Amidines, Isothioureas, and Guanidines as Nucleophilic Catalysts

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Abstract

Over the last ten years there has been a huge increase in development and applications of organocatalysis in which the catalyst acts as a nucleophile. Amidines and guanidines are often only thought of as strong organic bases however, a number of small molecules containing basic functional groups have been shown to act as efficient nucleophilic catalysts. This *tutorial review* highlights the use of amidine, guanidine, and related isothiourea catalysts in organic synthesis, as well as the evidence for the nucleophilic nature of these catalysts. The most common application of these catalysts to date has been in acyl transfer reactions, although the application of these catalysts towards other reactions is an increasing area of interest. In this respect, amidine and guanidine derived catalysts have been shown to be effective in catalysing aldol reactions, Morita-Baylis-Hillman reactions, conjugate additions, carbonylations, methylations, silylations, and brominations.

Introduction

Amidines and guanidines are important classes of compound that are found throughout nature that also have many uses within organic chemistry.[1-6] For example, the amino acid arginine (**1**) has a guanidine side chain whilst a number of natural products contain amidine units, such as noformycin (**2**) that has been isolated as a metabolite from actinobacteria. The two functional groups are also found within many medicinally active compounds. Pentamidine (**3**) contains two amidine units and is used to treat protozoan infections, whilst guanidine derived cimetidine (**4**) was the first blockbuster drug used to treat peptic ulcers (Figure 1).[3]

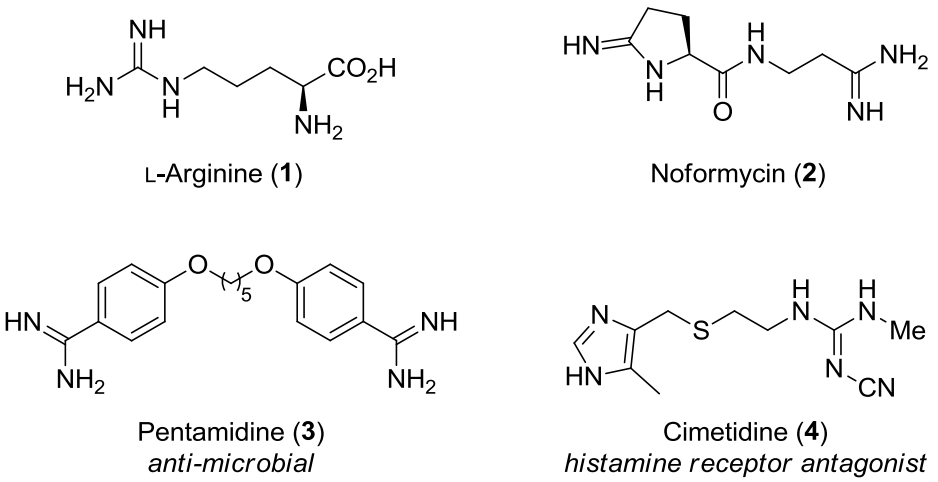


Figure 1. Examples of amidines and guanidines contained as fragments within natural products and drug molecules.

The most common use of amidines and guanidines in organic chemistry is as organic bases. They are some of the strongest neutral organic bases known due to the ability of their protonated forms to delocalise charge over two nitrogen atoms. The structures and pK_as of some of the most commonly used amidine and guanidine bases are presented in Figure 2.[3,7] These bases have been used widely in numerous organic reactions and have often been shown to be advantageous when compared with other types of organic bases. For example, the bicyclic amidines 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **5**) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **6**) are often used as bases in dehydrohalogenation reactions as they allow alkene bonds to be formed under milder conditions than when using other types of nitrogen bases.[1] The physical properties of amidines and guanidines also make them useful *N*-based donor ligands in coordination chemistry.[2]

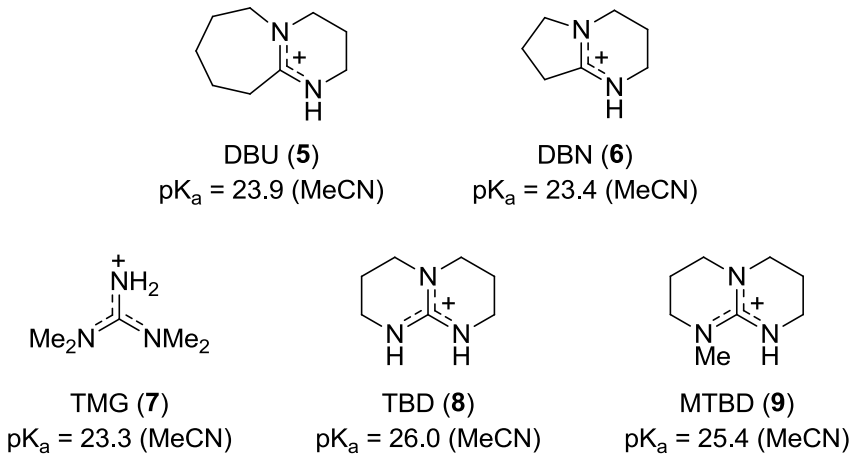
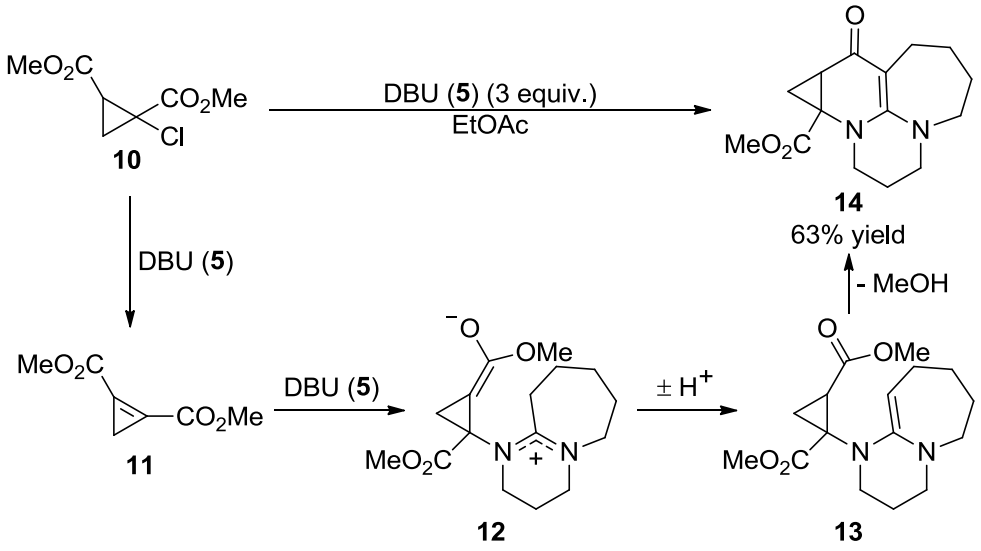


Figure 2. Structure and pK_as of some commonly used amidine and guanidine bases.

Traditionally, amidines and guanidines have been thought of as non-nucleophilic bases. However, with the recent increase in interest in organocatalysis,[8] a number of amidines and guanidines have also been shown to act as nucleophilic catalysts in a wide range of reactions. A number of structurally related isothiourea derivatives have also been prepared based upon the potential of amidines and guanidines as effective acyl transfer catalysts.[2,5,9] The structural diversity of accessable nucelophilic catalysts based around amidine, isothiourea, and guanidine cores, including those containing stereocentres, makes these catalysts applicable to a wide range of achiral and stereoselective reactions.

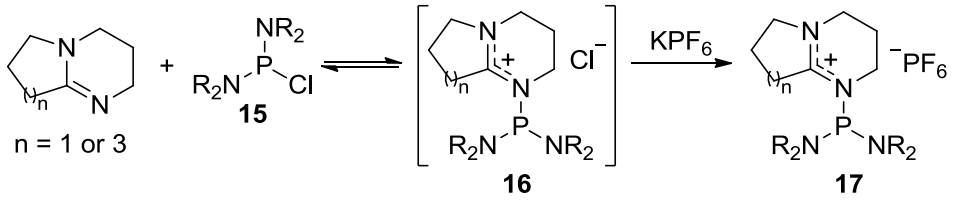
Nucleophilic Nature of Amidines and Guanidines

The amidine bases DBU (**5**) and DBN (**6**) have often been used as bases in dehydrohalogenation reactions however, in some cases unexpected side-products were obtained from these reactions. For example, in 1981 McCoy and Mal isolated and characterised an unusual tetracyclic dihydropyridin-4-one structure (**14**) from the dehydrohalogenation reaction of cyclopropane diester **10** using excess DBU (**5**) (Scheme 1). The authors postulated that the DBU (**5**) fragment was incorporated into the final product through nucleophilic attack of the α,β-unsaturated intermediate (**11**), although the generality of the process was not investigated further.[10]



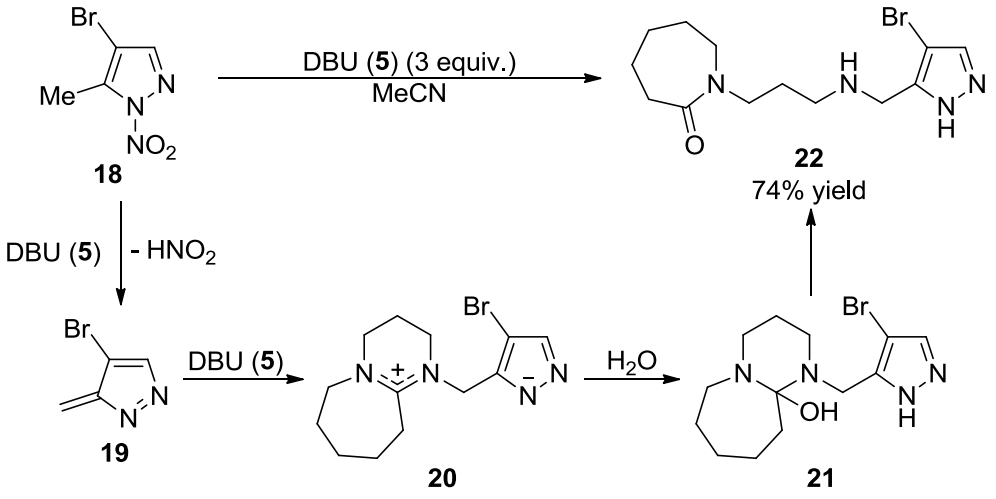
Scheme 1. Unexpected tetracyclic side-product (**14**) isolated from the dehydrohalogenation reaction of cyclopropane diester **10** with DBU (**5**).

In 1993, Bertrand and co-workers were the first to state explicitly that DBU (**5**) and DBN (**6**) could act as strong nucleophiles. They showed that both DBU (**5**) and DBN (**6**) reacted with chloro-phosphanes (**15**) to afford cationic phosphanes (**16**) that could be isolated and characterised if their chloride counter-ions were exchanged for hexafluorophosphate (Scheme 2). An X-ray crystal structure of one of the cationic phosphanes (**17**) showed that both amidine C-N bonds were of similar length, suggesting that the positive charge was delocalised over both nitrogen atoms.[11]



Scheme 2. The first direct evidence that DBU (**5**) and DBN (**6**) can act as nucleophiles *via* reaction with chloro-phosphanes (**15**).

Subsequently, there have been a number of reports of DBU (**5**) and DBN (**6**) being incorporated into molecules through nucleophilic addition pathways. For example, Lammers *et al*. were the first to show that bicyclic amidines could add to electrophilic carbon centres, demonstrating that they react with *N*-nitro-pyrazoles (**18**) to form lactam products (**22**) (Scheme 3). Mechanistically, DBU (**5**) first acts as a base to eliminate HNO_2 from pyrazole **19**, with a second equivalent of DBU (**5**) acting as a nucleophile that adds to the exocyclic alkene of pyrazole **19**. The resulting intermediate (**20**) is then hydrolysed by adventitious water to form the ε-lactam product (**22**).[12]



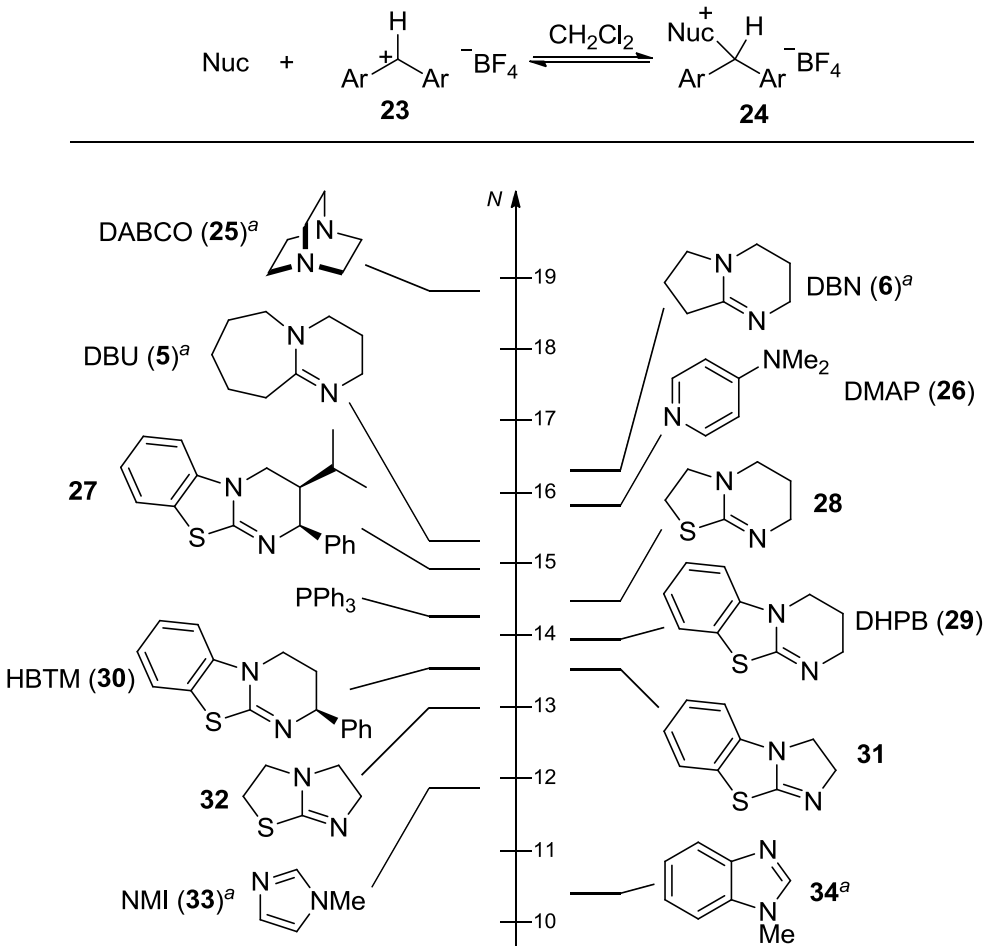
Scheme 3. a) Nucleophilic addition of DBU (**5**) to pyrazole (**19**) and subsequent hydrolysis reaction.

Recently, Mayr and co-workers have performed a number of kinetic experiments to compare the nucleophilicity of DBU (**5**) and DBN (**6**) with other common organocatalysts, including isothiourea derivatives that have been shown to be effective acyl transfer catalysts (*vide infra*).[13,14] The equilibrium between a range of nucleophilic catalysts and a number of benzhydrylium tetrafluoroborate anions (**23**) was studied photometrically. The results of these kinetic experiments were analysed using Equation 1, where k is the second order rate constant, s is the nucleophile-specific slope parameter, N is the nucleophilicity parameter, and E is the electrophilicity parameter. This analysis enabled the nucleophilicity parameter (N) of a number of organocatalysts to be compared directly (Scheme 4).[14]

$$\log k = s(E + N)$$

Equation 1. Nucleophilicity parameter (N) used to compare organocatalysts.

Remarkably, this study revealed that DBU (**5**), DBN (**6**), and recently synthesised isothiourea derivatives have comparable nucleophilicity to 4-(dimethylamino)pyridine (DMAP, **26**), which is generally considered to be one of the most powerful nucleophilic catalysts. DBN (**6**) was shown to be more nucleophilic than most of the catalysts studied, with only 1,4-diazabicyclo[2.2.2]octane (DABCO, **25**) exhibiting a greater N value.



Scheme 4. Relative nucleophilicities of selected nucleophilic catalysts. [a]Measurements made in MeCN. Modified scheme reprinted with permission from reference 14. Copyright 2011 American Chemical Society.

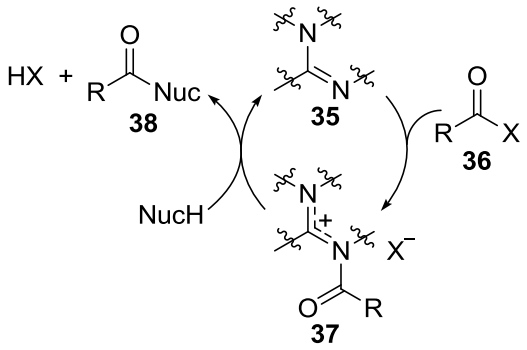
Zipse *et al*. performed an equally impressive study by calculating the methyl cation affinities of over 40 common organocatalysts.[15] Again, their computational method predicts that DBU (**5**), DBN (**6**), and bicyclic isothioureas have greater methyl cation affinities than many DMAP (**26**), imidazole, and cinchona alkaloid derivatives. Both studies revealed that bicyclic amidines (and presumably guanidines, although none were studied in either case) are considerably more basic than many other organocatalysts. The relatively high basicity of these amines most likely accounts for why they have received relatively limited attention as potential nucleophilic catalysts to date, because their use with acidic substrates can easily lead to their deactivation by competing protonation.

Amidines and Guanidines as Nucleophilic Catalysts

Despite the potential problems associated with their high basicity, amidine, guanidine, and isothiourea derivatives are becoming increasingly popular catalysts due to their highly nucleophilic nature. The remainder of this article will focus on the uses of these types of catalysts in synthesis. Fu and Tan have recently reviewed the use of guanidines as catalysts, focusing on more mechanistic aspects of their reactions.[6]

Acyl Transfer Reactions

Acyl transfer is the most familiar reaction known to be accelerated by the use of nucleophilic catalysts. It is therefore unsurprising that a range of amidine, guanidine, and related isothiourea catalysts have been shown to be successful acyl transfer agents. A generalised mechanism for acyl transfer catalysed by amidine and guanidine derivatives is shown in Scheme 5. In most reactions, the catalyst (**35**) nucleophilically attacks an acyl donor (**36**) (usually an acyl chloride, acid anhydride, or an ester) to generate an activated *N*-acyl intermediate (**37**) that, due to its charged nature, is more reactive than the parent acyl donor (**36**). A nucleophile then attacks the *N*-acyl intermediate (**37**), forming an acylated product (**38**), whilst regenerating the catalyst (**35**).

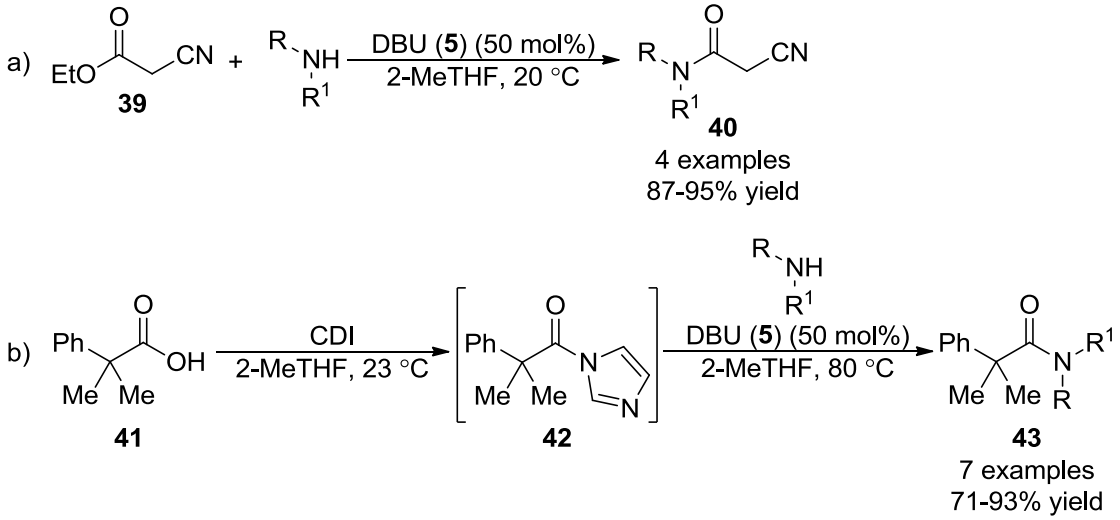


Scheme 5. General mechanism for acyl transfer catalysed by amidines and guanidines.

Amidations

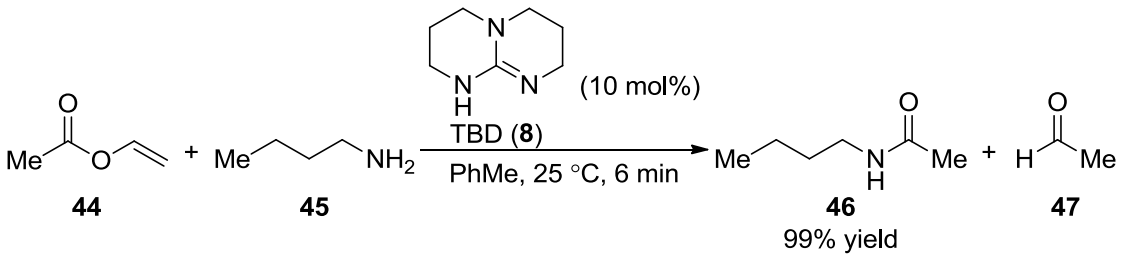
Vaidyanathan and co-workers have shown that DBU (**5**) is an efficient catalyst for amide formation from reactive esters and activate acids (Scheme 6). Initially the group found that DBU(**5**) accelerated the rate of amidation of ethyl cyanoacetate (**39**) with a small range of secondary amines (Scheme 6a).[16] This methodology was extended by using DBU (**5**) to catalyse the addition of amines to acyl imidazole **42**, which was formed *in situ* from the reaction of 2-methyl-2-phenyl propanoic acid (**41**)

with *N*,*N*'-carbonyldiimidazole (CDI) (Scheme 6b).[17] This sterically demanding substrate was chosen to demonstrate the efficiency of DBU (**5**) as a catalyst for difficult substrates and also to avoid side-reactions that could occur *via* α-deprotonation. It was found that the rate enhancement of amidation using DBU (**5**) was comparable with that observed with traditional additives such as hydroxybenzotriazole (HOBt). Mechanistically, DBU (**5**) is thought to nucleophilically activate both ethyl cyanoacetate (**39**) and acyl imidazole **42** to generate *N*-acyl DBU intermediates that are more reactive towards amines than their parent substrates.



Scheme 6. DBU (**5**) catalysed amidations of a) ethyl cyanoacetate (**39**) and b) acyl imidazoles (**42**).

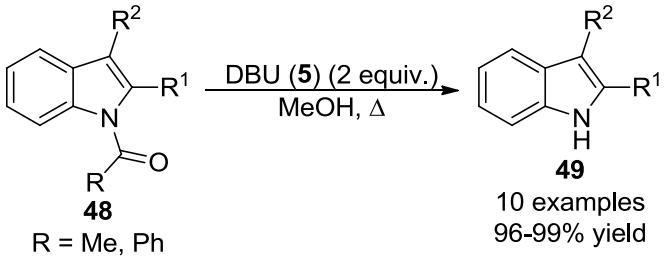
Waymouth *et al*. have shown that 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **8**) catalyses the formation of secondary amides from vinyl, benzyl and ethyl esters, as well as primary amides. For example, vinyl acetate (**44**) and butylamine (**45**) react to give an almost quantitative yield of *N*-butylacetamide (**46**) in only six minutes when using 10 mol% TBD (**8**), as compared with the 24 hours required for the uncatalysed process (Scheme 7). Kinetic studies suggest that TBD (**8**) reacts with the ester to form an *N*-acyl TBD intermediate, which is then nucleophilically attacked by the amine.[18]



Scheme 7. Amidation of vinyl acetate (**44**) with butylamine (**45**) catalysed by TBD (**8**).

Waymouth *et al*. have also shown that TBD (**8**) is an efficient catalyst for transesterifications and the ring-opening polymerisation of cyclic esters such as lactide, δ-valerolactone, and ε-caprolactone.However, detailed mechanistic and computational studies predicted that a hydrogen-bonding mechanism is favoured over nucleophilic catalysis in these cases.[18]

Chakrabarty *et al*. have found that amide bonds can also be cleaved using an amidine as a catalyst. A series of *N*-acetyl and *N*-benzoyl indoles (**48**) was deprotected by heating in methanol at reflux in the presence of two equivalents of DBU (**5**), forming the parent indoles (**49**) in high yields (Scheme 8).[19] Coin *et al*. also reported unexpected nucleophilic behaviour of DBU (**5**) towards peptide bonds, which limited its use as a base for the removal of Fmoc protecting groups in the total synthesis of the cyclic peptide cotransin.[20]



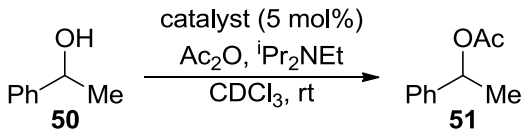
Scheme 8. Deprotection of *N*-acyl indoles (**48**) promoted by DBU (**5**).

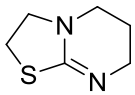
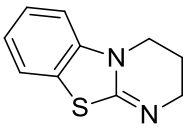
Esterifications

Okamoto *et al*. and Birman and co-workers have both investigated the use of amidine derivatives for the acylation of alcohols with acetic anhydride.[21,22] Selected results from Birman and co-workers on the acylation of 1-phenylethanol (**50**) with acetic anhydride using various nucleophilic catalysts are shown in Table 1. They found that DBN (**6**) was much more reactive than DBU (**5**), with the rate of

acylation comparable with that observed with DMAP (**26**) (Table 1, entries 1-3). A number of amidine derivatives were synthesised and tested in the reaction, with the isothioureas 2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine (THTP, **52**) and 3,4-dihydro-2H-pyrimido[2,1-*b*]benzothiazole (DHPB, **29**) proving to be more reactive than DMAP (**26**) (Table 1, entries 4 and 5).[22] Direct evidence for nucleophilic catalysis was observed by Okamoto *et al*. when a 1:1 mixture of DHPB (**29**) and acetic anhydride was analysed by ^{1}H NMR spectroscopy, which showed formation of significant amounts of an *N*-acetyl DHPB intermediate.[21] The increased reactivity of the isothiourea derivatives compared with the basic amidines has been attributed to increased stabilisation of the *N*-acetyl DHPB intermediate by nonbonded interactions between the sulphur atom and the carbonyl oxygen.

Table 1. Acylation of 1-phenylethanol (**50**) using amidine derivatives as catalysts.[a]

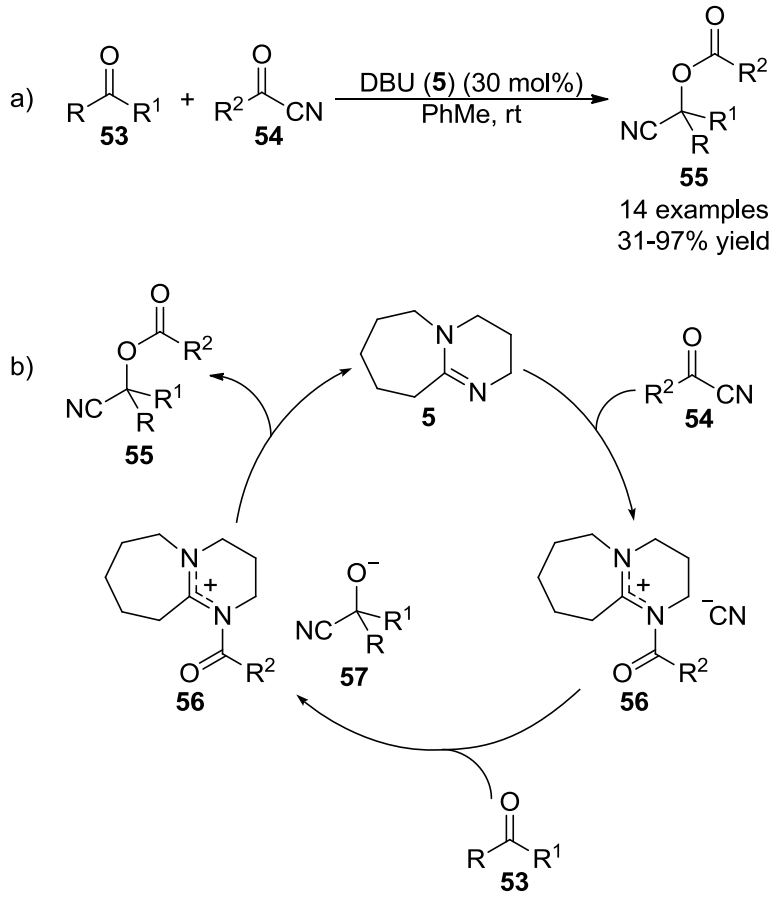


Entry	Catalyst	Substrate Conc. (M)	$t_{1/2}$[b]
1	DMAP (**26**)	0.1	5 min
2	DBN (**6**)	1	15 min
3	DBU (**5**)	1	17 h
4	 THTP (**52**)	0.1	2 min
5	 DHPB (**29**)	0.1	<2 min

[a]Data taken from reference 22. [b]Time to reach 50% conversion determined using ^{1}H NMR spectroscopic analysis.

Shi and Zhang have shown that DBU (**5**) catalyses the cyanoacylation of ketones (**53**) with acyl cyanides (**54**) (Scheme 9a).[23] Mechanistically, DBU (**5**) is thought to add to the acyl cyanide (**54**) to

generate an *N*-acyl DBU intermediate (**56**). The cyanide anion released during this addition can then undergo nucleophilic attack at the ketone (**53**) to give a cyanoalkoxide (**57**), which is then acylated by the *N*-acyl DBU species (**56**) (Scheme 9b).



Scheme 9. a) Cyanoacylation of ketones (**53**) by acyl cyanides (**54**) catalysed by DBU (**5**). b) Proposed mechanism.

Kinetic Resolutions

A number of enantiomerically pure nucleophilic catalysts have been used as acylation catalysts for the kinetic resolution of a wide range of substrates and this area has been reviewed recently by both Schreiner *et al.*[24] and Pellissier.[25] Some of the most active amidine and isothiourea catalysts developed for kinetic resolutions are shown in Scheme 10.

Birman and co-workers have developed a number of excellent catalysts for the kinetic resolution of secondary alcohols. Firstly, the enantiomerically pure amidine derivative (*R*)-2-phenyl-6-(trifluoromethyl)-2,3-dihydroimidazo[1,2-*a*]pyridine (CF_3-PIP, **60**) was shown to be active in the kinetic resolution of benzylic secondary alcohols (**58**, R = aryl, R^1 = alkyl) with acid anhydrides.[26] It

was found that the rate of acylation using catalyst **60** was increased by using one equivalent of $^{i}Pr_2NEt$, presumably by helping prevent catalyst deactivation by any acid generated during the reaction. The highest selectivity factors (*s*) of up to 85 were observed for the acylation of benzylic secondary alcohols with propanoic anhydride. The transition states for these reactions are proposed to involve π-π or cation-π interactions between the aryl group of the alcohol and the pyridinium ring of the catalyst. The favoured enantiomer for acylation is the one in which steric repulsions between the alkyl group of the alcohol and the acyl groups are minimised (Figure 3).

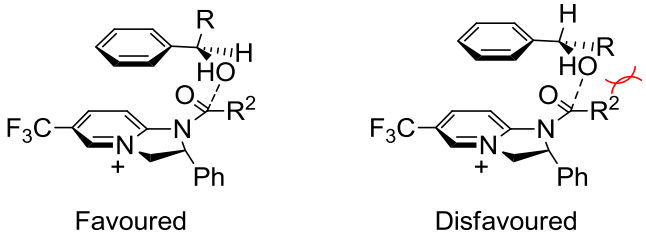
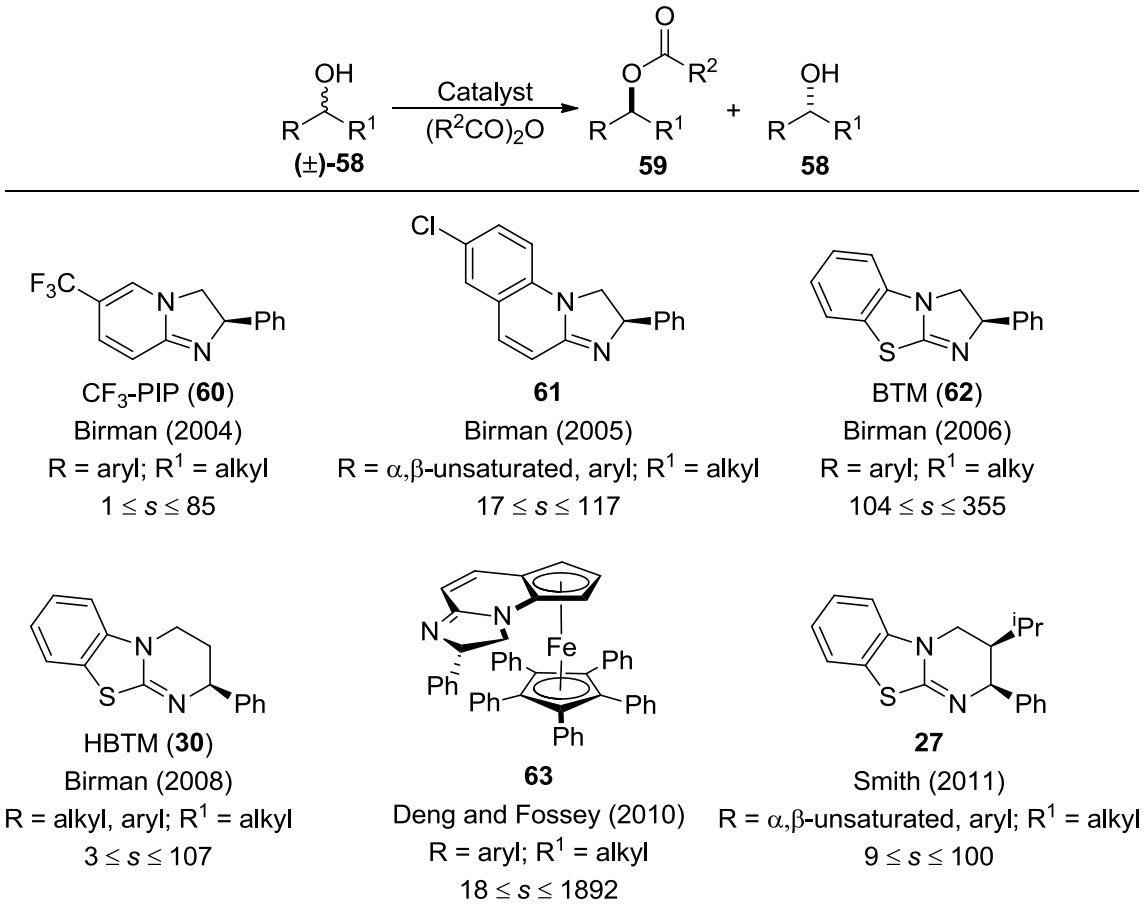


Figure 3. Proposed transition state for the resolution of aryl secondary alcohols using CF_3-PIP (**59**).

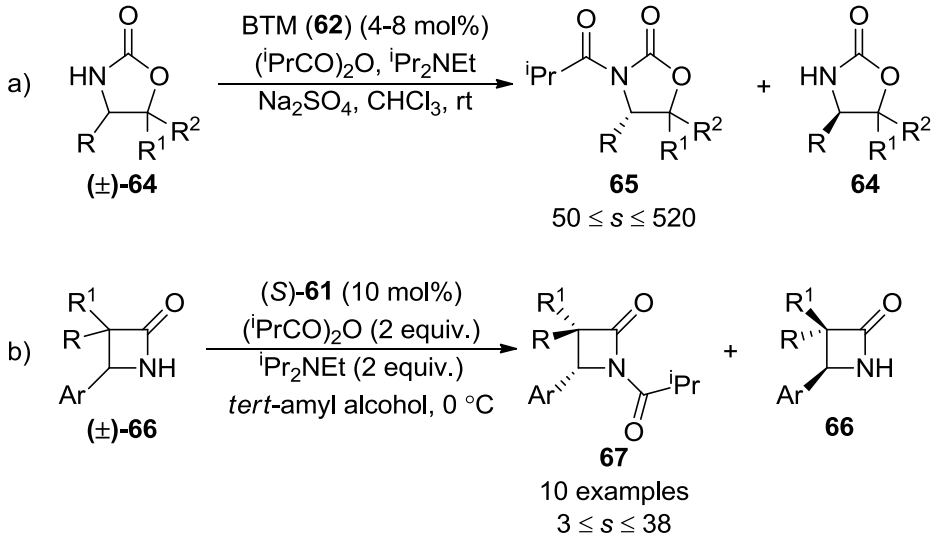
Birman and co-workers then developed a new catalyst that contains an additional aryl ring (**61**) for the resolution of cinnamoyl based allylic alcohols. The extended π-system of **61** allowed efficient π-stacking between the alkene and remote aryl fragments of the allylic alcohols with the catalyst, giving high *s* values for the resolution of a number of substrates using propanoic anhydride.[27] In 2006, Birman *et al*. employed enantiomerically pure benzotetramisole (BTM, **62**) as a catalyst for the kinetic resolution of benzylic alcohols.[28] It was found that BTM (**62**) was highly active and, unlike previously developed catalysts (**60** and **61**), could be used with isobutyric anhydride as an acyl donor, which allowed *s* values of up to 355 to be obtained. Extending the imidazoline ring of BTM (**62**) by one carbon atom to give catalyst **30**, named homobenzotetramisole (HBTM), allowed a number of 2-aryl-substituted cycloalkanols to be resolved with *s* values of up to 66 observed.[29] Rychnovsky *et al.* have developed a method of assigning the absolute configuration of enantiomerically pure secondary alcohols by comparing the relative rates of acylation using both (*R*) and (*S*)-HBTM (**30**) as catalysts.[30] Further substitutions to the HBTM (**30**) core by Birman *et al*.[31] and Smith *et al*.[32] have resulted in a number of catalytic variants that have been used as efficient catalysts for the kinetic resolution of

benzylic, cinnamoyl, propargyl, and cyclic secondary alcohols with acid anhydrides. Recently, Fossey and Deng *et al*. combined the principles behind Fu's highly successful planar chiral DMAP catalysts with Birman's amidine catalysts to prepare catalyst **63**, which was shown to give remarkable *s* values of up to 1892 for the resolution of benzylic alcohols with propanoic anhydride.[33]



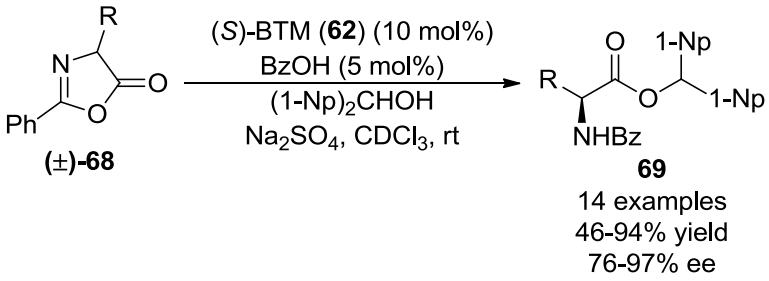
Scheme 10. Examples of amidine and isothiourea derivatives that have been used as catalysts for the kinetic resolution of secondary alcohols (**58**).

Birman and co-workers have also applied their amidine catalysts to the kinetic resolution of racemic 2-oxazolidinones (**64**) and 4-aryl-β-lactams (**66**) that proceed through an enantioselective *N*-acylation process (Scheme 11). It was found that BTM (**62**) was the most efficient catalyst for the kinetic resolution of 2-oxazolidinones (**64**) giving *s* values of up to 520 (Scheme 11a),[34] whilst catalyst **61** was optimal for the resolution of 4-aryl-β-lactams (**66**) (Scheme 11b).[35]



Scheme 11. Kinetic resolution of a) 2-oxazolidinones (**64**) and b) 4-aryl-β-lactams (**66**) using catalytic, enantioselective *N*-acylation protocols.

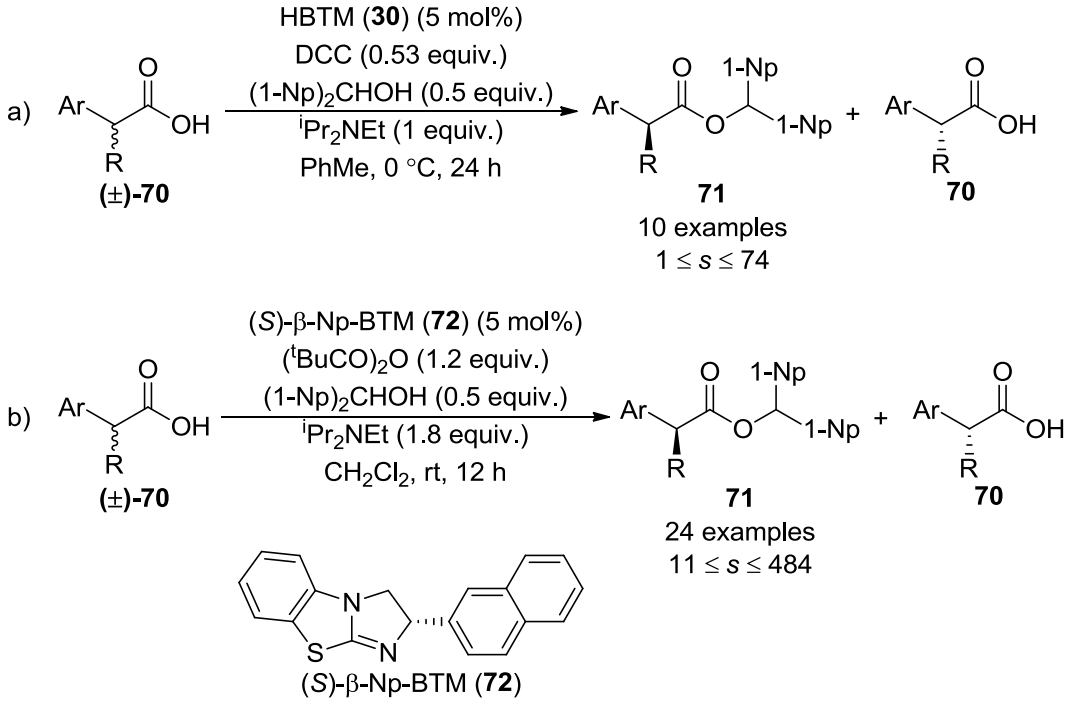
BTM (**62**) was also shown to be capable of catalysing the dynamic kinetic resolution of azlactones (**66**) to form α-amino acid derivatives (**69**) in high yields and good ee (Scheme 12).[36] The highest levels of enantioselectivity were observed using di(1-naphthyl)methanol as a nucleophile, which was rationalised by the increased steric demand of the alcohol and increased π-π interactions with the catalyst.



Scheme 12. Dynamic kinetic resolution of azlactones (**68**) using BTM (**62**) and di(1-naphthyl)methanol.

Isothiourea derivatives have also been used as catalysts for the kinetic resolution of α-aryl acids (**70**) (Scheme 13). Birman and co-workers employed half an equivalent of dicyclohexylcarbodiimide (DCC) to form a symmetrical anhydride of racemic acid (**70**) *in situ*, which was then kinetically resolved using HBTM (**30**) to provide the corresponding α-aryl esters (**71**) with high levels of enantioselectivity (Scheme 13a).[37] Shiina *et al*. have also used (*S*)-β-Np-BTM (**72**) for the kinetic

resolution of mixed anhydrides generated *in situ* from pivalic anhydride and α-aryl acids (**70**) (Scheme 13b). The catalyst (**72**) was shown to be highly selective, with the highest *s* values of up to 484 observed for *ortho*-substituted α-aryl acids.[38]

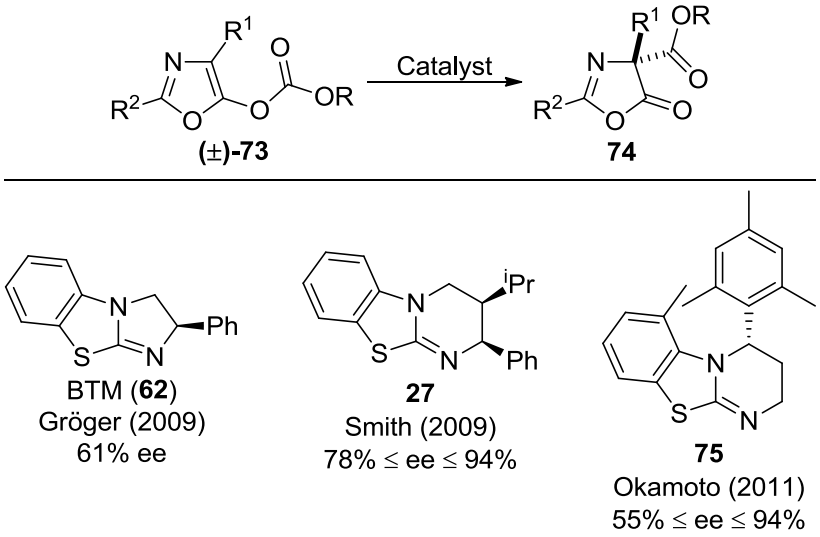


Scheme 13. Kinetic resolution of α-aryl acids (**70**) using a) HBTM (**30**) and DCC and b) (*S*)-β-Np-BTM (**72**) and pivalic anhydride.

C-Acylations

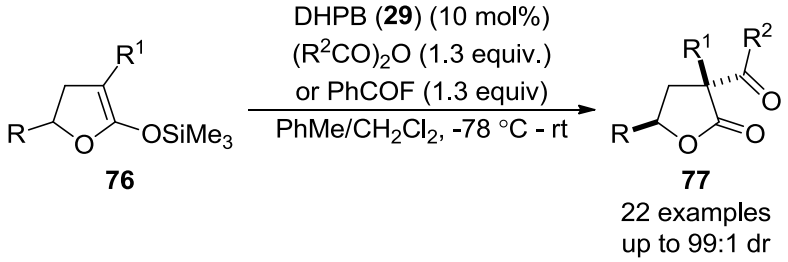
Smith *et al*. initially demonstrated that the achiral isothiourea DHPB (**29**) efficiently catalysed the *O*- to *C*-acyl transfer reaction (Steglich rearrangement) of oxazolyl carbonates (**73**).[39] Gröger and co-workers subsequently reported that enantiomerically pure BTM (**62**) could be used to form 4-carboxyazlactone products (**74**) enantioselectively with reasonable ee (Scheme 14).[40] Smith *et al*. then reported that HBTM derivative **27** gave higher yields and improved enantioselectivities for this rearrangement compared with BTM (**62**).[41] Catalyst **27** could also be used for the stereoselective rearrangement of furanyl enol carbonates, affording a mixture of lactone regioisomers, whose major regioisomer could be isolated in reasonable yield with good levels of ee.[42] Recently, Okamoto and co-workers have developed DHPB derivative **75** and shown it to be an effective catalyst for the

asymmetric rearrangement of oxazolyl carbonates (**73**), giving comparable enantioselectivities with those observed for the HBTM derivative **(27**).[43]



Scheme 14. Enantioselective *O*- to *C*-acyl transfer reactions of 5-oxazole carbonates (**73**) to their corresponding 4-carboxyazlactones (**74**).

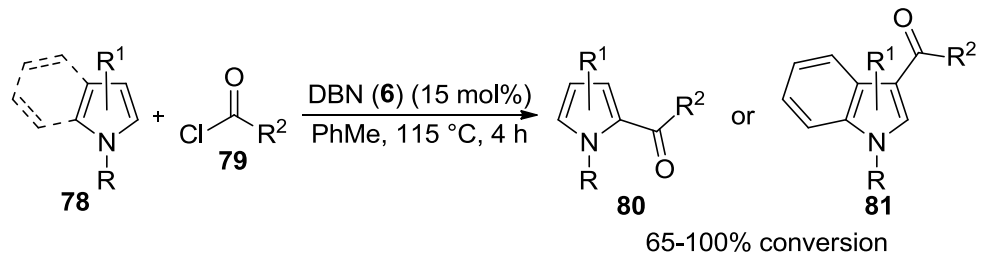
Smith *et al*. have developed the first isothiourea catalysed intermolecular *C*-acylation reactions of cyclic silyl ketene acetals (**76**), which avoids competing *O*-acylation that is often observed with enols and enolates.[44] It was found that DHPB (**29**) catalyses the *C*-acylation of a range of cyclic silyl ketene acetals (**76**) with either acid anhydrides or benzoyl fluoride (Scheme 15). The cyclic β-keto esters (**77**) formed contain chiral quaternary carbon centres and the reaction was found to be highly diastereoselective with up to 99:1 dr observed.



Scheme 15. DHPB (**29**) catalysed diastereoselective intermolecular *C*-acylation reactions of cyclic silyl ketene acetals (**76**).

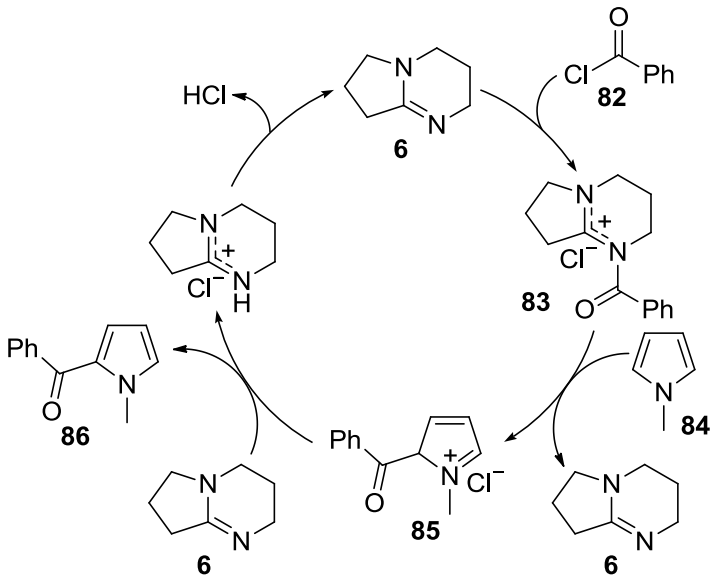
Bull, Williams, and Taylor have developed the first organocatalytic version of the Friedel-Crafts acylation reaction using DBN (**6**) as a catalyst. It was found that DBN (**6**) catalyses the regioselective

*C*2-acylation of pyrroles and *C*3-acylation of indoles using acyl chlorides (**79**) (Scheme 16).[45] The protocol was shown to work for a wide range of aromatic and alkyl acyl chlorides (**79**), as well as for a number of protected pyrroles and substituted indoles (**78**). The synthetic utility of the methodology was demonstrated for the synthesis of the non-steroidal anti-inflammatory drug Tolmetin.



Scheme 16. DBN (**6**) catalysed Friedel-Crafts acylation of pyrroles and indoles.

Detailed mechanistic studies on the reaction of *N*-methylpyrrole (**84**) with benzoyl chloride (**82**) have confirmed that DBN (**6**) acts as a nucleophilic catalyst in the reaction, forming an *N*-acyl DBN intermediate (**83**) with the acyl chloride (**82**) (Scheme 17). The structure of the intermediate (**83**) was confirmed by X-ray crystallographic analysis of an *N*-acyl DBN species as its tetraphenylborate salt.

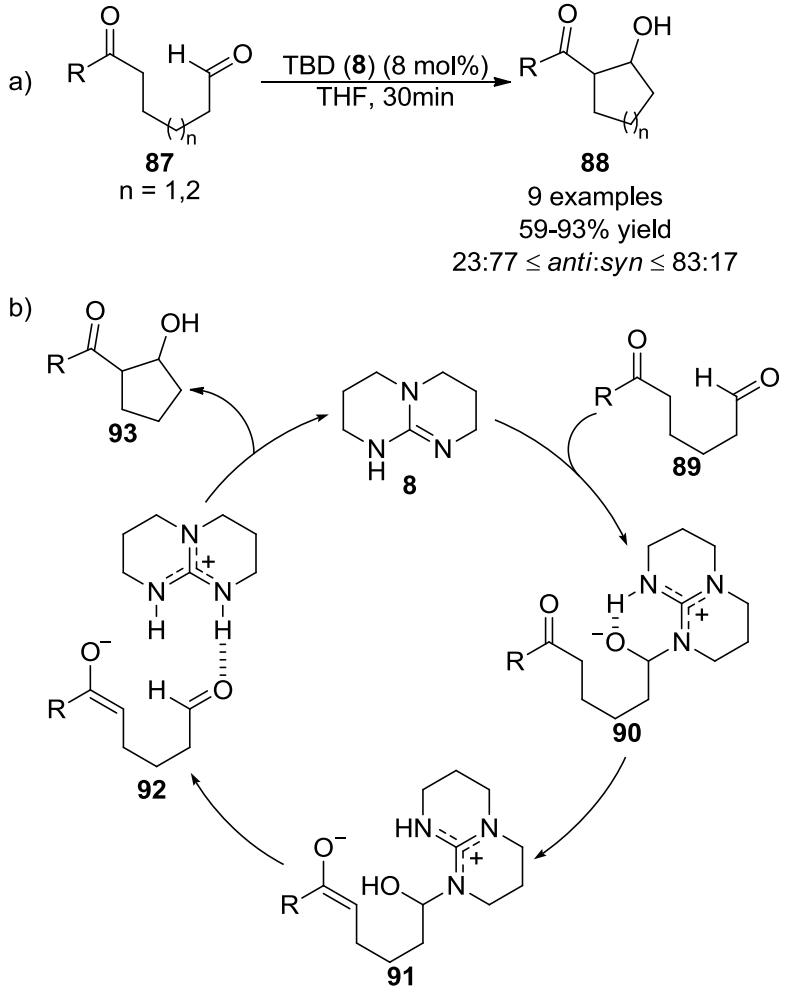


Scheme 17. Proposed mechanism for the DBN (**6**) catalysed *C*2-acylation of *N*-methylpyrrole (**84**).

Aldol Reaction

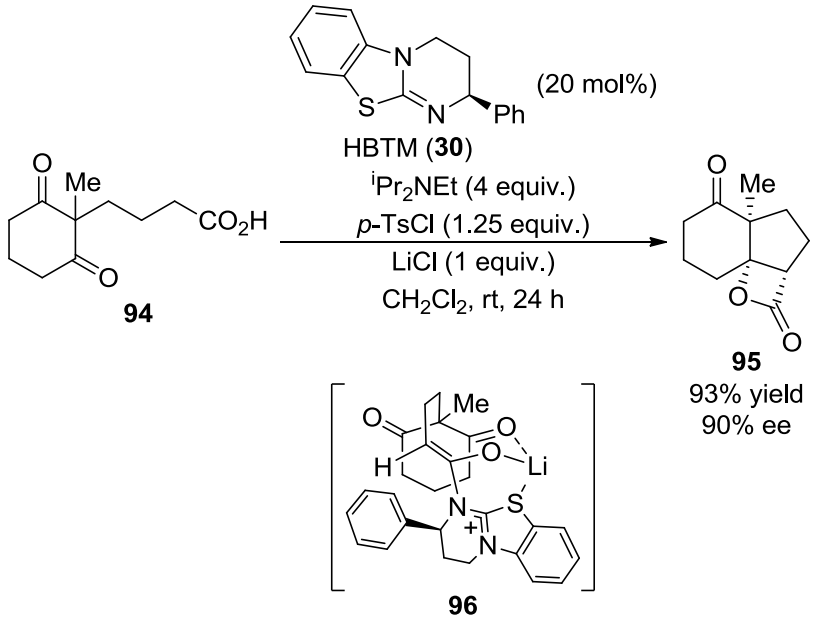
Baati and co-workers found that the guanidine TBD (**8**) was an efficient catalyst for the intramolecular aldol reaction of keto-aldehydes (**87**), forming cyclic aldol products (**88**) in reasonable

yields with modest levels of diastereoselectivity (Scheme 18a).[46] Whilst the cyclisation process could be promoted by TBD (**8**), the observation that 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, **9**) and 1,1,3,3-tetramethylguanidine (TMG, **7**) were much less active, despite their similar basicities, led the authors to propose an alternative mechanism in which the TBD (**8**) acts as a bifunctional catalyst (Scheme 18b). They proposed that TBD (**8**) initially acts as a nucleophile towards the aldehyde (**89**) to form a stabilised tetrahedral intermediate (**90**). Intramolecular proton transfer forms a ketone enolate (**91**), before the aldehyde is regenerated by release of a guanidinium cation. The guanidinium cation then hydrogen-bonds to the aldehyde functionality (**92**) to activate it towards intramolecular nucleophilic attack.



Scheme 18. a) Intramolecular aldol reaction catalysed by TBD (**8**). b) Proposed mechanism.

Romo *et al*. have shown that isothioureas can also catalyse the intramolecular aldol-lactonisation of keto-acids to form bi- and tri-cyclic lactones. For example, HBTM (**30**) was shown to catalyse the aldol-lactonisation of keto-acid **94** to form tricyclic lactone **95** in high yield with good levels of enantioselectivity (Scheme 19).[47] Mechanistically, the acid (**94**) is activated towards nucleophilic attack by HBTM (**30**) using *p*-TsCl to form an *N*-acyl HBTM intermediate, which can then be deprotonated to form the required enolate. It was found that using one equivalent of LiCl increased the yield of the reaction, presumably by acting as a Lewis acid to chelate the enolate and ketone into a chair-like transition state that enables the aldol reaction to proceed (**96**).

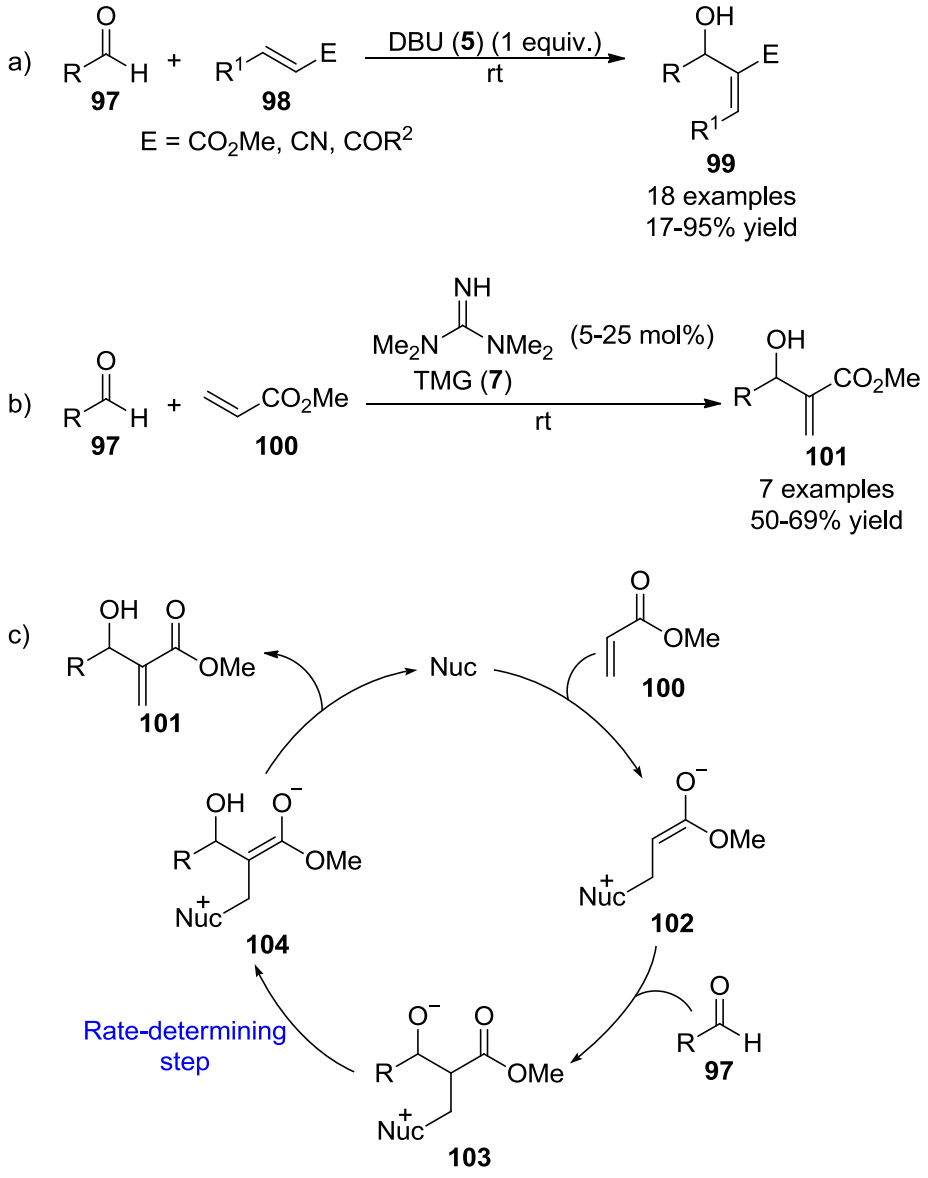


Scheme 19. HBTM (**30**) catalysed intramolecular aldol-lactonisation reaction to form a tricyclic lactone (**95**).

Morita-Baylis-Hillman Reaction

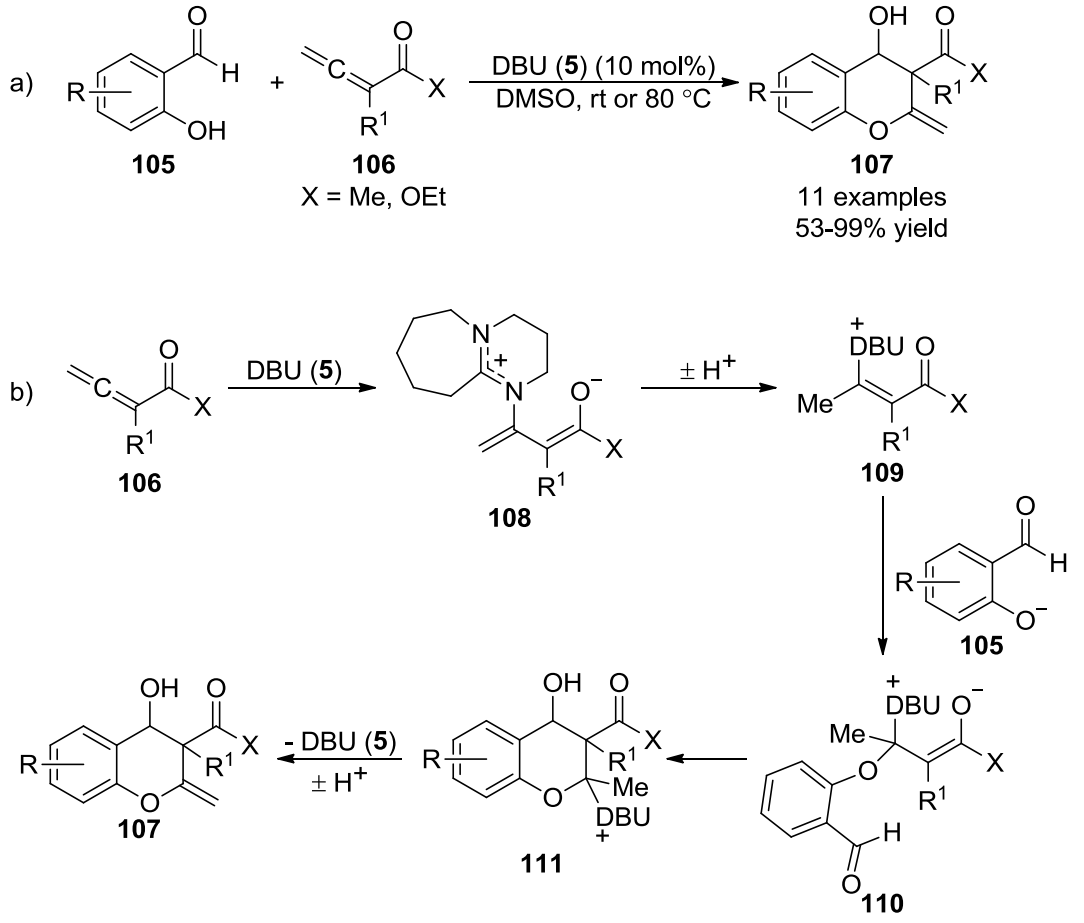
In 1999, Aggarwal and co-workers discovered that DBU (**5**) was an efficient catalyst for the Morita-Baylis-Hillman reaction, with rates of reaction faster than those observed with DABCO (**25**) (Scheme 20a).[48] Leadbeater and van der Pol showed that TMG (**7**) also catalyses the reaction between methyl acrylate (**100**) and a range of aldehydes (**97**) (Scheme 20b).[49] The rate-enhancement observed with DBU (**5**) and TMG (**7**) is attributed to increased resonance stabilisation of the β-ammonium enolate (**102**) formed from conjugate addition of the catalyst to the unsaturated substrate when compared with other tertiary amines (Scheme 20c). Cheng *et al*. subsequently found that DBU (**5**) catalysed the

Morita-Baylis-Hillman reaction of sterically demanding substrates in methanol.[50] The strong solvent dependence of the reaction led them to propose that the methoxide anion was the true catalyst of the reaction using DBU (**5**) in methanol. However, detailed computational studies by Aggarwal and Harvey *et al*. suggested that methanol increases the rate of the tertiary amine catalysed Morita-Baylis-Hillman reaction by allowing the rate-determining proton-transfer step to occur *via* a lower energy concerted pathway.[51]



Scheme 20. Morita-Baylis-Hillman reactions catalysed by a) DBU (**5**) and b) TMG (**7**). c) Proposed mechanism of the Morita-Baylis-Hillman reaction.

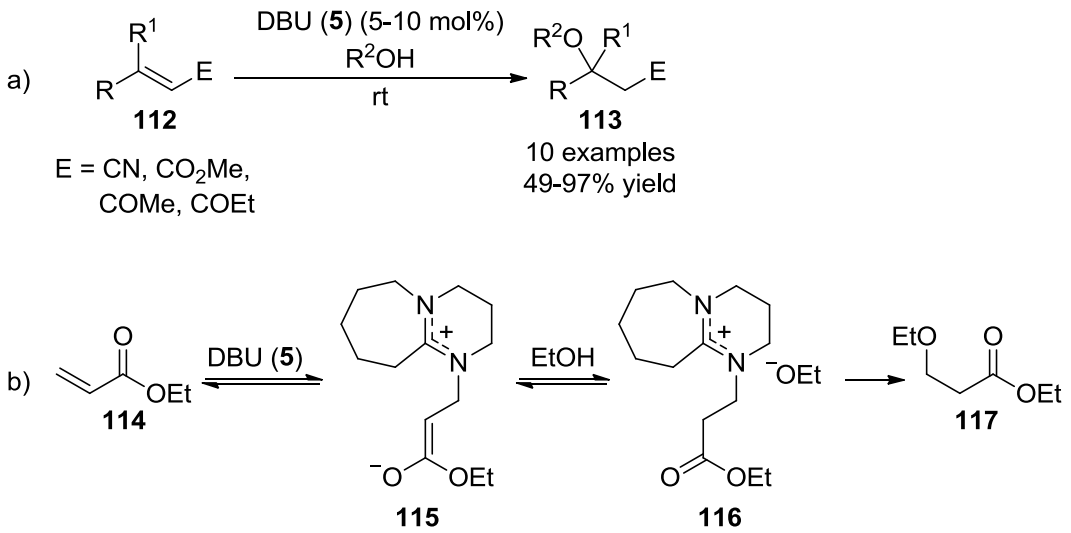
In a related process, Shi *et al*. have shown that 10 mol% DBU (**5**) can be used to catalyse the reaction of salicylic aldehydes (**105**) with allenes (**106**) to form 2*H*-1-chromenes (**107**) (Scheme 21a).[52] As observed with other α,β-unsaturated ketones, the DBU (**5**) is believed to activate the allene (**106**) through conjugate addition to form a β-ammonium enolate (**108**). The β-ammonium enolate **108** could then be protonated, allowing the salicylic aldehyde (**105**) to undergo a conjugate addition followed by an aldol reaction to form the products (**107**) (Scheme 21b). The authors propose a second possible cyclisation pathway in which the β-ammonium enolate **108** undergoes a Morita-Baylis-Hillman reaction with the salicylic aldehyde (**105**), however we believe that the conjugate addition/aldol pathway is more plausible.



Scheme 21. a) DBU (**5**) catalysed reaction of salicylic aldehydes (**105**) with allenes (**105**) to form 2*H*-1-chromenes (**107**). b) Potential mechanism *via* conjugate addition and intramolecular aldol reaction.

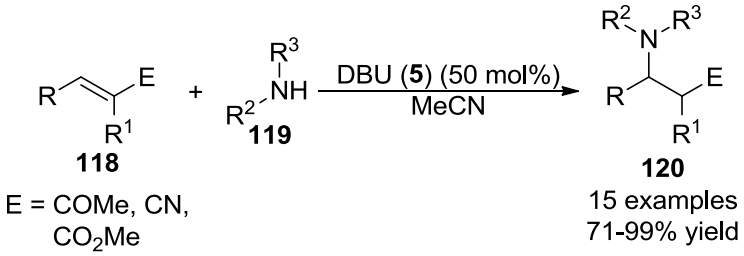
Conjugate Additions

Whilst screening tertiary amines as catalysts for the Baylis-Hillman reactions, Connon *et al*. observed a competing hydroalkoxylation reaction. This resulted in the development of a DBU (**5**) catalysed conjugate addition of alcohols to α,β-unsaturated nitriles, esters, and ketones (**112**) (Scheme 22a).[53] Mechanistically, the authors propose that the DBU (**5**) undergoes a conjugate addition to the α,β-unsaturated substrate (**114**) to generate a β-ammonium enolate intermediate (**115**), similar to those proposed for the Morita-Baylis-Hillman reaction. The enolate is then protonated by the alcohol solvent to generate a second charged DBU-intermediate (**116**) and an alkoxide anion. This alkoxide anion then undergoes an S_N2 reaction with the charged intermediate (**116**), with DBU (**5**) as the leaving group (Scheme 22b).



Scheme 22. a) DBU (**5**) catalysed conjugate addition of alcohols to α,β-unsaturated nitriles, esters, and ketones (**112**). b) Author's proposed mechanism for the addition of ethanol to ethyl acrylate (**114**).

Kim and co-workers have shown that DBU (**5**) catalyses the aza-Michael addition of a range of amines (**119**) to α,β-unsaturated ketones, nitriles, and esters (**118**) (Scheme 23).[54] Although no mechanism was proposed, Kim and co-workers speculate that the reactivity could not be explained by base catalysis alone. It is therefore possible that the reaction proceeds *via* a similar mechanism to that proposed by Connon *et al*. for their alcohol conjugate addition protocol (Scheme 22b).

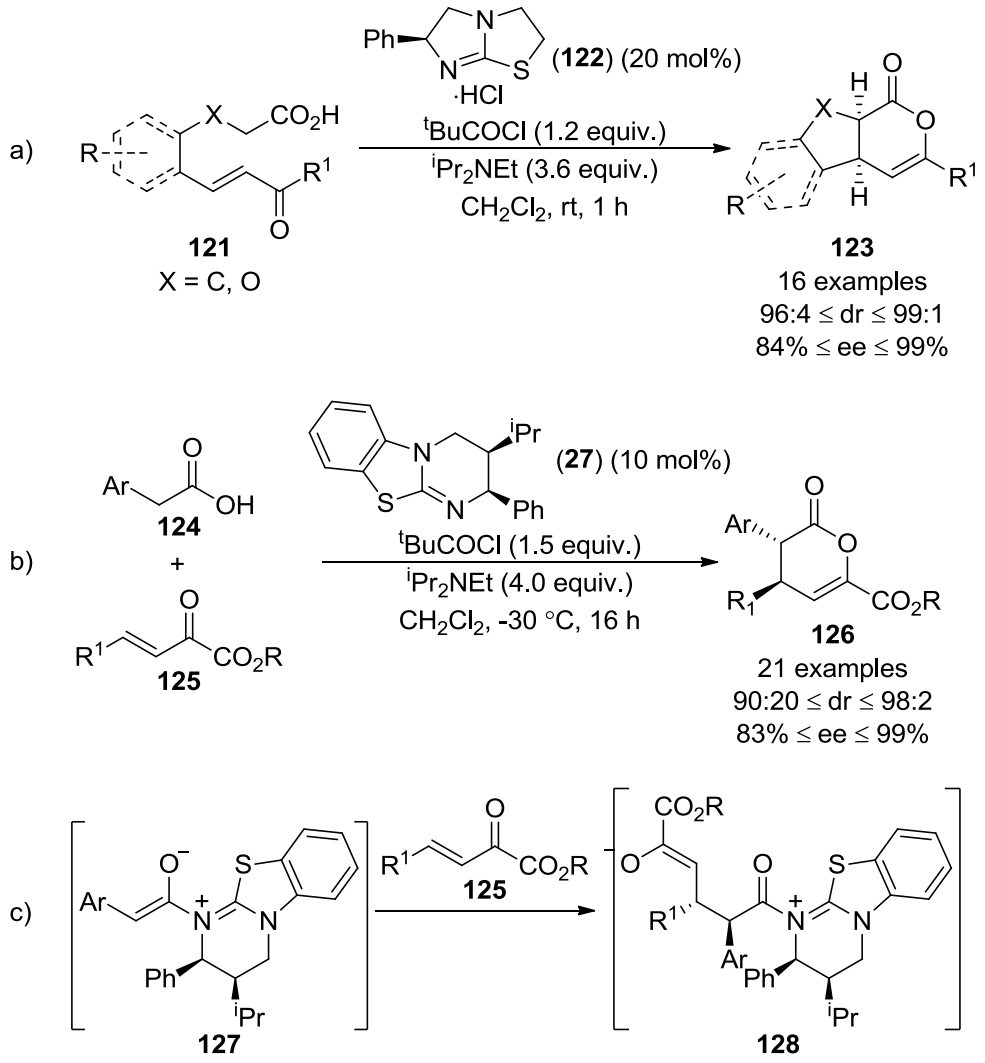


Scheme 23. DBU (**5**) catalysed aza-Michael addition of amines (**119**) to α,β-unsaturated ketones, nitriles, and esters (**118**).

Recently, Smith *et al*. have used isothioureas to catalyse intra- and inter-molecular Michael addition-lactonisation reactions (Scheme 24).[55] It was found that tetramisole (**122**) catalysed the intramolecular Michal addition-lactonisation sequence of a range of enone-acids (**121**) to form carbo- and hetero-cyclic lactones (**123**) in high yield with excellent levels of diastereoselectivity and ee (Scheme 24a). The lactone products (**123**) could be ring-opened using either methanol or isopropylamine to form the corresponding indene or dihydrobenzofuran carboxylates. Further optimisation allowed the process to be extended to the intramolecular reaction between arylacetic acids (**124**) and α-keto-β,γ-unsaturated esters (**125**) (Scheme 24b). In this case, HBTM derivative **27** was found to be the best catalyst, providing *anti*-dihydropyranones (**126**) with excellent levels of stereocontrol. The intra- and inter-molecular reactions are thought to proceed *via* similar stepwise Michael addition-lactonisation mechanisms. Firstly, the pivaloyl chloride reacts with the acid present to form a mixed anhydride, which can then be nucleophilically attacked by the isothiourea catalyst to form an *N*-acyl intermediate. The $^{i}Pr_2NEt$ present then deprotonates the *N*-acyl intermediate to form a zwitterionic species (**127**) that then undergoes a Michael addition onto the α,β-unsaturated ketone functionality (Scheme 24c). Subsequent lactonisation of the resultant enolate (**128**) gives the lactone product and releases the catalyst. This proposed mechanism also provides an explanation for the absolute configuration obtained if it is assumed that the Michael addition proceeds with the two pro-stereocentres adopting a staggered conformation to minimise unfavourable non-bonding interactions.

A number of guanidine catalysed conjugate additions have been reported over the last 15 years. However, whilst nucleophilic catalysis is theoretically possible with these examples, most reports

favour either general Brønsted base catalysis or hydrogen-bonding models to explain the role of the guanidine catalyst.[6]

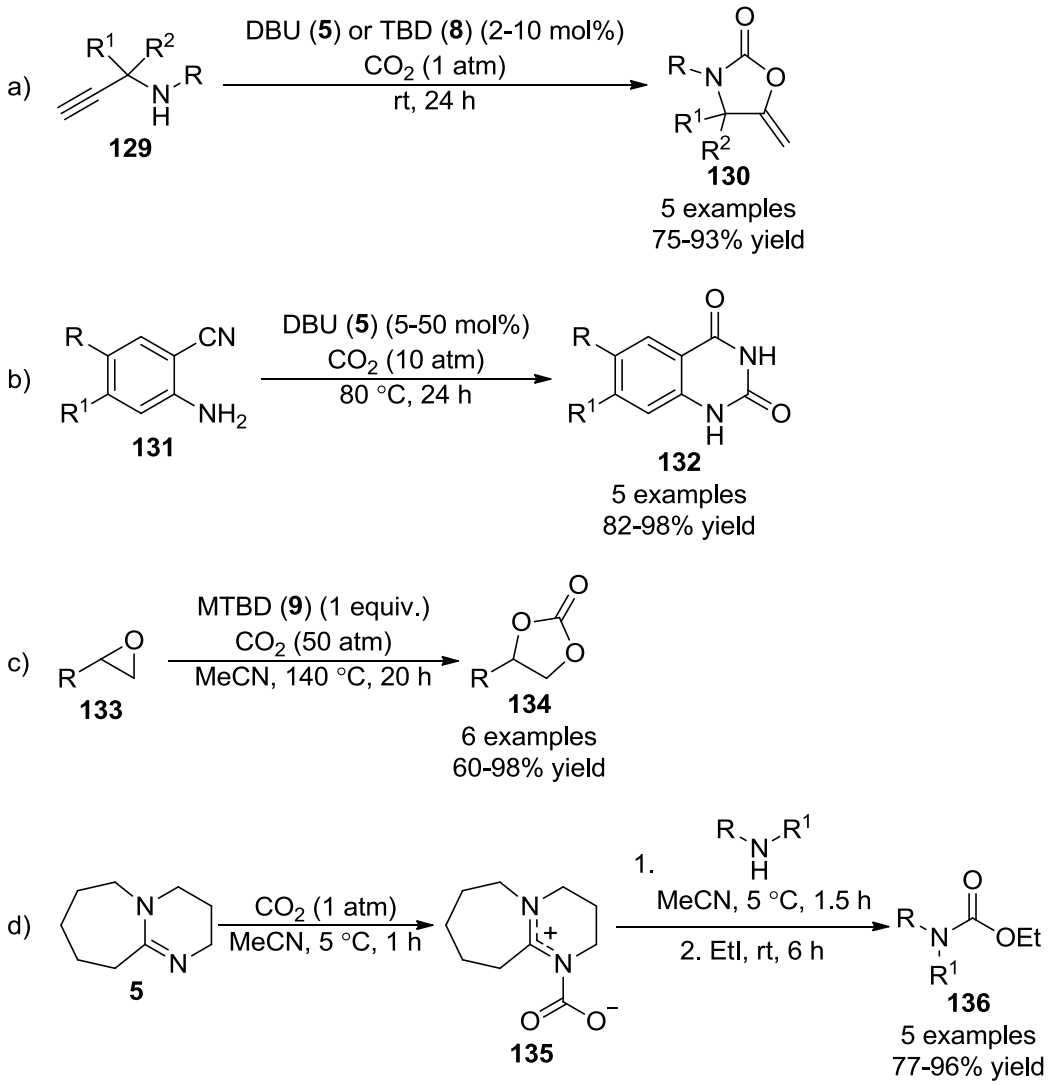


Scheme 24. a) Intramolecular Michael addition-lactonisation reaction. b) Intermolecular Michael-addition-lactonisation reaction. c) Proposed intermediates in the isothiourea **27** catalysed process.

Carbonylation Reactions

In 1996, Costa and co-workers showed that both DBU (**5**) and TBD (**8**) catalyse the reaction of acetylinic amines (**129**) with CO_2 to form 5-methylene-oxazolidin-2-ones (**130**) (Scheme 25a). Although no mechanism was proposed for the role of the amidine or guanidine catalysts it was found that the rate of reaction was independent of the pK_a of the catalyst.[56] Mizuno *et al*. then found that DBU (**5**) could catalyse the reaction between CO_2 and 2-aminobenzonitriles (**131**). The reaction readily occurs in one atmosphere of CO_2 when one equivalent of DBU (**5**) is used, whereas the use of

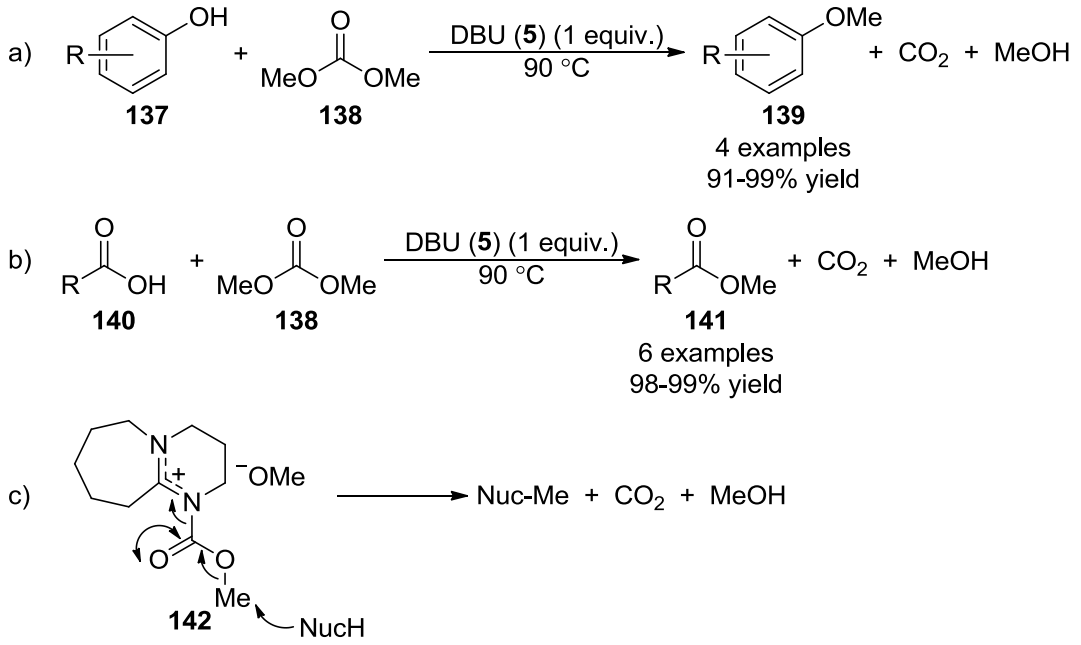
sub-stoichiometric amounts of DBU (**5**) required ten atmospheres of CO_2 (Scheme 25b).[57] Sartori *et al*. reported that the guanidine MTDB (**9**) catalysed the cycloaddition of CO_2 to epoxides (**133**) to form cyclic carbonates (**134**) (Scheme 25c).[58] Franco and co-workers were the first to suggest that CO_2 is nucleophilically activated by the amidine or guanidine catalysts when they showed that a DBU-CO_2 complex (**135**) reacts with amines. The initial addition products were trapped with ethyl iodide to form the corresponding ethyl carbamates (**136**) in high yields (Scheme 25d). The structure of the DBU-CO_2 complex (**135**) was subsequently confirmed by ^{13}C NMR spectroscopic analysis, although attempts to obtain an X-ray crystal structure resulted in the formation of a DBU-carbonic acid complex during the crystallisation process.[59]



Scheme 25. Examples of the nucleophilic activation of CO_2 using amidine and guanidine based catalysts.

Methylation Reactions

In 1990, Sennyey *et al*. found that tetrasubstituted guanidines could be used to catalyse the methylation of phenols (**137**) using dimethyl carbonate (**138**) at high temperature (180 °C).[60] Shieh *et al*. subsequently found that using one equivalent of DBU (**5**) was more efficient, enabling the methylation of phenols (**137**) at 90 °C (Scheme 26a).[61] Shieh *et al*. also found that DBU (**5**) and dimethyl carbonate (**138**) could be used for the methylation of acids (**140**) to form the corresponding esters (**141**) (Scheme 26b).[62] Extensive mechanistic studies have shown that DBU (**5**) and dimethyl carbonate (**138**) react to form an *N*-acyl carbamate (**142**), which acts as the methylating agent towards nucleophiles, releasing CO_2 and methanol as by-products (Scheme 26c).

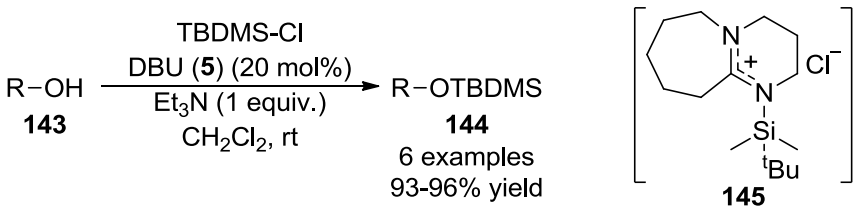


Scheme 26. DBU (**5**) and dimethyl carbonate (**138**) for the *O*-methylation of a) phenols (**137**) and b) acids (**140**). c) Proposed mechanism.

Silylation Reactions

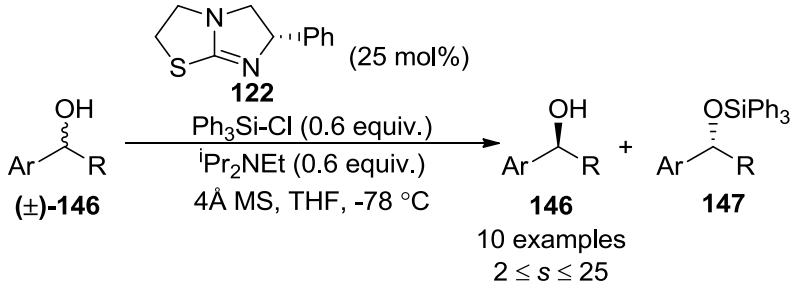
In 1985, Kim and Chang showed that DBU (**5**) could be used as a nucleophilic catalyst in the *tert*-butyldimethylsilylation of primary alcohols (**143**) (Scheme 27).[63] The silylation reaction can be performed using either one equivalent of DBU (**5**), or 20 mol% DBU (**5**) and one equivalent of triethylamine, providing *O*-silyl protected products (**144**) in high yields. The silylation methodology was shown to be regioselective for the protection of primary alcohols over secondary alcohols. The

DBU (**5**) is believed to attack the TBDMS-Cl to form an *N*-TBDMS DBU complex **145**, which then acts as the active silylating agent.



Scheme 27. Silylation of primary alcohols (**143**) catalysed by DBU (**5**).

Recently, Wiskur *et al*. have used the enantiomerically pure tetramisole (**122**) as a nucleophilic catalyst for the kinetic resolution of secondary alcohols (**146**) through enantioselective silylation (Scheme 28).[64] The highest enantioselectivities were observed using cyclic secondary alcohols (**146**) and triphenylsilyl chloride, giving *s* values of up to 25 that corresponds to an 88% ee for recovered alcohol at 52% conversion (**146**).

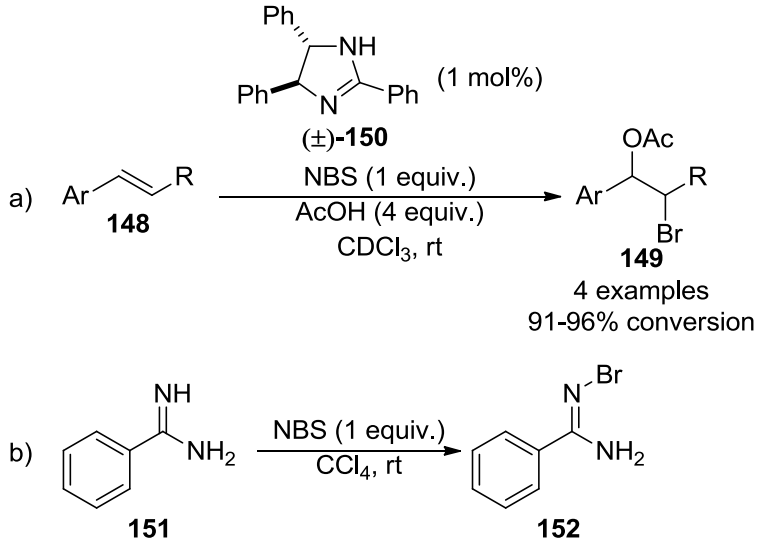


Scheme 28. Kinetic resolution of secondary alcohols (**146**) through enantioselective silylation reactions catalysed by tetramisole (**122**).

Bromination Reactions

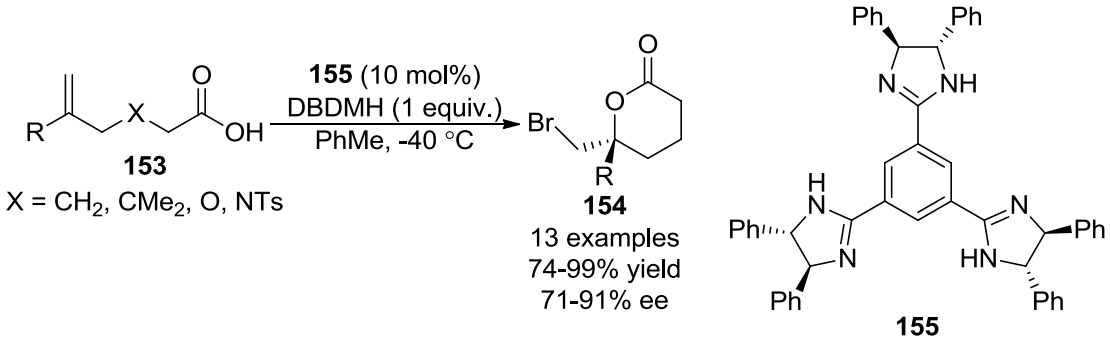
Braddock and co-workers have found that amidine and guanidines can be used as nucleophilic catalysts in bromination reactions. Firstly, the acyclic guanidine TMG (**7**) was shown to be a highly efficient catalyst for bromolactonisation and intermolecular bromoacetoxylation using *N*-bromosuccinimide (NBS).[65] The cyclic amidine (±)-*iso*-amarine (**150**) was also shown to catalyse the same reactions using NBS. The bromoacetoxylation of styrenes (**148**) was found to be highly regioselective for attack of acetic acid at the benzylic position of the bromonium ion (Scheme 29a).[65] The amidine and guanidine catalysts are thought to provide a more electrophilic source of bromine by

nucleophilically attacking NBS. An X-ray crystal structure of *N*-bromo-benzamidine (**152**), obtained from the reaction of benzamidine (**151**) with one equivalent of NBS, provides direct evidence for this mode of activation by amidines.



Scheme 29. a) Bromoacetoxylation catalysed by (±)-*iso*-amarine (**150**). b) Evidence for the activation of NBS by amidines.

Recently, Fujioka *et al*. have shown that the C_3-symmetric amidine derivative **155** can catalyse the asymmetric bromolactonisation reaction of a range of δ,ε-unsaturated acids (**153**) using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), forming the corresponding bromolactones (**154**) in high yields with good levels of enantioselectivity (Scheme 30).[66] In this case, formation of an ion-pair between



Scheme 30. Asymmetric bromolactonisation reaction catalysed by a C_3-symmetric amidine **155**.

the acid (**153**) and the catalyst (**155**) is thought to be important for asymmetric induction and it is unknown whether the catalyst (**155**) nucleophilically activates the electrophilic bromine source.

Conclusions

Amidines, guanidines, and isothioureas have been shown to act as nucleophilic catalysts in a wide range of reactions. In particular, the bicyclic amidines DBU (**5**) and DBN (**6**) and the guanidines TMG (**7**) and TBD (**8**) have been shown to be highly active nucleophilic catalysts in many cases, often offering advantages over more traditional nucleophilic catalyst. Enantiomerically pure derivatives of amidines, guanidines and, in particular, isothioureas have been successfully used in a number of asymmetric reactions. The potential of the amidine and guanidine functional groups to act as bifunctional catalysts, using combinations of nucleophilic, basic, and hydrogen-bonding behaviour, have also been exploited in a few processes. There is no doubt that further applications of amidine, guanidine, and isothiourea derived catalysts will continue to be discovered.

Acknowledgements

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