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# Acceleration of the DABCO-promoted Baylis–Hillman reaction using a recoverable H-bonding organocatalyst ☆

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**Abstract**—It has been shown that catalytic amounts (20–40 mol%) of bis-aryl (thio)ureas greatly accelerate the DABCO-promoted Baylis–Hillman reaction between a range of aromatic aldehydes and methyl acrylate in the absence of solvent. These robust organocatalysts are superior mole per mole promoters of the reaction than either methanol or water and are recoverable in high yield after the reaction by column chromatography.


The three-component Baylis–Hillman reaction[1] has recently emerged from relative obscurity to prominence as a carbon–carbon bond forming process that furnishes products of high functional-group density from relatively simple starting materials.[2] A significant drawback associated with these transformations is slow reaction rates (particularly those involving acrylates), a difficulty originally overcome by physical methods such as microwave irradiation and high pressure.[2] More recently, highly basic amines,[3] phosphines,[4] hydrogen bonding solvents,[5,6] salts (among other addenda)[6–8] and Lewis-acid catalysts (either alone[9] or in conjunction with a tertiary amine catalyst[10]) have been utilised to accelerate the reaction. The majority of these methods function by either activating the aldehyde component or stabilising the nucleophilic betaine intermediate **1**, the addition of which to the aldehyde is the rate-determining step of the reaction[11] (Fig. 1).

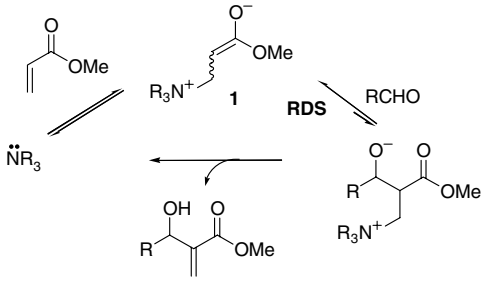


**Figure 1.** Baylis–Hillman reaction: catalytic cycle.

Despite possessing a flat, readily modifiable and rotationally restricted structure[12] with two mutually proximal N–H bonds available for hydrogen bond donation, the potential of bis-aryl ureas and -thioureas to serve as Lewis-acidic organocatalysts has only recently begun to be explored.[13,14] Given the accepted reaction mechanism (vide supra) and the known strong proclivity of aryl ureas and thioureas for carbonyl group[13c,15] and (in particular) anion binding,[16] it appeared that these species would hold promise as novel, stable and readily accessible co-catalysts for the tertiary amine-promoted Baylis–Hillman reaction. The candidate (thio)urea structures **2**–**7** (Fig. 2) chosen for this study reflect four main concerns; a desire to minimise p$K_a$ (thus maximising binding affinities),[16c,17,18] the avoidance of ionic or Lewis-basic carbonyl functionality, which could lead to possible self-quenching (or non-urea-based binding), the use of the most accessible catalyst structures and a necessity to render the catalysts as soluble as possible in Baylis–Hillman reaction media.

The Baylis–Hillman reaction is of quite wide scope with respect to the α,β-unsaturated component, however, the use of poor Michael acceptors such as acrylates often results in inconveniently long reaction times as compared to those involving the corresponding unsaturated aldehydes, ketones and nitriles. Similarly, nonactivated

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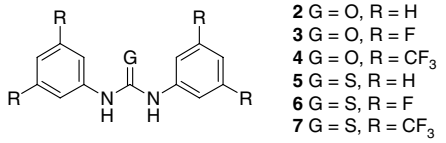



**Figure 2.** Candidate Baylis–Hillman reaction catalysts **2**–**7**.

aromatic aldehydes are significantly poorer substrates than either aliphatic or activated aromatic analogues.[2e] Therefore, to provide an instructive test of the catalysts' abilities to promote Baylis–Hillman processes, the pseudo-first-order rate constants for the reaction between methyl acrylate (1000 mol %) and benzaldehyde catalysed by both DABCO (100 mol %) and catalysts **3**–**7** were determined (Table 1).[19,20]

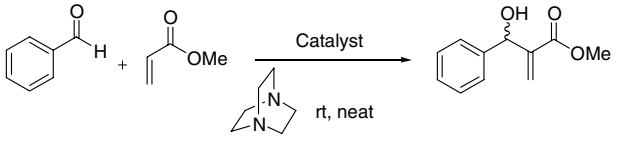
Gratifyingly, **3**–**7** (20% levels) accelerated the reaction relative to the 'uncatalysed' process (entry 1). The general inferiority of thioureas compared to ureas was unexpected;[13d,e] the reason for this is not yet clear, although it is noteworthy that examples of superior anion binding (particularly halide ions) of simple aryl ureas over aryl thioureas have been observed despite the latter possessing stronger H-bonding capabilities.[16d,f,21,22] In terms of stability and efficiency, catalyst **4** proved most effective. The significantly improved observed rates using **4** (20 mol %, entry 3) compared to either of the powerful hydrogen bond donors methanol or water (40%, entries 8 and 9) indicate that both urea hydrogen atoms are involved in catalysis. When it is considered that the formation of intermediate **1** is not rate determining,[11] the ability of **3**–**7** to promote the Baylis–Hillman reaction in the presence of 10 equiv of the Lewis-basic (relative to benzaldehyde) methyl acrylate is remarkable, and strongly points towards a mechanism involving the binding of Zwitterion **1** as opposed to direct activation of either methyl acrylate (which would not be expected to influence $k_{obs}$) or benzaldehyde (which should have less affinity for **3**–**7** than the acrylate) alone. This conjecture is supported by control experiments demonstrating that **4** is completely inactive in Baylis–Hillman reactions in the presence of equimolar TBAA (tetrabutylammonium acetate),[16] which can successfully compete with **1** for the urea N–H bonds and destroy the activity of **4**.[23] We would therefore postulate that catalysts **3**–**7** operate in the main via binding of either **1** (**8**) or possibly a Zimmerman–Traxler type transition state (**9**) for the addition of **1** to the benzaldehyde (Fig. 3).[24]

With significant catalytic activity and the supremacy of **4** over other (thio)ureas tested established, attention now turned to the question of reaction scope. The effect of **4** on Baylis–Hillman reactions between a range of activated and deactivated aromatic aldehydes and methyl acrylate, and on the reaction between acrolein/methyl vinyl ketone and benzaldehyde was determined (Table 2).

It was found that **4** (20 mol %) accelerated all reactions tested involving methyl acrylate regardless of the aldehyde employed. Good to excellent isolated yields of products were possible in reasonable reaction times for all substrates, even for the highly deactivated *p*-anisaldehyde and the traditionally challenging deactivated and hindered *o*-anisaldehyde (entries 7 and 11). The synthetic utility of **4** is illustrated by the poor adduct yields obtained in the urea-free control reactions involving deactivated substrates over the same time period (entries 2, 4, 6, 8, 10 and 12). Furthermore, in all cases the urea catalyst could be recovered unchanged after reaction by column chromatography in good to excellent yield and reused without any loss of activity. The Lewis-acidic properties of **4** are further underlined by its unsuitability as a catalyst for reactions involving acrolein and methyl vinyl ketone (entries 17 and 19), promoting instead rapid Michael acceptor decomposition in the presence of DABCO.

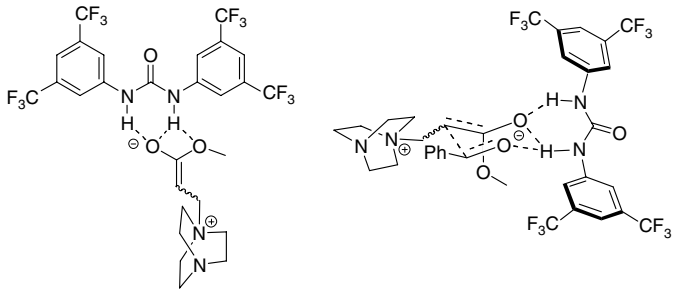
In view of these results demonstrating the compatibility of **4** with DABCO, the concept of preparing a tertiary amino/aryl urea hybrid catalyst incorporating both nucleophilic and H-bond activating moieties in one

**Table 1.** Acceleration of the Baylis–Hillman reaction between benzaldehyde and methyl acrylate in the presence of various H-bonding catalysts[a]




| Entry | Catalyst | Mol % | $k_{obs} \times 10^{-2}$ $(h^{-1})^{b,c}$ | $k_{rel}$ |
|---|---|---|---|---|
| 1 | — | 0 | 0.46 | 1.0 |
| 2 | **3** | 20 | 2.50 | 5.4 |
| 3 | **4** | 20 | 3.06 | 6.7 |
| 4 | **5** | 20 | 0.76 | 1.7 |
| 5 | **6** | 20 | 2.63 | 5.7 |
| 6 | **7** | 20 | 1.73 | 3.7 |
| 7 | **4** | 40 | 4.32 | 9.4 |
| 8 | MeOH | 40 | 1.15 | 2.5 |
| 9 | $H_2O$ | 40 | 0.72 | 1.6 |

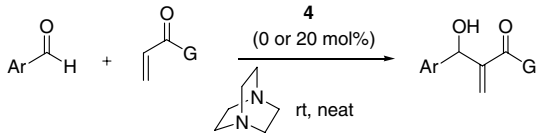
[a] Reagents and conditions: benzaldehyde (1.0 equiv), DABCO (1.0 equiv), methyl acrylate (10.0 equiv).
[b] Initial rates (<20% conversion).
[c] Determined by $^1H$ NMR spectroscopy using (*E*)-stilbene as an internal standard.



**8** **9**

**Figure 3.** Catalyst **4**: proposed mode(s) of action.

**Table 2.** Baylis–Hillman reactions involving a range of substrates catalysed by **4**[a]




| Entry | Ar | G | Mol% **4** | Time (h) | Product | Yield (%)[b] | Recovered **4** (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | OMe | 20 | 20 | **11** | 88 | 87 |
| 2 | $C_6H_5$ | OMe | 0 | 20 | **11** | 32 | — |
| 3 | *p*-$MeC_6H_4$ | OMe | 20 | 36 | **12** | 71 | 82 |
| 4 | *p*-$MeC_6H_4$ | OMe | 0 | 36 | **12** | 32 | — |
| 5 | *p*-$FC_6H_4$ | OMe | 20 | 42 | **13** | 92 | 86 |
| 6 | *p*-$FC_6H_4$ | OMe | 0 | 42 | **13** | 53 | — |
| 7 | *p*-$MeOC_6H_4$ | OMe | 20 | 96 | **14** | 71 | 88 |
| 8 | *p*-$MeOC_6H_4$ | OMe | 0 | 96 | **14** | 21 | — |
| 9 | 2-Furan | OMe | 20 | 2 | **15** | 88 | 89 |
| 10 | 2-Furan | OMe | 0 | 2 | **15** | 21 | — |
| 11 | *o*-$MeOC_6H_4$ | OMe | 20 | 72 | **16** | 81 | 78 |
| 12 | *o*-$MeOC_6H_4$ | OMe | 0 | 72 | **16** | 27 | — |
| 13 | *o*-$ClC_6H_4$ | OMe | 20 | 2 | **17** | 89 | 95 |
| 14 | *o*-$ClC_6H_4$ | OMe | 0 | 2 | **17** | 82 | — |
| 15 | *o*-$O_2NC_6H_4$ | OMe | 20 | 1 | **18** | 93 | 82 |
| 16 | *o*-$O_2NC_6H_4$ | OMe | 0 | 1 | **18** | 86 | — |
| 17 | $C_6H_5$ | H | 20 | 1 | **19** | 0[d] | — |
| 18 | $C_6H_5$ | H | 0 | 1 | **19** | 0[e] | — |
| 19 | $C_6H_5$ | Me | 20 | 2.5 | **20** | >15[f] | — |
| 20 | $C_6H_5$ | Me | 0 | 2.5 | **20** | 59 | — |

[a] Reagents and conditions: aldehyde (1.0 equiv), DABCO (1.0 equiv), Michael acceptor (3.0 equiv), rt.
[b] Refers to isolated yield after column chromatography for all reactions promoted by **4** (entries 1, 3, 5, 7, 9, 11, 13 and 15), corresponding yields of 'uncatalysed' reactions were determined by $^1$H NMR using (*E*)-stilbene as an internal standard.
[c] After column chromatography.
[d] Highly exothermic reaction on addition of acrolein resulting in a resinous product.
[e] Acrolein decomposition.
[f] Estimated by $^1$H NMR (relative integration of product and DABCO signals) after complete decomposition of methyl vinyl ketone.

molecule (by analogy with the known efficient catalyst 3-hydroxyquinuclidine) was appealing. Urea and thiourea derivatives of 3-amino quinuclidine **21** and **22** (Fig. 4) were prepared[25] and tested in the reaction between methyl acrylate and *o*-chlorobenzaldehyde (Scheme 1).

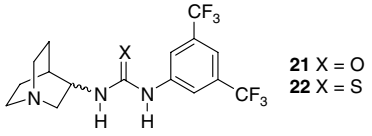
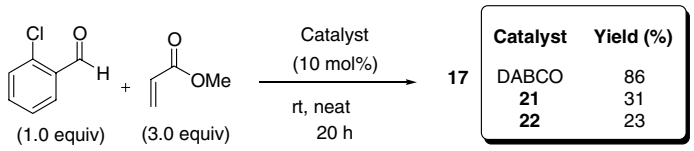



**Figure 4.** Hybrid catalysts **21** and **22**.

In contrast to **4**, the performance of both **21** and **22** was disappointing; both proving inferior to DABCO under the conditions employed. However this correlates well with recent findings by Aggarwal et al.[3i] who have convincingly demonstrated (contradicting hitherto accepted theory) that in quinuclidine derivative-catalysed Baylis–Hillman reactions, protonated amine p$K_a$ is the governing factor in determining catalyst efficiency, thus making quinuclidine itself a faster catalyst than




**Scheme 1.** Comparison between **21**, **22** and DABCO.

3-heteroatom substituted analogues, which are of reduced basicity/nucleophilicity and give lower reaction rates.[26]

In summary, it has been demonstrated for the first time that bis-aryl ureas such as **4** can serve as efficient, stable and recyclable DABCO-compatible organocatalysts for the Baylis–Hillman reaction involving both activated and challenging substrates, and in this capacity are considerably more powerful mole per mole promoters of the reaction than either methanol or water. Preliminary results implicate a mechanism involving binding to a Zwitterionic intermediate/transition state, a more definitive understanding of which is necessary before further catalyst optimisation/derivatisation and application in areas such as bifunctional catalysis and asymmetric catalysis can proceed. These studies are now underway in our laboratory.

*Supplementary material*: Experimental procedures, characterisation data for catalysts **4**, **21** and **22**, rate plots (Table 1), $^{1}H$ and $^{13}C$ NMR spectra for products **11**–**18** (Table 1).

## Acknowledgements

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18. Schreiner and Wittkopp[13d] has proposed that *meta*-electron withdrawing substituents also raise the barrier to rotation in thioureas, thus further minimising entropy loss on binding.
19. Surprisingly carbanilide (**2**) was unsuitable due to poor solubility.
20. As anticipated, ln[PhCHO] versus time plots for all reactions in Table 1 were linear, indicating no significant change in [DABCO] (and hence no significant interaction with **3**–**7** via H-bonding) over time. All correlation coefficients for the pseudo-first-order rate plots were $\geqslant 0.99$. A pseudo-second-order treatment of the data gave similar relative rates however given the volatility of methyl acrylate and the long reaction times involved, a pseudo-first-order treatment is preferred here.
21. This has been rationalised[16d] in terms of greater observed dimerisation constants for aryl thioureas compared to ureas; increased thiourea H-bonding ability seems more important than decreased sulfur (as opposed to oxygen) H-bond accepting ability. This may be significant in the above Baylis–Hillman reactions where catalyst concentrations are high. It should also be noted that the factors influencing the relative ability of ureas and thioureas to bind anions are not fully understood. For an example of superior thiourea binding in a bis(thio)urea system see Ref. 17.
22. It is noteworthy that some thiourea catalyst decomposition was observed after extended reaction times. Curran and Kuo[13a] has reported inferior aryl thiourea (vs aryl urea) stability at high temperatures (100 °C).
23. This binding could be observed as an immediate large ($t = 0$ h, $\Delta\delta = 4.40$ ppm) downfield shift of the $^1$H NMR N–H urea signal. While this experiment does not exclude the possibility of benzaldehyde activation (some association is both likely and beneficial, see also Ref. 13d) being the governing factor affecting $k_{obs}$, it does demonstrate the predilection of **4** (as expected from HASB theory) to bind to an oxyanion (once formed) in preference to either benzaldehyde or methyl acrylate.
24. The concept of increased reaction rates through the intermediacy of **9** is attractive, as stabilisation of **1** through sole binding with the urea (as in **8**) would increase the equilibrium concentration of the Zwitterion while concurrently decreasing its nucleophilicity.
25. See supplementary material.
26. Ref. 3i appeared during the preparation of this manuscript.