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Chiral aminophosphine phosphinite ligands and related auxiliaries Recent advances in their design, coordination chemistry, and use in enantioselective catalysis

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Contents

Abstract

Recent advances in the synthesis and coordination chemistry of aminophosphine phosphinite ligands (AMPP) and closely related auxiliaries are reviewed. Asymmetric catalytic reactions involving various organometallic AMPP complexes are presented.

Keywords: Aminophosphine phosphinite; Enantioselective catalysis; Enantioselective hydroformylation; Enantioselective hydrogenation; Enantioselective formation of C–C bonds; Chiral diphosphines

1. Introduction

Organometallic catalyzed transformations provide practical and effective synthetic methods for the production of bioactive substances and specific materials [1–4]. Enantioselective synthesis and catalysis have been

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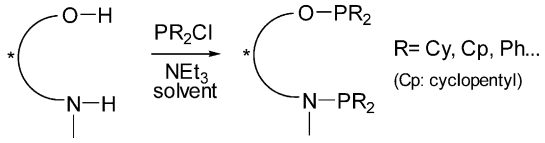


Scheme 1. General synthesis of AMPP ligands.

developed for large-scale preparations of optically pure compounds [4,5]. Among the various methods available to prepare a single enantiomer (resolution of racemates, asymmetric synthesis, enantioselective biocatalysis), the enantioselective catalysis based on chiral chemical catalysts has been under thorough investigation because of the high potential of the methodology. Spectacular enantioselection has been achieved in numerous reactions leading to well-known enantioselective transformations such as hydrogenation, hydroformylation, cyclopropanation, allylic substitution, organometallic addition to aldehydes, olefin isomerisation, olefin epoxidation and dihydroxylation, and so forth [4].

Generally, all asymmetric organometallic catalysts bear at least one chiral ligand. The reactivity and selectivity of a catalyst is adjustable through variation of the metallic centre and/or the chiral ligand. The extensive research carried out in that field has provided a great number of chiral ligands, the most successful have been chelating diphosphines which are applicable to a variety of transformations [6,7]. Key examples of chiral diphosphines are DIOP [8], DIPAMP [9] BPPFA [10], BPPM [11], BINAP [12], BIPHEMP [13], and DUPHOS [14]. Nevertheless, the exploration of other phosphorus containing chiral auxiliaries has also been a fast growing area [6,7,15]. In the early 1980s, the synthesis of new chiral diphosphine ligands based on natural amino alcohols provided the first members of a new family of auxiliaries successfully applied in the enantioselective hydrogenation of dehydroaminoacids [16–18]. A previous account covered the literature that appeared on the synthesis and use of such ligands up to 1997 [19]. Here, we will give an overview of the recent achievements in that field while describing the synthesis of new aminophosphine phosphinites and closely related ligands, the preparation of the chiral precatalysts and their use in asymmetric catalysis.

2. Synthesis of AMPP and closely related ligands

Chiral amino alcohols are the precursors of choice of AMPP ligands [16] and closely related bisphosphines [19]. If their preparation is largely based on natural amino alcohols, synthesized precursors have also been used (amino alcohols [20,21], amido alcohols [22], and diamines [23–25] (Scheme 1).

The purification of AMPP ligands often involves a filtration through basic alumina under nitrogen. Other procedures have also been reported, i.e. flash chromatography over silica gel under an air atmosphere [26–28] and silica gel chromatography of their diborane complex [29] (Scheme 2).

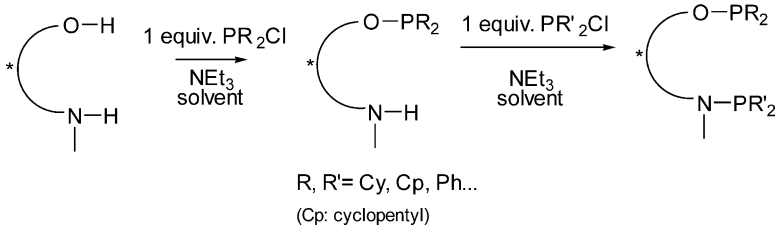
With regard to new ligand skeletons, carazolol [30], amino alcohol derived from ketopinic acid [28], and substituted 2-amino ethanols [26,31] were converted into the corresponding diphenylphosphino substituted AMPPs **1**, **2**, and **3**–**5**, respectively (Scheme 3). New cyclic AMPPs have been obtained starting from azetidine [32,33], indoline [33–35], and tetraisoquinoline carboxylic acids [32,33]. The resulting ligands, i.e. (*S*)-R,R-AzeNOP (**6**), (*S*)-R,R-IndoNOP (**7**), and (*S*)-R,R-QuinoNOP (**8**) (Scheme 3) are accessible in a few straightforward steps in moderate to high overall yields.

The preparation of $Cr(CO)_3$-complexed amino alcohols allowed one to introduce a second chirality and more steric hindrance on the aromatic ring of the indoline and tetraisoquinoline precursors. Two series of diastereomeric complexed amino alcohols [33,34,36] were obtained. The new AMPP precursors are presenting *syn* and *anti* relations between the $Cr(CO)_3$ unit and the stereogenic centre. Such precursors could easily be converted into the corresponding '*syn*' (**9** and **10**) and '*anti*' (**11** and **12**) chiral auxiliaries (Scheme 4).

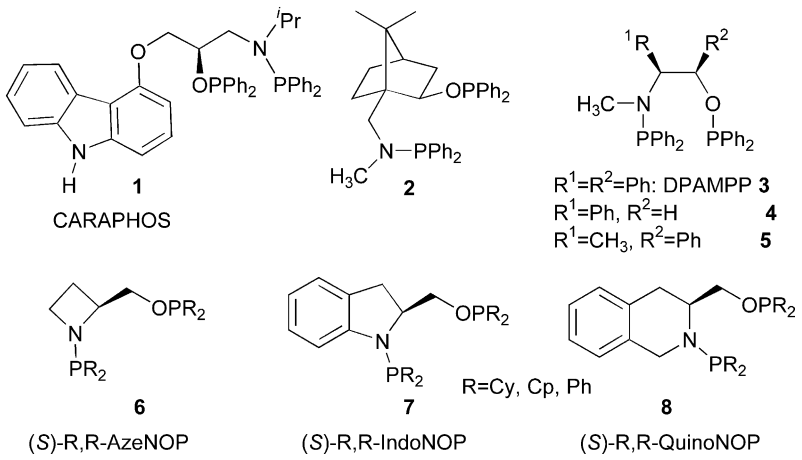
Amino acids could be converted directly into aminophosphine carboxyphosphinites (**13**–**15**) following the classical phosphinylation reaction of the α-amino acids (Scheme 5) [37].

A new series of bisaminophosphines (**16**) has been synthesised from L-glutaric acid following the general procedure outlined in Scheme 6 [38].

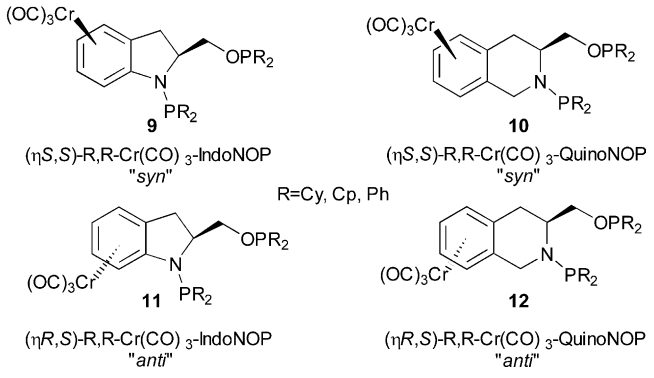
The next examples of new ligands include a new chiral skeleton and a variation of the substituents at the phosphorus atoms. Thus, new amidophosphine phosphinite ligands (*t*LANOP, **17**) [39] derived from the



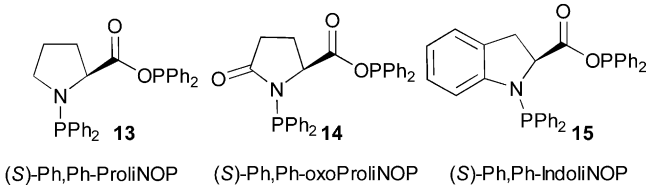
Scheme 2. Synthesis of 'mixed' AMPP ligands.



Scheme 3. AMPP ligands based on newly introduced skeletons.



Scheme 4. Chromium complexed AMPP ligands.



Scheme 5. Aminophosphine carboxyphosphinites.

chiral hydroxyamide (*R*)- or (*S*)-hydroxy-3,3-*N*-trimethylbutyramide have been prepared in 43–84% yields (Scheme 7). No formation of the desired ligands *t*LANOPs was observed when the classical procedure (PR_2Cl/Et_3N) was applied. The phosphinylation arose efficiently in the presence of a combination of BuLi and 5 mol% of a secondary amine (e.g. di*iso*propylamine).

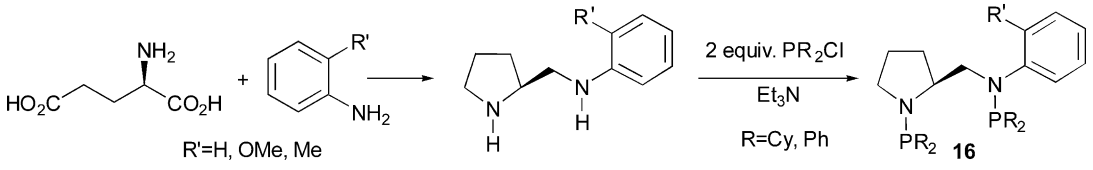
Ligands possessing new substituents on the phosphorus atoms have also been sought. The first example reports the straightforward synthesis of pyroglutamic acid based amidophosphine phosphinites (**18**, **19**) using the classical procedure [40] (Scheme 8).

Electron-deficient aminophosphonite phosphites (Scheme 9) based on (1*R*,2*S*)-ephedrine **20**(**a**–**d**), (*S*)-prolinol (**21**), and (*S*)-oxoprolinol (**22**) and chlorophosphites have been described [41,42]. The appropriate non-commercially available chlorophosphites were generally synthesised from diol and PCl_3 in a mixture of toluene and triethylamine [41–43].

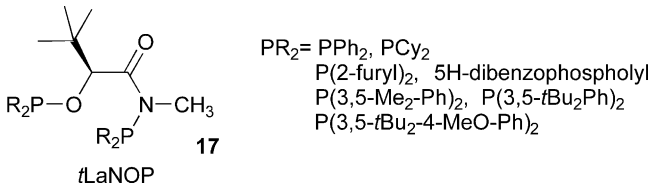
Finally, the asymmetric synthesis of AMPP ligands with one **23** or two **24** P-stereogenic centres has been reported using the borane methodology [28,29,44–46] (Scheme 10). The synthesis of these AMPP ligands is based on the reaction of the oxazaphospholidine borane complex with an organolithium reagent providing an intermediate, which is trapped by a chlorophosphinoborane. The borane can be easily removed by exchange with 1,4-diazabicyclo [2,2,2]octane (dabco). This procedure allows one to introduce various residues on the phosphorus moieties enantioselectively.

3. Palladium–AMPP complexes and related catalysis

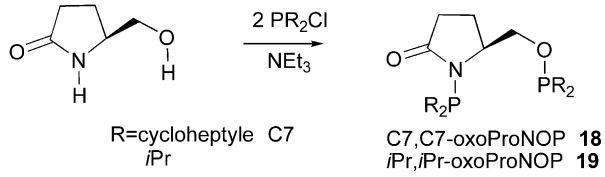
Only one recent report describes the synthesis and catalysis involving Pd–AMPP complexes, though, other Pd–AMPP complexes have been described.



Scheme 6. Synthesis of new bisaminophosphine ligands.



Scheme 7. New amidophosphine phosphinites ligands.



Scheme 8. Synthesis of AMPP ligands ex-(*S*)-oxoprolinol.

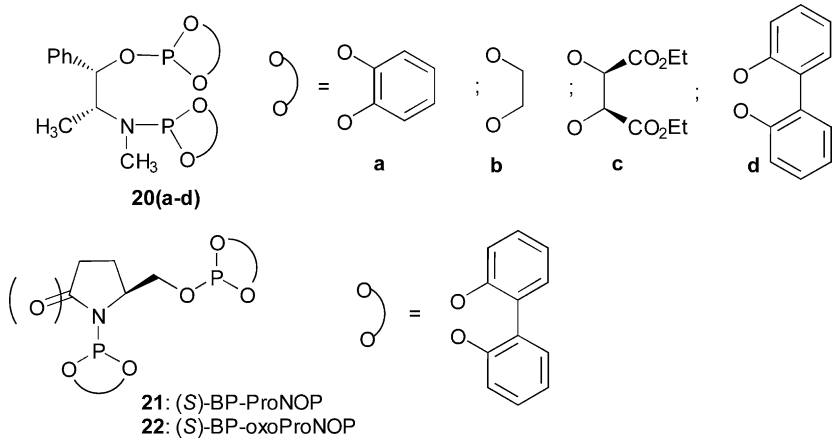
3.1. Synthesis and characterisation of Pd–AMPP complexes

Chiral orthometallated palladium complexes have been prepared to establish the absolute configuration of *t*LANOP ligands (**17**, Scheme 7) [39] and to determine whether the synthesis of AzeNOP ligands (**6**, Scheme 3) is proceeding with epimerisation or not [33]. Thus, the reaction of (*S*)-Ph,Ph-*t*LANOP with [Pd-(*R*)-η²-$Me_2NCH(CH_3)$-C_5H_4)$(NCMe)_2$]BF_4 **25** yielded the kinetic product **26** presenting a 7-membered chelating ring with a δ-boat conformation and the expected ligand configuration (Scheme 11).

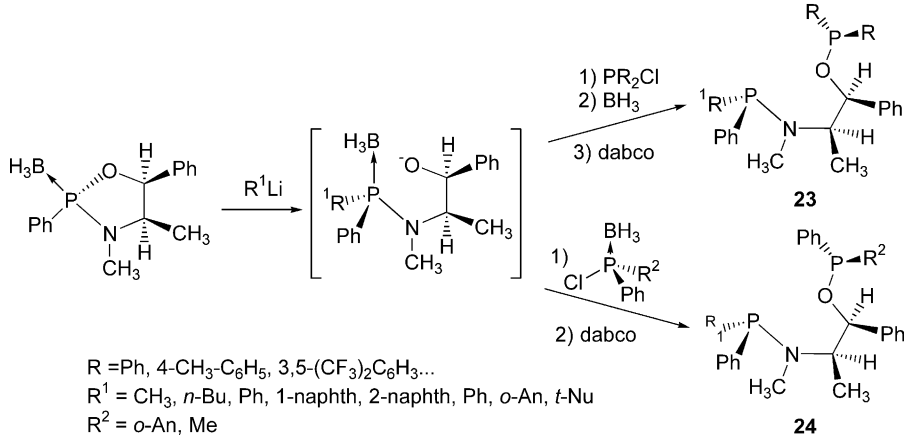
The reaction of di-μ-chlorobis[(*R*)-1-(dimethylamino)ethyl]-2-naphthenyl-C_2-*N*]dipalladium(II) with (*S*)-Ph,Ph-AzeNOP in methanol in the presence of $NaBF_4$ provided the corresponding [CN*Pd{(*S*)-Ph,Ph-AzeNOP}]Cl complex [33] presenting a single set of ^{31}P-NMR signals. This feature is indicative of the optical purity of the AMPP ligand and rules out the mentioned epimerization.

3.2. Palladium–AMPP catalysis

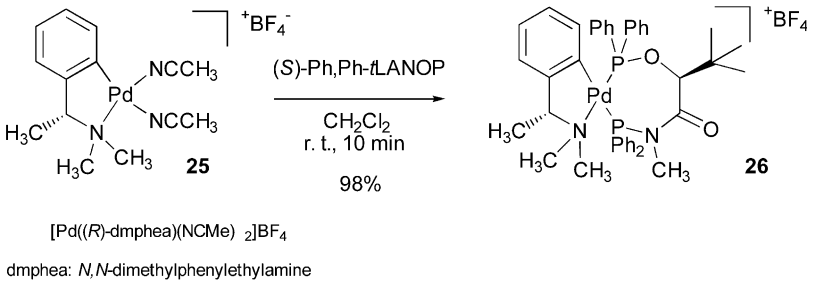
The palladium complexes Pd(η³-PhCH-CH-CHPh){(*S*)-Ph,Ph-ProNOP}X (X = BF_4 or PF_6) (Scheme 12) have been applied in the allylic alkylation of 1,3-diphenyl-2-propenylacetate **27** with sodium dimethylmalonate providing the substituted product **28** in 30% ee [47]. Only one new report described an identical



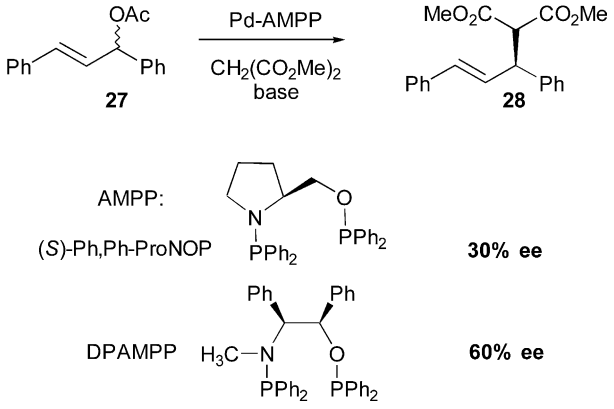
Scheme 9. Structure of aminophosphonite phosphite ligands.



Scheme 10. Synthesis of P-chiral AMPP ligands.



Scheme 11. Synthesis of a [Pd{AMPP}] complex.



Scheme 12. Palladium catalysed allylic substitution.

reaction [31] where it had been anticipated that a second stereogenic centre near the phosphinite moiety of the ligand would improve the stereocontrol of the reaction. Thus, a series of chiral AMPP (DPAMPPs, **3**–**5**, Scheme 3) derived from chiral 1,2-diphenyl-2-aminoethanols has been applied in the mentioned reaction. After variation of the Pd source, solvent, additive, AMPP, AMPP/Pd ratio, the highest ee obtained was 60% (Scheme 12).

Catalytic results have shown that this additional stereogenic centre induced a significant improvement of the enantioselectivity (from 11 to 60% ee). The configuration of the carbon adjacent to O–PPh_2 played also a key role in the allylation reaction. Nevertheless, the use of the corresponding amino-phosphinite ligand provided 95% ee in the same reaction [48].

4. Platinum–AMPP complexes and related catalysis

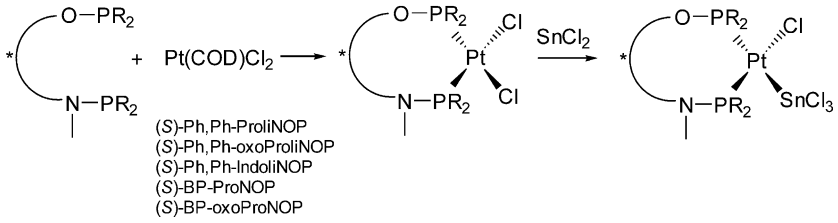
4.1. Synthesis and characterisation of Pt–AMPP complexes

Essentially two series of electron deficient ligands e.g. aminophosphonite-phosphite (BP-AMPP) (**21** and **22** Scheme 9) and aminophosphine-carboxyphosphinite (AMPCP) (**13**–**15**, Scheme 5) were used for the preparation of optically active platinum complexes $PtCl_2${BP-AMPP} [42] and $PtCl_2${AMPCP} [37] and applied in hydroformylation (see below). The reaction of $Pt(COD)Cl_2$ (COD: 1,5-cyclooctadiene) with one equimolar amount of diphosphine in dichloromethane at ambient temperature led quantitatively to the desired complexes (Scheme 13) which presented the typical ^{31}P-NMR patterns (two sets of signals). The major ones, which consists of two doublets resulting from the PN–PO coupling, were assigned to the –$NPPh_2$ (most upfield) and –$OPPh_2$ (most downfield) signals. The ^{195}Pt satellites appeared as doublets of minor intensity. In the case of Pt{BP-AMPP}Cl_2 complexes, the ^{31}P-NMR properties were almost identical to those generally observed with coupling values close to 12 Hz for J_{PO-PN} and J_{Pt-PO} and J_{Pt-PN} coupling values of 3950 and 3910 Hz, respectively. Interestingly, in the case of Pt{AMPCP}Cl_2 complexes, larger Pt–P coupling values were observed (ca. 5500 Hz for J_{Pt-PO} and ca. 5760 Hz for J_{Pt-PN}) associated with J_{PP} values between 4 and 28 Hz. These values are typical of phosphite ligands associated with platinum complexes [49]. The crystal structure of Pt{(*S*)-BP-ProNOP}Cl_2 established the *cis* chelation of the AMPP ligand [42]. The reaction of Pt{AMPCP}Cl_2 with stannous dichloride provided the complexes Pt{AMPCP}($SnCl_3$)Cl exhibiting a lowering of the J_{Pt-PO} values as a result from the coordination of the $SnCl_3$ *trans* to the PO moiety (Scheme 13).

Platinum complexes have also been used to attribute surprising ^{31}P-NMR chemical shifts obtained with ephedrine based AMPP ligands [40]. Indeed, an inversion of the order of the signals generally observed for AMPP ligands (PN most upfield and PO most downfield) has been confirmed by the NMR characterization of Pt{**20b**}Cl_2 (structure of **20b** given in Scheme 9).

4.2. Platinum–AMPP catalysis

The AMPCP (**13**–**15**) [37] and BP-AMPP (**21**, **22**) [42] containing platinum catalysts provided moderate branched to normal aldehyde ratios (i.e. from 30/70 to 66/34 and 53/47 to 66/34, respectively) in the hydroformylation of styrene (Scheme 14). The enantioselectivities into the branched aldehyde **29** are very low for the former ($< 5\%$ ee) and moderate for the latter (up to 44% ee). Interestingly, the reaction rate increased with the lowering of the electron density at the phosphorus



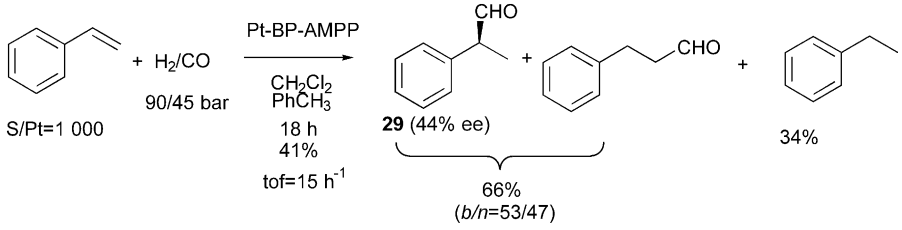
Scheme 13. Synthesis of platinum complexes.

atom of the BP-AMPP based catalysts (up to 38 h^{-1}) when compared to earlier described Pt–AMPP catalysts (up to 5 h^{-1}) [19]. However, the hydrogenation side reaction is occurring to some extent (up to 35%) [42]. Compared with earlier reported AMPPs, the BP-AMPP containing catalysts are more active than phenyl or cycloalkyl bearing AMPPs. However, from an enantioselectivity standpoint, cycloalkyl based ligands provide the highest ees (up to 56% ee) [50]. The most appropriate stereoelectronic properties are thus difficult to define in order to design new efficient AMPP ligands for the Pt-based enantioselective hydroformylation.

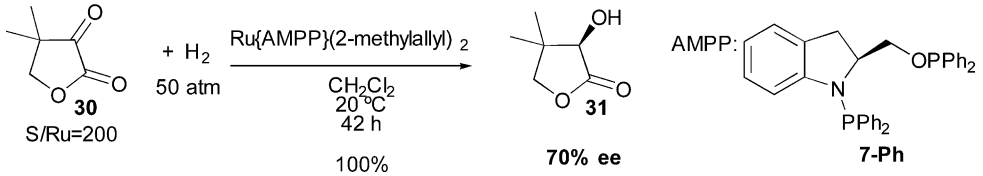
5. Ruthenium–AMPP complexes and related catalysis

Ruthenium diphosphine complexes are well known as very efficient catalysts for highly enantioselective hydrogenations [51]. Earlier reports described the synthesis of RuX_2(Arene){AMPP}, Ru{AMPP}(OCOR), and Ru{AMPP}(2-methylallyl)$_2$ and their use in the hydrogenation of α-functionalised ketones [52–54] and β-ketoesters [55]. For example, up to 79.5% ee were obtained for the reduction of α-substituted ketones. New AMPP ligands have only been applied in the hydrogenation of ketopantolactone **30** into pantolactone **31** in the presence of Ru{AMPP}(2-methylallyl)$_2$ bearing exclusively phenylsubstituted auxiliaries [52]. The enantioselectivities are in the 0–70% ee range [32,33,37]. A high enantiocontrol (70% ee) has been achieved with (*S*)-Ph,Ph-IndoNOP (**7-Ph**, Scheme 15) compared to (*S*)-Ph,Ph-QuinoNOP (47% ee, **8-Ph**, Scheme 3), (*S*)-Ph,Ph-AzeNOP (< 1% ee, **6-Ph**, Scheme 3), and (*S*)-Ph,Ph-oxoProliNOP (0% ee, **14**, Scheme 5). Nevertheless, for this transformation, the best AMPP ligand still remains (*S*)-Ph,Ph-oxoProNOP (79.5% ee) [52].

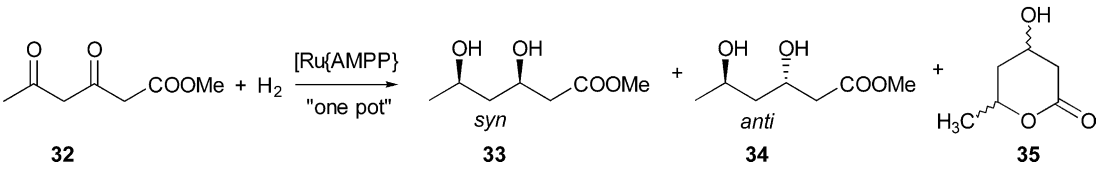
From an enantiocontrol standpoint, β-ketoesters are better substrates for Ru–AMPP catalysed hydrogenations (earlier reports related from 75 to 85% ee) [19,55]. The hydrogenation of simple and functionalised 1,3 diketones and β,δ-diketoesters [56] has been explored recently. The aim was to produce selectively enantiopure *syn*-diols which are key building blocks for the synthesis of important inhibitors of HMG-coenzyme A reductase. Methyl 3,5-dioxohexanoate **32** was used as a model substrate in the presence of the most efficient AMPP ligand described up to now (i.e. (*S*)-Ph,Ph-oxoProNOP) [57]. The ruthenium(II) catalysts investigated were obtained by protonolysis of Ru{(*S*)-Ph,Ph-oxoProNOP)}(2-methylallyl)$_2$ with various carboxylic and sulfonic acids (either chiral or not). A mixture of *syn* **33** and *anti* **34** diols is produced along with the cyclisation product hydroxylactone **35** for reactions carried out in chlorinated solvents or in methanol [57,58] (Scheme 16). The diastereoselectivities induced



Scheme 14. Platinum catalysed hydroformylation of styrene.



Scheme 15. Ruthenium–AMPP catalysed hydrogenation.



Scheme 16. Asymmetric hydrogenation of methyl-3,5-dioxohexanoate.

by these catalytic systems were in the 10/90-96/4 range, the highest being obtained with the ruthenium complex Ru{(*S*)-Ph,Ph-oxoProNOP}{(−)-MTPA}$_2$ obtained by protonolys with Mosher's acid (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in chlorinated solvents. Nevertheless, the enantioselectivity induced by this system into the *syn* isomer **33** is very low (5% ee). Compared to the AMPP based catalysts, other ruthenium complexes bearing atropisomeric diphosphines produced the *anti* diol **34** in up to 78% de and 95% ee. The lower enantioface discrimination of the Ru{AMPP} catalysts achieved during the hydrogenation of β,δ-diketoesters compared to β-ketoesters has been attributed to the competitive coordination of C=O (ester) and C=O (δ ketone) occurring during the hydrogenation of the first C=O group (β-ketone).

6. Iridium–AMPP complexes and related catalysis

Iridium–AMPP precatalysts, prepared from [Ir(COD)Cl]$_2$ and AMPP (oxoProNOP and IndoNOP bearing phenyl or cyclopentyl residues) have been applied in the hydrogenation of ketopantolactone **30** (Scheme 15). The hydrogenation proceeded efficiently at room temperature under 50 atm of hydrogen with low to moderate enantioselectivities (15–42% ee) [33,35].

Cyclic iminium salts **36** have been hydrogenated in the presence of iridium catalysts bearing ligands of the *t*LANOP and oxoProNOP types (Scheme 17) [39]. The former led to the highest enantioselectivities (up to 86% ee) compared to the oxoProNOP auxiliaries (11–27% ee). The increase of the steric hindrance of the aryl substituents on the phosphorus atoms led to a remarkable enhancement of the ees (for example: Ph, 19% ee; 3,5-*t*Bu aryl, 86% ee).

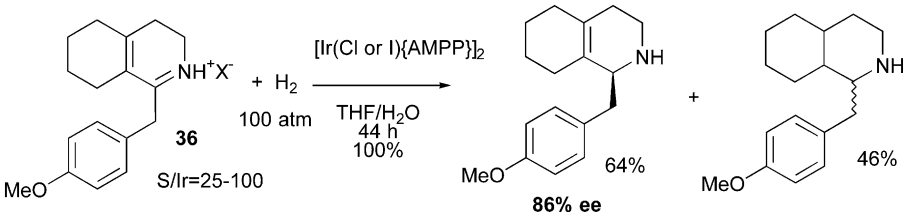
7. Rhodium–AMPP complexes and related catalysis

7.1. Synthesis of Rh–AMPP complexes

Several rhodium–AMPP have been synthesized or generated in situ and applied in enantioselective catalysis. Other complexes have been prepared in order to identify catalytic intermediates (vide infra).

Cationic rhodium complexes [Rh(COD){AMPP}]X (X = BF_4, ClO_4) have been prepared either by displacement of the COD ligand from the cationic precursor [Rh(COD)$_2$]X [59] by the AMPP species or by reaction of the neutral [Rh(COD)Cl]$_2$ [60] with the AMPP ligand in the presence of $AgBF_4$ [26] or $AgClO_4$ [61]. One report describes also the synthesis of cationic compounds starting from the borane complexed AMPPs. The complexes were prepared in a one pot procedure with three consecutive steps: decomplexation of the borane from the H_3B·AMPP compound, reaction with [Rh(COD)Cl]$_2$ in the presence of $AgBF_4$, and precipitation of the desired rhodium complex [62]. Another convenient procedure consisted in a ligand exchange reaction while reacting Rh(COD)(acac) and the AMPP followed by the addition of HBF_4 [30].

The most common procedure applied to prepare neutral rhodium–AMPP complexes is the displacement of the COD ligand from the neutral dimeric precursors [Rh(COD)X]$_2$ (X = Cl [60], OCOR [63], $OCOCF_3$ [63]). The trifluoroacetate bearing rhodium complexes have been the most widely used in ketone hydrogenations (vide infra). In situ generated complexes were also described. One procedure involves the carbon monoxide displacement of Rh(CO)$_2$acac by the AMPP providing the Rh{AMPP}(acac) compound [44]. Precatalysts were also obtained from a reaction between $Rh_4(CO)_{12}$ and the appropriate AMPP [41].



Scheme 17. Iminium salts asymmetric hydrogenation.

7.2. Characterisation of Rh–AMPP complexes

The ^{31}P-NMR spectra of neutral and cationic complexes exhibit the eight line AB parts of ABX (X = ^{103}Rh) spin systems, due to non-equivalence of the phosphorus atoms. Typical values for cationic complexes [Rh(COD){AMPP}]X are δ PO 110–140 ppm (J_{PP} = 17–30 Hz, J_{Rh-PO} = 167–173 Hz) and δ PN = 70–100 ppm (J_{Rh-PN} = 157–170 Hz). Surprisingly, a J_{PP} value of 653 Hz has been reported for [Rh(COD){(1*R*,2*S*-DPAMPP}]BF_4 (AMPP **3**) [26]. Such a large coupling value can be more certainly attributed to a Rh–AMPP complex presenting a *trans* relation between the two phosphorus nuclei (vide infra) [64]. The two enantiomeric complexes bearing the CARAPHOS (**1**) AMPP have been examined by circular dichroïsm [30].

An interesting study has been reported on the behaviour of Rh(I)-amidophosphine phosphinite species in methanol. Extensive NMR investigation allowed to characterise the dinuclear compounds existing in the two sym-trans and sym-cis forms containing two equivalents of the AMPP ligand *t*LANOP [Rh(μ-Cl){(*S*)-Ph-*t*LANOP}]$_2$ (**37**) [65] accompanied by the new isolable dinuclear cationic complex **38** possessing both a bridged chloride and a bridging AMPP (Scheme 18). The dynamic behaviour and the synthesis of other Rh-*t*LANOP complexes have also been described [64].

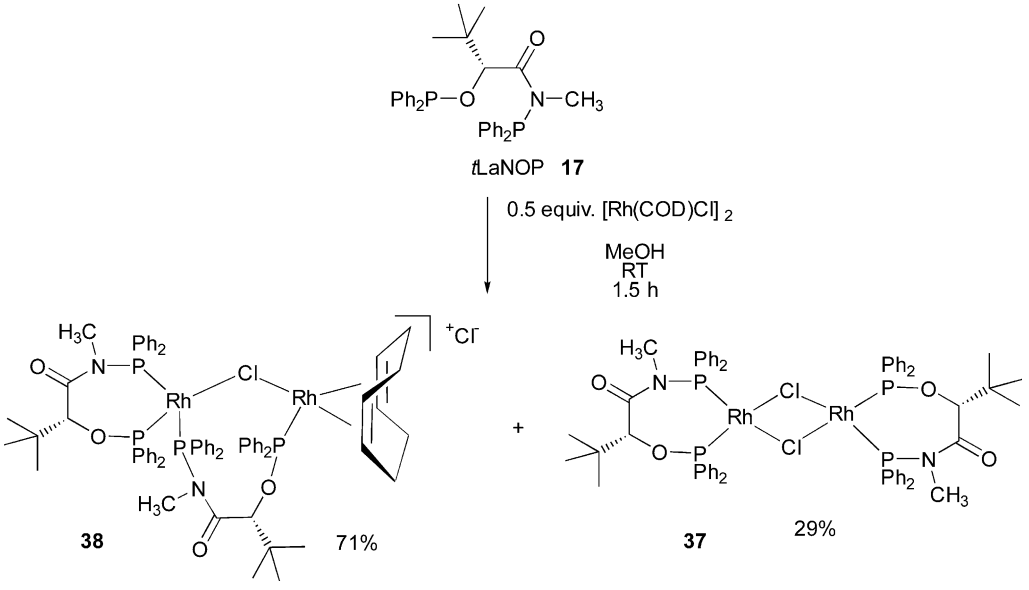
The crystal structures of the pseudo square planar [Rh(μ-Cl){(*S*)-Ph-*t*LANOP}]$_2$ (**37**), and the cationic [Rh(COD){(*S*)-Ph-*t*LANOP}]OTf (Tf: triflate) have been determined. The flat amide unit, Me–N–C=O is imparting rigidity to the chelate ring which is certainly beneficial to the enantiocontrol exerted by the corresponding catalysts (vide infra).

7.3. Enantioselective hydroformylation of C=C bonds

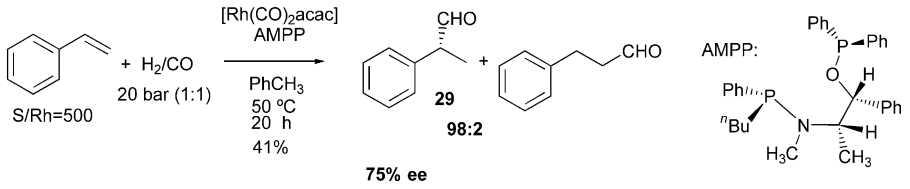
Recently, only two groups have reported on the use of ephedrine based AMPP ligands in the Rh catalysed hydroformylation of olefins. Thus, under mild conditions, the hydroformylation of styrene in the presence of electron deficient aminophosphonite phosphite auxiliaries provided the branched hydratropaldehyde **29** with high regioselectivities but with a low enantioselectivity (up to 20% ee) [41].

Ephedrine based aminophosphine phosphinites possessing a stereogenic centre at the nitrogen bonded phosphorus atom have been applied in the hydroformylation of styrene, vinylarenes, and vinylacetate [44]. For styrene, the highest enantioselectivities were obtained with the most electrondonating substituents at the OP moiety of the series (i.e. Ph and 4-CH_3-C_6H_5) (98% branched aldehyde, 75% ee) (Scheme 19). Conversely, electron deficient substituents on the PO end are detrimental to the enantioselective control exerted by the corresponding catalyst. Nevertheless, the catalysts are more active in the latter cases.

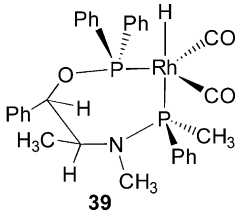
As earlier, efforts have been devoted to the detection and characterisation of catalytic intermediates. As a matter of fact, in solution, only one hydride species containing NP in an axial position and PO in an equatorial position has been detected. Hence, the ^{1}H- and ^{31}P-NMR analysis of a solution composed by the complex obtained from the reaction of [$Rh(CO)_2$acac] with two equivalents of an AMPP ligand under a syngas pressure of 20 bars (CO/H_2 = 1/1) allowed to characterise two species [44]. A catalytically inactive dinuclear carbonyl bridged complex has been identified along with one trigonal bipyramidal complex **39** presenting the PN



Scheme 18. Preparation of dimeric Rh–AMPP complexes.



Scheme 19. Hydroformylation of styrene catalysed by Rh–AMPP.



Scheme 20. Hydroformylation catalytic intermediate.

moiety in axial and PO in equatorial positions (Scheme 20).

The inactive complex could also give rise to the hydrido intermediate in various conditions (i.e. higher hydrogen partial pressure and lower complex concentrations). This indicates that the additional chirality at the phosphorus atom, which is bearing one relatively small and one large residue provides an efficient stereodifferenciation while favouring the coordination mode mentioned.

7.4. Enantioselective hydroboration of C=C bonds

A series of bisaminophosphines have been associated with the neutral rhodium complex $[Rh(COD)Cl]_2$ and used in the asymmetric hydroboration of norbornene (exo-norborneol **40**, 12–77% ee) (Scheme 21), styrene (1-phenylethanol, 30–42% ee) and enones (2-hydroxycyclohexanones, 8–15% ee) [38].

7.5. Enantioselective hydrogenation of C=N bonds

An aminophosphine phosphinite (propraphos) **41** has been evaluated along with other various diphosphines and diphosphites in the rhodium based hydrogenation of imines [65]. Although a full conversion was obtained under mild conditions (50 bar, 20 °C, S/Rh = 100), only a moderate enantioselectivity was attained (57% ee) (Scheme 22).

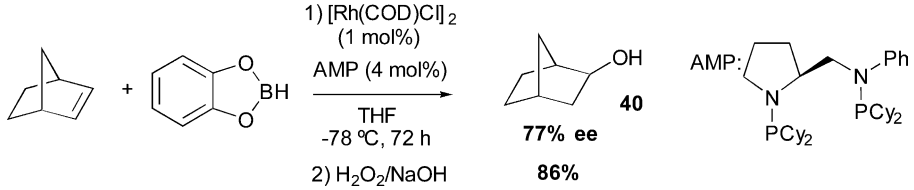
7.6. Enantioselective hydrogenation of C=C bonds

As already mentioned in the previous account [19], generally all the groups involved in the chemistry of AMPPs have directed their catalytic applications towards the asymmetric hydrogenation of functionalised olefins, particularly dehydroamino acids. All reactions were carried out in the presence of cationic Rh catalysts, usually generated in situ even though some publications report on the preparation and characterisation of the precatalysts (vide supra). Most of the efforts have been directed to the hydrogenation of the key substrate methyl α-acetamidocinnamate (Scheme 23, Table 1) providing the corresponding phenyl alanine derivative with high ees. A strong influence of the solvent on the catalytic activity and on the enantioselectivity is a general trend observed. However, the best results are regularly obtained in polar solvents. While using AMPP auxiliaries bearing a chiral phosphorus centre (structure type **23** and **24**, Scheme 10), it has been shown the important predominance of the chirality at phosphorus over that of the backbone [29].

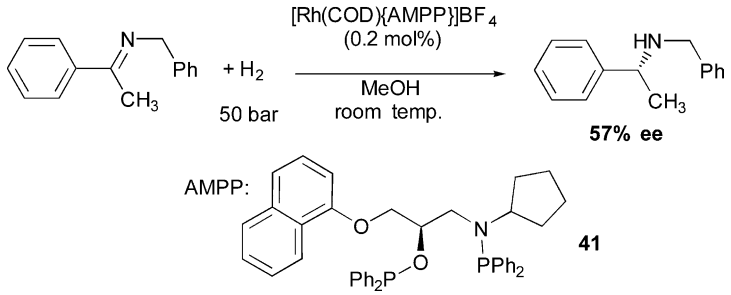
While varying the substituents on the phenyl ring [27] and specifically at the para position of non-proteinogenic aryl aminoacid precrusors [29], moderate to high enantioselectivities were obtained (62–90% ee). L-Homophenyl alanine has been produced via an optimised asymmetric hydrogenation of (*Z*)-2-acetamido-4-phenylcrotonate in the presence of DPAMPP ligands (95.7% ee, recrystallised > 99% ee) (Scheme 24) [27,61].

N-Boc protected amino acid precursors have also been hydrogenated with good ees (ca. 87% ee) while varying the para substituent of α-*N*-carbamato-cinnamate type substrates [30].

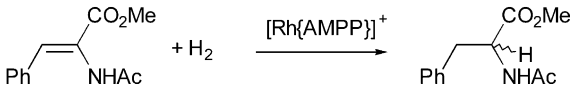
Finally, 4-oxoisophorone enol acetate has been hydrogenated into (*S*)-phorenol acetate, an intermediate in the synthesis of the natural pigment zeaxanthin in the presence of *t*LANOP and oxoProNOP type ligands with up to 95% ee (Scheme 25) [39].



Scheme 21. Asymmetric hydroboration catalysed by a Rh–AMPP complex.



Scheme 22. Asymmetric hydrogenation of an imine catalysed by a Rh–AMPP complex.



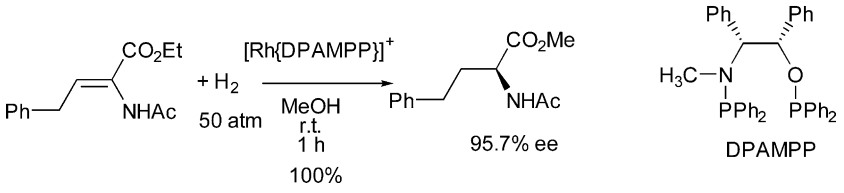
Scheme 23. Hydrogenation of acetamido-cinnamate.

Table 1
Enantioselective hydrogenation of methyl α-acetamido-cinnamate

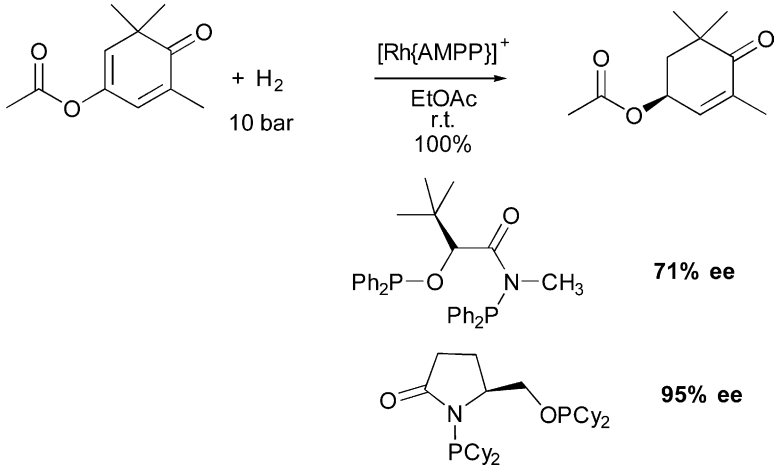
Ligand	Solvent	Conditions temperature, P_{H2}	Ee (%)	Reference
2	Acetone	25 °C, 35 atm	77	[28]
24	C_6H_6	r.t., 10 atm	99	[29,61]
3	MeOH	r.t., 50 atm	98.3	[26,27]
1	MeOH	25 °C, 1 atm	78	[30]

7.7. Enantioselective hydrogenation of C=O bonds

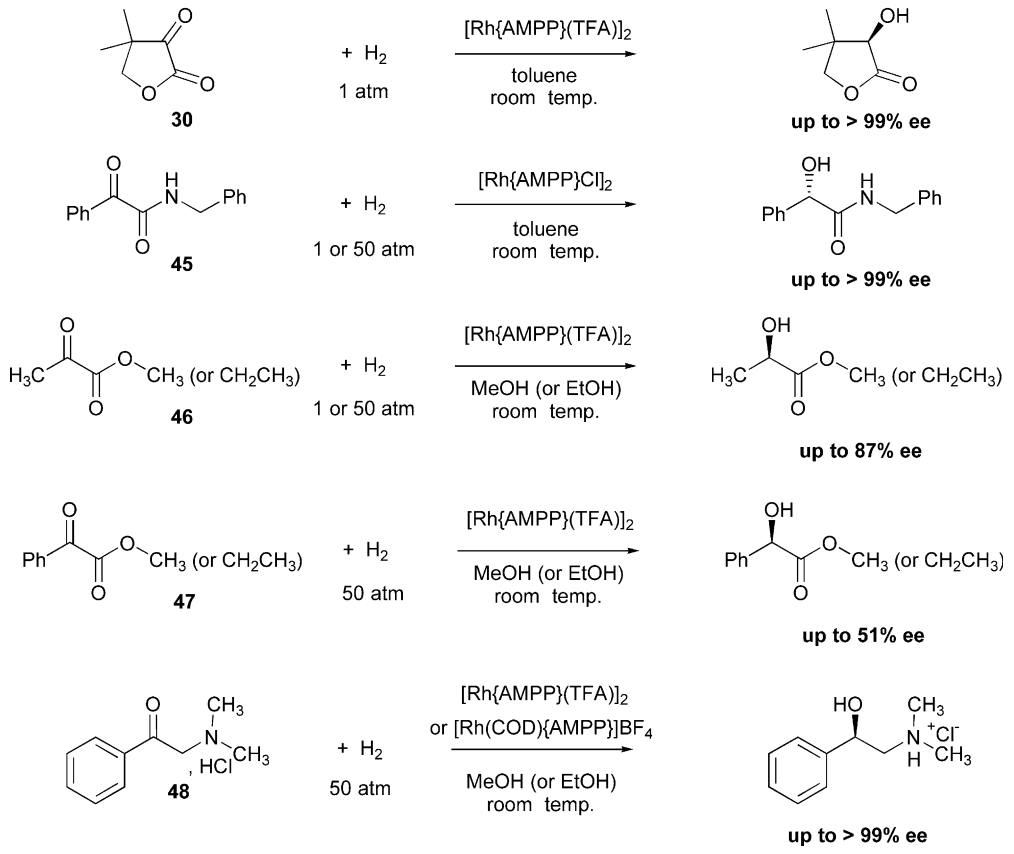
The design and development of enantioselective hydrogenation of ketones catalysed by Rh–AMPP has been an important focus of our research. More specifically, neutral rhodium complexes bearing AMPP possessing dicycloalkyl residues on their phosphorus atoms have induced very high enantiodifferentiations and good catalytic activities in apolar solvents in the mentioned transformation [19,25,66]. In addition to this fundamental trend, previous work had also established other specific tendencies related to the structure of the rhodium catalytic precursor. The non-chiral ancillary ligand plays a significant role and has to be selected according to the substrate to be hydrogenated [22,25,67–69]. Thus, it has been shown that, in the presence of dicycloalkyl-AMPP ligands, neutral rhodium precursors of the type $[RhCl\{AMPP\}]_2$ are best designed for the hydrogenation of ketoamides, whereas $[Rh\{AMPP\}(TFA)]_2$ behave generally best in the hydrogenation of ketoesters and the ketolactone, ketopantolactone (**30**, Scheme 26). Thus very interestingly,



Scheme 24. Preparation of L-homophenylalanine intermediate.



Scheme 25. Hydrogenation of 4-oxoisophorone enol acetate.

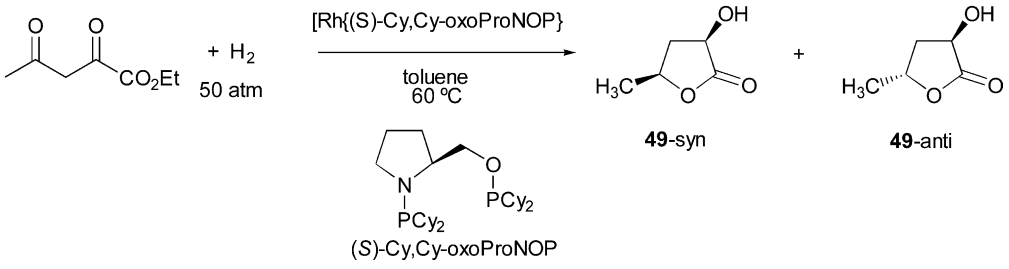


Scheme 26. Enantioselective hydrogenation of functionalised ketones.

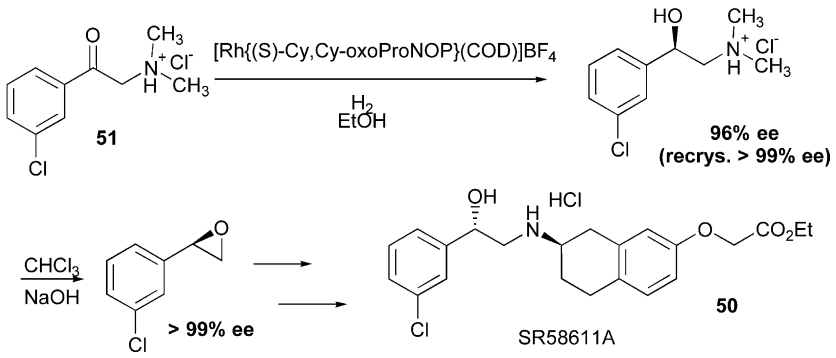
dicycloalkyl and diphenyl substituted AMPP ligands are complementary for the hydrogenation of either ketones or amino acid precursors. In other words, the catalytic systems composed by cationic rhodium complexes bearing diphenyl substituted AMPP are adapted to the hydrogenation of C=C bonds (vide supra) in polar solvents while neutral rhodium–AMPP (dicycloalkyl or dialkyl) are most appropriate for the hydrogenation of functionalised ketones in non polar solvents (vide infra).

The new synthesised dicycloalkyl AMPPs have been applied systematically in the hydrogenation of ketopantolactone **30**, *N*-benzylbenzoylformamide **45**, methyl (or ethyl) pyruvate **46**, phenylglyoxylate **47**, and an aminoketone **48** (Scheme 26).

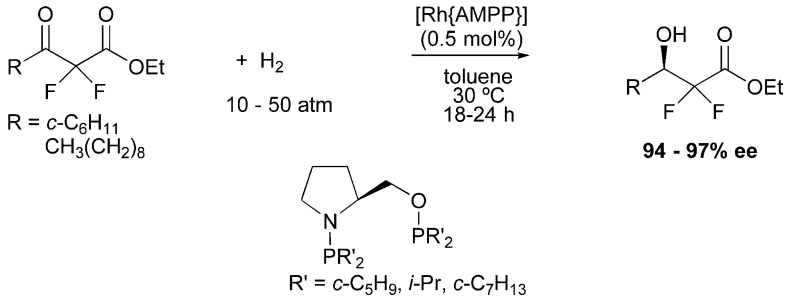
While using AMPP based on indoline carboxylic acid **7-Cy** and **7-Cp** and tetraisoquinoline carboxylic acid **8-Cy** and **8-Cp** (structures depicted in Scheme 3), very efficient hydrogenations could be performed on substrates **30**, **45**, and **48**. For the latter, it has to be mentioned that neutral and cationic precursors behave equivalently in terms of enantioselectivity as catalyses are carried out in methanol or ethanol in which most probably cationic species exist [70]. A beneficial effect on the enantioselectivity could be observed while using the 'right' diastereomer of the corresponding chromium tricarbonyl complexed AMPPs [33,36,43]. The highest enantioselective enhancement has been obtained for the hydrogenation of ketopantolactone **30** ($\Delta ee = 35\%$) when replacing the phenyl based ligand **8-Ph** by the corresponding $Cr(CO)_3$-complexed AMPP **12-Ph** (structure given Scheme 4) [36]. On the other hand, generally, highly enantioselective hydrogenation of phenylglyox-



Scheme 27. Asymmetric hydrogenation of a 2,4-dioxoester.



Scheme 28. Synthesis of a chiral chloro-epoxystyrene.



Scheme 29. Hydrogenation of difluoro oxocarboxylates.

ylate type substrates is still rather difficult to perform in the presence of AMPP ligands [71]. The use of methanol as solvent associated to **7-Cy** (Scheme 3) provided a moderate 51% ee into the hydrogenated product mandelate [35].

Rhodium–AMPP based enantioselective hydrogenations have been carried out efficiently for the preparation of particular chiral alcohols which are important intermediates in the synthesis of bioactive substances. As such, the diastereoselective and enantioselective sequential hydrogenation of α,β-diketoesters allowed one to prepare α-hydroxy-γ-butyrolactone **49** with moderate selectivity into *syn* and *anti* products (72/87-80/86) and good enantioselectivities (72/87 to 80/86% ee) (Scheme 27) in the presence of (*S*)-Cy,Cy-oxoProNOP [72,73].

The same AMPP ligand was used for the preparation of an intermediate in the synthesis of chiral atipycal β-adrenergic agonist SR58611A **50** (Scheme 28) [74]. The key step is the highly enantioselective hydrogenation of the aryl amino ketone **51**.

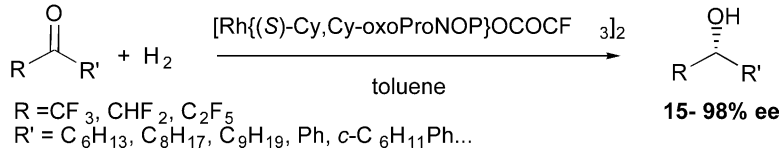
The same AMPP has been used successfully along with its di*iso*propyl, dicycloheptyl, and dicyclopentyl congeners for the highly enantioselective hydrogenation of 2,2-difluoro-3-oxocarboxylates (Scheme 29) [40].

Very interestingly, the catalytic asymmetric hydrogenation of simple trifluoro methyl ketones has been accomplished successfully using a neutral Rh–AMPP catalyst in toluene providing a variety of optically active α-trifluoro methyl alcohols with up to 98% ee (Scheme 30) [75].

Finally, a theoretical approach of the enantioselective hydrogenation of ketopantolactone with neutral rhodium–AMPP catalysts has been undertaken with molecular mechanics and extended Hückel calculations [76]. Essentially, the most stable catalytic intermediates have been considered and a rationale between the configuration of the prevailing produced pantolactone, catalytic intermediate structures, and the definition of the most nucleophilic hydride on rhodium has been seeked.

8. Conclusion

The synthesis and use in asymmetric catalysis of AMPP type chiral auxiliaries have remained under



Scheme 30. Hydrogenation of fluorinated ketones.

investigation during the last years. Several new auxiliaries have been prepared and utilised with success in asymmetric transformations. However, the full scope of the used of these ligands has not been totally defined. Up to now, they appear to be particularly well designed for the hydrogenation of C=C bonds. Furthermore, asymmetric hydrogenation of ketones is performed in a highly enantioselective manner using the most appropriate dialkylsubstituted AMPPs. The productivity of the rhodium-{(*S*)-Cy,Cy-oxoProNOP} based hydrogenation of ketopantolactone has been tested under industrial conditions and it was shown that this auxiliary can be truly efficient. Special attention is given nowadays to new technologies that meet technical, economic [22], and environmental requirements. Asymmetric catalysis falls within such new concerns. Thus, the extensive research devoted to the design of efficient chiral catalysts will be pursued. As such, the application of new AMPP type ligands will certainly be reported in the future.

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