First examples of metal and ligand accelerated catalysis of the Baylis–Hillman reaction

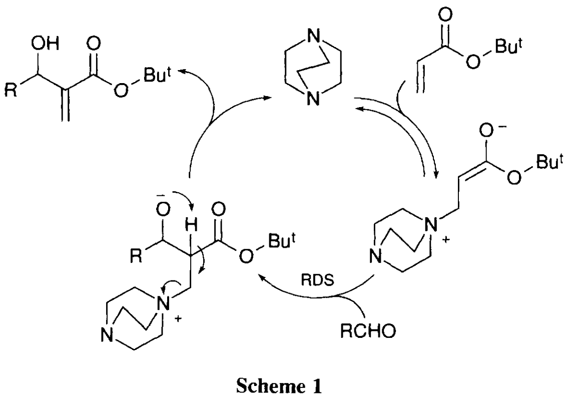
Varinder K. Aggarwal,*[a] **Gary J. Tarver**[a] **and Ray McCague**[b]

[a] *Department of Chemistry, University of Sheffield, Sheffield, UK S3 7HF*
[b] *Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE*

Lanthanides and group III metal triflates (especially La, Sm) accelerate the Baylis–Hillman reaction (reaction between an unsaturated ester and aldehyde catalysed by DABCO, for example) and further acceleration can be obtained upon addition of diol ligands such as binol.

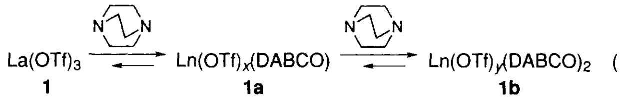
The coupling of an activated vinyl system with an aldehyde catalysed by a tertiary amine (the Baylis–Hillman reaction,[1] Scheme 1) suffers from low reaction rates and indeed can be inordinately slow with certain substrates *e.g.* the reaction of *tert*-butyl acrylate with benzaldehyde catalysed by 1,4-diazabicyclo[2.2.2]octane (DABCO) takes 28 days to go to completion when conducted in neat reagents.[2] Much attention has therefore focused on accelerating this reaction and it has been found that rate increases can be achieved using high pressure,[3] ultrasound[4] or microwave irradiation[5] but such methods suffer from requiring specialised equipment. Other methods include the use of water as solvent,[6] although this method has only been applied to acrylonitrile, and the use of activated aldehydes, which unfortunately limits the scope of the reaction.[7]

In attempting to develop a more general method for acceleration of the Baylis–Hillman reaction we have considered the use of Lewis acids as these should activate the aldehyde towards nucleophilic attack (this is believed to be the RDS of the reaction[2,8]). However, standard Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$) resulted in *deceleration* of the reaction, presumably due to formation of an amine–Lewis acid complex. This effectively sequesters the amine, preventing it from acting as a nucleophilic catalyst and renders the Lewis acid inactive. To weaken the Lewis acid–amine complex we needed a harder Lewis acid (more oxophilic) and to retain Lewis acid capability we needed a metal capable of binding multiple ligands. Lanthanides fulfil these criteria.[9,10] We therefore investigated a range of lanthanides and group III metal triflates in the above reaction (Scheme 1) and the results are presented in Table 1. We were pleased to find that, using just 5 mol% of catalyst, all of the lanthanide and group III metal triflates did indeed cause an acceleration of the reaction.†



Scheme 1

$La(OTf)_3$ and $Sm(OTf)_3$ provided the greatest acceleration and reaction with $La(OTf)_3$ was studied in greater detail. Reactions were carried out with varying amounts of DABCO (nucleophilic catalyst) in the presence of 5 mol% $La(OTf)_3$ and the rates compared to reactions conducted in the absence of the Lewis acid. The results are depicted graphically in Fig. 1. It was found that rates did not increase linearly with increasing DABCO concentration as might have been expected (the reaction is first order with respect to DABCO[2,8] presumably because increasing additions of DABCO resulted in effective dilution of the other reagents.† In the presence of Lewis acid, it was found that no reaction occurred until 10 mol% DABCO had been added, possibly because all the DABCO was associated with the Lewis acid to give **1b** [eqn. (1)]. Above this



$$\underset{\mathbf{1}}{La(OTf)_3} \rightleftharpoons \underset{\mathbf{1a}}{Ln(OTf)_x(DABCO)} \rightleftharpoons \underset{\mathbf{1b}}{Ln(OTf)_y(DABCO)_2} \quad (1)$$

concentration, DABCO performed its role as a nucleophilic catalyst and $Ln(OTf)_y(DABCO)_2$ **1b** presumably acted as a Lewis acid, with the reaction occurring *via* **2**. The non-linear increase in rate with increasing concentration of DABCO could again be accounted for by the diluting effect of additional DABCO.

It was thought that the presence of powerful nitrogen donor ligands on the metal would moderate its Lewis acidity and so we sought to displace them by taking advantage of the oxophilic nature of the metal. We therefore tested a number of diol ligands and discovered further rate enhancements particularly with (+)-binol.‡ We again studied the rate of reaction as a function of DABCO concentration in the presence of 5 and 10 mol% (+)-binol (Fig. 1).† It was discovered that this time, reactions occurred even at low concentrations (< 10 mol%) of DABCO indicating that the metal was no longer sequestering the amine and that, as the graphs had steeper gradients compared to the absence of (+)-binol, we had generated a stronger Lewis acid **3**. The departure from linearity at high DABCO concentration presumably results from a change in concentration of the different catalytic species present [*e.g.* shift of the equilibrium from **3** towards **1b**, eqn. (2)]. Thus, as we had predicted, the

$$\underset{\mathbf{1b}}{Ln(OTf)_y(DABCO)_2} \xrightleftharpoons{\text{binol}} \underset{\mathbf{3}}{Ln(OTf)_a(binol)_z} \quad (2)$$

lanthanum catalyst with oxygen donor groups **3** was superior to the lanthanum catalyst with nitrogen donors **1b**.

This constitutes another important reaction which shows ligand accelerated catalysis. There are few reactions in this class (*e.g.* Sharpless asymmetric epoxidation, dihydroxylation) but such reactions provide real opportunities in asymmetric synthesis.[11] Perhaps even more importantly, we have achieved

Table 1 Relative rate of Baylis–Hillman reaction using 100 mol% DABCO and 5 mol% metal catalyst

$M(OTf)_3$	k_{rel}
—	1
Sc	3.3
Sm	4.7
Eu	3.5
Gd	3.9
Yb	3.6
La	4.7

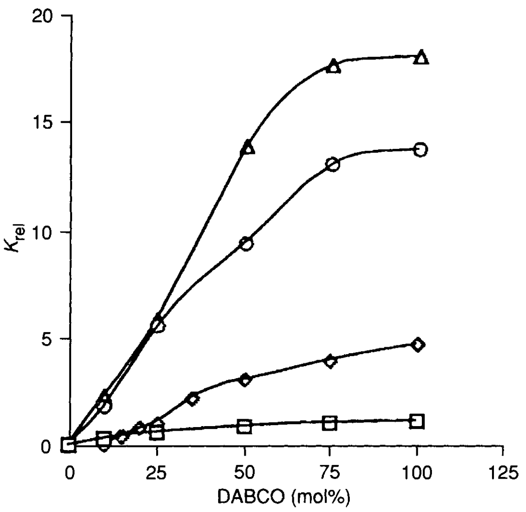
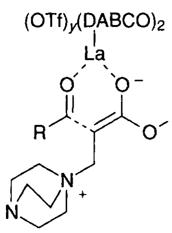


Fig. 1 Relative rate of reaction as a function of DABCO concentration for the Baylis–Hillman reaction between *tert*-butyl acrylate and benzaldehyde; (□) no metal or diol present, (◇) 5 mol% lanthanum triflate, (○) 5 mol% lanthanum triflate and 5 mol% binol, (△) 5 mol% lanthanum triflate and 10 mol% binol



2

Table 2 Relative rates of Baylis–Hillman reaction between acrylate derivatives and benzaldehyde using 100 mol% DABCO†

	K_{rel}	
Substrate	$La(OTf)_3$[a]	$La(OTf)_3$/(+)-binol[b]
Methyl acrylate	3.3	15.3
Ethyl acrylate	4.7	25.6
tert-Butyl acrylate	4.7	18.1
Acrylonitrile	2.2	6.2

[a] Relative rate of reaction in presence of 5 mol% $La(OTf)_3$. Rate in absence of metal and ligand is 1. [b] Relative rate of reaction in presence of 5 mol% $La(OTf)_3$ and 10 mol% (+)-binol.

significant levels of rate enhancement through the cooperative action of both Lewis acid and base catalysts.§ These catalysts were presumably able to fulfil their respective roles and to work effectively in unison to promote and enhance the rate of the reaction. Non-interacting pairs of Lewis acids and bases will no doubt have applications in other chemical reactions.¶

The system we have developed has been applied to the reaction of benzaldehyde with a range of unsaturated esters and nitriles (Table 2).‖ In each case rate increases were observed in the presence of the Lewis acid and further acceleration was obtained in the presence of the diol ligand.

We thank Chiroscience and Sheffield University for support of this work.

Footnotes

† Reactions using methyl, ethyl or *tert*-butyl acrylate as substrate were conducted at 25 °C in MeCN. Reactions using acrylonitrile as substrate were conducted at 25 °C in THF (to maintain homogeneity) at 2 mol dm^{-3} concentration. One equivalent of benzaldehyde, acrylate or acrylonitrile and the required amount of DABCO were added to a stirred mixture of lanthanide triflate (5 mol%) and ligand (0, 5 or 10 mol%) in acetonitrile (100 μl mmol^{-1} benzaldehyde) or THF (2 mol dm^{-3}). After 24 h one equivalent of ethyl cinnamate was added as internal standard. The reaction was then diluted and stopped by filtration through silica gel to remove DABCO and the lanthanide catalyst and the yield of the product was determined by GC. From this data the relative rate of reaction was calculated using the formula $K_{rel} = \{[1/(1 - X_{cat})] - /[1/(1 - X_{uncat})] - 1\}$ where X_{cat} and X_{uncat} are the concentrations of products in the catalysed and uncatalysed reactions respectively. This equation is derived from the second order rate equation and gives a straight line when plotting 1/[acrylate] against time.

‡ The product obtained was racemic. In a control experiment it was found that binol on its own [no $La(OTf)_3$, all other reagents present] did not cause any rate acceleration.

§ Chemical reactions cannot usually be accelerated by *both* Brönsted/Lewis acids and Brönsted/Lewis bases simultaneously as these catalysts usually react together and either annihilate each other or form strong complexes which are no longer able to act as catalysts. For a notable exception see ref. 12.

¶ Work is underway to develop a mathematical model to describe the principle of push–pull catalysis. The mechanistic considerations we have detailed in the paper are in accordance with this model, details of which will reported in due course.

‖ At present α,β-unsaturated ketones are not compatible with the reaction conditions and give mixtures of products including a dimer. It is known that DABCO can catalyse such dimerisation of α,β-unsaturated ketones (ref. 13).

References

1 D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001; S. E. Drewes and G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653.
2 Y. Fort, M. C. Berthe and P. Caubere, *Tetrahedron*, 1992, **48**, 6371.
3 J. S. Hill and N. S. Issacs, *J. Chem. Res. (S)*, 1988, 330.
4 G. H. P. Roos and P. Rampersadh, *Synth. Commun.*, 1993, **23**, 1261.
5 M. K. Kundu, S. B. Mukherjee, N. Balu, R. Padmakumar and S. V. Bhat, *Synlett*, 1994, 444.
6 J. Auge, N. Lubin and A. Lubineau, *Tetrahedron. Lett.*, 1994, **35**, 7947.
7 Aryl aldehydes complexed with $Cr(CO)_3$ give faster reactions compared to uncomplexed aldehydes: E. P. Kundig, L. H. Xu, P. Romanens and G. Bernardinelli, *Tetrahedron. Lett.*, 1993, **34**, 7049; E. P. Kundig, L. H. Xu and B. Schnell, *Synlett*, 1994, 413.
8 J. S. Hill and N. S. Issacs, *J. Phys. Org. Chem.*, 1990, 285.
9 S. Kobayashi, *Synlett*, 1994, 689.
10 G. A. Molander, *Chem. Rev.*, 1992, **92**, 29.
11 D. J. Berrisford, C. Bolm and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1059.
12 M. Shibasaki and H. Sasai, *Pure Appl. Chem.*, 1996, **68**, 523.
13 D. Basavaiah, V. V. L. Gowriswari and T. K. Bharathi, *Tetrahedron. Lett.*, 1987, **28**, 4591.

Received, 7th August 1996; Com. 6/05515J