Development of catalysts for the Baylis–Hillman reaction: the application of tetramethylguanidine and attempts to use a supported analogue

Nicholas E. Leadbeater * and Cornelia van der Pol †

Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS.
E-mail: nicholas.leadbeater@kcl.ac.uk

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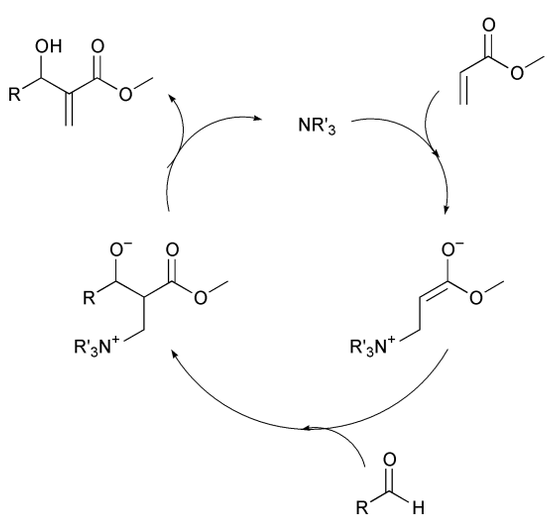
We show here that tetramethylguanidine (TMG) is a useful catalyst for the Baylis–Hillman reaction of aldehydes with methyl acrylate, showing good activity with a range of aldehyde substrates and, unlike many other catalysts or catalyst mixtures, it can be used to good effect with simple aliphatic aldehydes. We show that the activity of the catalyst is decreased when the reaction is run using solvents rather than solvent-free but, in the case where a solvent is necessary, dichloromethane offers the best results. Attempts to use supported or derivatised TMG complexes as catalysts for the reaction have been unsuccessful suggesting that the presence of an amine hydrogen is key to the activity of TMG. Attempts to use stabilised aliphatic phosphines as catalysts for the reaction have proven partly successful, with only modest yields of product being obtained with 2-(dicyclohexylphosphino)biphenyl and 2-(di-*tert*-butylphosphino)biphenyl. The Verkade superbase, $P(MeNCH_2CH_2)_3N$, proved inactive as a catalyst, an adduct with the acrylate being the only product formed.

Introduction

The Baylis–Hillman reaction offers a convenient synthetic route to highly functionalised molecules.[1] The reaction involves the coupling of an activated alkene with electrophiles (usually aldehydes) using a base (usually an amine) as a catalyst (Fig. 1). The proposed mechanism for the reaction is shown in Scheme 1. The densely functionalised products can be transformed selectively, for example, into epoxides, triols and anti-aldol products.[2] Whilst it has been used for the synthesis of natural products and other targets,[3,4] it is not without its problems. The reaction is very enigmatic and catalysts used are often very substrate specific. Another major drawback to date has been the poor reaction rates; the process taking anything



Scheme 1 Proposed mechanism for the amine catalysed Baylis–Hillman reaction.

† Study placement student from Hogeschool van Utrecht, The Netherlands.

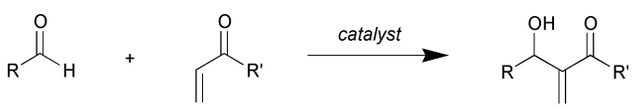


Fig. 1 The Baylis–Hillman reaction.

up to 28 days to reach completion. Recently there has been a resurgence in research activity based around the reaction and there have been a number of reports of catalysts and conditions that lead to rate acceleration.[5–11] Although these can prove useful in some situations, it is often the case that the catalysts used are very substrate specific and so there is no really universal catalyst that can be used and relied on for a range of substrates. In addition, a number of the catalyst systems reported to date either require a mixture of a number of components acting together as a catalyst mixture or else are air- and moisture-sensitive meaning that special conditions need to be used.

In our laboratories we have been looking at the development of catalysts that can be used in the Baylis–Hillman reaction and are readily available, have high activity and need no special conditions for use. We have looked at a range of catalyst candidates and at the conditions for optimal results. We report our findings here and show that in the case of many substrates 1,1,3,3-tetramethylguanidine (TMG) could be a catalyst of choice. We also report our attempts to prepare solid-supported analogues for use in the reaction.

Results and discussion

The base most often used as a catalyst for Baylis–Hillman chemistry is 1,4-diazabicyclo[2.2.2]octane, DABCO. This nucleophilic non-hindered base has been found to be reasonably versatile, working for a range of substrates. In addition, it is easily removed from the product mixture at the end of the reaction. More recently, however, Aggarwal and Mereu have reported that 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU, which is normally considered as a hindered non-nucleophilic base, is an excellent catalyst for Baylis–Hillman chemistry when used in

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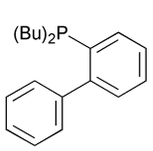
Table 1 Screening of **1** and **2** for activity in the Baylis–Hillman reaction[a]

Catalyst	Reaction time/h	Product yield (%)
1	6	6
1	16	9
1	48	12
2	6	14
2	16	31
2	48	36
2	144	36

[a] Using benzaldehyde and methyl acrylate as starting materials and 5 mol% phosphine catalyst. Reactions were run solvent-free and at room temperature.

a 1 : 1 : 1 ratio with alkene and electrophile.[8] The key to the activity of DBU is thought to be the fact that the β-ammonium enolate is stabilised through conjugation which increases its equilibrium concentration and results in enhanced rates. In addition to amines, recent reports suggest that some tertiary phosphines are also good catalysts for the reaction. Aliphatic phosphines have been shown to be the most active, in particular tributylphosphine, reported by Rafel and Leahy to catalyse the reaction rapidly at room temperature and even faster at 0 °C.[10]

The starting point for our work was to look at a number of amine and phosphine complexes that could potentially act as catalysts for the reaction. The problems with using aliphatic phosphines are that they are very susceptible to aerial oxidation and are also hard to extract from the product mixture. Recent reports in the literature have shown that sterically crowded dialkylbiphenylphosphines have the steric bulk and electronic properties similar to trialkylphosphines but are significantly more stable in the presence of air and moisture.[12] Consequently, we screened two such complexes for catalytic activity in the Baylis–Hillman reaction. Both 2-(di-*tert*-butylphosphino)-biphenyl, **1**, and 2-(dicyclohexylphosphino)biphenyl, **2**, showed catalytic activity in the reaction of benzaldehyde with methyl acrylate, although only producing product in significantly lower yield than that reported using tributylphosphine (Table 1). This being said, in our laboratory we were unable to reproduce the product yields using tributylphosphine as a catalyst, finding that product yields were not in excess of 45 to 50%. In an attempt to increase yields of product using **1** and **2** as catalysts we tried varying the catalyst concentration and reaction temperature but neither had a significant effect on the yield of product.



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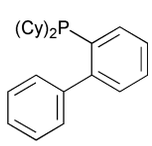

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To continue the studies, the Verkade superbase, P(MeN-$CH_2CH_2)_3$N **3**,[13] was assessed for activity. Proazaphosphatranes such as **3** have been used with much success as catalysts, promoters and nonionic bases in a range of organic transformations, these properties stemming from the partial transannulation between the phosphorus and bridgehead nitrogen atoms on formation of a cation.[14–16] However, we find that in the Baylis–Hillman reaction between benzaldehyde and methyl acrylate, **3** forms an adduct with the acrylate and no product is formed. This could well be attributed to the high nucleophilicity and basicity of proazaphosphatranes, **3** having a pK_a of 41.2 in acetonitrile and 26.8 in DMSO.[17]

We decided to move away from using tertiary phosphines as catalysts for the reaction and to look instead at substituted amine substrates capable of stabilising the intermediates

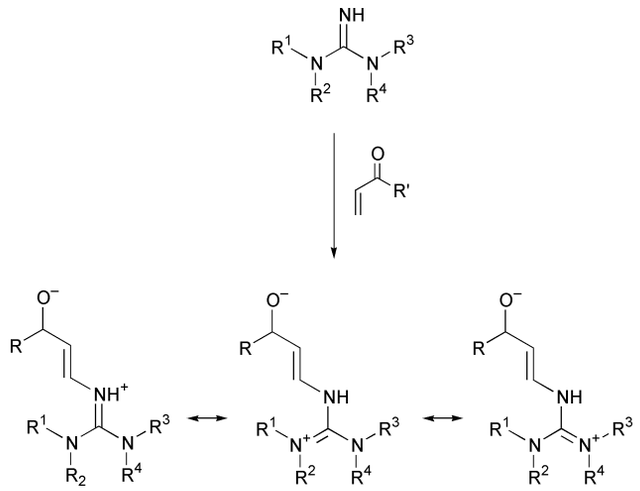
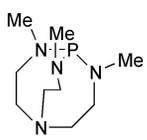


Fig. 2 Stabilisation of intermediates with substituted guanidines.

formed. Our attention focused on substituted guanidine substrates as there is potential for resonance stabilisation of the β-enolate formed with acrylates (Fig. 2). We are not the first to use substituted guanidines as catalysts for the reaction. Aggarwal and Mereu report the use of 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2,*a*]pyrimidine, **4**, but find it produces only modest yields of product (30%) over a period of two days.[8]



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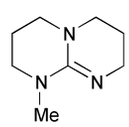

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We have focused our attention on tetramethylguanidine, TMG, ($R^{1–4}$ = Me in Fig. 2) as a potential catalyst candidate. We find that it shows good activity and low loadings of catalyst can be used. Optimisation studies were performed using benzaldehyde and methyl acrylate as substrates (Tables 2–4). At room temperature we find that the optimum yields of product are obtained when the reaction is run for 16 h using a ratio of benzaldehyde : methyl acrylate : TMG of 1 : 1 : 0.5 (Table 2). We find that decreasing the catalyst loading from 25 mol% to 5 mol% results in only a slight reduction of product yield. However, increasing the catalyst loading significantly results in a decrease in yield rather than, as may be expected, an increase. The exact reason for this is not fully understood but may explain why in the reports using **4**, where a benzaldehyde : methyl acrylate : **4** ratio of 1 : 1 : 1 is used, yields are so low.[8]

We were keen to shorten the reaction time to less than 16 h and find that after 6 h the product yield is only 13% less indicating that the majority of the product is formed in the first few hours of reaction and as the reaction reaches an equilibrium product formation slows. In order to try to speed up the reaction we studied the effects of varying the temperature on the product yield (Table 3). Rafel and Leahy report that, when using DABCO as a catalyst, the yields of product in the reaction are increased when the temperature is reduced from room temperature to 0 °C.[10] They suggest that this increase in yield is as a result of the preferential formation and subsequent rapid reaction of an ionically stabilised enolate. Using TMG we find that the opposite is true; the optimal yield of product is achieved at room temperature (25 °C) or slightly warmer (30 °C). Further cooling or warming of the reaction mixture results in a dramatic lowering in yield. The fact that the results are so different to those reported for DABCO suggests that the formation of an ionically stabilised enolate is not key to the activity of TMG as a catalyst and certainly supports the idea that the equilibrium concentration of the β-enolate

Table 2 Optimisation of TMG catalyst loading and reaction time[a]

Ratio of aldehyde : acrylate : TMG	Mol% TMG	Reaction time/h	Product yield (%)
1 : 1 : 0.1	5	6	58
1 : 1 : 0.1	5	16	64
1 : 1 : 0.25	12.5	6	66
1 : 1 : 0.25	12.5	16	67
1 : 1 : 0.5	25	6	68
1 : 1 : 0.5	25	16	73
1 : 1 : 1	50	6	31
1 : 1 : 1	50	16	50

[a] Using benzaldehyde and methyl acrylate as starting materials and TMG as catalyst. Reactions were run solvent-free and at room temperature.

Table 3 Optimisation of reaction temperature[a]

Mol% TMG	Temperature/°C	Product yield (%)
5	0	8
50	0	12
5	25	58
12.5	25	66
50	25	68
25	25	73
5	30	62
12.5	30	67
5	40	8

[a] Using benzaldehyde and methyl acrylate as starting materials and TMG as catalyst. Reactions were run solvent-free and for 6 h.

Table 4 Assessment of the effect of solvent on the reaction[a]

Solvent	Product yield (%)
None	58
Dichloromethane	53
Toluene	38
Hexane	32
THF	29
Dioxane	29
Acetonitrile	27

[a] Using benzaldehyde and methyl acrylate as starting materials, 5 mol% TMG as catalyst and 5 ml solvent. Reactions were run at room temperature for 6 h.

intermediate is increased by using a base that has the potential for stabilisation through conjugation. We are not certain as to why the reaction yield decreases so dramatically when the temperature is increased from 30 to 40 °C, but analysis of the product mixture shows some evidence of the TMG being rapidly decomposed or forming a polymeric product with the starting materials.

As both benzaldehyde and methyl acrylate are liquids, the reaction can be run without the need for solvent. However, this is not always the case as many potential substrates are solids. In addition, if the reaction is to be modified for using either polymer-supported reagents or catalysts a solvent would be necessary to ensure appropriate swelling of the resin. We therefore decided to investigate the effect of solvent on the reaction (Table 4). We find that addition of solvent (5 ml) to the benzaldehyde and methyl acrylate substrate mixture results in a decrease in overall yield. This decrease in yield is least in dichloromethane and greatest in acetonitrile, with THF, toluene, hexane and dioxane being in between these limits. To our knowledge, the use of dichloromethane as a solvent in Baylis–Hillman reactions has not been reported previously and may offer a route to increased yields using catalyst and procedures already reported in the literature as well as here using TMG.

To broaden the scope of the reaction, we studied the effects of changing the aldehyde on the yields of reaction. A range of

Table 5 TMG catalysed Baylis–Hillman reaction with various aldehydes[a]

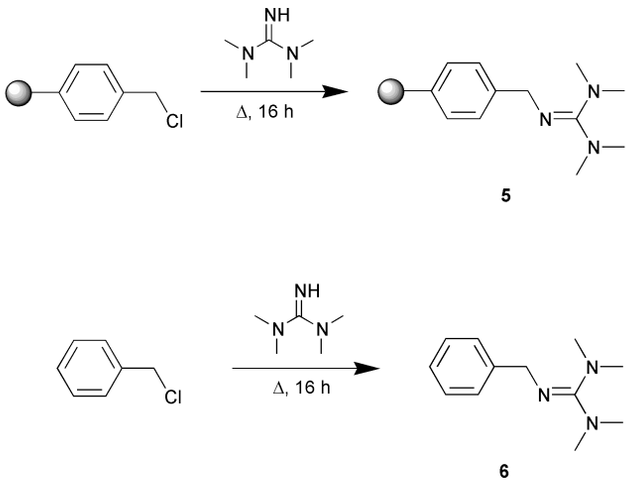
Aldehyde	Mol% TMG	Product yield (%)
Benzaldehyde	12.5	67
4-Chlorobenzaldehyde	12.5	65
Acetaldehyde	12.5	61
Propionaldehyde	5	63
Propionaldehyde	12.5	69
3-Phenylpropionaldehyde	12.5	55
(*E*)-Cinnamaldehyde	25	50
(*E*,*E*)-Hexa-2,4-dienal	5	0[b]

[a] Using aldehyde and methyl acrylate as starting materials and TMG as catalyst. Reactions were run in dichloromethane and at room temperature. [b] Polymerisation occurs

aldehydes were screened for activity in the reaction using methyl acrylate as the activated alkene and TMG as catalyst. Reactions were run in dichloromethane for 6 h using an aldehyde : acrylate : TMG ratio of 1 : 1 : 0.1. The results are shown in Table 5. As can be seen from the data, good yields of product are obtained with a range of aldehydes, the exception being hexa-2,4-dienal where polymerisation occurs. This is not totally unexpected as this substrate is known to readily polymerise in the presence of base. The fact that the reaction works well with acetaldehyde and propionaldehyde is particularly noteworthy. To date, Baylis–Hillman reactions involving simple aliphatic aldehydes are reported to give notoriously low yields of product or else the aldehyde decomposes in the presence of the catalyst mixture during the course of the reaction. Using TMG our results suggest that it is possible to circumvent these problems and obtain reasonable yields of the desired product, the remainder of the reaction mixture being unreacted starting materials.

When using an amine catalyst, one of the drawbacks of the Baylis–Hillman reaction is the work-up required at the end of the reaction. It is necessary to remove the amine from the reaction mixture by an aqueous work-up. Although this is not difficult, it creates an extra step in the procedure and produces quantities of aqueous waste. We wanted to try to avoid the work-up step by immobilising the amine catalyst onto a polymer support. The key advantage of attaching a catalyst to a polymer support is ease of separation from the product mixture at the end of a reaction; a simple filtration being all that is required. In addition, as the catalyst is easily removed from the reaction mixture, it can be re-used in subsequent reactions.

We prepared polymer-supported TMG, **5**, by simple reaction of Merrifield's resin with TMG (Scheme 2). The resin is suspended in dioxane and, after allowing time for swelling, an excess of TMG is added. The mixture is then refluxed for 16 h before filtering and washing away excess TMG leaving the product in a pure form. Elemental analysis shows that a loading of approximately 1 mmol TMG per g resin can be obtained from Merrifield's resin with a loading of approximately 4 mmol Cl per g. We find that a similar loading of TMG can be achieved using a lower loading of Merrifield's resin indicating



Scheme 2 Preparation of a polymer-supported analogue of TMG, **5**, and a homogeneous model, **6**.

that the limiting factor for replacement of Cl by TMG may well be the steric crowding of the support.

Having prepared and characterised the supported TMG we attempted to use it as a catalyst in the Baylis–Hillman reaction. Our observations were disappointing, finding that **5** was completely inactive as a catalyst. The reaction was run for 48 h using both dichloromethane and THF solutions of the reagents and also using solvent-free conditions. In none of these cases was any trace of product formed. We thought that one reason for the loss of activity of TMG on immobilisation might be the steric crowding in the environment of the polymer support. To investigate this we prepared benzyl-TMG, **6**, this acting as a homogeneous comparison to **5** (Scheme 2). This was prepared in a modification of the literature method in modest yield by thermolysis of a dioxane solution of benzyl chloride and TMG.[18] Screening the activity of **6** in the Baylis–Hillman reaction showed that, like **5**, it was inactive as a catalyst. This therefore suggests that the amine hydrogen on free TMG is key to the activity of this complex as a catalyst for the reaction. Substitution of this renders the complex inactive under the conditions used in our experiments.

Conclusions

We have shown that tetramethylguanidine, TMG, is a useful catalyst for the Baylis–Hillman reaction. It shows good activity with a range of aldehyde substrates and, unlike other catalysts or catalyst mixtures, it can be used with simple aliphatic aldehydes. We have shown that the activity of the catalyst is decreased when the reaction is run using solvents rather than solvent-free but, in the case where a solvent is necessary, dichloromethane offers the best results. To our knowledge this is the first time dichloromethane has been used as a solvent for the reaction and could prove useful for performing the reaction using other catalysts. Attempts to use supported or derivatised TMG complexes as catalysts for the reaction have been unsuccessful suggesting that the presence of an amine hydrogen is key to the activity of TMG. Attempts to use stabilised aliphatic phosphines as catalysts for the reaction have proven partly successful, with only modest yields of product being obtained with 2-(dicyclohexylphosphino)biphenyl, 2-(di-*tert*-butylphosphino)biphenyl. The Verkade superbase proved inactive as a catalyst, an adduct with the acrylate being the only product formed.

Experimental

General

Reactions were run in dried glassware and using distilled solvents. Reaction substrates and tetramethylguanidine were purchased from Lancaster and Aldrich. Verkade superbase, 2-(dicyclohexylphosphino)biphenyl, 2-(di-*tert*-butylphosphino)-biphenyl and tributylphosphine were acquired from Strem Chemicals. Merrifield resin (200–400 mesh, crosslinked with 2% divinylbenzene, 4.3 mmol Cl g^{-1} resin) was obtained from Fluka. All commercially available chemicals were used in reactions without further purification. ^{1}H- and ^{13}C-NMR spectra were recorded using a Bruker 360 MHz NMR spectrometer. Elemental analyses were run by Medac Ltd, Brunel Science Park, UK. All spectra were run in $CDCl_3$ using TMS as a standard. The Baylis–Hillman products are all known compounds. Physical and spectral data were compared with those reported in the literature.

Typical procedure for catalyst screening for activity in the Baylis–Hillman reaction

To a mixture of benzaldehyde (0.51 ml, 0.53 g, 5.0 mmol) and methyl acrylate (0.45 ml, 0.43 g, 5.0 mmol) was added the desired catalyst candidate. The reaction was stirred at the required temperature for the allotted time. The reaction was ended by addition of diethyl ether (20 ml). This solution was washed with 2 M HCl (20 ml) and then twice with water (2 × 15 ml). The organic extract was dried over magnesium sulfate, the solvent and any unreacted methyl acrylate were removed under vacuum and the product mixture was analysed.

Typical procedure for aldehyde screening for activity in the Baylis–Hillman reaction

To a mixture of aldehyde (5.0 mmol) and methyl acrylate (0.45 ml, 0.43 g, 5.0 mmol) in dichloromethane (1.5 ml) was added TMG (0.06 ml, 57.5 mg, 0.5 mmol). The reaction was stirred at room temperature for 6 h. The reaction was ended by addition of diethyl ether (20 ml) and the work-up was as in the case of benzaldehyde.

Preparation of TMG-methylpolystyrene, 5

To Merrifield resin (1 g, 4.3 mmol Cl) was added dioxane (50 ml) and the mixture allowed to stir for 30 min to ensure swelling of the resin. After this time TMG (2.72 ml, 2.47 g, 21.5 mmol) was added and the mixture heated at 70 °C for 16 h. At the end of the reaction the beads were washed twice with MeOH, DCM and hexane in this order. The white beads were dried overnight in a vacuum desiccator. The loading of amine on the support was determined by microanalysis and estimated at approximately 1 mmol TMG g^{-1} resin (analysis data: 72.69% C, 7.79 N, 8.70 H, 10.82 Cl).

Preparation of 2-benzyl-1,1,3,3-tetramethylguanidine, 6

To a dioxane solution (5 ml) of benzyl chloride (0.92 ml, 1.00 g, 8.0 mmol) was added TMG (1 ml, 0.92 g, 8.0 mmol) and the resultant mixture heated at 70 °C for 2 h. Diethyl ether (25 ml) was added and the mixture washed with water (25 ml) and dried over magnesium sulfate. The solvent was removed under vacuum and the resultant oily product purified by flash chromatography giving 3.6 mmol (44% yield) of **6** as a yellow oil. ^{1}H-NMR: δ 7.56–7.15 (m, 5H), 4.39 (s, 2H), 2.78 (s, 6H), 2.73 (s, 6H). ^{13}C-NMR: δ 134.5, 128.0, 127.2, 125.8, 53.1, 39.7 and 38.9.

Procedure for using 5 and 6 in the Baylis–Hillman reaction

To a dichloromethane solution (5 ml) of benzaldehyde (0.51 ml, 0.53 g, 5.0 mmol) and methyl acrylate (0.45 ml, 0.43 g, 5.0 mmol) was added TMG-methylpolystyrene (0.5 g, 0.5 mmol TMG). The reaction was stirred at room temperature and the reaction monitored using TLC. The reaction was ended after 48 hours after no evidence was found for product formation.

The reaction was repeated in THF and solvent-free but again with no success. Repeating the reactions using **6** in the place of **5** again did not lead to product formation.

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