the reactions were carried out under anhydrous conditions and in an atmosphere of argon unless otherwise indicated. Melting points were obtained using a Leitz microhotstage and are uncorrected. NMR spectra were recorded on Varian XL-200, Gemini 200 and 300 and Brucker 250 MHz intruments. Chemical shifts are expressed as parts per million (δ) relative to tetramethylsilane. Mass spectra were obtained using a Varian Matt 445 instrument, with electron impact (70 eV) and chemical ionisation gas (isobutane). IR spectra were taken with a Nicolet 500 FT instrument. Thin layer chromatography was performed on Merck 0.2 mm aluminium-backed TLC plates and visualised using ultra-violet light followed by development with alkaline $KMnO_4$ solution. Column chromatography was performed using Merck silica gel 60 (230-240 mesh) under pressure. Microanalyses were provided by the analytical department, University College London.

General experimental procedure

To a thick Teflon® tube were added sequentially the starting aldehyde **20** (1 eq), methyl vinyl ketone **19** (1 eq), the chiral amine **13-18** (0.1 eq; 10 mol%) and CH_2Cl_2 (concentration of the final solution ~ 1 M). The tube was stoppered and pressurised at the indicated pressure (Table 2) at 25°C for 20-26 hrs. Evaporation of the volatiles under vacuum followed by purification gave the optically active β'-hydroxy-enones in 40-50% yield. The enantiomeric excesses were measured by ^1H NMR in the presence of $Eu(hfc)_3$ or by chiral GC.

Preparation of 4-hydroxy-3-methylene-heptan-2-one (Table 2, Entry 4)[5,7]

Following the general experimental procedure outlined above, butanal (720 mg, 1 mmol), methyl vinyl ketone (0.7 g, 1 mmol), and quinidine (323 mg, 0.1 mmol, 10 mol%) dissolved in 10 ml CH_2Cl_2 were pressurised at 3 Kbars and 25°C for 26 hrs. After filtration through a pad of silica gel using ethyl acetate as the eluent and removal of the volatiles *in vacuo*, distillation (118-123°C, 760 mm Hg) gave the title compound (496 mg, 42%) as a colourless oil.

IR (neat) ν_{max} 3448, 1673, 1367 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ_H 6.15 (1H, s), 6.0 (1H, d, J = 1 Hz), 4.4 (1H, dt, J^1 = 7.0 Hz, J^2 = 7.5 Hz), 2.72 (1H, d, J = 7.0 Hz), 2.35 (3H, s), 1.6-1.38 (4H, m), 0.81 (3H, t, J = 7.1 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 200.5, 150.3, 125.5, 71.2, 38.4, 26.4, 19.0, 13.8. MS (m/z; EI) 143 (M+1), 141 (M-1). $[\alpha]_D^{25}$ = -1.6° (EtOH)

Preparation of 4-hydroxy-3-methylene-tridecan-2-one (Table 2, Entry 6)[5,7]

The above procedure was employed using the following quantities: decanal (1.56 g, 1 mmol), methyl vinyl ketone (0.7 g, 1 mmol), and quinidine (323 mg, 0.1 mmol, 10 mol%) in 10 ml CH_2Cl_2. The sample was pressurised at 10 Kbars and 25°C for 20 hrs. The crude compound was filtered through a pad of silica gel (eluent: ethyl acetate) and the crude product further purified by rapid column chromatography over silica gel using ethyl acetate/petrol (1:3) as the eluent. Removal of the volatiles under vacuum afforded the title compound

(904 mg, 40%) as a colourless oil.
IR ($CHCl_3$): ν_{max} 3600, 1665, 1370 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.10 (1H, s), 6.03 (1H, s), 4.43 (1H, t, J = 7.5 Hz), 2.88 (1H, bs), 2.38 (3H, s), 1.57 (2H, m), 1.28 (14 H, m), 0.86 (3H, t, J = 7.8 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 200.5, 150.5, 125.3, 71.0, 36.3, 31.8, 29.5, 29.4, 29.2, 26.4, 25.8, 22.5, 13.9. MS (m/z; CI) 244 ($M^+ + NH_4$). $[\alpha]_D^{25}$ = -6.1° (EtOH).

Preparation of 4-hydroxy-5-methyl-3-methylene-hexan-2-one (Table 2, Entry 11)[5,7]
Following the general experimental procedure, isobutyraldehyde (0.72 g; 1 mmol), methyl vinyl ketone (0.7 g, 1 mmol), and quinidine (323 mg, 0.1 mmol, 10 mol%) in 10 ml CH_2Cl_2 were pressurised at 3 Kbars and 25°C for 22 hrs. The crude product was purified by rapid filtration through a pad of silica gel (eluent: ethyl acetate) followed by distillation under reduced pressure to afford the title compound (740 mg, 52%) as a colourless oil (bp 88-91°C, 0.2 mmHg). IR ($CHCl_3$): ν_{max} 3600, 1670, 1620 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ_H 6.15 (1H, s), 5.97 (1H, d, J = 1.0 Hz), 4.09 (1H, d, J = 6.6 Hz), 2.72 (1H, b), 2.37 (3H, s), 1.87 (1H, m), 0.94 (3H, d, J = 6.5 Hz), 0.85 (3H, d, J = 6.6 Hz) ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 200.9, 149.2, 126.7, 77.3, 32.6, 26.5, 19.6, 17.5. MS (m/z; CI) 160 ($M^+ + NH_4$). $[\alpha]_D^{25}$ = -4.7° (EtOH).

Preparation of 1-cyclohexyl-1-hydroxy-2-methylene-butan-3-one (Table 2, Entry 15)[5,7]
The above experimental procedure was employed using the following quantities: cyclohexane carboxaldehyde (1g, 8.91 mmol), methyl vinyl ketone (0.75 ml, 8.91 mmol), and quinidine (288mg, 0.89 mmol, 10 mol%) in CH_2Cl_2 (10 ml). Pressure: 3 Kbars at 25°C for 21 hrs. The crude compound was filtered through a pad of silica gel using ethyl acetate as the eluent. Distillation under vacuum (b.p. 92-94°C, 0.2 mm Hg) afforded the title compound as a colourless oil (820 mg, 45%).
IR ($CHCl_3$): ν_{max} 3600, 1660, 1360 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.14 (1H, s), 5.92 (1H, d, J = 1.1 Hz), 4.07 (1H, dd, J^1 = 7.4 Hz, J^2 = 7.9 Hz), 2.74 (1H, d, J = 7.9 Hz), 2.37 (3H, s), 1.94-0.87 (11H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 200.7, 149.0, 126.5, 76.9, 42.5, 30.1, 28.3, 26.5, 26.3, 26.1, 25.9. MS (m/z; CI) 200 ($M^+ + NH_4$). Anal. Calc. for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.51; H, 10.19. $[\alpha]_D^{25}$ = -8.6° (EtOH).

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9. A number of diastereoselective routes have been described using chiral auxiliaires attached on the acrylate moiety or employing optically active aldehydes (ref. 3a). In his seminal review, Drewes mentions the use of chiral amines to catalyse the asymmetric Baylis-Hillman reaction. However, both the yields and the enantiomeric excesses are low (< 10%).
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17. When optically enriched BH adduct **21** (R=Cy) was resubjected to the reaction conditions (10 Kbars, 3 days), the e.e. decreased to about 10% e.e.. However, the yield of **21** was also much lower. We are grateful to a Referee to suggest this experiment.

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