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Chiral Ureas and Thioureas in Asymmetric Catalysis

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Abstract After an overview of chiral urea and thiourea synthetic methods, this review describes the main applications of urea and thiourea complexes in asymmetric catalysis. Some recent examples of thioureas as catalysts are also presented. Coordination chemistry of ureas and thioureas is briefly discussed.

Keywords Asymmetric catalysis · Coordination modes of ureas and thioureas · Thioureas · Transition metal complexes · Ureas

1 Introduction

Chiral diaza-molecules are relatively new ligands for asymmetric catalysis, but they are now widely used [1]. In several cases, they have efficiently replaced air-sensitive chiral phosphorus ligands. They have often led to high enantiomeric excesses in metal catalysed reactions, but they still suffer from limitations because of their relatively low stability to the reaction or work-up conditions. Even when immobilised, work up of the reaction has to be carefully optimised in order to preserve the nature of the ligand against chemical modifications or metal leaching. Some amine derivatisations are known to lead to functional groups with increased stability. Among these amine derivatives, ureas and thioureas possess N and O or S coordinating centres. Moreover, these molecules generally possess N – H functional groups, which could act as Brönsted acids, leading to deprotonation for metal complexation or selective formation of hydrogen bonding [2] for molecular recognition. Indeed, ureas and thioureas are often used for their molecular recognition properties [3–5]. Several supramolecular systems using the urea or thiourea groups as building blocks have been described during the last few years [6]. They exhibit original and fascinating properties, such as the autoassembly of multilayer structures [7]. Moreau has described macrochiral fibres of silica, which are formed as a result of the interactions between chiral ureas. These materials have been used to breed asymmetric induction during addition of zinc derivatives onto aldehydes. After generation of the first slight enantiomeric excess, the asymmetric autocatalytic reaction goes on and leads to a neat amplification of the reaction enantioselectivity [8]. Thioureas have also been used as complexing reagents to discriminate inorganic species [9] or as specific receptors for the detection of the presence of particular anions [10, 11]. Although these potential applications of ureas and thioureas are of broad interest both for economical and ecological reasons, we chose to focus on the use of these molecules only as ligands for transition metal catalysts or as or-

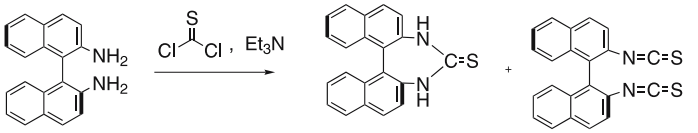
ganic catalysts (organocatalysts) for asymmetric synthesis. Binding sites with different characteristics are available on urea and thiourea functional groups. In terms of the HSAB model: the sulfur atom of thioureas should be considered as a soft Lewis base although the N – C = O function is of medium hardness and the oxygen atom itself could offer a hard basic site. Thioureas and ureas are potentially able to interact with most of the organometallic precursors and, in addition, are both strong hydrogen bond donors and hydrogen bond acceptors. All these interactions could be used to organise the catalytic site and control the selectivity of the catalysed reaction. Examples of chiral ureas and thioureas used in asymmetric transition-metal catalysed reactions are described in Sect. 4. One of the advantages of ureas and thioureas lies in their easy access, due to the commercial availability of many isocyanates and isothiocyanates. The possibility of using phosgene and thiophosgene and amine substrate in order to prepare either new isocyanate or isothiocyanate, as well as ureas or thioureas, is also a major advantage for the development of such derivatives. Moreover, the addition of nucleophilic amines onto isocyanate or isothiocyanates is carried out in short reaction periods, affording very high yields and selectivities. Such reactivity allows the use of parallel and combinatorial technologies, thus leading to some of the rare successes in high throughput screening catalyst discovery [12]. Finally, ureas and thioureas are valuable building blocks for the synthesis of five- and six-membered heterocycles [13, 14] which are useful as biomimetic models [15]. Indeed, thiourea- and urea-containing compounds have biological activity [16–19]. They are useful as fungicides, herbicides and rodenticides [20, 21] or against bacteria and microbial infection [22–25]. Some molecules bearing one of these particular functional groups show enzymatic inhibition [26–28]. Such applications are out of the scope of this article.

2
Synthesis of Chiral Ureas and Thioures

Chiral amines and diamines are readily available substrates for the synthesis of ligands for transition metal-catalysed reactions since they can easily be transformed into chiral ureas and thioureas. Therefore, several groups have prepared chiral symmetrical ureas and thioureas, dissymmetrical ureas and thioureas, amino-urea and thiourea derivatives. Finally polyureas and non-soluble polythioureas were also prepared and tested as ligands for asymmetric catalysis.

2.1
Symmetrical Ureas and Thioureas

Treatment of a chiral amine with phosgene is the cheapest way to prepare symmetrical ureas [29]. Nevertheless, due to the toxicity and reactivity of that reagent, it can advantageously be replaced by triphosgene [30] or 1,1′-carbonyldiimidazole [31–34] or other derivatives such as 1,1′-carbonyldi-2(1H)-pyridinone [35]. This procedure can be extended to thiophosgene (Scheme 1) and its thio-analogues, such as 1,1′-thiocarbonyldi-2(1H)-pyridinone to produce thioureas [36]; chiral diamines can thus be transformed into the corresponding monoureas or monothioureas.



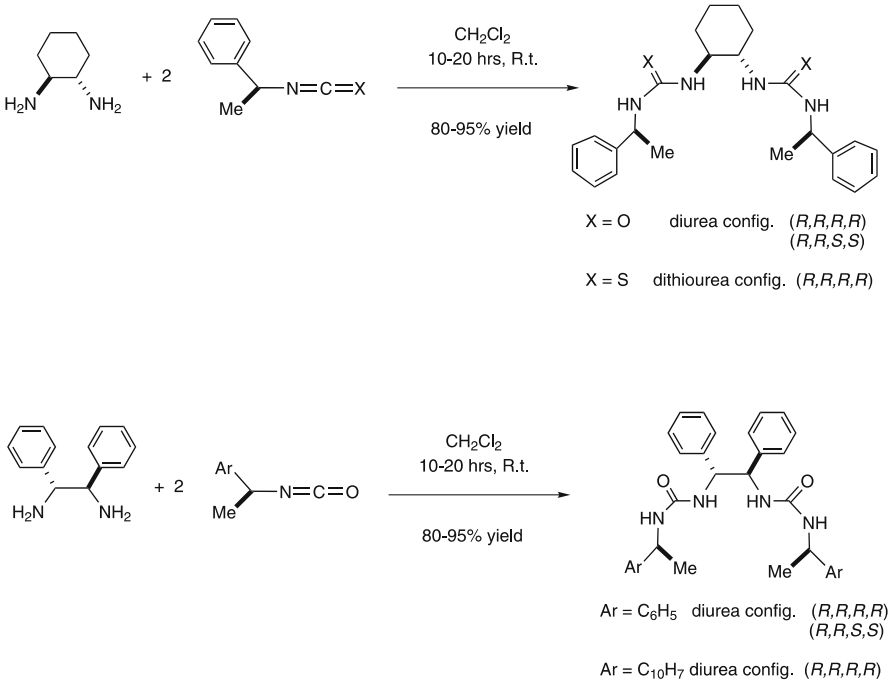
Scheme 1

2.2
Symmetrical Diureas and Dithioureas

Chiral diamines can also react with isocyanates or isothiocyanates to form chiral diureas and dithioureas. For example, a series of chiral C_2-symmetric diureas [37] or dithioureas [38] were easily prepared from the reaction of an optically active diamine with two equivalents of the desired isocyanate or isothiocyanate. The reaction takes place at room temperature in very good yields. Most of these reagents are commercially available or can be obtained by reaction of phosgene, thiophosgene or substitutes with primary amines. This procedure is also useful for the preparation of symmetrical diisocyanates or thiocyanates. Diureas and dithioureas with atropoisomeric chirality can be prepared from binaphtylamine (Scheme 1). By using chiral isocyanate [37] or thiocyanate [39] and chiral amines, urea or thiourea derivatives with four different stereogenic centres, Scheme 2 can be formed. In this way, match/mismatch effects could be observed in hydrogen transfer reactions (see Sect. 4.1.1).

2.3
Dissymetrical Ureas and Thioueas

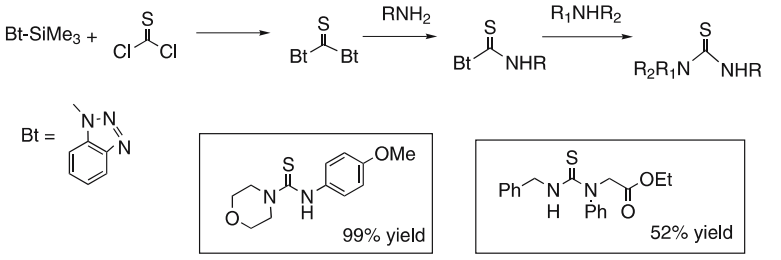
A recent paper from Katritsky summarises all the preparations of achiral dissymmetrical thioureas and proposes a new one, based on 1-(alkyl/arylthiocarbamoyl)benzotriazoles, which act as masked isothiocyanates. As described in the previous section, other *N*-heterocyclic derivatives can be used instead



Scheme 2

of benzotriazole. The thiocarbamoylbenzotriazole derivatives being stable compounds, substituted thioureas are prepared in high yields in a one-pot reaction using this procedure (Scheme 3) [40]. However, no chiral thiourea has been prepared using this method so far.

Since chiral amines are much more available than chiral isocyanates, ureas have often been obtained from reaction of an amine used as the chiral source with a stoichiometric amount of a non-chiral isocyanate [41]. Similarly, thioureas are obtained by reacting isothiocyanates with amines. The corresponding ureas and thioureas (examples in the following sections) are



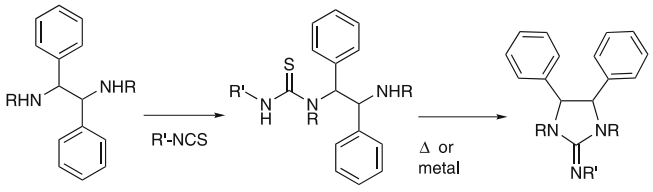
Scheme 3

obtained in excellent yields (> 70% yield for pure products). Chiral ureas can also be synthesised by reaction of chiral isocyanates with non-chiral amines. Chiral isothiocyanates have to be synthesised by known methods (see above) because only few are commercially available. However, the preparation of these derivatives is not necessary since heterocyclic urea and thiourea derivatives instead can be used for synthetic purposes: for example, the benzotriazolylthiourea intermediate is depicted in Scheme 3, but pyridyl and imidazolyl derivatives with related structures can also be used. With these compounds, the reactive function is masked during the purification step and can afterwards be substituted by an amine.

2.4
Amino-ureas and Amino-thioureas

Diamines can also react with only one equivalent of isothiocyanate to form bifunctionnal amine-thiourea ligands: 59–68% yields obtained for several alkyl isothiocyanates. However, reaction of phenylisocyanate with 1,2-diamines could also lead to the formation of the guanidine derivative by cyclisation and elimination of H_2S (Scheme 4) [42, 43].

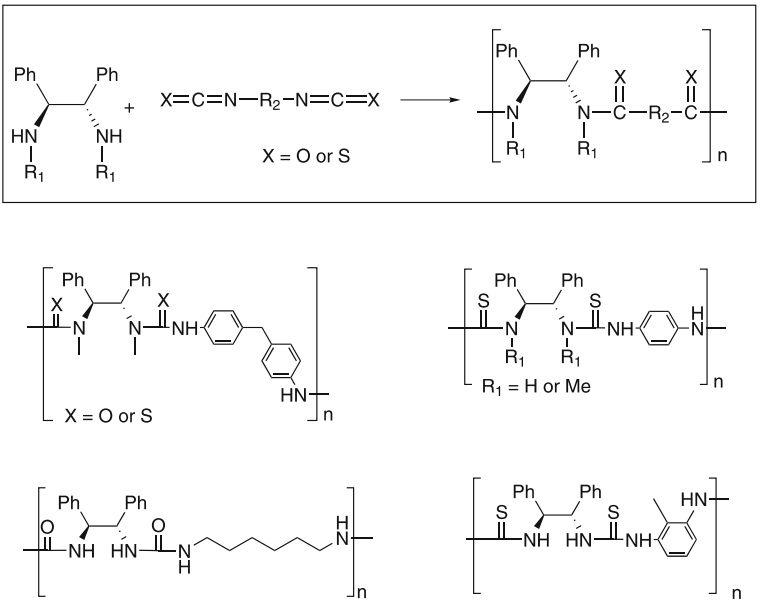
Moreau and co-workers have also prepared (1*R*, 2*R*)-1,2-diaminocyclohexane amino-urea and thiourea derivatives [43]. Diphenylethylenediamine-substituted monothioureas are more stable than the cyclohexyldiamine counterpart, but they can also rearrange to guanidine derivatives, especially at high temperature or in the presence of metal [43]. Under the same conditions, thioureas also rearrange to guanidines in the presence of amines. Selective formation of substituted guanidines from thiourea derivatives of diaminocyclohexane or diphenylethylenediamine were also reported in a recent paper from Ishikawa [44].



Scheme 4

2.5
Polyureas and Polythioureas

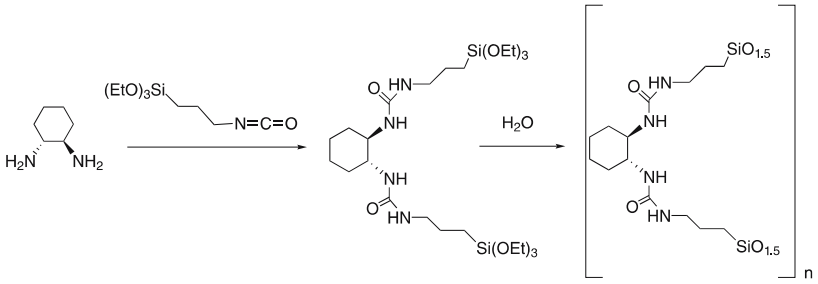
One of the limitations of the use of asymmetric catalysis comes from the difficulties of separating the chiral catalyst from the reaction medium and recycling it. Such systems are generally formed with chiral phosphane and/or



Scheme 5

diamine. Besides their relatively low stability, ligands of this type could only be transformed into insoluble catalytic materials via structural modifications, which are neither easy nor cheap [45]. Conversely, polyureas and polythioureas are readily available from diisocyanates or diisothiocyanates and chosen chiral diamines. The general preparation of polymer systems by this methodology is depicted in Scheme 5, as well as some polymer structures [46].

Linear polymers can be obtained by using diisocyanates or diisothiocyanates with diamines. In this case, the molecular weights are controlled by the solubility of the polymer in the chosen solvent. Due to the polarity and to the number of possible hydrogen bonds, such polymers are generally insoluble in classical solvents (MeOH, CH_2Cl_2) but are usually soluble in DMSO. A molecular weight of at least 2000 g/mol was estimated by NMR measurements [46]. A crosslinked insoluble material was prepared by using a mixture of di- and tri-isocyanate. In this case, the molecular imprinting effect could be performed (see Sect. 4.1.1). Insoluble materials are available by grafting ureas or thioureas onto insoluble polymers or inorganic materials. Urea and thiourea function can be used as linker for ligand immobilisation [47]. Moreau and co-workers achieved the immobilisation of polyurea ligands by sol-gel hydrolysis condensation giving hybrid materials: a left or right handed helix was autogenerated according to the chiral (*R*, *R*)-or (*S*, *S*)-diureidocyclohexane structure (Scheme 6) [48].



Scheme 6

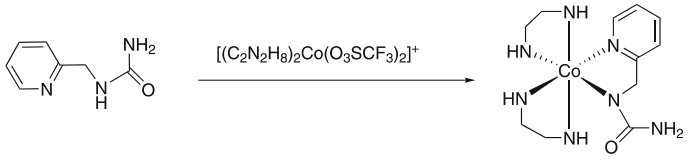
Substituted thioureas have been used as ligands for transition-metal catalysed reactions and as organocatalysts for organic synthesis. These points will be discussed in Sects. 4 and 5. We first present some aspects of the coordination modes of ureas and thioureas.

3
Coordination Chemistry

Several metal complexes have been described with urea, thiourea or dimethyl derivatives [49, 50]. We will focus in this section on the coordination chemistry of substituted ureas and thioureas used as neutral ligands as well as many ureato and thioureato anions complexed to metal centres.

3.1
Urea Coordination Modes to Transition Metals

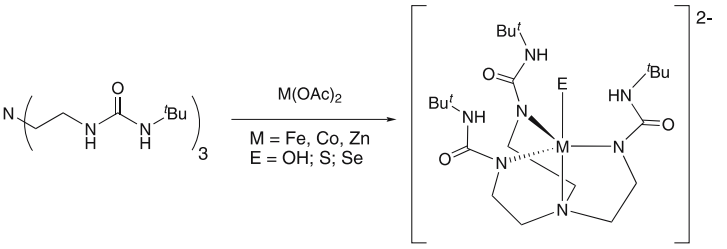
In transition metal complexes, two main coordination modes have been described for urea ligands: *N*-monohapto, or *N*,*O*-chelates. In the case of molecules containing more than one urea function, the molecules act as *N*,*N*-chelates, so that one of the urea functions always behaves as monohapto-ligand. For example, complexes of Co(III) with *N*-(2-pyridylmethyl)urea and ethylenediamine have been characterised by X-ray crystallographic analysis (Scheme 7). The urea group is coordinated through only one of its N



Scheme 7

atoms, while the pyridine moiety brings the second bond: thus the *N*-(2-pyridylmethyl)urea behaves as a *N*,*N*-bidentate ligand [51].

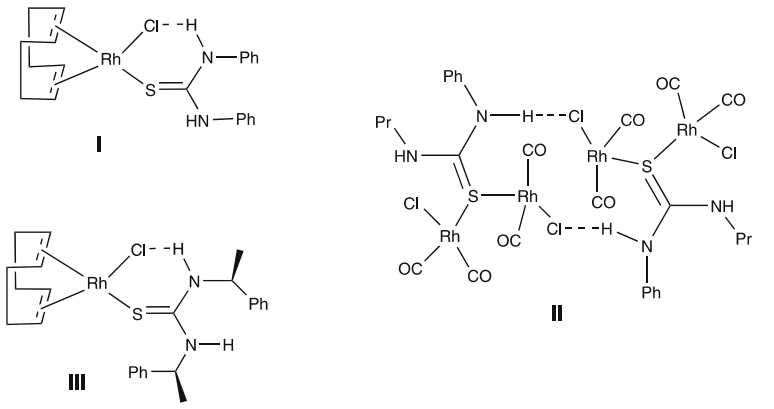
Iron(II) complex of tris(*N*′-*tert*-butylurea-ylato)-*N*-ethylene]aminato activates dioxygen at room temperature to afford an iron(III) complex containing a single terminal oxo ligand. X-ray structures show that the three urea molecules act as a tridentate *N*,*N*,*N*-ligand [52]. The tripodal ligand was also used to synthesise complexes of cobalt, iron or zinc with terminal hydroxo ligands (Scheme 8) [53].



Scheme 8

3.2
Thiourea Coordination Modes to Transition Metals

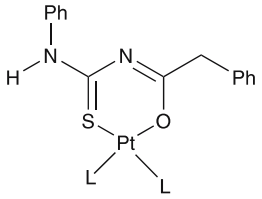
Platinum-thiourea complexes have been extensively studied because of their biological activity [54], but few have been used in catalysis. Neutral thioureas are able to coordinate to metal centres through their sulfur atom (Scheme 9) [55, 56]: monomeric (**I**) and oligomeric (**II**) species are known for Rh [57], and an X-ray structure has also been determined for the chiral complex **III** [58]. In many complexes hydrogen bonding has been observed



Scheme 9

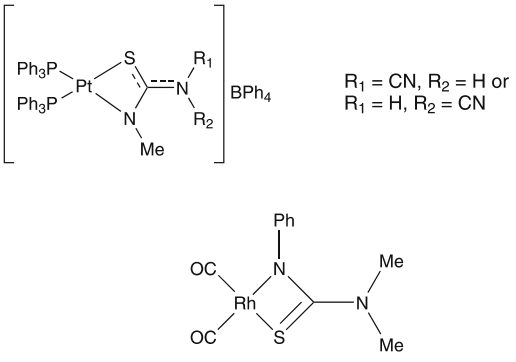
between halide ligands inside the coordination sphere and one of the hydrogen atoms of the NH thiourea moiety.

Due to their stability and their easy formation, many examples of transition metal complexes containing benzoyl-substituted thiourea ligands have been described [59–62]. Most of them concern Pt species in which the thiourea ligands behave as monoanions and are bounded to the metal centre through the S and O atoms, forming a six-member ring system (Scheme 10).



Scheme 10

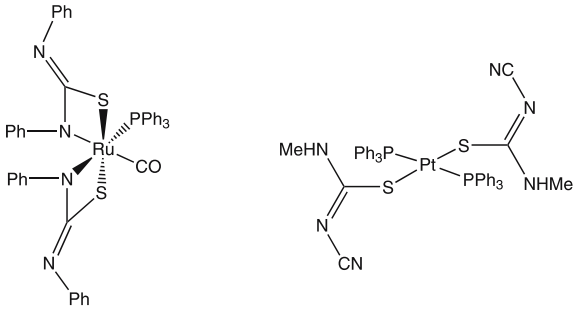
Non-ionic thiourea derivatives have been used as ligands for metal complexes [63, 64] as well as anionic thioureas and, in both cases, coordination in metal clusters has also been described [65, 66]. Examples of mononuclear complexes of simple alkyl- or aryl-substituted thiourea monoanions, containing *N*,*S*-chelating ligands (Scheme 11), have been reported for rhodium(III) [67, 68], iridium and many other transition metals, such as chromium(III), technetium(III), rhenium(V), aluminium, ruthenium, osmium, platinum [69] and palladium [70]. Many complexes with *N*,*S*-chelating monothioureas were prepared with two triphenylphosphines as substituents. ^{31}P NMR spectroscopy of these phosphorus complexes has been used for structure elucidation. Depending on the bulkiness of the thiourea substituents, a single isomer (bulky) or two isomers (small size, example in Scheme 11 with two possibilities for the relative position of the cyano group)



Scheme 11

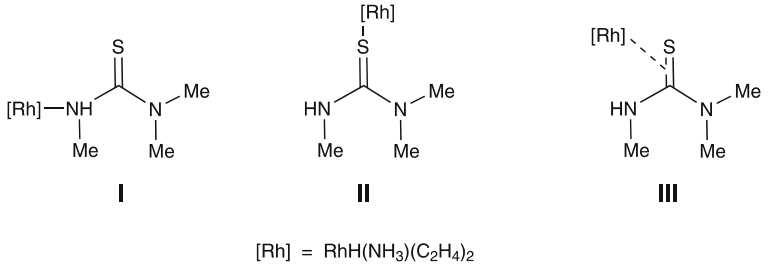
have been observed with Pt. A similar structure has been proposed for the related Rh complex (Scheme 11).

Platinum and ruthenium complexes have been characterised by positive-ion electrospray ionisation mass spectroscopy (ESMS) and in some cases X-ray diffraction spectroscopy. The S – C and C – N bond lengths in these species suggest a delocalisation and a double bond character in both the C – S and C – N bonds. For example, the Ru complex depicted in Scheme 12 contains two thiourea monoanions bonded in an *N*,*S*-chelating mode [71]. Bis(monoanion)-Pt complexes with thioureato ligands have also been prepared. A Pt complex with two substituted thioureas as ligand crystallises with two independent molecules, and the bond lengths and angles are similar for both. The single-crystal X-ray structure shows S-bonded thiourea anions *trans* to each other.



Scheme 12

Thiourea ligands can be bounded to the metal centre through one nitrogen atom, the sulfur atom, or the C = S double bond. These coordination modes were studied by density functional theory calculations for Rh-thiourea complexes (Scheme 13). No stable structure was attained by optimisation of the nitrogen coordination mode **I** but optimised geometries as trigonal-bipyramidal complexes were obtained for modes **II** and **III**. An η^2 coordination is determined for the latter complex through both S and C atoms. As this



Scheme 13

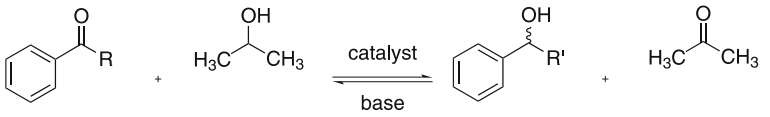
structure is 9 kcal/mol higher than **III**, the dimethyl-methyl-thiourea prefers an η^1 coordination mode which can be rationalised to other thioureas since it involves the S lone pair. Thioureas and ureas have therefore very distinct coordination modes.

4
Catalytic Activity of Urea- and Thiourea-Containing Complexes

4.1
Asymmetric Reduction

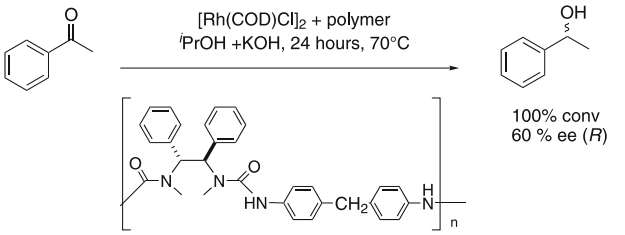
4.1.1
Hydrogen Transfer Reduction of C = O Bonds

The hydrogen transfer reaction (HTR), a chemical redox process in which a substrate is reduced by an hydrogen donor, is generally catalysed by an organometallic complex [72]. Isopropanol is often used for this purpose since it can also act as the reaction solvent. Moreover the oxidation product, acetone, is easily removed from the reaction media (Scheme 14). The use of chiral ligands in the catalyst complex affords enantioselective ketone reductions [73, 74].



Scheme 14

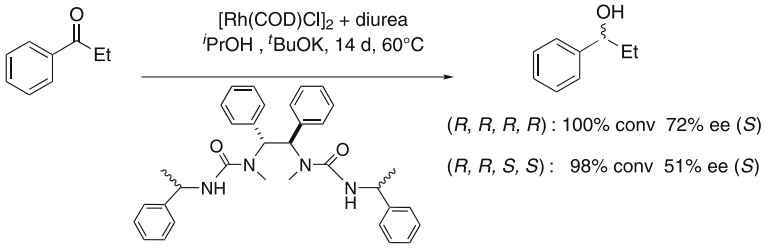
Polyureas were first used in HTR as an heterogeneisation method for Rh-diamine catalysts by incorporation of the chiral ligand into polymer backbones [75]. Various polyamides and polyureas were thus prepared and the influence of the structure of the polymers on catalytic activity was also investigated. When using the polyamide or the polyurea prepared with a flexible chain copolymer (e.g. hexamethylenediisocyanate), only low ee were observed. Moreover, with such material, no recycling could be performed. A rigid polymer was obtained using a commercially available mixture of methylenediphenyldiisocyanate and its trimer. Crosslinking was instantaneous, leading to a hard and insoluble material that gave better results in the polyurea-based catalyst for acetophenone reduction (Scheme 15) [46]. When the reaction was complete, the catalyst was recovered by filtration, washed and reused twice without loss of selectivity or activity (elemental analysis confirmed Rh quantitative complexation in the polymer). It is of great importance to prepare a rigid and cross-linked material to obtain highly selective



Scheme 15

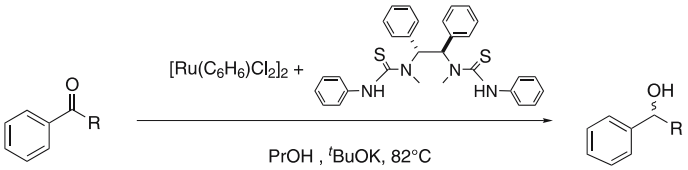
and reusable catalysts. The enantioselectivity of the catalyst was improved by the application of molecular imprinting technology, in which the imprinted material allowed 70% ee after careful optimisation of the cross-linking and synthesis parameters [76, 77].

Polyurea was used as both chiral ligand and support in an heterogeneous system but it should be used at higher temperatures than the diamine complex (60 °C instead of room temperature). Nevertheless, due to the higher stability of the polymer catalyst, increased turnover numbers are observed as well as similar ee values. A series of optically pure soluble diureas were easily obtained from chiral diamines and chiral diisocyanates, thus affording two types of stereogenic centres [78]. A match/mismatch double induction effect was noticed with cyclohexyl, as well as with diphenyl-derived ligands (Scheme 16). Even if encouraging enantioselectivities were observed, long reaction times were required: 7 days for the best result, obtained for propiophenone reduction in 80% ee (*R*).



Scheme 16

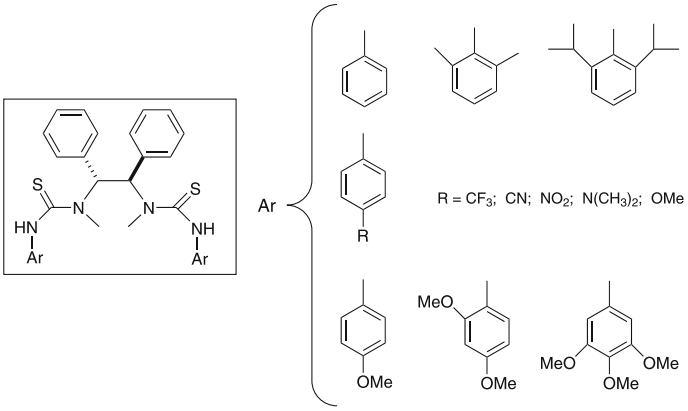
Chiral dithioureas, which are sulfur analogues of diureas, were thus evaluated as ligands for the asymmetric HTR of arylketones catalysed by Ru, Ir, Rh or Co species and compared to the corresponding urea ligands [38]. Ruthenium complexes afforded the best enantioselection for the reduction of arylketones catalysed with in-situ formed species from $[Ru(C_6H_6)Cl_2]_2$ and chiral *N*,*N*′-diphenyldithiourea (Scheme 17). Dithiourea complexes were more active and enantioselective [79] than the corresponding monothioureas or guanidine derivatives [38].



R	time (h)	% conv	% ee
Me	9	98	87 (*S*)
Et	17	96	91 (*S*)
^{i}Pr	17	92	94 (*S*)
^{t}Bu	48	93	85 (*R*)

Scheme 17

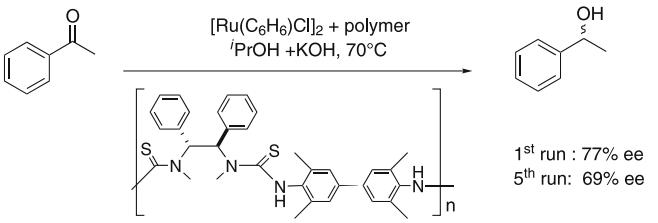
Effects on the nitrogen substitution was examined in the case of dithiourea ligands by replacing Me by H on each of the N atoms. The presence of methyl groups improves both the reaction rate and the asymmetric induction from 24% ee, 15% conv. in 3 days to 89% ee, 94% conv. in 1 day for acetophenone reduction [80]. A theoretical and experimental approach was undertaken for dithiourea-Rh catalysts to determine the influence of electron-withdrawing or electron-donating substituents as well as the influence of bulky substituents on the aromatic rings (Scheme 18). It appears that steric hindrance does not affect catalytic activity but that CF_3, CN, NO_2 causes a dramatic decrease in ee while OMe substituents slightly improve chiral induction.



Scheme 18

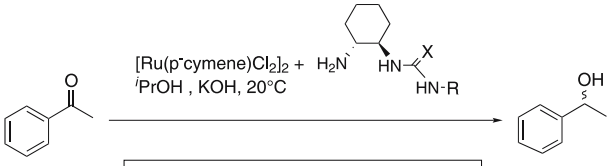
Heterogeneisation of such dithiourea catalysts was achieved by the synthesis of a series of chiral polythioureas from the corresponding chiral diamine and diisothiocyanate [81]. Results of the catalytic tests have shown that it is important to preserve the C_2-symmetry inside the polymeric material [82]

in order to obtain enantioselectivities close to those observed with the homogeneous catalyst. As for polyurea analogues, efficient polythiourea-based catalysts need a rigid spacer between the two thiourea units. Due to the low solubility of such polymers, the catalysts are easy to recover by filtration [83]. Using polythiourea as ligand and support associated with the Ru precursor, 77% ee was obtained for acetophenone reduction by hydride transfer. The catalyst could be recycled five times with only slight loss in reactivity and selectivity (Scheme 19) [82].



Scheme 19

Moreau and co-workers prepared (1*R*,2*R*)-1,2-diaminocyclohexane aminourea and thiourea derivatives and combined them to Ru precatalysts for the HTR of arylketones [43]. By comparing mono- and diurea ligand effects, it was found that monourea-containing catalysts were more efficient, giving (1*R*)-phenylethanol with ee values up to 83% (Scheme 20). The monourea catalyst was also more active and enantioselective than the corresponding monothiourea species, which surprisingly led to the opposite alcohol enantiomer (*S*) with moderate enantioselectivities (Scheme 20). Immobilisation of these polyurea ligands was achieved by sol-gel hydrolysis condensation giving hybrid materials: a left- or right-handed helix was autogenerated according to the chiral (*R*, *R*)- or (*S*, *S*)-cyclohexane structure [48].

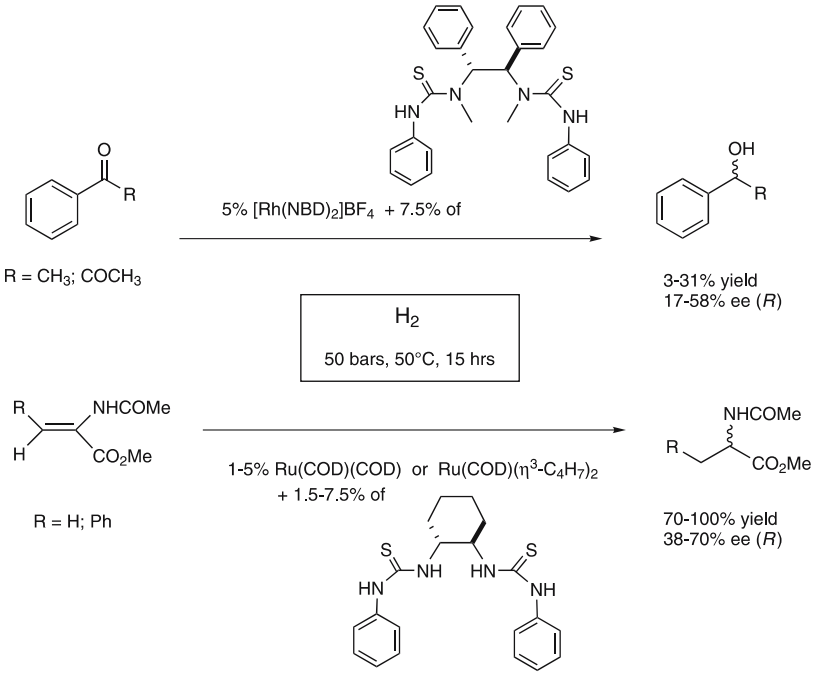


R	X	time (h)	% conv	% ee
Cy	O	4	73	83 (*R*)
Cy	S	4	20	22 (*S*)
^{t}Bu	O	18	54	66 (*R*)
^{t}Bu	S	22	72	36 (*S*)

Scheme 20

4.1.2
Hydrogenation of C = O and C = C Bonds

Enantioselective hydrogenation of C = O or C = C bonds has been widely studied over the last decade since it is a useful pathway to a wide variety of enantiomerically pure molecules. Asymmetric hydrogenation in the presence of transition metal catalysts was one of the two topics of the 2001 Nobel Prize for chemistry [84]. Many books [85–87] and reviews [88] give an overview of the catalysts employed, which often contain chiral phosphines. Among them BINAP is probably the most studied [89]. One of the most successful uses of such an ubiquitous ligand is the asymmetric hydrogenation of aromatic ketones. In such cases, the synergetic effect between diphosphine and diamine allows the reduction of aryl ketones with excellent enantioselectivities and impressive turnover rates. Nevertheless, other non-phosphorinated compounds have been developed for this purpose, in particular nitrogen-based ligands [1] such as amino alcohols, oxazolines, pyridines, phenantrolines, amines, ureas and thioureas. Various C_2-symmetric diamines, diureas and dithioureas were tested as chiral ligands combined with various Ru, Rh or Ir precatalysts for asymmetric hydrogenation of aryl ketones or enamides (Scheme 21). In both cases, thiourea complexes were much more efficient

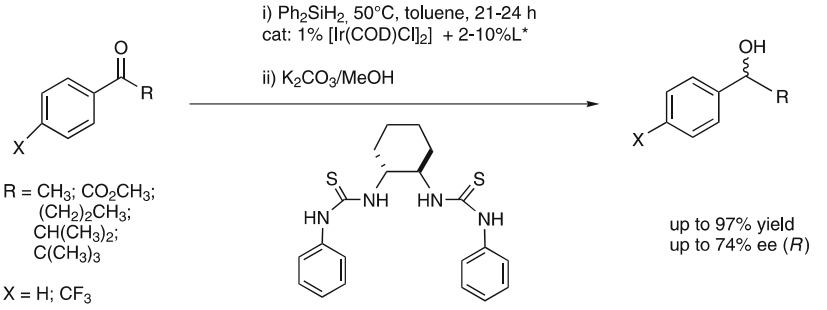


Scheme 21

than urea species: up to 58% ee for phenylglyoxylate methyl ester hydrogenation with cationic Rh/*N*,*N*′-diphenyldithiourea complex [90]. Better chiral induction was observed for the hydrogention of α-acetamidocinnamic methyl ester in 70% ee with diaminocyclohexanedithiourea/Ru catalyst [91]. Although relatively modest ee values were obtained, compared to the diphosphine counterpart, such results show that thioureas were able to act as alternative ligands for Rh- or Ru-catalysed hydrogenation.

4.1.3
Hydrosilylation

Enantioselective hydrosilylation of ketones is a versatile synthetic route to chiral secondary alcohols and it can be efficiently catalysed by several types of complexes, including Rh complexes, some Ti species and a few Fe species [92–94]. In contrast to other catalytic ketone reduction methods, asymmetric induction for hydrosilylation is often better with N ligands than with P ligands: oxazolines, pyridylimines or alkylamines. Brunner, Nishiyama and co-workers reported excellent ee values achieved with Rh Pybox [95] and Pythia [96, 97] complexes. Recently, our group developed a series of Ir catalysts for acetophenone hydrosilylation containing chiral C_2-symmetric diamines, dithioureas or monothioureas (Scheme 22). Better enantioselectivity is observed with dithiourea catalysts than with analogue diamine Ir species: up to 74% ee could be reached with a tenfold excess of ligand versus Ir precursor [39].



Scheme 22

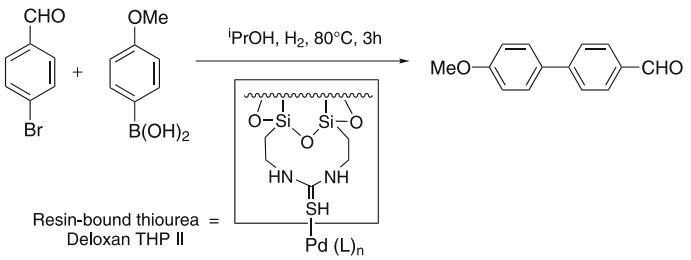
4.2
Oxidation and Reaction with Epoxides

Urea hydrogen peroxide adduct (UHP) was employed in metal-catalysed asymmetric epoxidation [98] and Baeyer–Villiger oxidation [99, 100]. Since the presence of urea does not change the course of the reaction, this will not be described here. Conversion of epoxides to halohydrins with elemental

halogen was accelerated in the presence of thiourea, but no chiral process has been described so far [101].

4.3 Formation of C–C Bonds

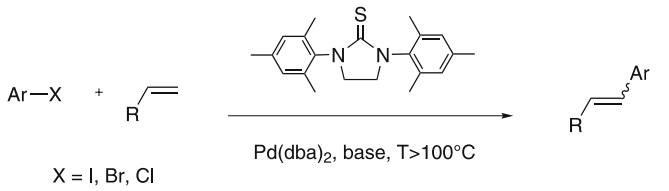
Carbon–carbon bond forming reactions via transition metal catalysts will be discussed in this section. Thiourea was also used as an organocatalyst and this topic will be discussed in the next section. Chiral polyureas were used for Pd-catalysed allylic substitution with dimethylmalonate but gave disappointing results. Chiral polyamide analogues prove to be much more efficient and selective for this reaction [75]. Thioureas were used as ligand in metal-catalysed organic synthesis. Thanks to the strong association of the sulfur atom and functional groups containing sulfur to transition metal, many examples reported the use of non-chiral thioureas. This was particularly true for Pd catalysts used for the Suzuki coupling (Scheme 23) [102], carbonylation reactions (see next section) and the Heck reaction [103]. They illustrate the potential of such types of ligand in catalysis and may inspire future developments in asymmetric catalysis.



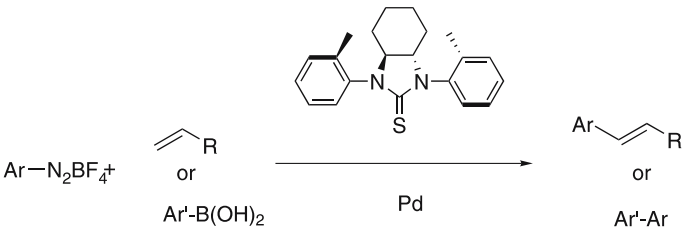
Scheme 23

The Pd-catalysed Heck reaction performed with thiourea as the ligand exhibit good activities for some catalysts. As for carbene ligands [104], steric hindrance improves catalytic results. Thus, thioureas wearing bulky substituents afford the formation of air- and moisture-stable Pd complexes [105]. For example, the catalyst obtained with 2 mol % $Pd(dba)_2$ and *N*,*N*′-dimesitylene-ethylene thiourea (Scheme 24) was still active even after 2 months in an air atmosphere.

In a very recent work, the Pd-catalysed cross-coupling reactions with arenediazonium salts under aerobic conditions in the presence of a chiral monothiourea ligand were reported (Scheme 25) [106]. Even if this ligand bears four chiral centres, no test in asymmetric Heck-type reaction has been described so far.



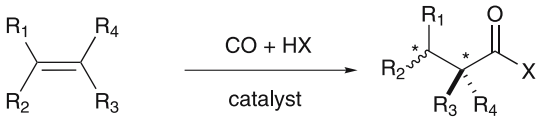
Scheme 24



Scheme 25

4.4 Reactions Involving CO

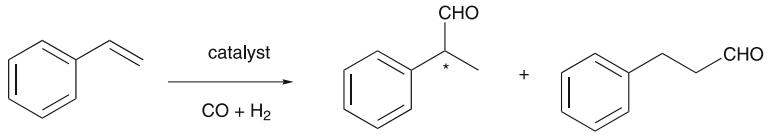
Hydrocarbonylation of olefins, hydroformylation, hydroesterification and hydroxycarbonylation are reactions which appear to be of particular interest. Indeed, they allow the simultaneous creation of a new C – C bond as well as the introduction of a functional group (aldehyde, ester and acids). One or two new stereogenic centres can thus be formed at the same time (Scheme 26). Despite the difficulty of using high carbon monoxide pressure, the already existing industrial processes prove that such reactions can be performed on a very large scale [107].



Scheme 26

4.4.1 Hydroformylation

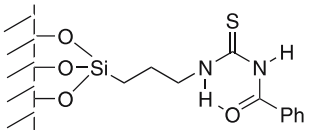
Hydroformylation has been extensively studied since it produces optically active aldehydes which could be important precursors for pharmaceutical and fine chemical compounds. Thus, asymmetric hydroformylation of styrene (Scheme 27) is a model reaction for the synthesis of ibuprofen or naproxen. Phosphorus ligands were used for this reaction with excellent results, espe-



Scheme 27

cially for the Rh-Binaphos system [107]. Sulfur ligands, such as thiols and thioethers, led to low enantioselectivities although a good activity is noted for this reaction [108]. Rhodium is the preferred metal for this reaction since it forms highly active and selective catalysts, leading to the main formation of aldehydes (instead of the hydrogenation product). The neutral dimeric complex $[Rh(COD)Cl]_2$ is generally used in the presence of a base (Et_3N). More sophisticated complexes can also be used. The branched aldehyde which presents a stereogenic centre is the major product, but some linear aldehyde is also obtained (Scheme 27, *i*: hydratropaldehyde/*n*: hydrocinnamaldehyde, $i/n = 90/10$ typically) [109].

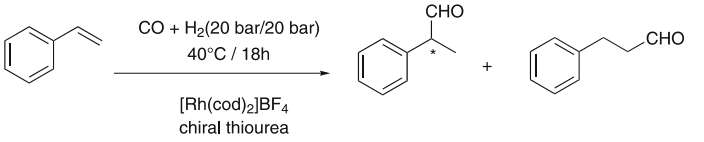
The major difficulty in this reaction consists in the formation of "naked Rh species" which are highly active and compete with the chiral species, which often have lower activity. Thus, neutral $[Rh(COD)Cl]_2$ and cationic $[Rh(COD)_2]BF_4$ precursors, without any additional ligand, are able to form active complexes for the catalytic hydroformylation of styrene [110]. It is difficult to determine if the ligand coordinates to the metal centre or not. In such cases, the stable Rh complexes act as a reservoir for the active naked species. Thus, amines or ureas are not bonded strongly enough to maintain the asymmetric catalytic cycle, and the formation of metallic Rh particles can be observed [111]. The asymmetric induction is then difficult to obtain in this reaction. Moreover, the optically active aldehyde can turn into the racemic product during the course of the reaction. Cauzzi showed that thiourea-functionalised silica xerogels containing Rh were effective and recyclable catalysts for hydroformylation (Scheme 28). In this particular case, it was not proven that the reaction occurred at the surface since leaching was observed, suggesting reaction in the homogeneous phase. However, regioselectivity towards the branched aldehyde increased for successive runs and the authors studied the Rh distribution at the surface and inside the core of the material. The spectroscopic data (IR and XPS) showed four different thiourea-Rh linkages with a decrease in the external Rh population. The Rh

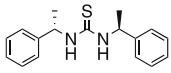
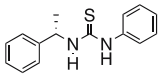


Scheme 28

species located in the core of the material were more selective towards the formation of the branched product [112, 113].

Some chiral mono-, acyl- and di-thioureas have been used as ligand for the Rh-catalysed asymmetric hydroformylation of styrene. Although thiourea ligands form inactive systems with $[Rh(COD)Cl]_2$ as the catalyst precursor, in standard conditions (40 °C, 40 bar CO + H_2: 1/1), the cationic Rh complex $[Rh(COD)_2]BF_4$ combined with monothioureas as the ligand showed moderate to good activity (Scheme 29) [114].



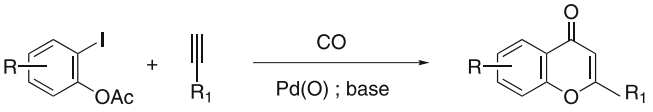
chiral thiourea	% ald. (%conv.)	b/n	% ee
	99 (18)	85/15	16 (-)
	98 (18)	91/9	24 (-)

Scheme 29

Excellent chemoselectivity (> 98%) was obtained with good regioselectivity (> 85%) but generally with very low enantioselectivity, except for a few ligands with ee up to 24%. An excess of monothiourea ligand (L/Rh= 2/1 and more) or a dithiourea ligand inhibited hydroformylation, except for ligands with C_2-symmetry (ee up to 16%) [115]. Monothioureas then had to be associated to phosphorus ligands in order to give active and stable hydroformylation catalysts. Recent work of Cauzzi et al. discusses this point, but without any chiral application [116].

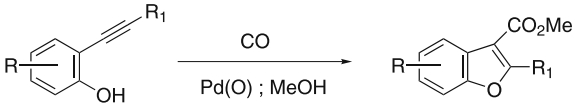
4.4.2 Alkoxycarbonylation

Thiourea was used as stabilising agent for zerovalent Pd species [117]. The Pd-thiourea (H_2NCSNH_2) catalysed carbonylation of terminal alkynes and allylic alcohols has been described by Chiusoli [118]. More recently, Pd-thiourea-catalysed carbonylative annulation was studied. The reaction proceeds between alkynes, iodophenol acetates and carbon monoxide, in the presence of dppp, thiourea (H_2NCSNH_2) and base at 40 °C. Flavones have been obtained in good yields (Scheme 30) [119].



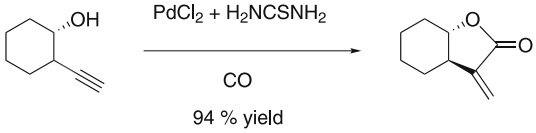
Scheme 30

2,3-Disubstituted benzo[*b*]furans were also prepared by intramolecular cyclisation in the presence of a $[Pd(thiourea)_4]I_2$ catalyst (thiourea = $H_2NCS\ NH_2$). No Pd precipitation occurred with this very stable thiourea complex (Scheme 31) [120].



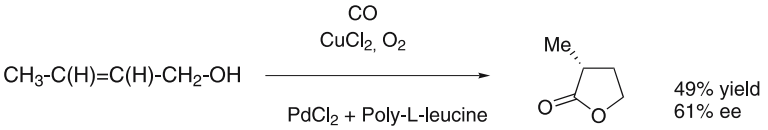
Scheme 31

Chiral lactones were also obtained by cyclocarbonylation of chiral acetylenic alcohols with Pd and thiourea (H_2NCSNH_2) (Scheme 32). No loss in chirality was observed, but large amounts of Pd and thiourea were used (10 mol %) since the catalyst deactivates by forming metal particles. The catalytic precursor (PdI_2 > $PdCl_2$) and the ratio of thiourea to Pd were very important, thiourea being necessary for this reaction. The active species was supposed to be $[Pd(thiourea)_3I]I$, which forms in situ from $[Pd(thiourea)_4]I_2$ and $[Pd(thiourea)_2]I_2$. It had to be a partially dissociated species since $[Pd(thiourea)_4](BF_4)_2$ was inactive [121].



Scheme 32

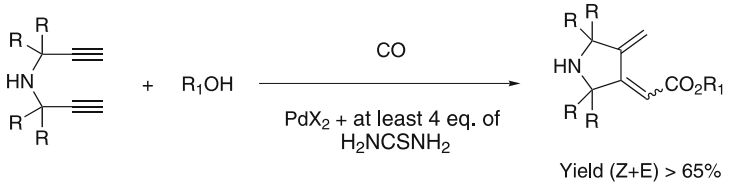
Chiral lactones were also formed by cyclocarbonylation [122] with chiral catalysts, such as Pd-poly-L-leucine catalytic system. For example, but-2-en-1-ol led to the corresponding cyclic chiral lactone in the presence of Pd catalysts with chiral ligands (Scheme 33). About 10 mol % of Pd(II) chloride



Scheme 33

and 4 – 40 mol % of the chiral ligand were needed for this reaction. The major drawback lay in the vinyl alcohol reagent, which required both CO (reducing agent) and oxygen [123].

Palladium salts are able to catalyse diyne carbonylation, so the reaction can be performed at room temperature under 1 atm of carbon monoxide. Thiourea (H_2NCSNH_2), which is added to stabilise the Pd catalyst (Scheme 34), is described as the best ligand for the efficiency of this reaction [124].

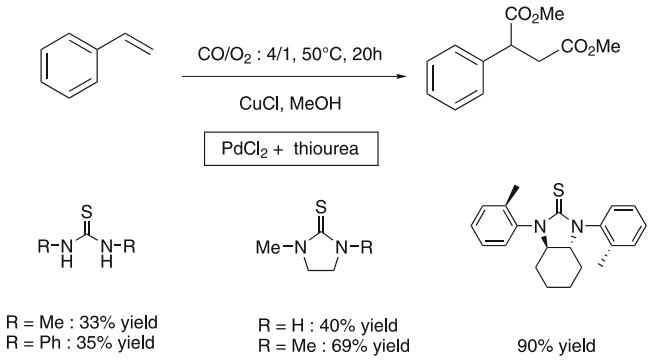


Scheme 34

Many other carbonylation reactions were carried out with thiourea [117], but no information about the use of chiral thioureas have been reported yet. Other Pd-catalysed hydrocarbomethoxylation reactions were studied with styrene and chiral phosphorus ligands, leading to low ee (52% with neomenthyldiphenylphosphine reported by Chiusoli) [125, 126]. All of these systems require large amounts of oxidising agents (e.g. $CuCl_2$ and O_2) to maintain a catalytic cycle, since the Pd(0) formed after one catalytic cycle had to be re-oxidised to Pd(II) [127, 128]. However, this could not be considered as a major drawback since the industrial Wacker process is currently using a Pd re-oxidation technology. Several metal-catalysed carbonylations were studied [129–135] with sometimes high enantioselectivities: 99% ee for the hydroesterification of styrene with the bis-diphenylphosphine derived from isosorbide [136]. Only nitrogen- and phosphorus-based auxiliaries were used [137–139] until recently. However, *N*,*N*′-disubstituted ureas can act as additives for Pd-catalysed hydrocarbonylation reactions. The accelerating effect was attributed to the interaction of the acidic urea protons with the catalysts, weakly coordinated by counter-ions [140]. A study on the use of chiral ureas or thioureas in such processes has not been performed yet.

4.4.3 Bismethoxycarbonylation

The Pd(II)-catalysed asymmetric carbonylation of olefins with a chiral thiourea as the ligand has been reported recently. Since these ligands are stable in the presence of oxidising agents, they prevent Pd precipitation and double-bond isomerisation (Scheme 35) [141].



Scheme 35

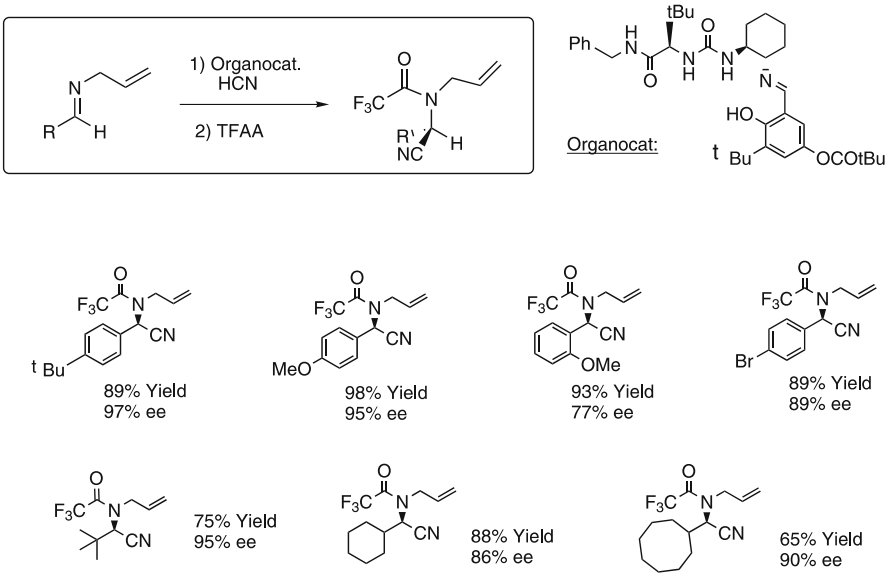
The authors underline that the saturated species $[Pd(thiourea)_4]I_2$ did not lead to bis(methoxycarbonylation) of styrene under the reported reaction conditions, but to styrene polymerisation [142, 143]. With a low-coordinated Pd complex such as $[Pd(tetramethylthiourea)]Cl_2$ [144, 145], the desired product was obtained in only 30% yield. Optimisation of the reaction parameters (Pd halide, oxidising agent, solvent, temperature and CO pressure) resulted in improving the yield to over 60%. The authors also investigated the effect of the substitution of the thiourea: higher yield of carbonylated product is obtained for substituted thioureas (Scheme 35). They explain that hindered thiourea ligands were more effective for the generation of the low-coordinated active Pd complex; no Pd precipitation was observed. Double-bond isomerisation did not occur when other olefin were used. Although chiral thioureas derived from diaminocyclohexane were tested, no asymmetric induction was reported.

5
Organocatalysis: Ureas and Thioureas as Organic Catalysts

Even if organocatalysis is a common activation process in biological transformations, this concept has only recently been developed for chemical applications. During the last decade, achiral ureas and thioureas have been used in allylation reactions [146], the Baylis–Hillman reaction [147] and the Claisen rearrangement [148]. Chiral organocatalysis can be achieved with optically active ureas and thioureas for asymmetric C – C bond-forming reactions such as the Strecker reaction (Sect. 5.1), Mannich reactions (Sect. 5.2), phosphorylation reactions (Sect. 5.3), Michael reactions (Sect. 5.4) and Diels–Alder cyclisations (Sect. 5.6). Finally, deprotonated chiral thioureas were used as chiral bases (Sect. 5.7).

5.1
Strecker Reaction: CN Addition

The Strecker reaction is a condensation of an aldehyde, ammonia and cyanide source (HCN), followed by hydrolysis of the resulting amino nitrile to the corresponding amino acid [149]. In addition to metal-catalysed asymmetric cyanations, organocatalysts have been developed such as chiral guanidino-diketopiperazine [150] (Lipton) and bicyclic guanidine [151] (Corey). Imine-containing urea and thiourea derivatives were developed by Jacobsen (Scheme 36) [148, 152–155]. In these catalytic processes, asymmetric Strecker reactions were performed using preformed imines followed by quenching of the cyano adduct with trifluoroacetic anhydride (TFAA, Scheme 36).



Scheme 36

5.1.1
Asymmetric Strecker Synthesis

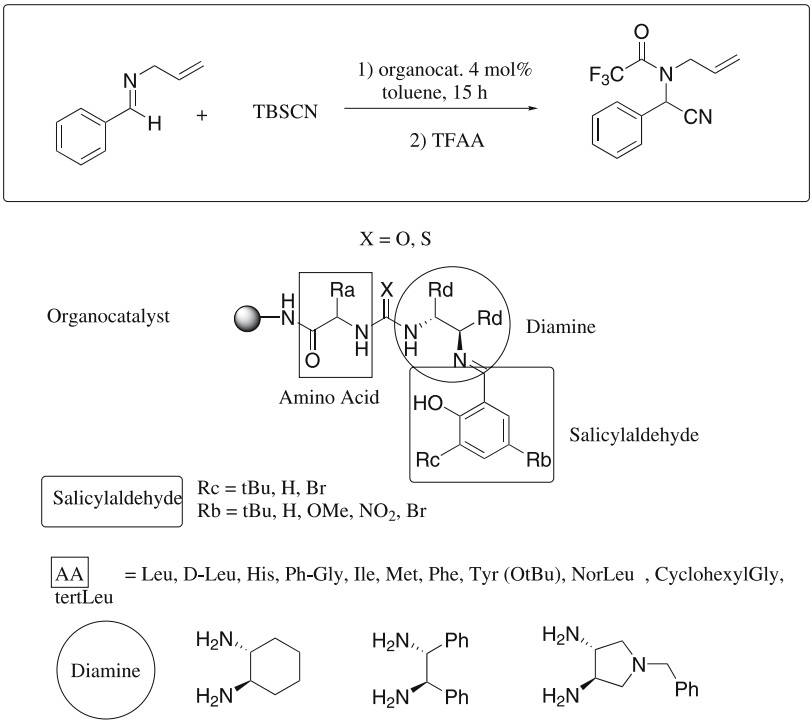
The asymmetric Strecker-type reaction developed by the Jacobsen group is suitable for both aliphatic and aromatic imines, giving high enantiomeric excesses for a wide range of substrates. In this reaction the urea derivative also acts as the catalyst (Scheme 36).

Other ureas and thioureas were tested for this reaction. All of the molecules contain an imino bond moiety, which appeared to be beneficial for

the catalysed hydrocyanation process, but urea or thiourea functional groups were of major importance.

5.1.2
Solid Phase Synthesis for High Throughput Screening

These catalysts were first tested as resin-bound derivatives via HTS, first with metals and then without. Three libraries of chiral molecules, based on three different enantiomerically pure diamines, bulky salicylidene moities and optically active *R*-amino acids were used for structure optimisation (Scheme 37 TBSCN = $^{t}BuMe_2SiCN$) [152].



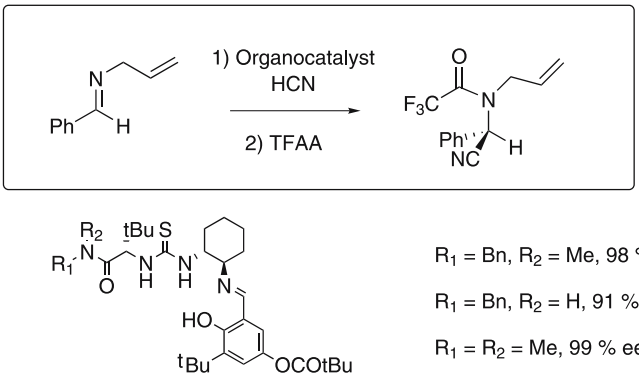
Scheme 37

The reaction was first tested with these substances as ligands but the organic molecule, in the absence of any added metal ion, proved to be the most enantioselective catalyst (library 1: 19% ee vs. less than 13% ee for the best metal catalyst). The effects of selective variations of the amino acid nature and of the salicylidene moiety on the diamine structure were investigated for urea and thiourea derivatives via HTS (library 2 : 48 urea compounds and

library 3 : 132 thiourea compounds) with the model substrate *N*-allyl benzaldimine.

5.1.3
Homogeneous Strecker Synthesis

The catalysts bearing a cyclohexylamine moiety combined with a bulky salicylidene compound linked via one thiourea function to a *tert*-leucine benzylamide (Scheme 38, R_1 = Bn, R_2 = H) was the most efficient. The test was performed in solution at – 78 °C, with HCN as the cyanide source. Excellent results were obtained: 78% isolated yield with 91% ee for the optimised substrate and 70–86% ee for other imine derivatives (65–92% isolated yield) [148, 152–157].

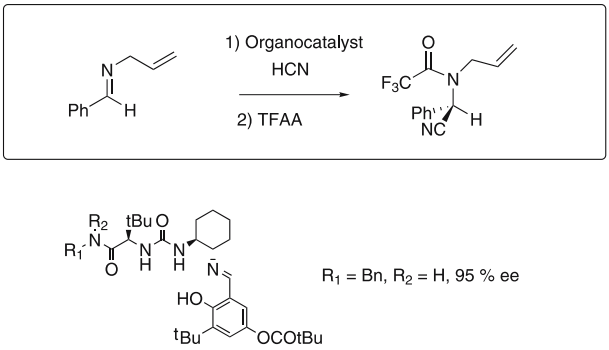


Scheme 38

5.1.4
Recent Developments: Urea vs. Thiourea Ligands

New organocatalysts prepared by the Jacobsen group showed that alkylation of the final amide bond increased the enantioselection (Scheme 38, compare R_2 = Me, 98% ee to R_2 = H, 91% ee). Thus, the reaction performed with *N*-allyl benzaldimine and with the dimethylamide-ending thiourea (Scheme 38 with R_1 = R_2 = Me) gave up to 99% ee. This compound is a structural analogue of the urea depicted in Scheme 36 [148, 152, 154].

Both the ureas and thioureas are highly suitable organocatalysts for the asymmetric Strecker synthesis. For example, the thiourea function was replaced by an urea function (note the opposite configurations). The organocatalysts thus obtained showed similar activity and slightly higher enantioselectivities with *N*-allyl benzaldimine (Scheme 39, 74% yield with 95% ee for R_1 = Bn and R_2 = H). Once again, better enantioselectivity (up to 99% ee) was at-



Scheme 39

tained with the dimethylamide-urea analogue (with opposite configurations, depicted in Scheme 36) [148, 152, 154].

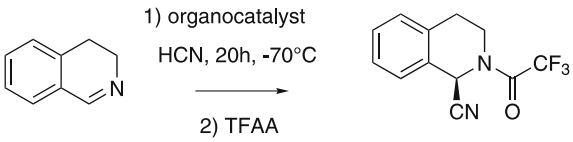
5.1.5
Structural Characteristics and Reaction Mechanism

Other organocatalysts were prepared for the Jacobsen-type Strecker synthesis. The characteristic structural components were reviewed recently and new catalysts were used [148]. From this large number of chiral products, it appeared that the use of thiourea instead of urea gave, in general, better results. The amide bond was more efficient than the ester bond. The reaction was not sensitive to the amino acid, but sensitive to the salicylaldimine substituents: the *ortho*-substituent had little effect, while changing the *para*-substituent from ester to *tert*-butyl lowered the ee of the product. Alkylation (MeO-, $^{t}BuCO_2$-) of the phenol also resulted in lower enantioselectivities. More details concerning the mechanism of the reaction were given: it was found that the Schiff base catalyst has a well-defined secondary structure in solution (NOE NMR). The hydrocyanation reaction proceeded according to a Michaelis–Menten kinetic model, with a first-order dependence on the thiourea and HCN, and saturation kinetics with respect to the imine substrate. Reversible hydrogen bond formation between the two urea or thiourea hydrogens and the imine was observed. The binding of the imine as the *Z* isomer was noticed. A broad variety of substrates were tolerated and the asymmetric induction was independent of their steric or electronic properties. The addition of HCN was supposed to take place over the diaminocyclohexane framework (Scheme 36) [153].

5.1.6
Other Substrates

The tertiary amide containing thiourea (Scheme 38 with $R_1 = R_2 = Me$) and urea (Scheme 36) were used for a wide range of substrates as depicted in

Scheme 36. The urea derivative gave similar results to the thiourea compound. Acyclic imines (mainly *E* isomers) and *Z* cyclic imines could also be used for this process (Scheme 40, 91% ee) [148, 152, 154].



Scheme 40

5.1.7 Industrial Applications

The Jacobsen group has also shown that the recycling of the resin-bounded catalyst can be successfully performed [152, 154]. Moreover, they have developed an efficient method for the hydrolysis of the aminonitrile into the corresponding amino acid. This method was applied for the commercial production of optically active *R*-amino acids at Rhodia ChiRex (e.g. *tert*-leucine): the catalyst was immobilised on a resin support (4 mol %, 10 cycles) and the intermediate hydrocyanation adduct was trapped by simply replacing TFAA with $HCOOH/Ac_2O$, for example. Highly crystalline formamide derivatives were thus obtained in excellent yields (97–98% per cycle) with very high enantioselectivities (92–93% per cycle) [158].

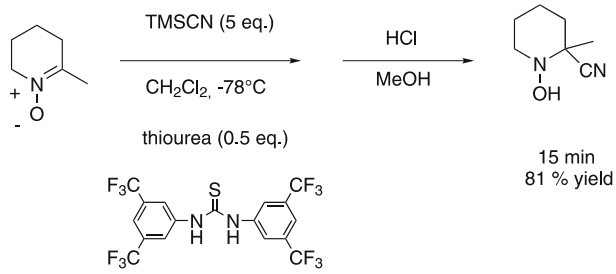
Jacobsen and co-workers also described the highly enantioselective hydrocyanation of ketimines with the urea analogue. After recrystallisation of the corresponding Strecker adduct, formylation and hydrolysis, the *N*-benzyl *R*-methylphenylglycine, was obtained. The *R*-amino acid hydrochloride is obtained in 93% overall yield with > 99.9% ee on a gram scale [149].

5.1.8 Nitrone Cyanation

Finally, nitrone cyanation were performed with non-chiral urea and thiourea derivatives, the latter being more efficient for this process. No chiral compound has been described yet (Scheme 41) [159].

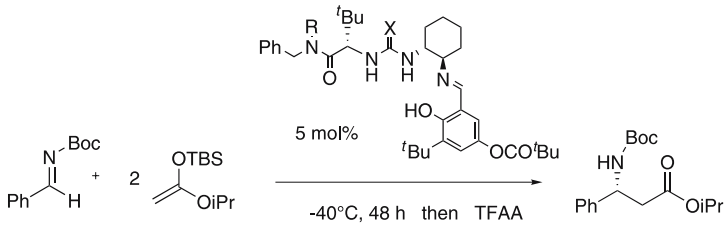
5.2 Mannich Reactions

Similar organocatalytic species to those successfully used for the Strecker reaction were used for the asymmetric Mannich reaction. Catalyst structure/enantioselectivity profiles for the asymmetric Strecker and Mannich reactions were compared by the Jacobsen group [160]. The efficient thiourea



Scheme 41

ligands used for the Strecker reaction (80–99% ee) showed lower activity in the Mannich reaction (44–97% ee). However, similar enantioselectivities were obtained both for the urea- and the thiourea-containing molecules. The model reaction was the asymmetric silylketene acetal addition to *N*-Boc benzaldimine (Scheme 42).



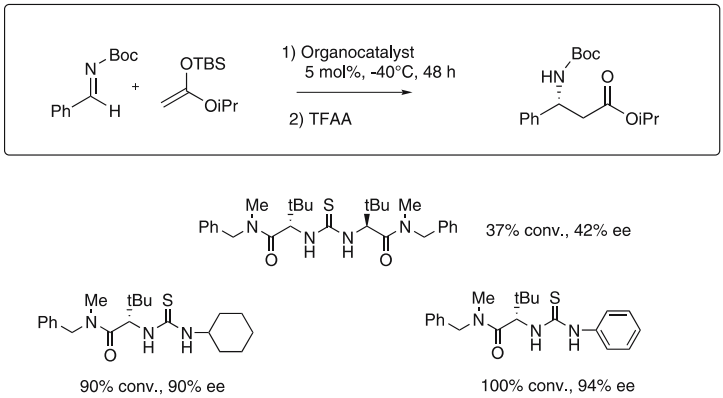
X	R	% conv.	% ee
O	H	92	81
S	H	90	91
	Me	96	97

Scheme 42

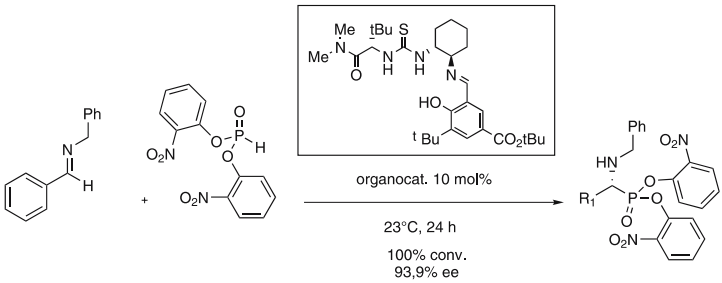
New catalysts were prepared after optimisation of the ligand structure. The most efficient organocatalyst for this reaction was an amido-thiourea derivative (Scheme 43). Interestingly, dissymmetrical ligands were more efficient and selective for this reaction.

5.3 Phosphorylation

The Jacobsen group also studied the thiourea-catalysed enantioselective hydrophosphonylation of imines (Scheme 44) [160]. Many examples were de-



Scheme 43



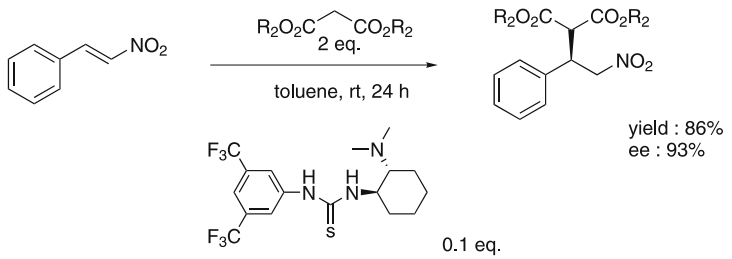
Scheme 44

scribed with excellent enantioselectivities (> 90%) for both substrates after phosphite optimisation (*o*-nitrobenzyl > Ph, 2-cyanoethyl). Aliphatic imines can also be used.

5.4 Michael Reactions

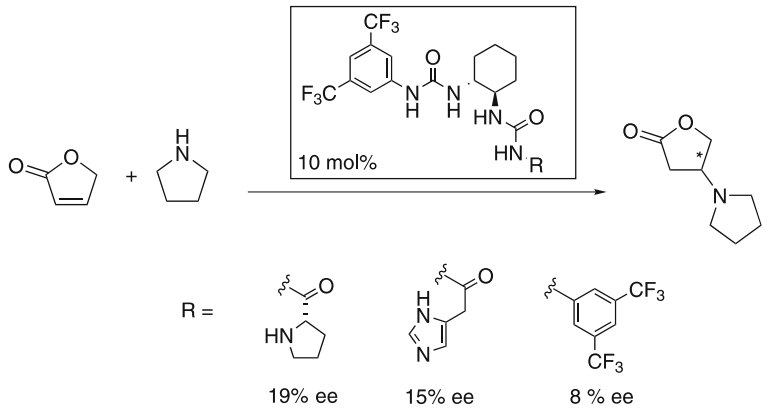
The enantioselective Michael reaction of malonates to nitroolefins catalysed by bifunctional amino-thioureas has recently been reported by Takemoto [161]. Excellent ee (75–93%) were obtained with diethylmalonate after solvent optimisation, toluene being the best solvent both for the activity and for the selectivity. Substituted malonates were then reacted with various nitroolefins under the same conditions. Excellent enantioselectivities were observed (Scheme 45).

This bifunctionnal amino-thiourea organocatalyst led to high selectivity because it was activating both the nitrone and the malonate, in its enol form, due to the acidic hydrogen atoms of the thiourea. Thus, the amino-thiourea catalyst promoted the Michael reaction of malonates to various nitroolefins



Scheme 45

with high enantioselectivities (81–93% ee). The authors reported that the reaction was also successful without solvent. Very recently, Nagasawa reported the use of chiral ureas for the hetero-Michael reaction [162]. Non-chiral ureas, guanidines and thioureas accelerated the racemic reaction of pyrrolidine with γ-crotonolactone. The asymmetric conjugate addition was then performed with chiral ureas. The most successful representatives are reported in Scheme 46.

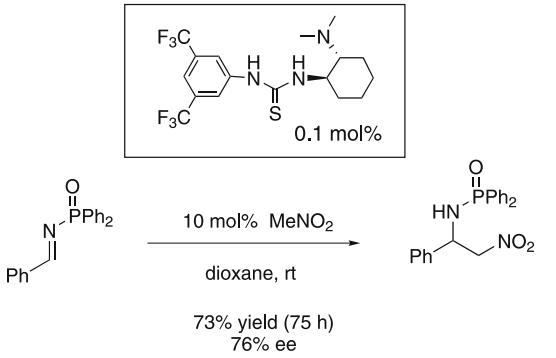


Scheme 46

The asymmetric induction depended on the solvent and on the R group. The best enantioselectivities were obtained in toluene (Scheme 46). Despite of the low ee values, those results show the importance of the R group, suggesting possible enhancement.

5.5
Aza-Henry and Nitroaldol Reactions

An enantioselective aza-Henry reaction catalysed by the same bifunctional organocatalyst was recently reported by the same group (Scheme 47) [163].



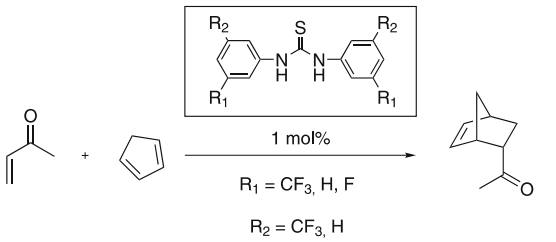
Scheme 47

The aza-Henry reaction is the nucleophilic addition of nitroalkanes to imines to give nitroamine derivatives. This reaction was also studied with metal-based catalysts [164].

Preliminary studies on the racemic reaction of protected imines with nitromethane showed that the thiourea and the amine mutually weakened their reactivities. However, the bifunctional amino-thiourea led to good results. Enantioselectivity of the adduct depended on the protecting group, $P(O)Ph_2$ affording the best results (76% ee). Then, other aromatic imines substrates were successfully phosphorylated with good to high enantioselectivities (63–76% ee).

5.6 Diels–Alder Reactions

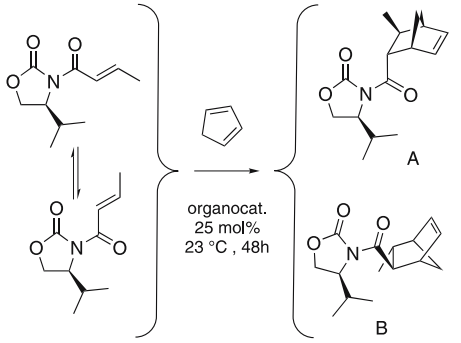
Diels–Alder reactions [165] using thiourea as organocatalyst were recently examined [166]. Kinetic measurements showed that accelerations of the relative reaction rates were more dependent on the thiourea substituents than on the substrates or the solvent (even in highly coordinating polar solvents like wa-



Scheme 48

ter). The catalysts increased the reaction rates and endo-selectivities of Diels–Alder reactions between cyclopentadiene and vinylketones (Scheme 48).

Aromatic thioureas were more active than alkyl (octyl, cyclohexyl) derivatives. Thioureas with trifluoromethyl substituents were even more effective. The same group also showed that these organocatalysts can act as weak Lewis acids and are thus able to alter the stereochemistry of the Diels–Alder reaction between cyclopentadiene and chiral acrylamide derivatives (Scheme 49) [167].

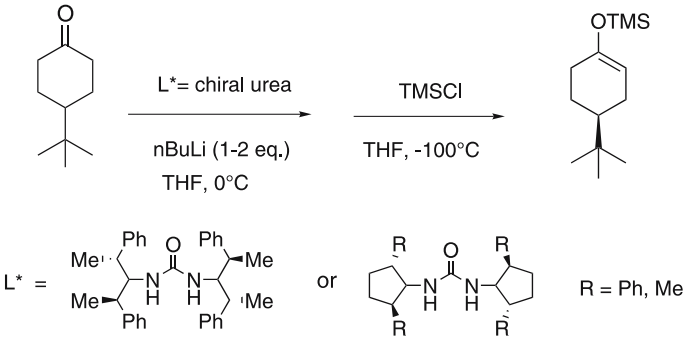


R_1	R_2	A	B	yield
CF_3	H	77	23	74%
CF_3	CF_3	81	19	78%

Scheme 49

5.7 Thioureas as Chiral Bases

Asymmetric deprotonation of prochiral cyclic ketones (Scheme 50) was performed with chiral ureas in the presence of butyllithium. Yields were good (85–88%) with high enantioselectivities (83–87%). Moderate enantioselectivity is obtained with the cyclopentyl-containing urea (Scheme 50: 37% ee with R = Ph; 7% ee with R = Me) [168, 169].



Scheme 50

6 Conclusion

Although the use of optically pure ureas and thioureas in asymmetric catalysis mainly appeared in this last decade, their potential as chiral inductors is already very important. In this relatively short time period, urea and thiourea species have found an application in numerous domains of asymmetric catalysis. This can be explained by both the easy synthesis of such compounds and the diversity of their chemical properties. Many chiral amines and diamines are available, thus enabling the straightforward synthesis of various series of optically pure ureas and thioureas in very good yields. As the formation of urea and thiourea complexes is very easy and fast, they are ideal for solid phase synthesis and high-throughput screening. On another hand, the easy polyaddition of diamines onto isocyanates or isothiocyanates opens a way to supported catalytic systems affording the recovery of the chiral active species. Various coordinating modes of urea and thiourea groups to metallic centres can be observed since they can act as L- or X-ligand types, and are thus able to present either hard or soft properties. The chemical versatility of these groups allows the formation of various complexes with several types of transition metal precursors. Some of these organometallic complexes proved to be both efficient and selective catalysts in asymmetric reductions. In some cases, similar results to those obtained with the best known phosphine ligands have been attained. In addition to their Lewis base properties, ureas and thioureas are also able to form several types of hydrogen bonding (acceptor or donor) which confer organocatalyst properties. It is therefore not surprising that these molecules are used as efficient and selective organocatalysts for important asymmetric transformations, such as the Strecker reaction. Many other enantioselective reactions also appear possible in the presence of such thiourea-based organocatalysts. Two examples have been described by the time of writing this review: the Pictet–Spengler reaction [170], which provides a highly enantioselective access to a range of substituted tetrahydro-β-carbolines, and the Baylis–Hillman reaction, for which a drastic rate increase is observed during the formation of allylic alcohols. In the later case, the bis-thiourea catalyst was quantitatively recovered by silica-gel column chromatography [171]. In this review we describe many applications of ureas and thioureas for asymmetric metal-catalysed reactions and often noted that thioureas lead to more active and enantioselective complexes than ureas. As the organocatalytic properties, including metal interactions, of chiral thioureas are widely observed, they are a very promising type of compound and their use in asymmetric catalysis will probably expand very rapidly during the next decade.

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