Rate Acceleration of the Baylis−Hillman Reaction in Polar Solvents (Water and Formamide). Dominant Role of Hydrogen Bonding, Not Hydrophobic Effects, Is Implicated

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Received August 30, 2001

A substantial acceleration of the Baylis−Hillman reaction between cyclohexenone and benzaldehyde has been observed when the reaction is conducted in water. Several different amine catalysts were tested, and as with reactions conducted in the absence of solvent, 3-hydroxyquinuclidine was found to be the optimum catalyst in terms of rate. The reaction has been extended to other aldehyde electrophiles including pivaldehyde. Attempts to extend this work to acrylates was only partially successful as rapid hydrolysis of methyl and ethyl acrylates occurred under the base-catalyzed and water-promoted conditions. However, *tert*-butyl acrylates were sufficiently stable to couple with relatively reactive electrophiles. Further studies on the use of polar solvents revealed that formamide also provided significant acceleration and the use of 5 equiv of formamide (optimum amount) gave faster rates than reactions conducted in water. Using formamide, further acceleration was achieved in the presence of $Yb(OTf)_3$ (5 mol %). The scope of the new conditions was tested with a range of Michael acceptors and benzaldehyde and with a range of electrophiles and ethyl acrylate. The origin of the rate acceleration is discussed.

A number of physical and chemical methods have been developed to accelerate the notoriously slow Baylis−Hillman reaction.[1] These efforts not only allow reactions to proceed more rapidly but also allow previously unreactive partners to couple. Of these methods, the chemical methods have the advantage of not requiring specialized equipment, and so are especially attractive. We previously reported that the combination of a metal catalyst and co-ligand (5 mol % $La(OTf)_3$ and 80 mol % triethanolamine) provided up to a 40-fold increase in rate,[2] and recently, Kobayashi showed that lithium perchlorate in ether can lead to increased rates.[3] We have also discovered that DBU is a better catalyst than 3-hydroxyquinuclidine (which was previously regarded as the optimum catalyst[4]) and provides rate accelerations of up to 50-fold over the standard amine catalyst (DABCO).[5] We demonstrated that these new conditions provided significantly increased rates and also increased the scope of the Baylis−Hillman reaction. However, there is still scope for further improvements.

It is well-known that protic solvents (e.g., methanol, ethylene glycol) accelerate the Baylis−Hillman reaction, through either stabilization of the enolate by hydrogen bonding or by activation of the aldehyde again through hydrogen bonding or indeed both.[2,4] As the initial addition of the tertiary amine to the Michael acceptor is reversible, a solvent that is able to solvate *both* the enolate and the ammonium cation should provide a further acceleration as it should increase the concentration of intermediate **1** (Scheme 1). Strongly polar solvents, especially water, should be able to provide such solvation and thereby enhance rates.[6] Furthermore, there is the additional possibility of achieving acceleration through hydrophobic effects[7] as the Baylis−Hillman reaction shows a large negative volume of activation ($\Delta V^{\ddagger} = -70$ cm^3 mol^{-1}).[8] Indeed, Augé has shown that the Baylis−Hillman reaction between acrylonitrile and various aldehydes can be accelerated in water.[9] However, it was not clear whether the origin of the acceleration was due to hydrophobic effects as the key test results involving salting in and out agents were ambiguous: generally, both salting-in (CsI) and salting-out (LiCl) agents caused a small reduction in rate, although LiI and NaI caused a small increase in rate. It was curious that they had chosen to study reactions involving acrylonitrile as this is already a relatively fast-reacting substrate in the Baylis−Hillman reaction. We have focused on slower reacting substrates, which are very much in need of acceleration: β-substituted enones and acrylates. In this paper, we describe

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10.1021/jo016073y CCC: $22.00
Published on Web 12/27/2001

Scheme 1. Baylis−Hillman Reaction

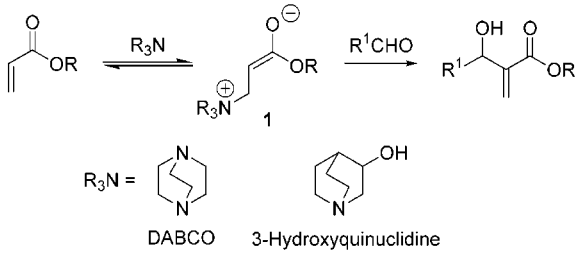

Table 1. Effect of Different Amine Catalysts on the Rate of the Baylis−Hillman Reaction in Water[a]

entry	catalyst	rate (% min^{-1})	k_{rel} (DABCO)
1	DABCO	0.17	1.0
2	4-DMAP	0.35	2.1
3	3-HDQ	0.44	2.6
4	3-HDQ with GnCl[b]	1.62	9.5
5	3-HDQ with LiCl[b]	0.86	5.1

[a] Reaction conditions: 2.0 mmol of cyclohexenone, 1.0 mmol of PhCHO, 1.0 mmol of catalyst, and 1.0 mL of water were stirred at rt. [b] 2.0 mmol of cyclohexenone, 1.0 mmol of PhCHO, 1.0 mmol of 3-HDQ, and 1.0 mL of 4 M salt solution. GnCl = guanadinium chloride. The rate of each reaction was determined at low conversion (<10%) by ^{1}H NMR.

the use of polar solvents to accelerate a broad range of Baylis−Hillman reactions.

We began our studies with the reaction between cyclohexenone[10] and benzaldehyde in water and investigated the effect of different amine catalysts on reaction rates (Table 1). DMAP has been compared with DABCO and found to be superior in the reaction between cyclohexenone and formaldehyde in THF/water.[11] We found that DMAP was indeed better than DABCO, but as with reactions conducted neat, 3-hydroxyquinuclidine gave the fastest rates (Table 1).[12]

To test whether the origin of the acceleration in water was due to hydrophobic effects, salting-in [guanidinium chloride (GnCl)] and salting-out (LiCl) agents were tested (Table 1, entries 4 and 5).[7,13] If hydrophobic effects were operative, salting-in agents should decelerate the reaction while salting-out agents should accelerate the reaction. The results obtained showed that both GnCl and LiCl caused an increase in the rate of these water-promoted reactions. As both salting-in and salting-out agents caused an increase in rate, this means that hydrophobic effects are not the primary cause for the acceleration observed. These results concur with Augé's observations.[9]

(10) β-Substituted enones were previously regarded as unreactive substrates in Baylis−Hillman reaction (see ref 1c), but we have found that cyclohexenone displays moderate reactivity and certainly greater the *tert*-butyl acrylate (see ref 5).

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(12) This finding surprised us as the rate acceleration of 3-HDQ over DABCO has been attributed to hydrogen bonding either intra- or intermolecularly (ref 4). Clearly, hydrogen bonding cannot be responsible for the increase in rate of 3-HDQ relative to DABCO *in water* and this prompted us to investigate the origin of the rate acceleration further. We have found that in the absence of steric effects there is a correlation between the pK_a of the base and its rate in the Baylis−Hillman reaction, and this can account for the enhanced rate of 3-HDQ [pK_a 9.9 (see: Grob, C. A. *Helv. Chim. Acta*, **1985**, *68*, 882)] relative to DABCO [pK_a 8.7 (see: Hine, J.; Chen, Y.-J. *J. Org. Chem.*, **1987**, *52*, 2091)]. Full details of these investigations will be reported in due course.

(13) (a) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613−5617. (b) Schmitt, M.; Bourguignon, J. J.; Wermuth, C. G. *Tetrahedron Lett.* **1990**, *31*, 2145−2148. (c) Dack, M. R. J. *Chem. Soc. Rev.* **1975**, *4*, 211−220.

Table 2. Coupling of Cyclohexenone with Different Carbonyl Compounds in Water[a]

entry	carbonyl compound	time (h)	yield (%)
1	benzaldehyde	4	82
2	*o*-anisaldehyde	24	74
3	isobutyraldehyde	17	59
4	pivaldehyde	10 d	36
5	formalin[b]	4	99

[a] Reaction conditions: 2.0 mmol of 2-cyclohexen-1-one, 1.0 mmol of carbonyl compound, 1.0 mmol of 3-hydroxyquinuclidine, and 1.0 mL of water. [b] 5 equiv of formalin was used with 1.0 mmol of 2-cyclohexen-1-one.

Table 3. Coupling of *tert*-Butyl Acrylate with Carbonyl Compounds in Water[a]

entry	carbonyl compound	time (h)	yield (%)
1	*p*-nitrobenzaldehyde	4	97
2	*o*-nitrobenzaldehyde	4	80
3	*o*-chlorobenzaldehyde	48	53
4	*o*-anisaldehyde	17	33
5	2,2,2-trifluoroacetophenone	72	40
6	formalin[b]	10 d	88
7	glyoxylic acid[c]	4	56

[a] Reaction conditions: 2.0 mmol of *tert*-butyl acrylate, 1.0 mmol of carbonyl compound, 1.0 mmol of 3-hydroxyquinuclidine, and 1.0 mL of water. [b] 1.0 mmol of *tert*-butyl acrylate, 3.0 mmol of formalin, 1.0 mmol of 3-HQD, and 1.0 mL of water. [c] 1.0 mmol of NEt_3 was also added to neutralize the acid.

The optimum catalyst, 3-hydroxyquinuclidine, was screened with a range of electrophiles (Table 2). As benzaldehyde worked so well, providing high yields in short reaction times (Table 2, entry 1), we only investigated relatively difficult/unusual substrates. *o*-Anisaldehyde is a hindered and deactivated aldehyde but still gave good yields after only 1 day (Table 2, entry 2). Hindered aliphatic aldehydes such as isobutyraldehyde (Table 2, entry 3) worked well although in the case of pivaldehyde (Table 2, entry 4) required longer reaction times. The use of pivaldehyde in the Baylis−Hillman reaction is rare, and this is only the second report on its use.[5] Aqueous formaldehyde (formalin) also coupled extremely efficiently under these conditions (Table 2, entry 5).

The use of acrylates with 3-hydroxyquinuclidine in water was less successful due to rapid hydrolysis particularly of the methyl and ethyl esters.[14] The problem of ester hydrolysis or transesterification is a general problem when acrylates are employed with alcohol solvents to enhance rates, and this is clearly accentuated if the acrylate is attached to a solid support for combinatorial synthesis.[15] However, we considered the use of *tert*-butyl esters, which are much less rapidly hydrolyzed, but this benefit has to be balanced against the fact that *tert*-butyl acrylate is a notoriously slow partner in the Baylis−Hillman reaction.[1c] In the event, *tert*-butyl acrylate was sufficiently stable at short reaction times to allow coupling to occur with reactive electrophiles (Table 3). *It is notable that in most cases high yields were obtained with this highly unreactive substrate after only a few hours.* However, aliphatic aldehydes were not

(14) During the course of this work, Hu reported the use of water to promote Baylis−Hillman reactions involving methyl acrylate and also noted that partial hydrolysis of the acrylate occurred. He used the less basic amine, DABCO, in which case the rate of hydrolysis will be slower compared to the use of 3-HQD. Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413−5418.

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Table 4. Reaction between *tert*-Butyl Acrylate and Benzaldehyde in Different Solvents/Conditions[a]

entry	solvent	rate (% min^{-1})	k_{rel} (neat)
1	acetonitrile	5×10^{-6}	0.001
2	neat	5×10^{-3}	1
3	formamide	0.11	22
4	formamide (5 equiv)[b]	0.23	46
5	water	0.18	37
6	water/$Sc(OTf)_3$[c]	0.059	12
7	water/$Yb(OTf)_3$[c]		
8	*N*-methylformamide	0.022	4
9	formamide/$Ti(OiPr)_4$[d]	0.31	62
10	formamide/$Al(OiPr)_3$[d]	0.32	64
11	formamide/$Yb(OTf)_3$[d]	0.33	66
12	formamide/$La(OTf)_3$[d]	0.24	48

[a] Reaction conditions: 2.0 mmol of *tert*-butyl acrylate, 1.0 mmol of PhCHO, 1.0 mmol of 3-hydroxyquinuclidine, and 1.0 mL of solvent. [b] 2.0 mmol of *tert*-butyl acrylate, 1.0 mmol of PhCHO, 1.0 mmol of 3-hydroxyquinuclidine, and 5.0 mmol (220 μL) of formamide. [c] 2.0 mmol of *tert*-butyl acrylate, 1.0 mmol of PhCHO, 1.0 mmol of 3-hydroxyquinuclidine, 1 mL of water, and 0.05 mmol of Lewis acid were stirred at rt. [d] 2.0 mmol of *tert*-butyl acrylate, 1.0 mmol of PhCHO, 1.0 mmol of 3-hydroxyquinuclidine, 5.0 mmol of formamide, and 0.05 mmol of Lewis acid were stirred at rt.

compatible with these conditions, and this limitation prompted us to investigate other polar solvents (Table 4).

We were particularly interested in the use of formamide as, like water but to a lesser extent, it is known to contribute to hydrophobic acceleration[7] and because it has an even higher dielectric constant (ϵ_r = 111 vs 78.5 for water)[16] will be better able to stabilize the charged intermediate. A further advantage of using formamide was the fact that there was no possibility of ester hydrolysis. We were pleased to find that the use of formamide did indeed provide an acceleration over reactions conducted neat (Table 4, entries 2 and 3). *N*-Methylformamide, which has an even higher dielectric constant than formamide (ϵ_r = 182 vs 111),[16] was also tested but gave a lower[17] rate indicating that the rate acceleration is not dominated by the solvents ability to solvate/stabilize the charged intermediates.

It seems that the origin of the rate acceleration observed with water, formamide, and *N*-methylformamide is dominated by hydrogen bonding but with smaller contributions from hydrophobic effects (with water) and solvent polarity. The small increase in rate observed when salts (GnCl or LiCl) are added to water could be due to the solvation of the cation, which will increase the hydrogen bond donor ability of water.

Further studies on concentration revealed that 5 equiv of formamide was optimum (Table 4, entry 4) and provided a rate acceleration that was similar to water. Similar experiments on concentration with water showed that the rate increased up to 0.2 M (Table 4, entry 5) and then plateaued.[18] For comparison, rates of reaction conducted neat and in acetonitrile (2 M) are given (Table 4, entries 1 and 2) and serve to demonstrate the high level of acceleration that can be achieved in the polar protic solvents (>10^4 fold increase in rate). Further studies with the optimized concentration of formamide revealed that additional acceleration could be achieved using Lewis acid (Table 4, entries 9−12).[2] We believe that formamide coordinates to the Lewis acid, which results in even more polarized NH bonds leading to increased hydrogen bond donor ability and therefore increased rates. These new conditions (Table 4, entry 11) provided significantly higher rates than using water alone. In contrast to the use of formamide, no additional rate acceleration was observed with $Sc(OTf)_3$ or $Yb(OTf)_3$ (Table 4, entries 6 and 7) in water. *As these conditions are now the best to date*, we tested a range of different Michael acceptors with benzaldehyde (Table 5) and a range of different electrophiles with ethyl acrylate (Table 6) using both stoichiometric and catalytic quantities of 3-hydroxyquinuclidine.

Table 5. Reaction of Different Michael Acceptors with Benzaldehyde under Optimized Conditions

		stoichiometric[a]		catalytic[b]	
entry	alkene	time[c] (h)	yield (%)	time[c] (h)	yield (%)
1	methyl acrylate	6	74	17	78
2	ethyl acrylate	3.75	80	17	84
3	*tert*-butyl acrylate	14	96	48 (72)	59 (71)
4	acrylonitrile	4	95	4	97
5	methyl vinyl ketone[d]	10 min	10		
6	2-cyclohexen-1-one	24	63	96	63
7	2-cyclopenten-1-one	24	70	24	10

[a] Reaction conditions: 1.2 mmol of Michael acceptor, 1.0 mmol of PhCHO, 5.0 mmol of H_2NCHO, 1.0 mmol of 3-hydroxyquinuclidine, and 0.05 mmol of $Yb(OTf)_3$. [b] 1.2 mmol of Michael acceptor, 1.0 mmol of PhCHO, 1.25 mmol of H_2NCHO, and 0.1 mmol of 3-hydroxyquinuclidine were stirred at rt under an argon atmosphere. [c] No further increase in yield after the times reported. [d] Rapid decomposition of methyl vinyl ketone took place under reaction conditions.

Table 6. Reaction of Different Carbonyl Compounds with Ethyl Acrylate under Optimized Conditions[a,b]

		stoichiometric[a]		catalytic[b]	
entry	carbonyl compound	time[c] (h)	yield (%)	time[c] (h)	yield (%)
1	*o*-chlorobenzaldehyde	4	99	6	99
2	*o*-anisaldehyde	12	90	96 (120)	66 (75)
3	*p*-anisaldehyde	28	18	96	30
4	*o*-nitrobenzaldehyde	2	95	2	95
5	isobutyraldehyde	72	71	42	21
6	cyclohexylcarboxaldehyde	72	88	42	42
7	trifluoroacetophenone	20	37	72	46
8	pivaldehyde	8 d	31		

[a] Reaction conditions: 1.2 mmol of ethyl acrylate, 1.0 mmol of carbonyl compound, 5.0 mmol of H_2NCHO, 1.0 mmol of 3-hydoxyquinuclidine, and 0.05 mol of $Yb(OTf)_3$. [b] 1.2 mmol of ethyl acrylate, 1.0 mmol of carbonyl compound, 1.25 mmol of H_2NCHO, and 0.1 mmol of 3-hydroxyquinuclidine were stirred at rt under an argon atmosphere. [c] No further increase in yield after the times reported.

All the acrylates and acrylonitrile reacted efficiently (Table 5, entries 1−4) under both stoichiometric and catalytic conditions. Less reactive enones coupled smoothly (Table 5, entries 6 and 7) but more reactive enones led to polymerization (Table 5, entry 5). This is typical of reactive enones, which are usually reacted in the presence of solvent to slow the reaction to prevent polymerization. Indeed, with reactive enones more conventional catalyst systems can be employed for efficient coupling.

Ethyl acrylate coupled efficiently with most aldehydes (Table 6). Particularly noteworthy is the unusually high reactivity of *o*-anisaldehyde relative to *p*-anisaldehyde.

(16) *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; Reichardt, C., Ed.; VCH Verlagsgesellschaft: Weinheim, 1988.

(17) These results parallel Augé's observations who observed that rate of Baylis−Hillman reaction between acrylonitrile and benzaldehyde in different solvents followed the order $H_2O \approx H_2NCHO >$ MeNHCHO (ref 9).

(18) Reactants are not soluble in water, which is why there is no peak in the rate of reaction with amount of water used. The reaction is zero order in water (ref 9).

This is presumably due to the superior ability of the ortho isomer to bind the Lewis acid and thus activate the aldehyde. Aliphatic aldehydes (Table 6, entries 5 and 6) coupled efficiently under stoichiometric conditions, but at the longer reaction times required under the catalytic conditions, product decomposition was observed. Activated ketones worked moderately well, but simple ketones (acetone) were not effective (Table 6, entry 7). Pivaldehyde (Table 6, entry 8) worked moderately well, and indeed, this is only the second use of pivaldehyde in the Baylis−Hillman reaction with any Michael acceptor.[5]

In conclusion, we have developed new conditions for accelerating the Baylis−Hillman reaction, which we believe are now the best to date. These improved conditions employ either water as solvent or small amounts of formamide and $Yb(OTf)_3$. Using the formamide and $Yb(OTf)_3$, rate enhancements of up to 120-fold have been achieved in the coupling of methyl acrylate with benzaldehyde over standard DABCO-catalyzed reaction. These new conditions will be particularly appropriate for solid-phase Baylis−Hillman reactions of acrylates as high rates without premature cleavage of the ester from the resin should be achieved. Hindered and deactivated aldehydes can now be coupled efficiently, and attempts to encourage unactivated ketones to couple is underway.

Experimental Section

Reagents. Methyl, ethyl, and *tert*-butyl acrylate were used as purchased. Cyclohexenone, cyclopentenone, formamide, and all aldehydes were distilled prior to use. DABCO was purified by sublimation under vacuum prior to use. DMAP and 3-hydroxyquinuclidine were used as purchased without further purification. All Lewis acids (except $Ti(OiPr)_4$) were stored in a vacuum desiccator and used without further purification. $Ti(OiPr)_4$ was distilled under reduced pressure prior to use.

General Procedure for the Baylis−Hillman Reaction (Tables 1 and 2). To a stirred mixture of 2-cyclohexen-1-one (2.0 mmol) and carbonyl compound (1.0 mmol) in water (1.0 mL) at room temperature was added the amine catalyst (1.0 mmol). The reaction was stopped by dilution with diethyl ether and washed with 2 M HCl, followed by water. After drying over sodium sulfate, filtration, and evaporation, the crude mixture was analyzed by ^{1}H NMR.

General Procedure for the Baylis−Hillman Reaction (Table 3). To a stirred mixture of *tert*-butyl acrylate (256 mg, 2.0 mmol) and carbonyl compound (1.0 mmol) in water (1.0 mL) at room temperature was added 3-hydroxyquinuclidine (127 mg, 1.0 mmol). The reaction was stopped by dilution with diethyl ether and washed with 2 M HCl, followed by water. After drying over sodium sulfate, filtration, and evaporation, the crude mixture was purified by column chromatography.

2-[Hydroxy(2-nitrophenyl)methyl]acrylic Acid *tert*-Butyl Ester. *tert*-Butyl acrylate (256 mg, 2.0 mmol), *o*-nitrobenzaldehyde (151 mg, 1.0 mmol), and 3-hydroxyquinuclidine (127 mg, 1.0 mmol) were reacted in water (1.0 mL). The mixture was purified by column chromatography using petroleum ether/diethyl ether (1:1) as eluant to produce the adduct as a yellow oil (233 mg, 80%): R_f 0.3 (petroleum ether/diethyl ether, 1:1); IR (film) 3452, 2932, 1709, 1528 cm^{-1}; ^{1}H NMR (250 MHz; $CDCl_3$) 1.3 (s, 9H), 3.7 (bs, 1H), 5.6 (s, 1H), 6.0 (s, 1H), 6.2 (s, 1H), 7.4 (td, J = 7.5 Hz, 1.5 Hz, 1H), 7.5−7.65 (m, 2H), 7.85 (d, J = 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) 27.8, 67.6, 81.7, 124.5, 125.5, 128.6, 128.8, 133.4, 136.6, 142.1, 148.5, 165.1; MS (CI) *m*/*z* (rel intensity) 297 (MNH_4^+, 29), 241 (100), 206 (19); HRMS (CI) (*m*/*z*) calcd for $C_{14}H_{21}O_5N_2$ 297.1450, found $C_{14}H_{21}O_5N_2$ 297.1436. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H 6.1; N 5.0. Found: C, 60.1; H 6.1; N 5.0.

2-(2,2,2-Trifluoro-1-hydroxy-1-phenylethyl)acrylic Acid *tert*-Butyl Ester. *tert*-Butyl acrylate (256 mg, 2.0 mmol), 2,2,2-trifluoroacetophenone (174 mg, 1.0 mmol), and 3-hydroxyquinuclidine (127 mg, 1.0 mmol) were reacted in water (1.0 mL). Purification by column chromatography using petroleum ether/diethyl ether (2:1) as eluant gave the adduct as a colorless oil (120 mg, 40%): R_f 0.27 (petroleum ether/diethyl ether, 2:1); IR (film) 3420, 2980, 1720 cm^{-1}; ^{1}H NMR (250 MHz; $CDCl_3$) 1.3 (s, 9H), 5.5 (s, 1H), 5.95 (s, 1H), 6.45 (s, 1H), 7.25−7.4 (m, 3H), 7.5−7.65 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) 27.7, 79.0 (q, $^2J_{CF}$ = 29 Hz), 83.5, 124.5 (q, $^1J_{CF}$ = 280 Hz), 126.9, 127.8, 128.2, 128.8, 129.1, 130.1, 135.5, 137.4, 166.2; MS (EI) (*m*/*z*) 302 (M^+, 12), 177 (100), 159 (59); HRMS (EI) (*m*/*z*) calcd for $C_{15}H_{17}O_3F_3$ 302.1130, found 302.1125.

2-[Hydroxy(2-chlorophenyl)methyl]acrylic Acid *tert*-Butyl Ester. *tert*-Butyl acrylate (256 mg, 2.0 mmol), *o*-chlorobenzaldehyde (141 mg, 1.0 mmol), and 3-hydroxyquinuclidine (127 mg, 1.0 mmol) were reacted in water (1.0 mL). Purification by column chromatography using 5% ethyl acetate in hexane as eluant gave the adduct as a yellow oil (143 mg, 53%): R_f 0.32 (10% ethyl acetate in hexane); IR (film) 3426, 2933, 1710 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 1.45 (s, 9H), 3.2 (d, J = 4.5 Hz, 1H), 5.54 (t, J = 1.1 Hz, 1H), 5.95 (bd, J = 4.5 Hz, 1H), 6.26 (d, J = 1.1 Hz, 1H), 7.2−7.4 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) 28.0, 69.5, 87.1, 125.7, 127.0, 128.1, 129.0, 129.4, 132.9, 136.8, 138.7, 165.8; MS (EI) (*m*/*z*) 268 (M^+, 6), 154 (76), 139 (74), 57 (100). Anal. Calcd for $C_{14}H_{17}ClO_3$: C, 62.6; H 6.4. Found: C, 62.3; H 6.4.

2-Hydroxy-3-methylenesuccinic Acid 4-*tert*-Butyl Ester. *tert*-Butyl acrylate (256 mg, 2.0 mmol), glyoxylic acid monohydrate (92 mg, 1.0 mmol), triethylamine (101 mg, 1.0 mmol), and 3-hydroxyquinuclidine (127 mg, 1.0 mmol) were reacted in water (1.0 mL) to give the adduct as a colorless oil (114 mg, 56%): IR (film) 3580−2350, 2980, 1721 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 1.45 (s, 9H), 3.1 (bs, 1H), 4.8 (s, 1H), 5.8 (s, 1H), 6.2 (s, 1H), 7.5 (bs, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) 27.9, 70.2, 83.6, 128.9, 137.9, 166.8, 174.2; MS (CI) (*m*/*z*) 220 (MNH_4^+, 83), 203 (MH^+, 12), 164 (100), 147 (34); HRMS (CI) (*m*/*z*) calcd for $C_9H_{15}O_5$ 203.0919, found 203.0919.

Monitoring of Water-Based Reactions (Table 4). To a stirred mixture of *tert*-butyl acrylate (256 mg, 2.0 mmol), benzaldehyde (106 mg, 1.0 mmol), and water (1.0 mL) at room temperature was added 3-hydroxyquinuclidine (127 mg, 1.0 mmol). At selected time points, an aliquot (yield between 0 and 10%) of the reaction mixture was quenched with 2 M HCl/brine (1:1, 0.5 mL), extracted with $CDCl_3$ (0.5 mL), passed through a hydrophobic filter (Whatman IPS filter media catalog no. 6987-1299), and analyzed by ^{1}H NMR.

Monitoring of Formamide-Based Reactions (Table 4, Entry 11). To a stirred mixture of *tert*-butyl acrylate (256 mg, 2.0 mmol), benzaldehyde (106 mg, 1.0 mmol), and formamide (225 mg, 5.0 mmol) at room temperature were added ytterbium triflate (32 mg, 0.05 mmol) and 3-hydroxyquinuclidine (127 mg, 1.0 mmol). At selected time points (yield between 0 and 10%), an aliquot of the reaction mixture was removed, diluted with $CDCl_3$, and analyzed by ^{1}H NMR.

General Procedure for the Baylis−Hillman Reaction under Optimum Catalytic Conditions (Tables 5 and 6). To a stirred mixture of carbonyl compound (1.0 mmol), Michael acceptor (1.2 mmol), and formamide (1.25 mmol) at room temperature under argon was added 3-hydroxyquinuclidine (0.1 mmol). After the time indicated, the reaction was stopped by dilution with ether and washed with 2 M HCl, followed by water. After drying over sodium sulfate, filtration, and evaporation, the crude mixture was purified by column chromatography.

General Procedure for the Baylis−Hillman Reaction under Optimum Stoichiometric Conditions (Tables 5 and 6). To a stirred mixture of carbonyl compound (1.0 mmol), Michael acceptor (1.2 mmol), and formamide (5.0 mmol) at room temperature under argon were added 3-hydroxyquinuclidine (1.0 mmol) and $Yb(OTf)_3$ (0.05 mmol). After the time indicated, the reaction was stopped by dilution with ether and washed with 2 M HCl, followed by water. After drying over sodium sulfate, filtration, and evaporation, the crude mixture was purified by column chromatography.

2-[Hydroxy(2-methoxyphenyl)methyl]acrylic Acid Ethyl Ester. Ethyl acrylate (120 mg, 1.2 mmol), *o*-anisaldehyde

(136 mg, 1.0 mmol), formamide (225 mg, 5.0 mmol), ytterbium triflate (31 mg, 0.05 mmol), and 3-hydroxyquinuclidine (127 mg, 1.0 mmol) were reacted. Purification by column chromatography using 10% ethyl acetate in hexane as eluant gave the adduct as a pale yellow oil (212 mg, 90%): R_f 0.11 (10% ethyl acetate in hexane); IR (film) 3473, 2938, 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 1.2 (t, $J = 7$ Hz, 3H), 3.5 (d, $J = 6$ Hz, 1H), 3.75 (s, 3H), 4.1 (q, $J = 7$ Hz, 2H), 5.65 (s, 1H), 5.75 (d, $J = 6$ Hz, 1H) 6.2 (s, 1H), 6.75−7.0 (m, 2H), 7.15−7.25 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) 14.1, 55.4, 60.8, 68.3, 110.5, 120.7, 125.4, 127.7, 128.9, 129.2, 141.6, 156.6, 166.7; MS (EI) (*m*/*z*) 236 (M^+, 36), 190 (33), 135 (100); HRMS (EI) (*m*/*z*) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1048. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H 6.8. Found: C, 66.2; H 6.8.

Registry Numbers (Provided by the Authors). The following known compounds showed identical data with the literature: 2-(hydroxyphenylmethyl)acrylic acid methyl ester, 29540-54-3;[19] 2-(hydroxyphenylmethyl)acrylic acid ethyl ester, 37442-45-8;[19] 2-(hydroxyphenylmethyl)acrylic acid *tert*-butyl ester, 135513-98-3;[19] 2-[hydroxy(2-nitrophenyl)methyl]acrylic acid ethyl ester, 198902-99-7;[20] 2-[hydroxy(4-nitrophenyl)-methyl]acrylic acid ethyl ester, 88039-47-8;[21] 2-[hydroxy(2-chlorophenyl)methyl]acrylic acid ethyl ester, 88039-46-7;[22] 2-[hydroxy(4-methoxyphenyl)methyl]acrylic acid ethyl ester, 88039-45-6;[23] 2-hydroxymethylacrylic acid ethyl ester, 121065-74-5;[24] 2-[hydroxy(2-isopropyl)methyl]acrylic acid ethyl ester, 135638-64-1;[25] 2-[hydroxy(2-cyclohexyl)methyl]acrylic acid ethyl ester, 145316-19-4;[26] 2-[hydroxy(2-*tert*-butyl)methyl]acrylic acid ethyl ester, 252756-39-1;[27] 2-(hydroxyphenylmethyl)-2-cyclohexen-1-one, 94348-71-7;[28] 2-[hydroxy(2-methoxyphenyl)-methyl]-2-cyclohexen-1-one, 254729-46-9;[5] 2-(hydroxymethyl)-2-cyclohexen-1-one, 105956-40-9;[11a] 2-(1-hydroxy-2-methylpropyl)cyclohexen-1-one, 94348-72-8;[29] 2-(1-hydroxy-2,2-dimethylpropyl)cyclohexen-1-one, 189870-31-3;[30] 2-(1-hydroxyphenylmethyl)cyclopenten-2-one, 122617-89-4;[31] 3-(hydroxyphenylmethyl)but-3-en-2-one, 73255-39-7;[32] 2-(hydroxyphenylmethyl)acrylonitrile, 19362-96-0,[33] 2-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)acrylic acid ethyl ester, 8063518.[34]

Acknowledgment. We thank EPSRC and GSK for support of this work.

Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016073Y

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