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# Correlation between p$K_a$ and Reactivity of Quinuclidine-Based Catalysts in the Baylis−Hillman Reaction: Discovery of Quinuclidine as Optimum Catalyst Leading to Substantial Enhancement of Scope

Varinder K. Aggarwal,* Ingo Emme, and Sarah Y. Fulford

*University of Bristol, School of Chemistry, Cantock's Close, BS8 1TS Bristol, U.K.*

*v.aggarwal@bristol.ac.uk*

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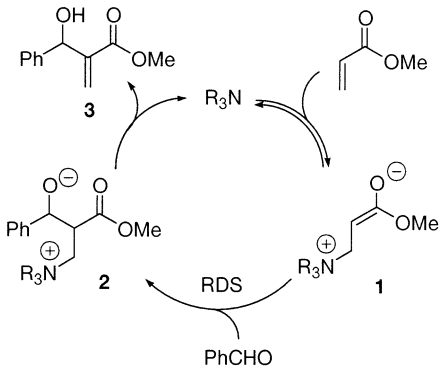
The reactivity of a variety of quinuclidine-based catalysts in the Baylis−Hillman reaction has been examined, and a straightforward correlation between the basicity of the base and reactivity has been established, without exception. The following order of reactivity was established with p$K_a$'s of the conjugate acids (measured in water) given in parentheses: quinuclidine (11.3), 3-hydroxyquinuclidine (9.9), DABCO (8.7), 3-acetoxyquinuclidine (9.3), 3-chloroquinuclidine (8.9), and quinuclidinone (7.2). The higher than expected reactivity of DABCO, based on its p$K_a$, was analyzed by comparing the relative basicity of DABCO and 3-acetoxyquinuclidine *in DMSO*. It was found that in aprotic solvent, DABCO was 0.6 p$K_a$ units more basic than 3-acetoxyquinuclidine, thus establishing a direct link between p$K_a$ of the amine and its reactivity. In contrast to previous literature work that reported the contrary, quinuclidine, which has the highest p$K_a$, was found to be the most active catalyst. The reaction profile with quinuclidine showed significant autocatalysis, which suggested that the presence of proton donors might further enhance rates. Thus, a series of additives bearing polar X−H bonds were investigated and it was found that methanol, triethanolamine, formamide, and water all provided additional acceleration. Methanol was found to be optimum, and the powerful combination of quinuclidine with methanol was tested with a host of aldehydes and Michael acceptors. Not only were the reactions more efficient and faster than previously reported, but now new substrates that were previously unreactive could be employed. Notable examples include the use of acetylenic aldehydes and the employment of vinyl sulfones, acrylamides, $\delta$-lactones, and even $\alpha,\beta$-unsaturated esters bearing a $\beta$-substituent.

## Introduction

The Baylis−Hillman reaction[1] is an exquisite reaction as simple starting materials are converted into densely functionalized products in a catalytic process without generating waste or byproducts (Scheme 1).[2] However, the reaction has traditionally suffered from low reaction rates and limited substrate scope. There has, therefore, been considerable interest in enhancing reaction rate as through this endeavor both practicality and scope can be improved.

The rate-determining step (RDS) of the Baylis−Hillman reaction is the reaction between the ammonium enolate **1** and the aldehyde (Scheme 1).[3] Thus, increasing the amount of the enolate or activation of the aldehyde will result in increased rates. We first demonstrated that the use of lanthanides resulted in modest rate enhancement and that further acceleration could be achieved by the addition of alcohol ligands, e.g., binol and triethanolamine.[4] We believed that the primary source of acceleration in these systems was due to the enhanced acidity of the OH group of the additive as a result of metal binding,

**SCHEME 1. Catalytic Cycle of the Baylis−Hillman Reaction**




(1) Baylis, A. B.; Hillman, M. E. D. *Offenlegungsschrift* 2155113, **1972**; U.S. Patent 3,743,669; *Chem. Abstr.* **1972**, *77*, 34174q.

(2) For reviews, see: (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (d) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670.

(3) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, *3*, 285−288.

(4) (a) Aggarwal, V. K.; Tarver, G. J.; McCague, R. *Chem. Commun.* **1996**, 2713−2714. (b) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183−7189. (c) For other examples of metal-accelerated Baylis−Hillman reactions, see: Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539−1542.

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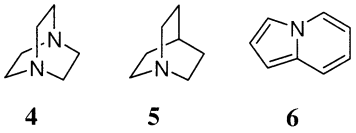


**4** **5** **6**

**FIGURE 1.** The original catalysts used by Baylis and Hillman.

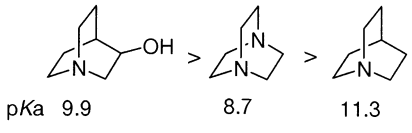
which resulted in enhanced hydrogen-bonded activation of the aldehyde.[4b] We[5] and others[6] have also shown that enhanced rates could be achieved by conducting reactions in water or formamide. In these highly polar solvents, we believe that rate acceleration is achieved by not only hydrogen-bonded activation of the aldehyde but also by increasing the amount of the zwitterionic intermediate **1** by solvation.

Most methods for promoting the Baylis−Hillman reaction have largely focused on activation of the aldehyde. We have also considered methods for increasing the amount of the ammonium enolate **1** through stabilization of the ammonium ion. This should provide increased concentrations of the reactive intermediate without having a negative impact on the rate of the subsequent reaction between the enolate and aldehyde as the enolate is not stabilized.[7] We showed that amidines[8] (DBU in particular) and guanidines[8,9] provided substantial increases in rate, and we believe this occurs by stabilization of the ammonium ion through delocalization. However, while good rates were achieved with DBU, the reaction was limited to non-enolizable aldehydes.

A good measure of an amine's basicity is the p$K_a$ of its conjugate acid. DBU has a high p$K_a$[10] but is also sterically hindered, a feature that usually results in severely reduced rates. The high rate increase observed with DBU indicates that, in this specific case, the basicity of the amine is more important than its steric hindrance. However, in the absence of steric effects, there should be a good correlation between reaction rate and p$K_a$, as amines with high p$K_a$ should give higher concentrations of the ammonium enolate.

In the original paper by Baylis and Hillman, three amine catalysts were tested, DABCO **4**, quinuclidine **5**, and pyrrocoline **6**, but their relative efficiencies were not clearly stated (Figure 1).[1,11]

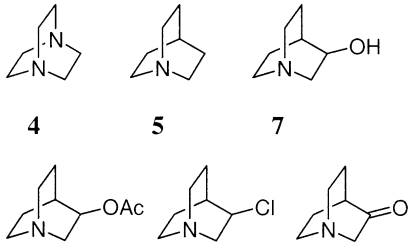
Long reaction times have been reported using DABCO, and in the search for more active catalysts, Drewes found that 3-hydroxyquinuclidine **7** showed considerably faster rates.[12] The superiority of 3-hydroxyquinuclidine over



p*K*a 9.9 8.7 11.3

**7** **4** **5**

**FIGURE 2.** Previously reported activities of quinuclidine-based catalysts in the Baylis−Hillman reaction with p$K_a$'s.



**4** **5** **7**

**8** **9** **10**

**FIGURE 3.** Catalysts investigated in the Baylis−Hillman reaction: DABCO **4**, quinuclidine **5**, 3-hydroxyquinuclidine **7**, 3-acetoxyquinuclidine **8**, 3-chloroquinuclidine **9**, and 3-quinuclidinone **10**.

DABCO and quinuclidine[13a,b] and the superiority of DABCO over quinuclidine[13c] were confirmed, and indeed, for some time 3-hydroxyquinuclidine was regarded as the optimum catalyst for the Baylis−Hillman reaction. Thus, on the basis of the literature reports, 3-hydroxyquinuclidine **7** was better than DABCO **4**, which was better than quinuclidine **5** (Figure 2). However, in comparing the three quinuclidine-based catalysts, for which steric differences would be expected to be insignificant, the expected correlation between p$K_a$[14] and reaction rate was clearly not apparent. On the basis of p$K_a$, quinuclidine should have been the best catalyst but was reported to be the worst. We therefore tested a broader range of quinuclidine-based catalysts to examine whether a correlation between rate and p$K_a$ existed and have reexamined the activity of quinuclidine. We now report that there is a direct correlation between p$K_a$ and reaction rate and that quinuclidine is in fact the best catalyst to date. This new discovery provides substantial improvements in rate and a very substantial increase in scope of the Baylis−Hillman reaction.

## Results

A series of reactions were conducted between 2-pyridinecarboxaldehyde (1 equiv),[15] methyl acrylate (1.2 equiv) and different quinuclidine-based catalysts (Figure 3). Reactions were conducted neat, and 5 mol % catalyst was employed to ensure homogeneity of all of the reaction

(5) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510−514.

(6) (a) Yu, C. Z.; Liu, B.; Hu, L. Q. *J. Org. Chem.* **2001**, *66*, 5413−5418. (b) Jenner, G. *High Pres. Res.* **1999**, *16*, 243−252. (c) Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *35*, 7947−7948.

(7) Stabilisation of the enolate would also provide increased concentrations of **1** but would also result in reduced reactivity of **1**.

(8) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311−2312.

(9) Leadbetter has also shown that guanidines are good catalysts: Leadbeater, N. E.; van der Pol, C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2831−2835.

(10) p$K_a$ refers to the p$K_a$ value of the conjugate acid of the amine catalysts. The p$K_a$ of DBU is 11.3. Höfle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

(11) The catalysts appear in separate claims of the patent in the order DABCO, pyrrocoline and quinuclidine. It is not clear if this order reflects the order or importance of the catalysts.

(12) (a) Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495−500. (b) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1565−1572.

(13) (a) Markó, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015−1024. (b) Bailey, M.; Markó, I. E.; Ollis, D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509−4512. (c) Ciganek, E. *Org. React.* **1997**, *51*, 207. In this review, personal communications between S. E. Drewes, N. D. Emslie, and Ciganek are cited.

(14) (a) The p$K_a$ values of quinuclidine, 3-hydroxyquinuclidine, 3-acetoxyquinuclidine, 3-chloroquinuclidine, and 3-cyanoquinuclidine were taken from: Grob, C. A. *Helv. Chim. Acta* **1985**, *68*, 882−886. (b) The p$K_a$ values of 3-quinuclidinone and DABCO were taken from: Hine, J.; Chen, Y.-J. *J. Org. Chem.* **1987**, *52*, 2091−2094.

(15) 2-Pyridinecarboxaldehyde was chosen as 3-hydroxyquinuclidine showed the highest solubility in it.

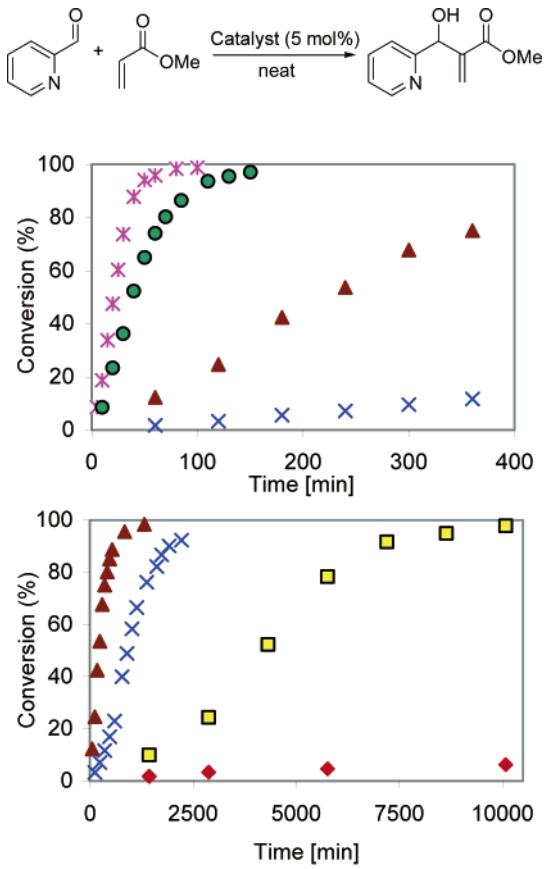



**FIGURE 4.** Effect of different quinuclidine-based catalyst on the rate of the Baylis−Hillman reaction. Conversion represents the ratio of the Baylis−Hillman product: unreacted aldehyde (determined by $^1$H NMR). The reaction was performed using quinuclidine (pink asterisks, QD), 3-hydroxyquinuclidine (green circles, 3-HQD), diazabicyclo[2.2.2]octane (dark red triangles, DABCO), 3-acetoxyquinuclidine (blue X, 3-AcOQD), 3-chloroquinuclidine (yellow squares, 3-ClQD), and 3-quinuclidinone (red diamonds, QD=O).

**TABLE 1. Effect of the Basicity of Quinuclidine-Based Catalyst on the Rate of the Baylis−Hillman Reaction**

| catalyst | rate[a] (%/min) | p$K_a$[b] | $k_{rel}$ |
|---|---|---|---|
| quinuclidine (QD) **5** | 1.8 | 11.3[c] | 9.0 |
| 3-hydroxyquinuclidine (3-HQD) **7** | $8.8 \times 10^{-1}$ | 9.9[d] | 4.3 |
| 3-acetoxyquinuclidine (3-AcOQD) **8** | $3.1 \times 10^{-2}$ | 9.3 | 0.15 |
| 3-chloroquinuclidine (3-ClQD) **9** | $8.2 \times 10^{-3}$ | 8.9 | 0.04 |
| diazabicyclo[2.2.2]octane (DABCO) **4** | $2.1 \times 10^{-1}$ | 8.5[e] | 1 |
| 3-quinuclidinone (QD=O) **10** | $1.3 \times 10^{-3}$ | 6.9 | 0.006 |

[a] Initial rates (<20% conversion). [b] All p$K_a$'s were determined in water.[14] [c] Quinuclidine was found to be more basic than 3-hydroxyquinuclidine in DMSO by 0.4 p$K_a$ units. [d] 3-Hydroxyquinuclidine was found to be more basic than DABCO in DMSO by 0.3 p$K_a$ units. [e] DABCO was found to be more basic than 3-acetoxyquinucidine in both DMSO and $CD_3CN$ by 0.6 p$K_a$ units.

mixtures (3-hydroxyquinuclidine was the least soluble, and it was only possible to dissolve 5 mol % of this catalyst in the reaction mixture). Aliquots were removed at various time intervals, and the extent of the reaction was determined by NMR. The results are presented in Figure 4 and Table 1. From this simple analysis, it was clear that there was a broad correlation between reaction rate and p$K_a$ of the quinuclidine base. Quinuclidine,

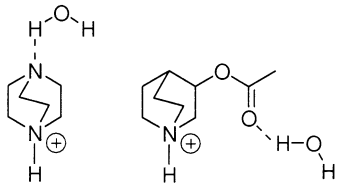


**FIGURE 5.** Hydrogen-bonded diazabicyclo[2.2.2]octane ammonium salt and 3-acetoxyquinuclidine ammonium salt.

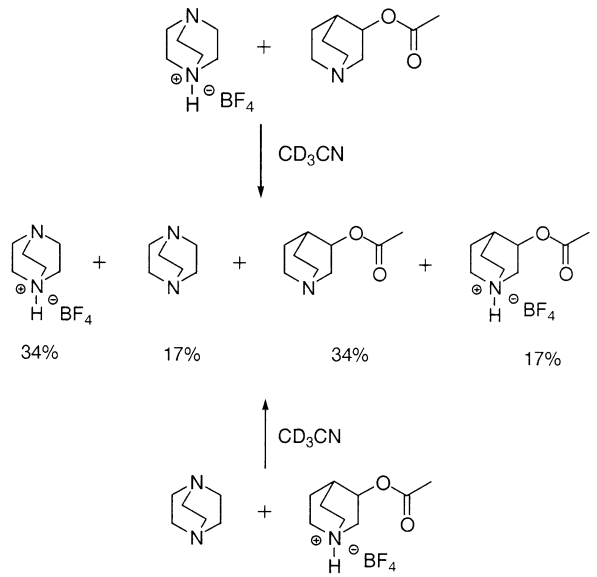
which has the highest p$K_a$, provided the fastest rate, and quinuclidinone, which has the lowest p$K_a$, gave the lowest rate. *We were surprised at the high reactivity of quinuclidine, as previous reports*[13] *had indicated that it was a poor catalyst.* Attempts to reproduce the literature results by using different quality catalysts (sublimed, used directly from the commercial supplies, aged by leaving open to air, and aged over an atmosphere of $CO_2$) were all unsuccessful: *all forms of the catalyst were almost equally effective.* The correlation between p$K_a$ and rate applied to all substrates except DABCO, which showed a higher than expected rate based on p$K_a$, but as DABCO possesses two basic nitrogens, it was possible that its higher effective molarity was responsible for its enhanced rate. However, even at lower loadings (2.5 mol %) DABCO still gave faster rates than both 3-acetoxyquinuclidine and 3-chloroquinuclidine.

We were intrigued as to the origin of the increased reactivity of DABCO, which had a p$K_a$ of 8.5, over 3-acetoxyquinuclidine, which had a p$K_a$ of 9.3. The p$K_a$ values of the quinuclidines have been determined in water and we suspected that the p$K_a$ of DABCO might be lowered as a result of hydrogen bonding of the second nitrogen with water (Figure 5). In contrast, hydrogen bonding between the acetate of 3-acetoxyquinuclidine and water is likely to be much weaker, and therefore, hydrogen bonding will not have a significant effect on its p$K_a$. We therefore wanted to determine the relative basicity of DABCO and 3-acetoxyquinuclidine in aprotic media, the medium in which our Baylis−Hillman reactions were conducted. To achieve this, we measured the equilibrium between a 1:1 mixture of DABCO·$HBF_4$ and 3-acetoxyquinuculidine (Scheme 2) and, as a control, a 1:1 mixture of 3-acetoxyquinuclidine·$HBF_4$ and DABCO (see the Supporting Information for full details).[16] Irrespective of which salt we started with we obtained the same equilibrium ratio in favor of the DABCO salt (2.0:1), thus demonstrating that DABCO was indeed a stronger base than 3-acetoxyquinuclidine in aprotic solvent.[17] A ratio of 2.0:1 correlates to an increase in p$K_a$ of DABCO relative to 3-acetoxyquinuclidine by 0.6.[18] Using the same technique, we also established that 3-hydroxyquinuclidine was a stronger base than DABCO

(16) The equilibrium ratio was determined by NMR in $CD_3CN$ and DMSO-$d_6$. The $BF_4^-$ salt was employed as it was considerably more soluble than the $Cl^-$ salt in $CD_3CN$. Furthermore, some hydrolysis of the acetate occurred upon treatment of 3-acetoxyquinuclidine with aqueous HCl. No hydrolysis occurred upon treatment of the same base with $HBF_4$ in $Et_2O$.

(17) A second independent test verified our supposition that hydrogen-bonding of the second nitrogen of DABCO was responsible for its reduced p$K_a$ relative to 3-acetoxyquinuclidine in protic media. When reactions were conducted in water, 3-acetoxyquinuclidine showed similar rates to DABCO but when the DABCO concentration was halved (to take into account the presence of two nitrogens), the reaction using 3-acetoxyquinuclidine was faster.

**SCHEME 2. Determination of Relative Basicity of DABCO and 3-Acetoxyquinuclidine**




(1.5:1 ratio, increase in p$K_a$ by 0.3) and that quinuclidine was a stronger base than 3-hydroxyquinuclidine (1.6:1 ratio, increase in p$K_a$ by 0.4) in aprotic media (see the Supporting Information for full details). With these "corrections" in the p$K_a$'s, *the correlation between p$K_a$ and reaction rate applied to all of the quinuclidine-based catalyst without exception*. This correlation between rate of the Baylis−Hillman reaction and p$K_a$ of the base will be an extremely useful parameter in the design of alternative quinuclidine-based catalysts, which can of course be extended to all amine catalysts, including chiral ones. However, for more general amine catalysts, rates of reaction will depend on both the basicity of the amine and steric hindrance around the nitrogen atom.

The origin of rate acceleration of 3-hydroxyquinuclidine over DABCO was initially believed to be due to an intramolecular hydrogen bond between the hydroxyl group and the enolate **11**,[12] but subsequent modeling studies showed substantial strain in such an intermediate.[13c] Since then, the model has been revised and the origin of the rate of acceleration has been ascribed to the ability of 3-hydroxyquinuclidine to protonate the developing zwitterionic intermediate intermolecularly **12** (Figure 6).[2b,c] However, our previous work showed that

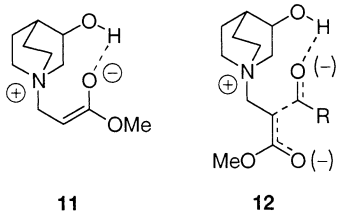



**FIGURE 6.** Proposed intramolecular hydrogen bonding involved in Baylis−Hillman reactions using 3-hydroxyquinuclidine.

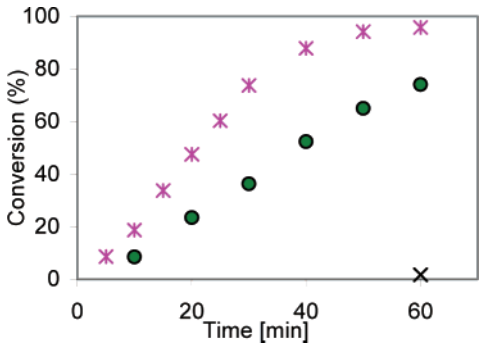



**FIGURE 7.** Reaction profiles of quinuclidine, 3-hydroxyquinuclidine (pink asterisks, QD), and 3-hydroxyquinuclidine (green circles, 3-HQD).

for reactions conducted in water 3-hydroxyquinuclidine was still superior to DABCO,[5] indicating that hydrogen bonding was not the primary reason for enhanced rates. From that observation and the current study, it is clear that, *rather than hydrogen bonding, it is the higher p$K_a$ of 3-hydroxyquinuclidine relative to DABCO that is responsible for its enhanced reactivity*. The hydroxyl group of 3-hydroxyquinuclidine does still play a role in enhancing rates although only a minor one.

A closer analysis of the reaction profile of quinuclidine revealed a sigmoidal curve with a point of inflection instead of a parabolic curve (Figure 7). *This implies autocatalysis*; i.e., the product of the reaction is enhancing the rate. The origin of this rate acceleration is presumably the hydroxyl of the product, which activates one or both of the components as described above. In fact, autocatalysis should be observed with other amine catalysts that are devoid of hydroxyl groups, but as far as we are aware, this has not been previously reported for the Baylis-Hillman reaction. Indeed, pronounced autocatalysis was observed with the other quinuclidine based catalysts: 3-acetoxyquinuclidine, DABCO, and 3-chloroquinuclidine (Figure 4). 3-Hydroxyquinuclidine showed much less pronounced autocatalytic behavior presumably because a hydroxyl group was already present at the start of the reaction. Thus, to enhance rates further with quinuclidine as catalyst, hydroxyl groups needed to be present at the start of the reaction. Thus, reactions were conducted in the presence of protic additives:[19] water, methanol, formamide and triethanolamine and the results are presented in Figure 8. Further substantial rate enhancements were indeed observed with all of the additives particularly methanol, formamide and triethanolamine.[20] We decided to focus further efforts on methanol as it is easier to evaporate and may aid solubility of

(18) The increase in p$K_a$ for DABCO relative to 3-acetoxyquinuclidine was calculated as follows:

$$[B_1H^+][B_2] \rightleftharpoons [B_1][B_2H^+]$$

$$K = \frac{[B_1][B_2H^+]}{[B_1H^+][B_2]}$$

$$K = \frac{K_a(B_2)}{K_a(B_1)}$$

$$pK_a(B_2) - pK_a(B_1) = -\log_{10}\frac{[B_1][B_2H^+]}{[B_1H^+][B_2]}$$

$$pK_a(B_2) - pK_a(B_1) = -\log_{10}\frac{[0.34][0.34]}{[0.17][0.17]}$$

$$pK_a(B_2) - pK_a(B_1) = \mathbf{0.6}$$

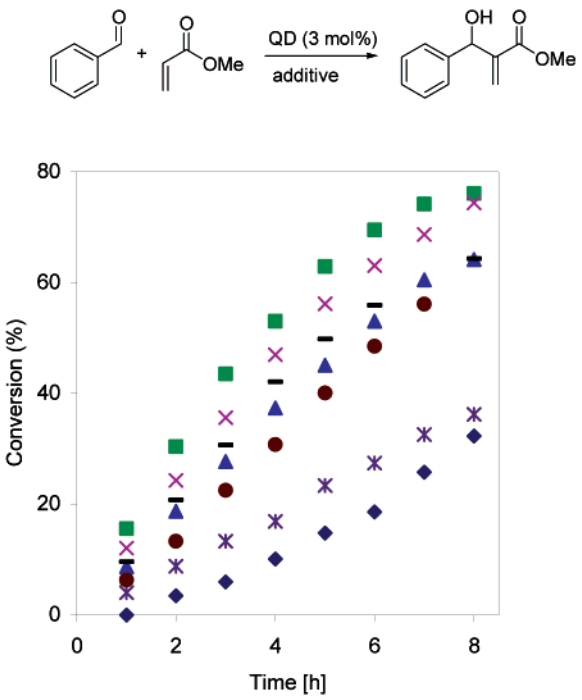



**FIGURE 8.** Effect of different additives on the rate of the Baylis−Hillman reaction using no additive (dark blue diamonds), 0.25 equiv of water (purple asterisk), 0.25 equiv of formamide (blue triangles), 0.25 equiv of methanol (dark red circles), 0.75 equiv of methanol (pink X), 1.50 equiv of methanol (black dashes), and 0.10 equiv of triethanolamine (green squares).

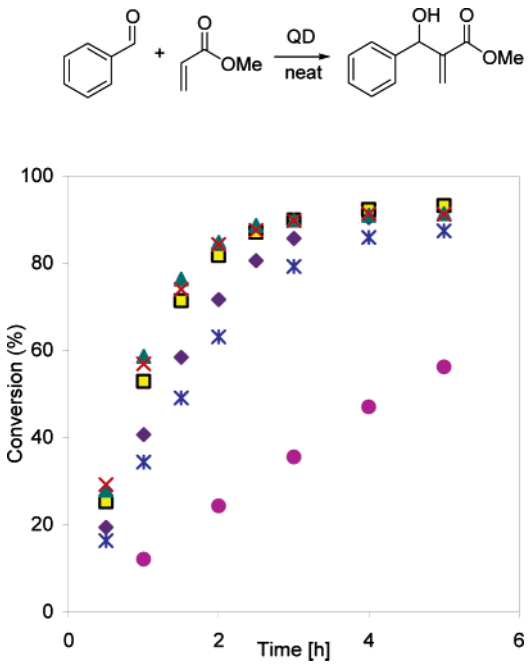



**FIGURE 9.** Effect of the amounts of catalyst on the rate of the Baylis−Hillman reaction using 3 mol % (pink circles), 10 mol % (blue asterisks), 25 mol % (red X), 50 mol % (green triangles), 75 mol % (yellow squares), and 1 equiv (purple diamonds) of quinuclidine.

any solid starting materials, which can be problematic for the reactions that are conducted neat.[21] Optimization of the amount of methanol revealed that 0.75 equiv gave faster rates than 0.25 and 1.5 equiv. Variation in the amount of quinuclidine revealed that higher catalyst loading did not necessarily lead to higher rates: optimum rates were achieved with 25, 50, and 75 mol % and so the lower loading of quinuclidine was selected for further study (Figure 9).

Having established the optimum conditions for the Baylis−Hillman reaction, we explored the scope and limitations of the reaction. Where possible, we have compared our results with the current best results reported. It should be noted that our conditions usually employ 25 mol % catalyst whereas most of the literature examples require 1 equivalent or even greater amounts of the amine catalyst.

We initially investigated reactions of methyl acrylate with a variety of aldehydes (Table 2). Simple aliphatic and aromatic aldehydes worked well (entries 1−4), providing adducts in shorter reaction times and higher yields than has previously been observed. *p*-Methoxybenzaldehyde (entry 4) was, as expected, found to be a slow reacting aldehyde and gave similar results in terms of yield and reaction time to the use of 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene. The electron-deficient aromatic aldehydes in entries 5 and 6 were solid aldehydes that posed additional problems as such reactions could not be conducted neat. With these substrates a minimum amount of dimethylformamide was added to the initial suspension to dissolve all of the reactants and the reactions were monitored as before. Again, higher yields and shorter reaction times were achieved with our improved system. Cinnamaldehyde provided another dramatic example of the efficiency of the new conditions (entry 9): a 62% yield after 3 h was obtained whereas the previous highest yield was 43% after 24 h.

Acetylenic aldehydes[24] could also be employed for the first time although curiously, the methyl ether **13** was obtained when the reaction was conducted in the presence of methanol whereas the normal Baylis−Hillman adduct **14** was obtained just using quinuclidine (Scheme 3). Treatment of **14** under the same Baylis−Hillman conditions provided the methyl ether **13** but only in a low yield (40%, plus 60% starting material), suggesting that there may be additional pathways for its formation in the Baylis−Hillman reaction conducted in the presence of methanol.

(19) The use of protic additives to enhance the rates has been described previously although not in the context of autocatalysis; see refs 6c and 12, also: Basaviah, D.; Sarma, P. K. S. *Synth Commun.* **1990**, *20*, 1611; Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611−5614. Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241−1244.

(20) 2-Propanol and trifluoroethanol were also tested as additives, but they showed less rate enhancement than methanol.

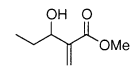
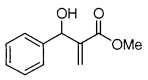
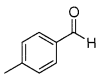
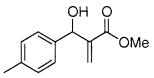
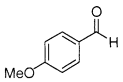
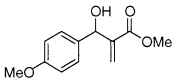
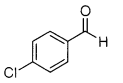
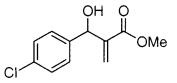
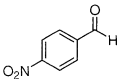
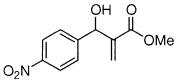
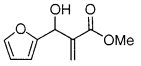
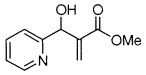
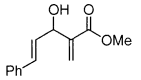
(21) A reviewer suggested the possibility that the amine deprotonated the alcohol (methanol or Baylis−Hillman product) and that the resulting alkoxide was the true catalyst under these conditions. However, in the attempted reaction between methyl acrylate and benzaldehyde, sodium methoxide in methanol did not give any Baylis−Hillman product, showing that methoxide itself is unable to catalyse this reaction.

(22) Rosa, N. J.; Afonso, C. A. M.; Santos, A. G. *Tetrahedron* **2001**, *19*, 4189−4194.

(23) Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.

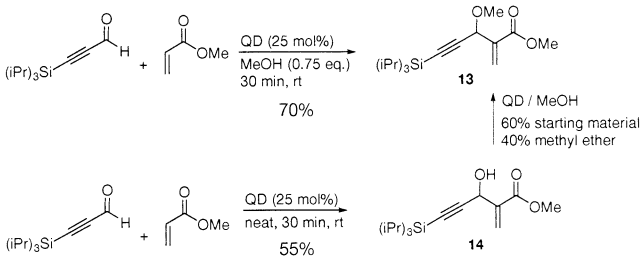
(24) Activated acetylenic fluoro ketones have been employed in the Baylis−Hillman reaction: Venkat-Ram-Reddy, M.; Rudd, M. T.; Veeraraghavan-Ramachandran, P. *J. Org. Chem.* **2002**, *67*, 5382−5385.

**TABLE 2. Baylis−Hillman Reaction of Aldehydes with Methyl Acrylate[a]**

| Entry | Substrate | Product | Conditions | Time | Yield (%) | Previous Optimum Results |
|---|---|---|---|---|---|---|
| 1 |  |  | A | 7 h | 83 | 14 h, 83%[a,6a] |
| 2 |  |  | A | 3 h | 88 | 6 h, 89%[b,8] |
| 3 |  |  | A | 9 h | 82 | 24 h, 61%[c,22] |
| 4 |  |  | A<br>B | 48 h<br>48 h | 62<br>67 | 48 h, 62%[b,8]<br>24 h, 39%[c,22] |
| 5 |  |  | C<br>(8 M) | 3 h | 88 | 24 h, 72%[c,22] |
| 6 |  |  | C<br>(2.75 M) | 0.5 h | 94 | 1 h, 95%[b,8] |
| 7 |  |  | A | 1 h | 84 | 20 h, 85%[a,6a] |
| 8 |  |  | A | 20 min | 96 | 1 h, 100%[a,6a] |
| 9 |  |  | A | 3 h | 62 | 24 h 43 %[c,22]<br>45min, 15%[d,23] |

[a] Conditions employed: (A) aldehyde (1 equiv), methyl acrylate (1.2 equiv), quinuclidine (0.25 equiv), methanol (0.75 equiv); (B) aldehyde (1 equiv), methyl acrylate (1.2 equiv), quinuclidine (1 equiv), methanol (0.75 equiv): (C) aldehyde (1 equiv), methyl acrylate (1.2 equiv), quinuclidine (0.5 equiv), methanol (0.75 equiv), DMF (minimum amount). Literature conditions: (a) 1:3:1 aldehyde/acrylate/DABCO, 1,4-dioxane/$H_2O$ (1:1, v/v), rt; (b) 1:1:1 aldehyde/acrylate/DBU, rt; (c) 1:1.1:1 aldehyde/acrylate/DABCO, rt, 100 $\mu$L/mmol [bmim][$PF_6$]; (d) 1:10:0.5 aldehyde/acrylate/DABCO, microwave (domestic oven, 650 W).

**SCHEME 3. Baylis−Hillman Reaction of Propargylic Aldehydes**

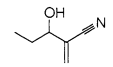
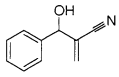
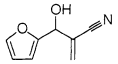
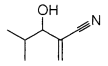



Reactions with acrylonitriles were also tested and again higher yields at shorter reaction times were achieved (Table 3). Among others, previous conditions have employed high pressure to achieve high yields after very short reaction times, but our simple chemical system was once again found to be highly effective for all substrates tested.

Acrylamides are very poor Michael acceptors and until earlier this year[30] had not succumbed to the Baylis−Hillman reaction. The recently reported conditions employed DABCO (1 equiv) in water and moderate to high yields were achieved, but only with highly reactive aldehydes. We found that using our conditions but with additional methanol or DMF to dissolve the acrylamide, faster reactions were achieved (Table 4, entries 1−3). Furthermore, less reactive electrophiles could now be employed (e.g. benzaldehyde, entry 4) whereas in the

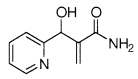
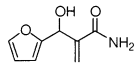
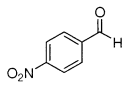
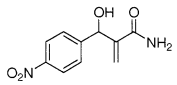
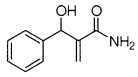
(25) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007−5010.
(26) Reddy, L. R.; Rao, K. R. *Org. Prep. Proced. Int.* **2000**, *32*, 185−188.
(27) (a) Kundu, M. K.; Bhat, S. V. *Synth. Comm.* **1999**, *29*, 93−101. (b) Kundu, M. K.; Sundar, N.; Kumar, S. K.; Bhat, S. V.; Biswas, S.; Valecha, N. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 731−736.
(28) Hill, J. S.; Issacs, N. S. *J. Chem. Res., Miniprint* **1988**, *10*, 2641−2676.
(29) Basavaiah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1987**, *17*, 587−592.
(30) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219−223.

**TABLE 3. Baylis–Hillman Reaction of Aldehydes with Acrylonitrile[a]**

| Entry | Substrate | Product | Conditions | Time | Yield (%) | Previous Optimum Results |
|---|---|---|---|---|---|---|
| 1 |  |  | A | 3 h | 81 | 5 min, 5 kbar, 70%[a,25] |
| 2 |  |  | A | 1 h | 87 | 1 h 70% [b,26]<br>4 h 97%[c,5]<br>5 min, 5 kbar, 95 %[a,25] |
| 3 |  |  | A | 20 min* | 78 | – [d,27] |
| 4 |  |  | A | 6 h | 76 | 5 d, 74% [e,28]<br>40 h, 66%[f,29] |

[a] Conditions employed: (A) aldehyde (1 equiv), acrylonitrile (1.2 equiv), quinuclidine (0.25 equiv), methanol (0.75 equiv). Literature conditions: (a) 1:1:1 aldehyde/acrylonitrile/DABCO, 5 kbar; (b) 1:1:1 aldehyde/acrylonitrile/DABCO, $\beta$-cyclodextrin complex, solid-state conditions; (c) 1:1.2:1 aldehyde/acrylontirile/3-HQD, $H_2NCHO$ (5 equiv), $Yb(OTf)_3$ (0.05 equiv); (d) no condition or yield given; (e) 1:1:0.06 aldehyde/acrylonitrile/DABCO; (f) 1:1.5:0.15 aldehyde/acrylonitrile/DABCO. *After 20 min rapid decomposition was observed.

**TABLE 4. Baylis–Hillman Reaction of Aldehydes with Acrylamide[a]**

| Entry | Substrate | Product | Conditions | Time | Yield (%) | Previous Optimum Results |
|---|---|---|---|---|---|---|
| 1 |  |  | MeOH (14 M) [a] | 5 h | 83 | 24 h, 89% |
| 2 |  |  | MeOH (13 M) [a] | 5 h | 66 | – (48 h, 61% [c]) |
| 3 |  |  | MeOH (75 mol%)<br>16 M DMF [a] | 4 h | 65 | 24 h, 95% |
| 4 |  |  | MeOH (7.5 M) [b] | 3 d | 55 | – |

[a] Conditions employed: (a) aldehyde (1 equiv), acrylamide (1 equiv), quinuclidine (0.5 equiv) in methanol; (b) aldehyde (1 equiv), acrylamide (1 equiv), quinuclidine (1 equiv) in methanol. Literature conditions: 1:1:1 DABCO/aldehyde/acrylamide, 5 mL of water, rt; (c) compared with 3-hydroxy-2-methylene-3-(5-hydroxymethylfuran-2-yl)propionamide.

previous system they were inert. Other slow-reacting substrates have also been examined (vinyl sulfones), and once again, our new catalyst system was found to be markedly superior to existing processes (Table 5).[31] This is most dramatically illustrated in the reaction between phenyl vinyl sulfone and benzaldehyde. Using DABCO, 57% yield was achieved after 21 days, but under our conditions we obtained 63% yield after just 1 day (entry 2).

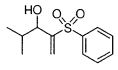
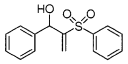
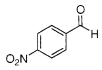
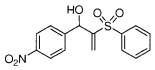
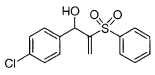
We were even able to extend the Baylis-Hillman reaction to a new class of Michael acceptors, $\alpha,\beta$-unsaturated $\delta$-lactones, which gave good yields of the corresponding adducts with aromatic aldehydes (Table 6).[33] Finally the power of the new methodology is illustrated with methyl crotonate, a substrate which only participates in the Baylis-Hillman reaction under microwave irradiation,[23] and is even unreactive at 10 kbar pressure.[25] Using quinuclidine and methanol, at ambient pressure, methyl crotonate reacted with 2-pyridinecarboxaldehyde, furnishing the Baylis–Hillman adduct in 25% yield after 21 days (Table 6). We are currently exploring the combination of the newly discovered chemical method for accelerating the Baylis–Hillman reaction with known physical methods (high pressure/microwave

(31) Under standard conditions, employing methanol as additive, an inseparable side product was obtained. Side products were also observed when DMF was used, but these were minimised when dioxane was utilised.

(32) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1998**, *44*, 6095–6106.

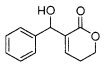
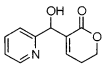
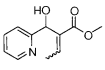
(33) A chiral $\alpha,\beta$-unsaturated $\gamma$-lactone has recently been used in the Baylis–Hillman reaction. Standard conditions were ineffective, but the method of Hu (ref 6a) was successfully employed. A mixture of $\alpha$, $\gamma$, and $\alpha + \gamma$ "aldol" products was obtained in nearly racemic form from enantiomerically pure lactone (15% ee measured by rotation), which shows that a significant pathway is via enolization by DABCO rather than conjugate addition: Franck, X.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 1449–1451.

**TABLE 5. Baylis−Hillman Reaction of Aldehydes with Phenyl Vinyl Sulfone[a]**

| Entry | Substrate | Product | Conditions | Time | Yield (%) | Previous Optimum Results. |
|---|---|---|---|---|---|---|
| 1 |  |  | E | 72 h | 40 | – |
| 2 |  |  | E | 24 h | 63 | 21 d, 57%[b,32] |
| 3 |  |  | F (1 M) | 24 h | 69 | – |
| 4 |  |  | F (2.6 M) | 96 h | 75 | – |

[a] Conditions employed: (E) aldehyde (2.5 equiv), phenyl vinyl sulfone (1 equiv), quinuclidine (0.25 equiv); (F) aldehyde (1 equiv), phenyl vinyl sulfone (1.2 equiv), quinuclidine (0.25 equiv), dioxane (minimum amount). Literature conditions: (b) phenyl vinyl sulfone (1 equiv), aldehyde (large excess), DABCO (0.1 equiv).

**TABLE 6. Baylis−Hillman Reaction of Aldehydes with 5,6-dihydro-2*H*-pyran-2-one and Methyl Crotonate[a]**

| Entry | Substrate | Product | Conditions | Time | Yield (%) | Previous Optimum Results. [b] |
|---|---|---|---|---|---|---|
| 1 |  |  | D | 72 h | 70 | – |
| 2 |  |  | D | 7 h | 69 | – |
| 3 |  |  | B | 21 d | 25 | – |

[a] Conditions employed: (B) aldehyde (1 equiv), 5,6-dihydro-2*H*-pyran-2-one (1.2 equiv), quinuclidine (1 equiv), methanol (0.75 equiv); (D) aldehyde (1 equiv), 5,6-dihydro-2*H*-pyran-2-one (1.2 equiv), quinuclidine (0.25 equiv). Literature conditions: (b) no previous optimum results, new compounds.

irradiation) to reduce reaction times with these especially difficult substrates.

In summary, we have found that there is a direct correlation between p$K_a$ and activity of quinuclidine-based catalysts in the Baylis−Hillman reaction: the higher the p$K_a$, the faster the rate. Presumably, high p$K_a$ provides enhanced stabilization of the intermediate ammonium enolate, resulting in its increased concentration without compromising its reactivity, which in turn leads to faster rates. Even though the p$K_a$'s are measured in $H_2O$ and the Baylis−Hillman reactions are conducted in aprotic media, the correlation nevertheless applied to all quinuclidine-based catalyst except for DABCO. Analysis of the p$K_a$ of DABCO (8.7 in $H_2O$) revealed that while it was indeed a weaker base than 3-acetoxyquinuclidine (9.3 in $H_2O$) in $H_2O$, in DMSO the situation was reversed. This correlated with reactivity: DABCO was superior to 3-acetoxyquinuclidine in aprotic media but in $H_2O$ showed similar reactivity. It is believed that the second nitrogen of DABCO is involved in hydrogen bonding in $H_2O$, which results in a lower than expected p$K_a$. The origin of the rate acceleration of 3-hydroxyquinuclidine over DABCO had previously been ascribed to hydrogen bonding but it is now believed that its higher p$K_a$ is the primary factor for its increased rate. Not only can the correlation between p$K_a$ and rate be used to predict the reactivity of other potential catalysts but it can also be incorporated into the design of new chiral catalysts for the asymmetric Baylis−Hillman reaction. In this analysis, the parent compound quinuclidine, which had the highest p$K_a$ of all the quinuclidines and had previously been reported to be a poor catalyst, was reevaluated and found to be the best catalyst to date.

The reactions of all the quinuclidine-based catalysts devoid of hydroxyl groups showed significant autocatalysis. The origin of the autocatalysis was the hydroxyl group of the Baylis−Hillman product, which promoted the reaction through hydrogen bonding. This observation led to the addition of hydrogen bond donors to further enhance the rate of the reaction. A number of additives were effective (methanol, formamide, triethanolamine, water) and methanol was found to be optimum. This new combination of quinuclidine and methanol is the most effective system to date for catalyzing the Baylis−Hillman reaction and was found to be general for a broad range of substrates. Reaction of a variety of aldehydes with methyl acrylate and acrylonitrile was found to give adducts in higher yield and shorter reaction times than any previous catalytic system. The same was observed with acrylamides, and vinyl sulfones. Furthermore, the new system allowed previously unreactive partners to couple (benzaldehyde with acrylamide) and allowed new Michael acceptors to be employed (α,*β*-unsaturated *δ*-lactones and crotonates) for the first time. No doubt this new system will find broad application in synthesis.

## Experimental Section

**General Methods.** Chromatography: Flash chromatography was performed on silica gel (400−630 mesh). TLC was performed on aluminum-backed silica plates precoated with silica (0.2 mm), which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), Δ, PMA/Δ, potassium permanganate. Infrared spectra: Only selected absorbances ($\nu_{max}$) are reported. $^1$H NMR spectra: These were recorded at 400 MHz. Chemical shifts ($\delta_H$) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (*J*) are reported to the nearest 0.1 Hz. $^{13}$C NMR spectra: These were recorded at 100 MHz. Chemical shifts ($\delta_C$) are quoted in ppm referenced to the appropriate solvent peak. Mass spectra: Only the molecular ions ($M^+$) and major peaks are reported with intensities quoted as percentages of the base peak. Solvents and reagents: Commercial grade solvents were dried and purified by standard procedures as specified in *Purification of Laboratory Chemicals*, 3rd ed. (Perrin, D. D.; Armarego, W. L. F. Pergamon Press: New York, 1988). Amine catalysts were obtained from commercial sources and were sublimed prior to use, although it was later found that they could be employed without further purification. All aldehydes were either distilled or sublimed before use. Acrylonitrile and methyl crotonate were distilled before use. Methyl acrylate, phenyl vinyl sulfone, 5,6-dihydro-2*H*-pyran-2-one, and acylamide were obtained from commercial sources and used directly.

**General Procedure for the Baylis−Hillman Reaction.** To a stirred mixture of the substrate aldehyde (1.0 mmol) and

Michael acceptor (1.2 mmol) were added quinuclidine (0.25 mmol) and methanol (0.75 mmol). The homogeneous reaction mixture was stirred at ambient temperature, and the reaction progress was monitored by NMR. Upon completion or as indicated, the reaction mixture was purified by flash column chromatography on silica gel, eluting with diethyl ether and petroleum ether to give the desired product.

**3-Triisopropylsilylethynyl-3-methoxy-2-methylenepropionic Acid Methyl Ester (13).** A mixture of triisopropylsilanylpropynal (127 mg, 0.603 mmol), methyl acrylate (62.3 mg, 0.724 mmol), quinuclidine (17 mg, 0.15 mmol), and methanol (19.6 mg, 0.603 mmol) was stirred for 30 min at room temperature. Column chromatography on silica ($Et_2O$/hexane 1:2) gave 131 mg (70%) of **13** as a colorless oil ($R_f = 0.8$, $Et_2O$/hexane 1:2): IR (neat) 2943, 2866, 1729, 1640, $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.05−1.12 (m, 21 H), 3.44 (s, 3 H), 3.79 (s, 3 H), 5.07 (s, 1 H), 6.23 (s, 1 H), 6.38 (s, 1 H); $^1H$ NMR ($C_6D_6$) $\delta$ 0.98−1.18 (m, 21 H), 3.31 (s, 3 H), 3.34 (s, 3 H), 5.17 (s, 1 H), 6.23 (s, 1 H), 6.29 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.2, 18.6, 52.1, 55.9, 69.3, 89.3, 102.9, 127.6, 138.0, 165.9; $^{13}C$ NMR ($C_6D_6$) $\delta$ 11.3, 18.6, 51.2, 55.9, 69.6, 88.3, 104.4, 126.1, 138.9, 165.3; MS *m*/*z* 295 (4) [$M^+ - CH_3$], 279 (20), 267 (38), 133 (100), 105 (83). Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74; O, 15.46; Si, 9.05. Found: C, 65.84; H, 10.10.

**3-Hydroxy-2-methylene-5-triisopropylsilanylhex-1-en-4-ynoic Acid Methyl Ester (14).** A mixture of methyl acrylate (166 mg, 1.94 mmol), triisopropylsilanylpropynal (336 mg, 1.61 mmol), and quinuclidine (45 mg, 0.40 mmol) was stirred for 30 min at room temperature. Column chromatography on silica (hexane/$Et_2O$ 4:1) gave 273 mg (55%) of **14** as a colorless oil ($R_f = 0.40$, hexane/$Et_2O$ 1:1): IR (neat) 3464, 2944, 2866, 1714 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (s, 21 H) 2.98 (br s, 1 H), 3.81 (s, 3 H), 5.25 (s, 1 H), 6.16 (d, $J = 0.7$ Hz, 1 H), 6.31 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 11.1, 18.6, 52.2, 62.7, 88.2, 104.9, 126.7, 139.5, 166.4; MS (FAB) *m*/*z* 295 [$M^+$] (15), 279 (100), 253 (70), 237 (10). Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52; O, 16.19; Si, 9.47. Found: C, 64.72; H, 9.31.

**2-(Furan-2-ylhydroxymethyl)acrylonitrile (Table 3, entry 3).** A solution of furfuraldehyde (340 mg, 3.54 mmol), acrylonitrile (225 mg, 4.25 mmol), quinuclidine (98.4 mg, 0.88 mmol), and methanol (85.0 mg, 2.65 mmol) was stirred for 20 min at room temperature. Column chromatography on silica (hexane/$Et_2O$ 2:1) gave 531 mg (78%) of the product as an orange liquid ($R_f = 0.3$): IR (neat) 3418, 2230, 1625, 1502, 1397 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.45 (br s, 1H), 5.37 (s, 1H), 6.15 (d, $J = 1.2$ Hz, 1H), 6.20 (d, $J = 1.2$ Hz, 1H), 6.40 (dd, $J = 3.1$ Hz, $J = 1.7$ Hz, 1H), 6.44 (dd, $J = 3.1$ Hz, $J = 0.9$ Hz, 1H), 7.44 (dd, $J = 1.7$ Hz, $J = 0.9$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 67.9, 108.8, 110.8, 116.6, 123.5, 131.2, 143.5, 151.6; MS *m*/*z* 149 (40) [$M^+$], 132 (90), 97 (100), 53 (9); HRMS (EI) calcd for $C_8H_7NO_2$ 149.0476, found 149.0477.

**3-Furan-2-yl-3-hydroxy-2-methylenepropionamide (Table 4, Entry 2).** A solution of acryl amide (230 mg, 3.23 mmol), furfuraldehyde (311 mg, 3.23 mmol), and quinuclidine (150 mg, 1.62 mmol) in methanol (250 $\mu$L) was stirred for 5 h at room temperature. Column chromatography on silica (EtOAc to EtOAc/MeOH 10:1) gave 355 mg (66%) of the product as a colorless solid ($R_f = 0.45$, EtOAc; mp 83−84 °C): IR (neat) 3375, 3188, 1660, 1630, 1604, 1433, 1142, 1011, 950, 734 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 5.49 (d, $J = 5.8$ Hz, 1 H), 5.65 (s, 1 H), 5.74 (d, $J = 5.8$ Hz, 1 H), 5.86 (s, 1 H), 6.13 (d, $J = 3.1$ Hz, 1 H), 6.36 (dd, $J = 3.1$ Hz, $J = 1.8$ Hz, 1 H), 7.04 (br s, 1 H), 7.53 (br s, 1 H), 7.56 (d, $J = 1.8$ Hz, 1 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 65.4, 106.9, 110.8, 118.8, 142.6, 145.6, 156.4, 169.1; MS *m*/*z* 167 (23) [$M^+$], 150 (24), 122 (100), 95 (79), 68 (41). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38; O, 28.71. Found: C, 57.33; H, 5.63; N, 8.22.

**2-(4-Methyl-3-hydroxypentenyl) Phenyl Sulfone (Table 5, Entry 1).** A mixture of phenyl vinyl sulfone (504 mg, 3.00 mmol), isobutyraldehyde (540 mg, 7.49 mmol), and quinuclidine (83 mg, 0.75 mmol) was stirred for 4 days at room temperature. Column chromatography on silica ($Et_2O$/$CH_2Cl_2$/hexane 10:70:30) gave 245 mg (40%) of the product as a colorless oil ($R_f = 0.3$, $Et_2O$/$CH_2Cl_2$/hexane, 10:70:30): IR (neat) 3502, 2965, 1388, 1367, 1291 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.76 (d, $J = 6.8$ Hz, 3 H), 0.89 (d, $J = 6.8$ Hz, 3 H), 1.97 (dqq, $J = 6.5$ Hz, 6.5 Hz, 6.5 Hz, 1 H), 2.32 (br s, 1 H), 4.08 (d, $J = 6.4$ Hz, 1 H), 6.07 (s, 1 H), 6.46 (s, 1 H), 7.53−7.59 (m, 2 H), 7.62−7.67 (m, 1H), 7.87−7.92 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 16.7, 19.5, 32.1, 74.4, 125.7, 128.3, 129.3, 133.7, 139.3, 152.5; MS (CI) *m*/*z* 241 (32) [$MH^+$], 223 (100), 197 (20), 143 (58); HRMS (CI) calcd for $C_{12}H_{17}O_3S$ 241.0894, found 241.0898. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; O, 19.97; S, 13.34. Found: C, 59.69; H, 6.87.

**3-(Hydroxyphenylmethyl)-5,6-dihydropyran-2-one (Table 6, Entry 1).** A mixture of 5,6-dihydro-2*H*-pyran-2-one (293 mg, 2.98 mmol), benzaldehyde (264 mg, 2.49 mmol), and quinuclidine (69 mg, 0.62 mmol) was stirred for 3 days at room temperature. Column chromatography on silica ($Et_2O$/$CH_2Cl_2$/hexane 8:50:30) gave 340 mg (70%) of the product as a colorless oil ($R_f = 0.5$. $Et_2O$): IR (neat) 3412, 2902, 1693 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.46 (m, 2 H), 3.55 (d, $J = 4.8$ Hz, 1 H), 4.29−4.40 (m, 2 H), 5.57 (d, $J = 4.8$ Hz, 1 H), 6.69 (t, $J = 4.4$ Hz, 1 H), 7.28−7.45 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 24.2, 66.3, 72.3, 126.7, 127.9, 128.5, 135.0, 140.8, 164.8; MS (EI) *m*/*z* 204 (52) [$M^+$], 186 (32), 127 (43), 105 (100), 77 (74); HRMS (EI) calcd for $C_{12}H_{12}O_3$ 204.0782, found 204.0786.

**2-(Hydroxypyridin-2-ylmethyl)but-2-enoic Acid Methyl Ester (Table 6, Entry 3).** A mixture of methyl crotonate (126 mg, 1.25 mmol), pyridine-2-carboxaldehyde (112 mg, 1.04 mmol), and quinuclidine (116 mg, 1.04 mmol) was stirred for 3 weeks at room temperature. Column chromatography on silica (hexane/EtOAc 7:3) gave 54 mg (25%) of the two isomers of the product in a 63:37 ratio as colorless oil ($R_f = 0.50$, 0.55 (hexane/EtOAc, 1:1), which could be partly separated using column chromatography on silica: IR (neat) 3388, 3059, 2951, 1708 $cm^{-1}$; MS (EI) *m*/*z* 207 (21) [$M^+$], 190 (100), 108 (55), 78 (63); HRMS (EI) calcd for $C_{11}H_{13}NO_3$ 207.0891, found 207.0895. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76, O, 23.16. Found: C, 63.53; H, 6.54; N, 6.62.

Major isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 2.05 (d, $J = 7.3$ Hz, 3 H), 3.69 (s, 3 H), 4.90 (br s, 1 H), 5.47 (br s, 1 H), 6.42 (q, $J = 7.3$ Hz, 1 H), 7.19−7.25 (m, 1 H), 7.34 (d, $J = 7.8$ Hz, 1 H), 7.68 (dt, $J = 7.8$, $J = 1.5$, 1 H), 8.55 (d, $J = 4.9$ Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 15.8, 51.3, 74.4, 121.0, 122.5, 134.4, 136.9, 140.3, 148.0, 160.1, 167.4.

Minor isomer: $^1H$ NMR ($CDCl_3$) $\delta$ 2.00 (d, $J = 7.3$ Hz, 3 H), 3.65 (s, 3 H), 4.98 (br s, 1 H), 5.79 (br s, 1 H), 7.15 (q, $J = 7.3$ Hz, 1 H), 7.17−7.21 (m, 1 H), 7.37 (d, $J = 8.0$ Hz, 1 H), 7.68 (dt, $J = 8.0$ Hz, $J = 2.0$ Hz, 1 H), 8.54 (d, $J = 4.9$ Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.5, 51.7, 69.0, 120.1, 122.1, 133.6, 136.8, 141.8, 148.1, 161.0, 167.4.

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**Supporting Information Available:** $^1H$ NMR spectra for all compounds, reaction profiles for the quinuclidine-based catalysts, and $^1H$ NMR spectra showing the equilibrium ratio of the $HBF_4$ salts used to determine the relative basicity of the quinuclidine-based catalysts in aprotic media. This material is available free of charge via the Internet at http://pubs.acs.org.

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