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Superior amine catalysts for the Baylis–Hillman reaction: the use of DBU and its implications†

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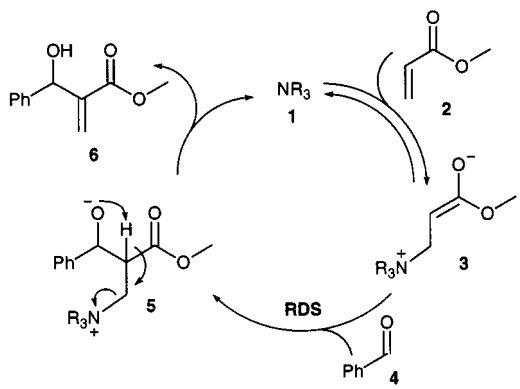
DBU, which is normally regarded as a hindered and non-nucleophilic base, is in fact the optimum catalyst for the Baylis–Hillman reaction, providing adducts at much faster rates than using DABCO or 3HQD; the scope of the Baylis–Hillman reaction is enhanced using this catalyst and implications of this finding are discussed.

The Baylis–Hillman reaction has great synthetic utility as it converts simple starting materials into densely functionalised products.[1] However, it suffers from low reaction rates (especially for acrylates) and this often limits the range of substrates that are tolerated. Whilst acceleration can be achieved by physical methods this usually requires specialised apparatus. We recently described a chemical method for accelerating the reaction: the use of $La(OTf)_3$ and triethanolamine as cocatalysts, which provided up to 40 fold rate increase over the use of DABCO alone.[2]

Structural variations of the amine catalyst have been probed and DABCO and 3-hydroxyquinuclidine (3-HQD) provide the highest rates. Indeed, if the optimum features of the catalyst are that it should be nucleophilic and unhindered, it is hard to imagine superior ones.[3] Here we describe our study on the nature of the catalyst and the discovery that much higher rates can be achieved with alternative structures.

The rate-determining step of the Baylis–Hillman reaction is the reaction of the aldehyde **4** with the ammonium enolate **3** (Scheme 1).[3] This enolate is formed by conjugate addition of the nucleophilic amine **1** to the Michael acceptor **2** (a reversible process) and therefore to obtain faster rates, higher *concentrations* of the enolate are required. Amines which can shift the equilibrium towards the enolate **3** by stabilising this species should achieve this. We therefore screened a range of amines which all had the potential for the positive charge on nitrogen to be stabilised through conjugation with another heteroatom (Table 1). Of the aromatic heterocyclic catalysts (entries 1, 2) only DMAP gave any Baylis–Hillman adduct,[4] but at a rate only slightly higher than DABCO (Table 2, entries 1, 3). None of the amidine catalysts (entries 4, 5) were stable under the reaction conditions except for DBU **7**, which not only gave a clean reaction but also the fastest rate (Table 1, entry 6; Table 2, entry 6). The substituted guanidine gave a lower yield due to a competing side reaction involving the acrylate (entry 7).



Scheme 1

In comparison with other commonly used catalysts (Table 2), DBU was over an order of magnitude faster than the current best catalyst (3-HQD, entry 4) and superior to the DABCO–$La(OTf)_3$–triethanolamine system that we have developed (entry 2).[2] Even at 10 mol% loading, DBU was superior to both stoichiometric DABCO or 3-HQD (Table 2, entry 5).[5]

We investigated the scope of the DBU-catalysed Baylis–Hillman reaction by reacting benzaldehyde with a range of Michael acceptors (Table 3), and methyl acrylate (Table 4) and cyclohex-2-en-1-one (Table 5) with a range of electrophiles.

Notable examples from Table 3 include a fast reaction with *tert*-butyl acrylate (entry 3; DABCO gives 65% yield after 28 d[6]), and a very rapid reaction with cyclohex-2-en-1-one (entry 5).[7] Methyl vinyl ketone (MVK) is not a suitable substrate with DBU (*vide infra*) but, in any case, is a fast reacting substrate with other catalysts (*e.g.* DABCO).

Notable examples from Table 4 include reaction with 4-anisaldehyde which gave a good yield after just 2 days (entry 5; DABCO gives 90% after 20 d[8]), reaction with the notoriously difficult, hindered and deactivated 2-anisaldehyde (entry 4) and

Table 1 Amine catalysts in the Baylis–Hillman reaction[a]

Entry	Nucleophilic compound	*t*/h	Yield (%)
1	Dimethylaminopyridine	96	87
2	1-Methylimidazole	120	0
3	2-Methyl-2-oxazoline	120	0
4	*N*-Methyl-4,5-dihydroimidazole	1	10[c]
5	DBN	2 min	13[d]
6	DBU	6	89
7	Substituted guanidine[d]	48	30

[a] Reactions conducted on 2 mmol scale using 1:1:1 ratio of benzaldehyde:methyl acrylate:catalyst. [b] Complex mixture of products. [c] A fast reaction occurred but the catalyst decomposed rapidly. [d] 1,3,4,6,7,8-Hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine.

Table 2 Comparison of DBU with the other catalytic systems[a]

Entry	Catalytic system	Reaction rate[b]	k_{rel}	*t*/h	Yield (%)
1	DABCO	0.016	1	120	91
2	DABCO–$La(OTf)_3$–$N(CH_2CH_2OH)_3$[c]	0.511	31.9	12	83
3	Dimethylaminopyridine	0.038	2.4	96	87
4	3-Hydroxyquinuclidine	0.076	4.8	30	91
5	DBU[d]	0.163	10.2	24	75
6	DBU	0.762	49.5	6	89

[a] Reactions conducted on 2 mmol scale using 1:1:1 ratio of benzaldehyde:methyl acrylate:catalyst. [b] % Product per minute. [c] 1 equiv. of DABCO, 0.05 equiv. $La(OTf)_3$ and 0.5 equiv. $N(CH_2CH_2OH)_3$. [d] 0.1 equiv.

† Experimental and spectroscopic data, and further references, are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/2311/

Table 3 Reactions of activated alkenes with benzaldehyde[a]

Entry	Alkenes	*t*/h	Yield (%)
1	Methyl acrylate	6	89
2	Ethyl acrylate	24	80
3	*tert*-Butyl acrylate	72	74[b]
4	Acrylonitrile	3	92
5	Cyclohex-2-en-1-one	0.5	60[c]

[a] Reactions conducted on 2 mmol scale using 1:1:1 ratio of benzaldehyde: alkene : DBU. [b] No side products; 20–25% benzaldehyde and acrylate recovered. [c] No benzaldehyde remained, 30% cyclohex-2-en-1-one recovered.

Table 4 Reactions of carbonyl compounds with methyl acrylate[a]

Entry	Aldehyde	*t*/h	Yield (%)
1	Benzaldehyde	6	89
2	2-Nitrobenzaldehyde	1.5	95
3	4-Nitrobenzaldehyde	1	95
4	2-Anisaldehyde	4	25[b]
5	4-Anisaldehyde	48	62
6	Propionaldehyde	24	17[b]
7	Trimethylacetaldehyde[c]	70	20[b]
8	2,2,2-Trifluoroacetophenone	2	60[d]
9	2,2,2-Trifluoroacetophenone[e]	48	78

[a] Reactions conducted on 2 mmol scale using 1:1:1 ratio of carbonyl compound: acrylate: DBU. [b] Low yield due to decomposition of aldehyde. [c] Reaction performed in presence of 0.05 equiv. $La(OTf)_3$. [d] Product found to be unstable in presence of high concentration of catalyst. [e] 0.1 equiv. DBU used.

Table 5 Reactions of aldehydes with cyclohex-2-en-1-one[a]

Entry	Aldehyde	*t*/h	Yield (%)
1	Benzaldehyde	0.5	60
2	2-Anisaldehyde	50 min	70
3	Cyclohexanecarbaldehyde	7	73
4	Trimethylacetaldehyde[b]	21	75

[a] Reactions conducted on 2 mmol scale using 1:1:1 ratio of aldehyde: cyclohex-2-en-1-one : DBU. [b] 1.2 equiv. cyclohex-2-en-1-one and 0.05% $La(OTf)_3$ used.

for the first time reactions with pivaldehyde (entry 7)[9] and trifluoroacetophenone (entries 8, 9). Pivaldehyde required $La(OTf)_3$ to promote the reaction as no adduct was obtained without it. $La(OTf)_3$ often enhances the rates and gives higher yields of adducts (Table 4, entry 7; Table 5, entry 4) but when used with benzaldehyde a less clean reaction was observed and the additional acceleration was minimal. Aldehydes with enolisable protons gave low yields of Baylis–Hillman adducts because of competing aldol reactions.[10]

Notable examples from Table 5 include high yielding reactions with all the difficult aldehydes (2-anisaldehyde, entry 2; pivaldehyde, entry 4; even the aliphatic enolisable aldehyde cyclohexanecarbaldehyde, entry 3), demonstrating the effectiveness and superiority of this catalyst. Again $La(OTf)_3$ (5 mol%) was required in the reaction with pivaldehyde (entry 4); in its absence 44% yield of adduct was obtained after 4 days. Evidently with faster reacting enones compared to acrylates, enolisable aldehydes are better tolerated.

There is one example of the use of DBU as a catalyst for the Baylis–Hillman reaction although no comment was made on its rate.[11,12] The focus of the paper was on α-alkylation of enones with acrylates as acceptors and it was proposed that DBU acted as a base rather than a nucleophile, with the reaction occurring *via* a diene enolate rather than a β-enolate. This was supported by their observation that reaction between MVK and acetaldehyde only returned starting material. Our observation that

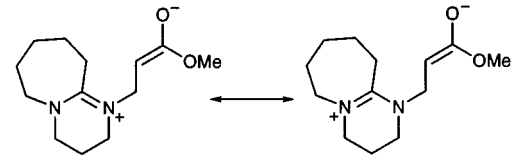


Fig. 1

acrylates work extremely well with DBU as a catalyst indicates that enolisation is *not* a requirement and that the reaction must proceed *via* the β-ammonium enolate derived from DBU and the acrylate. Furthermore we have not been able to reproduce some of their results: when we repeated the reaction between MVK and acetaldehyde we obtained polymeric material instead, no MVK was returned.

We were surprised that DBU worked so well as it is considered to be a non-nucleophilic hindered base; features that are diametrically opposite to what is normally required of amine catalysts for the Baylis–Hillman reaction. DABCO, for example, is one of the best amine catalysts and is an unhindered, nucleophilic base. The incorporation of substituents α to nitrogen result in substantial reduction in rates and this has been ascribed to the lower nucleophilicity of the base due to steric hindrance.[13] In fact, a more likely explanation is that the additional substituent contributes substantial steric hindrance to the β-ammonium enolate intermediate **3** which results in a shift in the equilibrium back to starting materials. In contrast, with DBU the intermediate β-ammonium enolate is stabilised through conjugation (Fig. 1), which increases its equilibrium concentration, and this results in significantly enhanced rates. These studies reveal that to achieve high rates in the Baylis–Hillman reaction the nucleophilicity of the amine is much less important than factors which stabilise the intermediate β-ammonium enolate.

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Notes and references

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