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Metal- and Ligand-Accelerated Catalysis of the Baylis−Hillman Reaction

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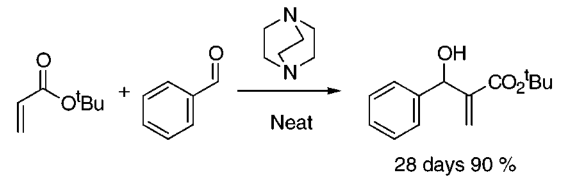
The Baylis−Hillman reaction, the coupling of an unsaturated carbonyl compound/nitrile with aldehydes, is a valuable reaction but is limited in its practicality by poor reaction rates. We have endeavored to accelerate the reaction using Lewis acids and found that while conventional Lewis acids gave reduced rates group III, and lanthanide triflates (5 mol %) gave increased rates. The optimum metal salts were La(OTf)$_3$ and Sm(OTf)$_3$, which gave rate accelerations (k_{rel}) of approximately 4.7 and 4.9, respectively, in reactions between *tert*-butyl acrylate and benzaldehyde when using stoichiometric amounts of DABCO. At low loadings of DABCO (up to 10 mol %), no reaction occurred due to association of DABCO with the metal. Use of additional ligands to displace the DABCO from the metal was studied, and the rate of reaction was found to increase further in most cases. Of the ligands tested, at 5 mol %, (+)-binol gave one of the largest rate accelerations (3.4-fold) and was studied in more detail. It was found that reactions occurred even at low DABCO concentration so that here the Lewis base and Lewis acid were able to promote the reaction without interference from each other. While the (+)-binol (and other chiral ligands) failed to provide any significant asymmetric induction, a substantial nonlinear effect was observed with binol. Thus, use of racemic binol gave no effect on the rate. In seeking to maximize the rate attainable, more soluble (liquid) ligands were studied. Diethyl tartrate and triethanolamine gave rate enhancements of 5.2× and 3.5× at 50 mol %, respectively, versus 1.5× and 2.3× at 5 mol %. The best protocol was to use 100 mol % DABCO, 50 mol % triethanolamine, and 5 mol % La(OTf)$_3$. This gave overall rate accelerations of between 23-fold and 40-fold depending on the acrylate and approximately 5-fold for acrylonitrile. A simple acid wash removed the reagents, leaving the product in the organic phase. While triethanolamine accelerated the reaction without the lanthanum triflate (18−22-fold at 80 mol %), the reaction in the presence of the metal salt was faster. The system was tested synthetically on various substrates and found to give good rate accelerations with both activated (benzaldehyde and *p*-nitrobenzaldehyde) and less activated aldehydes (anisaldehyde and cyclohexanecarboxaldehyde) with acrylates. The limited amount of dimerized acrylate in the latter reactions is noteworthy and should extend the range of substrates that can be made by the Baylis−Hillman reaction using our optimum conditions.

Introduction

The Baylis−Hillman reaction is an exquisite reaction: cheap and readily available starting materials are converted, using a suitable catalyst, into densely functionalized products.[1,2] However, the reaction suffers from poor reaction rates, e.g., the reaction of *tert*-butyl acrylate with benzaldehyde using 10 mol % DABCO catalyst takes 28 days to complete (Scheme 1).[3]

The mechanism of the Baylis−Hillman reaction is shown in Scheme 2.[4] Attempts have been made to increase the rate of the Baylis−Hillman reaction (the RDS is highlighted) through either physical or chemical means, but there are disadvantages associated with most of the methods.

Scheme 1. Reaction of *tert*-Butyl Acrylate with Benzyaldehyde



The reaction can be accelerated by high pressure (the Baylis−Hillman reaction has a very high negative activation volume: −70 cm^3 mol^{-1}), but this method requires sophisticated equipment.[5,6] Ultrasound[7] and microwave irradiation[8] have been reported to give increases in rate but again require somewhat specialized equipment. Conducting reactions at 40 °C provides an increase in rate of up to 2-fold,[7] but a recent report that reactions carried out at 0 °C gave rate increases of up to 40-fold seemed the simplest and most effective method for

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[1] Drewes, S. E.; Ross, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670.

[2] Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062.

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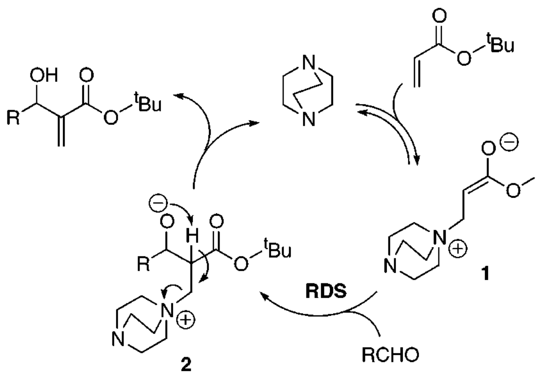
Scheme 2. Mechanism of the Baylis-Hillman Reaction



increasing reaction rate.[9] However, we have been unable to reproduce this result.

Modest increases in rates have been observed in the presence of hydrogen bond donors by using methanol as solvent[10] or using 3-hydroxyquinuclidine[10,11] or ω-hydroxy esters.[12] The increase in rate by hydrogen bonding can be attributed to either stabilization of the intermediate aza enolate **1** (thereby increasing its concentration) or by activation of the aldehyde or indeed both. Conducting reactions in water[13] or fluorinated solvents[14] also results in increased rates as a result of hydrophobic and fluorophobic effects, respectively. The use of phosphines, which are more nucleophilic catalysts than tertiary amines, result in increased rates.[9,15] The most active phosphines are aliphatic phosphines, but they are also very susceptible to air oxidation. Increasing the activation of carbonyl compounds on either the donor or acceptor also results in increased rates. For example, trifluoroethyl acrylate reacts ~2.5× faster than ethyl acrylate,[3] and aldehydes undergo the Baylis–Hillman reaction more readily than keto esters or ketones.

We have considered the possibility of using Lewis acids to promote the Baylis–Hillman reaction. In the same way that hydrogen bonding promotes the Baylis–Hillman reaction, Lewis acids should also lead to increased rates by either stabilization of the intermediate aza enolate (thereby increasing its concentration) or activation of the aldehyde or both. In this paper, we provide a full account of our studies in this area.[16]

Results

Reactions were conducted using *tert*-butyl acrylate and benzaldehyde with 1 equiv of DABCO and 5 mol % different Lewis acids. After 24 h, the reactions were stopped and the yields measured by gas chromatography (see the Experimental Section for full details). The results are shown in Table 1.

Table 1. Baylis–Hillman Reactions Using 100 Mol % DABCO and 5 Mol % Lewis Acid Catalyst[a]

Lewis acid	k_{rel}[b]	Lewis acid	k_{rel}[b]
	1	$Ti(OEt)_4$	<0.1
$BF_3 \cdot OEt_2$	<0.1	$Sc(OTf)_3$	3.3
$TiCl_4$	<0.1		

[a] Reactions were conducted on 1 mmol scale using a 1:1:1 ratio of *tert*-butyl acrylate/benzaldehyde/DABCO. Reactions stopped after 24 h. [b] Relative to reactions using 100 mol % DABCO as catalyst and no Lewis acid.

Table 2. Effect of Lanthanide Catalysts on the Rate of the Baylis–Hillman Reaction[a]

metal catalyst	yield (%)	k_{rel}[b]
none	3.8	1
$Sc(OTf)_3$	11.6	3.3
$Yb(OTf)_3$	12.3	3.6
$Gd(OTf)_3$	13.2	3.9
$Eu(OTf)_3$	12.1	3.5
$Sm(OTf)_3$	16.3	4.9
$La(OTf)_3$	15.9	4.7

[a] Reactions conducted on 1 mmol scale using a 1:1:1 ratio of *tert*-butyl acrylate/benzaldehyde/DABCO with the addition of 5 mol % metal catalyst and 100 μL of MeCN. Reactions stopped after 24 h. [b] Relative to reactions using 100 mol % DABCO as catalyst and no Lewis acid.

It was found that conventional Lewis acids ($BF_3 \cdot OEt_2$, $TiCl_4$) resulted in deceleration of the reaction, whereas the use of $Sc(OTf)_3$ resulted in an acceleration. We presume that the standard Lewis acids formed strong DABCO–Lewis acid complexes[17] which neutralized the Lewis acid and in addition removed some of the DABCO from the system so that there was less catalyst available for reaction, resulting in reduced rates. In contrast, $Sc(OTf)_3$, being a much harder Lewis acid, is likely to form a weaker and more labile DABCO–Lewis acid complex. This complex may still function as a Lewis acid as there should still be free sites on the metal to allow coordination of the aldehyde and therefore accelerate the reaction. We therefore screened a range of hard Lewis acids, the lanthanides (Table 2). As some catalysts were not completely homogeneous under neat reaction conditions, all reactions were conducted with 100 μL of MeCN. This proved to be the optimum solvent.

The catalysts are listed in order of increasing atomic radii of the metal, and there is a general trend of increase in reaction rate with increasing size of the metal cation.

$La(OTf)_3$ and $Sm(OTf)_3$ provided the greatest acceleration, and reaction with $La(OTf)_3$ was studied in greater detail as it is more economical. 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 Figure 1 (and in the Supporting Information, Table 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[3,4]) 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

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[15] Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992**, *33*, 1045–1048.

[16] Aggarwal, V. K.; Tarver, G. J.; McCague, R. *J. Chem. Soc., Chem. Commun.* **1996**, 2713–2714.

[17] It has recently been found that sulfides can catalyze the Baylis–Hillman reaction in the presence of $TiCl_4$. Presumably, this combination of reagents does not lead to the formation of strong Lewis acid–Lewis base complexes. Kataoka, T.; Iwama, T.; Tsujiyama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 197–198.

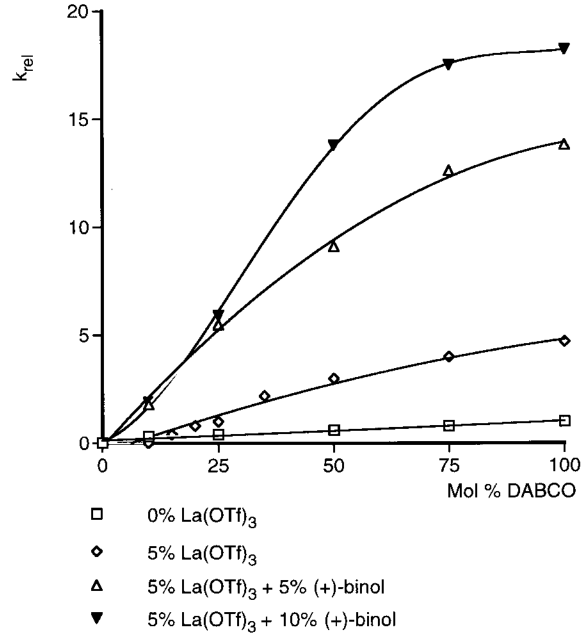
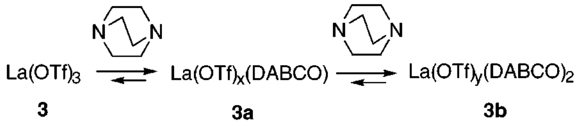
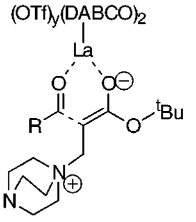


Figure 1. Effect of amount of DABCO on reaction rate. Reactions were conducted on a 1 mmol scale using a 1:1 ratio of *tert*-butyl acrylate/benzaldehyde with 0.1 mL of CH_3CN; $k_{rel} = 1$, $[La(OTf)_3] = 0$, $[(+)\text{-binol}] = 0$, $[DABCO] = 100$ mol %.

added, possibly because all the DABCO was associated with the Lewis acid to give **3b**. This is consistent with the formation of $La(OTf)_n(DABCO)_2$ complex which performs its role as a Lewis acid and at concentrations above 10 mol % the DABCO can perform its role as a nucleophilic catalyst. The reaction is believed to occur via the metal complex **4**. The nonlinear increase in rate with increasing concentration of DABCO could again be accounted for by the diluting effect of additional DABCO.





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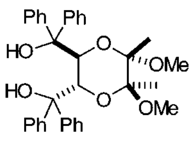
It was thought that the binding of DABCO to the Lewis acid to give **3b** not only resulted in sequestration of the nucleophilic catalyst but may also have moderated the Lewis acidity of the metal due to the powerful nitrogen donor ligands (amine ligands are better donors than ethers). We therefore sought to displace the nitrogen donor ligands with alternative groups by taking advantage of the oxophilic nature of the metal and so tested a broad range of oxygen-rich ligands with several metals and discovered further rate enhancements (Table 3).

No clear correlation between the structure of the ligand and rate acceleration emerged from this study. For example, some diol ligands gave good rate accelerations (Table 3, entries 2–4) but some did not (Table 3, entries 5–7). Salen, bisoxazoline, and amino alcohol ligands also gave mixed results. Triethanolamine gave good rate accelerations with $La(OTf)_3$ (Table 3, entry 10), but more substituted analogues gave lower rates (Table 3, entries 11 and 12). Similarly, hindered salens gave considerably lower rates than less substituted salens (Table 3, entries 13–15). The optimum ligand/metal combination in terms of rate acceleration was (*R*,*R*)-(+)-hydrobenzoin with $Yb(OTf)_3$ (Table 3, entry 6).



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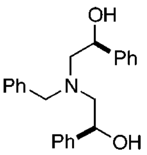

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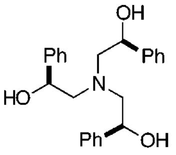

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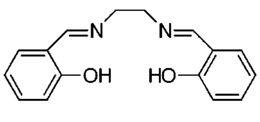

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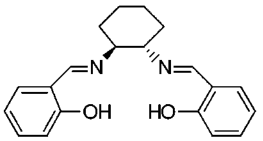

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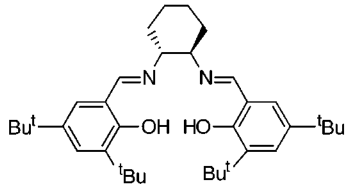

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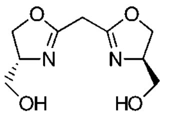

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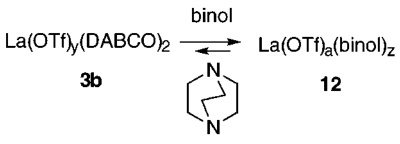
Unfortunately, the highest enantiomeric excess obtained using any of the chiral ligands was only 5% [(+)-diisopropyl tartrate with $Yb(OTf)_3$].

Although (*R*,*R*)-(+)-hydrobenzoin with $Yb(OTf)_3$ gave the highest rate, (+)-binol gave the highest rates with a range of metals (the optimum being $La(OTf)_3$, Table 3, entry 2), and so a series of reactions were now performed with this metal–ligand combination in order to optimize the amount of DABCO and ligand. The results are depicted in Figure 1 (and Supporting Information, Table 1).

It was discovered that, now, in the presence of binol, reactions occurred even at low concentrations (<10 mol %) of DABCO, indicating that the metal was no longer sequestering the amine. Also, as the graphs had steeper gradients compared to the absence of (+)-binol a stronger Lewis acid (**12**) must have been generated. The departure from linearity at high [DABCO] presumably results from a change in concentration of the different catalytic species present (e.g., shift of the equilibrium from **12** toward **3b**) or from dilution of the reaction. Thus, the lanthanum catalyst with oxygen donor groups **12** was superior to the lanthanum catalyst with nitrogen donors **3b**.



These results show that the best accelerations were obtained using stoichiometric amounts of DABCO and

Table 3. Effect of Metal and Ligand Catalysis on Relative Reaction Rate[a,b]

entry	ligand	$Sc(OTf)_3$	$Yb(OTf)_3$	$Eu(OTf)_3$	$La(OTf)_3$
1	none	3.3	3.6	3.5	4.7
2	(+)-binol	9.4	14.4	12.8	14.6
3	(+)-diethyl tartrate	5.2	9.7	5.5	7.3
4	(+)-−iisopropyl tartrate	3.5	9.5	4.6	8.1
5	(+)-TMTDA[c]	4.1	8.0	3.6	4.0
6	(*R*,*R*)-(+)-hydrobenzoin	3.5	16.2	5.8	5.3
7	(+)-1,1,2-triphenylethanediol	3.2	5.2	2.2	5.9
8	(+)-TADDOL **5**	2.9	4.5	3.8	4.7
9	ethylene glycol	3.3			
10	triethanolamine	4.65			10.8
11	amino diol **6**	3.3	3.6		
12	amino triol **7**	3.1			4.4
13	Salen ligand **8**	5.7			
14	Salen ligand **9**	7.0			
15	Salen ligand **10**	2.31	6.3	5.2	4.0
16	bisoxazoline **11**	3.6			
17	*N*-methylephedrine	2.87	5.8	3.2	4.4

[a] Reactions conducted on 1 mmol scale using a 1:1:1 ratio of *tert*-butyl acrylate/benzaldehyde/DABCO; 5 mol % metal catalyst, 5 mol % ligand and 100 μL of MeCN. [b] k_{rel} relative to 100 mol % DABCO without Lewis acid. [c] (+)-*N*,*N*-Tetramethyltartaric acid diamide.

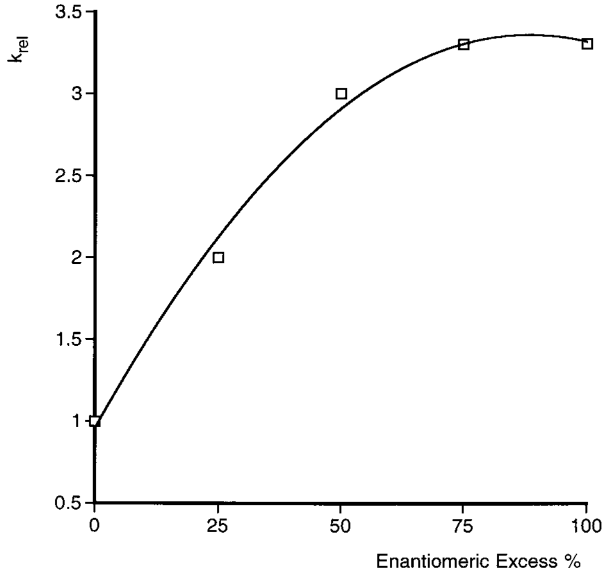


Figure 2. Effect of enantiomeric excess of binol on reaction rate. Reactions were conducted with a 1:1:1 ratio of *tert*-butyl acrylate, benzaldehyde, and DABCO on a 1 mmol scale with 5 mol % $La(OTf)_3$ and 5 mol % binol; $k_{rel} = 1$ for reaction with racemic binol.

10 mol % (+)-binol. Increasing the amount of binol further (25 mol %) did not result in further rate increases due to reaction viscosity.

Dependence of Reaction Rate on Enantiomeric Excess of Binol. Racemic binol gave much poorer acceleration of the Baylis−Hillman reaction than enantiomerically pure binol. To understand this effect, a series of reactions were conducted using 5 mol % binol of variable enantiomeric excesses in combination with 5 mol % $La(OTf)_3$ (Figure 2, Supporting Information, Table 2). The results clearly showed a nonlinear relationship between the relative rate of reaction with enantiomeric excess of the ligand. This indicates that more than one ligand is bonded to the metal or that a 2:2 complex (or greater) of metal and ligand are formed. The positive nonlinear effect indicates that the meso complex is more stable and less reactive than the chiral complex.

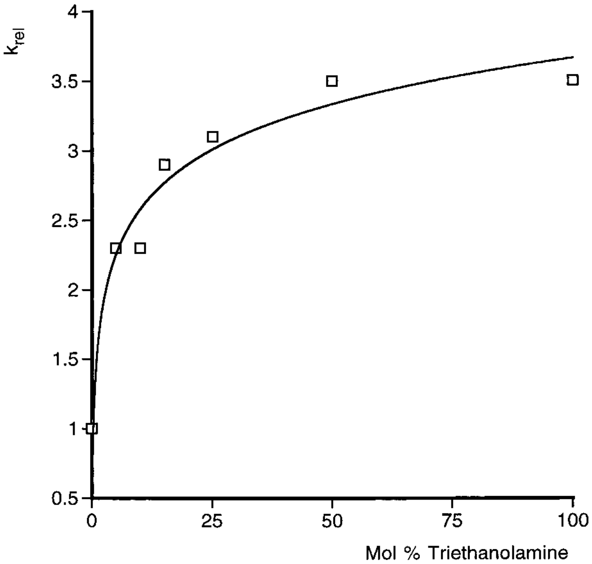


Figure 3. Effect of triethanolamine on reaction rate. Reactions were conducted with a 1:1:1 ratio of *tert*-butyl acrylate, benzaldehyde, and DABCO on a 1 mmol scale with 5 mol % $La(OTf)_3$; $k_{rel} = 1$, $[N(CH_2CH_2OH)_3] = 0$.

Nonlinear effects are normally associated with variations in enantiomeric excess of product with variation in enantiomeric excess of ligand.[18−20] In this case, all products were racemic. Nevertheless, for reactions that show ligand-accelerated catalysis[21] it is interesting to apply this concept to relative reaction rates.

Effect of Ligand Concentration. Enantiomerically pure binol is expensive, and so cheaper ligands were sought that would give comparable levels of acceleration. Diethyl tartrate and triethanolamine had been found to give moderate rate accelerations (1.8× and 2.2×, respectively) but less than binol (3.4×) at 5% loading. As higher ligand loading led to increased rates, we decided to investigate the effect of increased concentrations of diethyl tartrate and triethanolamine. As these ligands were both liquids at room temperature, much higher loadings were indeed possible.[22] The results are summarized in Figures 3 and 4 and in the Supporting Information, Table 3.

Increased amounts of ligands (triethanolamine and diethyl tartrate) led to increased rates up to approximately 50 mol % loading of ligand. Above this level, the rate either plateaued (as in the case with triethanolamine) or began to reduce (as in the case with diethyl tartrate). Presumably, at high ligand concentrations the metal is completely saturated and it is difficult for the aldehyde to coordinate and so the Lewis acidity is lowered. High ligand concentrations also dilute and

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[21] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

[22] (+)-Binol loading was limited to 10%, as above that amount the reaction became extremely viscous and no further acceleration was observed.

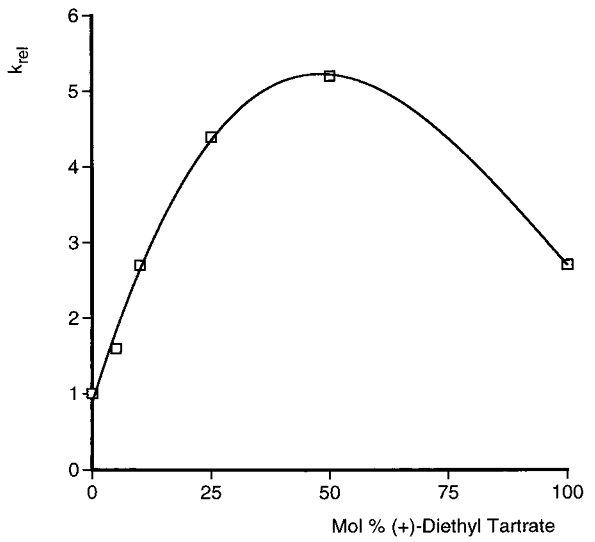
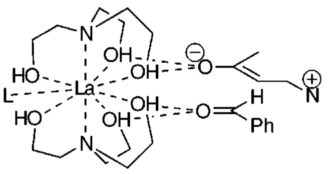


Figure 4. Effect of diethyl tartrate concentration on reaction rate. Reactions were conducted on a 1 mmol scale using a 1:1:1 ratio of benzaldehyde/*tert*-butyl acrylate/DABCO with 5 mol % La(OTf)$_3$, $k_{rel} = 1$, [(+)-diethyl tartrate] = 0.

therefore slow the reaction. These results show that the optimal loading of triethanolamine and diethyl tartrate is ∼50 mol %. Diethyl tartrate gave the best overall acceleration (5.2×); triethanolamine and binol gave similar but slightly lower optimal rate increases (3.5× and 3.9×, respectively). Due to the relative cost of triethanolamine (£0.05/g) and its ease of removal, triethanolamine was selected as the ligand of choice in these reactions.

A series of acrylates together with acrylonitrile were tested using the new system (5 mol % La(OTf)$_3$, 50 mol % triethanolamine), and as this seemed to be the optimum set of conditions, accurate rate data were obtained by monitoring reactions at short time and determining yields by GC (see the Experimental Section). Graphs were plotted of yield against time (see the Supporting Information), and the gradients of the straight line plots gave the rate of reaction. The results are summarized in Table 4. The expected increases in rate were observed in the presence of La(OTf)$_3$[23] with further rate increases in the presence of triethanolamine for all substrates. The optimized conditions provided rate increases of 23−40-fold depending on the acrylate used but much smaller rate increases for acrylonitrile.

X-ray crystal structures of lanthanide triflate−triethanolamine complexes have been reported for presidium and ytterbium[24] and provide some insights into the origin of the rate acceleration observed with lanthanum. The X-ray structures show a nine-coordinate metal center bearing two tetradentate triethanolamine ligands and one THF molecule. Additional THF molecules and triflates hydrogen bond to the triethanolamine ligands bound to the metal. Thus, it is possible that in the absence of THF the ninth ligand on the metal center is the azaenolate **1** or the aldehyde; either case would increase the of rate the Baylis−Hillman reaction. Indeed, the nucleophilic base DABCO may be too bulky to occupy the ninth position, and so the Lewis acid and Lewis base would be able to perform their respective roles without interference from each other. However, in the presence of an excess of triethanolamine, the ninth ligand is more likely to be a hydroxyl group of the excess reagent. In this case, rate acceleration would result from increased strengths of hydrogen bonds between the triethanolamine ligands bound to the metal and the azaenolate or between the triethanolamine ligands and the aldehyde or indeed both (see below). If this is indeed the origin of the rate acceleration, it is perhaps not surprising that low enantioselectivity was observed with the chiral ligands due to the lack of control in orientation of the hydrogen bonds.



A control experiment using 50 mol % triethanolamine without La(OTf)$_3$ was also conducted, and considerable rate enhancements were observed. We therefore carried out reactions with varying amounts of triethanolamine to determine the optimum concentration for maximum rate to determine if the metal catalyst was required (Figure 5). It was found that 80 mol % triethanolamine gave the highest rate accelerations (18−22-fold for different acrylates, Table 4) but that the rates were lower than those using the combination of metal and ligand. To determine whether the origin of the rate acceleration was simply due to hydrogen bonding, a similar study was conducted with methanol (Figure 6). In this case, it was found that approximately 240 mol % gave the highest rate accelerations[25] (3−11-fold for different acrylates, Table 4), but this time the rates were substantially lower compared to triethanolamine itself. This indicated that rate accelerations observed with triethanolamine were not simply due to hydrogen bonding alone but must involve a cooperative effect from multiple hydrogen bonding sites and the amino group.

A series of reactions using different acrylates and aldehydes were conducted on a synthetic scale to explore the scope and limitations of this optimized process (Tables 5 and 6).

High yields of products were obtained using a range of acrylates over a short reaction time. We were even able to extend the range of acceptors to include cyclohexanecarboxaldehyde[26] and anisaldehyde.[27,28] However, the reaction is still limited to relatively reactive acceptors

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[23] The slightly higher relative rates observed with La(OTf)$_3$ compared to earlier rate studies is because reactions are no longer being diluted with 100 μL of MeCN. In addition, more accurate measurements are now being made. We are currently obtaining five different samples from a single reaction and analyzing them. This was not practical in the initial stages when a very large number of different reactions were conducted.

[24] Hahn, F. E.; Mohr, J. *Chem. Ber.* **1990**, *123*, 481−484. We thank one of the reviewers for highlighting this paper to us.

[25] It had previously been shown that 10 mol % MeOH results in a 1.5-fold rate enhancement. No further tests were conducted. See ref 10.

[26] For reaction of cyclohexanecarboxaldehyde with methyl acrylate see ref 7. No yield was given, but the half-life for the reaction using 20 mol % DABCO was 10 days.

[27] For reaction of anisaldehyde with methyl acrylate, see: Foucaud, A.; El Guemmout, F. *Bull. Chim. Soc. Fr.* **1989**, 403−408. They reported 90% yield after 20 days using 15 mol % DABCO.

[28] Methyl acrylate has a tendency to dimerize, and with less reactive acceptors this is the major product (see refs 29 and 30). Under our optimum conditions, the rate of reaction with the aldehyde is enhanced relative to dimerization.

Table 4. Kinetic Studies of Reactions of Acrylates with Benzaldehyde[a]

	methyl acrylate		ethyl acrylate		*tert*-butyl acrylate		acrylonitrile	
catalytic system	rate (% per min)	k_{rel}	rate (% per min)	k_{rel}	rate (% per min)	k_{rel}	rate (% per min)	k_{rel}
DABCO	0.016	1	0.009	1	0.002	1	0.412	1
DABCO, $La(OTf)_3$[b]	0.148	9.2	0.112	12.4	0.013	6.5	0.972	2.36
DABCO, $La(OTf)_3$,[b] $N(CH_2CH_2OH)_3$[c]	0.511	31.9	0.357	39.7	0.046	23	2.091	5.07
DABCO, $N(CH_2CH_2OH)_3$[d]	0.306	19.2	0.196	22.0	0.036	18	1.146	2.78
DABCO, CH_3OH[e]	0.148	9.2	0.100	11.1	0.006	3	0.623	1.51

[a] Reactions conducted on 1 mmol scale using 1:1:1 ratio of benzaldehyde/acrylate/DABCO. [b] $La(OTf)_3$ 5 mol %. [c] Triethanolamine 50 mol %. [d] Triethanolamine 80 mol %. [e] CH_3OH 240 mol %.

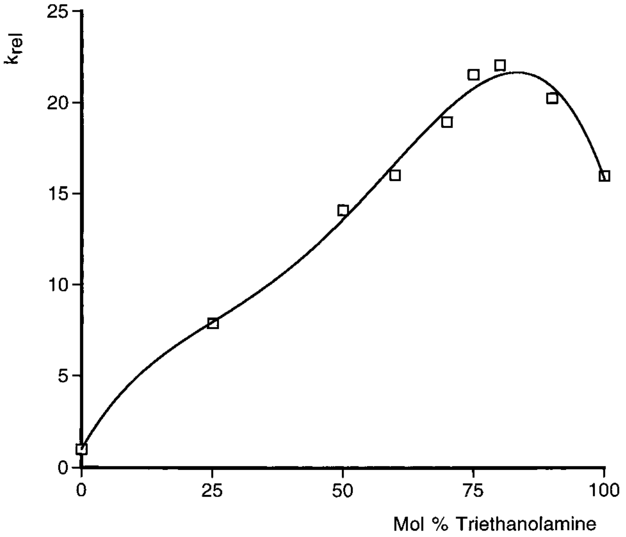

Figure 5. Effect of triethanolamine concentration on reaction rate. Reactions were conducted on a 1 mmol scale using a 1:1:1 ratio of ethyl acrylate/benzaldehyde/DABCO; $k_{rel} = 1$, $[N(CH_2CH_2OH)_3] = 0$.

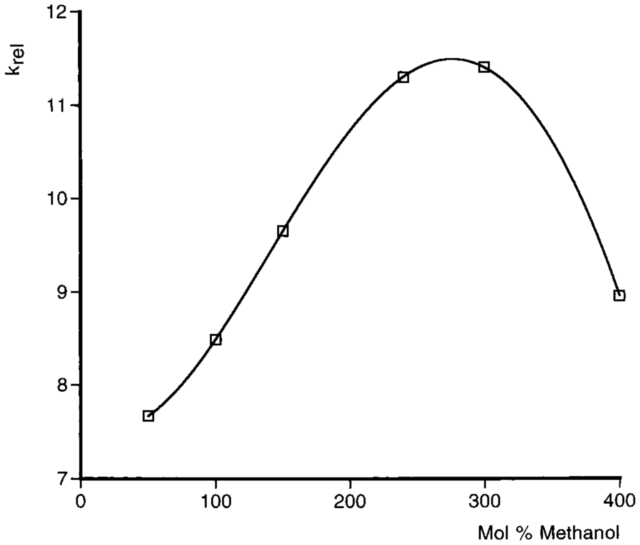

Figure 6. Effect of methanol concentration on reaction rate. Reactions conducted on a 1 mmol scale using a 1:1:1 ratio of ethyl acrylate/benzaldehyde/DABCO; $k_{rel} = 1$, $[CH_3OH] = 0$.

as ketones (cyclohexanone was attempted) gave mostly dimerized acrylates.[29,30]

Conclusions

In the above study, our principal discovery has been that scandium and lanthanide triflate catalysts, at 5 mol %, catalyzed the Baylis–Hillman reaction with a rate acceleration (k_{rel}) of up to 4.9 when using 1 equiv of DABCO. At low loadings of DABCO (up to 10 mol %), no reaction occurred, and this is consistent with the formation of a metal–DABCO complex ($La(OTf)_n(DABCO)_2$) so that the DABCO was no longer available as a nucleophilic catalyst. At the higher loadings of DABCO, this complex, despite the amino ligands, performed as a Lewis acid catalyst representing a rare example of where a base and a Lewis acid can coexist and cocatalyze a reaction.[31]

The second discovery was that a further increase in rate was achieved when using catalytic amounts of oxygen-rich donor ligands such as (+)-binol, L-diethyl tartrate, and triethanolamine. Reactions now occurred at low levels of DABCO (<10 mol %), so it is evident that the lanthanide no longer associates with DABCO but with the oxide ligand due to the metal's oxophilicity. A substantial nonlinear effect on rate with enantiomeric composition of binol was observed. Thus, while (+)-binol at 5 mol % gave a rate acceleration of 3.4-fold, racemic binol gave no greater rate than in its absence. This is consistent with the formation of a complex $La(OTf)_n(binol)_2$ in which the meso complex is more stable and less reactive than the chiral complex. Given the presence of two chiral ligands on the metal, it was disappointing that no significant enantiomeric excesses were observed with the chiral phenols/alcohols. We believe that the intermediate azaenolate and aldehyde react on the surface of the metal–ligand complex where acceleration is provided by increased strengths of hydrogen bonds between the hydroxyl groups of the ligands and the two reacting species. The lack of control in orientation of the hydrogen bonds is the probable explanation for the low enantioselectivity.

To maximize the reaction acceleration, ligands more soluble than binol were needed. The protocol discovered to give the best practicality was to use 100 mol % DABCO, 50 mol % triethanolamine, and 5 mol % $La(OTf)_3$. This gave an acceleration of up to 40-fold for an acrylate and approximately 5-fold for acrylonitrile, and a simple acid wash procedure allowed recovery of the product from the reagents. While triethanolamine alone (80 mol % was optimum) gave a rate acceleration of up to 22-fold, the acceleration is clearly greater when the lanthanum triflate is present. The preferred system was demonstrated to be effective synthetically on a variety of different acrylates and aldehydes both more and less reactive than benzaldehyde, demonstrating the general-

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Table 5. Yield of Baylis−Hillman Products in Reactions of Acrylates with Benzaldehyde[a]

	methyl acrylate		ethyl acrylate		*tert*-butyl acrylate		acrylonitrile	
catalytic system	time (h)	yield (%)	time (h)	yield (%)	time (h)	yield (%)	time (h)	yield (%)
DABCO, $La(OTf)_3$,[b] $N(CH_2CH_2OH)_3$[c]	12	83	12	84	72	74	1.5	92
DABCO, $N(CH_2CH_2OH)_3$[d]	24	88	24	91	72	65	4	88
DABCO, CH_3OH[e]	24	71	24	78	48	35	7	86

[a] Reactions conducted on 1 mmol scale using 1:1:1 ratio of benzaldehyde: acrylate: DABCO. [b] $La(OTf)_3$ 5 mol %. [c] Triethanolamine 50 mol %. [d] Triethanolamine 80 mol %. [e] CH_3OH 240 mol %.

Table 6. Reactions of Aldehydes with Methyl Acrylate in the Presence of 5 Mol % $La(OTf)_3$ and 50 Mol % Triethanolamine[a]

aldehyde	time	yield[b] (%)
p-nitrobenzaldehyde	3 h	90
anisaldehyde	2 days	65
cyclohexanecarboxaldehyde	5 days	37[c]

[a] Reactions conducted on 1 mmol scale using 1:1:1 ratio of aldehyde/methyl acrylate/DABCO, 5 mol % $La(OTf)_3$ and 50 mol % triethanolamine. [b] Isolated yield of pure product. [c] ~25% of dimerized methyl acrylate detected by ^1H NMR.

ity of this method. Additionally, it is noteworthy that reduced amounts of dimerized acrylates were obtained.

We anticipate that these new reaction conditions, by giving enhanced reaction rates, could extend the range of products that can practically be made by the Baylis−Hillman reaction.

Experimental Section

Amino diol **6**,[32] salen ligands **8**−**10**,[33] and bisoxazoline **11**[34] were prepared as described in the literature. Amino triol **7**[35] was a gift from Dr. Nugent. All other reagents were commercially available. The Baylis−Hillman products are all known compounds.

Reaction Monitoring (Tables 1−3, Supporting Information Tables 1−3). Reactions were conducted at 25 °C under neat reaction conditions or diluted with 100 μL of MeCN. Benzaldehyde (1 mmol, 102 μL), acrylate (1 mmol), and DABCO (0.1 mmol, 11.2 mg) were mixed, and then the required Lewis acid (0.05 equiv) was added. A control reaction was also run without Lewis acid. After 24 h, ethyl cinnamate (1 equiv, 168 μL) was added to the reaction mixture as internal standard. The reaction was then diluted with ethyl acetate and stopped by filtration through silica gel to remove both DABCO and the Lewis acid catalyst, and the yield of the product was determined by GC. From these data, the relative rate of reaction was calculated using the formula $k_{rel} = [(1/(1 - X_{cat.})) - 1/(1/(1 - X_{uncat})) - 1]$, where $X_{cat.}$ and X_{uncat} are the concentrations of products in the catalyzed and uncatalyzed reactions, respectively (see Supporting Information). This equation is derived from the second-order rate equation and gives a straight line when plotting 1/[acrylate] against time.

Reaction Monitoring (Table 4). To a stirred mixture of acrylate (4.92 mmol, 1 equiv) and benzaldehyde (0.5 mL, 4.92 mmol, 1 equiv) at room temperature under nitrogen were added DABCO (552 mg, 4.92 mmol, 1 equiv), lanthanum triflate (144 mg, 0.25 mmol, 5 mol %), and triethanolamine (0.33 mL, 2.46 mmol, 50 mol %). In kinetic studies, five samples were taken (0.1 mL using a Pipetman Gilson syringe) at fixed short periods of time and filtered through a short silica gel column using a solution of the internal standard, ethyl cinammate in CH_2Cl_2 (0.15 M, 0.5 mL, 0.075 mmol), and flushed with further CH_2Cl_2 (~1.5 mL), and the resulting solutions were used for the GC analysis.

Calculation:

$$\text{yield (\% product)} = \frac{\text{(area product)(int. stand. mol)(total weight)}}{\text{(area int. stand.)(acrylate mol)(sample weight)}} 100\rho$$

where ρ = GC correction factor (ratio between internal standard and product peak area of a equimolar solution).

Typical Procedure of Optimized Process (Tables 5 and 6). To a stirred mixture of acrylate (4.92 mmol, 1 equiv) and aldehyde (4.92 mmol, 1 equiv) at room temperature under nitrogen were added DABCO (552 mg, 4.92 mmol, 1 equiv), lanthanum triflate (144 mg, 0.25 mmol, 5 mol %), and triethanolamine (0.33 mL, 2.46 mmol, 50 mol %). After the time indicated, the reaction was stopped by dilution with ether (30 mL) and washed with HCl (2%, 20 mL) followed by water (20 mL). After drying over $MgSO_4$, filtration, and evaporation, the crude mixture was purified by column chromatography, eluting with petroleum ether/diethyl ether (2:1), to give the adduct as an oil. The product had data identical to those in the literature.

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Supporting Information Available: Data for Figures 1−4 and graphs of experimental rate data for Table 4 (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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