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REVIEW

# Organocatalytic Transfer Hydrogenation and Hydrosilylation Reactions

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**Abstract** The reduction of different carbon–carbon or carbon–heteroatom double bonds is a powerful tool that generates in many cases new stereogenic centers. In the last decade, the organocatalytic version of these transformations has attracted more attention, and remarkable progress has been made in this way. Organocatalysts such as chiral Brønsted acids, thioureas, chiral secondary amines or Lewis bases have been successfully used for this purpose. In this context, this chapter will cover pioneering and seminal examples using Hantzsch dihydropyridines **1** and trichlorosilane **2** as reducing agents. More recent examples will be also cited in order to cover as much as possible the complete research in this field.

**Keywords** Transfer hydrogenation · Organocatalysis · Hantzsch ester · Trichlorosilane · Phosphoric acid · Aminocatalysis · Thioureas · Lewis bases · Reduction · Hydrosilylation

## 1 Introduction

The reduction of different carbon–carbon or carbon–heteroatom double bonds is an important transformation that generates in many cases new stereogenic centers. Particularly, the asymmetric reduction of prochiral ketimines represents one of the most important methods and straightforward procedures for preparing chiral amines. This approach is one of the key reactions and powerful tools in synthetic organic

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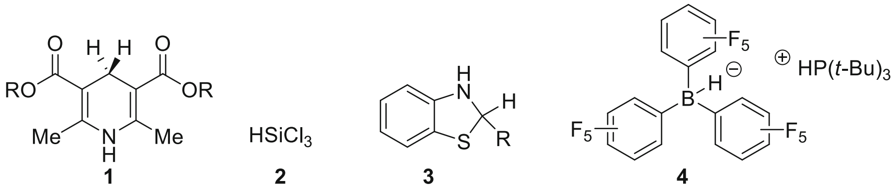



**Fig. 1** Model reducing agents

chemistry, which provides precious building blocks for natural products, pharmaceutical, and other fine chemical industries [1]. Until the last decade, available chemical catalysts for the enantioselective reduction of these substrates were mostly limited to chiral transition metal complexes, which often required elevated pressures and/or the use of additional additives to afford high yields and ee values (for reviews, see [2–10]). However, with the increasing interest during the last years in the development of the organocatalysis field [11–13], the organocatalytic version of these transformations has attracted more attention, and remarkable progress has been made in this way (For selected reviews on organocatalytic transfer hydrogenations, see [14–20]). The organocatalytic transfer hydrogenation is carried out by four fundamentally different approaches (Fig. 1): (1) reduction with Hantzsch dihydropyridines **1**, mainly catalyzed by chiral Brønsted acids, which activate the electrophilic substrates (for reviews, see: [21–26]); (2) hydrosilylation with trichlorosilane **2**, catalyzed through chiral Lewis-bases, which, in contrast, activate the nucleophilic hydride source [27–30]; and more recently, (3) transfer hydrogenation using benzothiazolines **3** as the reducing agent (Benzothiazoline **3** was firstly introduced by Akiyama's group for asymmetric transfer hydrogenation reactions: [31, 32]; [33]) and (4) hydrogen activation by frustrated Lewis pair **4** [34].

Interestingly, **1a–c** and **2** are commercially available, while **1d–e** must be synthesized. Trichlorosilane **2** is cheaper than the other reagents and **1a** is the most expensive one. Trichlorosilane **2** has shown a great spectrum of reactivity, as the reader will find in the second part of this chapter.

Although this field has been extensively reported, only pioneering and seminal examples using Hantzsch dihydropyridines **1** and trichlorosilane **2**, as reducing agents, will be disclosed in this chapter. More recent examples will be also cited in order to cover as much as possible the complete research in this field.

## 2 Hantzsch Esters as Hydride Source

Inspired by Nature, and trying to reproduce the enzymatic reductions using NAD(P)H as cofactor in living organisms, many research groups have focused part of their investigation on the development of new environmentally friendly and successful reducing agents trying to simulate its reactivity. That is the case of

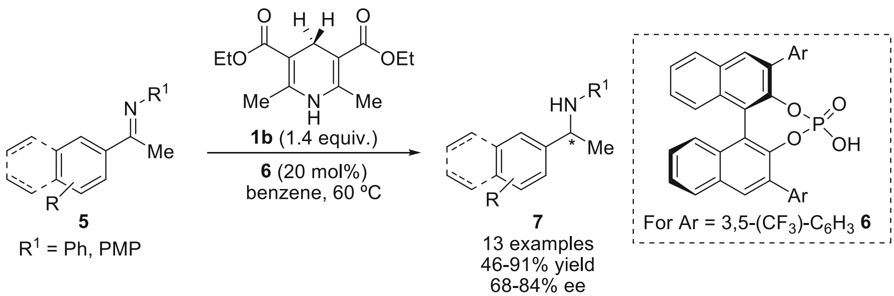
Hantzsch esters **1** as a hydride source [35, 36], which were initially synthesized following a multicomponent approach as an interesting synthetic example of 1,4-dihydropyridines. Although, it was only in the last decade when Hantzsch esters **1** became a key piece in the reduction processes using organocatalysts, the first reported example of transfer hydrogenation using this hydride source without metals is dated from 1989 ([37], for earlier examples on the transfer hydrogenation of imines with Hantzsch esters **1**: [38–40]). In the next pages, the pioneering enantioselective examples using Hantzsch dihydropyridines **1** in organocatalysis, and the most recent advances in this subarea of research will be briefly covered.

## 2.1 Chiral Phosphoric Acid Catalyzed Transfer Hydrogenation

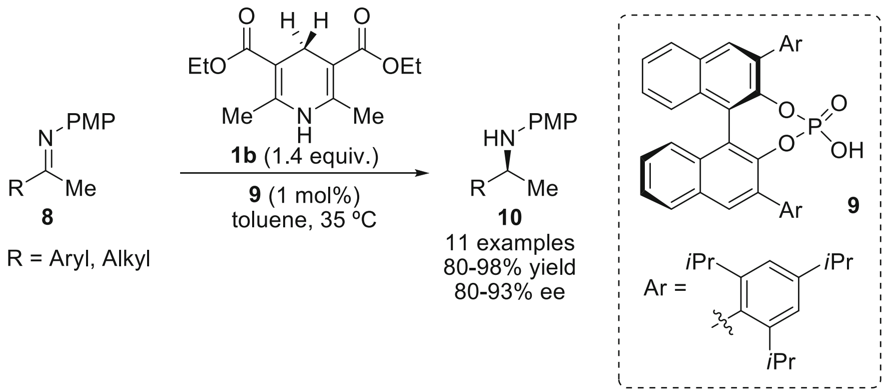
The reduction of imines is potentially useful for the synthesis of enantiomerically pure amines, since chiral amines appear in numerous interesting compounds in nature, and they have also a remarkable use as ligands in metal catalysis or as chiral organocatalysts. However, until 2001, this approach had been mainly explored using metal catalysts [2–10].

The first enantioselective Brønsted acid-catalyzed transfer hydrogenation of ketimines using Hantzsch ester **1b** was reported by Rueping's [41] (Scheme 1) and, independently, by List's groups (Scheme 2) [42] affording excellent results in terms of enantioselectivity and reactivity and, in both cases, using chiral phosphoric acid derivatives **6** and **9**. Interestingly, in the latter case, the authors significantly improved the results employing 20-fold reduction in the catalyst loading.

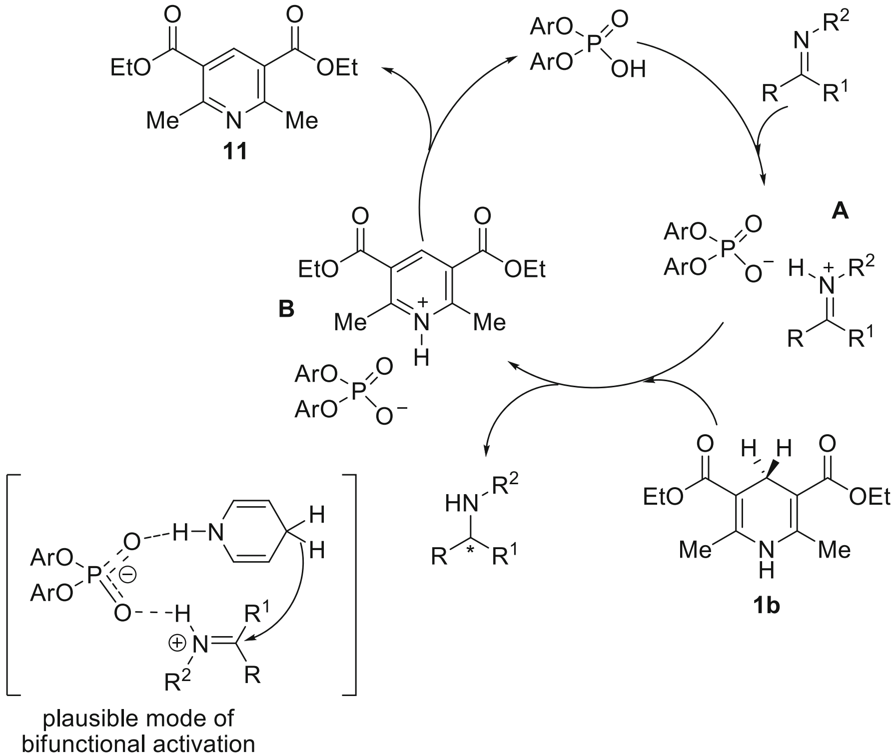
Based on previous studies where the imines were reduced with Hantzsch dihydropyridines in the presence of achiral Lewis [43] or Brønsted acid catalysts, [44] joined to the capacity of phosphoric acids to activate imines (for reviews about chiral phosphoric acid catalysis, see: [45–58]), the authors proposed a reasonable catalytic cycle to explain the course of the reaction (Scheme 3) [41]. A first protonation of the ketimine with the chiral Brønsted acid catalyst would initiate the cycle. The resulting chiral iminium ion pair **A** would react with the Hantzsch ester **1b** giving an enantiomerically enriched amine product and the protonated pyridine salt **B** (Scheme 3). The catalyst is finally recovered and the byproduct **11** is obtained in the last step. Later, other research groups also supported this mechanism (for mechanistic studies of this reaction, see: [59–61]).




**Scheme 1** Reduction of imines using phosphoric acid **6** as catalyst




**Scheme 2** Reduction of imines using Brønsted acid **9** as catalyst




**Scheme 3** Proposed catalytic cycle for the reduction of ketimines

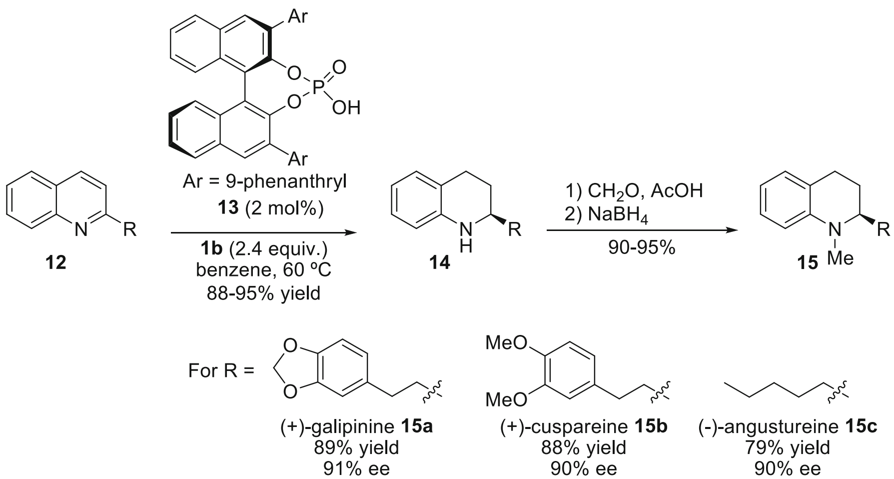
Since these seminal organocatalytic reports, other groups have used the same strategy for the reduction of different interesting imine derivatives such as MacMillan [62] [It is important to remark that as declared by the authors, the complete details of MacMillan's group concerning reductive amination were first published via oral presentation in August 2005 in presentations in Germany, Wales, Japan, and the USA prior to submission of their manuscript on this field (October 23rd, 2005) (see Ref. [21], You [63, 64], and Antilla [65]).

Because of the importance of chiral nitrogen on heterocycles constituting the structural core of many natural alkaloids and synthetic drugs, a great extension of this protocol has been performed during the last decade mainly by Rueping's group, affording different and valuable chiral heterocyclic products. In the next pages some pivotal examples reported by this research group will be disclosed and commented on.

Thus, Rueping and co-workers used their abovementioned methodology for the interesting activation of quinolines **12** by catalytic protonation and subsequent transfer hydrogenation, which involved a 1,4-hydride addition, isomerization, and final 1,2-hydride addition to generate the desired 1,2,3,4-tetrahydroquinolines **14** in a cascade process (Scheme 4) [66]. These compounds have proven to be interesting synthetic scaffolds in the preparation of pharmaceuticals and agrochemicals [67]. In this context, and having developed a general and enantioselective protocol, the authors demonstrated the applicability of this new methodology to the synthesis of biologically active tetrahydroquinoline alkaloids: galipinine **15a** [68, 69], cuspareine **15b**, [69, 70], and angustureine **15c** [69] (Scheme 4) (for a report on the achiral transfer hydrogenation of differently substituted quinolines, see also [71]) (for similar methodologies as an extension of this approach, see: [72–78]; for transfer hydrogenation of 1,2-dihydroquinolines, see: [79]).

Biologically active tetrahydroquinoline alkaloids **15** were prepared by simple *N*-methylation of intermediates **14** to lead the desired natural products in good overall yields and high enantioselectivities (for examples of dual catalysis, see: [80, 81], for more recent examples, see: [82–84]).

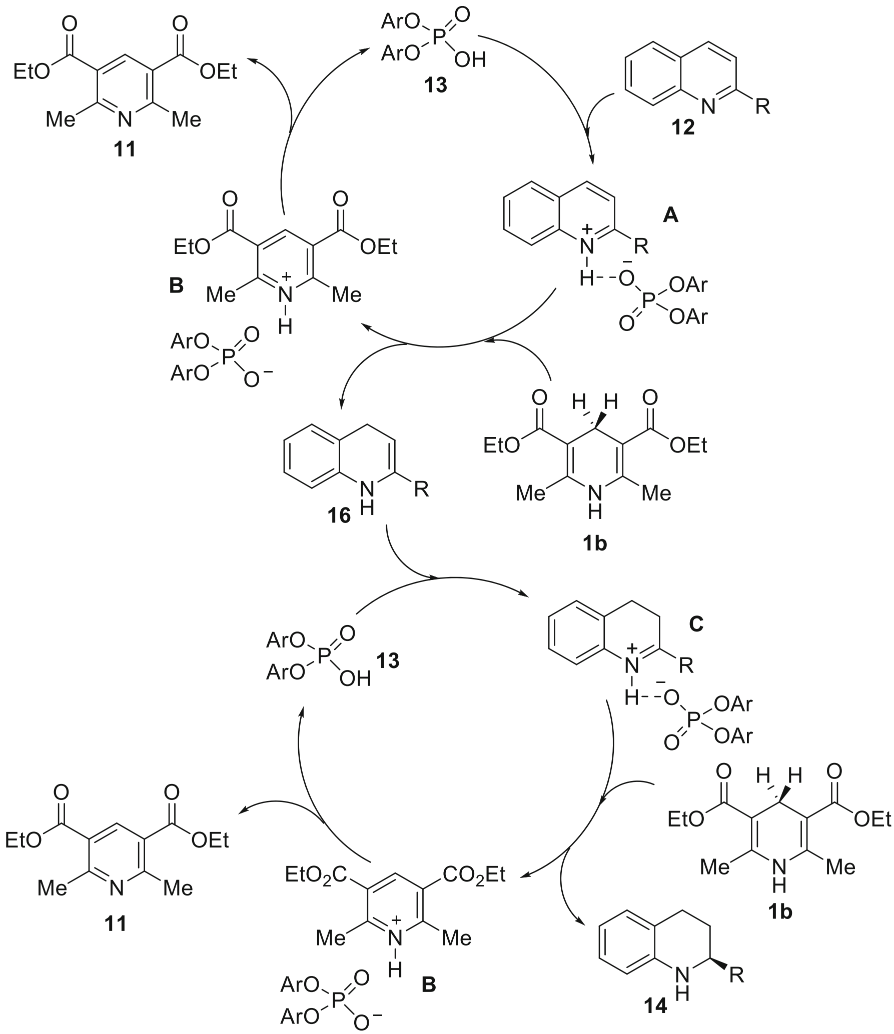
To explain the obtained products, the authors hypothesized that the first step should be the protonation of the quinoline **12** through the phosphoric acid catalyst **13** to generate the iminium ion **A** (Scheme 5). Transfer of a first hydride from the




**Scheme 4** Syntheses of biologically active tetrahydroquinoline alkaloids **15**

dihydropyridine **1b** would generate the enamine intermediate **16** and pyridinium salt **B**, which would regenerate the acid catalyst **13** and release pyridine **11**. The enamine **16** would interact with another molecule of Brønsted acid **13** to produce iminium **C**, which would receive the attack of a second molecule of hydride giving rise to the desired tetrahydroquinoline **14**. Subsequent proton transfer would recycle again the Brønsted catalyst **13** and would generate a second equivalent of pyridine **11** (Scheme 5).

The reduction of quinolines was applied to the asymmetric preparation of the anti-bacterial agent (*R*)-flumequine **18** [85, 86], starting from quinoline **12a** and generating the key tetrahydroquinoline intermediate **14a** for the total synthesis and using **17** as catalyst (Scheme 6) [87].




**Scheme 5** Mechanism for the cascade transfer hydrogenation of quinolines **12**

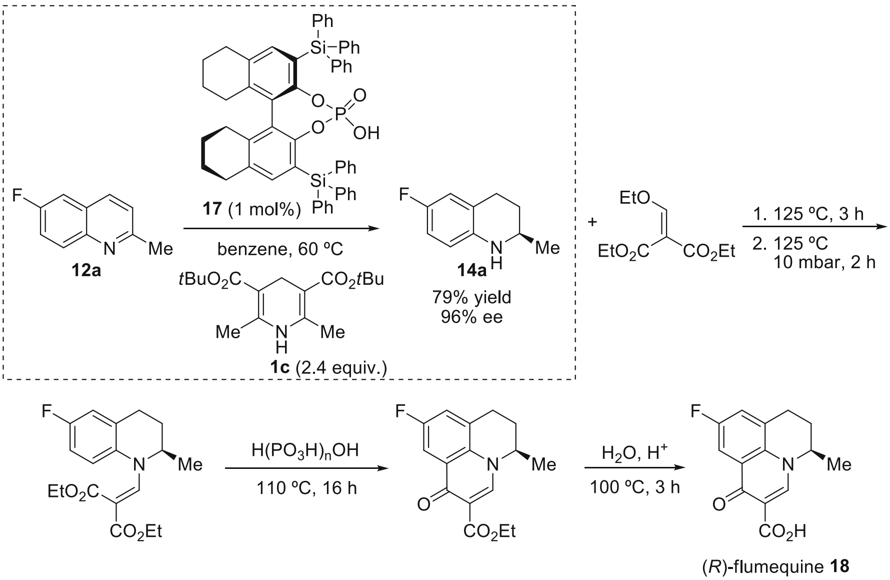
Gong and co-workers developed the first step-economical synthesis of the previously described process. The approach involves a Friedländer condensation [88, 89] followed by a transfer hydrogenation catalyzed by a combination of an achiral Lewis acid and a chiral Brønsted acid. This affords the direct conversion of 2-aminobenzaldehyde derivatives **19** and ketones **23** into highly optically active 1,2,3,4-tetrahydroquinoline derivatives **22** and **24**, with enolizable dicarbonyl compounds **20** (Scheme 7) [90].

The Lewis acid (LA) is believed to only participate in the catalyzed Friedländer condensation, while the chiral phosphoric acid (B*-H) could participate in the first condensation to give **25** and in the asymmetric transfer hydrogenation of **A** (Scheme 8). The success of this approach relies in the compatibility and synergic effect of both catalysts, the Lewis acid, and the chiral Brønsted acid.

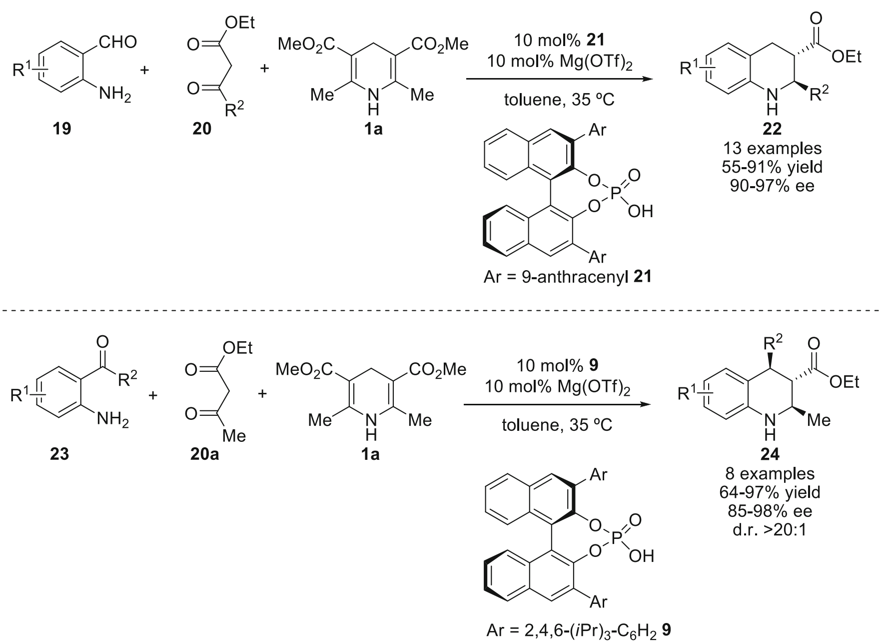
Rueping's group pioneered the first example of a catalyzed enantioselective reduction of pyridines giving rise to direct access to enantiomerically pure piperidines **26** (Fig. 2) [91].

The applicability of this new method was demonstrated in the formal synthesis of *diepi*-pumiliotoxin C **31** from the pumiliotoxin family (Scheme 9) [91]. Hence, the reduction of pyridine **29a**, which can be readily prepared according to Bohlmann and Rahtz's procedure starting from **27** and **28** [92, 93], gives the corresponding (*S*)-2-propylhexahydroquinolinone **30a** as a key intermediate for the subsequent transformation (Scheme 9) [94].

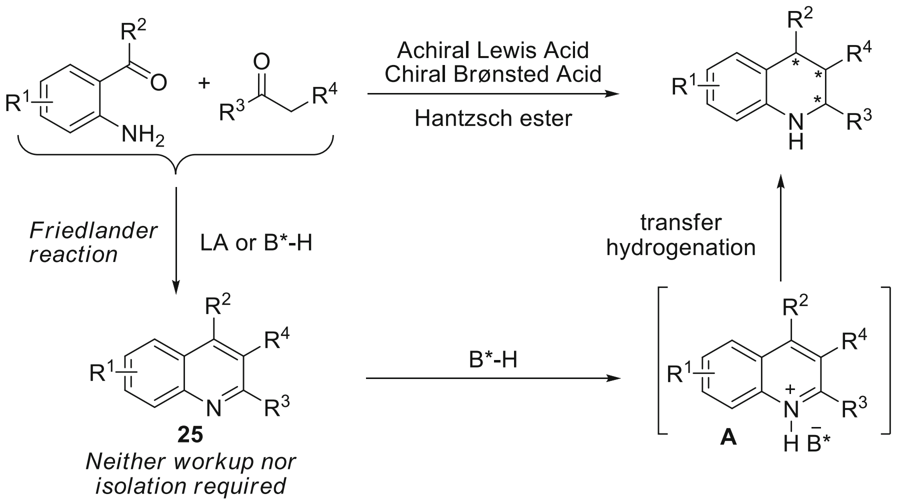
A plausible mechanism of the reduction was also proposed to explain the final products. Thus, in the first step, the pyridines **29** would be activated through catalytic protonation by the phosphoric acid catalyst **21**, resulting in the formation of a chiral ion pair **A** (Scheme 10). A subsequent hydride transfer from the Hantzsch




**Scheme 6** Synthesis of (*R*)-flumequine **18**




**Scheme 7** Step-economical syntheses of tetrahydroquinolines **22** and **24**




**Scheme 8** Proposed mechanism

ester **1b** would afford adduct **B**, which would be transformed into the iminium ion **C** through an isomerization. A second hydride transfer would render the desired product **26** or **30**, and **21** would be regenerated (Scheme 10).

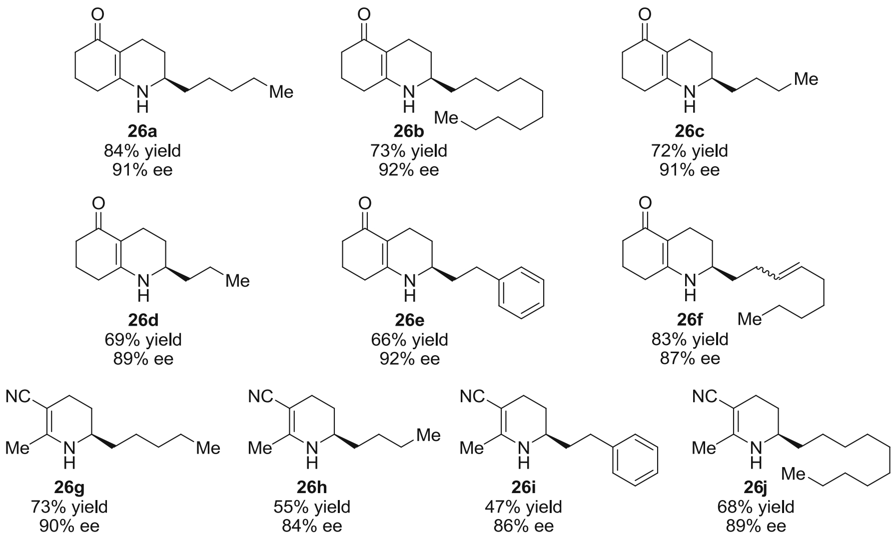
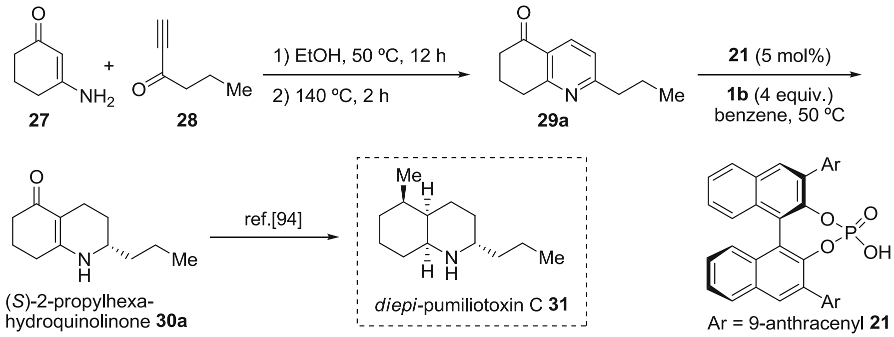



**Fig. 2** Scope of reduction of pyridines

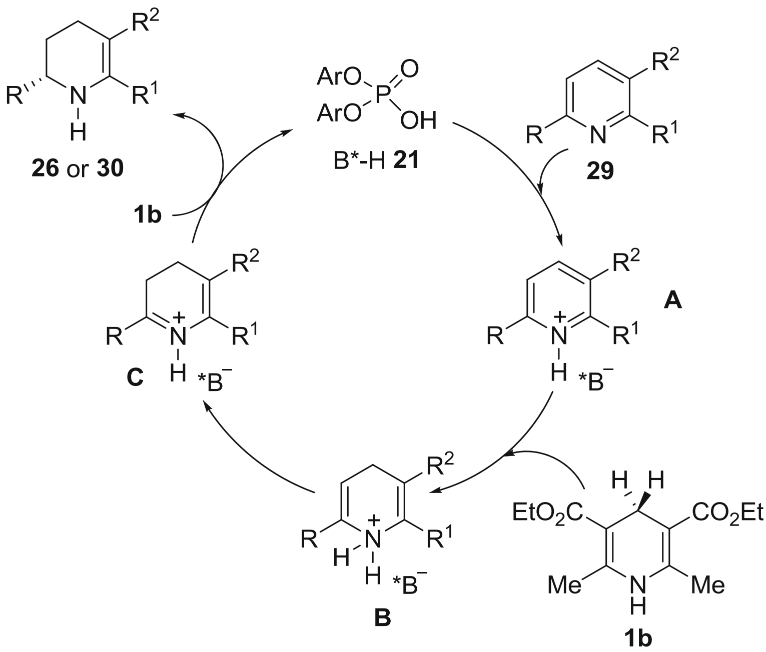



**Scheme 9** Formal synthesis of *diepi*-pumiliotoxin C **31**

The same research group developed a similar protocol for the reduction of benzoxazines **32**, benzothiazines **33,** and benzoxazinones **34** as key examples of heterocyclic compounds (Fig. 3) [95].

With the increasing interest experienced by enantioselective domino reactions as powerful tools for the direct construction of enantioenriched complex targets starting from simple and readily available precursors, many investigations have been developed in this area of research, where the organocatalysis has gained an important position [96–98].

In this context, Rueping's group envisioned the asymmetric organocatalytic multiple-reaction cascade version of the abovementioned process in which a six-step sequence was catalyzed by the chiral Brønsted acid catalyst **21** providing direct access to a broad scope of valuable tetrahydropyridines **26** and azadecalinones **35** with high enantioselectivities (Scheme 11) [99].




**Scheme 10** Proposed mechanism giving rise to piperidines **26** and **30**

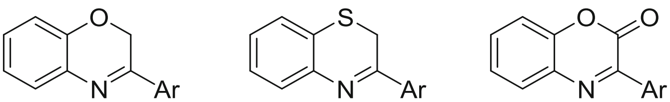


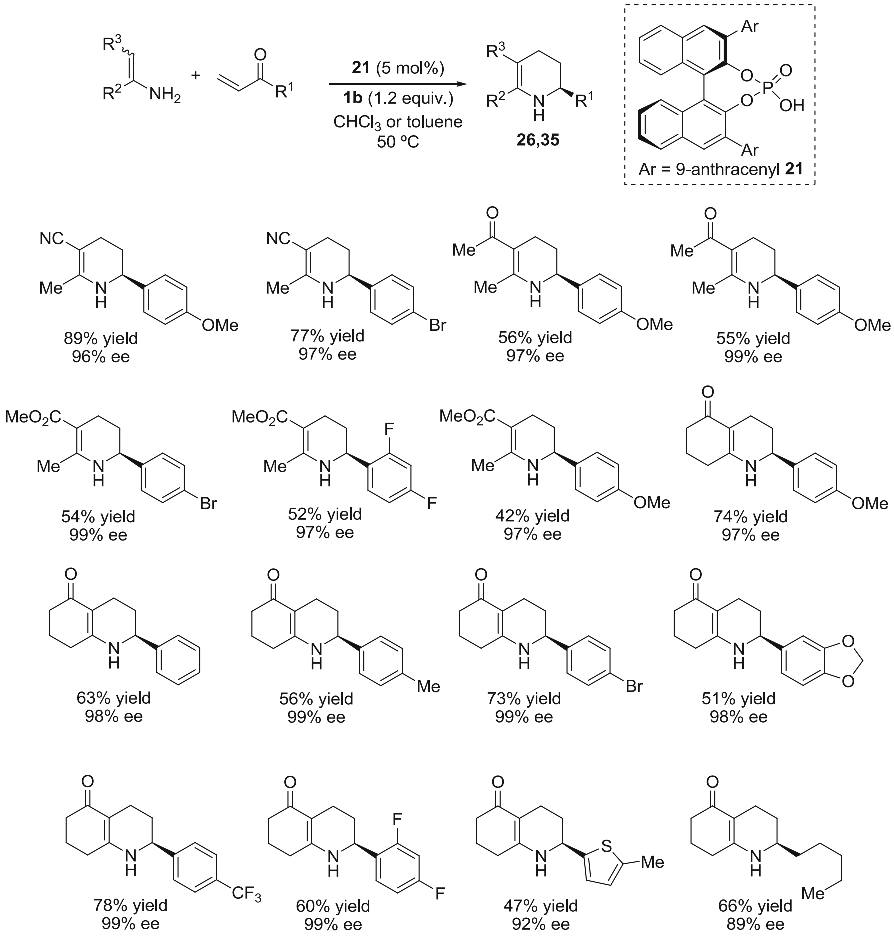

**Fig. 3** Model heteroaromatic compounds reduced

An interesting mechanism was suggested by the authors to explain the final products obtained through this methodology, where the chiral Brønsted acid catalyst **21** would participate in the six reaction steps proposed (Scheme 12).

Other interesting examples of catalytic transfer hydrogenation have been also described for the transformation of quinoxaline and quinoxalinones into the corresponding 2-tetrahydroquinoxalines **36** (Fig. 4) and 3-dihydroquinoxalinones **37** (Fig. 5) [100], with a structural core which exhibits remarkable biological properties [101–104].

Interestingly, Shi, Tu, and co-workers developed the tandem version of the abovementioned protocol comprising a cyclization/transfer hydrogenation strategy leading to enantioenriched tetrahydroquinoxalines **36** and dihydroquinoxalinones **37** from readily accessible materials with excellent results in terms of reactivity and enantioselectivity (Scheme 13) [105].

In order to explain the stereochemical outcome observed in this process, the authors proposed a plausible reaction pathway and transition state on the basis of

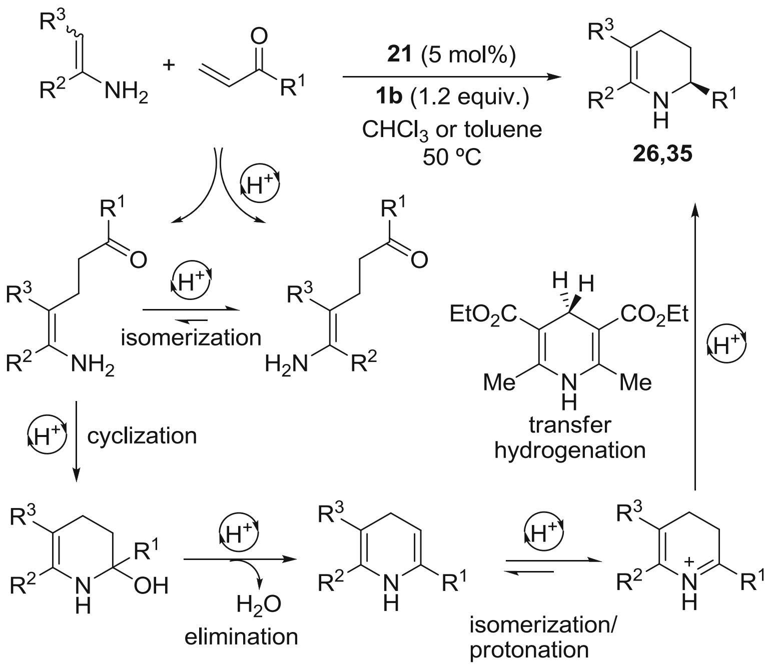



**Scheme 11** Synthesis of tetrahydropyridines **26** and azadecalinones **35**

their experimental results and previously reported calculations on transfer hydrogenation of imines [59–61] (Scheme 14). In this mechanism, the phosphoric acid catalyst **21** would act in a bifunctional mode, and the attack of the hydride in the TS justifies the absolute (*R*)-configuration observed in final products **36** and **37**.

Rueping and co-workers have recently developed a highly enantioselective synthesis of differently substituted tetrahydroquinolines **40** via a first photocyclization of substituted 2-aminochalcones **38** and subsequent Brønsted acid catalyzed asymmetric reduction of the in situ generated quinoline **39**, to give final products in moderate to high yields and with excellent enantioselectivities (Scheme 15) [106, 107].

The same research group applied the above methodology for the synthesis of valuable 4*H*-chromenes **43** in good yields and with excellent enantioselectivities. The approach consists of a dual light and Brønsted acid mediated isomerization–cyclization reaction starting from enones **41** to yield 2*H*-chromen-2-ol intermediates **A**. The subsequent Brønsted acid catalyzed elimination of water leads to an




**Scheme 12** Proposed mechanism for the cascade reaction

unprecedented intermediary chiral ion pair between a benzopyrylium ion and a chiral phosphate anion **B**. The following transfer hydrogenation exclusively occurs in the 4-position, providing the desired enantioenriched 4*H*-chromenes **43** (Scheme 16) [108].

Recently, a pioneering organocatalytic asymmetric reduction strategy for the synthesis of chiral 1,1-diarylethanes **46** with high efficiency and enantioselectivity was reported by Zhu, Lin, Sun, and co-workers (Scheme 17) [109].

A plausible reaction mechanism is hypothesized by the authors. The electron-rich styrene substrate **44** would be protonated by phosphoric acid catalysts **45** to generate the tertiary carbocation intermediate **A**. The neutral resonance structure **B**, activated by B*-H would receive the subsequent hydride addition giving the observed products **46** and regenerating the chiral acid catalyst **45** (Scheme 18).

To support the reaction mechanism and to better understand the role of each species, the authors performed B3LYP-D3 density functional theory (DFT) calculations. Interestingly, the method was applied to a broad spectrum of substrates, and a lead compound with impressive inhibitory activity against a number of cancer cell lines was also identified.

## 2.2 Aminocatalysis Promoted Transfer Hydrogenation

Another great area of research in organocatalysis that has experienced an incredible growth has been aminocatalysis. Proof of this progress is the huge number of works

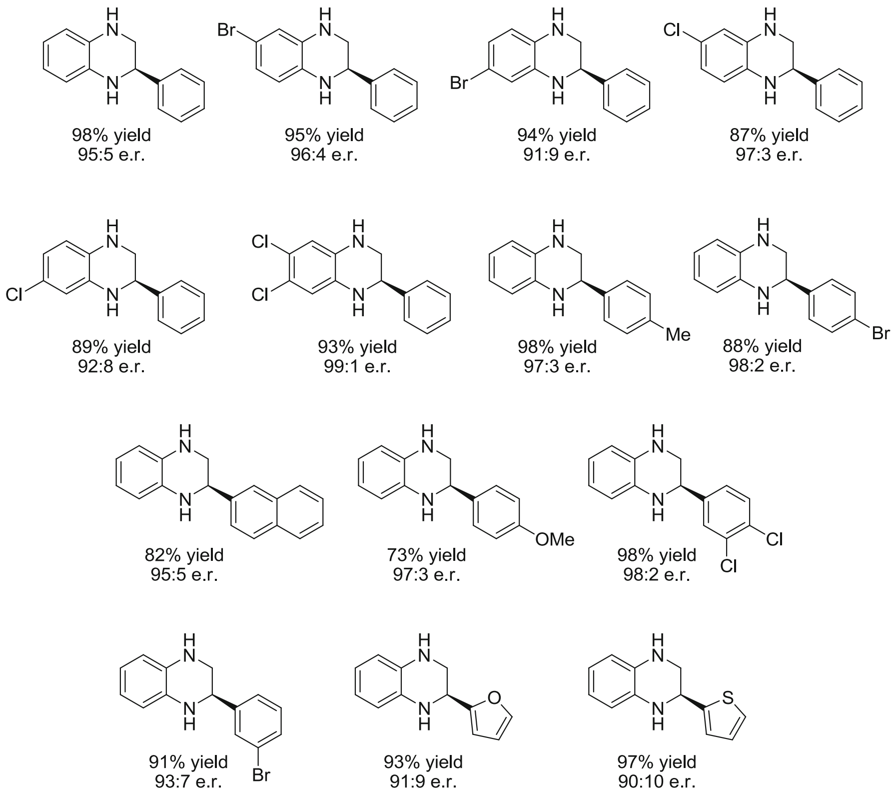



**Fig. 4** Scope of the reaction for the generation of 2-tetrahydroquinoxalines **36**

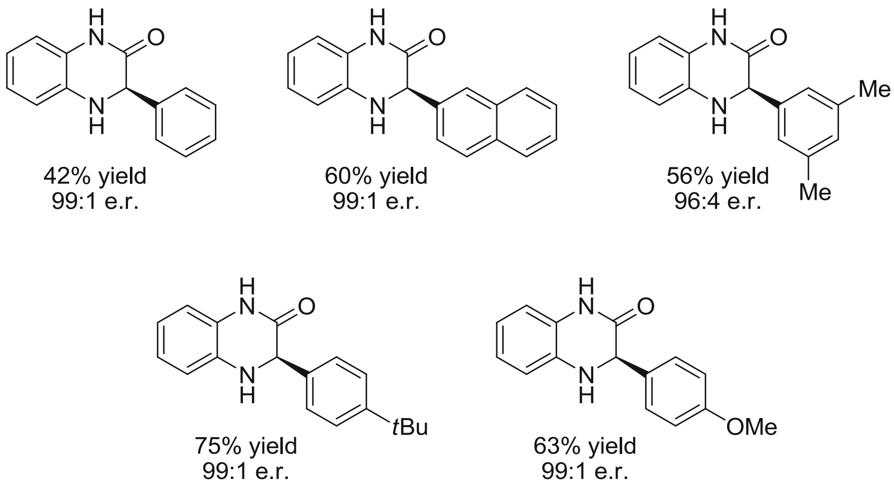
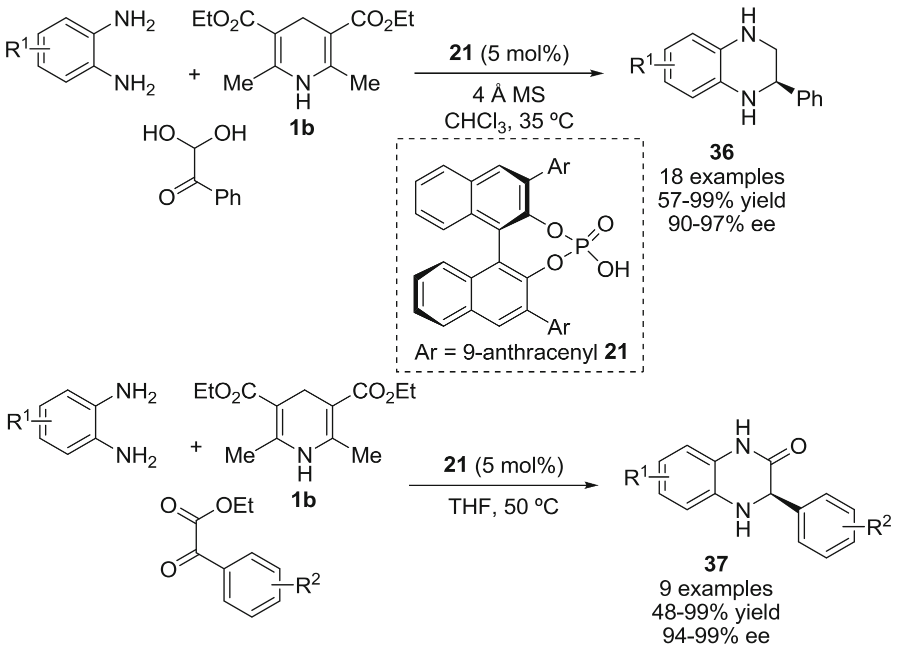
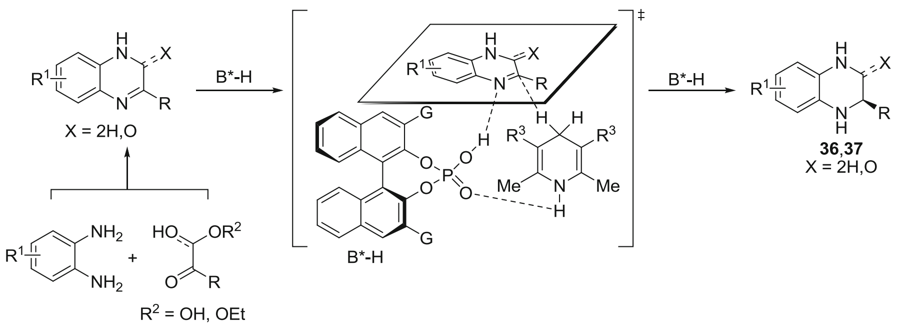



**Fig. 5** Scope of the reaction for the generation of 3-dihydroquinoxalinones **37**



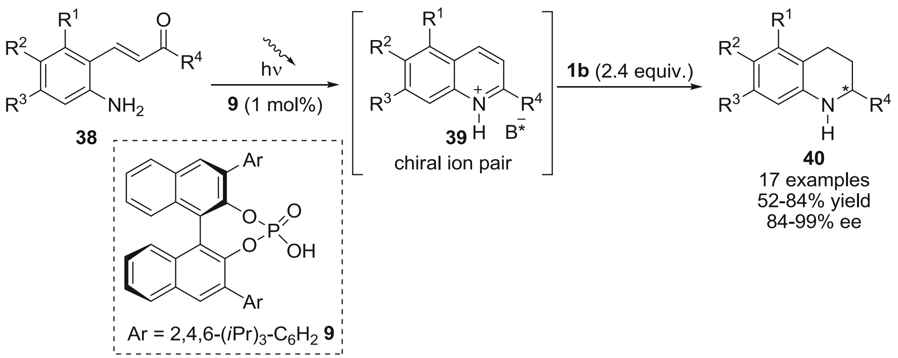

**Scheme 13** Tandem approach for the preparation of **36** and **37**



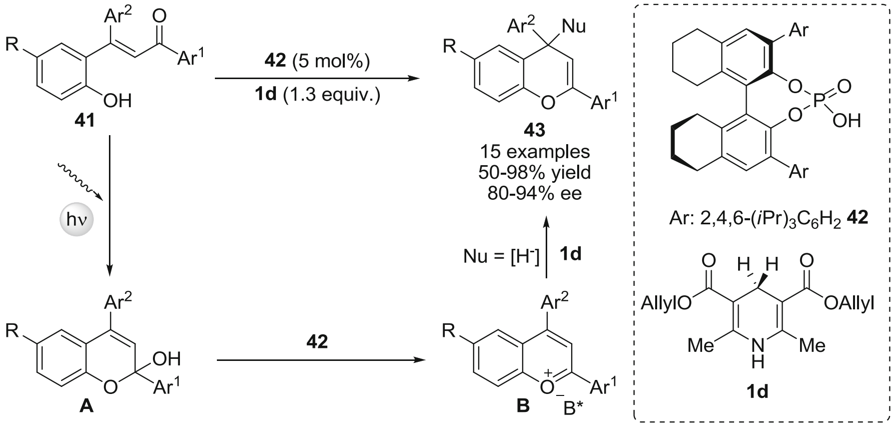

**Scheme 14** Plausible reaction pathway and transition state

focused on this field (for selected reviews concerning the aminocatalysis field, see: [110–129]). Among all of them, pivotal contributions related to transfer hydrogenations have been also developed in this area. Although less explored than the phosphoric acid catalyzed examples, these pivotal works will be recovered in the next examples.

In 2004, List and co-workers [130] pioneered only one chiral example of a novel iminium catalytic conjugate reduction of α,β-unsaturated aldehyde **47a** (Scheme 19a). In 2005, and independently, List's (Scheme 19b) [131] and MacMillan's groups (Scheme 19c) (as reported by the authors in Ref. [21], the complete details of their studies into transfer hydrogenation were first published via oral presentation on




**Scheme 15** Photocyclization-asymmetric reduction of **38**

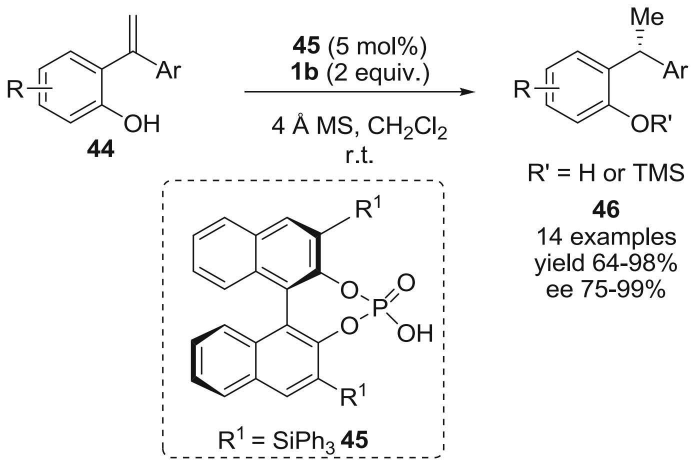



**Scheme 16** First asymmetric Brønsted acid catalyzed hydrogenation of benzopyrylium ion **B**

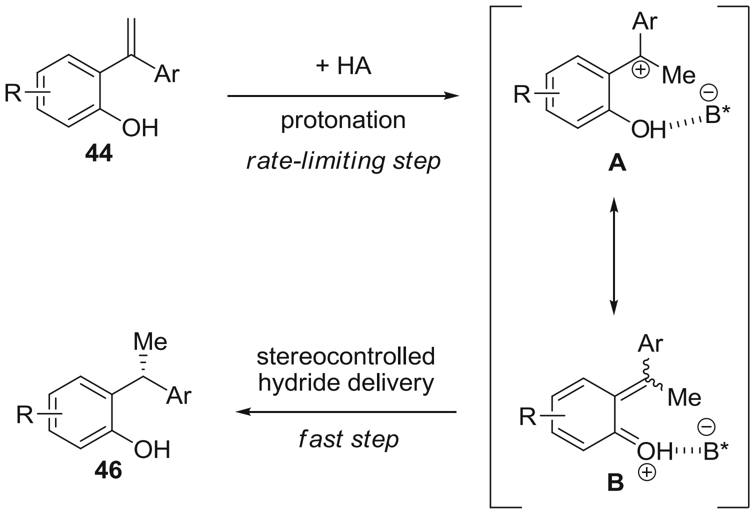
March 1st, 2003, at the Eli Lilly Young Award symposium, Indianapolis. Their work was further communicated in >15 presentations in Europe, USA, Australia, and Asia prior to submission of their manuscript (October 10th, 2004) [132]) reported two more extensive protocols for the enantioselective conjugate reduction of α,β-unsaturated aldehydes **47** and **51** using chiral imidazolinone catalysts **50** and **52**.

List's group proposed a reasonable mechanism to explain the observed absolute configuration in their final products **49**. The process would firstly proceed by formation of iminium ion **54**, which could isomerize quickly via dienamine **55** (Scheme 20). The authors assume that the rate determining step would be the hydride transfer from **1a** to iminium (*E*)-**54** via the transition state **A**, which would occur faster than (*Z*)-**54** [$k(E) > k(Z)$] and, as a result, the enantiomer *R* would be predominantly formed (Scheme 20) [131].

Later, the first enantioselective organocatalytic transfer hydrogenation involving cyclic enones was reported by MacMillan and co-workers following an operationally simple and rapid protocol that allowed access to chiral *β*-substituted




**Scheme 17** Enantioselective synthesis of 1,1-diarylethanes **46**

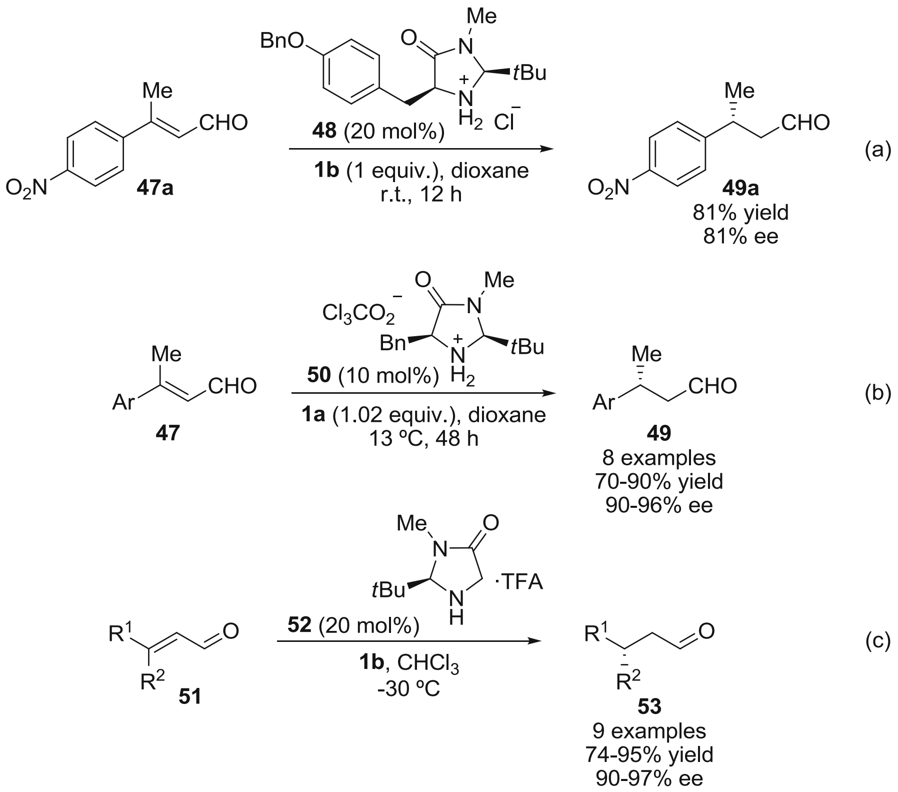



**Scheme 18** Plausible reaction mechanism

cycloalkenones **58** with very good yields and high enantioselectivities (Scheme 21) [133] (for an application of this methodology by the same research group, see: [134]).

In order to explain the sense of the asymmetric induction observed in final products **58**, the authors proposed a plausible attack of the hydride based on the selective engagement of the Hantzsch ester reductant **1c** over the *Si* face of the *cis*-iminium isomer **A** (Scheme 22).

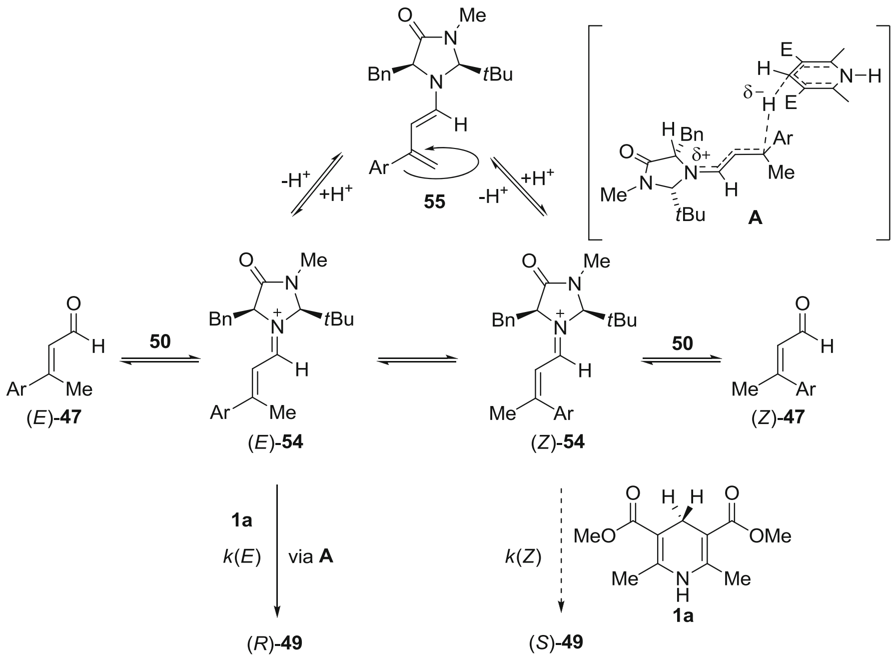
Interestingly, in this work the authors compared the efficiency of esters **1b**, **1c** and **1d**, in order to observe a possible structural effect of them over the




**Scheme 19** Pioneering examples of conjugated reduction of α,β-unsaturated aldehydes

enantioselectivity and the reactivity of this process. In fact, a significant impact on both aspects was found with a plausible correlation on the size of the ester functionality at the 3,5-dihydropyridine site (**1b**: Et, 96 % conversion, 74 % ee; **1d**: *i*-Pr, 78 % conversion, 78 % ee and **1c**: *t*-Bu, 86 % conversion, 91 % ee). The enantiocontrol results were explained in terms of electronic factors between the hydrogen substituents at the 4-position and the nitrogen lone-pair. The boat conformation found for **1c** would facilitate the overlap between one H (4-position) in an axial orientation with the nitrogen lone-pair in the ground state. In contrast, the **1b** ring is found in a planarized form wherein poor π-orbital overlap between the analogous C–H bond and nitrogen renders a less reactive hydride reagent. This hypothesis is consistent with not only an increase in enantiocontrol when using the more bulky *tert*-butyl Hantzsch ester **1c** but also improved reaction rate and efficiency [21, 133].

Bringing together the concept of aminocatalysis and the activation mode of chiral phosphoric acids, List and co-workers introduced the concept of *asymmetric counter anion directed catalysis* (ACDC) and they applied this idea to the asymmetric reduction of enals **47** (Scheme 23) [135]. The catalytic species is formed by an achiral ammonium ion **60** and a chiral phosphate anion **59** derived from 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **9** (TRIP).




**Scheme 20** Mechanistic hypothesis of the organocatalytic asymmetric transfer hydrogenation

All reduced β,β-disubstituted enals **49** were obtained in good yields (up to 90 %) and excellent enantioselectivities (up to 99 % ee). Moreover, the methodology was applied to the interesting reduction of citral **61** into the (*R*)-citronellal **62** and to the asymmetric reduction of farnesal **63**, in all cases with excellent enantioselectivies and high yields (Scheme 24).

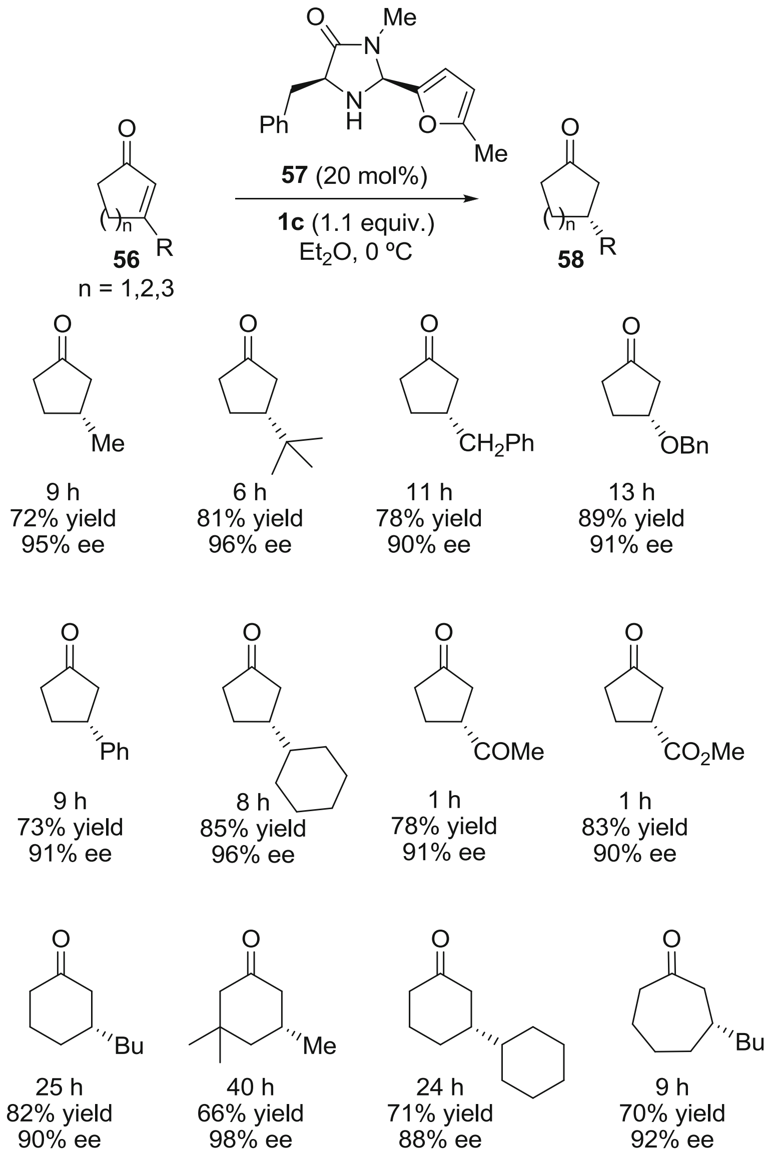
Remarkably, the same final enantiomer was obtained in the products even starting from *Z* enals, which is in agreement with a stereoconvergent catalytic system and a rapid *E*–*Z* equilibration, as detected by NMR spectroscopic studies. The mechanism is believed to occur via an iminium ion intermediate since salts of tertiary amines seem to be ineffective.

An extension of this work was reported by the same research group for the asymmetric conjugate reduction of α,β-unsaturated ketones **65**, affording final reduced products **67** with high yields and good to excellent enantioselectivities (Scheme 25) [136].

More recently, Lear and co-workers applied this new concept as a key synthetic step in the high yielding route leading to the (−)-platensimycin core ([137], for further studies in this field, see also: [138–140]).

## 2.3 Thiourea-Catalyzed Transfer Hydrogenation

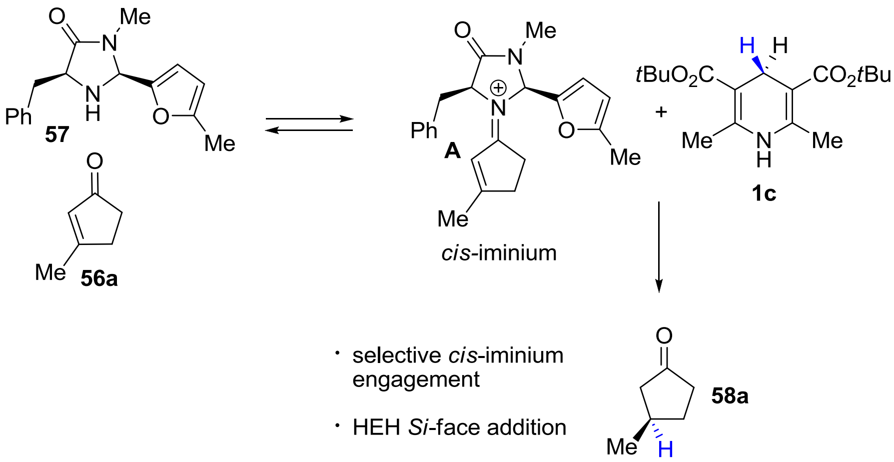
Another big family of organocatalysts that has been successfully used in hydrogen transfer, although less explored, is the chiral thiourea organocatalysts (for pivotal reviews concerning chiral thioureas, see: [141–154] and for the pioneering use of



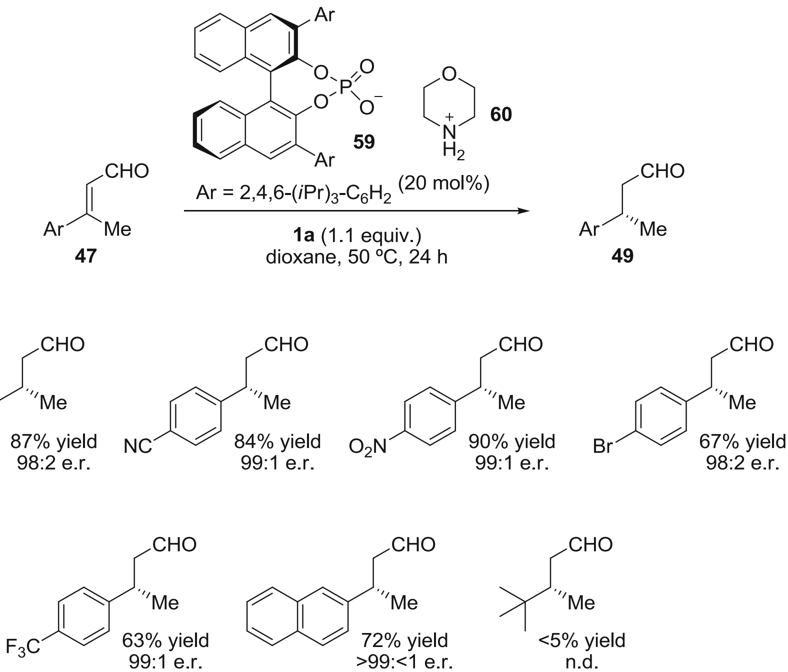

**Scheme 21** Scope of the organocatalytic enone hydrogenation

non-chiral thioureas in a transfer-hydrogenation reaction, see: [155]). In this context, List and co-workers reported the first example of conjugate reduction of nitroolefins **68** mediated by thiourea organocatalyst **69** (Scheme 26) ([156], for the non-enantioselective version of this reaction, see: [157]).

As disclosed, the process was suitable for a broad substrate scope, leading to final products **70** with high yields and enantioselectivities for diverse β-alkylsubstituted nitrostyrenes **68**.



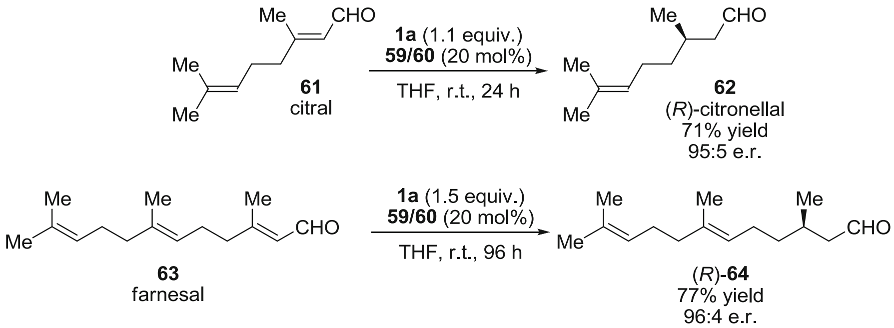

**Scheme 22** Enantioselective hydride addition mechanism




**Scheme 23** ACDC approach applied to the reduction of enals **47**

The reaction could proceed via a hydrogen-bonding interaction between the NH of the thiourea moiety and the nitro group and further enantioselective attack of the hydride from the Hantzsch ester **1c**.

An extension of this work was reported by the same research group using β-nitroacrylates **71** and the same thiourea organocatalyst **69** with the main aim of

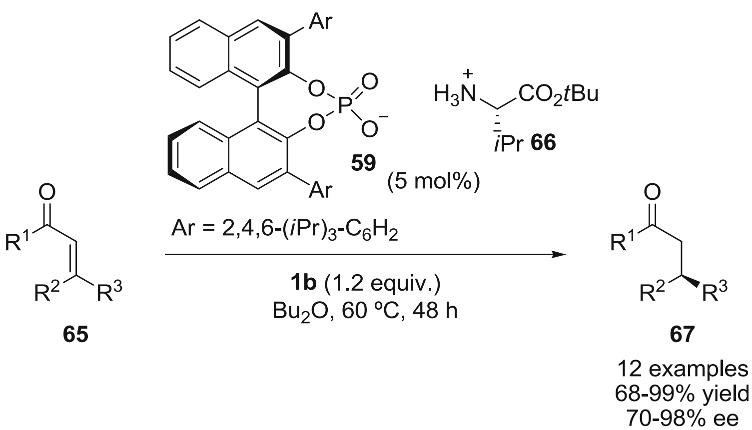



**Scheme 24** Catalytic asymmetric transfer hydrogenation of citral **61** and farnesal **63**

preparing the corresponding saturated *β*-nitroesters **72** in high yields and enantioselectivities, which can be easily converted into β$^2$-amino acids via hydrogenation (Scheme 27) ([158], for other developed methods of asymmetric transfer hydrogenation of nitroolefins using thioureas, see: [159, 160]).

The same approach was used by Benaglia's group for the enantioselective organocatalytic reduction of β-trifluoromethyl nitroalkenes **73**, with the aim of achieving chiral *β*-trifluoromethyl amines **75** (Scheme 28) [161]. The authors also performed the organocatalyzed reduction of α-substituted-β-trifluoromethyl nitroalkenes, although with poorer results. The stereochemical result of the reaction and the behavior of thiourea catalyst **74** were discussed based on computational studies and DFT transition-state analysis.

Simultaneously, although independently, Bernardi, Fochi and co-workers developed an extraordinary additional example of highly enantioselective transfer hydrogenation using *β*-trifluoromethyl nitroalkenes to give easy access to optically active *β*-trifluoromethyl amines with excellent results [162].




**Scheme 25** Asymmetric reduction of ketones **65**

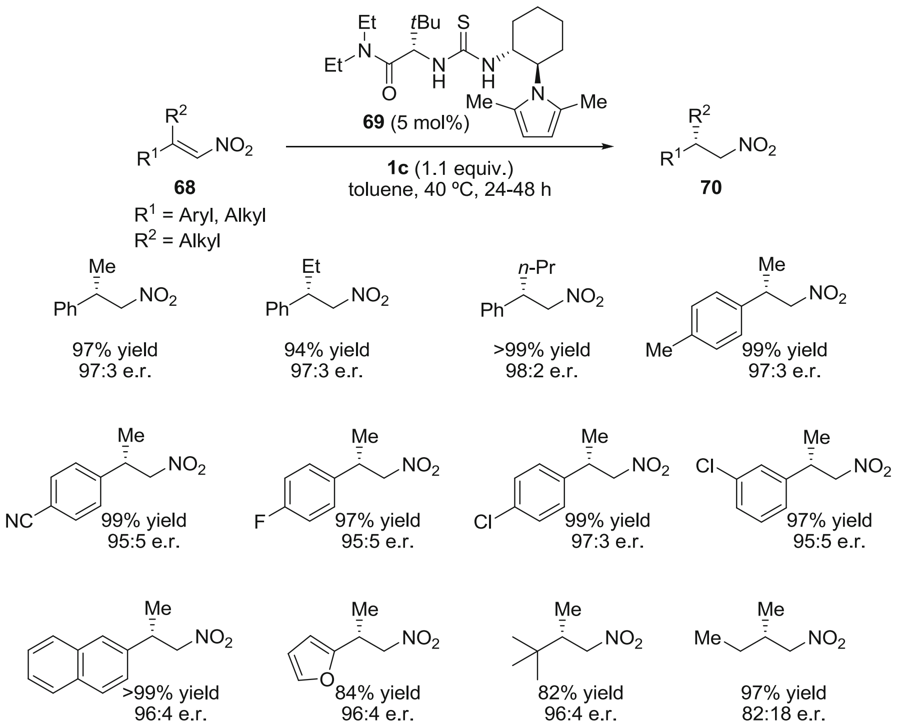
# 3 Trichlorosilane-Mediated Stereoselective Reduction of C=X Bonds

In the last decade, great progress has been made in the development of highly enantioselective Lewis basic organocatalysts for the reactions of trichlorosilyl derivatives as the reducing agents. The **2** is activated by the base moiety of the catalyst to generate an hexacoordinate hydridosilicate (for the activation of trichlorosilyl reagents by Lewis bases, see also: [163, 164]). Here is reported the successful application on the enantioselective reduction of prochiral ketimines, ketones and C=C bond using trichlorosilane **2** as an effective hydride source.

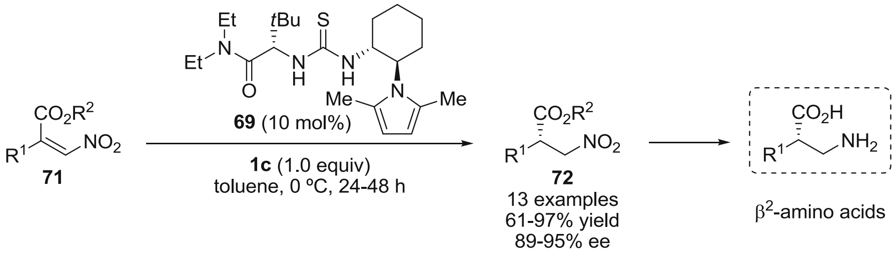
## 3.1 Reduction of Ketimines

### *3.1.1 N-Formylpyrrolidine Derivatives*

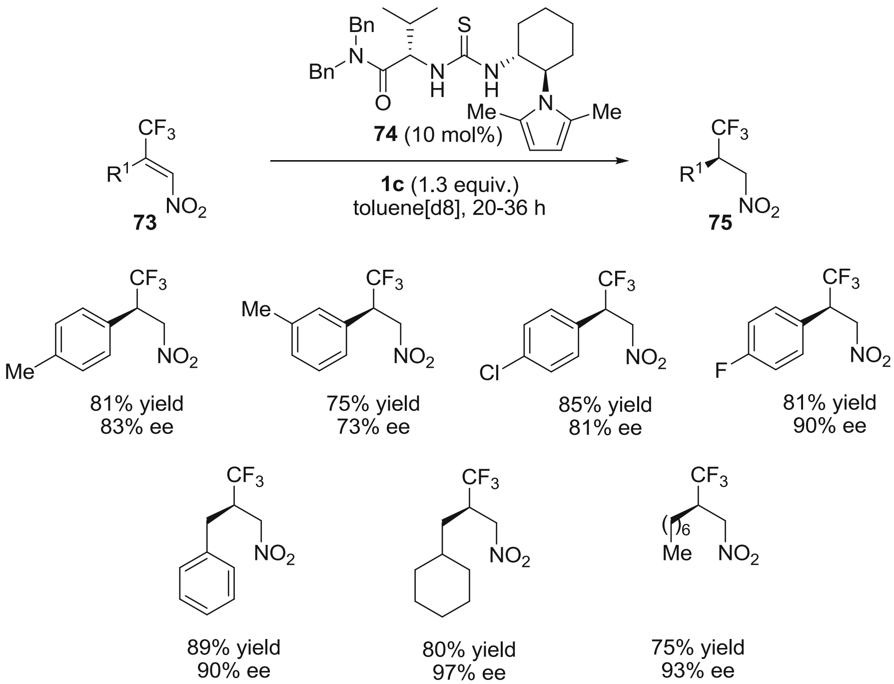
In a pioneering work, Matsumura and co-workers presented a new finding where trichlorosilane **2** activated with *N*-formylpyrrolidine derivatives **77** was an effective catalyst for the reduction of imines **76**. Reducing agent **2** showed much higher selectivity towards the imino group rather than the carbonyl group, because the carbonyl moiety in the catalysts was not reactive against the reduction (Scheme 29) [165]. Later, Tsogoeva's group demonstrated the use of pyrrolidine **78** as a




**Scheme 26** Thiourea promoted asymmetric transfer hydrogenation




**Scheme 27** Asymmetric reduction of β-nitroacrylates




**Scheme 28** Organocatalyzed reduction of fluorinated nitroolefins **73**

suitable catalyst for ketimines reduction, although only for one example and using HMPA as additive [166]. More recently, Lewis base **79** was successfully employed for the hydrosilylation of α-imino esters as direct precursors of α-amino acids ([167], for the use of additional picolinoyl catalyst derivatives, see also: [168–172]).

The role of the carbonyl groups in the catalysts seemed to be responsible for the silicium activation (for other pyrrolidine derivatives, see: [173–175]). In order to explain the sense of the stereoselectivity in final products, Matsumura's group suggested that the reduction predominantly proceeded through a transition state **A** rather than the most hindered transition state **B**, justifying the major enantiomer observed (Fig. 6). This mechanistic proposal was an early hypothesis, which was later modified by other authors on the basis of more experimental results (see below).

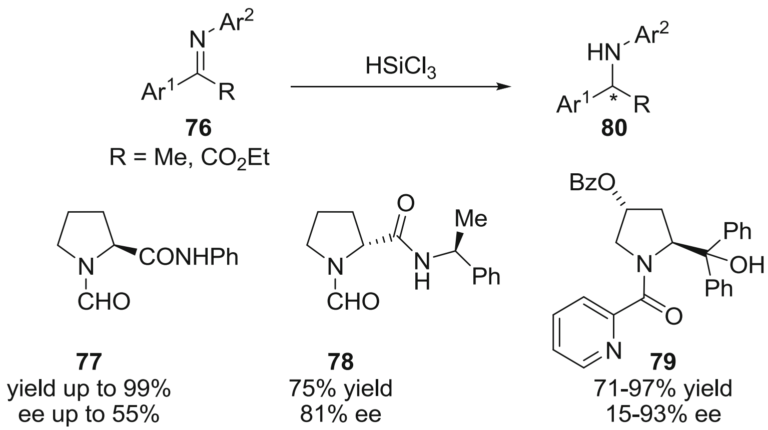
### 3.1.2 L-Valine-Derived N-methyl Formamides

Malkov, Kočovský, and co-workers have developed different L-valine-based Lewis basic catalysts such as **81** [176, 177], for the efficient asymmetric reduction of ketimines **76** with trichlorosilane **2**, or catalyst **82** [178] with a fluorous tag, which allows an easy isolation of the product and can be used in the next cycles, while preserving high enantioselectivity in the process. Sigamide catalyst **83** [179, 180] and Lewis base **84** [181] were employed in a low amount (5 mol%) affording final chiral amines **80** with high enantioselectivity (Scheme 30) [182]. Interestingly, **83** was used for the enantioselective preparation of vicinal α-chloroamines and the subsequent synthesis of chiral 1,2-diaryl aziridines. In these developed approaches the same absolute enantiomer was observed in the processes.

From these studies, the authors suggested different important conclusions: (1) the structure–reactivity studies showed that the product configuration seems to be controlled by the nature of the side chain of the catalyst scaffold, and the electronic properties of the substituents in the phenyl ring on the Lewis base. Interestingly, catalysts of the same absolute configuration may induce the formation of the opposite enantiomers of the product; (2) hydrogen bonding and arene–arene interactions between the catalyst and the imine appear to be crucial for the success of determining the enantiofacial selectivity; (3) the activation of trichlorosilane seems to be in agreement with a bidentate coordination with both carbonyl groups of the amide moiety in the catalyst, as previously invoked (Fig. 7) [176]. It is remarkable that the mode of activation in this case differs from that proposed previously by Matsumura's group in Fig. 6 [165].

### 3.1.3 L-Pipecolinic Acid Derived N-Formamides

Sun and co-workers developed a novel Lewis basic organocatalyst **86** (Scheme 31), easily synthesized from commercially available L-pipecolinic acid. The catalyst **86** promoted the reduction of *N*-aryl ketimines **85** with $HSiCl_3$ **2** in high yield and




**Scheme 29** Reduction of imines with *N*-formylpyrrolidine-based catalysts

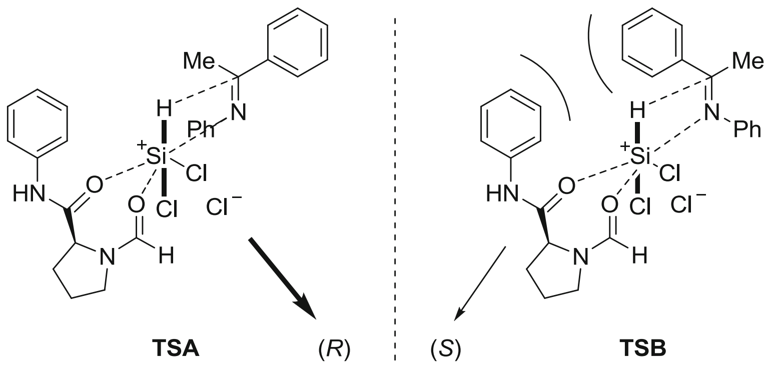


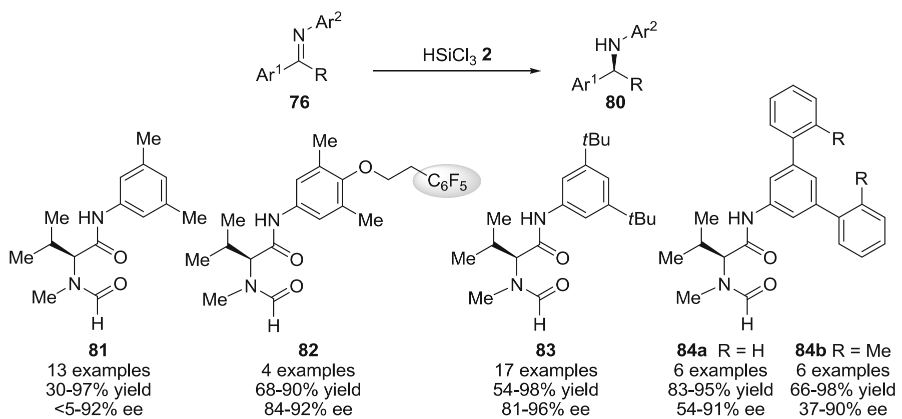

**Fig. 6** Mechanism of hydrosilylation of imines

excellent ee values under mild conditions with an unprecedented spectrum of substrates [183]. The same group also found that the L-pipecolinic acid derived *N*-formamide **87** was a highly effective Lewis basic organocatalyst for the same reaction [184].

On the basis of the experimental results, the methoxy group on C2′ has proven to be critical for the high efficiency of catalyst **87** in the reduction of the imines. A hexacoordinate silicon transition structure was proposed to justify the experimental observations. In a more extended mechanistic study *N*-funtionalized pipecolinamides **88** were proposed as an example of efficient catalyst after several variations in the C2 and the *N*-protected group ([185], for more recent L-pipecolinic basic organocatalysts for hydrosilylation of imines, see: [186, 187]).

### 3.1.4 Piperazine Lewis base Organocatalyst

Sun and co-workers envisioned that the piperidinyl ring on the abovementioned catalysts could be replaced by a piperazinyl backbone, considering that the




**Scheme 30** Pioneering examples of L-valine-based Lewis basic catalysts

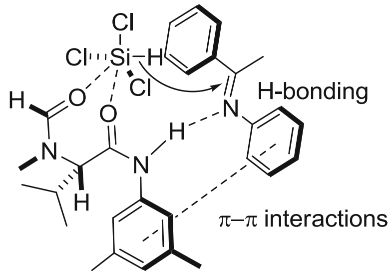


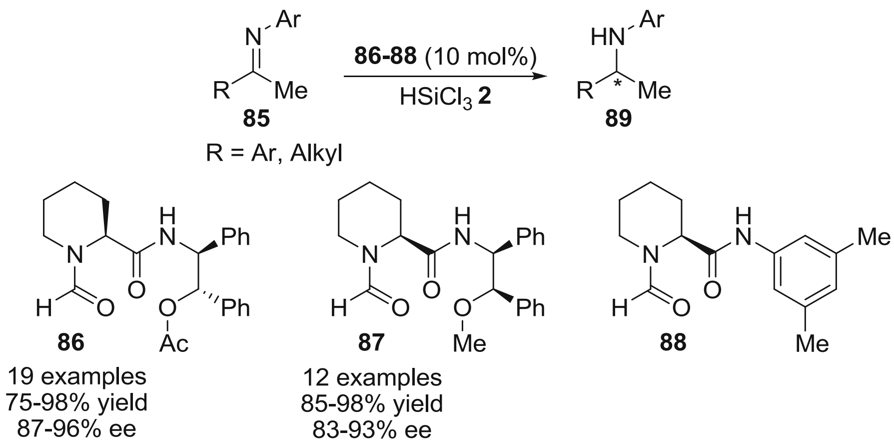

**Fig. 7** Mechanism of hydrosilylation of imines

additional secondary amino group on the 4-position (N4) should provide a suitable site to introduce structural variations and thus accurately to modify the catalytic properties. In this context, a new catalyst **91** was designed (Scheme 32) [188, 189], which promoted the unprecedented reduction of the relatively bulky ketimines **90**, becoming a complementary structure to the existing catalytic systems. The reductions of both *N*-aryl acyclic methyl ketimines and non-methyl ketimines **90** were catalyzed for a broad spectrum of substrates affording the desired chiral amines **92** in high yields and with high ee values.

Unfortunately, other *N*-substituted phenyl ketimines **93a–e** afforded lower ee values compared with **90**. The *N*-benzyl ketimine **93e** was also proven to be an unsuitable substrate using **91** as catalyst. The authors found that the arene sulfonyl group on N4 and the 2-carboxamide groups were crucial for the high enantioselectivity of the process and the efficiency of the catalytic system.

### 3.1.5 S-Chiral Sulfinamide Derivatives

Although stereogenic sulfur centers had been used as the source of chiral auxiliaries and ligands [190–195], organocatalysts incorporating chirality solely through the sulfur atom had been almost overlooked in the literature before the development of



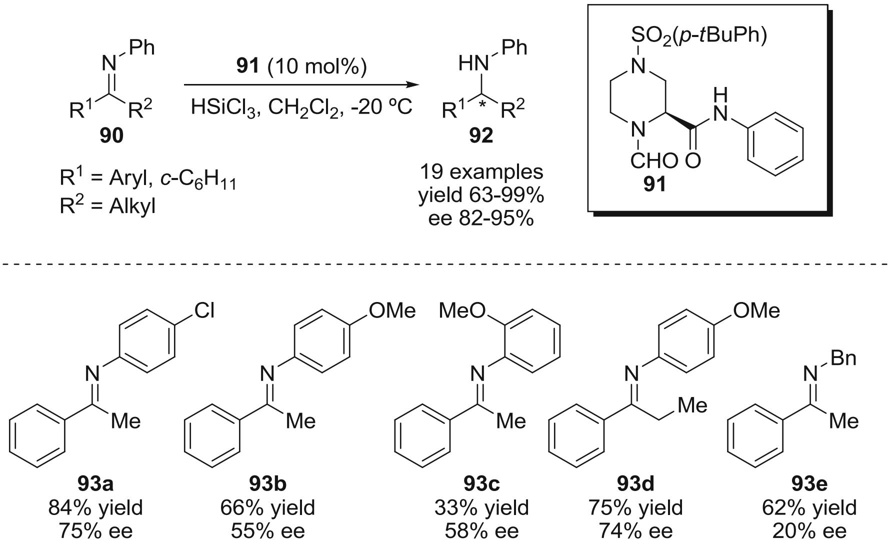

**Scheme 31** Model L-pipecolinic acid derived *N*-formamide catalysts **86–88**

this subarea of research. In this context, Sun's group developed the first highly effective example of sulfinamide organocatalyst **95** to promote the asymmetric hydrosilylation of ketimines with **2** in high yield and enantioselectivity (Scheme 33) [196]. Having in mind the idea that two molecules of monosulfinamide catalyst could participate in the mechanism of the reaction (Fig. 8), the same authors designed bissulfinamide **96** [197] incorporating two sulfinamide units, which efficiently promoted the asymmetric reduction of *N*-aryl ketimines in high yields and improved enantioselectivities (Scheme 33). Compound **96** resulted to be a better catalyst than the former monosulfinamide **95**.

The same group developed a new Lewis base organocatalyst **97,** which included stereogenic atoms represented by a sulfinamide group and a α-amino acid framework bearing Lewis basic carboxamide functionality, both for the activation of $HSiCl_3$ **2**. Excellent enantioselectivities and high yields for a wide range of aromatic *N*-alkyl ketimines were achieved (Scheme 33) ([198], for more recent examples belonging to the same research group, see also: [199, 200]).

### *3.1.6 Supported Lewis Base Organocatalysts*

With the increasing interest in developing catalysts able to be easily separated from the final product, many efforts have been devoted to the preparation of immobilized structures (for reviews on polymer-supported organocatalysts, see: [201–204], for a more recent example, see also: [205]). In this field, Kočovský's group has also reported interesting Lewis base supported catalysts for the efficient asymmetric hydrosilylation of ketimines with silane **2**. The first reported example was an *N*-methylvaline-derived Lewis basic formamide anchored to a polymeric support with




**Scheme 32** Reduction of imines using piperazine Lewis base derivative **91**

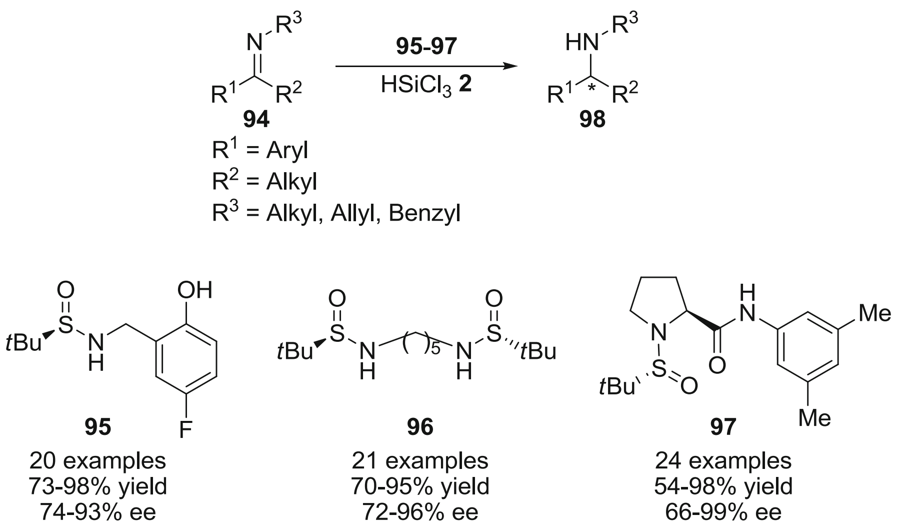
a varying spacer **100**. This protocol represented a considerable simplified procedure to isolate the catalyst from the crude of the reaction, which is not a trivial task, for instance on a large scale protocol (Scheme 34). The polymer-supported catalyst was reused at least five times without any loss of activity [206].

The same research group designed a soluble catalyst **102** with the main aim of avoiding the problems associated with the heterogeneous systems, and related to the common supported catalysts [207]. The main advantage of this system is the inverted solubility pattern that this catalyst exhibits, since it is soluble in non-polar solvents and insoluble in polar media (Fig. 9). This feature simplified the recovery (up to 99 %) and re-use of the catalyst at least five times without loss of activity, improving the results obtained with catalyst **100** (for the preparation of other immobilized catalysts easily recoverable, see: [208]).

In order to enable the isolation procedure of the organocatalysts, Kočovský's group also reported an alternative approach using a dendron-anchored organocatalyst **103** to efficiently reduce the imines with trichlorosilane **2** [209]. The isolation procedure of the catalyst from the crude was substantially simplified, since most of the catalyst (≥90 %) could be recovered by precipitation and centrifugation (Fig. 10).

## 3.2 Reduction of Ketones

Although the reduction of imines has been widely explored, as described above, the reduction of carbonyl groups has been less studied until now. Specifically, the reduction of ketones is more limited due to the low reactivity shown by these compounds. In this field, the pioneering works using trichlorosilane as reducing agent and a chiral Lewis base were reported by Matsumura and co-workers in 1999,




**Scheme 33** Example of efficient sulfinamide organocatalysts **95–97**

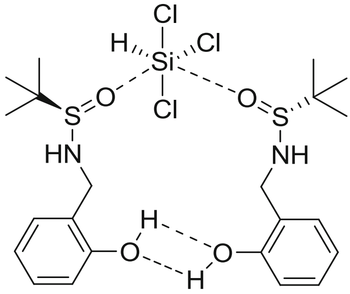
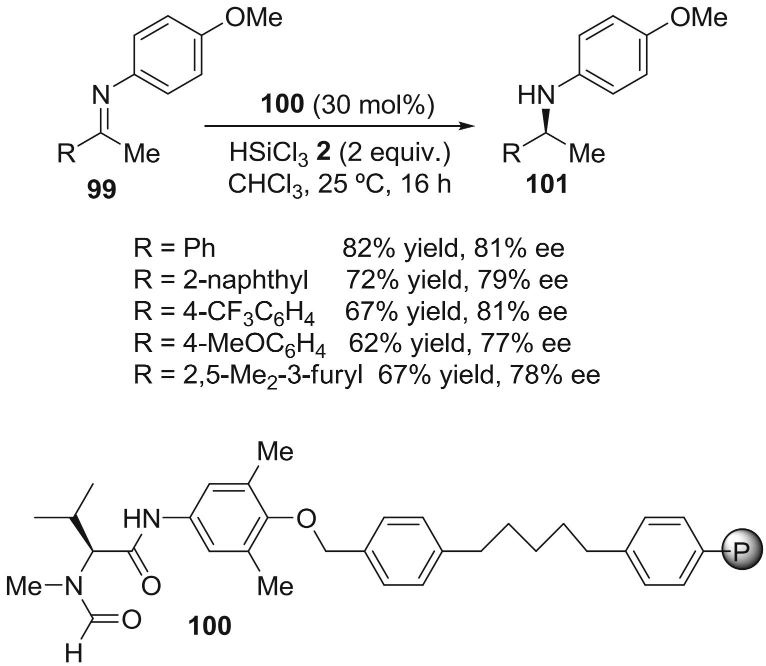


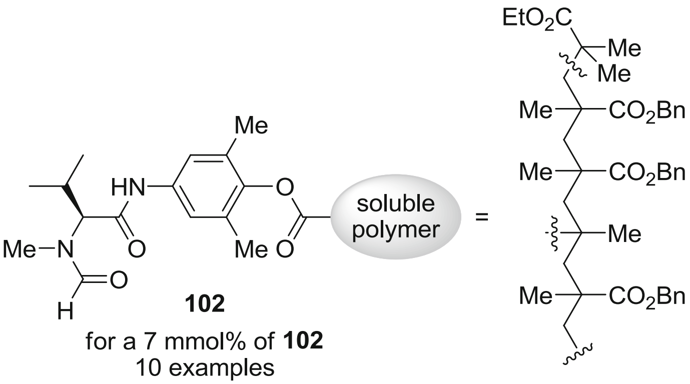
**Fig. 8** Mode of action of monosulfinamide organocatalysts




**Scheme 34** Application of polymer-supported organocatalyst **100**

affording low to moderate enantioselectivities (for the seminal enantioselective work using Lewis base to reduce carbonyl groups, see: [210], for pioneering works using chiral lithium salts, see: [211–213]). More recently and independently, Malkov, Kočovský, and co-workers [214] and Matsumura's group [215], reported isoquinolinyloxazoline **105** and *N*-formylpyrrolidine **106**, respectively, as new catalysts to significantly improve the enantioselectivity of the process in comparison with the pioneering work (Scheme 35).

In these examples the carbonyl compounds were limited to aromatic ketones. Based on the experimental results, the authors proposed the following TS to explain the enantioinduction observed in their work (Fig. 11) [214].




**102**

for a 7 mmol% of **102**
10 examples
70-90% yield
55-91% ee

**Fig. 9** Soluble supported catalyst **102**

The **2** would be chelated by the catalyst forming an activated hydrosilylating species, while a second molecule of $HSiCl_3$ would likely activate the ketone by coordination to the oxygen atom. The attack of the hydride would take place from the less hindered *Si* face. Additionally, the π–π interaction between the heteroaromatic ring of the catalyst and the aromatic ring in the ketone would stabilize the system.

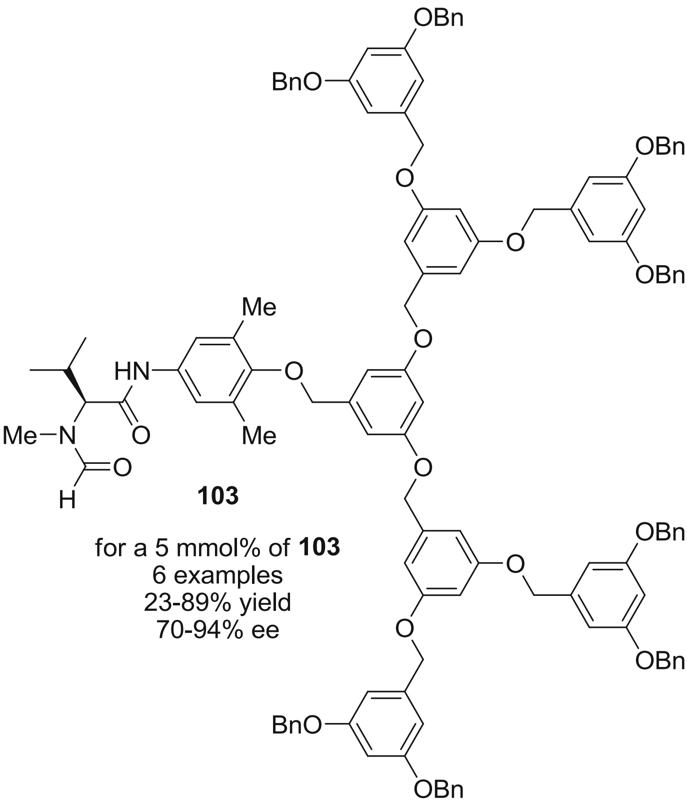
Later, Sun's group also used their pipecolinic acid derivative **87** for the first efficient reduction of aliphatic and aromatic ketones with silane **2** in moderate to high enantioselectivity [184]. A plausible transition state was proposed in order to explain the results observed, where the catalyst **87** would act as a tridentate activator and would promote the hydrosilylation of ketones through the heptacoordinate silicon structure depicted in Fig. 12.

It is remarkable that the hydrosilylation procedure has been successfully used for the synthesis of important targets. Matsumara and co-workers demonstrated the applicability of their developed method in the preparation of optically active lactone **109** from keto ester **108** in 93 % yield with 97 % ee (Scheme 36) [215]. Lactone **109** is an important building block for the synthesis of a variety of biologically active substances [216–218].

### 3.3 Reduction of β-Enamino Esters

In the last decade, increasing efforts have been devoted to the asymmetric preparation of structurally diverse β-amino acids (for selected reviews, see: [219–222]), due to their involvement in the synthesis of peptidomimetics and as valuable building blocks.

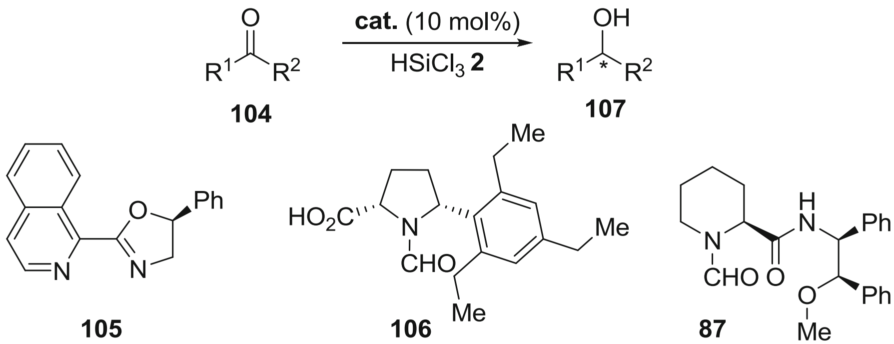
In this field of research, enantiomerically enriched β-amino acids could be also obtained through transfer hydrogenation using β-enamino esters ([223], for pioneering works using metals, see: [224, 225]). This approach was initiated by Matsumura and co-workers [173] reporting a single example using catalyst **111**




103

for a 5 mmol% of **103**
6 examples
23-89% yield
70-94% ee

**Fig. 10** Dendron-anchored organocatalyst **103**




**104** **107**

**105**
7 examples
35-93% yield
70-94% ee

**106**
11 examples
61-94% yield
93-97% ee

**87**
13 examples
81-99% yield
53-93% ee

**Scheme 35** Enantioselective reduction of ketones **104**

**Fig. 11** Activation proposal

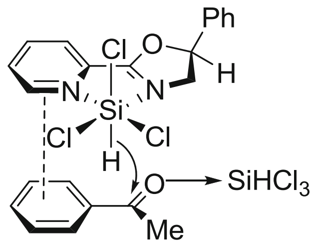
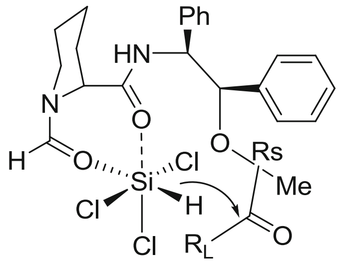
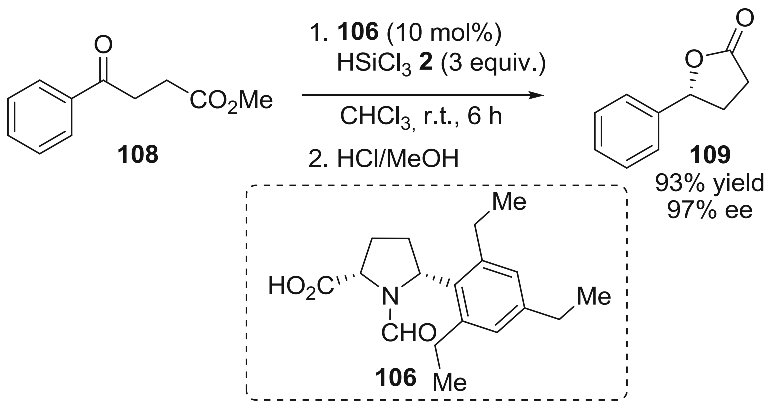



**Fig. 12** Role of pipecolinic acid derivative **87**

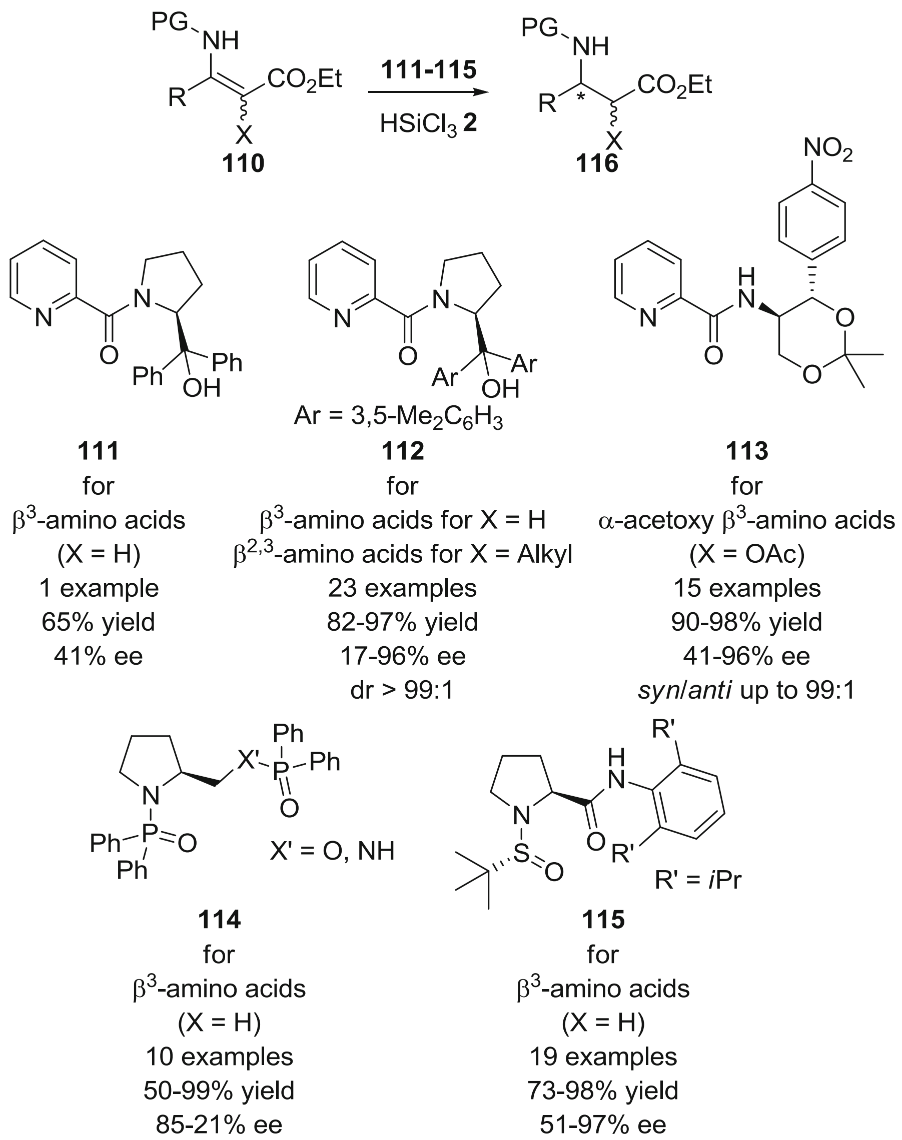



(Scheme 37). Later, the methodology was improved by Zhang's group with Lewis base catalyst **112** [226] and **113** [227], and also Benaglia and co-workers with catalysts **114** (Scheme 37) [228]. Remarkably, Sun's group reported an interesting methodology using water as additive and the Lewis base catalyst **115** [229]. The addition of 1 equiv. of water resulted to be crucial for the success of both reactivity and enantioselectivity of the process (Scheme 37). All these approaches were potentially useful for the preparation of enantiomerically enriched β-amino acid derivatives, which in all cases was achieved with good yield and good enantioselectivies [230].

Interestingly, in order to extend the applicability of the reduction of β-enamino esters, the protocol developed by Zhang and co-workers using catalyst **113** was



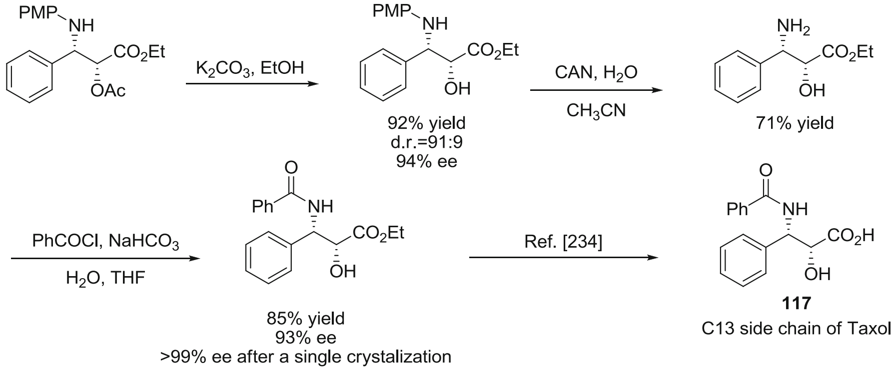

**Scheme 36** Synthesis of optically active lactone **109**



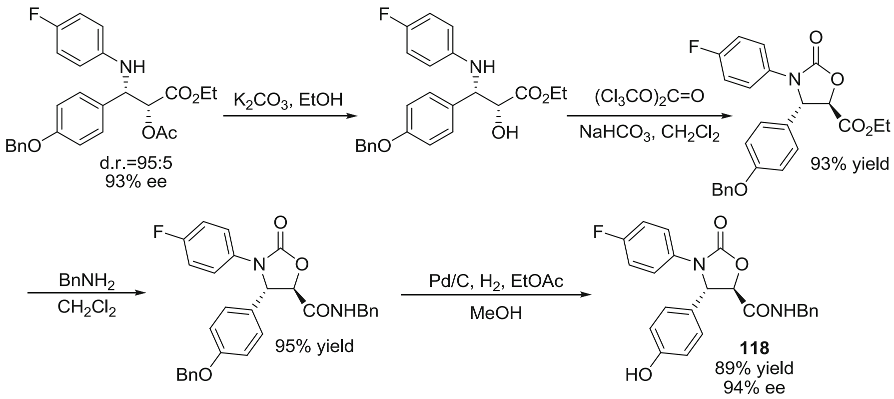

**Scheme 37** Reduction of β-enamino esters **110** (for other examples of reduction of enamines, see: [231–233])

successfully applied in the synthesis of the taxol C13 side chain **117** and oxazolidinone **118**, which is a potent hypocholesterolemic agent (Schemes 38, 39) [227].

Malkov, Kočovský, and coworkers also reported the interesting synthesis of $\beta^{2,3}$-amino acids, in which synthesis is still a challenge, using organocatalyst **83** (Scheme 40) [236]. This approach is based on the fast equilibration between the




**Scheme 38** Enantioselective synthesis of the taxol C13 side chain **117** [234]



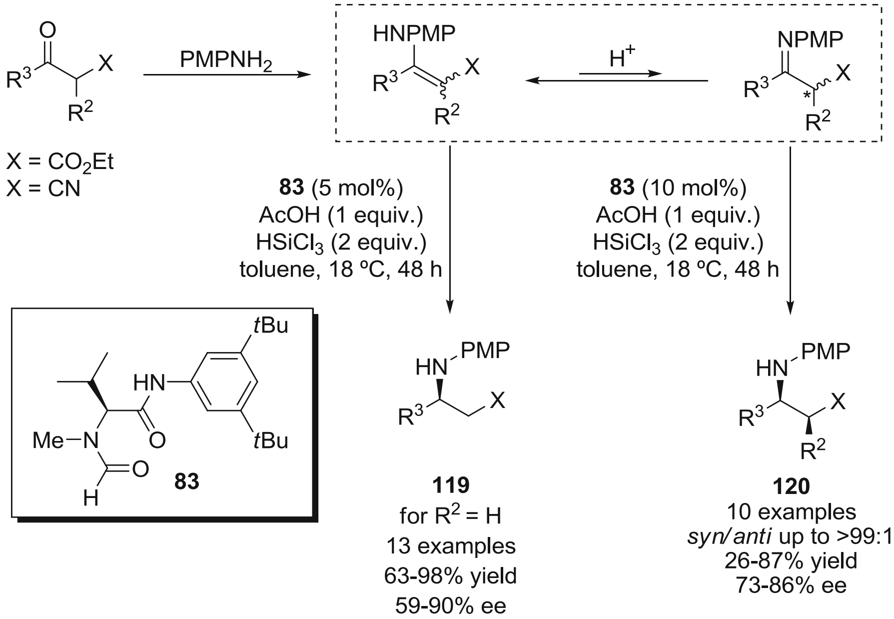

**Scheme 39** Enantioselective synthesis of oxazolidinone **118** [235]

enamine and imine forms. A subsequent reduction of the equilibrated mixture with $HSiCl_3$, afforded the corresponding amino esters and amino nitriles with good results.

AcOH was used in order to maintain the concentration of $H^+$ constant. Although the presence of $H^+$ also catalyzed the competing nonselective reduction, under the optimized reaction conditions, the use of one equivalent of AcOH provided a good compromise between reactivity and selectivity.

## 4 Conclusions

A great number of organocatalytic examples of reduction of different C=N, C=O and C=C double bonds affording new stereogenic centers has been illustrated. The organocatalytic transfer hydrogenation has been mainly focused on the pioneering examples using Hantzsch dihydropyridines **1** and trichlorosilane **2** as hydride




**Scheme 40** Enantioselective synthesis of $\beta^3$- and $\beta^{2,3}$-amino acid derivatives **119** and **120**

sources, although other reducing agents have being explored in the last few years. Organocatalysts such as chiral Brønsted acids, thioureas, and chiral secondary amines or Lewis bases have been successfully used in all the reported examples. As reflected in the numerous examples, this field is the focus of great interest. This is proof of the importance that the asymmetric transfer hydrogenation arouses, and the power of this approach to achieve the final target. Certainly, in the near future new hydride sources and novel organocatalysts will be designed to achieve this goal in a greener and more environmentally friendly manner.

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