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Review

Applications of Hantzsch Esters in Organocatalytic Enantioselective Synthesis

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Abstract: Hantzsch esters (1,4-dihydropyridine dicarboxylates) have become, in this century, very versatile reagents for enantioselective organic transformations. They can act as hydride transfer agents to reduce, regioselectively, a variety of multiple bonds, e.g., C=C and C=N, under mild reaction conditions. They are excellent reagents for the dearomatization of heteroaromatic substances, and participate readily in cascade processes. In the last few years, they have also become useful reagents for photoredox reactions. They can participate as sacrificial electron and hydrogen donors and when 4-alkyl or 4-acyl-substituted, they can act as alkyl or acyl radical transfer agents. These last reactions may take place in the presence or absence of a photocatalyst. This review surveys the literature published in this area in the last five years.

Keywords: 1,4-dihydropyridine dicarboxylates; transfer hydrogenation; transfer-alkylation; photoredox catalysis; chiral phosphoric acid; enantioselective catalysis; reduction; alkylation; dearomatization; radical transfer; electron donor-acceptor complexes

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1. Introduction

1,4-Dihydropyridine dicarboxylates, or Hantzsch esters (HEs) as they are known in honor of Arthur Rudolph Hantzsch—who first published methods for the synthesis of dihydropyridines in 1882 [1]—have become in recent years important agents for enantioselective transfer hydrogenation (ETH) [2,3]. The reduction of C=C and C=N functional groups can be achieved, even in heteroaromatic systems, particularly in the presence of a Lewis or Brønsted acid catalyst to activate the hydrogen acceptor. When chiral catalysts are used, the synthetic transformations proceed in an enantioselective manner, and very high levels of induction are achieved. The organocatalysts more frequently used for this purpose have been chiral amines, phosphoric acids, thioureas, or squaramides.

The HEs are structurally related to "Nature's reducing agents", the dihydropyridine-based nucleotides NADH (reduced nicotinamide adenine dinucleotide), and the closely related NADPH (reduced nicotinamide adenine dinucleotide phosphate). These substances are the cofactors which are more often used in cells for enantioselective biochemical hydrogenations [4]. Their use as hydride reducing agents was inspired by Nature, and the first applications in organocatalytic enantioselective reactions were published in 2004, independently, by the groups of List [5] and then MacMillan [6].

Prior to these discoveries, transition metal-catalyzed ETH had become a well-established branch of catalysis, particularly when performed with Ru(II) catalysts—complexed to chiral monotosylated 1,2-diamines or amino alcohols, with isopropyl alcohol or the HCOOH/Et_3N azeotrope as the hydrogen source [7,8]. These systems were very much explored by Noyori and co-workers during the 1990s, displaying ees >90%, and turnover numbers (TONs) and frequencies (TOFs) approaching those obtained in transition metal (TM)-catalyzed hydrogenation reactions, which contributed greatly to the development of this field [9].

Several catalysts based on other metals, ligands, and hydrogen donors have been shown since to work as well [8]. TM-catalyzed ETH with alcohols or HCOOH as hydrogen sources is (it refers to Transition metal-catalyzed ETH) particularly efficient for the asymmetric reduction of ketones and imines [10]. C=C double bonds are reduced only when conjugated and if -additional electron-withdrawing groups are present in the conjugated system, otherwise the unsaturated alcohol is obtained e.g., with enones and enals. C=C double bond reduction is observed with nitroalkenes. Thepartial reduction of triple bonds has rarely been reported. Aromatic or heteroaromatic systems cannot be reduced. Hantzsch esters have also been used as hydride donors with transition metals as catalysts [3,8].

In contrast with the TM-catalyzed systems, the biomimetic approach with an organocatalyst-HE combination will reduce a C=C double bond chemoselectively in preference to the C=O bond in an unsaturated system, e.g., in an α,β-unsaturated ketone, it will also reduce C=N bonds, and even heteroaromatic systems [2]. It does not reduce C=O bonds. This can be done with transition metals in combination with Hantzsch esters [11,12].

HEs are on their own an important class of calcium channel blockers and some are commercialized for the treatment of hypertension, e.g., nifedipine, amlodipine, or nimodipine [13]. The capacity of HEs to react as hydride donors is related to the energy gain obtained when the aromatic pyridine by-product is formed.

In more recent years, along with developments in visible light-driven photochemistry, new roles have been discovered for HEs as sacrificial reductants via single-electron-transfer (SET) and hydrogen sources in photochemical reactions [14,15]. Generally, the electron is transferred to a photoredox catalyst, which subsequently acts as an electron shuttle. The reverse process of stepwise reduction is also possible, i.e., hydrogen atom transfer (HAT) first, then SET. The first example in visible-light photocatalysis was demonstrated by Kellogg and coworkers, who reduced a phenacyl sulfonium salt with *N*-methyl HEs with $Ru(bpy)_3Cl_2$ as a photocatalyst under visible light [16,17]. HEs have since even been used as dehalogenating agents [18,19]. However, there have been examples in which single-electron transfer occurs upon visible light irradiation in the absence of photocatalysts [14,20].

In 2013, it was found that 4-alkyl-substituted Hantzsch esters (4R-HEs) can break the C–C bond and release the alkyl radical under condition of photocatalysis [21]. Several applications of this chemistry have been published since, but examples of organocatalytic enantioselective alkylation reactions using this approach are still scarce [22,23]. Not all HEs are capable of transferring an alkyl group. Whereas when R = Bn, *tert*-Bu, cyclohexyl, allyl, transfer can occur, when R is aromatic, e.g., Ph or thienyl, the HE will not function as a radical transfer agent [24]. The reasons for this are still not clear, although they are already being investigated by theoretical studies in the hope of finding ways of designing new HE alkylating agents [24].

Besides in the reduction of unsaturated double bonds, or alkyl transfer reactions, HEs have been applied in several cascade processes. Since they run under mild reaction conditions, frequently at room temperature, and the reactions are generally simple to operate without the need for specialized equipment as in high-pressure hydrogenation reactions, they have found many applications even in target-oriented synthesis. Applications in other types of chemistry are being explored and some progress has been made, as for example in the reduction of tertiary alcohols, described later in this review. Figure 1 shows the structures of HEs found in this review.

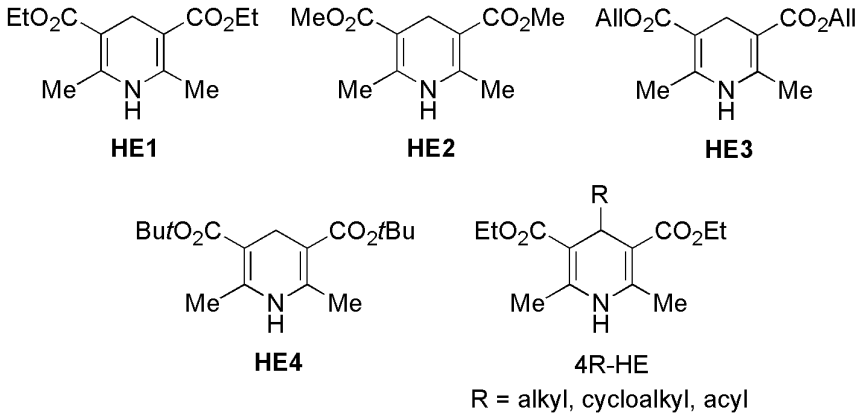


Figure 1. The Hantzsch esters most frequently used in enantioselective reactions during the period covered by this review.

The review surveys the literature on organocatalytic enantioselective reactions of HEs published since 2018. Metal-catalyzed processes are not included, and neither are biocatalytic processes. It is meant to be an update on our previous review in Org. Biom. Chem., published in 2017, where the reader can find references to works published prior to that date [2]. For reviews on related topics, see also references [25,26]. The information herein is divided into two main sections: HEs in enantioselective transfer hydrogenation, and HEs in "transfer-alkylation" and other photoredox radical reactions. The first section is further divided according to the class of chiral organocatalyst involved in the ETH reaction.

2. Enantioselective Transfer Hydrogenation

2.1. Brønsted Acids as Catalysts

2.1.1. Phosphoric Acid-Catalyzed Reactions

BINOL (1,1′-bi-2-naphthol)-derived Brønsted acids, and more particularly chiral phosphoric acids (CPAs), are a class of compounds that has proved to be robust, with extremely active catalysts promoting many types of highly enantioselective reactions [25–29]. Their applications in transfer hydrogenation have been particularly successful. They can be easily synthesized to incorporate several types of substituents.

NMR studies of the binary complexes between different CPAs and aromatic N-arylimines showed the formation of strong, charge-assisted hydrogen bonds in these catalyst/substrate complexes, which result from the formation of a network of CH–π and π–π interactions [30,31]. This information suggests that the stereoselectivity that they convey stems from the noncovalent interactions [29,32,33].

The sense of chiral induction in ETH catalyzed by CPAs has been rationalized in terms of a three-point contact model based on steric interactions; it assumes a bifunctional activation mode by the catalyst towards the HE and the substrate simultaneously [34].

a. Synthesis of Dihydropyrimidinones (DHPMs)

DHPMs are a class of compounds that often display interesting pharmacological activity [35,36]. This biological activity can depend on the configuration of chiral centers present in the molecule; hence, methods of enantioselective synthesis are of great interest. For example, the (*S*)-enantiomer of Monastrol is a more potent inhibitor of Eg5 ATPase activity than the (*R*)-enantiomer [37]. 2-Hydroxypyrimidines **1** were used recently to prepare enantiomerically-enriched 3,4-dihydropyrimidin-2(1*H*)-ones **2** via organocatalytic transfer hydrogenation, a dearomatization reaction catalyzed by a chiral CPA, (*R*)-**C1**—also known as TRIP—and a Hantzsch ester as a hydrogen source [38]. A highly chemoselective partial hydrogenation of the pyrimidines could be achieved at 40 °C, and the products incorporated a chiral center at C-4.

This was the first report of an asymmetric biomimetic transfer hydrogenation of pyrimidines. Both the yield and the ees were strongly dependent on the electronic nature of

the substituents. The best results were obtained when R^1 and R^2 were aryl groups with electron-donating substituents (≥97% yield, 91–>99% ee), but the ee dropped considerably if one of these groups was methyl (36%). The reduction of unsymmetrical multi-substituted 2-hydroxypyrimidines yielded inseparable mixtures. In such cases, dihydrophenanthridine (DHPD), a weaker donor than **HE1**, proved to be a better hydride transfer agent. Unfortunately, it was only when one of the R groups (at position 4) was methyl that a positive result could be obtained. When other alkyl substituents were present in the 2-hydroxypyrimidine ring, the transfer hydrogenation failed to take place. The stereoselectivity observed in these reactions is in agreement with the reaction model in which there are two hydrogen bonding interactions, and the steric hindrance built up by the "three-point contact model" favors a *Re* face approach of the reagents, as shown in TS1, rather than as in TS2 (Figure 2) [1].

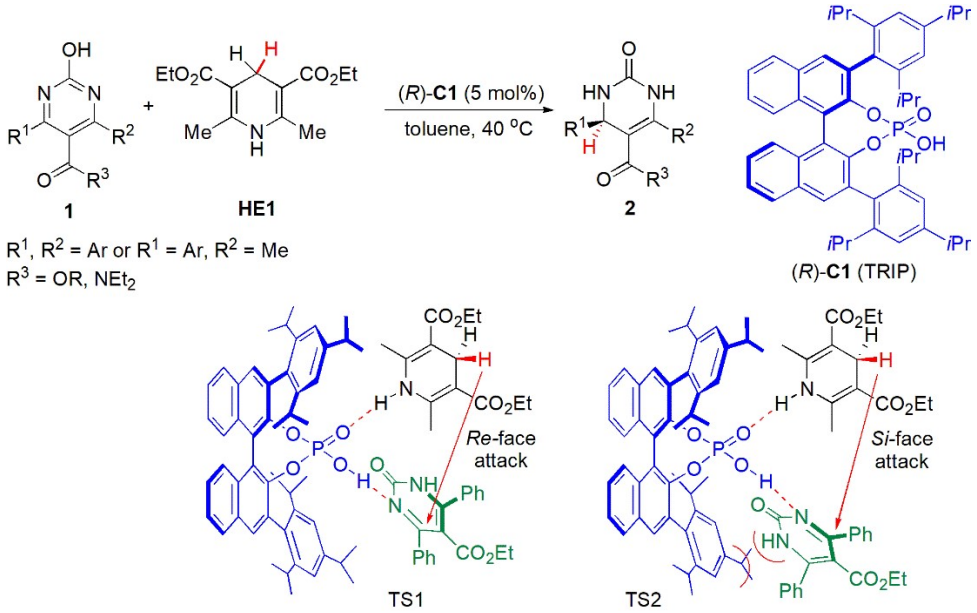


Figure 2. Enantioselective synthesis of 3,4-dihydropyrimidin-2(1*H*)ones from 2-hydroxypyrimidines [38].

The synthesis of the alkyl-substituted DHPMs was subsequently achieved from pyrimidin-2-ones **3**, via 1,4-reduction with the same CPA and **HE1** combination (Figure 3) [39]. Although *N*-methyl substituted substrates were used, there was no reduction of the C=N bond to yield a 1,2-reduced product, and the 1,4-reduced product was obtained exclusively. The reaction worked well with several alkyl substituents in the pyrimidin-2-one ring. The DHPMs **4** were obtained with very high yields and ees, with either electron-rich or electron-poor aryl substituents present in the aryl ring at C-4.

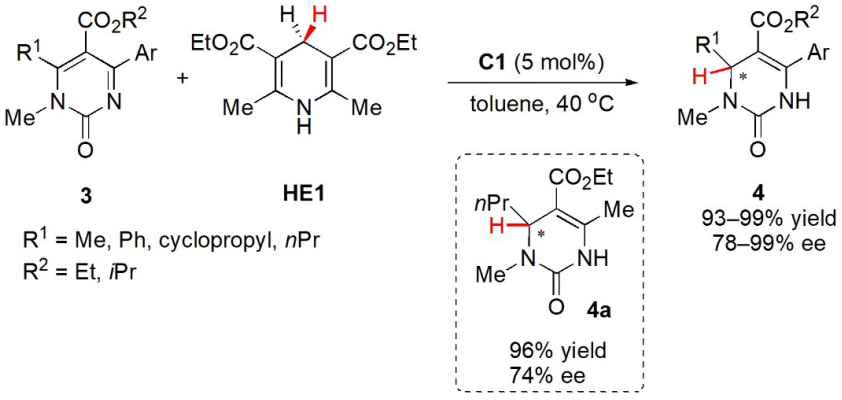


Figure 3. Enantioselective 1,4-reduction of pyrimidin-2-ones to 3,4-dihydropyrimidin-2(1*H*)-ones [39].

In a more recent development, chiral non-racemic phosphonyl ester-substituted DHPMs were synthesized by a redox deracemization reaction [40]. This procedure involved an oxidation reaction to destroy the stereocenter in racemic phosphonyl-substituted dihydropyrimidines *rac*-**5**, pre-prepared from the known corresponding pyrimidin-2-ols by reaction with a phosphite and zirconium tetrachloride (Figure 4). This was followed by ETH to regenerate the chiral carbon center bearing the vicinal phosphonic ester group, which gave rise to a series of optically active phosphonate substituted DHPMs (*R*)-**5** with up to 96% ee. The oxidation and transfer hydrogenation reactions could be performed in one pot with DDQ as an oxidant, with the chiral catalyst and reducing agent being added once the oxidation was complete, as evidenced by TLC. It was assumed that the reaction proceeded via the oxidation of the racemic starting mixture to an aromatic intermediate I, followed by a CPA-facilitated reversible isomerization to yield tautomer II. 1,2-Hydrogenation of the C=N bond yielded the final product. This hypothesis was supported by an additional experiment with a hydroxyl-protected substrate, for which no reaction could be observed under the standard conditions. A large range of diversely substituted substrates could be used successfully. However, if R^1 = Me, the ee dropped to 5% with a 94% yield. The nature of the phosphonyl ester substituents was also important, and the best results were obtained when they were diisopropyl. When these were phenyl groups, no ETH was observed. The reaction could also be performed on a gram-scale, e.g., with **5a** (**5**: R^1 = Ph, R^2 = H), to afford the corresponding product in 92% yield and 96% ee.

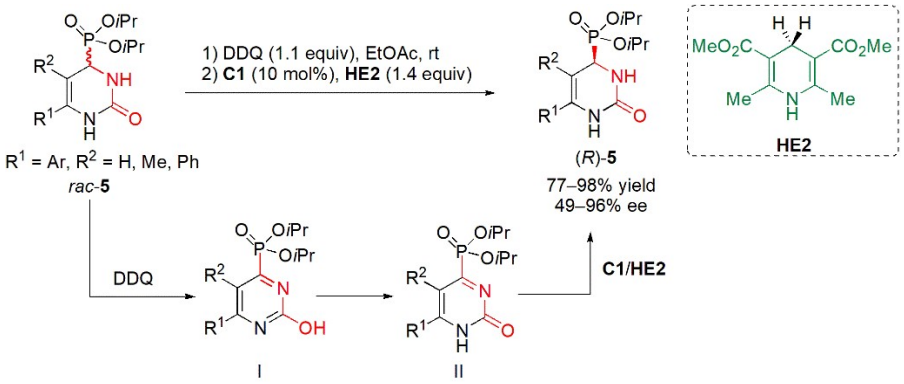


Figure 4. Redox deracemization of phosphonate-substituted dihydropyrimidines [40].

b. Reactions of indoles

ETH has been widely used in the past for the synthesis of polycyclic indole derivatives [2,41–43]. Cascade reactions involving catalytic asymmetric dearomatization (CADA) have been used, for example, for the asymmetric synthesis of tetrahydro-β-carbolines. The highly enantioselective synthesis of these substances has been described recently by a CPA-catalyzed sequential enamine isomerization/Pictet–Spengler reaction of indolyl dihydropyridines [44].

The spiroindolenine framework has been generally regarded as a key intermediate in Pictet–Spengler reactions, and the possibility of being able to capture in situ and manipulate further these intermediates frequently involved in the synthesis of indole derivatives could allow access to novel indole derivatives [45]. In a recently published procedure, this was achieved [46]. Starting from indolyl dihydropyridines **6** bearing a three-carbon tether, the tetrahydrospiro[indoline-3.1′-quinolizine] core **7** was obtained when the substrate was exposed to a reaction with chiral CPA (*S*)-**C2** and **HE1**, via an enamine isomerization/spirocyclization/transfer hydrogenation sequence (Figure 5). A gram-scale synthesis was also possible, without deterioration of the results. Good yields and very high ees were obtained generally, with only one diastereoisomer in most cases. Relative (*syn*) and absolute (*S*,*S*) configurations were determined by X-ray crystallographic analysis.

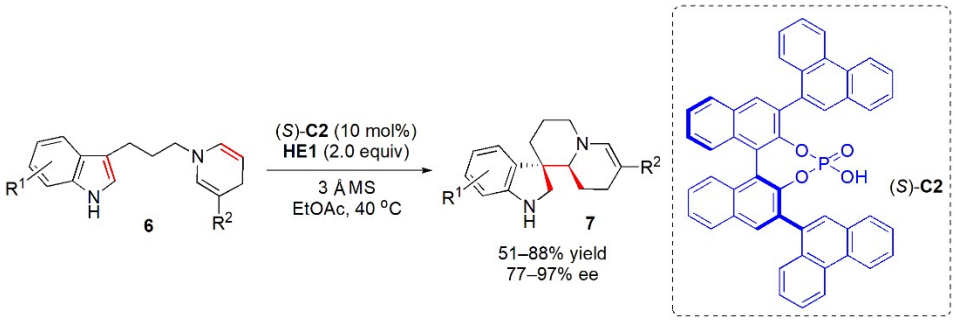


Figure 5. Catalytic enantioselective synthesis of spiroindolines [46].

The 1,1-diarylmethinyl stereocenter is a structural motif present in a large number of natural products and biologically active molecules [47]. One of the most direct approaches to obtain this structural unit is the asymmetric addition to the 1,1-diaryl C=C and C=X double bonds. Nevertheless, this is not a trivial matter, since it requires effective discrimination between two (often) sterically similar aryl groups. The use of directing groups has been the main way to resolve the problem, together with metal catalysis. An organocatalytic approach was recently developed, which allows discrimination between non-directing aryl and heteroaryl groups, thus providing access to highly enantioenriched triarylmethanes [48]. It relies on the formation of an intermediate indole imine methide from indoles **8**, bearing racemic tertiary alcohol moieties at position C-3 (Figure 6). Chiral indole triarylmethanes **10** could be obtained in a highly enantioselective fashion when the substrates were treated with a chiral phosphoric acid, namely **C3** in the presence of benzothiazoline **9** as a hydride transfer agent. In this case, when a Hantzsch ester **HE1** was employed instead **9**, the products were obtained in high yields, but the ees were low.

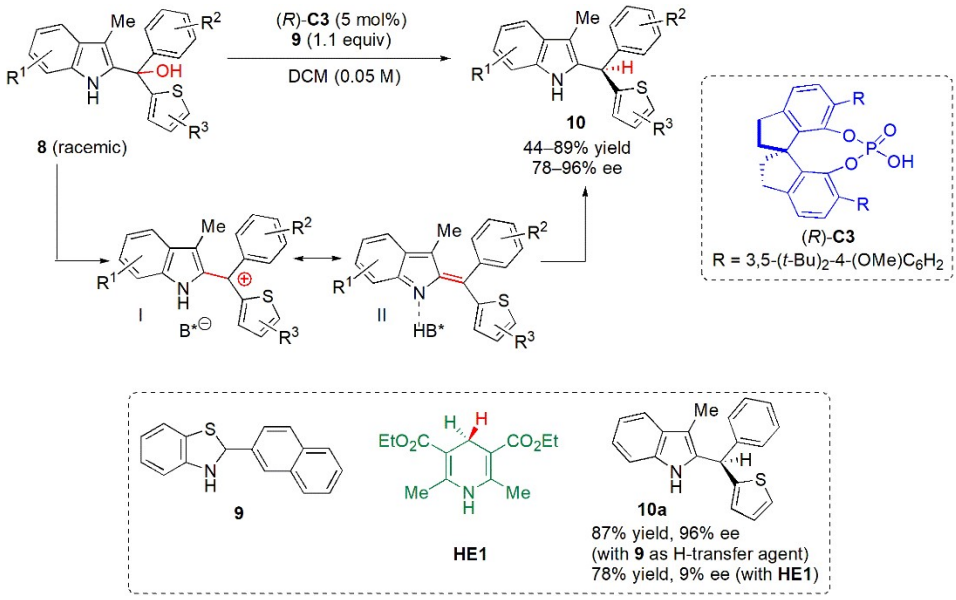


Figure 6. Enantioselective synthesis of bioactive indole-containing triarylmethanes [48]. B* = chiral acid counterion.

The reaction is assumed to go via an acid-catalyzed dehydration to yield an indolyl cation I1, paired with a phosphate counter anion, which may be in equilibrium (or pseudo resonance) with the respective activated indole imine methide form I2. Subsequently, the hydride source approaches benzylic carbon from the sterically most favorable side to deliver the product **10**. DFT (density functional theory) calculations suggested that the key interaction for discrimination of the two aryl groups is mainly π–π stacking.

c. Reactions of quinolines

Quinolines were the first heteroaromatic substrates to be reduced by organocatalytic transfer hydrogenation, a feat which opened the door to a new area of research, allowing dearomatization reactions based on hydrogenation to become simplified, since they can now be performed without the need to use hydrogen gas and high pressures without specialized equipment. It also simplified the synthesis of alkaloids, many of which contain these heterocycle frameworks. Since the first report with 2-substituted quinolines in 2007 [49], several developments have taken place. Recent reports are mostly related to applications in cascade reactions or to the development of novel catalysts.

In 2018, 2-aminochalcones **11** were utilized in a synthetic route involving a one-pot sequential procedure to produce tetrahydroquinolines (THQs) **13**, and for the first time the whole transformation could be achieved with a single catalyst (Figure 7) [50]. The synthetic process involves the initial formation of a quinoline, which is subsequently reduced to the corresponding THQ derivative **12**, i.e., a cyclization followed by an asymmetric reduction. In previous reports on the organocatalytic synthesis of this heterocyclic skeleton, starting from 2-aminochalcones, two catalysts were required, one for each of these steps, which required compatibility between the two to exist. In this new procedure, a chiral CPA is the only catalyst.

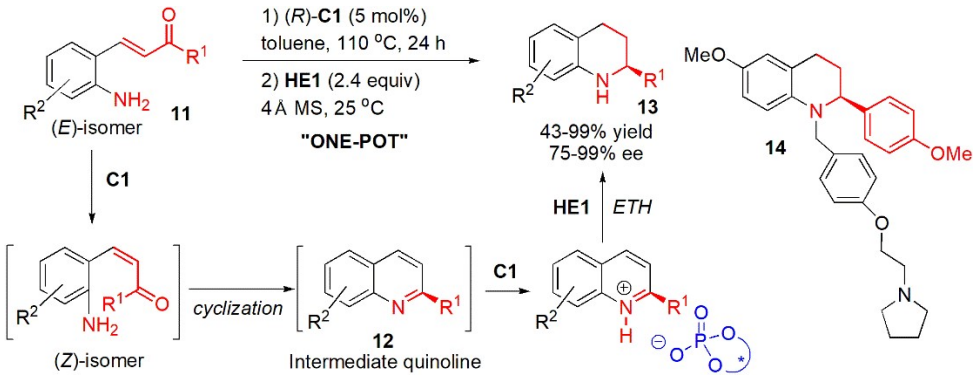


Figure 7. Enantioselective synthesis of THQs from 2-aminochalcones via a consecutive one-pot reaction catalyzed by (*R*)-**C1** [50].

Although the dehydrative cyclization of 2-aminochalcones appears to be the most straightforward way to obtain 2-substituted quinolines, in practice, the conversion does not take place, because the chalcone exists in a stable (*E*)-configuration which places the amino group too far from the carbonyl group for any condensation reaction to take place. By using the phosphoric acid, the double bond in the unreactive (*E*)-configuration isomerizes to the (*Z*)-configuration and at the high temperature in which the reaction takes place, the condensation occurs. Once the cyclization is complete, as evidenced by TLC, a Hantzsch ester (**HE1**) is added at room temperature, and through the usual hydrogen transfer reactions, the heterocycle is reduced to yield the final desired product. The co-addition of molecular sieves helps to improve the yields. Several THQs could be obtained in high yields and excellent ees, with the reaction being relatively insensitive to the nature of functional groups present in the substrate. The method was applied to the synthesis of an estrogen receptor modulator (**13**).

In the mechanism generally accepted for the dearomatization of quinolines by ETH with a CPA/HE combination, two molecules of hydride donor are required to convert one molecule of quinoline to the desired final product, and each working on one of two subsequent catalytic reduction cycles (Figure 8) [49]. In the first cycle, the quinoline is reduced by a 1,4-hydride addition to a dihydroquinoline (DHQ), which subsequently enters the second cycle. One equivalent of Hantzsch pyridine is formed as a by-product. Upon DHQ protonation by the Brønsted acid and isomerization to an iminium, a second hydride addition occurs, a 1,2-addition. This is the enantio-determining step, during which the

Hantzsch ester is released as an ion pair with the CPA. After proton transfer, the CPA is regenerated and a second equivalent of Hantzsch pyridine is obtained.

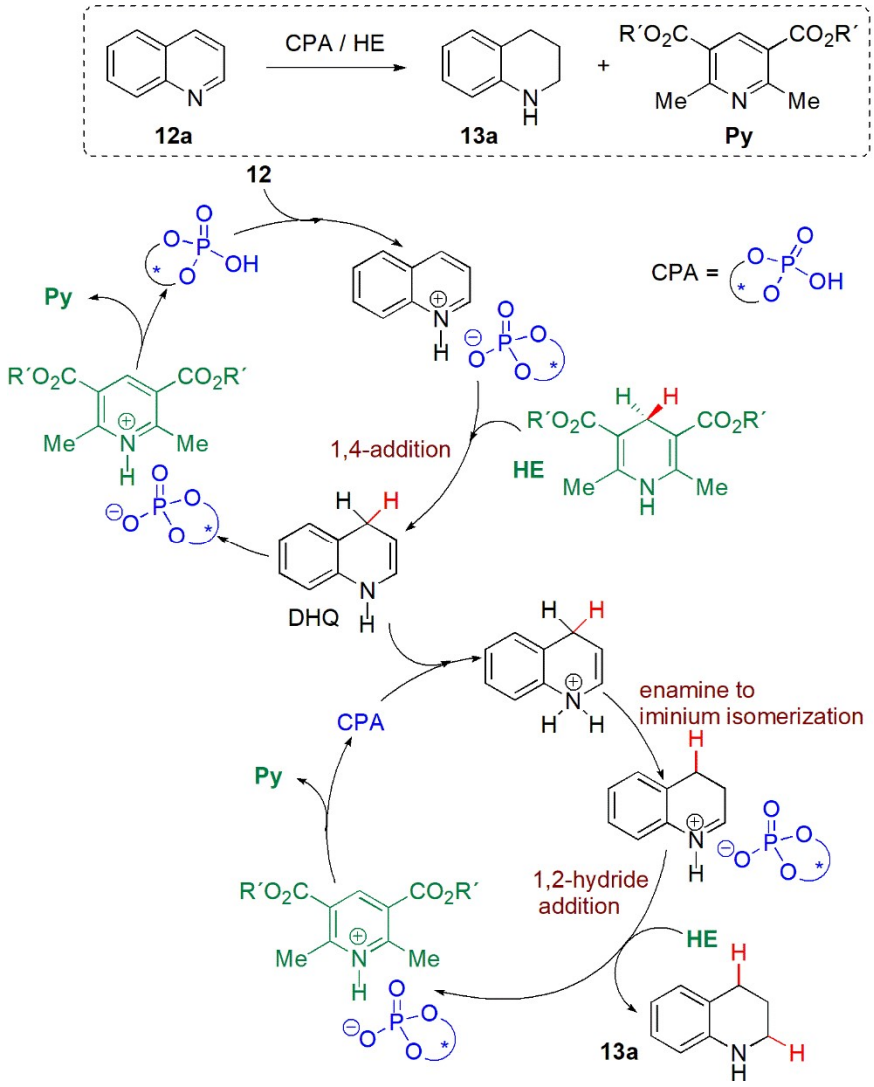


Figure 8. The mechanism initially proposed for the ETH of quinolines [49].

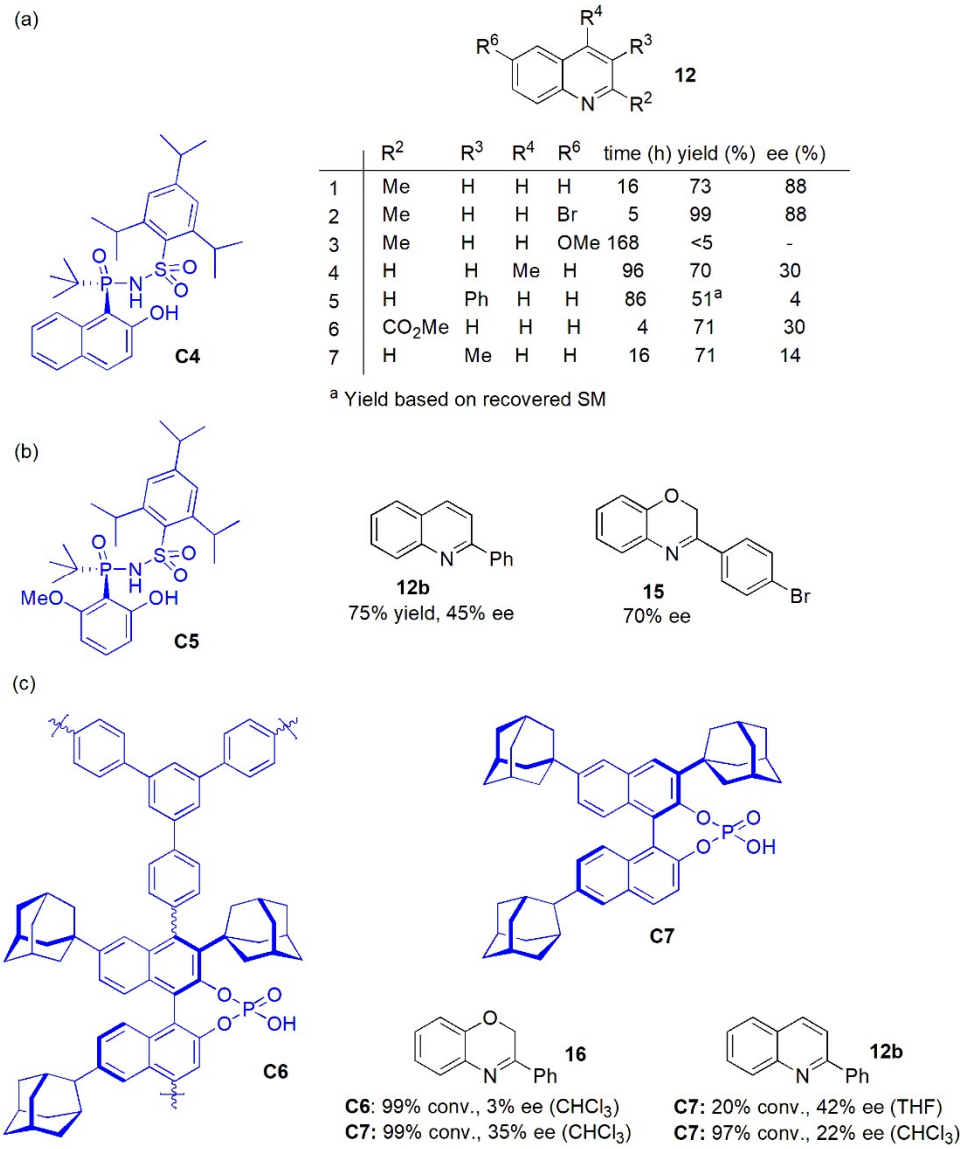
The availability of catalysts that provide efficient chiral differentiation is of prime importance in this field. Since in ion-pair complex formation the chiral counteranion tends to remain in the vicinity of the positively charged nitrogen atom, the highest enantio-differentiating effect is expected to be on the vicinal carbon atom, and less on the other carbons in the ring. The design of new catalysts also looks at the possibility of enhancing chiral discrimination at other centers in the molecule. In addition, improving catalyst acidity can lead to reaction rate enhancements, and this is another aspect being studied.

In 2019 new P-chiral, *N*-phosphoryl sulfonamide Brønsted acids were described and evaluated in the ETH of quinolines [51]. The catalyst shown to perform better was catalyst **C4**, the properties of which compared favorably with those of BINOL-derived phosphoric acids with a small substrate-binding pocket. The results obtained with 5 mol% **C4** in the ETH of quinolines with a variety of substitution patterns in the presence of **HE1**, at rt, are shown in Figure 9a. Further recrystallizations could improve the ees.

A related chiral-at-phosphorus catalyst, **C5**, was prepared and evaluated in ETH reactions with **HE1** (Figure 9b) [52]. This catalyst was less reactive, requiring a temperature of 60 °C for substrate conversion to the THQ within a reasonable time, 48 h in the case of the 2-phenyl-substituted quinoline. With this more difficult substrate, with 10 mol% of **C5**,

a slightly lower yield and ee was obtained than with **C5**. A lower selectivity was observed in the reduction of 2*H*-benzo [1,4] oxazine **15**.

The immobilization of CPAs on heterogeneous supports for easier separation and recovery from reaction solutions, and recyclability, also continues to be a subject of interest since the first reports in 2010 [53,54]. Instead of the classical immobilization with prefabricated supports, a "bottom-up" approach can also be used, with the catalyst being embedded into the polymer network [55,56]. Such catalysts include the recently prepared adamantyl-BINOL-based chiral porous aromatic polymers (Ad-BINOLPAFs), which contain hindered BINOL-derivatives bearing bulky groups embedded into a porous Polymeric Aromatic Framework (**C6**) (Figure 9c) [57]. They were evaluated in ETH, with **HE1** as a hydride donor, but although the yields of the products obtained were high, they were almost racemic. A free adamantyl-derived BINOL (**C7**), used for comparison, afforded moderate ees.



	R^2	R^3	R^4	R^6	time (h)	yield (%)	ee (%)
1	Me	H	H	H	16	73	88
2	Me	H	H	Br	5	99	88
3	Me	H	H	OMe	168	<5	-
4	H	H	Me	H	96	70	30
5	H	Ph	H	H	86	51[a]	4
6	CO_2Me	H	H	H	4	71	30
7	H	Me	H	H	16	71	14

[a] Yield based on recovered SM

Figure 9. ETH of quinolines with chiral-at-phosphorus catalysts **C4** (**a**) and **C5** (**b**) and (**c**) with adamantyl-BINOL derived catalysts **C6** and **C7** [57].

The ETH of quinolines has been the subject of theoretical studies to determine the nature of the enantiocontrol in CPA-catalyzed reactions [29,58]. In the mechanism generally accepted for this reaction (Figure 8), it is assumed that the CPA acts as a Lewis

base−Brønsted acid (LBBA) bifunctional catalyst, not simply as an acid that can simultaneously activate the two reaction partners in the second catalytic cycle—the quinoline in its iminium form and the Hantzsch ester (Figure 10). Both (*Z*) and (*E*)-configured iminium ions are suitable substrates. This was the basis of a DFT study performed in 2008, with a simplified PA catalyst, i.e., a biphenol-derived CPA with mesityl substituents on its 3,3′-positions. It was concluded from this study that the enantioselectivity is established in the hydride transfer step and that there are two transition states mostly responsible for the enantioselectivity observed, one leading to the major enantiomer of the product, 15 kJ/mol higher in energy than the other [58].

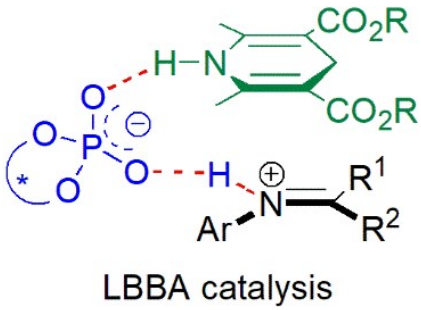


Figure 10. Complexation between the catalyst and the reagents in LBBA catalysis in the ETH of quinolines. The secondary (non-covalent) interactions are not shown [58].

In a new DFT study described in 2018, an alternative proposal was made, in which the enantioselectivity would be achieved not in the hydride transfer step, but rather in the coordination of HE to the CPA-DHQ complex by selective association [59]. According to this model, using a (*R*)-BINOL-derived CPA, stereochemical control occurs through the preferential formation of a three-component complex either from the side leading to the (*S*)-enantiomer, or from the side leading to the other, on which HE insertion in the active site is easier. Therefore, the catalytic reaction is under Curtin−Hammett control, and the origin of enantiocontrol relates to "dynamic kinetic selection" between two prochiral conformers. The calculations reproduced the experimental data well.

d. Miscellaneous

Enantioselective reductive amination is another type of reaction that may be achieved by ETH. The first example performed with the help of CPA/HE combinations was described in 2006 [60]. In a reaction between an amine and a ketone, the enantioselective reduction of the imine intermediate was achieved in high yields and ees. Reductive amination reactions utilizing simple aldehydes and amines were subsequently described [61], and later the chiral phosphoric acid-catalyzed asymmetric amination of α-branched cyclic ketones [62]. An application in a complex cascade reaction was also reported [63].

Recently, the reductive amination of β-tetralones was described for the first time [64]. Upon the reaction of β-tetralones **17** with anilines **18** when CPA **C1** was used as catalyst and Hantzsch ester **HE1** as hydride donor, various chiral β-aminotetralins **19** were obtained in good yields with good to high ees (Figure 11a). However, the product was almost racemic when a *p*-hydroxyaniline was used as a reaction partner and it was also low when a *p*-methoxyaniline was reacted with a tetralone bearing a methoxy group at position 8. Steric effects were also important since there was almost no reaction with a 2-methoxy-substituted aniline. The related reductive amination of α-tetralones was unsuccessful, since they were unreactive under the same reaction conditions.

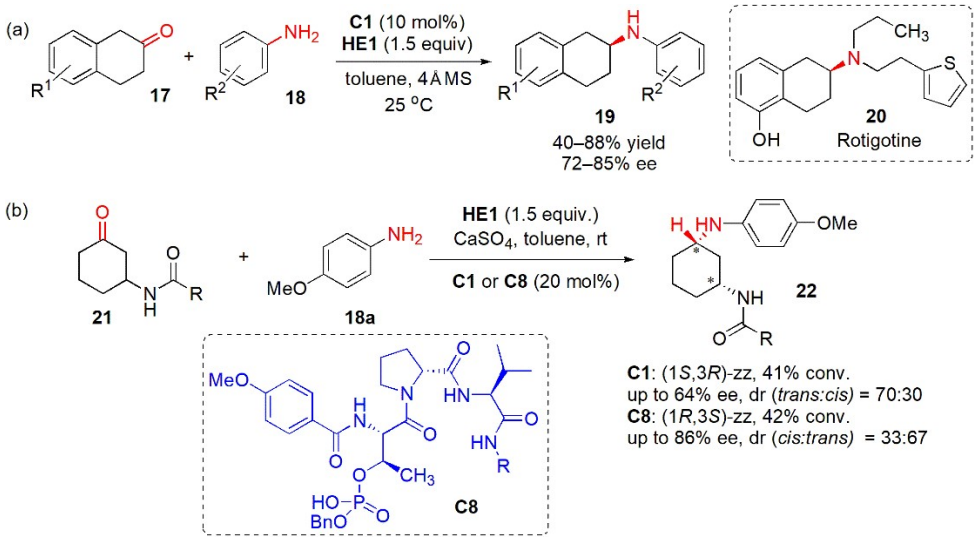


Figure 11. (**a**) Enantioselective synthesis of β-aminotetralins [57]; (**b**) Phosphothreonine-catalyzed reductive aminations of 3-amidocyclohexanones [59].

The utility of the new protocol was demonstrated in the enantioselective synthesis of rotigotine (**20**), a dopamine agonist of the non-ergoline class, used for the treatment of Parkinson's disease and restless legs syndrome [65]. Previous catalytic protocols relied mainly on the asymmetric hydrogenation of cyclic enamides derived from β-tetralones with transition metals, e.g., Ir, Ru, or Rh, as catalysts. These catalysts are more expensive, and extra care is required to ensure that there is no metal residue left, particularly in the synthesis of targets of pharmaceutical interest.

The reductive amination of 3-amido cycloalkanones **21** was explored in 2018. Since there is the possibility of producing *cis*- and *trans*-substituted products, the study was directed at developing catalysts capable of exhibiting divergent selectivities [66]. A range of phosphothreonine (*p*Thr)-embedded peptide catalysts was developed, with different amino acid sequences, and their potential, tested in this reaction. Up to 86% ee was obtained with **C8** [dr (*trans:cis*) 33:67], in a reaction with *p*-anisidine (**18a**) and **HE1** (Figure 11b). When the same reaction was performed with (*S*)-TRIP (**C1**), the opposite selectivity was obtained (64% ee, dr (*trans:cis*) 70:30. NMR studies and DFT calculations performed at the time suggest that secondary interactions between the substrate and the catalyst are responsible for the selectivity observed. A parallel kinetic resolution of the substrates appeared to be in operation as well.

Oxocarbenium ions, derived from cyclic ethers, are another functional group of interest for ETH. However, these reactions have been challenging. Some success has been achieved with pyrilium ions. The cyclization of chalcones **23** was achieved via the corresponding benzopyrilium ions **24**, to yield enantio-enriched 4*H*-chromenes **25** through ion-pair catalysis provided by a CPA, but additional activation was required (Figure 12a) [67]. The reaction proceeded well with light activation at 300 nm, with the benzopyrilium ions being formed in situ (Figure 11a).

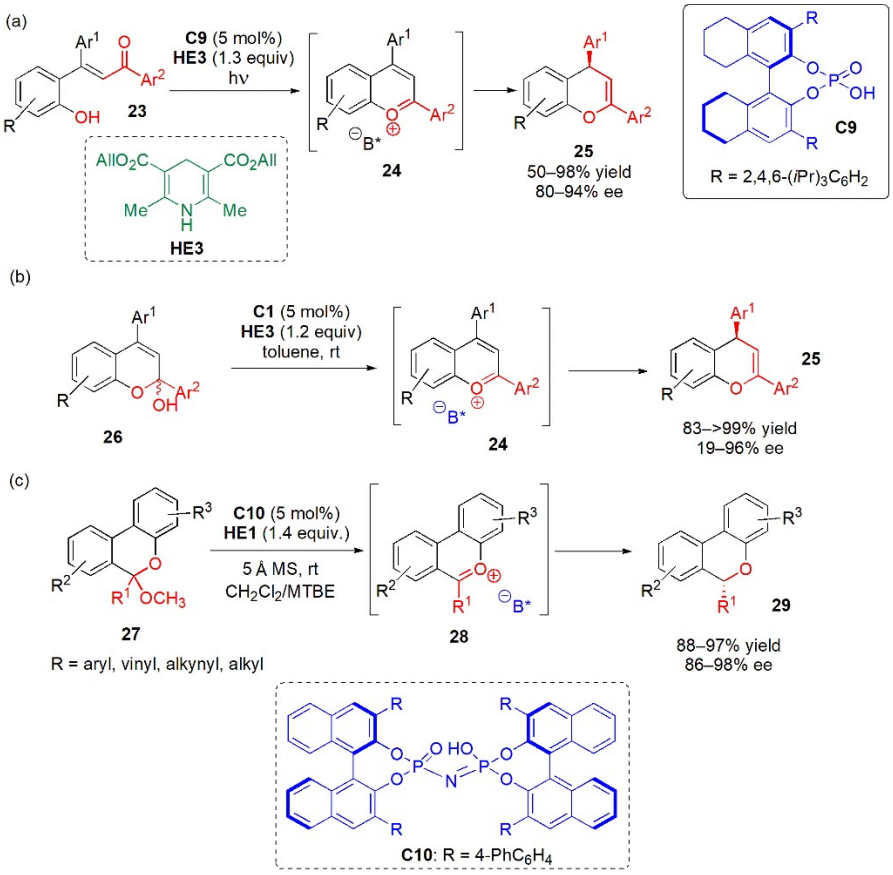


Figure 12. (**a**) Light-assisted asymmetric ion-pair catalysis in the ETH of pyrilium ions to produce chiral 4*H*-chromenes [67]; (**b**) Synthesis of chiral 4*H*-chromenes from racemic 2*H*-chromen-2-ols [68]; (**c**) Synthesis of chiral benzo[*c*]chromenes by ETH [69]. $B^{\ominus}$ = Chiral acid catalyst counteranion.

The 1,4-reduction of benzopyrilium ions was also achieved starting from racemic 2*H*-chromen-2-ols **26** after CPA activation (Figure 12b) [68]. In this case, light was not necessary, and cat **C1** (TRIP) allowed the formation of the required chiral ion-pair **24** by the dehydration of the substrate. Products **25** were obtained in up to 96% ee.

In 2018, chiral α-substituted 6*H*-benzo[*c*]chromenes **29** were obtained from the corresponding ketals through chiral imidodiphosphoric acid-catalyzed ETH [69]. Catalytic enantioselective methods to prepare these enantioenriched skeletons had so far remained elusive [70], despite the fact that this is an important structural element of many biologically-active compounds [71]. The reaction proceeds through the formation of an oxocarbenium intermediate (**28**) in the presence of **C10**, followed by a very efficient ETH, to afford the desired products with very high yields and ees.

2.1.2. Disulfonimide-Catalyzed Reactions

Although chiral CPAs have been very successful in enantioselective synthesis, there have been occasions in which a more acidic catalyst was required. The disulfonimide catalysts (DSIs) were then introduced, and they have been successfully applied in the ETH of *N*-alkylimines [72,73]. The products of these reactions are more basic than the related *N*-arylamines, which can be obtained by ETH of *N*-arylamines with CPA catalysis, and they cause catalyst inhibition, slowing down reactions. The more acidic DSIs work quite well with the *N*-alkylimines. The catalytic reactions are thought to take place with mechanisms similar to those of CPAs. In a 2019 study to determine whether these stronger Brønsted acids form binary complexes with charge-assisted H-bonds or whether pure ion pairs without H-bond contribution are formed, it was observed, by means of NMR spectroscopy, that complexes with a high ion-pair character were formed, but unexpectedly

weak H-bonds were still detected [74]. Due to the high acidity, a significant weakening of the H-bond exists, but the presence of five H-bond acceptors allows an enormous mobility of the imine in the binary DSI complexes. In fact, these catalysts are so strongly acidic that they even catalyze the ETH of NH–imine hydrochloride salts, e.g., **30**. This was reported in a 2020 study (Figure 13) [75]. The big challenge was to have the chiral acid catalyst, present in catalytic amounts, competing successfully with a stoichiometric amount of an achiral acid as a starting material **30**. Crystalline primary amine salts **31** were obtained in this study with good yields, as well as ees with **C11** as a catalyst and **HE4**. Kinetic studies and acidity data suggest that the reactions go via a bifunctional catalytic activation mode.

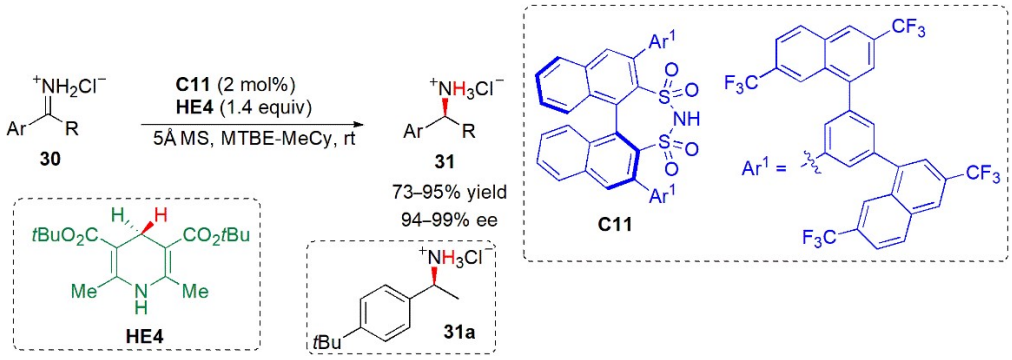


Figure 13. Highly enantioselective disulfonimide-catalyzed ETH of NH–imine hydrochloride salts [75].

Prior to this report, the known examples of imine reduction were limited to *N*-aryl or *N*-alkyl imines. For unsubstituted N–H imines only one report was known, involving the rhodium/bis(phosphine)thiourea-catalyzed asymmetric high-pressure hydrogenation (10 atm) of N–H imine hydrochloride salts, which nevertheless provided the products in excellent yields and ees [76]. The new disulfonimide procedure was also tried on a 5 g scale, and the desired product (**31a**) was obtained in 95% yield (98% ee), without requiring column chromatography purification.

Recent NMR spectroscopic studies about the ternary complex of a catalyst, substrate, and reagent in ion pair catalysis, such the transfer hydrogenation of imines catalyzed by chiral DSIs, together with quantum chemistry calculations, showed that the expected catalyst/imine H-bond switches to an unexpected O–H–N structure, previously unknown [77]. This arrangement facilitates the hydride transfer from the Hantzsch ester in the transition states. Since there are very high isomerization barriers which prevent fast pre-equilibration, the reaction barriers from the ternary complex to the transition states determine the enantioselectivity. It was concluded from this study that the weak H-bonding, the H-bond switching, and the special geometrical adaptation of substrates in the complex formed by the catalyst explain the robustness towards more challenging substrates.

2.2. Bifunctional Catalysts Based on Thioureas, Squaramides and Related Substances

Bifunctional catalysts of this type are usually combined with chiral amines or cinchona alkaloids, and recently also amides, phosphines, or sulfides on a modular basis. They are bifunctional dual H-bond donor catalysts, which activate the reactants by H-bonding and other noncovalent interactions [78]. They have been particularly successful in the ETH of β-nitroolefins [2]. During the period of time covered by this review, a few methods were described of enantioselective 1,4-conjugate addition reactions of the hydride ion promoted by bifunctional catalysts based on these structural units. They were utilized in sequential reactions jointly with other steps.

Although hydride Michael addition reactions have been reported for a few substrates, until recently the organocatalyzed transfer hydrogenation of α,β-unsaturated esters had not been demonstrated. The first report involved an isothiourea-catalyzed reaction of *para*-nitrophenyl esters **32** using a Hantzsch ester **HE1** in 2021 [79]. Good to excellent yields of

products **33** were observed using α,β-unsaturated aryl esters bearing electron-withdrawing β-substituents with a racemic isothiourea (**C12**), but the reaction was also quite sensitive to the substitution pattern of the double bond, e.g., α-substituted-α,β-unsaturated esters were unreactive under the typical reaction conditions (Figure 14). Interestingly there was no reaction in toluene, but it proceeded well in benzene at 80 °C. When a chiral isothiourea (**C13**) was employed instead, a good yield but a moderate ee (52%) were obtained. In this case benzene as well as toluene could be used as solvents, but with benzene a higher ee can be obtained at a lower temperature.

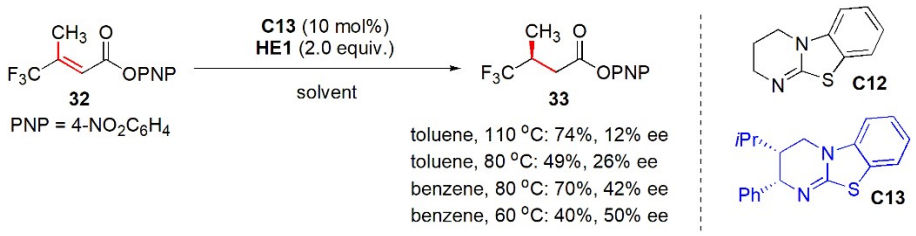


Figure 14. Isothiourea-catalyzed ETH of α,β-unsaturated esters [79].

In 2021 a method providing a stereodivergent entry to β-branched β-trifluoromethyl α-amino acid derivatives which involved a sequential (one-pot) catalytic asymmetric process was described (Figure 15) [80].

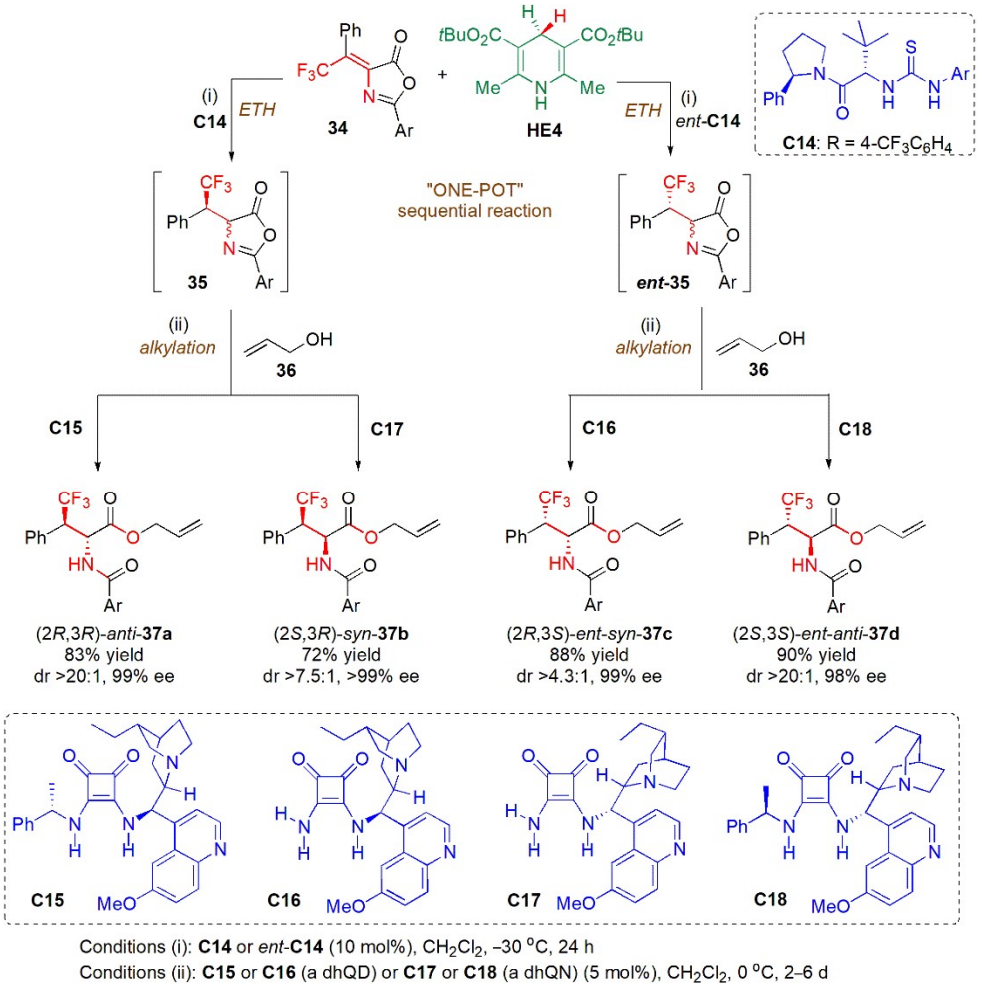


Figure 15. One-pot diastereodivergent, enantioselective synthesis of the stereoisomers of **37** with different catalyst combinations [80].

Amongst the possible ways of obtaining β-branched α-amino acids and their derivatives, the hydrogenation of suitable precursors is a plausible approach. However, since hydrogenation is a stereospecific reaction, the relative configuration of the final product depends on the E/Z geometry of the substrate. Hence, in order to prepare a certain diastereoisomer, a suitable parent olefin has to be prepared first, and the required selectivity may not always be obtainable. The olefin may also not be prone to undergo asymmetric hydrogenation, and long synthetic routes to bypass this problem may be necessary during target-oriented synthesis. A bifunctional thiourea-catalyzed process was devised to obtain the target amino acids based on the enantioselective reduction of Erlenmeyer–Plöchl azlactones, followed by the dynamic stereoselective ring opening. This process is a formal hydrogenation of the azlactone olefin, and in contrast to catalytic hydrogenation, it fixes the configurations of the two hydrogenated centers in different steps, making stereodivergency possible. An enantioselective transfer hydrogenation—dynamic ring opening via alkylation sequential reaction of compounds **34**—was thus developed as shown in Figure 15 [80]. Each one of the two steps was optimized independently until catalysts were found which gave the best results for each. In step (i), the ETH and the configuration of the first chiral center is established, giving rise to intermediates **35** which are alkylated by allyl alcohol **36**, a step which established the configuration of the second chiral center. The synthesis of all four diastereoisomers of **37** is a representative example (Figure 15).

2.3. Amines as Catalysts

Amines have been known to be useful organocatalysts for ETH with Hantzsch esters since 2005 [81]. The reduction of α,β-unsaturated aldehydes to the corresponding saturated aldehydes by Hantzsch ester **HE1** in the presence of a chiral imidazolinone, which afforded products with high ees and yields, was described then. The reaction was highly regioselective, with the double bond being reduced exclusively. Given the versatility of amines in reacting to form either enamines or imines, they have been applied to the ETH of a few other substrates since [2]. In 2018, a novel cascade process was described, involving 2-hydroxy cinnamaldehydes **38** and 1-aza-1,3-butadienes (**39**/**40**), which made possible the diversified synthesis of chromane-containing polyheterocyclic compounds **41**/**42** (Figure 16) [82].

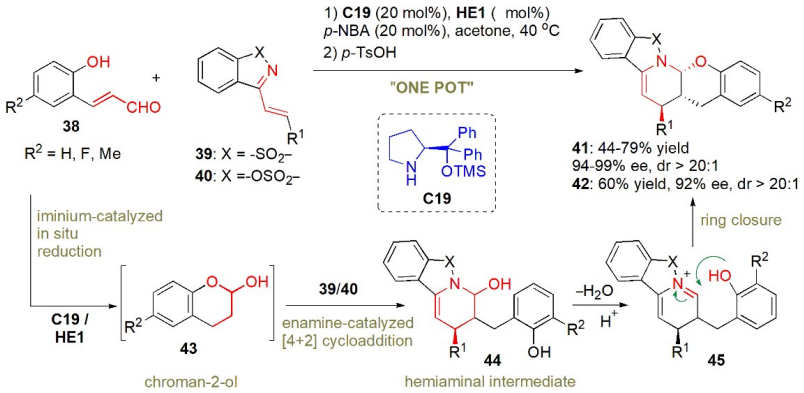


Figure 16. Synthesis of chromane-containing polycyclic compounds [82].

It was assumed that the reaction goes via a one-pot [4 + 2] cycloaddition/iminium ion-induced aminal formation cascade. Initially, a chroman-2-ol (**43**) is obtained through iminium ion formation/reduction and cyclization of compounds **38** in the presence of **HE1** and amine **C19**. An enamine-catalyzed [4 + 2] cycloaddition (or inverse-electron-demand aza-Diels−Alder reaction) ensues, generating hemiaminal intermediate **44** by reacting with the 1-aza-1,3-butadiene **39**/**40**. Subsequently, an acid-catalyzed iminium ion formation of the hemiaminal intermediate **106** provides the polycyclic product **103** by ring closure. Similarly, the 1-aza-1,3-butadiene **45** yields the product **41**/**42**. The final products were obtained with drs >20:1 and very high ees.

It was also found that if the hydride transfer agent **HE1** was not added to the reaction mixture, a different reaction pathway was followed, and functionalized chromane derivatives bearing a ketimine moiety suitable for further transformations could be obtained.

3. Hantzsch Esters in "Transfer-Alkylation" and Other Photoredox Radical Reactions

The developments in photoredox catalysis in recent years have led to the discovery of Hantzsch ester-mediated radical alkylation reactions and related transformations [22,23]. When irradiated by light of a suitable frequency, RHEs can absorb light and reach an electronically excited state. Upon excitation, they become strong reducing agents, and they can activate other substances capable of accepting electrons by single-electron transfer (SET). They can form electron donor-acceptor (EDA) complexes by weak electrostatic interactions between themselves and an electron-deficient acceptor, and undergo a photoinduced electron transfer (PET) process and subsequently homolytic cleavage, to generate C(sp^3)-centered alkyl radicals for further reactions, e.g., C-C bond formation, with other substances [83–85]. When the reactions take place in the presence of a chiral catalyst, high ees can be reached. An oxidant is not required. There are methods that require a photocatalyst and others that do not. Although this is a fairly new approach in enantioselective synthesis, a few examples have already been published. The 4R-HEs have a similar structure to HEs but on average they have a higher oxidation potential ($E^{ox}_{1/2}$ = +1.05 V vs. SCE), and they are more stable in photochemical reactions [22].

Besides this radical-mediated strategy, other photoredox reactions have been developed. They rely on the use of an HE as a sacrificial reductant by SET, which can also be a hydrogen source (as opposed to hydride).

The first reported alkylation relying on 4R-HEs and a chiral organocatalyst was described in 2019. It was the enantioselective organocatalytic addition to enals **46** of acyl radicals generated photochemically from alkyl HEs **47** to produce 1,4-dicarbonyl compounds **48** (Figure 17) [86]. The preparation of such 1,4-dicarbonyl compounds in a stereoselective manner is usually difficult, since joining two carbonyl groups in a 1,4-relationship requires a polarity inversion of one of the carbonyl substrates, i.e., some form of umpolung reactivity. Besides the use of the Stetter reaction of which there are not yet many intermolecular examples, or of acylsilanes, an intermolecular Giese-type addition of acyl radical intermediates to αβ-unsaturated carbonyl compounds is an alternative way to achieve this link, but thus far, an enantioselective catalytic version of this radical approach had not yet been described. The main problem was the high reactivity of the acyl radicals which hinders an appropriate stereocontrol. This secondary amine-catalyzed reaction which developed with alkyl-HEs as acyl transfer agents proceeded well at rt when the solution was irradiated with visible light (460 nm). The products were obtained with high yields and ees. The procedure developed could be applied to the synthesis of serotonin 5HT1A receptor antagonists **49**, and even incorporated into a reaction cascade for the stereodivergent synthesis of 2,3-difunctionalized 1,4-dicarbonyl compounds (Section 2.1 Brønsted acids were used as catalysts).

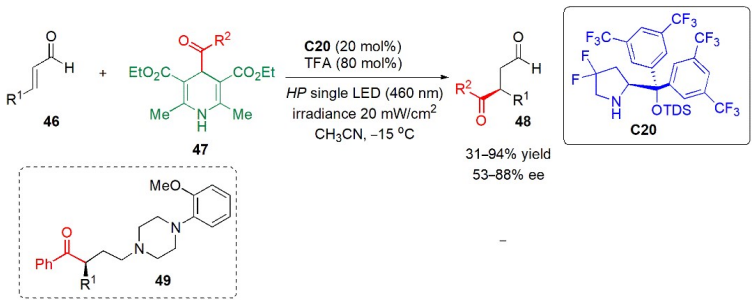


Figure 17. Enantioselective synthesis of 1,4-dicarbonyl compounds via acyl radical conjugate addition to chiral imines derived from enals [86].

In 2019, an enantioselective radical addition method using vinyl pyridines to prepare γ-functionalized pyridines was described. It relied on asymmetric cooperative photoredox catalysis mediated by visible light (Figure 18) [87]. Prior to this report, methods to functionalize vinyl pyridines at either the α-position [88,89] or the β-position [90] using Brønsted acid organocatalysis in combination with photoredox catalysis were known. However, as the distance between the α-amino radical and the nitrogen-coordinated chiral catalyst increases, the efficacy of enantiofacial induction diminishes, and indeed in the functionalization at the β-positions, the ees obtained were only moderate, suggesting that if a similar strategy were to be followed for the γ-functionalization of pyridines, the difficulty in obtaining good ees would increase. Such asymmetric reductive intermolecular coupling reactions had not yet been reported prior to this example. The addition of aldehydes to vinyl pyridines leading to γ-functionalized products had been previously achieved with enamine catalysis [91].

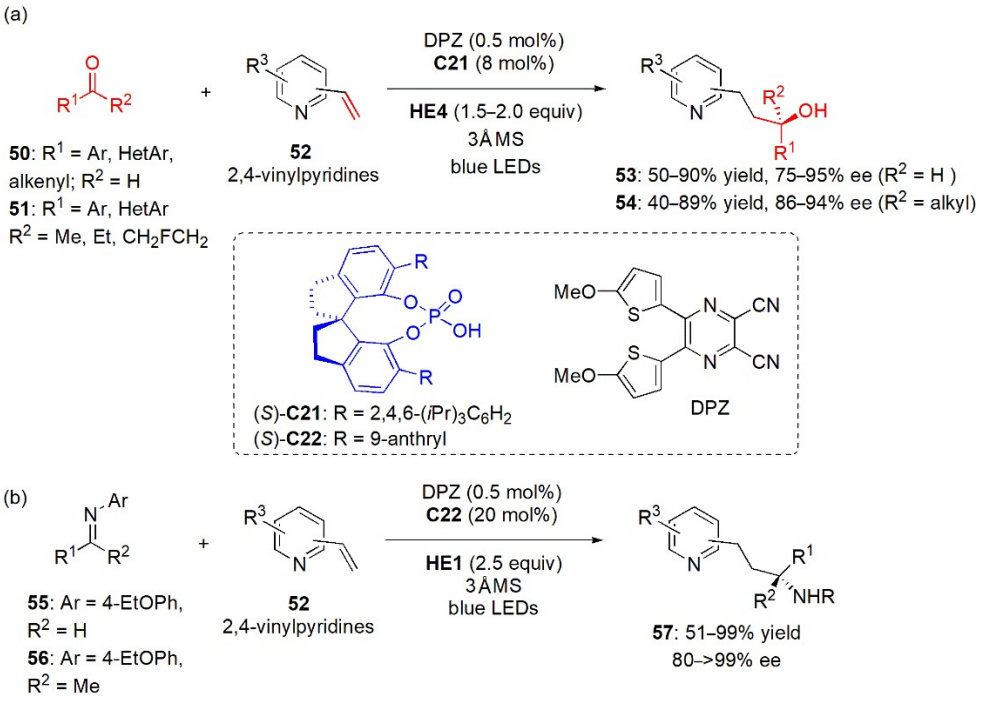


Figure 18. (**a**,**b**) Catalytic enantioselective addition of prochiral radicals to vinylpyridines under photoredox conditions and CPA catalysis [87].

In the new procedure, a Hantzsch ester was used as a sacrificial electron/hydrogen donor to obtain the required prochiral radical species. A photocatalyst, dicyanopyrazine (DPZ), was required besides the HE; otherwise, there was no reaction. If the HE was replaced by another tertiary amine, e.g., iPr$_2$Net, there was no reaction either. There was no reaction even in the absence of the CPA.

The reactions of aldehydes **50** and ketones **51** with the vinyl pyridines **52** (Figure 18a), as well as of imines, **55**/**56** proceeded well. Chiral γ-secondary and tertiary hydroxyl-substituted pyridines (**53**/**54**) and amino-substituted pyridines **57** were obtained in high yields with good to excellent enantioselectivities (Figure 18b). Although 18 successful examples were presented with aldehydes and pyridines bearing various substituents, pyridines with 4-bromo, 5-Br, Cl, or Me and 6-Me, Br, OMe were unreactive in reactions with aldehydes. Also unreactive were alkyl aldehydes, presumably because of the difficulty in reducing them to the corresponding radicals. Alkyl-substituted ketimines were also unreactive.

DFT calculations support the existence of a ternary transition state involving both reactants and the CPA. The authors proposed two different mechanisms, based on a

difference in the PCET process for the reaction, since both the CPA and PyH^+ can be involved in this process. They are exemplified for imine **55a** in Figure 19a,b.

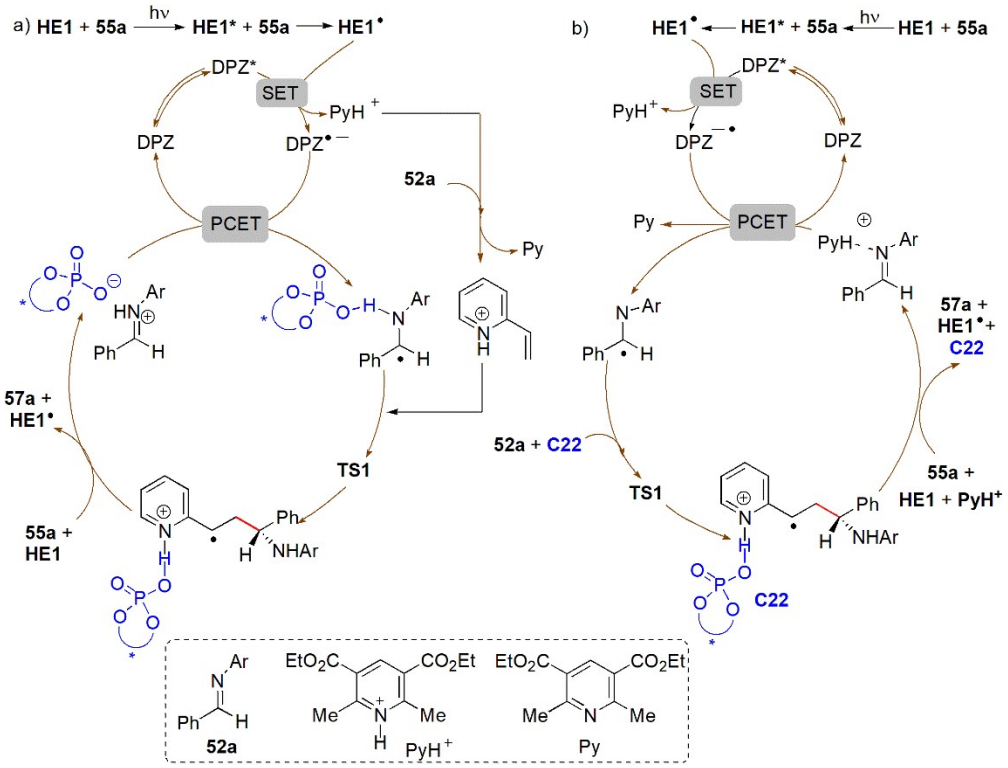


Figure 19. (**a**,**b**). Alternative mechanisms proposed for the catalytic enantioselective addition of prochiral radicals to vinylpyridines under photoredox conditions and CPA catalysis [87].

In 2019, a method of performing a Hantzsch ester-mediated Minisci-type C2-alkylation of quinolines, isoquinolines, and pyridines was described (Figure 20) [92]. Primary, secondary, and tertiary *N*-(acyloxy)phthalimide esters (NHPI) **58** were used as alkylating agents. Visible light [blue LED light (456 nm)] and CPA (**C1**) activation were required. Both electron-withdrawing and electron-donating substituents on the heterocyclic rings were well-tolerated, and ee values in the range 53–99% were obtained for products **59**. The lowest ees were obtained with the isoquinolines. It was assumed that the reaction mechanism involved the excitation of an electron-donor acceptor (EDA) complex **A**, formed from weak electrostatic interactions between the Hantzsch ester and NHPI. Electron transfer caused fragmentation of the NHPI, generating a reactive radical species R• via **C**–**E**, with loss of CO_2, which added to the *N*-heterocycle producing the nitrogen-centered radical cation **G** (Figure 21). Oxidation of **G** and deprotonation gave rise to quinolinium **H**, as well as **D** and another molecule of the radical R•. Further deprotonation (by **12a** or **D**) then delivered the desired product, as well as **F** or phthalimide.

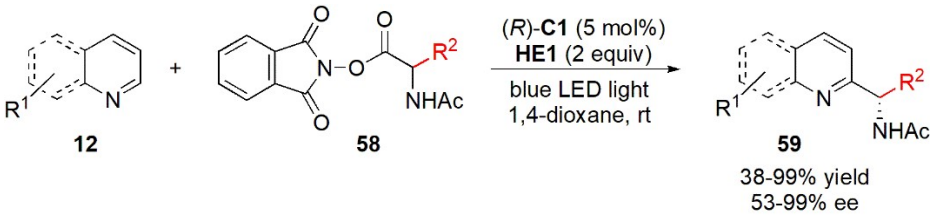


Figure 20. Enantioselective Minisci-type alkylation of *N*-heteroarenes by *N*-(acyloxy)phthalimide esters [92].

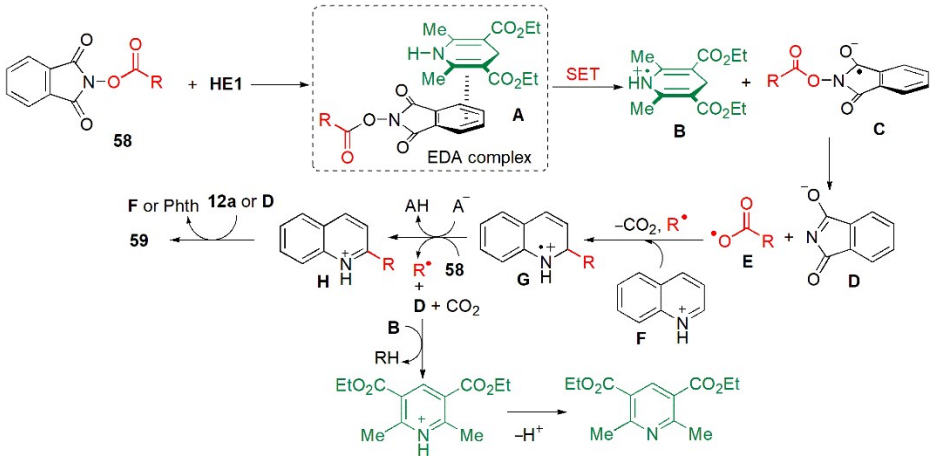


Figure 21. Mechanism proposed for the enantioselective Minisci-type alkylation of *N*-heteroarenes by *N*-(acyloxy)phthalimide esters. HA = **C1** [92].

Previous methods described for the carbon-carbon bond formation reaction have required the need for excess amounts of the oxidant, strongly acidic conditions, and high reaction temperatures. The new method bypasses these needs with the reactions being performed at rt. The reaction mechanism was studied by means of a few simple experiments. For example, in the presence of 3 equiv of TEMPO there was no reaction, suggesting that this photoredox-mediated C(sp^3)–C(sp^2) bond formation proceeds via a radical pathway.

In 2022, a strategy for the hydroalkylation of non-terminal alkenyl pyridines **60** was described (Figure 22) [93]. This method creates two adjacent stereocenters in a single step via the enantioselective addition of prochiral radical species to C-C bonds on internal alkenes. Until said date, no photocatalyst-free photochemical method had yet been described [94]. Pyridines remain the most frequently found motif in pharmaceuticals, agrochemicals, and natural products, and chiral pyridines are frequently used as ligands as well [95]. Compared to terminal alkenyl pyridines, the challenges to overcome in this functionalization are the lower reactivity of internal alkenes, the possibility of *E* to *Z* isomerization and the stereochemical control. CPA catalysis was used which not only activates all the reactants involved and provides asymmetric induction, but also accelerates the formation of the EDA complex.

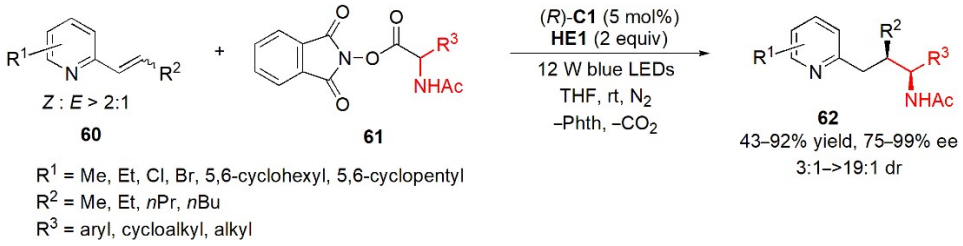


Figure 22. Enantioselective hydroalkylation of internal alkenylpyridines [93].

The redox-active esters **61** were prepared from natural and unnatural amino acids. The products **62**, bearing adjacent β and γ tertiary stereocenters, were obtained with good yields and high ees. There was good functional group tolerance and good drs were obtained, the lowest 3:1 when R^2 = R^3 = Me. Further studies were performed towards understanding the reaction mechanism. The reaction was completely inhibited by TEMPO, suggesting that a radical process was involved. When isomeric mixtures of alkenyl pyridines with different *Z*:*E* ratios were reacted, higher stereoselectivities were obtained for lower ratios of (*E*)-olefin in the isomeric mixtures, which suggests that a photoinduced *E* to *Z* isomerization might be taking place. Spectrophotometric and kinetic studies suggested that there may be an aggregation between the HE and the NHPIs, i.e., that EDA complex formation prior to SET events is plausible. Further bathochromic shifts and absorption enhancement were also

observed with increasing concentrations of (*R*)-TRIP, which together with kinetic studies suggested that the CPA may interact with this complex to form a ternary EDA complex, which could accelerate the SET process. The mechanism proposed is shown in Figure 23.

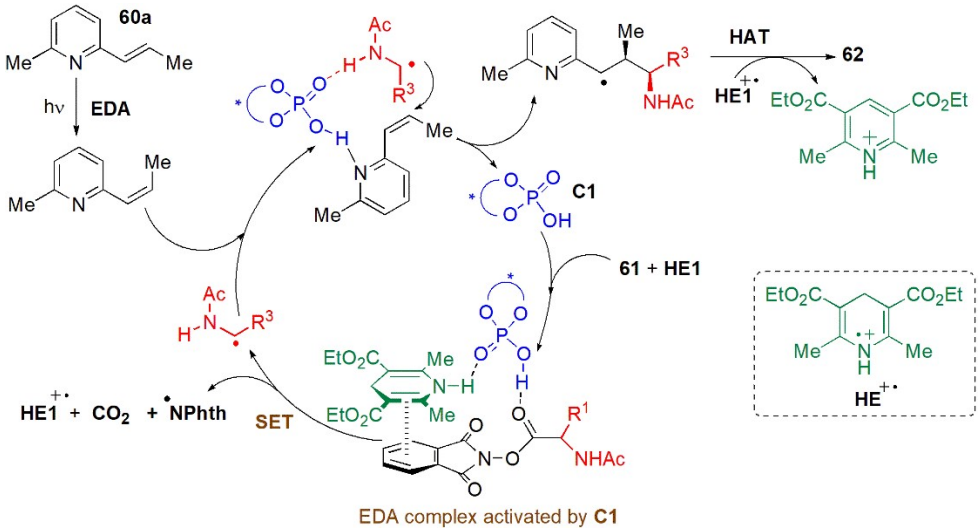


Figure 23. Mechanism proposed for the enantioselective hydroalkylation of internal alkenylpyridines [93].

A photoinduced enantioselective sulfonylation of 1-(arylethynyl)naphthalen-2-ols **63** was described in 2023 [96]. An inorganic sulfite, sodium hydrogen sulfite, was used as the sulfur dioxide surrogate, and 4-substituted Hantzsch esters **64** as radical alkylating agents (Figure 24). Prior to this example, a reaction between MBH acetate, a 4-substituted Hantzsch ester, and $NaHSO_3$ (sodium hydrogen sulfite) was described using 9-mesityl-10-methylacridinium tetrafluoroborate (Mes-Acr^+) as the photocatalyst under visible light irradiation. For one example a chiral tertiary amine catalyst was used, but although the desired chiral allylic sulfone was obtained, a moderate yield and ee were observed (43%, 33% ee) [97]. The synthesis of axially chiral styrenes by a photoinduced asymmetric radical reaction was reported, along with a sulfur dioxide insertion reaction which also proceeded with excellent enantioselectivity and regioselectivity [98]. Potassium alkyltrifluoroborates and potassium metabisulfite were the alkylating agents and sulfur dioxide source in this case.

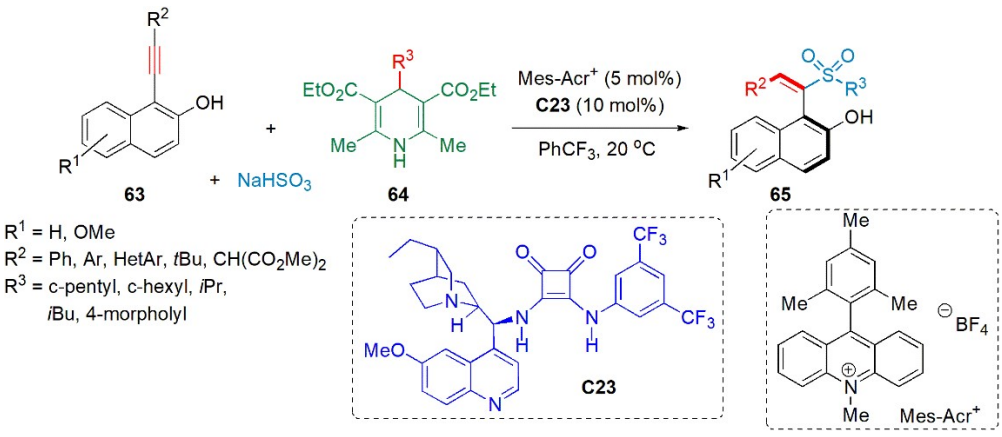


Figure 24. Enantioselective sulfonylation of 1-(arylethynyl)naphthalen-2-ols [96].

In the new three-component reaction, with 4-alkyl Hantzsch esters as alkylating agents, the axially chiral (*S*,*E*)-1-(1-(alkylsulfonyl)-2-arylvinyl)naphthalen-2-ols **65** were produced in good yields with excellent ees. Excellent regioselectivity and chemoselectivity were observed as well. It was assumed that the reaction goes via the formation of an intermediate

allene (**I**) formed in the presence of the chiral bifunctional organocatalyst, squaramide-based **C104**. The mechanism proposed for the reaction is shown in Figure 25. It is assumed that an alkyl radical is produced by the action of the photocatalyst on 4R-HE **64**, which reacts with sulfur dioxide to produce sulfonyl radical **II**. Under the influence of the chiral catalyst, compounds **63** isomerize to the respective allenes, to which the sulfonyl radical adds yielding anionic intermediate **V** after a reductive single-electron transfer with an excited photocatalyst. Intermediate **V** isomerizes to **VI**, which by protonation yields the desired product **65**.

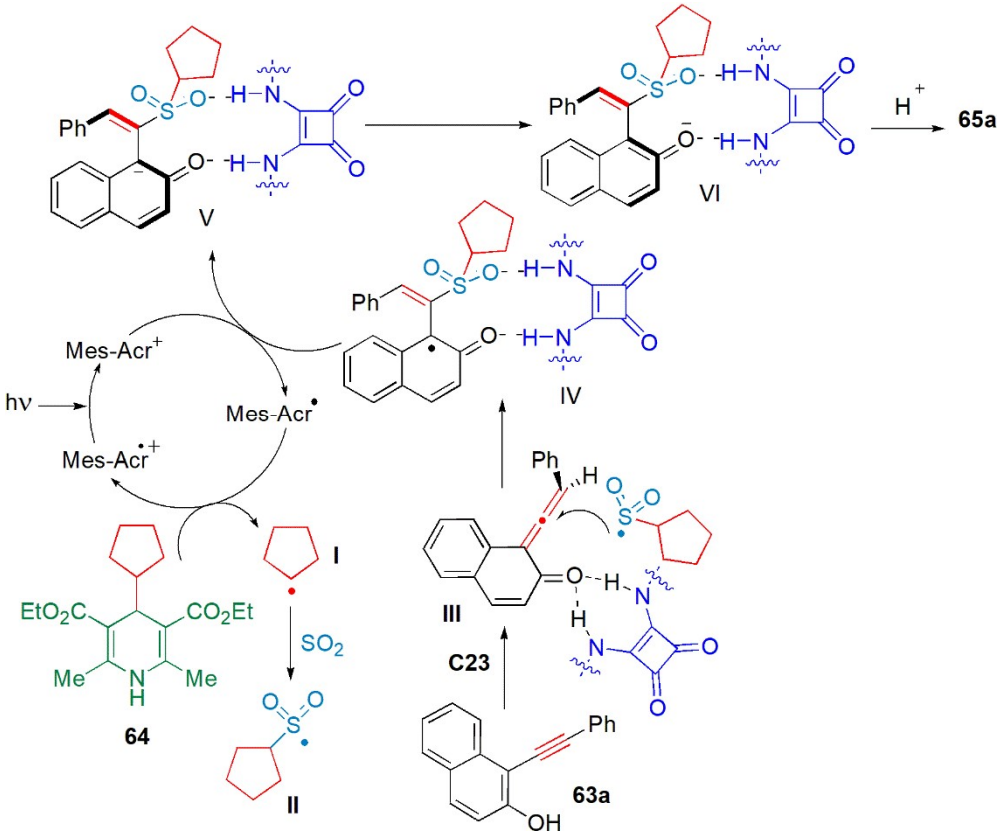


Figure 25. Mechanism proposed for the enantioselective sulfonylation of 1-(arylethynyl)naphthalen-2-ols [96].

4. Conclusions

Hantzsch esters are very versatile reducing reagents which have proved to be efficient hydride transfer agents for a variety of reactions. The latest developments in photoredox chemistry have unveiled new roles for Hantzsch esters, namely as radical reductants and proton sources. In addition, 4-substituted Hantzsch esters have been developed as alkylating and acylating reagents for radical reactions. The first enantioselective examples in which Hantzsch esters act as radical reductants or transfer agents have been published only in the last five years. Given the high regioselectivities, yields, and ees obtained, it is expected that this new avenue in synthesis will give rise to many new developments; particularly since Hantzsch esters can be readily prepared, the reactions take place under mild conditions, and in many cases not even a photocatalyst was required. Much remains to be explored in this emerging area of research, and the authors hope that the present review will help to stimulate further developments.

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