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Review

Synthesis of β-aminoacid derivatives *via* enantioselective hydrogenation of β-substituted-β-(acylamino)acrylates

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Contents

Abstract

This review presents recent advances in enantioselective hydrogenation of β-amidoacrylates by means of rhodium and ruthenium catalysis. It reveals the strong efforts, which have been devoted to the discovery of new ligands and catalysts during the last decade. Metal catalysts containing optically pure bidentate and monodentate phosphorus ligands have made possible the generation of very efficient catalytic systems for the production of β-aminoacid derivatives under mild and green conditions from a variety of (*E*)- and (*Z*)-β-aryl- and β-alkyl-(β-acylamino)acrylates.

Keywords: β-Amido esters; Enantioselective hydrogenation; Catalysis; Ruthenium; Rhodium

1. Introduction

Enantiomerically pure β-aminoacid derivatives are building blocks of choice for the preparation of β-peptides. This type of peptides usually presents high enzymatic stability and three-dimensional structures of interest [1]. Some β-aminoacids themselves are biologically active products, for instance *cis*-pentacine shows high antibiotic and antifungal activities [2], and emeriamine exhibits hypoglycemic and anticetogenic properties (Scheme 1) [3]. A variety of polyfunctional linear products [4], as well as macrocycles [5] incorporating β-aminoacid substructures have revealed interesting biological activities (Scheme 1).

Due the high potential of such compounds in pharmaceutical industry, the preparation of chiral β-aminoacids has been intensively studied [6]. The main approaches for stereoselective synthesis of β-aminoacids are based on homologation of α-aminoacids [7], enzymatic resolution [8], enolate addition to imines [9], Curtius rearrangement [10], conjugate addition of nitrogen nucleophile to α,β-unsaturated derivatives [11], aminohydroxylation [12], etc. However, the catalytic asymmetric hydrogenation of β-acetamidoacrylates, which involves clean atom economical reactions and offers the preparation of both (*R*)- and (*S*)-enantiomers in the presence of chiral ruthenium(II) or rhodium(I) complexes represents one of the most

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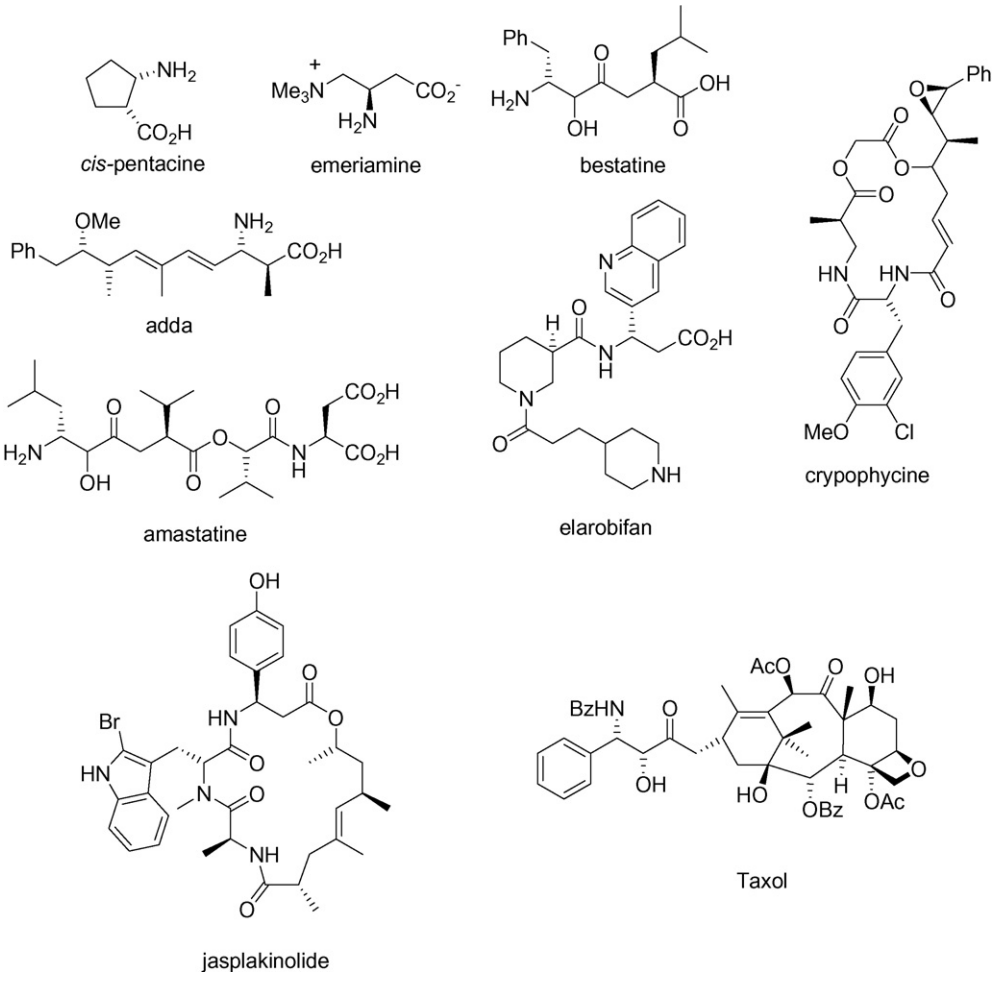
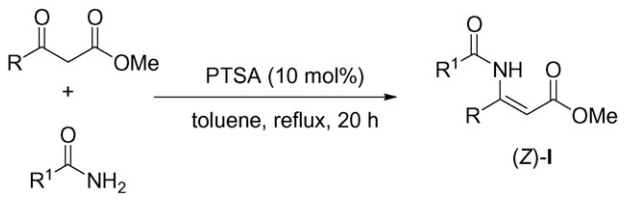


Scheme 1. Some biologically active compounds with a β-aminoacid substructure.

promising method for a large scale industrial preparation of optically pure β-aminoacids.

2. Preparation of β-(acylamino)acrylates

The most direct methods to prepare β-(acylamino)-acrylates start from β-ketoesters. We have prepared β-(acylamino)acrylates according to a procedure previously used in our laboratory to synthesize *N*-acylenamines from ketones [13]. Condensation of primary amides with β-ketoesters in the presence of a catalytic amount of *para*-toluenesulfonic acid (10 mol%) in refluxing toluene with elimination of water in a Dean Stark apparatus led to the formation in satisfactory yields to (*Z*)-β-(acylamino)acrylates ((*Z*)-**I**), exclusively (Scheme 2).

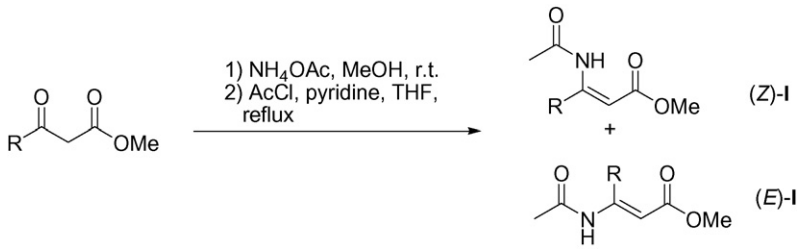


Scheme 2. Direct preparation to (*Z*)-β-(acylamino)acrylates.

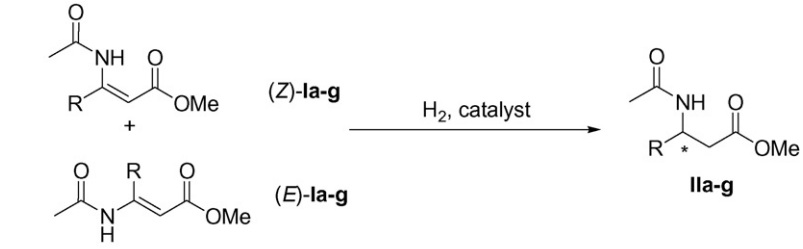
Another method, which has been more often used, is a two-step transformation of β-ketoesters into enaminoesters upon treatment with ammonium acetate in methanol at room temperature followed by acylation with acyl chloride or anhydride in THF (Scheme 3) [14]. With this method, (*Z*)/(*E*) mixtures of stereoisomers are usually obtained, the thermodynamically more stable (*Z*)-isomer stabilized by hydrogen bonding being predominant. Whereas β-alkyl-(β-acylamino)acrylate stereoisomers can be easily separated by column chromatography, this separation is not always easy from β-aryl derivatives.

3. Enantioselective hydrogenation of β-(acylamino)acrylates

As a preamble, it is useful to point out that the two β-(acylamino)acrylate stereoisomers have different reactivities and behaviours in metal-catalyzed asymmetric hydrogenation. Initial studies showed that the (*E*)-isomers led to better or excellent enantioselectivities, but the asymmetric hydrogenation of the (*Z*)-isomers was more problematic. For these reasons, and also for the potential of the resulting β-aminoacid derivatives, the prochiral (*Z*)- and (*E*)-β-(acylamino)acrylates have recently become model compounds in enantioselective hydrogenation according to Scheme 4.



Scheme 3. Two-step preparation of β-(acylamino)acrylates.



R= Me(**a**), *i*Bu(**b**), *t*Bu(**c**), Ph(**d**), Et (**e**), *i*Pr(**f**), *n*Pr (**g**)

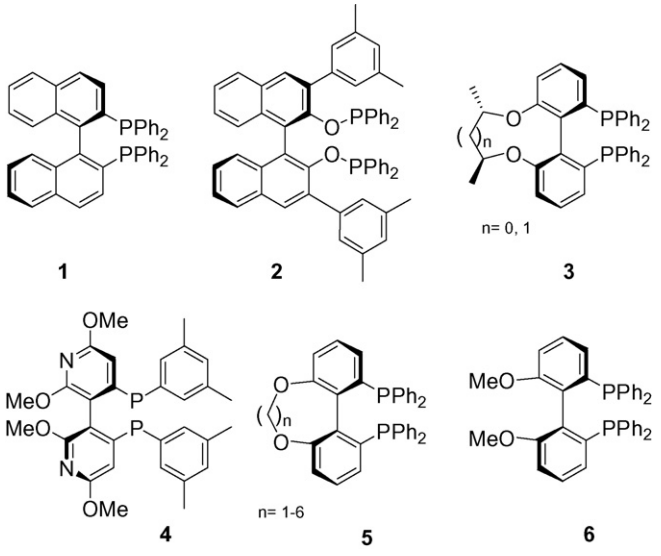
Scheme 4. General scheme for the enantioselective hydrogenation of β-(acylamino)acrylates.

3.1. Ruthenium-catalyzed enantioselective hydrogenation of β-(acylamino)acrylates

The first use of ruthenium catalysts for the enantioselective hydrogenation of β-(acylamino)acrylates was reported by Noyori in 1991 [15]. The chiral ligand (*R*)-Binap **1** (Scheme 5) was incorporated in the ruthenium precursor $Ru(O_2CCH_3)_2$(**1**), and the first tests carried out from 3-substituted-3-acetylaminoprop-2-enoates **Ia**,**b**,**d** in methanol at room temperature revealed the following features: (i) the (*Z*)-isomers were more reactive than the (*E*)-isomers but very low enantioselectivities were obtained from the (*Z*)-isomers (<5%), (ii) the (*E*)-isomers **Ia**,**b** were converted into the corresponding β-amidoesters **IIa**,**b** in more than 90% ee, (iii) the hydrogenation reactions could be performed under relatively low hydrogen pressure at room temperature but under these conditions they required long reaction times during which time the β-amido group could be cleaved, and (iv) the absolute configuration of the stereogenic centre of the major enantiomer obtained by hydrogenation of the (*E*)- and (*Z*)-isomers were opposite starting from the aliphatic compounds **Ia**,**b**, and identical when R was a phenyl group in **IId**.

The low enantioselectivities obtained from the (*Z*)-isomers, together with the different major configurations of the β-amido esters resulting from hydrogenation of one or the other starting stereoisomer represented a serious drawback for the use of $Ru(O_2CCH_3)_2$(**1**) as catalyst for the direct hydrogenation of (Z)/(E) mixtures of the substrates. Other [Ru((*R*)-Binap)] precatalysts generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and **1** led to lower enantioselectivities for the hydrogenation of **Id** (31% ee) when the reaction was carried out in ethanol at 50 °C under 5.5 bar of H_2 [16]. Also containing binaphthyl atropoisomery, the C_2-symmetrical bis-phosphinite ligand **2** bearing bulky aromatic substituents at the 3,3′ positions of the binol backbone, provided excellent catalysts in association with $[RuCl_2(p\text{-cymene})]_2$ as ruthenium source [16]. Under 5.5 bar of H_2 in EtOH at 50 °C for 20 h, a variety of (*E*)/(*Z*)-mixtures of aromatic substrates of type **Id** with various substituted phenyl groups (C_6H_4-*p*-X: X = F, Cl, Br, Me, MeO, CH_2Cl) were hydrogenated in excellent enantioselectivities (>96% ee in most cases). This catalytic system appears as one of the best for the enantioselective hydrogenation of β-aryl-β-acylaminopropenoates.

Other ruthenium catalysts designed on the basis of the chiral biphenyl scaffold have been tested. From ligands **3**, where the phenyl groups are tethered by a chiral bridge, $[RuCl(C_6H_6)$(**3**)]Cl complexes were prepared and used for the hydrogenation of (*E*)-**Ia**,**c**,**e**–**g** in methanol at 0 °C to room temperature under

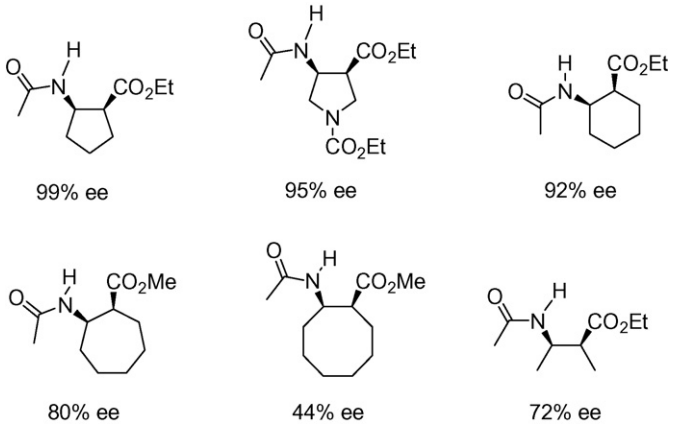


Scheme 5. Diphosphine ligands used in ruthenium-catalyzed hydrogenation of β-(acylamino)acrylates.

17 bar of H_2 [17]. All types of ligands with the (*SSS*), (*RSS*), and (*SRR*) configurations led to very good enantioselectivities. Almost perfect hydrogenations (ee >99.6%) were obtained from the 3-*tert*-butyl-substituted substrate **Ic**. The configuration of the stereogenic centre in compounds **IIa**,**c**,**e**–**g** was controlled by the configuration of the binaphthyl motive.

The dipyridyldiphosphine **4** was also used to prepare the [RuCl(C_6H_6)(**4**)]Cl complex which performed the enantioselective hydrogenation of β-alkyl-β-acetamidoprop-2-enoates **Ia**,**c**,**e**–**g** at room temperature under 4 bar of H_2. The (*E*)-substrates were hydrogenated with excellent enantioselectivities (>97% ee), the best one (99.7% ee) being also obtained from **Ic** featuring the bulky *tert*-butyl substituent [18]. It is worth noting that with the same (*R*)-**4** ligand, when *R* = Me (**Ia**), Et (**Ie**), *n*Pr (**Ig**), (*S*)-**IIa,e,g** were the major compounds, whereas when *R* = *i*Pr (**If**) and *t*Bu (**Ic**), e.g. α-branched alkyl substituents, the (*R*)-**IIc**,**f** products were preferentially formed. Under similar conditions, the (*Z*)-**Ia** substrate led to poor enantioselectivity (37.5% ee) and the opposite (*R*)-**IIa** enantiomer was produced.

The above examples concern the enantioselective hydrogenation of trisubstituted olefinic bonds. The asymmetric hydrogenation of tetrasubstituted olefins is usually more challenging. However, the enantioselective hydrogenation of cyclic β-(acetamido)acrylates was successfully performed with an *in situ* generated system, which had previously been used for the hydrogenation of other types of endocyclic tetrasubstituted olefins such as enones [19], and enamides [20]. Thus, by mixing Ru(methallyl)$_2$(cyclooctadiene), a chiral diphosphine and HBF_4·Me_2O (molar ratio: 1/1/2) in CH_2Cl_2, a catalytic material was isolated after evaporation of the solvent. Tunaphos ligands **5** provided very efficient and selective catalysts which led to five-membered *cis*-β-amido esters in more than 99% ee in alcoholic solvent at room temperature under 50 bar H_2 pressure (Scheme 6) [21]. Hydrogenation with other biaryl ligands such as Binap (**1**) and MeO-Biphep (**6**) also gave high enantioselectivities. With larger rings, the enantioselectivity decreased from 92% for a six-membered ring to 44% for a eight-membered ring, and an intermediate value of 72% was obtained from the acyclic tetrasubstituted ethyl 3-acetamido-2-methylbut-2-enoate.



Scheme 6. Enantioselective hydrogenation of cyclic β-(acylamino)acrylates with C3-Tunaphos ligand (**5**, *n* = 3).

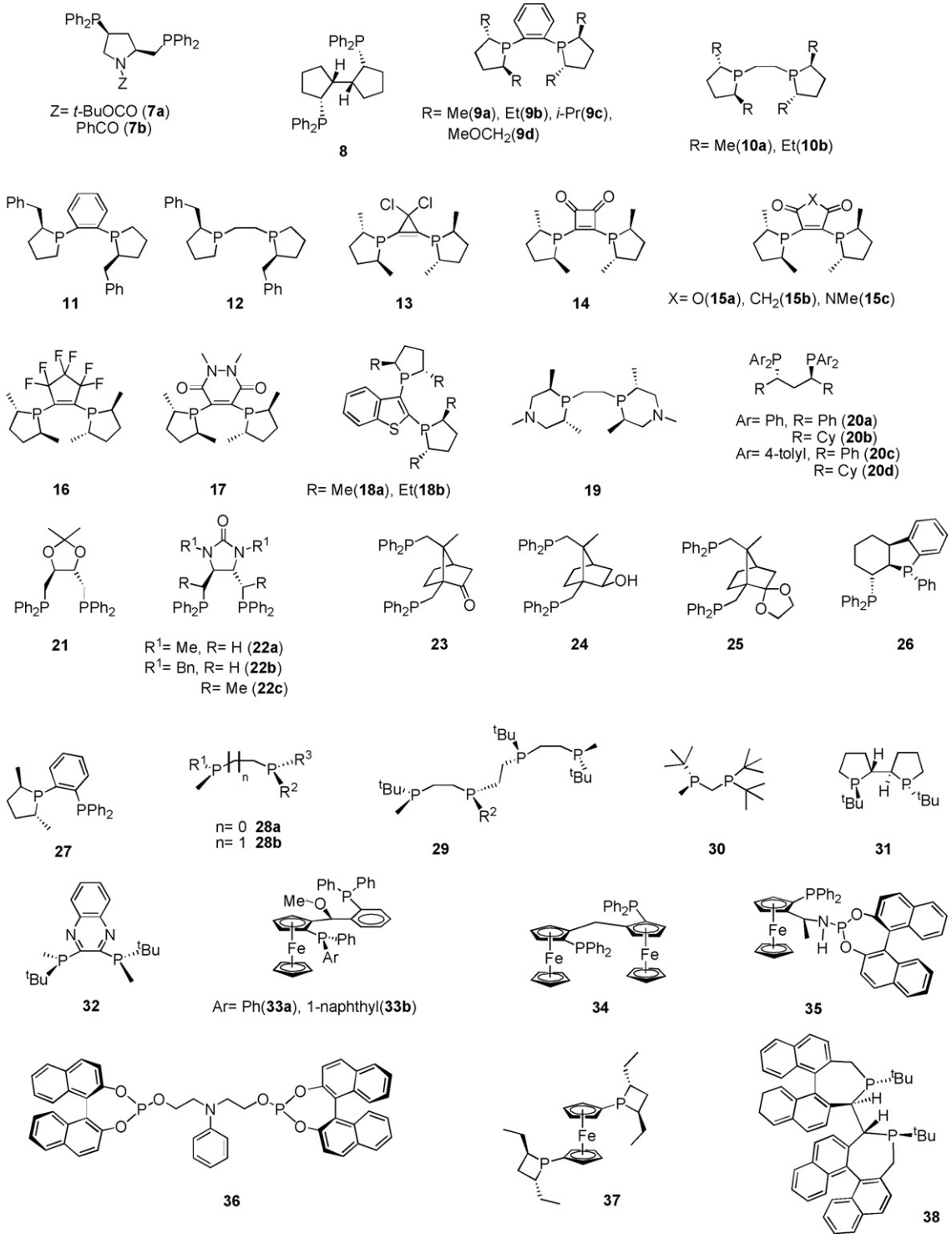
As a conclusion, it appears that selected ruthenium catalysts containing atropoisomeric binaphthyl or biphenyl-based diphosphine ligands are able to perform the hydrogenation of β-(acylamino)acrylates under mild conditions (room temperature, low hydrogen pressure) in protic solvents, especially methanol, with high enantioselectivity. From β-arylacrylates, both (*Z*)- and (*E*)-substrates are concomitantly hydrogenated with high enantioselectivity into the same major enantiomer, whereas β-alkylacrylates usually lead to the formation of the opposite enantiomers with much higher enantioselectivity from the (*E*)-stereoisomer.

3.2. Rhodium-catalyzed enantioselective hydrogenation of β-(acylamino)acrylates

3.2.1. Rhodium catalysts based on bidentate phosphorus ligands

3.2.1.1. Description of efficient catalytic systems. After the initial and promising results obtained by Achiwa in 1978 [22] with [Rh(**7b**)] catalyst (55% optical purity), it took about 20 years before the report of valuable enantioselectivities higher than 95% appeared. These results were obtained by using a cationic rhodium precursor combined with an optically pure diphosphine such as (*R,R*)-BICP (**8**) or (*R,R*)-Me-DuPhos (**9a**) (Scheme 7) [23]. The important information, which came out from this study was that the (*E*)-isomer was hydrogenated faster than the (*Z*)-isomer and that both stereoisomers of aliphatic and aromatic substrates led to the same β-acetylamino ester enantiomer. The hydrogenation could be performed at room temperature in an aprotic solvent such as toluene under low hydrogen pressure (3 bar) for the (*E*)-isomer but required higher pressure for the (*Z*)-isomer (20 bar). It was latter shown that with Et(**9b**)- and Me(**9a**)-DuPhos ligands, the enantioselective hydrogenation of both stereoisomers could be efficiently performed at room temperature under low hydrogen pressure (1 bar) in methanol [24]. Under similar hydrogenation conditions, the absolute configuration of the hydrogenated products **II** depended on the chiral ligand but also on the nature of the substituent at the disubstituted position of the double bond, and higher enantiomeric excesses were obtained from the (*E*)-isomer (up to 99.6%) than from the (*Z*)-β-(acylamino)acrylates [23]. With these ligands, β-arylacrylates led to lower enantioselectivities than β-alkylacrylates.

A variety of bis(phospholane) ligands have been tested in combination with rhodium precursors. BPE ligands (**10a**,**b**) [25], 2,5-bis(oxymethyl)-bis(phospholanes) **9d** [26,27], 2-monosubstituted bis(phospholanes) **11**, **12** [28], and bis(phospholanes) **13**–**17** [29,30] with various tunable backbones have been investigated (Scheme 7). Most of these ligands, except **13**, led to high enantioselectivities for the hydrogenation of both (*E*)- and (*Z*)-(acylamino)acrylates after optimization of the reaction conditions (solvent, hydrogen pressure, temperature). From aliphatic substrates (**I**, *R* = alkyl), the enantiomeric excesses obtained from the (*E*)-isomers are always higher than those resulting from hydrogenation of the (Z)-isomers. When R is an aromatic substituent, this tendency is not always respected.



Scheme 7. Bidentate ligands used in rhodium-catalyzed hydrogenation.

The unsymmetrical bidentate phospholanes **18a**,**b** based on the benzothiophene scaffold have been incorporated in [$Rh^{(I)}$(cyclooctadiene)(**18**)]BF_4 complexes, which were tested as catalysts in the hydrogenation of (*E*)-**Ib** and (*Z*)-**Ia** in methanol at room temperature under 14 and 5 bar of hydrogen pressure, respectively [31]. The good enantioselectivities observed were located in the range of 87–90%, which is in line with the results obtained with C_2-symmetrical bis(phospholanes). The bis(azaphosphorinane) **19**, presents a C_2-symmetrical structure with a flexible ethylene bridge connecting two 6-membered heterophosphirane rings was found to give very efficient Rh(I) catalysts operating in dichloromethane at room temperature under 1 bar of hydrogen [32]. Thus, methyl, ethyl, and isopropyl esters derived from the β-alkyl-

β-(acetylamino)acrylates (*E*)-**Ia**,**b**,**e–g** were fully hydrogenated within 24 h with enantioselectivities higher than 99%, whereas (*Z*)-**Ia** acrylates were obtained in 96% ee.

1,3-Diphosphines **20** with a chiral tether leading to a six-membered chelate ring after coordination to a rhodium(I) centre have been prepared from 1,3-diols [33]. The corresponding rhodium complexes were efficient catalysts able to perform the hydrogenation of β-dehydroaminoesters at room temperature in various solvents such as MeOH, CH_2Cl_2 and CF_3CH_2OH [33,34]. Starting from (*E*)-**Ia**, excellent ee's (up to 98%) were achieved whatever the diphosphine used. From (*Z*)-**Ia**, the enantioselectivities were lower, especially with ligands **20b,d** containing the purely aliphatic backbone. It was also found that the benzyl ester usually provided better results than the methyl ester.

The 1,4-diphosphine DIOP (**21**) exhibited poor activity for the hydrogenation of (*E*)- and especially (*Z*)-**I** isomers [27,35]. However, other 1,4-diphosphines such as **22** bearing two (**22a**,**b**) or four (**22c**) stereogenic centres, have revealed an interesting potential in asymmetric hydrogenation of β-(acylamino)acrylates [35–37]. With these ligands it is remarkable that under similar reaction conditions, namely in different solvents (MeOH, CH_2Cl_2, THF, acetone) at room temperature under 1 bar of H_2 pressure, the (*Z*)-isomers were hydrogenated with the same or higher ee values than the (*E*)-isomers. With ligand **22a**, the best ee obtained from (*Z*)-**Ia** (ethyl ester) reached 97.4% in THF [35], and similar values were obtained when ligands (*S,S*)-**22b** and (*R,S,S,S*)-**22c** were used in *i*PrOH [37]. A series of diastereomeric oxygenated diphosphines (**23**–**25**) prepared from the camphor core were also tested in the hydrogenation of β-dehydroamino esters and acids but they showed relatively low reactivities and enantioselectivities during the hydrogenation of (*Z*)- and (*E*)-**Ia** and the corresponding acids [38,39]. The unsymmetrical mixed diphosphino-phospholane ligands **26** [40], **27** [41] able to generate five-membered chelates upon coordination to the rhodium centre provided disappointing enantioselectivities.

Aliphatic electron-rich P-chirogenic 1,1- and 1,2-diphosphines were introduced in 2001 for the hydrogenation of β-(acylamino)acrylates [42]. The reactions carried out in THF at room temperature and an initial H_2 pressure of 3 bar in the presence of 1 mol% of [Rh(norbornadiene)(**28a** or **28b**)]BF_4 gave fast conversion of (*E*)-β-alkyl substrates **I** within 2 h into the β-(acylamino) esters **II** with enantiomeric excesses in the range of 95–99%, whatever the nature of the ester (methyl or ethyl) and the R group (Me(**Ia**), Et(**Ie**), *n*Pr(**Ig**)). From the aliphatic (*Z*)-**Ia**, **Ie** substrates, various rhodium catalysts with symmetrical and unsymmetrical diphosphine ligands provided complete conversion but moderate enantioselectivities (up to 72% ee) [43]. The tetraphosphine **29** based on similar aliphatic structures have made possible the preparation of the binuclear rhodium complex [Rh_2(norbornadiene)$_2$(**29**)][PF_6]$_2$ [44]. Under 3 bar H_2 pressure, in methanol at room temperature, (*E*)-**Ia** was hydrogenated within 2 h with 99% ee, and (*Z*)-**Ia** was converted into **IIa** in 71% ee [44]. Improvement of the enantioselectivity from the aliphatic (*Z*)-isomers was obtained when the [Rh(cyclooctadiene)(**30**)]BF_4 complex, containing the unsymmetrical and bulky diphosphine **30** was used [45]. The aliphatic β-(acetamido)acrylates **Ia**,**b**,**c**,**f** were hydrogenated with complete conversion within 15 min at room temperature in THF under 0.4–1.5 bar [45]. The enantiomeric excesses obtained from the (*E*)-**I** isomers were higher than 99%, and located in the range of 92–99% from the (*Z*)-**I** isomers. It is noteworthy that the lower the pressure, the higher the enantioselectivities, and as already observed with ruthenium catalysts [18], the substrates featuring an α-branched R substituent at the β-position (**Ic,f**) led to the (*S*)-**II** enantiomers, whereas the substrates **Ia**,**b**,**g** provided the (*R*)-**II** enantiomers, when hydrogenated in the presence of the same catalyst. [Rh(norbornadiene)(TangPhos **31**)]SbF_6 has also been used efficiently for the hydrogenation of (*E*)/(*Z*) mixtures of both β-alkyl and β-aryl(acylamino)acrylates in THF at room temperature under low pressure [46]. Thus a 1:1 mixture of (*E*)- and (*Z*)-**Ia** led to **IIa** with 99.5% ee. As far as aryl (acylamino)acrylates are concerned, electron-rich substrates with a *p*-alkoxyphenyl substituent gave slightly higher ee's (>98%), whereas *ortho*-substituted phenyl substituents led to lower enantioselectivities (74–83% ee) [46]. An example of diphosphine based on dialkylphosphino groups linked *via* an aromatic quinoxaline backbone (**32**) has revealed high efficiency (99.7% ee for the formation of **IIa** from (*E*)-**Ia** under 3 bar of H_2 pressure in MeOH) [47].

Ferrocene-based diphosphines such as **33** [48] and **34** [49] have been recently tested with rhodium precursors for the hydrogenation of β-alkyl(acylamino)acrylates but with low efficiency in term of enantioselectivity. However, with some of these ferrocene-based ligands, the most interesting improvements were observed for the enantioselective hydrogenation of β-aryl(acylamino)acrylates. The catalytic system generated *in situ* from [Rh(cyclooactadiene)$_2$]BF_4 and the unsymmetrical mixed ferrocenylphosphine-phosphoramidite ligand **35** was very efficient for the hydrogenation of a variety of (*Z*)-β-aryl(acylamino)acrylates in more than 96% ee under 10 bar of hydrogen in dichloromethane at 5 °C for 12 h [50]. From (*Z*)- and (*E*)-β-alkyl(acylamino)acrylates, good enantioselectivities were also obtained (92–99% ee) with the same catalytic system, but with this ligand **35** the (*Z*)- and (*E*)-**I** stereoisomers led to the opposite enantiomers **II**, which seems to be specific of this ligand bearing three different types of chirality. On the contrary, the bis(phosphate) ligand **36** led to poor enantioselectivities [51]. With the ferrotane ligand **37**, the (*E*)-alkyl substrates **I** were hydrogenated in more than 99% ee, whereas the (*Z*)-alkyl substrates led to modest enantioselectivity. On the contrary, (*E*)-β-aryl(acetylamino)acrylates were hydrogenated with excellent enantioselectivities (>99% ee) in the presence of [Rh(MeOH)$_2$(**37**)]BF_4 as catalyst precursor in methanol under 1 bar H_2 pressure at 25 °C with a substrate/catalyst ratio of 100 [52]. [Rh(norbornadiene)(**38a**)]SbF_6 is another very efficient catalyst for the enantioselective hydrogenation of aromatic substrates such as **Id** under mild conditions [53]. More than 99% ee was obtained upon hydrogenation of a variety of (*Z*)-β-aryl-β-(acetylamino)acrylates with donor and acceptor substituents in *para*- and *ortho*-positions on the phenyl group at room temperature under 1.5 bar in THF for

24 h. Surprisingly, with this catalyst, under similar conditions the enantiomeric excess of **IIa** was higher upon hydrogenation of (*Z*)-**Ia** (99.2%) than (*E*)-**Ia** (32.7%) [53]. Finally, it is worth noting that α-substituted and α,β-disubstituted-β-(acetylamino)acrylates have been hydrogenated in the presence of Rh(DuPhos) catalysts but the enantioselectivities remained moderate (up to 67% ee) [54].

3.2.1.2. Influence of parameters and mechanistic aspects in rhodium diphosphine catalytic systems. In most catalytic systems, a strong influence of the solvent has been found both on enantioselectivities and reaction rates. The hydrogenation reactions are slower and require higher H_2 pressure in non-polar solvents such as dichloromethane or toluene, than in polar protic solvents [23,35,36]. (*Z*)-isomers usually react faster than (*E*)-isomers in polar protic solvents (MeOH, *i*PrOH), and the reverse situation is observed in aprotic solvents (toluene, THF) [24,25,36]. Effects of reaction temperature on enantioselectivities have been observed during the hydrogenation of both stereoisomeric substrates in THF and in methanol with rhodium-diphosphine catalysts. In general, an optimum temperature to obtain high enantioselectivity has to be selected for each type of ligand (DuPhos or BPE) [14,25,55]. The hydrogen pressure has a slight influence during the hydrogenation of (*E*)-stereoisomers with rhodium-Duphos type catalysts, but is an important parameter for hydrogenation of the (*Z*)-stereoisomers, which leads to the best enantioselectivities at low hydrogen pressure [14,24,25]. Study of the consumption of H_2 in methanol revealed first-order kinetics for both **Ia** stereoisomers with Et-DuPhos as chiral ligand, whereas zero-order kinetics were observed for the hydrogenation of (*Z*)-**Ia** with Dipamp as ligand [55]. All these observations provided evidence that the reaction proceeded *via* first coordination of the prochiral substrate before activation of hydrogen (the so-called unsaturated route) [14,55]. Recently, Heller has shown that the enantioselective hydrogenation of β-aryl-β-(acetamino)acrylates, with cationic Rh(DuPhos) and Rh(Dipamp) complexes followed the unsaturated route, and that the major catalyst–substrate complex led to the major enantiomer of the product [56]. This proposed mechanism contrasts with that involved with α-(acylamino)acrylates, where the catalyst–substrate complex dominant in the solution leads to the minor enantiomer [57].

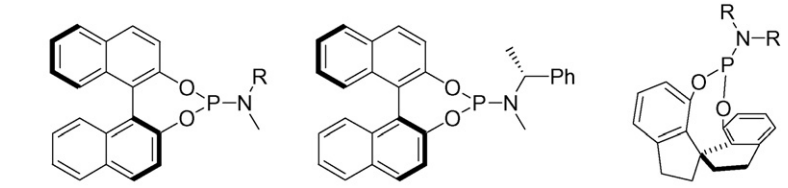
With an electron-rich diphosphine ligand such as **28b**, a $[Rh(H)_2(\mathbf{28b})(CD_3OD)_2]BF_4$ intermediate resulting from activation of dihydrogen has been detected at low temperature, which indicated the possibility of the other mechanism based on initial formation of rhodium-hydride species prior to coordination of the substrates [42].

3.2.2. Rhodium catalysts based on monodentate phosphorus ligands

Whereas the search for new ligands concentrated on diphosphine systems, new chiral monodentate ligands, especially phosphoramidites, phosphites and phosphonites, derived from 2-binaphthyl-1,1′-diol (Binol) emerged as efficient catalysts for asymmetric hydrogenation of olefins [58]. In this case, the chirality arises from the atropoisomeric binolate moiety. The catalytic species, usually generated from $[Rh(cod)_2][BF_4]$ and two equivalents of the optically pure ligand provide efficient hydrogenation catalysts and good enantioface differentiation during hydrogenation of prochiral carbon–carbon double bonds.

The first hydrogenation of β-(acylamino)acrylates catalyzed by cationic rhodium complexes generated *in situ* from $[Rh(cod)_2]BF_4$ and two equivalents of MonoPHOS **39a** or ligands **39b**, **40** (Scheme 8) was described by Feringa [59]. The (*E*)- and (*Z*)-β-(acylamino)acrylate isomers showed different behaviours during their asymmetric hydrogenation. Indeed, with the (*Z*)-isomer, the best enantioselectivities (77–95% ee) were obtained in isopropanol under 10 bar of hydrogen in the presence of 1 mol% of precatalyst, with substrates bearing an aliphatic R group [59,60]. The same reaction conditions allowed to reach 92–94% ee during the hydrogenation of β-aryl-β-(acylamino)acrylates, which is among the best ee's obtained with rhodium complexes. The use of an aprotic solvent such as ethyl acetate decreased the enantioselectivity down to 3% ee. From the (*E*)-isomer, hydrogenation reactions performed in isopropanol gave low conversions (49–52%) and enantiomeric excesses (52–64%). Complete conversions and better enantiomeric excesses (83–99% ee) were obtained in dichloromethane, whatever the ligand used. The ligand with a methyl and a benzyl substituent on the nitrogen atom (**39b**) seems to be the best alternative for the hydrogenation of these (*E*)-substrates since the enantiomeric excesses varied from 98% to 99% ee under 10 bar of hydrogen.

The Rh complexes of SIPHOS (**41**) catalyze the hydrogenation of (*Z*)/(*E*) mixtures of β-aryl-β-(acylamino)acrylates in good to excellent enantioselectivities (up to 94% ee) [61]. Lower enantioselectivities were obtained for β-alkyl-β-dehydroamido esters (87–89%). Screening of the reaction conditions showed that dichloromethane was the best solvent and that increasing hydrogen pressure led to higher reaction rates without spoiling

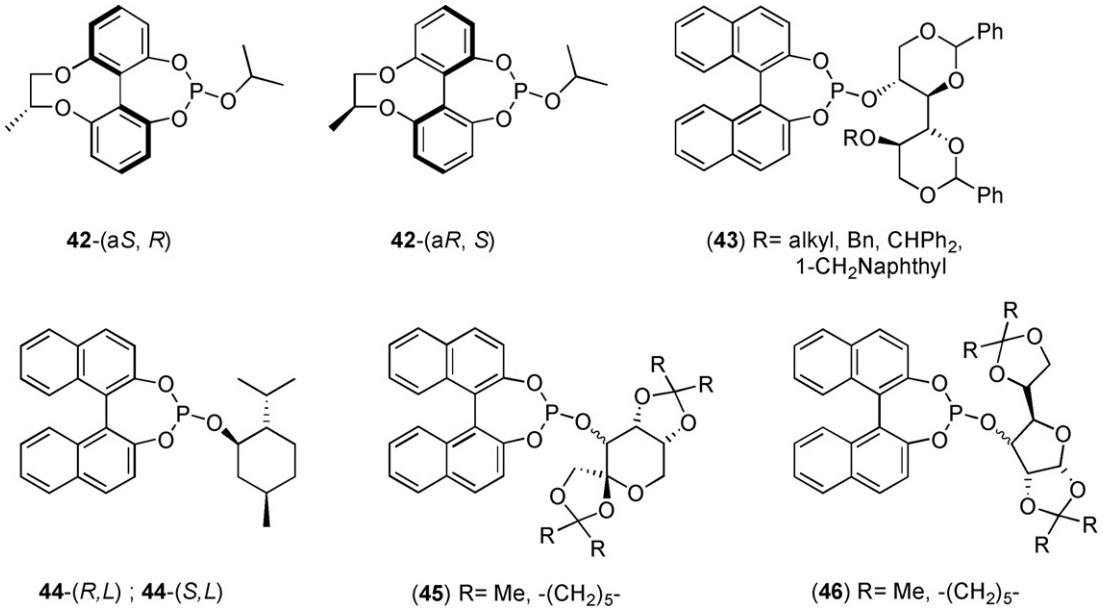


R = Me (*S*)-MonoPhos **(39a)**
R = CH_2Ph **(39b)**

(*S*)-**(40)**

(*S*)-SiPhos **(41)**
R= Me, Et, *i*Pr

Scheme 8. Some selected phosphoramidite ligands.



Scheme 9. Some monophosphite ligands.

the enantiomeric excesses. The SIPHOS ligand with smaller alkyl groups on the *N*-atom (namely the methyl substituent) afforded higher enantioselectivity.

Phosphite ligands (Scheme 9) were also used for the enantioselective hydrogenation of β-dehydroamido esters. Starting from 2,2′,6,6′-tetrahydroxybiphenyl, the synthesis of both enantiomers of the monophosphite **42** was performed [62]. The first application of rhodium-monophosphite catalyst in hydrogenation of (*Z*)-(acetamido)acrylate was carried out with this ligand, and led to low enantiomeric excess (11% ee).

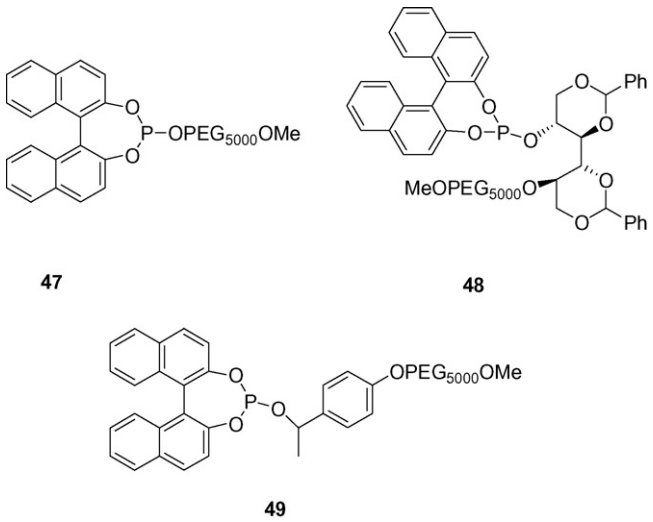
A variety of (Binol)P-OR phosphites, where R is a chiral group (terpene or carbohydrate moiety), were reported by Zheng [63] and Bruneau [64]. With a menthyl motive (**44**), ee's up to 94% were obtained from (*E*)-β-dehydroamido esters at 25 °C under 15 bar of hydrogen pressure in dichloromethane. It is worth mentioning that these ligands **44** can be easily prepared from racemic binaphthol by successive recrystallization in ether at room temperature, and at 0 °C. The absolute configuration of the stereogenic centre of the major enantiomer arising from the hydrogenation of the (*E*)- and (*Z*)-isomer was imposed by the configuration of the binaphthyl fragment. Similar observations were made with a ligand **43** bearing a mannitol fragment.

With (D)-glucose or (D)-fructose as carbohydrate backbones (ligands **45** and **46**, respectively) the hydrogenation of a series of (*E*)-β-alkyl- and β-aryl-β-(acylamino)acrylates **I** was performed in dichloromethane at room temperature under high pressure of hydrogen (30 bar). Excellent enantioselectivities were observed in both cases (up to 98.4% ee for β-alkyl- and 93% ee for β-aryl-β-(acetamido)esters **II**) [65].

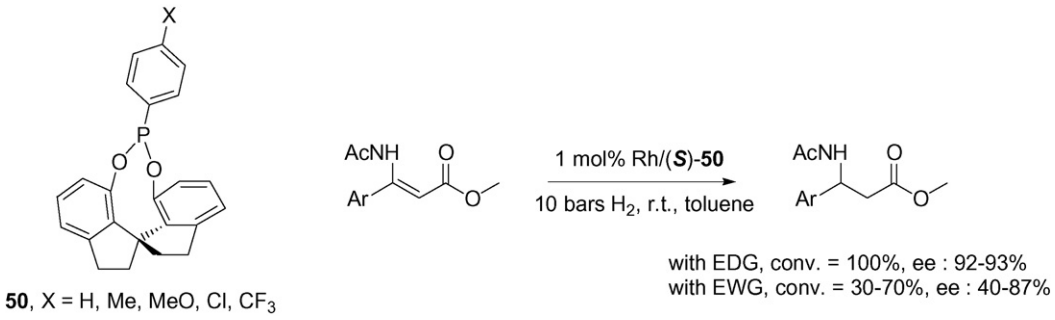
To overcome difficult separations and propose recycling processes, immobilized chiral phosphites have been developed. The introduction of a polyethyleneglycol (PEG) side chain (Scheme 10) resulted in a class of highly effective polymeric monophosphites, and enantioselective hydrogenations of β-alkyl-β-(acylamino)acrylates were reported by Zheng [66] and Chen [67]. Phosphite **47** induced the hydrogenation of (*E*)- and (*Z*)-**I** in excellent ee's (96–99.9%).

Monodentate phosphonites have not been used extensively in this reaction. However, in order to study the electronic effects of ligands directly connected to the phosphorus atom, Zhou and co-workers reported the synthesis of chiral spirophosphonite ligands and their evaluation in the enantioselective hydrogenation β-dehydroaminoacid derivatives (Scheme 11) [68]. With an electron-donor substituent on the aromatic ring, the β-aryl-β-(acylamino)acrylates were obtained with higher enantiomeric excesses than with phosphoramidite SIPHOS **41**. With an electron-withdrawing group on the phenyl ring, the reactivity and enantioselectivity were decreased.

More electron-rich monodentate ligands were also involved in asymmetric hydrogenation. Then, Beller and Gladiali reported the use of 4,5-dihydro-3*H*-dinaphtophosphepines **51** as chi-

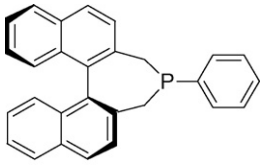


Scheme 10. Monophosphites with polymeric fragments.



Scheme 11. Monophosphonites ligand.

ral ligand in the enantioselective hydrogenation of various β-dehydroamido acid derivatives (Scheme 12) [69].



(**51**)

Scheme 12. Monophosphepine ligand.

The most general features which emerge from these studies on monophosphepines are the following: (i) alcohols, such methanol, ethanol and isopropanol, are the preferred solvent, (ii) the (*Z*)-isomer gives higher enantioselectivities than the *E*-isomer, which is in sharp contrast with most of the other monodentate ligands, (iii) the absolute configuration of the acetamidoester **II** depends on the geometry of the starting carbon–carbon double bond, and (iv) high temperatures have a negative effect on the enantioselectivity. The decrease is more important for the (*E*)-isomer than for the (*Z*)-isomer.

From all these results, it appeared that monodentate phosphorus ligands represent an excellent alternative to bidentate ligands. They offer also the advantage to be readily accessible, diverse and inexpensive as compared to various efficient bidentate ligands. An additional possibility offered by monodentate ligands is the introduction of two different ligands in the coordination sphere of the metal. This opens the route to combinatorial chemistry. The initial breakthroughs were made independently in 2003 by Reetz [70] and Feringa [71], who used mixtures of phosphorus ligands. By mixing two ligands (L^a and L^b) in the presence of rhodium precatalyst, three complexes, which are in equilibrium with one another, can be formed: RhL^aL^a and RhL^bL^b (homocombination), and RhL^aL^b (heterocombination). If the heterocombination dominates, due to the enhanced reactivity and enantioselectivity, then ee's will be better than in separate experiments involving pure L^a and L^b.

Convincing examples, which clearly outlined that selected heterocombinations of chiral P-ligands provided more reactive and enantioselective catalytic systems in hydrogenation of (*Z*)-β-(acylamino)acrylates, were reported by Feringa [71]. Thus, using a combination of monophosphoramidite ligands **39** and **41** in dichloromethane, enhancement of the reactivity and the enantioselectivity were observed. Similarly, Reetz [72] demonstrated that mixtures of Binol-derived phosphites and phosphonites were effective in this reaction. Starting from various (*E*)-β-alkyl or (*E*)-β-aryl β-dehydroamidoacid derivatives, enantiomeric excesses of 94–99% were reached. Mixtures of Binol-derived phosphonites and phosphates with achiral phosphorus ligands or configurationally fluxional atropisomeric phosphites [73], or mixtures of chiral TROPOS phosphites and phosphoramidites based on biphenol [74], were also applied in the hydrogenation of β-dehydroamidoacid derivatives. All three catalytic systems proved to be more selective than the corresponding homocombination system. The former one was the most effective (up to 98% ee) and involved two rapidly interconverting diastereomers. Such results are of practical importance because half of the ligand system derives from a cheap achiral compounds.

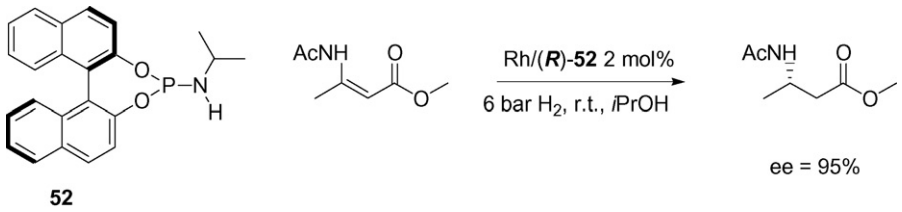
The preparation of phosphoramidites by reaction of a chlorophosphite with a primary or a secondary amine in the presence of triethylamine in toluene is very straightforward and opens the route of libraries of ligands. Using this protocol, a library of 32 ligands, combining unsubstituted Binol and 32 different amines, was prepared and tested by the DSM group in the hydrogenation of the methyl-(*Z*)-3-acetamido-2-butenoate [75–76]. Conversions varied from few to complete and ee's ranged from 0 to 92%. This screening revealed also that the new ligand **52** provided the fastest catalyst and the best enantioselectivity for this substrate in isopropanol at room temperature under 6 bar of hydrogen pressure (Scheme 13).

Due to the flexibility of the phosphoramidite synthesis, such ligands are suitable for high throughput experimentation (HTE).

As a general conclusion to Section 3.2, it appears that efficient rhodium catalysts are now available for the synthesis of β-amidoesters from β-acetamido acrylates. From the (*E*)-β-alkyl stereoisomers a variety of mono- and bidentate ligands are able to induce good enantioselectivities. From (*Z*)-β-alkyl (Table 1), and β-aryl-β-(acylamino)acrylates (Table 2), more specific ligands have also revealed excellent activities.

4. Perspectives

Most of the current approaches required an *N*-acyl or *N*-carbamoyl protecting groups on the β-dehydroaminoacid substrates to achieve high enantioselectivities, *via* chelation between the substrate and the metal. The major drawbacks of this strategy are the difficulty to protect and remove this



Scheme 13.

Table 1
Selection of efficient rhodium catalysts containing a bidentate ligand or a homocombination of monophosphorus ligands for the hydrogenation of (*Z*)-3-(acetamido)but-2-enoates

Ligand	H_2 pressure (bar)	Solvent	Ee (%)	Ref.
19	1	CH_2Cl_2	96	[32]
22a	7	CH_2Cl_2	95	[35]
30	1.5	THF	99	[45]
31	1.5	THF	98.5	[46]
32	3	MeOH	99.2	[47]
35	10	CH_2Cl_2	93	[50]
38	1.5	THF	99.2	[53]
40	10	*i*PrOH	94	[59]
47	10	CH_2Cl_2	97	[66]

Table 2
Selection of efficient rhodium catalysts containing a bidentate ligand or a homocombination of monophosphorus ligands for the hydrogenation of 3-phenyl-3-(acetamido)prop-2-enoates

Ligand	H_2 pressure (bar)	Solvent	Ee (%)	Ref.
30	1.5	THF	96	[45]
31	1.5	THF	93.8	[46]
35	10	CH_2Cl_2	>99	[50]
37	1	MeOH	99	[52]
38	1.5	THF	>99	[53]
40	10	*i*PrOH	92	[59]
41	100	MeOH	90	[68]
46	30	CH_2Cl_2	93	[65]
50	100	CH_2Cl_2	93	[68]

protecting-chelating group without racemization at the stereogenic centre. To avoid these extra steps, one solution might be either the enantioselective hydrogenation of β-*N*-alkyl- or β-*N*-aryl-enaminoesters or a direct reductive amination of β-ketoesters.

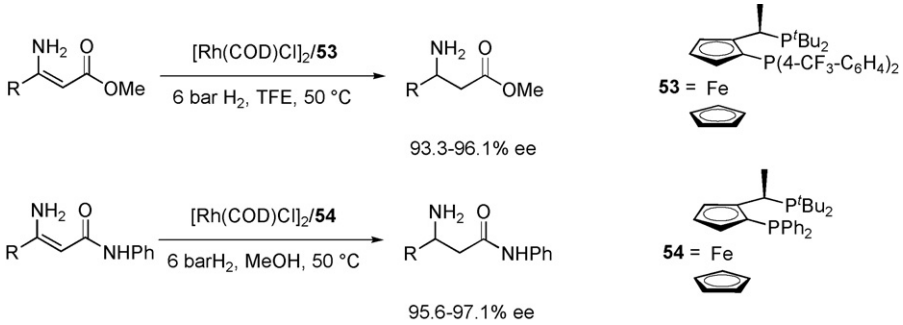
The first enantioselective hydrogenation of unprotected enamines was reported by the Merck group in 2004 [77]. In the presence of Rh-ferrocene diphosphine complexes (**53** or **54**) in trifluoroethanol (TFE) or methanol, the corresponding unprotected aminoesters and aminoamides were isolated in high yields and high enantiomeric excesses (Scheme 14).

Kinetic studies provided some information on the reaction rate [78]. As a result, the *in situ* protection of the resulting amine with Boc_2O led to enhanced rate without any loss of selectivity. Thus, in the presence of Boc_2O, the higher activity of the catalyst allowed to perform the hydrogenation under lower hydrogen pressure (3 bar of H_2 instead of 7 bar). During the process development, the sources of variation arising from all reaction parameters were examined [79]. These studies resulted in the identification of ammonium chloride as the species able to promote both high conversions and high enantioselectivities. It is worth mentioning that the level of ammonium chloride has to be maintained between 500 and 1500 ppm (0.38–1.14 mol%) with respect to the enaminoamide in order to obtain reproducible yields and ee's.

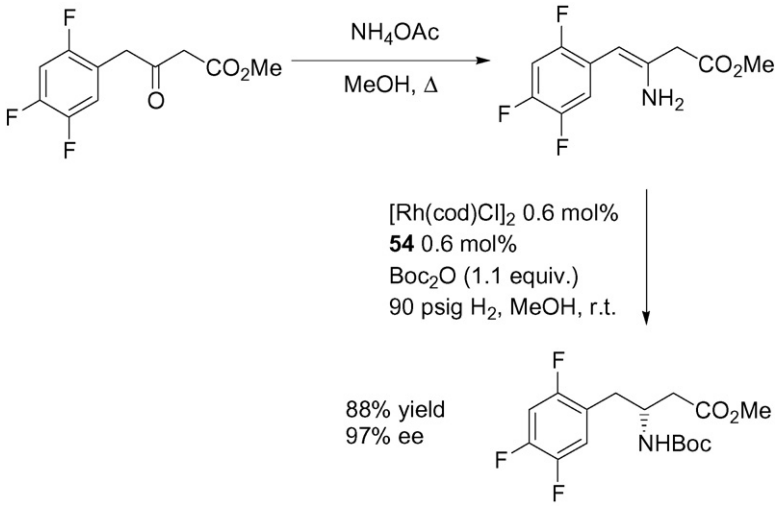
Application of this asymmetric hydrogenation of enamines has led in a concise approach to the synthesis of (*R*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid, a potential drug for the treatment of type II diabetes (Scheme 15) [80].

In 2005, Zhang reported the hydrogenation of β-*N*-aryl-enaminoesters in the presence of a catalytic amount of Rh-Tangphos (**31**) in TFE at 50 °C [81]. The corresponding aminoesters were obtained in good conversions and high ee's (up to 96.3%, Scheme 16).

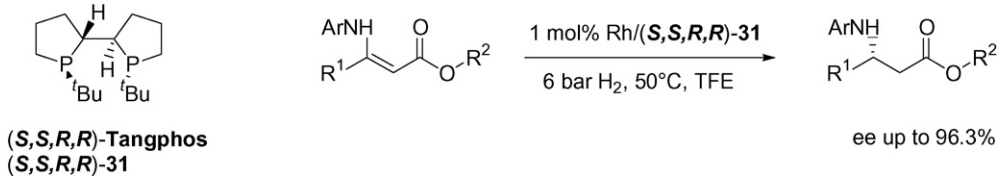
The first, and up to now sole direct reductive amination examples were reported by the Lanxess and the Takesago groups [82,83]. For instance, at Lanxess, the chiral β-amino esters were obtained in a one-pot synthesis from β-ketoesters and ammonium acetate under a pressure of hydrogen in the presence of [RuCl(*p*-cymene) ((*R*)-**54**)]Cl or $Ru(OAc)_2$((R)-**54**) as catalyst. From acyclic β-ketoesters, the chemoselectivity in favour of the aminoester and the enantioselectivity were excellent, from cyclic



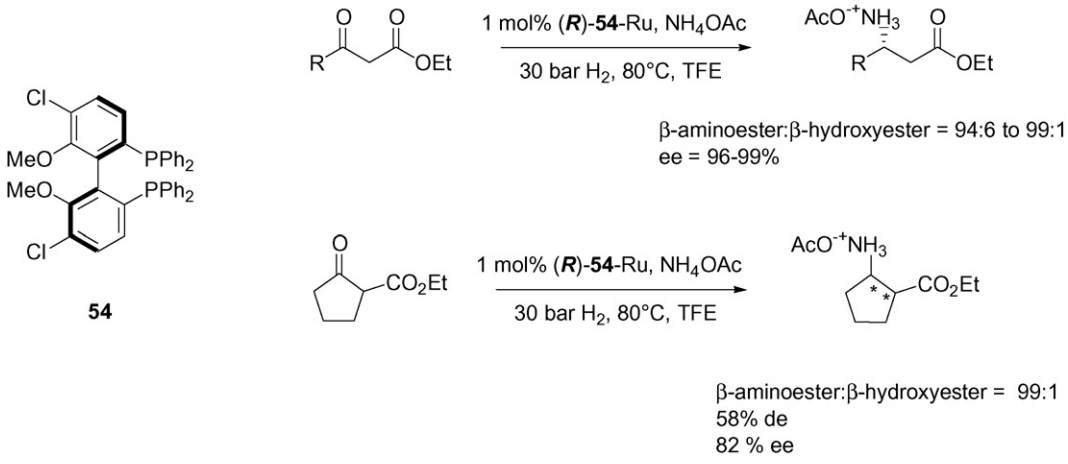
Scheme 14. Enantioselective hydrogenation of β-enaminoesters and amides.



Scheme 15.



Scheme 16.



Scheme 17. Direct enantioselective reductive amination of β-ketoesters.

β-ketoester the chemoselectivity in favour of the aminoester was still high but the diastereo- and the enantioselectivity were moderate (Scheme 17).

5. Conclusion

The preparation of β-aminoacid derivatives *via* enantioselective hydrogenation of β-enaminoacid derivatives is now possible from a variety of substrates due to the discovery of highly efficient catalytic systems. These substrates now constitute model compounds for the evaluation of the performance of new catalysts. The difficulties due to the different reactivities of (*Z*)- and (*E*)-β-(acylamino)acrylates have been overcome thanks to the preparation of bidentate and monodentate ligands able to generate efficient ruthenium and rhodium catalysts. The efficient ruthenium catalysts are based on bidentate diphosphine ligands. With rhodium, bidentate ligands have also revealed very high efficiencies, but the possibility of using monodentate phosphorus ligands provides a variety of active combinations detected by combinatorial and high throughput techniques.

The direct enantioselective reductive amination of β-ketoesters is very attractive and the first results recently obtained have opened the way to further promising studies in this direction.

Acknowledgements

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