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**PERSPECTIVE**

# Trichlorosilane mediated asymmetric reductions of the C═N bond

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Chiral amines are key components in numerous bioactive molecules. The development of efficient and economical ways to access molecules containing this functional group still remains a challenge at the forefront of synthetic chemistry. Of the methods that do exist, the trichlorosilane mediated organocatalytic reduction of ketimines offers significant potential as an alternative strategy. In this perspective, we wish to highlight the progress made in the past decade in this field and offer a direct quantitative comparison to transition-metal mediated process.



## 1. Introduction

The asymmetric reduction of a ketimine (C═N bond) represents a powerful and practical route toward the synthesis of enantiomerically enriched amines. Whilst there has been much interest in the transition metal mediated reduction of such substrates,[1] the analogous organocatalytic process has seen far less development despite offering several advantages over the metal-catalysed counterpart, including the avoidance of pressurised hydrogen gas and issues associated with use and recovery of transition-metal species. Amongst the organocatalysed reductions of ketimines that have been developed, those that use trichlorosilane as the reductant have seen substantial interest in recent years. Trichlorosilane is a colourless, readily available material primarily manufactured and used in the organosilicon industry. The reagent accounts for 75% of the world's production of polycrystalline silicon through the Siemens process, in which high purity silicon rods are exposed to trichlorosilane at elevated temperatures, leading to decomposition of the trichlorosilane and additional silicon to be deposited onto the rods.[2] Within synthetic chemistry, in order to be an effective reducing agent, trichlorosilane needs to be activated through coordination of a Lewis base, the result of which induces formation of a hexacoordinate hydridosilicate complex, believed to be the reductant. Should the Lewis base be chiral, then the potential exists for stereoselective hydride delivery and thus access to a range of synthetically important enantiomerically enriched species, including chiral amines.

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**Simon Jones**

*Simon Jones received his first degree from the University of Southampton followed by a Ph.D. at the University of Wales, Cardiff. After postdoctoral positions at Arizona State University and the University of Oxford, he took up his first academic appointment at the University of Newcastle upon Tyne in January 1999 and moved to the University of Sheffield in June 2003. Dr Jones' research group work on developing new ways to prepare small molecule chiral building blocks, using a combination of chiral auxiliary and catalyst strategies, as well as using synthetic methods to enable new approaches for the imaging of biological processes.*

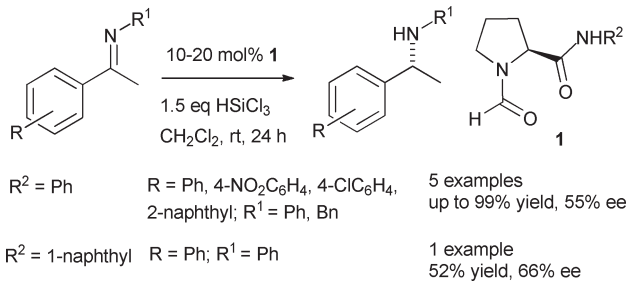
**Christopher Warner**

*Christopher Warner was born in Leicester, U.K. in 1987. Chris received his undergraduate degree from the University of Sheffield, spending the third year studying at the University of Queensland, and completed his undergraduate project in 2009 working on developing methodology for the synthesis of butenolides with Dr Simon Jones. He started his Ph.D. studies at the University of Sheffield in 2009 in Dr Jones' laboratory on the development of new classes of organocatalysts and their application in asymmetric synthesis.*

It is hoped that this brief review will provide the reader with an insight into the current literature, and where available, a rationale into the transition state models proposed to account for the observed stereoselectivity.[3] The perspective will also offer for the first time a quantitative comparison between the transition metal mediated and organocatalytic reduction of a ketimine and hence demonstrate the power of this relatively new methodology.

## 2. Trichlorosilane mediated C=N reduction

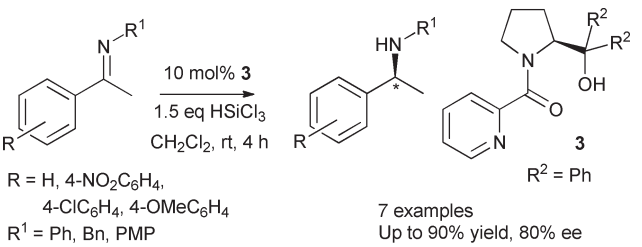
In 1996, Kobayashi and co-workers demonstrated that DMF could activate trichlorosilane toward the reduction of a variety of organic substrates.[4] This system reduced aldehydes, aldimines and ketones, albeit under different conditions. $^{29}$Si NMR spectroscopic studies identified the *in situ* formation of a six-coordinate silicon intermediate leading to the hypothesis that DMF was acting as a Lewis base coordinating to the silicon atom and activating the silane toward the reduction. Five years later, the first enantioselective reduction of a ketimine using a chiral Lewis base was reported by Matsumura.[5] The proline-derived chiral formamide **1** facilitated the reduction of a variety of *N*-phenyl and benzyl protected aryl-methyl ketimines with excellent yield and moderate enantioselectivity (Scheme 1). The 1-naphthyl derived catalyst showed slightly enhanced selectivity, but reduced catalytic activity.




**Scheme 1**

In order to rationalise the (*R*)-configuration of the resulting amines, the authors proposed two transition state models **2a** and **2b** (Fig. 1), where adverse steric interactions would exist between the aromatic rings of the substrate and catalyst in model **2b**.

The same group also identified a series of *N*-picolinoylpyrrolidine derived catalysts capable of inducing high enantioselectivity.[6] A detailed structure/activity relationship demonstrated the necessity for a 2-picolinoyl derivative with the corresponding 3- and 4-analogues displaying significantly lower catalytic activity. The authors also noted that a hydroxyl group was pivotal for high enantioselectivity, as replacement with a hydrogen atom or a Lewis basic ester or amide moiety resulted in a pronounced reduction in the observed enantioselectivity. The optimum catalyst **3** ($R^2$ = Ph) was used for the reduction of a representative set of *N*-aryl acetophenone derivatives, in addition to examples of *N*-benzyl, and α-iminoester β-enaminoester substrates, all in good yield and enantioselectivity (Scheme 2).




**Scheme 2**

The key requirement of the hydroxyl group to induce high enantioselectivity led Matusmura to hypothesise the existence of a hydrogen bonding interaction between the tertiary alcohol and the ketimine in transition state models **4a** and **4b**. It was proposed that steric interactions between the phenyl groups of the catalyst and the protecting group of the ketimine would disfavour transition state **4b**, and thus lead to the (*S*)-configured amine (Fig. 2).

Work from the same laboratories prepared a related catalyst **5**. This was shown to exhibit broadly similar activity and selectivity with a small variety of *N*-aryl acetophenone derived imines (Scheme 3).[7]

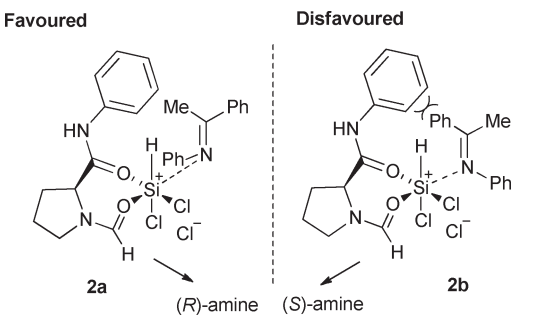



**Fig. 1** Matsumura's proposed transition state model for catalyst **1**.

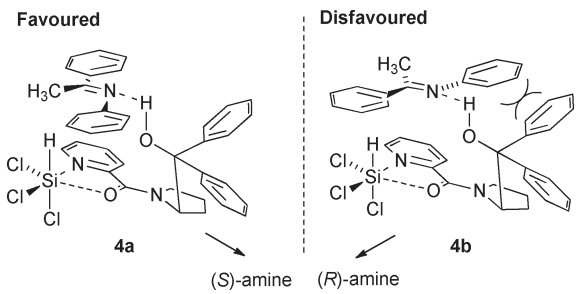
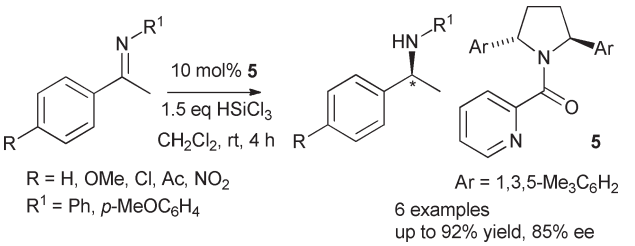
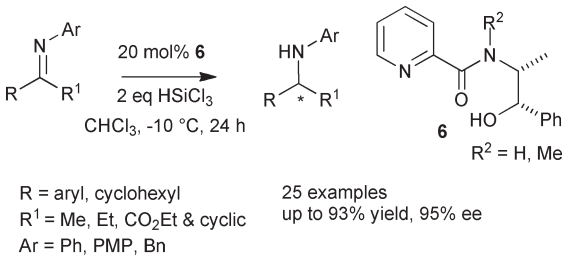



**Fig. 2** Matsumura's proposed transition state model for catalyst **3**.



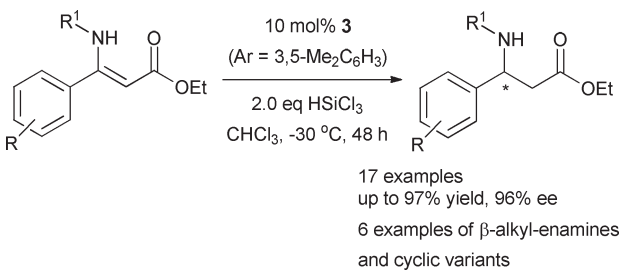

**Scheme 3**

The picolinoyl catalyst sub-class was extended by Zhang *et al.* using a number of chiral amino-alcohols.[8] Two sets of catalyst were investigated, one with a secondary amide linkage, the other with a tertiary amide. Examination of the effect of having either one or two pre-installed stereogenic centres led the authors to conclude that the stereodirecting group adjacent to the amino group was essential for reactivity, although this site was very sensitive to the nature of this group; methyl provided better results than phenyl. Also crucial was the role of the amide *N*-methyl group, since this catalyst series consistently delivered better enantioselectivities than the series without. This could be due to a chiral-relay effect, with the pre-installed stereogenic centres inducing an additional stereodirecting element, although the authors did not speculate upon this. Once again, the role of a terminal hydroxyl group was shown to be essential for high selectivity. Catalyst **6** was shown to affect the reduction of a wide variety of ketimines in generally good yield and enantioselectivity (Scheme 4).




**Scheme 4**

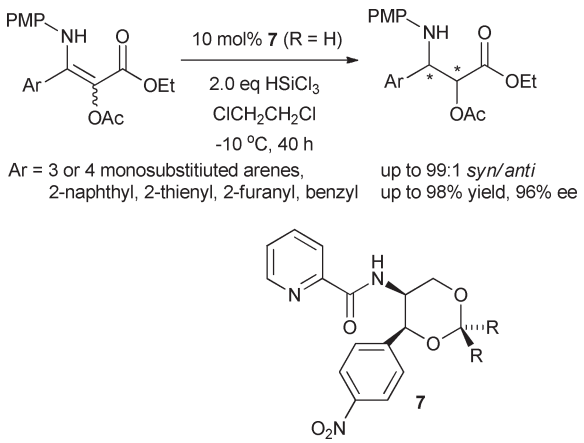
This group were also the first to report an in-depth study of the enantioselective reduction of a range of β-enamino esters.[9] Derivatives of catalyst **3** ($R^2$ = Ph, *p*-$MeC_6H_4$, 3,5-$Me_2C_6H_3$) displayed good activity and enantioselectivity, whilst 4-methoxy-prolines were less selective. Catalyst *ent*-**6** ($R^2$ = Me) led to modest selectivity but with a reversal of the sense of enantioselectivity. The best catalyst **3** ($R^2$ = 3,5-$Me_2C_6H_3$) was taken on for reaction optimisation, the optimal conditions being 10 mol% catalyst at -30 °C for 48 h. These conditions were applied to 24 substrates; those with a variety of β-aryl *N*-aryl enamino-esters were generally reduced in excellent yield and enantioselectivity, but some β-alkyl enamino-esters were less well tolerated (Scheme 5).




**Scheme 5**

To account for the experimentally observed enantioselectivity, the authors proposed that the reaction proceeds *via* reduction of the imine tautomer, outlining two transition state models analogous to those presented by Matsumura (Fig. 2), with the added stabilisation of arene–arene interactions between the pyridine ring and the β-aryl group of the substrate.

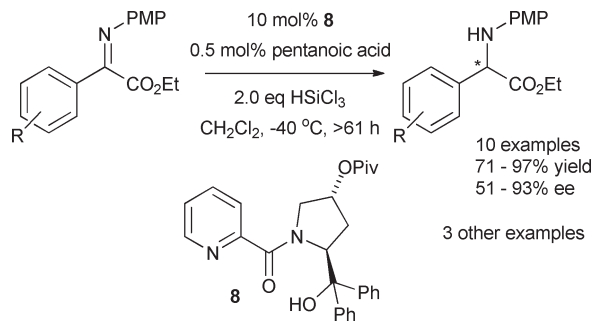
More recent studies from this group have extended the substrate scope to include α-acetoxy-β-enamino esters using acetal-based picolinoyl catalysts **7** (Scheme 6).[10] Other than the commercial availability of the amino-alcohol required to make this catalyst, the authors do not comment on the rationale for their choice of catalyst, or whether other catalysts could be employed. In addition, use of the catalyst **7** (R = H) was essential for ensuring that diastereoselectivities were greater than 90%. A wide range of *N*-aryl β-aryl and heteroaryl substrates were reduced in good yield (up to 98% yield) and selectivity (up to 99 : 1 *syn* : *anti* and 96% ee). A single example of a β-alkyl substrate provided the only enantioselectivity less than 77% (41%). Interestingly, Zhang noted the sluggish nature of the reaction in dehydrated solvent, suggesting that trace quantities of water in un-treated commercial solvent reacted with trichlorosilane to generate a Brønsted acid that promoted tautomerisation of the enamine to the reactive imine tautomer.



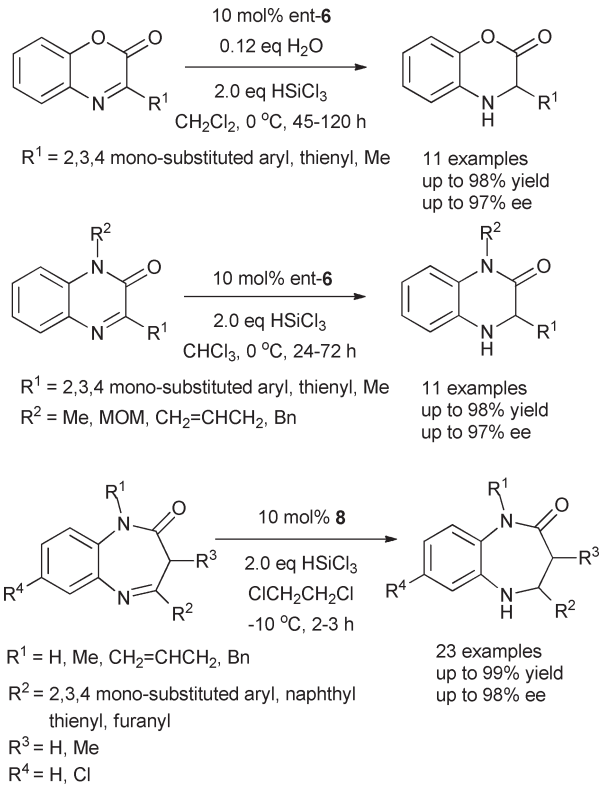

**Scheme 6**

The authors have also demonstrated the hydrosilylation of α-imino esters with picolinoyl-proline derived catalysts.[11] Nearly all of the 17 catalysts screened displayed good to excellent activity, but varied in their selectivity. The *O*-pivaloyl *trans*-4-hydroxy-L-proline **8** derivative was chosen for further optimisation, with low temperatures and prolonged reaction times being essential. Also crucial for efficiency was the addition of small quantities of pentanoic acid (Scheme 7). The authors demonstrated the applicability on substrates that led to a range of substituted phenylglycine derivatives, and three other substrates, including one aliphatic imine.

The catalysts developed by this group have also been used for the stereoselective synthesis of chiral heterocyclic building blocks such as dihydrobenzoxazinones and dihydroquinoxalinones,[12] and dihydrobenzodiazepinones,[13] using catalysts *ent*-**6** ($R^2$ = Me) and **8**, respectively (Scheme 8). Noteworthy from these reports are the comments on the role of additives; benzoxazinone substrates require water to increase the yield and selectivity, while quinoxalinones and benzodiazepinones do not.



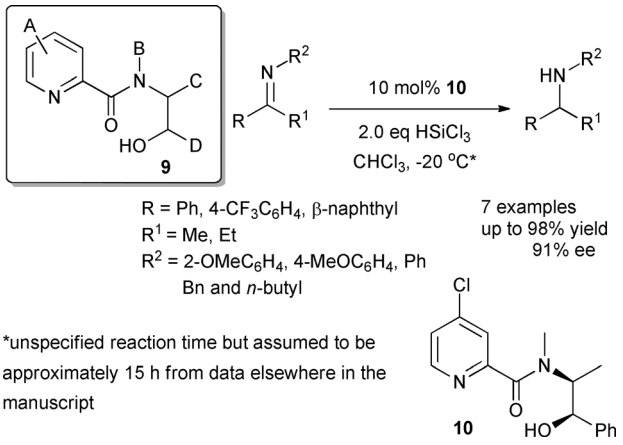

**Scheme 7**



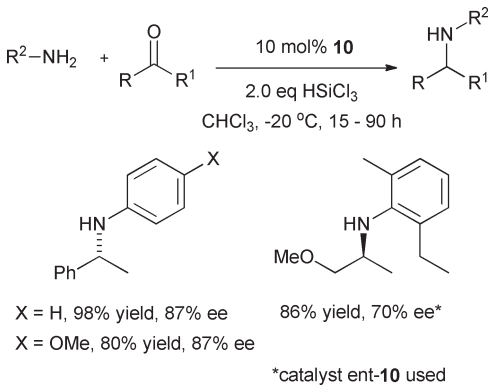

**Scheme 8**

Benaglia has reported an extensive exploration of picolinoyl derived catalysts of general type **9**, the optimum being a 4-chloropyridine derivative **10** of Zhang's catalyst **6** ($R^2$ = Me) (Scheme 9).[14] This catalyst showed enhanced reactivity and enantioselectivity and facilitated reduction of (1-phenylethylidene)-phenylamine with 1 mol% catalyst loading. In addition, excellent reactivity and selectivity was observed using 10 mol% loading towards the reduction of a representative class of *N*-aryl aryl-alkyl ketimines, as well as *N*-alkyl ketimines of acetophenone and a cyclic analogue. Transition states models to account for the observed selectivity were proposed that were analogous to those put forward by Matsumura and Zhang.

Perhaps one of the most important disclosures in this work was the ability to affect the asymmetric reductive amination with un-activated ketones. Three examples were presented with catalyst **10** being demonstrated to be superior to catalyst **6**, delivering products in excellent yields and moderate to excellent selectivity with 10 mol% catalyst (Scheme 10).




**Scheme 9**



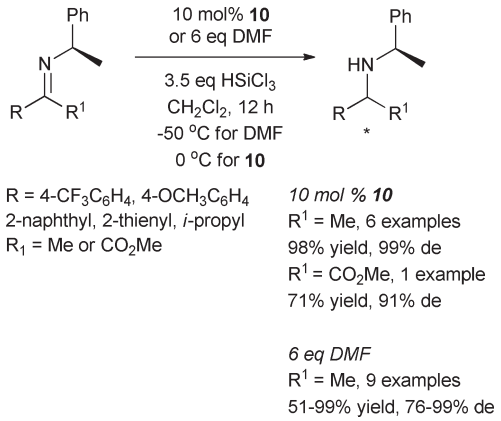

**Scheme 10**

To improve upon the selectivity of the ketimine reduction process further, the hydrosilylation of a range of substrates derived from (*R*)-1-phenylethylamine were examined.[15] Optimisation of the reaction conditions identified that 10 mol% of catalyst **10** facilitated complete diastereoselective reduction of a range of electronically different acetophenone derived ketimines, as well as α-imino esters. This methodology was also applicable for the complete diastereoselective reduction of a dialkyl imine, with the imine derived from *iso*-butyl ketone being reduced in 98% yield and 99% de. The authors also found that comparable levels of diastereoselectivity were attained through use of DMF as the catalyst, albeit with the need for a large excess of the achiral Lewis base at lower reaction temperature (Scheme 11).[16]

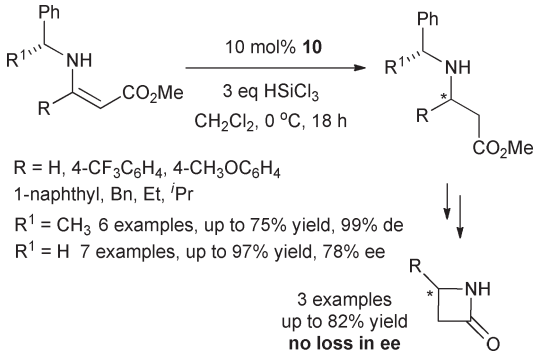
Benaglia has also used catalysts of type **10** to reduce a representative series of *N*-benzyl and *N*-α-methylbenzyl β-enaminoesters (Scheme 12).[17] In each case, enhancement of the enantioselectivity was observed when using substrates with the additional stereodirecting group, even with β-alkyl enamines, although the enantioselectivity was lower than for β-aryl enamine substrates (~75% ee *vs.* 99% ee, respectively). Three of the β-amino acids products were then transformed to enantiomerically enriched β-lactams.

A second class of chiral picolinamides derived from enantiomerically pure chiral diamines has also been reported by this group to be effective toward the reduction of *N*-aryl and *N*-alkyl ketimines.[18] Screening of a number of analogues identified the

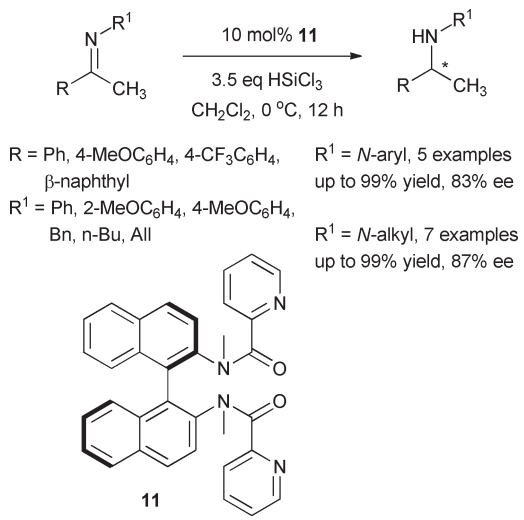



**Scheme 11**



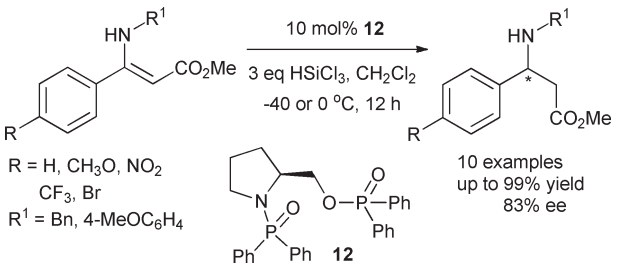

**Scheme 12**

methylated *bis*-picolinamide **11** as the most effective catalyst, with the resulting *N*-aryl and *N*-alkyl amines being isolated in excellent yield and moderate to good enantioselectivity (Scheme 13). Whilst no mechanistic details or models for the selectivity were reported, the authors noted that methylation of both amide-nitrogen atoms was pivotal for high enantioselectivity. These catalysts were also evaluated for the reduction of other substrates[15,17] but were not as effective as catalyst **10**.



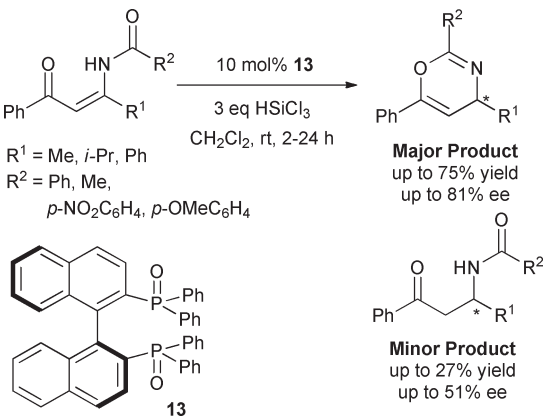

**Scheme 13**

Most recently, Benaglia has disclosed the potential of a range of chiral phosphinamides derived from proline to promote the hydrosilylation of β-enamino esters (Scheme 14).[19] In nearly all cases, catalyst **12** was shown to be the most effective toward the reduction, with a range of electron rich and electron deficient substrates reduced in up to 99% yield and 83% ee. The selectivity of the process could be improved further by adopting the double stereodifferentiation approach employing an additional α-methylbenzylamine stereodirecting group. No mechanistic details or an explanation for the stereochemical outcome of the reduction were reported.




**Scheme 14**

Benaglia's group was not the first to describe the use of phosphorus-derived Lewis base catalysts. The synthesis of enantioenriched 4*H*-1,3-oxazines has been reported through the trichlorosilane mediated reductive cyclisation of *N*-acylated-β-amino enones (Scheme 15).[20] Examination of a number of phosphine oxide organocatalysts identified BINAPO **13** as the most selective catalyst, with the oxazine derived from 3-amino-1-phenylbutane-1,3-dione being isolated in 56% yield and 71% ee. Somewhat surprisingly, the expected product of the reaction, the acyclic *N*-acylated β-amino ketone was only isolated in 13% yield and 4% ee. From the limited examples reported, it was noted that the absolute configuration of this acyclic product was opposite to those of the oxazine and thus suggested the existence of two independent mechanistic pathways. The authors proposed conjugate reduction of the *N*-acylated β-amino enone and ensuing cyclisation of the enolate, eliminating $HOSiCl_3$, would afford the observed oxazine. The uncyclised minor product was believed to originate from the 1,2-reduction of the *N*-acyl imine generated *via* equilibration of the enamide.

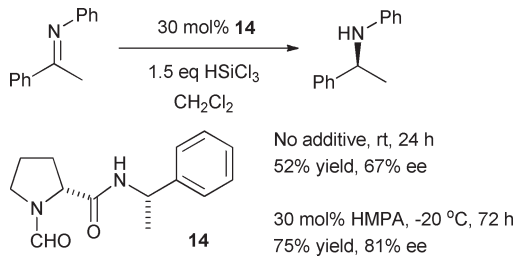



**Scheme 15**

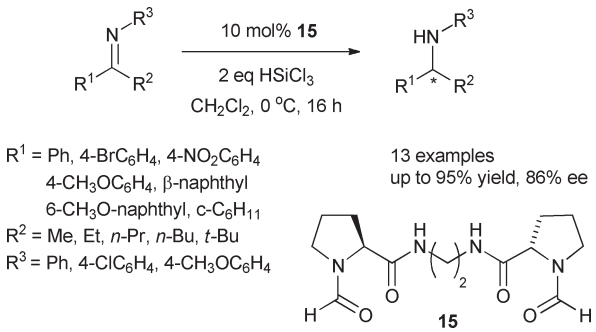
Most recently, methodology to prepare γ-amino alcohols has been reported by the same group by a reductive aldol-like process catalysed by chiral phosphine oxides and using trichlorosilane as the reductant source.[21] In spite of the high diastereoselectivity observed, attempts at introducing an enantioselective process only sought to induce low to moderate levels of enantioselectivity (up to 40% ee), again using BINAPO **13**.

In 2007, Tsogoeva reported the chiral formamide **14** as a moderately active and selective catalyst for the synthesis of *N*-phenyl-1-phenylethylamine from reduction of the corresponding ketimine.[22] Of particular interest are the need for high catalyst loadings (30 mol%) compared to Matsumura's catalyst **1**, the essential requirement of an additional stereogenic centre to ensure high selectivity, and the use of HMPA as an additive that enhanced both reactivity and selectivity. No rationale was put forward for the role that such additives might play (Scheme 16).

In the same year, Sun reported the $C_2$-symmetric chiral tetramide **15** derived from proline to be effective toward the reduction of a representative set of *N*-aryl ketimines (Scheme 17).[23] Crucial for high activity and selectivity was the length of the diamine, with any deviation significantly eroding the performance of the catalysts. Whilst no mechanistic data was reported, the authors proposed two transition state models with heptacoordinate silicon species to account for the synergistic effects of the two diamide units and the absolute configuration of the amine product obtained (Fig. 3).




**Scheme 16**




**Scheme 17**

The authors were also the first to report the organocatalytic reduction of aliphatic ketimines.[24] Diastereomeric pipecolinic acid derivatives bearing three stereogenic centres were screened with the optimum catalyst being found to be acetate **16**. The stereogenic centre at the β-position was found to be the most crucial for obtaining high levels of stereoselectivity. Catalyst **16**

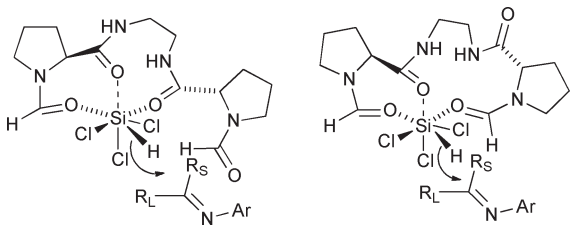
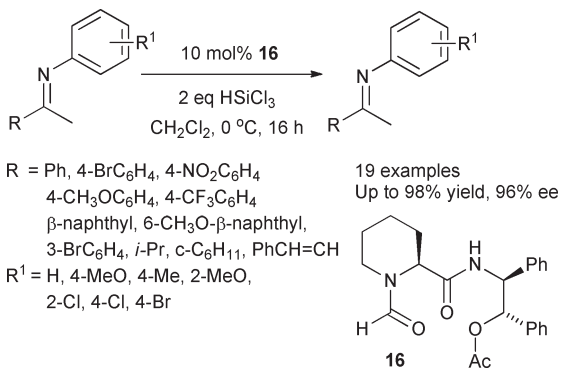


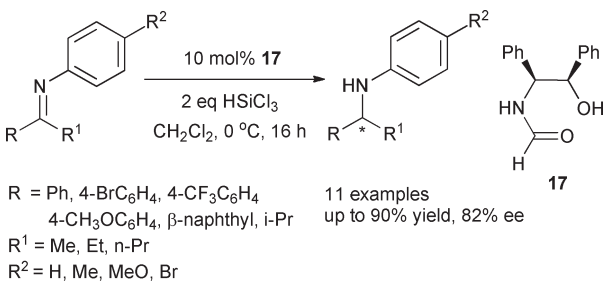
**Fig. 3** Sun's proposed transition state model for catalyst **15**.

was shown to reduce a diverse range of ketimines in excellent yield and enantioselectivity (up to 98% yield, 96% ee). This work was also the first to demonstrate the independence of ketimine geometry on the selectivity of the reaction, thus implying a substrate equilibration pathway prior to reaction (Scheme 18).




**Scheme 18**

A related catalyst bearing a methyl ether instead of an acetate was also shown to behave in a similar manner.[25] Further investigation found that remarkably simple formamides could act as catalysts, the best being alcohol **17**, which was found to reduce a number of *N*-aryl ketimines in yields ranging from 62-90% and enantioselectivities from 67-82% ee (Scheme 19).[26] The only exception to this was the ketimine derived from isobutyroacetophenone, which was reduced in 31% ee.




**Scheme 19**

Ensuing work demonstrated that catalyst **18** based upon a piperazine scaffold could reduce a very similar series of ketimines under similar conditions as catalyst **16** (Scheme 14).[27] However, catalyst **18** was significantly more sensitive to the nature of the nitrogen protecting group, with substituted aromatics and benzyl groups leading to serious erosion in yield and

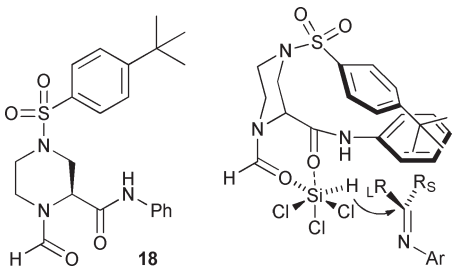
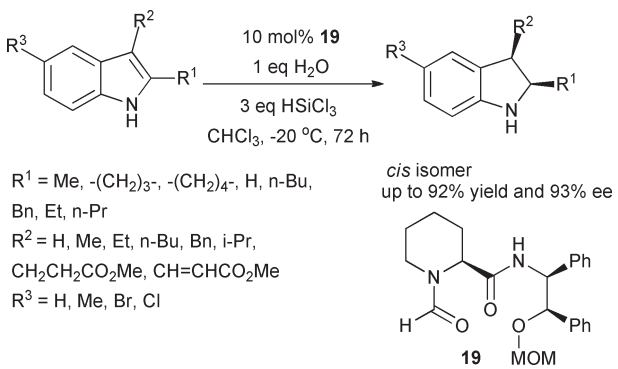


**Fig. 4** Catalyst **18** and corresponding proposed transition state model.

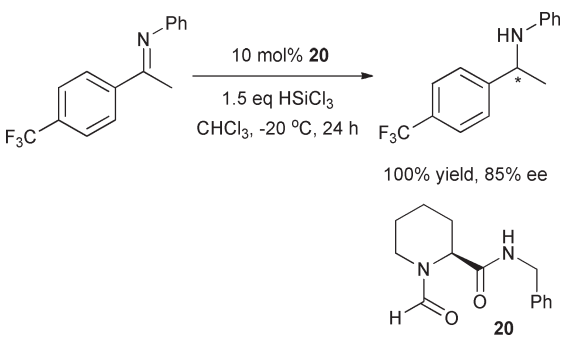
selectivity. A transition-state model was proposed to account for the observed selectivity (Fig. 4).

Most recently, Sun has shown that chiral pipecolic acid catalysts can affect the highly diastereo- and enantio-selective reduction of 2,3-substituted indoles (Scheme 20).[28] Crucial to this methodology was the addition of one equivalent of water which was postulated to generate HCl necessary to facilitate isomerisation of the indole to the reactive iminium species. Interestingly, picolinoyl hydroxy-proline catalysts proved to be more effective for the reduction of substrates bearing a large group at the 2-position.



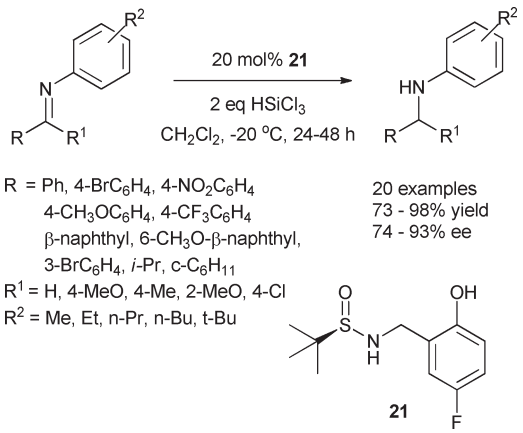

**Scheme 20**

Collados has also developed a series of 13 pipecolic acid derivatives as catalysts for this process.[29] All were evaluated in the reduction of a single *p*-trifluoromethylphenyl ketimine, with catalyst **20** providing the best yield and enantioselectivity (Scheme 21).




**Scheme 21**

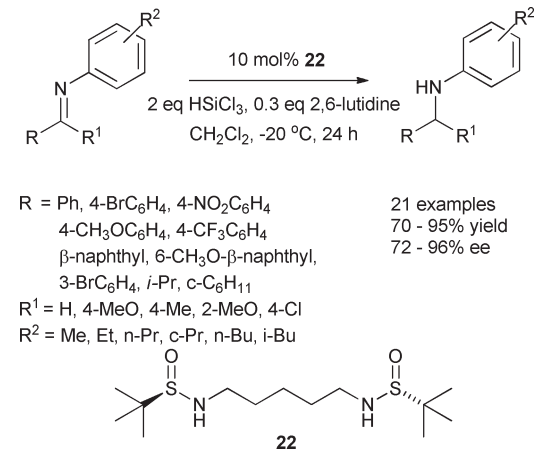
Sun has also developed a series of *S*-chiral sulfinamide organocatalysts (Scheme 22).[30] A number of catalysts were easily prepared from commercially available (*R*)-*t*-butylsulfinamide and evaluated in the reduction of a benchmark substrate. Pivotal to the activity of the optimised catalyst **21** was the position of the phenol moiety. Movement to either the *meta* or *para* position had a detrimental effect upon the enantioselectivity. The importance of the *ortho* OH group was further supported by the observation that either methylation or acetylation of this group resulted in a dramatic decrease in the reactivity and selectivity of the reaction. Addition of an electron withdrawing group *para* to the phenol moiety resulted in a further increase in selectivity implying that the phenol behaved as a Brønsted acid rather than a coordination site for trichlorosilane. From a mechanistic perspective, the authors made several interesting observations; (i) the Brønsted acidic phenol needed to function in an intramolecular role as external additives did not work; (ii) a positive, non-linear effect was observed implying that more than one molecule was observed in the rate-determining step; (iii) that the reaction becomes heterogeneous after initiation. With an optimal catalyst in hand, the authors demonstrated its applicability in the reduction of a standard range of representative substrates.



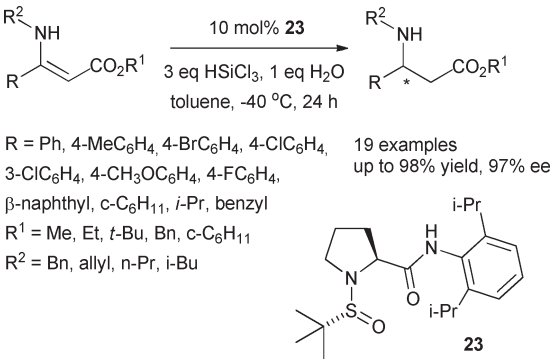

**Scheme 22**

The realisation that catalyst **21** exhibited a non-linear effect led to the development of a series of catalysts incorporating two tethered sulfinamides.[31] Screening of a variety of flexible aliphatic chain lengths as well as more restricted linkers *via* the incorporation of a phenyl ring eventually led to the development of the $C_2$-symmetric catalyst **22**. This catalyst now exhibited a linear effect of the product ee in relation to the catalyst ee, and facilitated the reduction of a variety of *N*-phenyl protected aryl and aliphatic ketimines in up to 96% yield and 94% ee (Scheme 23). Of interest and pivotal to the observed enantioselectivity was the presence of 0.3 equivalents of 2,6-lutidine, any deviation in the amount of additive only led to a detrimental effect upon the selectivity. No explanation however, as to the origins of the effect of the additive were indicated.

Most recently, chiral proline derived sulfinamides **23** have been used for the enantioselective reduction of a range of *N*-alkyl protected β-enamino esters (Scheme 24).[32] In this particular case, the use of Brønsted acidic additives was essential to




**Scheme 23**




**Scheme 24**

obtain high yields of product, with 1 equivalent of water being identified as optimum. The additives were suggested to accelerate the rate of enamine–imine tautomerisation and increase the electrophilicity of the imine tautomer by protonation of the nitrogen atom.

In 2004, Kočovský and Malkov reported the *N*-methyl-(*S*)-valine derived formamide **24** as a highly selective catalyst at 10 mol% loading for the reduction of predominantly *N*-aryl acetophenone-derived ketimines (Fig. 5).[33,34] Significantly, the most active catalyst **24** did not require the conformational restriction provided by a ring-system to be effective, the stereodirecting effects being attributed to a combination of arene–arene interactions, hydrogen bonding, and chiral relay effects of the stereochemically-labile *N*-methyl group. These deductions were made from a comprehensive programme of catalyst synthesis and evaluation with a range of substrates, all of which proceeded in good to excellent yields and selectivities. The authors proposed a transition state model (Fig. 5) in which the silicon atom is coordinated by the two carboxamide groups and a key catalyst-substrate hydrogen bond is responsible for binding of the substrate. The important *N*-aryl groups then participate in π–π stacking between catalyst and substrate.

A minor modification of catalyst **24** resulted in Sigamide® **25**, which was taken forward as the catalyst of choice and is now commercially available.[35,36] A huge number of ketimines were investigated bearing, aryl, heteroaryl and aliphatic substituents

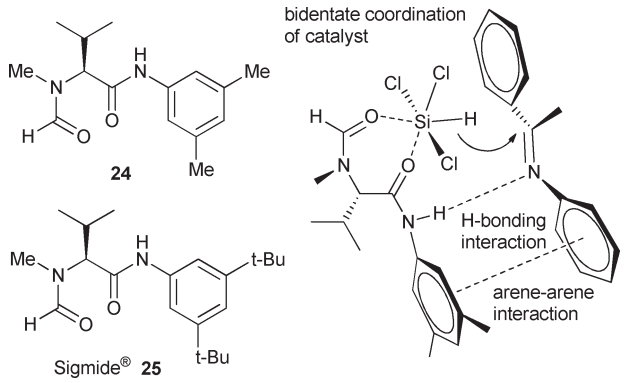
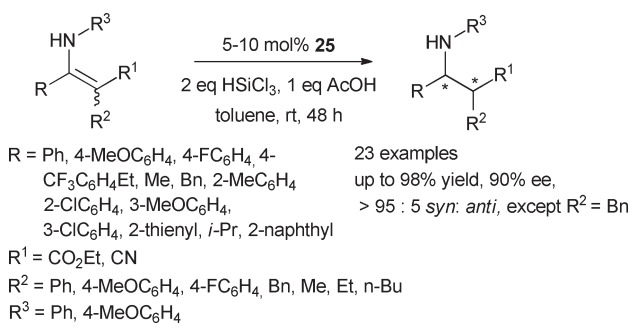



**Fig. 5** Catalysts **24** and **25** and corresponding transition state model.

and in all cases good to excellent levels of enantioinduction were observed, especially when there was an appreciable steric difference between the two groups of the ketimine backbone. Sigamide® **25** has also been used for the reduction of α-chloroketimines,[37] the products of which were transformed into aziridines; the same products were also be generated by a one-pot reductive amination protocol.

Typically Sigamide® **25** can be used at as little as 5 mol% loading with no adverse effects on the reaction outcome. In their 2009 treatise, Kočovský and Malkov also present the most comprehensive discussion as yet published on the likely mechanism of action of these chiral formamide catalysts, noting the independence of ketimine geometry on the product selectivity and the importance of the role of Brønsted acid additives.

Sigamide® **25** has also been shown to be applicable for the reduction of a variety of β-enamino esters and nitriles.[38] The authors noted that pivotal for the activity and selectivity of the catalyst was the introduction of precise quantities (1 equivalent) of acetic acid, it's role being suggested to facilitate tautomerisation of the β-enamino ester/nitrile to the imine form, the active substrate for hydrosilylation. A diverse range of aromatic and aliphatic substituted enamines were well tolerated under the optimised conditions and thus led to the corresponding $\beta^3$ and $\beta^{2,3}$-amino esters being isolated in good yield, high enantioselectivity and in the case of the $\beta^{2,3}$-amino esters complete diastereoselectivity (Scheme 25). In order to account for the latter, a fast equilibrium of the starting achiral enamine and the reactive ketimine was proposed, thus leading to the observed selectivity *via* dynamic kinetic resolution.




**Scheme 25**

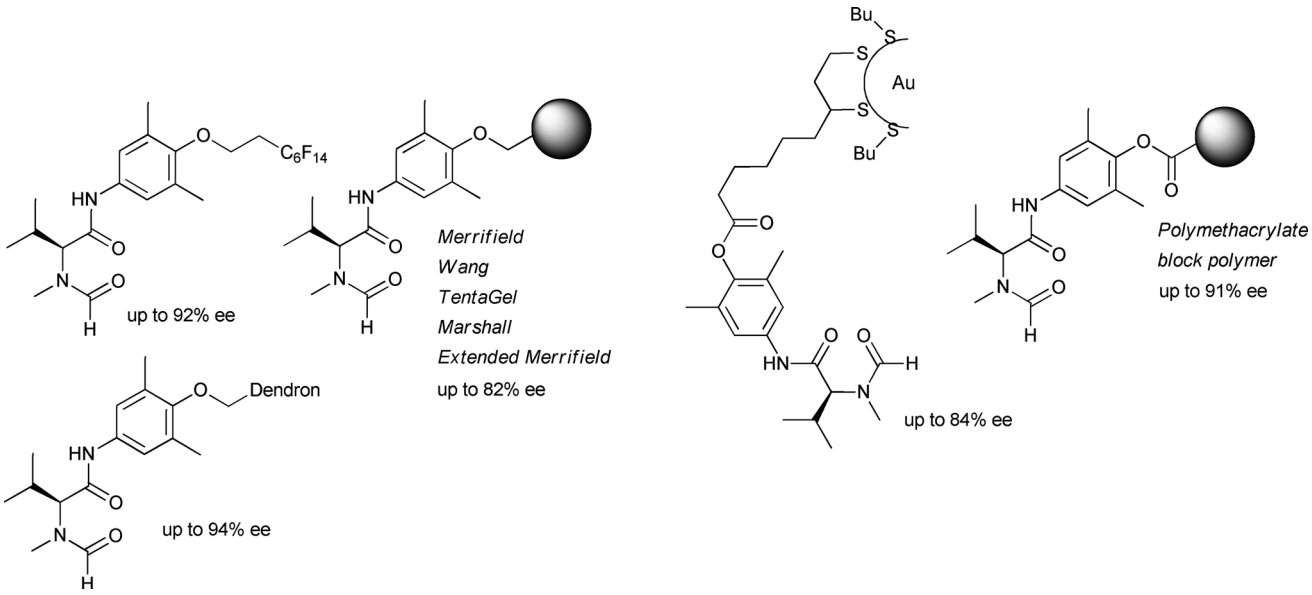
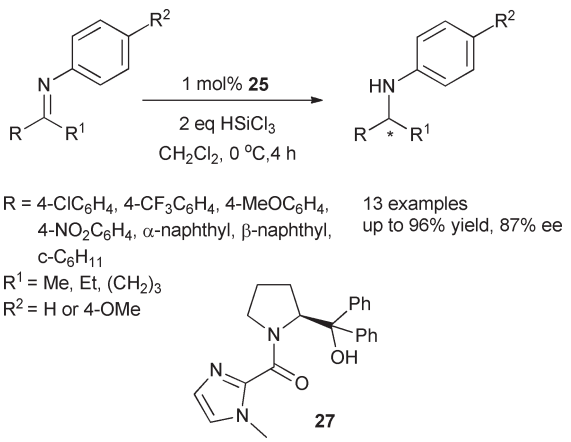



**Fig. 6** Supported and recoverable chiral Sigamide® catalysts.

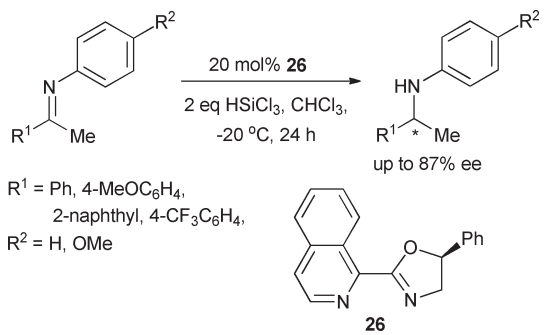
A number of functionalised Sigamide® derivatives have been prepared with groups attached to facilitate the recovery and re-use of the catalysts (Fig. 6). Recovery strategies that have been employed include attachment of the catalyst to fluorinated tags (enabling recovery by filtration through a pad of fluorous silica),[35] traditional polymeric Merrifield, Wang, Tentagel and Marshall resins,[39] gold nanoparticles,[40] block polymethacrylate polymers,[41] and third generation dendrons.[42] In all cases, detailed comparisons were made of the results obtained with the recoverable reagents and those with conventional solution-phase reactions.

The same group have also demonstrated the effectiveness of the isoquinoline containing oxazoline organocatalyst **26** toward the asymmetric reduction of ketimines in up to 87% ee (Scheme 26).[43] A limited range of examples were presented, however, this catalyst is one the few to be able to perform the reduction of both ketimine and ketone substrates in good yield and selectivity.

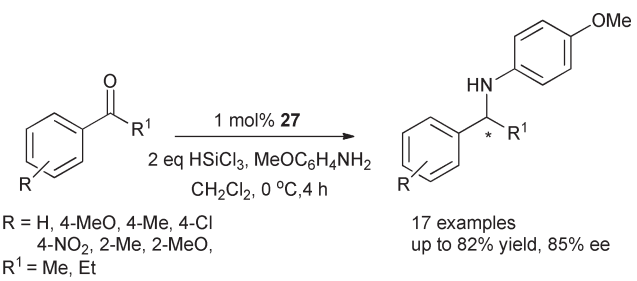
Research from my group has a long standing interest into the development of bifunctional catalysts incorporating an imidazole ring,[44] and as a consequence led us to report a series of such species in 2009, the *N*-methylated imidazole bifunctional catalyst **27** derived from proline being found to be the best to facilitate the highly enantioselective reduction of a variety of ketimines at 1 mol% catalyst loading and short reaction time of 4 h (Scheme 27).[45]




**Scheme 27**




**Scheme 26**




**Scheme 28**

A detailed structure activity relationship identified that akin to the work of Matsumura, a di-aryl tertiary alcohol was pivotal for high enantioselectivity, with phenyl being chosen as best for simplicity of preparation. Removal of the carbonyl group adjacent to the imidazole ring led to a detrimental effect on both the yield and selectivity of the reduction. Investigation into the substrate scope of the catalyst demonstrated that a range of electron rich and electron deficient aryl and aliphatic ketimines as well as substrates that exhibit a *E*/*Z* ketimine geometry could be reduced in excellent yield (up to 96% yield) and enantioselectivity (up to 87% ee).

Most recently, we have reported the highly selective reductive amination of a diverse range of ketones and aryl and aliphatic amines in up to 82% yield and 85% ee at only 1 mol% catalyst

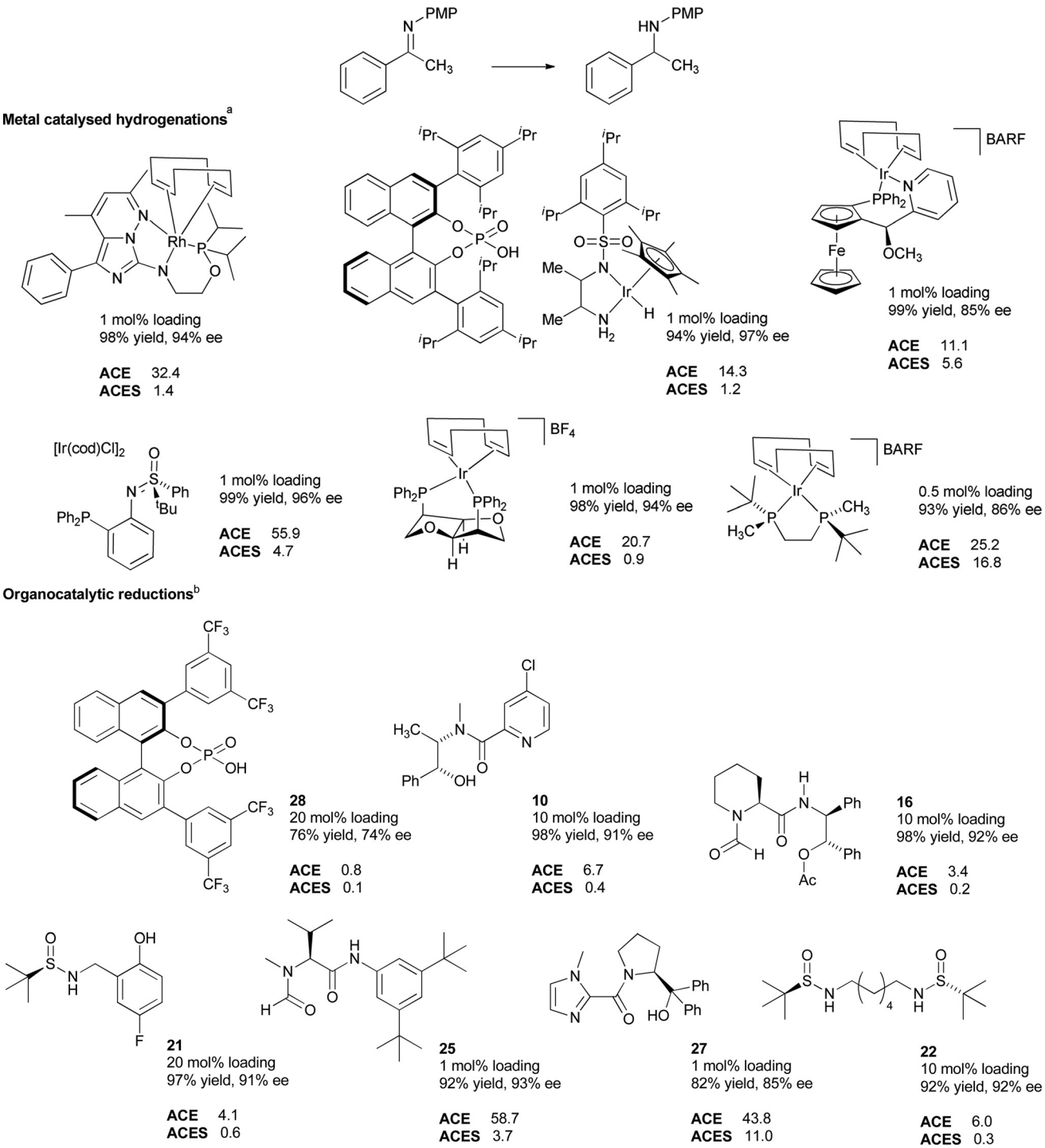



**Fig. 7** Comparison of efficiency of selected enantioselective catalysts. [a] Unless drawn otherwise, all calculations assume [M(cod)Ligand] as the active catalytic species; [b] In all cases trichlorosilane is employed as the reducing agent, except for catalyst **28** which utilises a Hantschz dihydropyridine as the reductant.[50]

loading (Scheme 28).[46] Crucial to the success of this work was optimisation of the *in situ* conditions that facilitated formation of the imine substrate. Introducing TMS-OTf as a Lewis acid additive sought to increase the yield of the reaction but at a deleterious effect to the selectivity of the reduction. However, by simply increasing the concentration of the reaction, an increase in the yield was obtained whilst having no adverse effect upon the selectivity.

In this work we also demonstrated a two-step one pot reductive amination strategy in which the ketimine was formed using microwave irradiation and then subsequently subjected to our reduction conditions. This protocol offers considerable time savings compared to the classical reductive amination protocol (8h 40 min *vs.* 24 h), and extends the substrate scope to include a range of *N*-alkyl amines, providing the desired targets in good yield and enantioselectivity (up to 76% yield, 86% ee).

## 3. Transition metal *vs.* organocatalyst

The increasing focus on the development of environmentally friendly and sustainable manufacturing processes has resulted in catalysis being a pinnacle technology in the 21st century, with demand estimated to be ~850,000 tons in 2007 and is projected to increase by 3.5–4% until 2012.[47] However, in spite of this, no generally accepted measure for the effectiveness of a catalytic reaction exists, with at present the anecdotal phrases "good reaction" and "bad reaction" being the closest to such a description.

Recently, El-Fayyoumi, Todd and Richards have reported a theoretical approach to modelling catalyst efficiency.[48] The ACE (Asymmetric Catalyst Efficiency) calculator proposes that assuming other things are equal, then *a ligand of low molecular mass able to induce asymmetry in a given substrate is more efficient than one of high molecular mass*. The authors propose a straightforward formula as a quantitative means of measuring the effectiveness of a given catalyst:

$$ACE = \frac{MW(product)}{MW(catalyst)} \times \frac{1}{mol\%} \times \frac{ee}{100} \times Yield$$

To allow for a direct comparison between the metal mediated and organocatalysed processes used to prepare chiral amines, the reduction of the *N*-PMP ketimine derived from acetophenone was chosen as the benchmark substrate with a selection of representative catalysts. Using the above formula, the ACE values for both classes of reduction were calculated as well as the corresponding ACES (asymmetric catalyst efficiency speed) value defined as ACE/t (Fig. 7).[49] This data clearly shows that both Sigamide® **23** and our organocatalyst **25** are comparable and in many cases more efficient than their iridium and rhodium counterparts and thus demonstrate the potential of this type of organocatalysed reduction as an attractive alternative to the analogous transition metal process.

## 4. Summary and outlook

The use of sub-stoichiometric amounts of a readily available organic compound of low molecular weight to promote reactions in the absence of costly transition metals is an alluring prospect for the organic chemist, well exemplified in the Lewis base catalysed trichlorosilane mediated reduction of a ketimine. As shown in this perspective, the developments that have already been made in this field have led to catalysts that offer comparable efficiencies to transition metal catalysts, and there is no doubt that further developments will continue to be made in the near future as our understanding of this reaction grows.[51]

## Acknowledgements

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