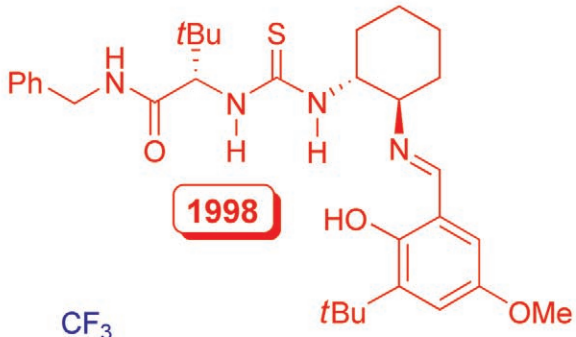

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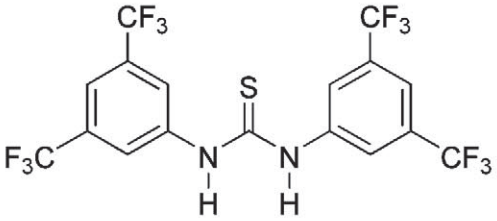

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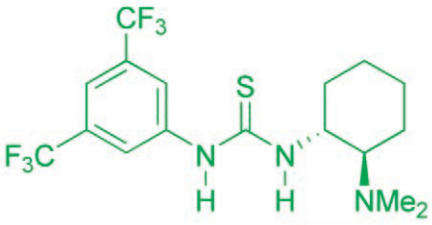
Organocatalysis mediated by (thio)urea derivatives



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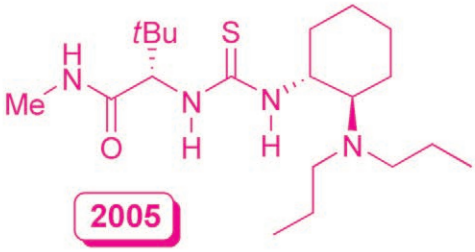

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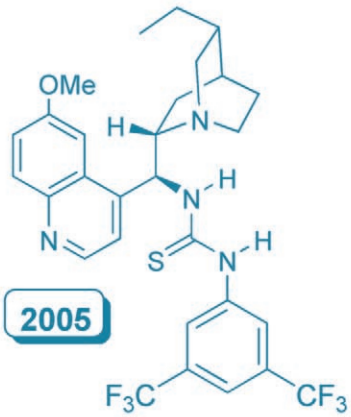

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Organocatalysis Mediated by (Thio)urea Derivatives

Stephen J. Connon*[a]

Abstract: Over the last decade the potential for *N,N*-dialkyl(thio)urea derivatives to serve as active metal-free organocatalysts for a wide range of synthetically useful reactions susceptible to the influence of general acid catalysis has begun to be realised. This article charts the development of these catalysts (with emphasis on the design principles involved), from early "proof-of-concept" materials to contemporary active chiral (bifunctional) promoters of highly selective asymmetric transformations.

Keywords: asymmetric catalysis · hydrogen bonding · organocatalysis · thiourea · urea

Introduction and Background

The activation of an electrophilic reaction component by a metal-based (or metal-ion based) Lewis acidic additive is a time-honoured strategy for the catalysis of chemical reactions. In the majority of cases not involving substrate ionisation, the dramatic improvements in both rate and selectivity possible under the influence of metal(-ion)-based catalysis is ascribable to a lowering of the lowest unoccupied molecular orbital's energy upon coordination of a Lewis basic substrate heteroatom to the catalyst.[1,2] Extensive research in this area coupled with parallel advances in ligand design have given rise to plethora of (chiral) Lewis acidic metal-based catalysts, the steric and electronic properties of which can be controlled with considerable precision.[3]

The advent of these systems has revolutionised organic synthesis, and while the scope for further development and discovery in this broad field undoubtedly remains vast, the use of strongly Lewis acidic metal-based catalysts is not without potential drawbacks. Principal among these are 1) product inhibition (binding of the product to the catalyst) which can limit (or prevent) catalyst turnover, requiring a strongly Lewis acidic "catalyst" to be employed at loadings up to and beyond 100 mol%, and 2) the strong oxophilicity of several catalytically useful metal ions (e.g., Fe^{3+}, Al^{3+}, B^{3+}, Sn^{4+} and Ti^{4+}), which can necessitate the rigorous exclusion of air/moisture from the reaction and limit functional-group/solvent compatibility. Attempts to circumvent these difficulties over the last decade have led to the successful introduction of catalysts based on ions of more polarisable metals (particularly the lanthanides) that exhibit much improved catalytic properties, many of which are active in aqueous media.[4]

More recently, with a view to designing more selective, robust, environmentally benign and functional-group tolerant catalysts, chemists have begun to reconsider use of the simplest Lewis acid: the proton. Brønsted acid catalysis of a multitude of reactions (e.g., Fischer esterification, acetal/ketal formation and ester hydrolysis) has been known for decades; however, in general, the use of strong acid catalysts is often impractical due to a lack of selectivity, for example, protonation of the reaction product leading to decomposition/epimerisation/polymerisation or inactivation of a "nucleophilic" (and hence often basic) reaction component. Therefore, taking their cue from natural enzymatic systems, chemists have begun to explore the exploitation of weak acid–base interactions/hydrogen bonding as a basis for catalyst design.[5] Fortunately, a wide range of synthetically useful reactions—particularly (but by no means exclusively) those involving additions to C=O and C=N bonds in which reaction is accompanied by a dramatic change in heteroatom basicity—are susceptible to the influence of general acid catalysis and thus can potentially be promoted by weakly acidic metal-free small organic molecules that stabilise the transition state (TS) of the reaction through either hydrogen bonding or a degree of proton transfer.[6]

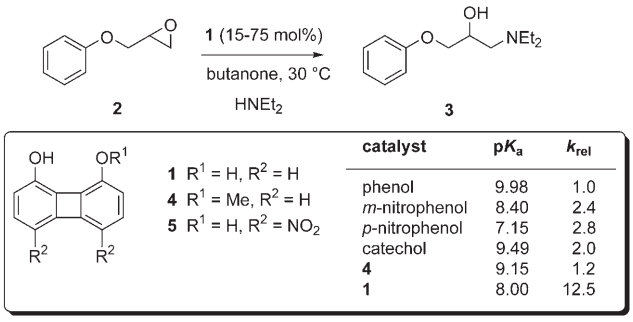
While such general acid organocatalytic systems inherently lack the strong enthalpic substrate-binding abilities usually associated with metal(-ion)-based Lewis acid catalysts

[a] Dr. S. J. Connon
Centre for Synthesis and Chemical Biology
School of Chemistry, University of Dublin, Trinity College
Dublin 2 (Ireland)
Fax: (+353) 1-671-2826
E-mail: connons@tcd.ie

and thus often possess inferior turnover frequencies (TOF) for which comparisons are possible, this need not necessarily be seen as disadvantageous. These same properties potentially allow for greater control of binding chemoselectivity in catalyst design (ideally only the TS resulting from reaction at a single substrate functional group should be bound by the catalyst), and it therefore follows that the twin menaces of product inhibition and catalyst air/moisture sensitivity are generally less problematic in well-designed organocatalytic systems. Perhaps most importantly, the high functional group tolerance of these materials and their general ease (and economy) of construction/modification through standard synthetic techniques facilitates the design and fine-tuning of chiral systems for stereoselective synthesis, as the almost limitless exploitation of the surfeit of Lewis acidic (hydrogen-bond donating) and (if necessary) Lewis basic functional groups available from the chiral pool is unhindered by potential interactions with metal-ion centres.[7,8]

Early Successes: From Biphenylenediols to Efficient *N,N′*-Diarylthio(urea) Catalysts

In an often-overlooked series of seminal studies, Hine et al. demonstrated that the conformationally rigid 1,8-biphenylenediol (**1**) was capable of forming two strong hydrogen bonds to the oxygen atom of Lewis basic substrates such as hexamethyl phosphoramide (HMPA) and 1,2,6-trimethyl-4-pyridone,[9] and effectively promoted the aminolysis of phenyl glycidyl ether (**2**) in butanone (Scheme 1). A Brønsted plot based on catalysis of this reaction by a range of substituted phenols indicated that **1** promoted the conversion of **2** with an efficiency per hydroxy group that would expected from a phenol 600 times as acidic, and that both hydroxyl groups participated in catalysis.[10] Further investigation identified the dinitrobiphenylenediol derivative **5** as a material with considerably improved hydrogen-bond-donating properties.[11] Later Kelly and co-workers[12] reported the promotion of the Diels–Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes and ketones by 3,6-dipropyl derivatives of **5** (40–50 mol%), and proposed double hydrogen-bond donation to the dienophile (**6**; Figure 1) as an explanation for the catalysis observed.[13] This was consistent with a theory proposed by Jorgensen based on computational studies to rationalise the observed acceleration of Diels–Alder reactions and Claisen rearrangements in H_2O relative to nonprotic solvents (**7**).[14,15]



Scheme 1. Catalysis of epoxide ring-opening by **1**.

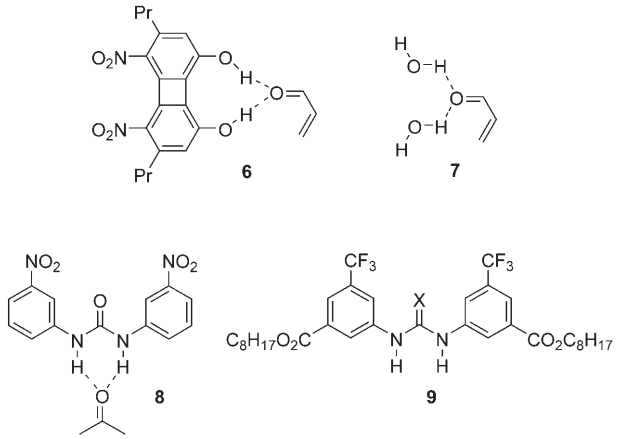
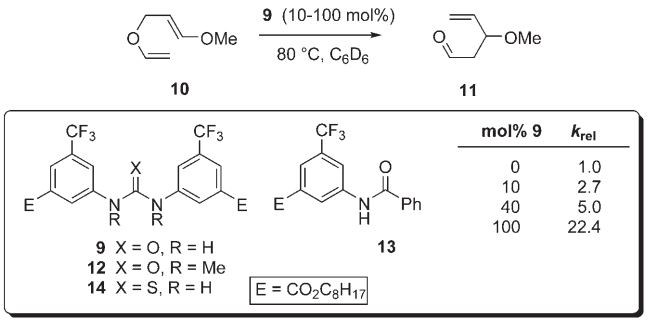


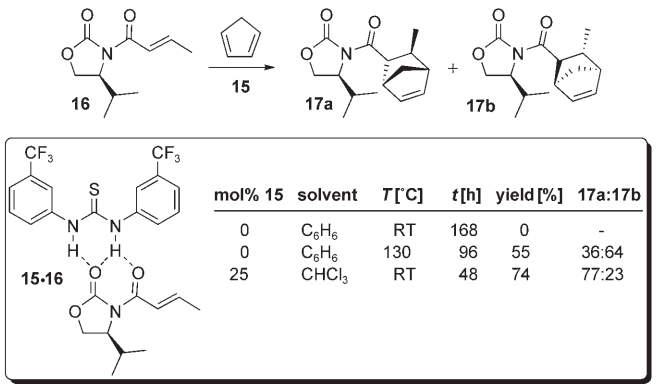
Figure 1. Rationale for the catalysis of the Diels–Alder reaction by **6** (Kelly) and H_2O (**7**: Jorgensen) through double hydrogen-bond donation; a representation of the binding between *m*-nitrocarbanilide and acetone (**8**) and Curran's urea catalyst (**9**).

Although the biphenylenediol catalysts possessed only moderate reactivity and solubility profiles, the pioneering work of Hine and Kelly established that general acid catalysis by conformationally restricted metal-free diprotic acids is a valid strategy upon which to base organocatalyst design. At around this time, Etter et al.[16,17] observed hydrogen bond-directed co-crystallisation of *N,N′*-diarylureas (in particular 3,3′-dinitrocarbanilide (**8**)) with compounds incorporating a wide variety of Lewis basic functional groups, such as nitroaromatics, ethers, ketones[18] and sulfoxides. In each case the donation of two hydrogen bonds by a single urea molecule to the Lewis base was implicated.[19] The precedents set by the aforementioned studies for efficient catalysis by rigid bidentate hydrogen-bond donors and the demonstration of binding between ureas and Lewis bases provided the basis for the development of urea-based organocatalysts.

The first such example came from Curran et al. who found that substoichiometic amounts of diarylurea **9** enhanced both the yield and diastereoselectivity of the allylation of cyclic α-sulfinyl radicals with allyltributylstannane.[20] The choice of functionality installed on the diarylurea backbone deserves comment: the nitro group from the strong Lewis base binding *m*-nitrocarbanilide was substituted for an electron-withdrawing group more compatible with radical processes (i.e., CF_3) and lipophilic side chains were utilised to improve solubility in common organic solvents. Later the same group reported the promotion of the Claisen rearrangement of **10** by using catalytic quantities of **9** (Scheme 2). At medium to high catalyst loadings useful rate



Scheme 2. Diiaryl(thio)urea catalysis of the Claisen rearrangement.

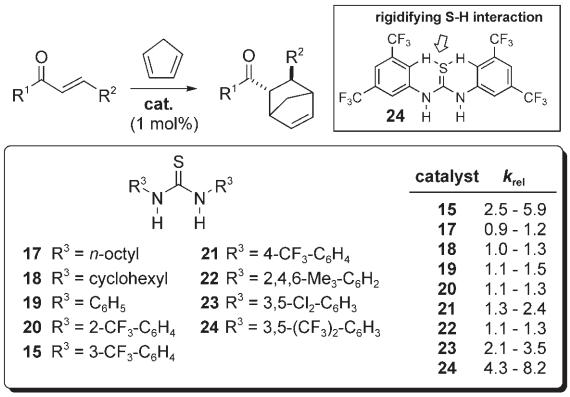


Scheme 3. Diarylthiourea catalysis of the Diels–Alder reaction.

acceleration was possible. The failure of either dialkylurea **12** or benzanilide **13** to promote the reaction efficiently strongly suggested—in line with Hine's findings (vide supra)—the involvement of both urea protons in catalysis.[21] For the first time thiourea derivatives (e.g., **14**) were also shown to hold promise as hydrogen-bonding catalysts.[22]

Schreiner has established that diarylthioureas can catalyse the Diels–Alder reaction between cylclopentadiene and α,β-unsaturated carbonyl compounds.[23,24] To avoid the solubility problems often associated with the use of diarylureas, more soluble thiourea analogues were investigated, thereby dispensing with the requirement for long-chain alkyl substituents. For a hydrogen-bonding catalyst to be effective it must ideally bind most efficiently with the TS and not with either the starting materials, products or itself; therefore the removal of the Lewis basic ester linkage from **14** and the retention of the strongly electron-withdrawing (yet poor hydrogen bond accepting) CF_3 moiety was advantageous in terms of limiting the catalyst's ability to self-associate. This, combined with the relatively high acidity[25] (facilitating Lewis base binding) and poor hydrogen bond acceptor ability of thioureas (again limiting self-association of thiourea relative to urea derivatives), made **15** an attractive starting point for catalyst design. Preliminary binding studies determined that **15** possessed a large dimerisation entropy and thus could self associate efficiently only at low temperatures, while efficient binding to one equivalent of the dienophile **16** was observed at room temperature. A comparison of the measured and calculated C=O IR absorptions for complex **15·16** implicated binding of the catalyst to both carbonyl moieties of the oxazolidinone as shown in Scheme 3. These findings were supported by the efficient catalysis of the Diels–Alder reaction between **16** and cyclopentadiene with a concomitant switch in the major diastereomer formed (and an improvement in d.r.) consistent with catalysis via **15·16**.[23]

Subsequently the evaluation of a small library of symmetrical *N,N′*-disubstituted thiourea derivatives as promoters of the [4+2] cycloaddition of a series of α,β-unsaturated aldehydes/ketones to cyclopentadiene shed light on the key steric and electronic requirements for catalytic activity in these systems. Thioureas derived from aliphatic amines or simple anilines were poor catalysts, as were diarylureas incorporating *ortho*-substituents (Scheme 4). Only diarylthioureas with powerful electron-withdrawing groups in the *meta*- or *para*-positions possessed appreciable activity, with

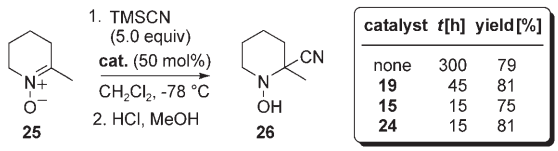


Scheme 4. Catalyst optimisation.

tetrasubstituted catalyst **24** proving to be the most effective candidate structure tested across a range of five different dienophiles.[24] It is worth noting that diarylthiourea-mediated catalysis of the reaction was found to persist even in aqueous solvent. In view of the generally weak enthalpic binding between thioureas and carbonyl compounds,[23,26] the results were rationalised in terms of the importance of entropic effects; specifically, it was proposed that the (computationally determined)[24] rotational barrier of catalyst **24** is relatively high due to an attractive interaction between the *ortho*-hydrogen atoms, which are polarised by the adjacent electron-withdrawing substituent, and the Lewis basic sulfur heteroatom (Scheme 4). This rigidifying interaction would minimise entropy loss upon binding of the substrate and thus facilitate catalysis. It is also likely, however, that enthalpic factors also contribute to the high activity of **24**; that is, the *m*-CF_3 substituents ($\sigma_m = 0.46$)[27] would significantly augment the acidity of the N–H protons relative to those in **19**.

Diarylureas and -thioureas have also been successfully employed in the additions of nucleophiles to nitrones. Take-

moto and co-workers[28] disclosed the catalytic cyanation of nitrones promoted by a variety of diaryl(thio)ureas (Scheme 5). The reactions were significantly accelerated in



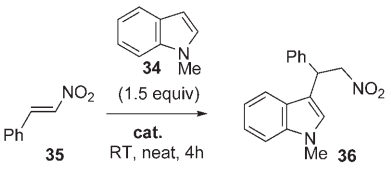
catalyst	t[h]	yield[%]
none	300	79
19	45	81
15	15	75
24	15	81

Scheme 5. Addition of TMSCN to nitrones catalysed by thiourea catalysts.

the presence of relatively high loadings of catalyst, the relative activities of which were broadly in line with that found by Schreiner[24] (vide supra). Efficient catalysis of the addition of silylketene acetals to nitrones by **24** was also demonstrated.

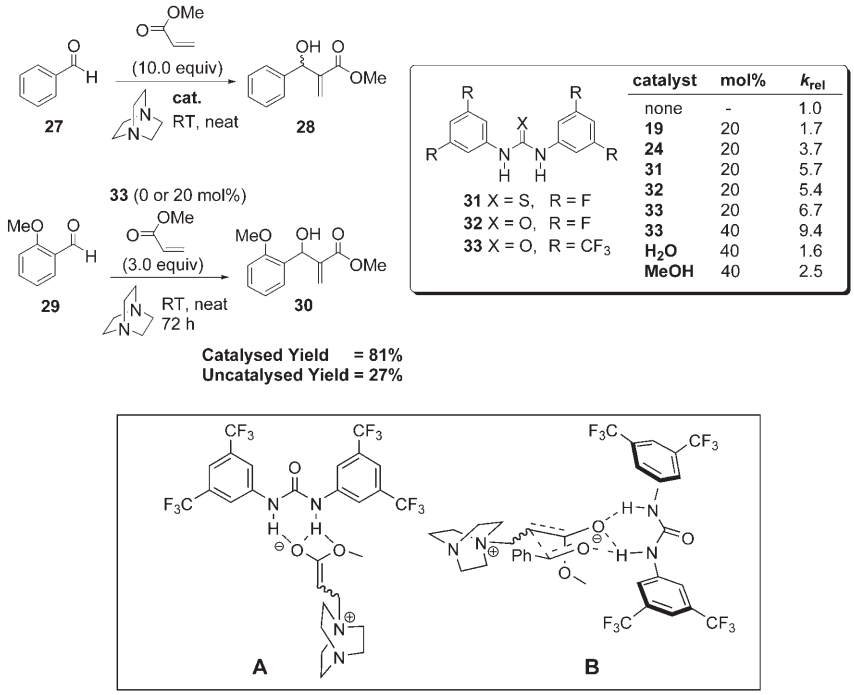
Our group reported that Lewis (Brønsted) acidic diarylureas can be synergistically utilised in conjunction with basic (nucleophilic) tertiary amines in the catalysis of the notoriously slow Baylis-Hillman reaction between methyl acrylate and aromatic aldehydes.[29] By using substoichiometric catalyst loadings, rate acceleration of the addition of methyl acrylate to benzaldehyde (**27**) approaching an order of magnitude was possible (Scheme 6). While the precise catalyst mode of action is unclear, the known anion-binding proclivities of (thio)urea derivatives[30] and the ability of the catalysts to effectively promote the reaction in the presence of ten equivalents of methyl acrylate strongly indicates a mechanism involving binding to (and stabilisation of) the Zwitterionic ammonium enolate intermediate (binding scenario **A** or **B**, Scheme 6), the addition of which to the aldehyde has been proposed to be the rate-determining step of the reaction.[31,32] It is notable that optimal catalyst **33**[33] is a considerably superior mole per mole promoter of the reaction than the traditional additives water or methanol.[34] The potential synthetic utility of **33** is underlined by the smooth reaction between challenging substrates **29** and methyl acrylate in the presence of a tertiary amine co-catalyst to afford **30** in good yield under optimised conditions. The catalyst could also be efficiently recovered for reuse after reaction by column chromatography.

Electrophilic aromatic substitution reactions have also been shown to be susceptible to the influence of catalysis by diaryl(thio)urea hydrogen-bond donors. For example the addition of indole **34** to nitroolefin **35** to afford adduct **36** is accelerated considerably presence of 10 mol% **24** or **33** (Scheme 7). The methodology was found to be applicable to several electron-rich aromatic substrates such as indoles, pyrroles and *N,N*-dialkylanilines.[35]



catalyst	mol%	conv.[%]	yield[%]
none	-	19	-
24	10	100	94
33	10	100	-

Scheme 7. Catalysis of Friedel–Crafts type reactions.



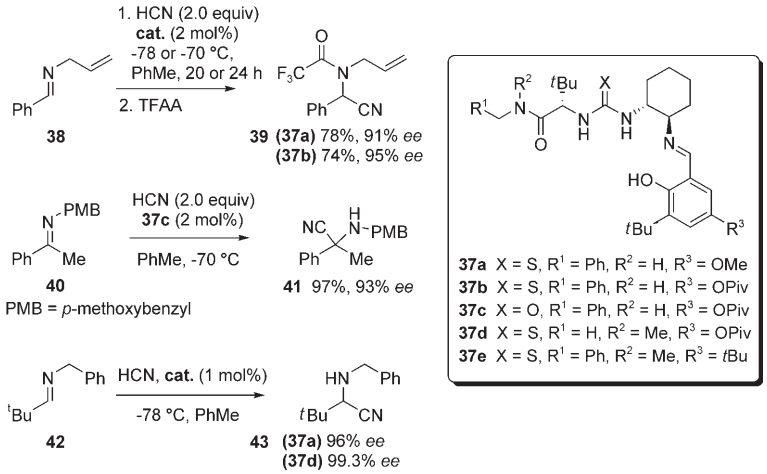
catalyst	mol%	k_{rel}
none	-	1.0
19	20	1.7
24	20	3.7
31	20	5.7
32	20	5.4
33	20	6.7
33	40	9.4
H_2O	40	1.6
MeOH	40	2.5

Scheme 6. Diaryl(thio)urea catalysed Baylis–Hillman reactions.

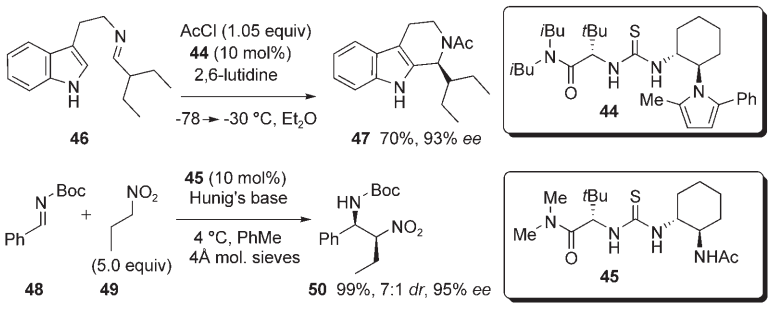
Chiral (Thio)ureas for Asymmetric Organocatalysis

The ready availability of enantiopure chiral building blocks bearing primary amino functionalities from the chiral pool and other sources greatly facilitates the synthesis of asymmetric (thio)ureas. Therefore given the excellent general stability, high conformational rigidity[36] and Lewis base binding proclivities[16,17,19] of thio(urea) derivatives, it is perhaps unsurprising that chiral analogues are rapidly emerging as versatile, functional group tolerant and easily prepared/modified catalyst templates for the promotion of a wide range of synthetically useful asymmetric carbon–carbon bond forming processes.

Schiff base derived catalysts: In the course of studies involving a combinatorial approach to the design of catalysts for the metal-ion-promoted asymmetric Strecker reaction, Jacobsen et al. observed that in the case of one particular urea-derived ligand the control reaction, that is, in the absence of metal ion, furnished the product with the highest enantioselectivity. A combination of subsequent parallel library and conventional linear optimisation studies resulted in the identification of **37a** (Scheme 8) as an efficient and highly enantioselective catalyst for the addition of HCN to aromatic and aliphatic *N*-allyl amines.[37] Further optimisation[38] led to the development of **37b** and its robust and readily synthesised[39] urea-derivative **37c**, which is compatible with a broad range of imine substrates including traditionally challenging keto–imine derivatives (Scheme 8).[40,41]



Scheme 8. (Thio)urea-catalysed asymmetric Strecker reactions.

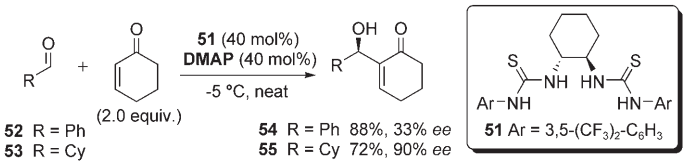


Scheme 9. Simplified (thio)urea derivatives for the asymmetric Pictet–Spengler and nitro Mannich reactions.

Mechanistic and binding studies determined that these urea-catalysed Strecker reactions displayed Michaelis–Menten kinetic behaviour (implying reversible substrate binding), and that catalyst binds the imine (*Z*)-isomer preferentially through double hydrogen-bond donation to the imine lone pair, in a fashion directed by the minimisation of steric interactions between the catalyst and large imine substituents. This insight guided the design of an improved catalyst **37d**, possessing remarkable reactivity and selectivity profiles (Scheme 8).[42] The utility of these materials is not confined to the Strecker reaction; they have also found application in other imine-addition processes, such as the asymmetric Mannich,[43,44] imine hydrophosphonylation[45] and aza Baylis–Hillman reactions.[46]

Interestingly, it has recently been shown that considerable structural simplification of the **37a–e** is possible without an accompanying loss of enantioselectivity.[44] This allows a certain latitude for fine-tuning of catalyst structure to suit the requirements of individual reaction classes, and has led to the development of simplified (yet superior to **37a–e**) analogues **44** and **45** for the efficient promotion of the asymmetric Pictet–Spengler,[47] acyl Mannich[48] (catalyst **44**) and nitro Mannich (aza Henry catalyst **45**)[49] reactions (Scheme 9).

Nagasawa and co-workers[50] have applied chiral diaryl thiourea derivatives to catalysis of the asymmetric Baylis–Hillman reaction. *trans*-1,2-Diaminocyclohexane-derived bis-thiourea **51** promoted the *N,N*-4-dimethylaminopyridine (DMAP)-mediated addition of cyclohexenone to a range of activated aldehydes. While aromatic aldehydes proved to be generally mediocre substrates in terms of selectivity, the analogous aliphatic electrophiles were converted to the Baylis–Hillman adducts with moderate to excellent enantioselectivity (Scheme 10). The high selectivity, sense of stereoinduction observed and superiority of **51** over monothiourea analogues prompted the authors to propose that both thiourea moieties are involved in the TS of the rate-determining (and stereocentre-forming) step.[31,32]



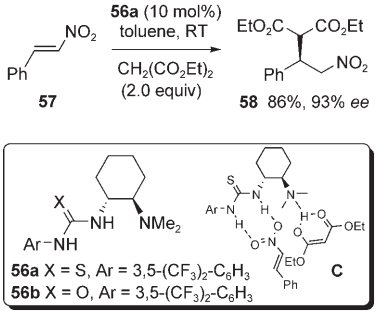
Scheme 10. Thiourea-catalysed enantioselective Baylis–Hillman reactions.

Chiral bifunctional (thio)urea catalysts: The excellent functional group tolerance of the thio(urea) catalysts stems from

their relatively weak enthalpic binding with organic Lewis basic nucleophiles, such as alcohols and amines. As is often the case, the penalty for high (chemo)selectivity can be a general lack of activity relative to benchmark metal(-ion)-based catalyst systems, often leading to long reaction times at temperatures required to attain high enantioselectivity.

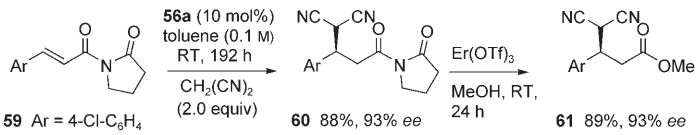
There is undoubtedly a limit to which the strength of the binding interactions between simple (thio)urea catalysts and electrophilic substrates can be modulated by catalyst design without either sterically hindering substrate recognition or adversely effecting catalyst stability. Recently the concept of exploiting the high functional group tolerance of these materials by incorporating a Lewis basic nucleophile-activating functionality into the catalyst structure has begun to be explored. Such bifunctional catalysts mimic natural enzymatic systems by activating both electrophile and nucleophile simultaneously,[51] allowing scope for significantly improved catalytic activity, and perhaps, more importantly, allow a greater degree of stereocontrol over the addition event. The majority of these prototype systems represent a hybrid strategy that borrows heavily from the design principles set down in the seminal work of Curran, Jacobsen and Schreiner outlined above involving the installation of readily tunable aromatic functionality (to maximise the catalyst's rigidity and hydrogen-bond-donating ability) at one (thio)urea nitrogen atom, and chiral (in this case Lewis basic) functionality at the other.

The first (thio)urea-based bifunctional catalyst reported was tertiary amine **56a** (Scheme 11), which was capable of the efficient promotion of the addition of malonate esters to β-nitrostyrenes with excellent enantioselectivity.[52] The authors found that both the tertiary amine and the thiourea moieties were requisite for efficient and selective catalysis, and posited a model to explain the sense of stereoinduction observed that involved deprotonation of the malonate pronucleophile by the tertiary amine followed by the addition of the resultant nucleophile to a single face of the thiourea-bound nitroolefin (**C**, Scheme 11). Subsequent studies demonstrated that a range of β-ketoester pronucleophiles were also compatible with the reaction, allowing the catalyst to be employed at lower loadings of 2 mol% without compromising enantioselectivity.[53] The synthetic utility of this organo-catalysed reaction was later demonstrated by its use as a key step in a stereoselective total synthesis of the medicinally relevant alkaloid (−)-epibatidine.[54]



Scheme 11. Takemoto's bifunctional catalysis of the addition of malonate esters to nitroolefins.

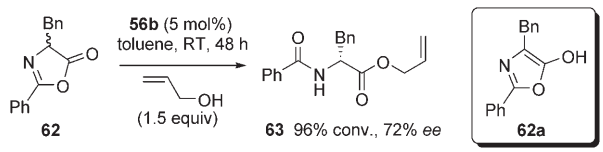
Takemoto and co-workers have also reported the enantioselective addition of the highly acidic malononitrile to α,β-unsaturated imides, such as **59**, catalysed by **56a** (Scheme 12).[55] The lability of the imide moiety is advantageous; for example, **60** could be readily methanolysed to give **61** in high yield (Scheme 12), thereby providing access to the products from addition to the corresponding α,β-unsaturated esters. Presumably, this general strategy could also be utilised to prepare the corresponding aldehydes and carboxylic acids. It is of interest that while malononitrile is an excellent pronucleophilic substrate in the addition to α,β-unsaturated imides, it gave poor selectivity in the addition to nitroolefins, while the best 1,3-dicarbonyl substrates for the nitroolefin addition reaction (vide supra) gave no reaction with α,β-unsaturated imides.[55]



Scheme 12. The addition of malononitrile to **59** catalysed by bifunctional organocatalyst **56a**.

Catalyst **56a** has also been used to promote asymmetric nitro Mannich (aza Henry) reactions between *N*-phosphinoyl[56] and *N*-Boc imines,[57] as well as simple nitroalkanes. While yields of adduct using a variety of aromatic aldehyde-derived imines were uniformly good using either protecting group, higher enantioselectivity was obtained in reactions involving *N*-Boc imine substrates.[57]

Berkessel et al. have successfully applied **56a** and its urea derivative **56b** to the dynamic kinetic resolution (DKR) of racemic azalactones. For example, the addition of allyl alcohol to the (DL)-phenylalanine-derived azalactone **62** catalysed by **56b** gave amide **63** in good conversion and enantioselectivity (Scheme 13). Given that tertiary amines alone gave only very slow conversion of azalactones, while urea derivatives without the tertiary amine functionality were inactive catalysts, it seems possible that the catalyst mode of action involves binding of the substrate to **56b** (which was demonstrated qualitatively by ^{1}H NMR spectroscopy in the case of **62**) followed by general base catalysis of the subsequent ring-opening reaction by the dimethylamino group. The tertiary amino moiety also promotes the racemisation



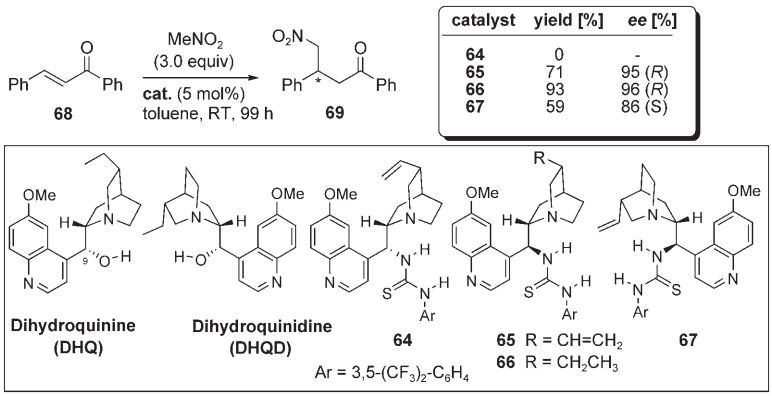
Scheme 13. Dynamic kinetic resolution of azalactones catalysed by **56b**.

of **62** (via the aromatic enol **62a**) to ensure that the faster binding/reacting enantiomer of the racemate is constantly replenished as the reaction progresses.[58] A short time later second-generation *N,N'*-dialkyl(thio)urea derivatives were prepared, the application of which in the DKR of **62** demonstrated that the catalyst aromatic group is not essential for either high activity or selectivity in this reaction.[59]

Very recently, Hedrick et al. have expanded the scope of bifunctional organocatalysis to include polymerisation reactions. The use of 5 mol% of *rac*-**56a** pyrenebutanol ([monomer]/[initiator] = 100) was found to initiate the living polymerisation of lactide with minimal competing transesterification observed. The authors demonstrated that the catalysis was bifunctional in nature,[60] and while it is still early days, it seems likely that in future the synthetic utility of bifunctional catalytic strategies will not be confined to the synthesis of small molecules.

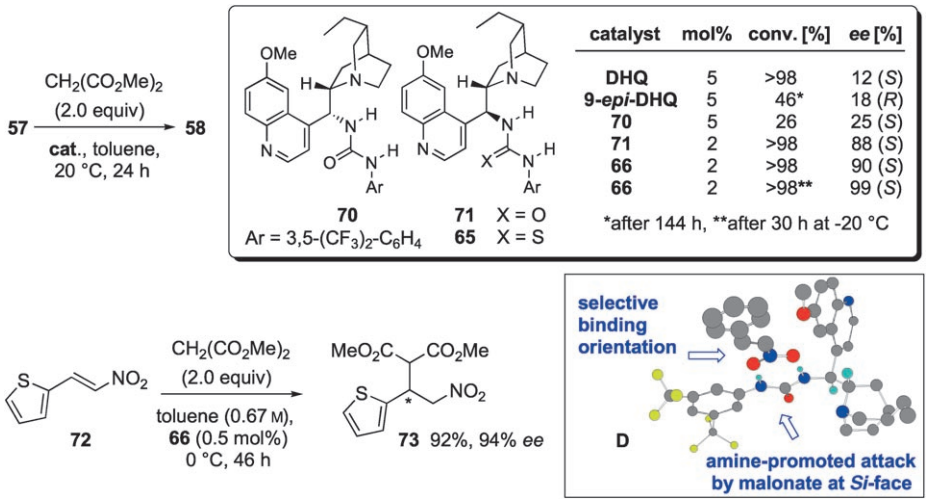
Soós et al. and our group have independently investigated the use of (thio)urea-substituted cinchona alkaloid derivatives as bifunctional catalysts. The cinchona alkaloid backbone incorporates both a basic quinuclidine moiety and a secondary alcohol in a well-defined chiral environment. The substitution of the C-9 hydroxy group for a (thio)urea moiety not only enhances the (bifunctional) catalytic potential of these materials, but also (since secondary alcohol configuration can be readily inverted) allows the influence of the *relative* stereochemistry at the Lewis basic and Lewis acidic groups on both activity and selectivity to be determined. Soós prepared four thiourea-substituted cinchona alkaloid catalysts **64**–**67** (Scheme 14) and evaluated their performance in the asymmetric addition of nitromethane to chalcones.[61] Surprisingly (given the ubiquity of cinchona alkaloid derivatives as ligands/catalysts asymmetric synthesis) the thiourea derivative of "natural" stereochemistry at C-9 (i.e., **64**) was inactive in the addition of nitromethane to **68**, as was quinine itself. However analogues of **64** of inverted stereochemistry at C-9[62] proved both active and highly selective bifunctional catalysts for the same reaction. These results strongly indicate—as one might expect in a bifunctional system—that a relative stereochemical arrangement of the catalyst Lewis/Brønsted acidic and basic groups conducive to their synergistic operation is a prerequisite for chiral bifunctional catalyst design.

Our group prepared a range of (thio)urea-substituted derivatives of **DHQ** and **DHQD** for the asymmetric catalysis of the addition of diethylmalonate to nitroolefins.[63] We found that while neither epimerisation of **DHQ** at C-9 (**9-*epi*-DHQ**, Scheme 15) nor substitution of the C-9 hydroxy group with an *N*-arylurea moiety without epimerisation (catalyst **70**, Scheme 15) improved catalyst activity (the opposite occurred in fact, although a small increase in enantioselectivity was observed), a combination of both modifications results in an extremely active and selective catalyst of "unnatural" stereochemistry at C-9 (**71**, Scheme 15). The same trend was also observed in the corresponding **DHQD**-derived materials. A selectivity model (**D**, Scheme 15) based on these findings and MM2 calculations was put forward to account for both catalyst activity and the sense of stereoinduction observed in the addition of dimethylmalonate to a single face of **57** catalysed by **71**. Thiourea **66** offered a small further increase in both activity and selectivity, and could convert a range of activated and deactivated aliphatic



catalyst	yield [%]	ee [%]
64	0	-
65	71	95 (*R*)
66	93	96 (*R*)
67	59	86 (S)

Scheme 14. Asymmetric bifunctional catalysis of the addition of nitromethane to chalcone.



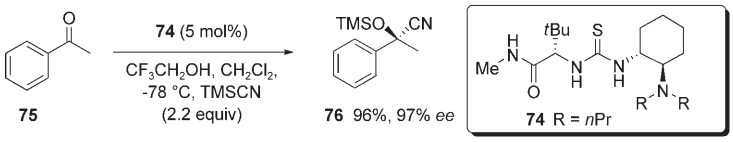
catalyst	mol%	conv. [%]	ee [%]
DHQ	5	>98	12 (*S*)
9-*epi*-DHQ	5	46*	18 (*R*)
70	5	26	25 (*S*)
71	2	>98	88 (*S*)
66	2	>98	90 (*S*)
66	2	>98**	99 (*S*)

*after 144 h, **after 30 h at -20 °C

Scheme 15. Bifunctional catalysis of the addition of dimethylmalonate to nitroolefins.

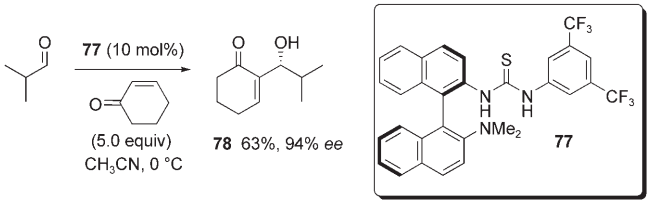
and aromatic nitroolefins with good to excellent yield and enantioselectivity. The high activity of these catalysts (which are on a par with benchmark metal-based systems[64]) is highlighted by the smooth transformation of **72** into **73** promoted by 0.5 mol% **66** under mild reaction conditions with excellent yield and selectivity. Very shortly after this report, Dixon et al. disclosed similar results using a cinchonine-derived analogue of **67** (at loadings of 10 mol%).[65]

Very recently, Jacobsen and co-workers modified the structural backbone of Schiff-base catalysts **37a–e** to incorporate tertiary amino functionality. Thiourea **74** was demonstrated to be optimal for the highly efficient and selective catalytic asymmetric cyanosilylation of ketones. In the presence of low catalyst loadings and a stoichiometric amount of 2,2,2-trifluoroethanol additive impressive levels of efficiency and selectivity were obtained if the ketone substrate bore an sp^2-hybridised substituent (Scheme 16).[66]



Scheme 16. Bifunctional organocatalytic cyanosilylation of ketones.

An axially chiral thiourea-based bifunctional catalyst has been recently developed by Wang et al. for the promotion of challenging enantioselective Baylis–Hillman reactions. Compound **77** was found to promote the addition of cyclohexenone to a range of aromatic and aliphatic aldehydes with good to excellent yields and selectivity (Scheme 17).[67] The same catalyst was later found to also catalyse the addition of efficient and enantioselective addition of 2,4-pentadione to (*E*)-β-nitrostyrenes.[68]



Scheme 17. Bifunctional catalysis of asymmetric Baylis–Hillman reactions.

Summary and Outlook

It is just over a decade since the disclosure of the first (thio)urea-based catalyst. From humble beginnings (in terms of catalyst activity) it has now been demonstrated that these materials can serve as conformationally rigid catalyst templates that are tunable from both steric and electronic standpoints to a considerable degree, and which when suitably substituted can efficiently transfer stereochemical information to the products of a diverse array of addition reactions. The realisation that (thio)ureas are wholly compatible with a range of Lewis bases has allowed the development of bifunctional systems, which while adding an extra level of complexity to catalyst design, provides new opportunities regarding not only the rate-enhancing simultaneous activation of both the electrophile and nucleophile, but also in terms of allowing greater control over the chiral environment in which they encounter one another. We are now moving into an exciting phase of this young field beyond what could be described as "proof-of-concept", as successive bifunctional catalyst generations begin to approach (on a reaction-by-reaction basis) the activity and selectivity profiles more often associated with metal-based systems. It seems likely that the studies outlined above will stimulate further research towards the design of robust, readily assembled, environmentally benign, highly active and selective metal-free organocatalysts for an ever-widening range of challenging and synthetically important processes.

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