24
Enantioselective Hydrogenation: Phospholane Ligands

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24.1
Introduction and Extent of Review

The ability to efficiently synthesize enantiomerically enriched materials is of key importance to the pharmaceutical, flavor and fragrance, animal health, agrochemicals, and functional materials industries [1]. An enantiomeric catalytic approach potentially offers a cost-effective and environmentally responsible solution, and the assessment of chiral technologies applied to date shows enantioselective hydrogenation to be one of the most industrially applicable [2]. This is not least due to the ability to systematically modify chiral ligands, within an appropriate catalyst system, to obtain the desired reactivity and selectivity. With respect to this, phosphorus(III)-based ligands have proven to be the most effective.

Amongst the hundreds of chiral phosphorus-based ligands developed since the seminal studies of Knowles and Horner [3], only a select few ligand families have had a revolutionary impact on the field. The highly modular chiral C_2-symmetric phospholane ligands (DuPhos^{TM} and BPE), developed by Burk and coworkers at DuPont, are one such example. As a result, much effort has been directed towards building on this breakthrough discovery and extending both the design and application of this ligand class.

In this chapter, we review the growing family of phospholane-based chiral ligands, and specifically examine their applications in the field of enantioselective hydrogenation. In general, this ligand class has found its broadest applicability in the reduction of prochiral olefins and, to a significantly lesser extent, ketones and imines; this is reflected in the composition of the chapter. Several analogous phosphacycle systems have also been included, where appropriate.

Whilst trying to be comprehensive, we have also intended to introduce a strong applied flavor to this summary. In the industrial case, catalyst performance is critically judged on overall efficiency, namely catalyst productivity and activity as well as enantioselectivity. As a result, turnover numbers (TONs) and turnover frequencies (TOFs) have been included or calculated whenever possible and meaningful.

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However, the reader should be aware of the danger of comparing systems tested under nonequivalent conditions (e.g., *in situ* versus preformed catalysts or alternative solvents). It is also worth noting that as this chapter is dedicated to applications in enantioselective hydrogenation, there may be many examples of phospholane-containing ligands that do not feature. Since this is by no means the first review of this type [2, 4], hopefully those reviews dealing with more general enantioselective applications will capture these aspects [5].

24.2
Phospholane Ligands: Synthesis and Scope

24.2.1
Early Discoveries and the Breakthrough with DuPhos and BPE

The first reported application of phospholane-based ligands for enantiomeric hydrogenation was described by Brunner and Sievi in 1987 [6]. Unfortunately, these *trans*-3,4-disubstituted phospholanes (**1–3**) were derived from tartaric acid, and proved to be relatively unselective for the rhodium-catalyzed hydrogenation of (*Z*)-*α*-(*N*-acetamido)cinnamic acid (6.6–16.8% ee). This was, presumably, due to the remoteness of the chiral centers from the metal coordination sphere failing to impart a significant influence. This was also found to be the case with several other bi- and tridentate analogues [7].

The fundamental discovery by Burk et al. that the analogous *trans*-2,5-disubstituted phospholanes formed a more rigid steric environment led to the introduction of the DuPhos and BPE ligand classes (Fig. 24.1) [8–13]. Subsequently, these ligands have been successfully employed in numerous enantiomeric catalytic systems [4a, 5], the most fruitful and prolific being Rh-catalyzed hydrogenations. The reduction of *N*-substituted *α*- and *β*-dehydroamino acid derivatives,

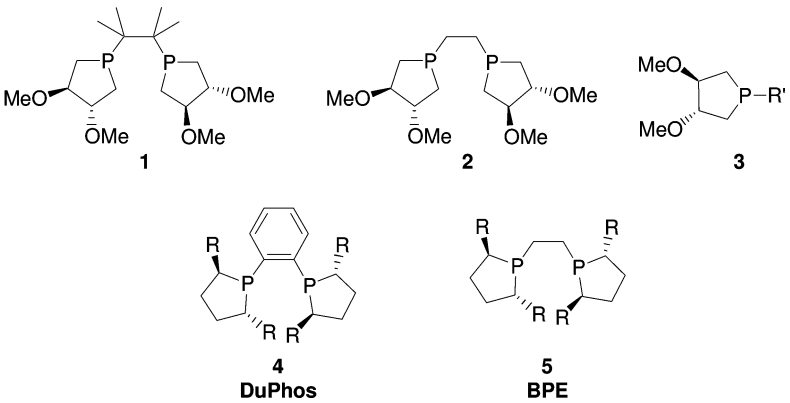


Fig. 24.1 The first phospholanes to be used for enantiomeric hydrogenation.

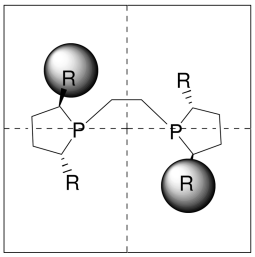
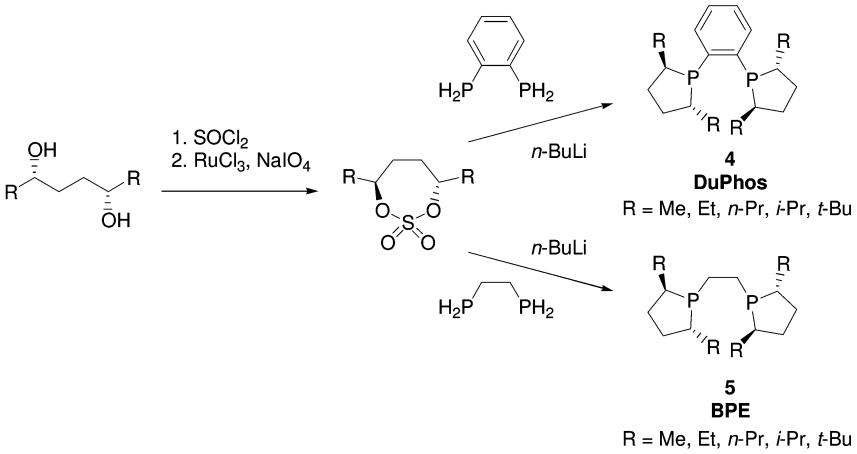


Fig. 24.2 The steric quadrant model for 2,5-disubstituted phospholanes.



Scheme 24.1 The synthesis of *trans*-2,5-dialkyl-phospholanes, DuPhos.

β-dehydroamino alcohols, *N*-acylhydrazones, *N*-substituted enamides, enol esters, *α*,*β*-unsaturated acid and *β*-keto ester derivatives have all been achieved in exceptionally high enantioselectivity [4a, 14–21]. Furthermore, the combination of robustness, high activity, and excellent selectivity has rendered these ligands suitable for commercial-scale industrial applications [2d, 4b, 22, 23]. A simplistic, qualitative guide to explaining the high degree of selectivity observed has been provided in part by the quadrant model (Fig. 24.2) [4a]. By having two of the four phospholane substituents project into the open coordination plane of the metal, steric interactions influence the reaction pathway, though some dispute as to the validity of this model has recently been raised [24].

The conventional synthesis of *trans*-2,5-dialkyl phospholanes starting from a chiral 1,4-diol is shown in Scheme 24.1. Originally, these 1,4-diols were obtained via electrochemical Kolbe coupling of single enantiomer *α*-hydroxy acids [25], but this method proved to be commercially impracticable and has since been replaced by more viable biocatalytic routes [26]. Reaction of the chiral 1,4-diol with thionyl chloride followed by ruthenium-catalyzed oxidation with so-

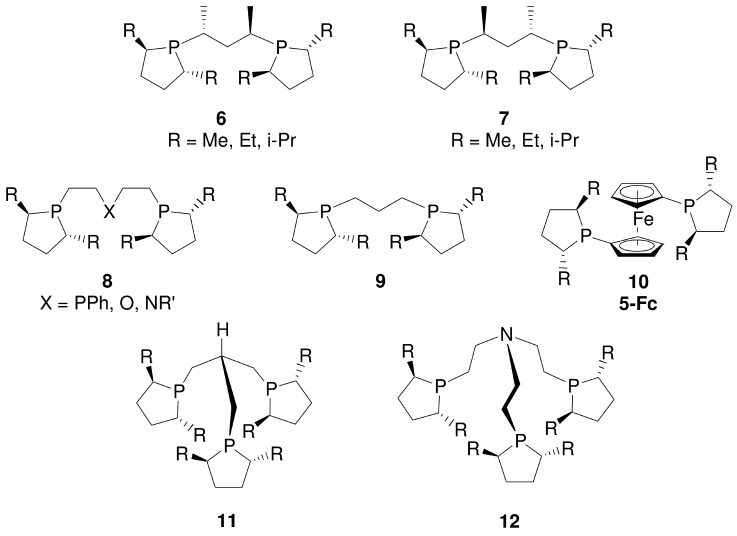
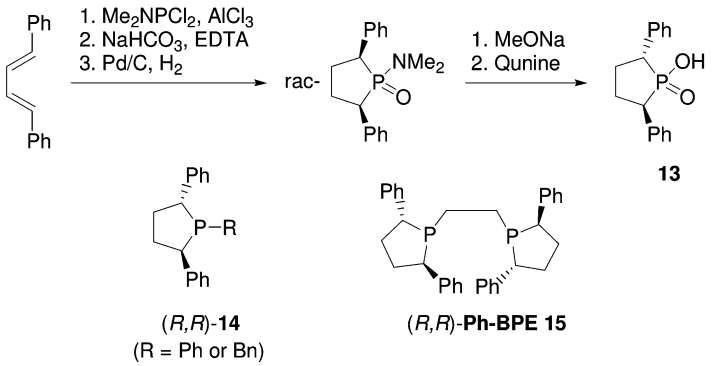


Fig. 24.3 Multidentate 2,5-disubstituted phospholanes displaying wide backbone diversity.

dium periodate yields the cyclic sulfate [27]. Treatment with 2 equiv. of a strong base, such as BuLi, and addition of a primary phosphine affords the tertiary phospholane with net inversion of stereochemistry. Practical methods have been developed for the large-scale manufacture of these ligands [28]. An alternative method via lithium phosphides was originally applied, but this was handicapped by excessive P–P bond formation [8], in addition to partial racemization of the phospholane chiral centers [11, 29]. Clearly, multidentate ligands may be obtained if a moiety containing more than one primary phosphine is used, and indeed numerous examples with a wide diversity of backbones were reported by Burk et al. (Fig. 24.3) [8, 10, 11, 29, 30].

Unfortunately, *trans*-2,5-diaryl phospholanes cannot be prepared using the traditional method described above for the alkyl derivatives; the basic conditions employed tend to induce elimination reactions with the corresponding cyclic aryl sulfate or dimesylate [31]. In 1991, Fiaud and co-workers reported a route to single enantiomer *trans*-1,2,5-triphenylphospholane oxide via epimerization of the previously reported *cis*-isomer and liquid chromatographic separation of the racemate [32]. Later, an alternative approach was developed using a chelotropic reaction between 1,4-diphenylbuta-1,3-diene and a dichloroaminophosphine (Scheme 24.2) [31]. After reduction, epimerization and hydrolysis, a diastereomeric salt resolution of the resulting racemic *trans*-2,5-diphenyl phospholanic acid could now be achieved, yielding the enantiomerically pure phospholane synthon **13**. This was ultimately converted to a series of monodentate 2,5-triphenylphospholane ligands (**14**), and shown to give reasonable to high enantioselectivities for the hydrogenation of (*Z*)-methyl-2-acetamidocinnamate (MAC), itaconic acid and esters, and *N*-acetyl enamides [31, 33]. This procedure has since



Scheme 24.2 Preparation, resolution and resulting ligands from 2,5-diaryl phospholanic acid.

been used to prepare the bidentate bisphospholane, Ph-BPE **15** (Scheme 24.2) [34]. This has been shown to have excellent levels of selectivity and activity for the hydrogenation of a range of olefinic substrates when compared to the dialkyl analogues [34, 35].

Although the DuPhos and BPE family of ligands have been shown to form active asymmetric hydrogenation catalysts with a range of transition metals (namely Ru, Ir, Pt, Pd and Au), none has shown the high degrees of selectivity and activity typically reported for the Rh-based catalysts. On the whole, the most successful results have been obtained with preformed mononuclear, cationic complexes employing the diolefin co-ligands 1,5-cyclooctadiene (COD) or norbornadiene (NBD). There has been some debate regarding COD precatalysts being uneconomic for use in industrial processes when compared with the NBD analogues [36]. A study performed at high catalyst loadings (molar substrate to catalyst ratio (SCR) = 100) showed there to be a rate difference for some substrates due to the NBD precatalyst forming the active species faster, but with no difference in enantioselectivity. However, when more industrially practical conditions were applied (SCR 2000 to 10 000), this effect became insignificant to the catalyst's overall productivity; furthermore, it was shown to be substrate-dependent [37]. In fact, the experimental conditions (e.g., stirring rate) were found to have a far more dramatic effect than the choice of precatalyst. For this class of reaction, hydrogen mass transfer into solution is the most important individual process parameter to affect the overall reaction rate [38].

In general, the choice of counteranion has a minor effect on catalyst performance, with typical examples being selected from BF_4^-, OTf^-, PF_6^-, or $BARF^-$. In one example, however, it was noted that [(*R,R*)-Et-DuPhos Rh COD]OTf gave superior selectivity for the reduction of *β-β*disubstituted *α*-dehydroamino acid derivatives than the corresponding BARF complex when performed in a range of solvents, including supercritical carbon dioxide [39].

In recent years, considerable effort has been made to immobilize homogeneous hydrogenation catalysts because of the obvious potential advantages, such as improved separation and catalytic performance [4b, 40]. Although beyond the

remit of this chapter, it is worth mentioning that significant success has been achieved with several examples involving catalysts based on phospholane ligands [41].

Unsurprisingly, the immense success of DuPhos and BPE has created considerable interest in this ligand class, resulting in a vast number of variants appearing over the past few years. This has partly been driven by a desire to circumvent the original patents, but also by others in an attempt to explore certain mechanistic or design theories. On the whole, these ligands display similar properties to DuPhos and BPE with variable degrees of selectivity and activity when applied to enantioselective hydrogenation. This expansion has been partly facilitated by the modular nature of these ligands [4a], with modifications to the backbones, phospholane substituents, and second chelating site. A summary of these ligands concludes this section.

24.2.2 Modifications to the Backbone

The structures depicted in Figure 24.4 all display alterations to the original DuPhos and BPE backbones, and a concomitant variation in the ligand bite angle. In general, these have been prepared using the traditional cyclic sulfate method with the corresponding primary diphosphine. Pringle et al. have successfully applied a chiral *trans*-1,2-diphosphinocyclopentane to the synthesis of matching and mis-matching bidentate phospholanes **16** [24]. Hydrogenation of MAC was achieved with 77% to 98% ee, depending on the relative chirality of the backbone and 2,5-positions of the phospholane rings, with the overall stereochemis-

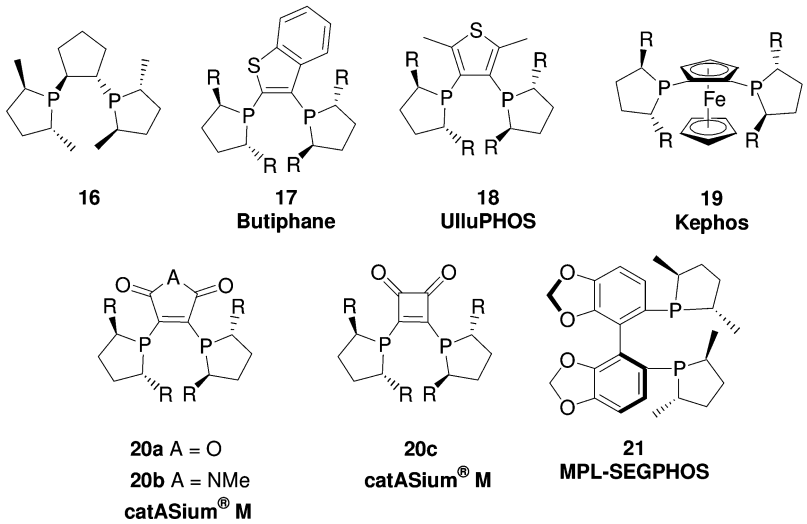


Fig. 24.4 DuPhos and BPE analogues with modified backbones.

try of the product being determined by the phospholane moieties. The sulfur heterocycle-based ligands, Butiphane (**17**) [42, 43] and UlluPHOS (**18**) [43, 44], have both been reported to be applicable for the Rh-catalyzed enantiomeric reduction of simple *α*-dehydroamino acid and itaconate derivatives, giving comparable results to Me-DuPhos in each case. Interestingly, the synthesis of Butiphane, together with that of several other benzo[b]thiophene-based ligands, was facilitated by the use of *N*,*N*-dialkyl-aminophosphine-containing intermediates acting as directing groups in the *ortho*-lithiation of the backbone. Several ferrocenyl-1,2-diphosphines, including Kephos (**19**), have also recently been reported to be effective for the reduction of several standard model substrates [45].

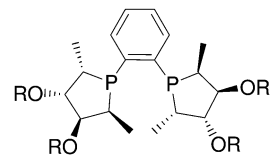
One exception to the use of primary phosphines is in the reported syntheses of the catASium® M class of ligands **20** [46–49]. In one report, reaction of the cyclic sulfate with $P(TMS)_3$ yields the TMS-protected secondary phospholane, which could then be reacted with the appropriate 1,2-dichloro species [46]. An alternative procedure to the same intermediate involves preparation of 1-phenylphospholane via the bismesylate, subsequent lithium-induced P–Ph cleavage, and quenching with TMSCl [49]. The ligand based on 2,3-dichloromaleic anhydride (**20a**; originally referred to as MalPHOS [46]) has been shown to be effective for the chiral reduction of *α*- and *β*-dehydroamino acid derivatives and itaconate derivatives.

An interesting approach to investigating the relationship between the position of enantiodescriminating sites in a number of chiral ligands and enantioselectivity in enantioselective hydrogenation has been proposed by Saito et al. [50]. In this report, (*aS*,*S*,*S*)-MPL-SEGPHOS (**21**) was used for the reduction of MAC, albeit in 75% ee.

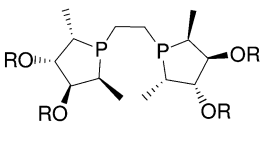
24.2.3
Modifications to the Phospholane Substituents

In recent years, numerous DuPhos and BPE analogues have been introduced that contain structural variations at the 2,5-positions of the phospholane segments and/or additional stereogenic centers (Fig. 24.5).

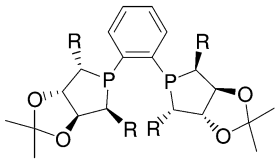
Several groups have independently reported the synthesis of D-mannitol-derived phospholanes with either ketal, ether or hydroxy substituents in the 3,4-positions. The earliest ligand class, Rophos containing either a 1,2-benzene (**22**) or 1,2-ethane backbone (**23**), was introduced by Börner, Holz and co-workers in 1998 [51]. By taking advantage of the difference in reactivity between the primary and secondary alcohols, the mannitol framework could be manipulated to prepare the cyclic sulfate and, ultimately, the desired diphosphine. These were applied to the Rh-catalyzed hydrogenation of a range of olefinic substrates, all with excellent enantioselectivity. The research groups of Zhang [52] and Rajan-Babu [53] have both reported the synthesis of the *iso*-propylidene ketal bisphospholane **24** (R = Me or Et) and the tetrahydroxy bisphospholane **25** (R = Me or Et). Surprisingly, whilst ligand **24** (KetalPhos) was described as being inactive for the hydrogenation of dehydroamino acid derivatives when the catalyst was



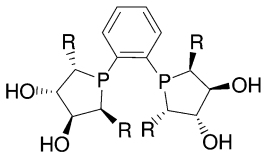
22
Rophos
R = Bn, *t*-Bu



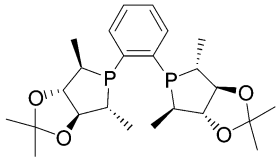
23
Rophos
R = Bn, *t*-Bu



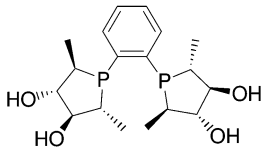
24
KetalPhos
R = Me, Et, Pr, Bn, $CH_2CH_2CH(CH_3)_2$



25
R = Me, Et, Pr, Bn, $CH_2CH_2CH(CH_3)_2$



26



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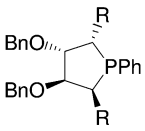
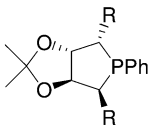
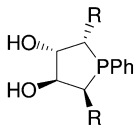


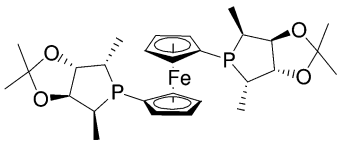
28
R = Me, Bn



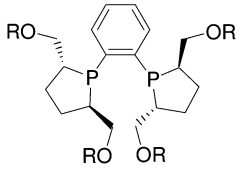
29
R = Me, Et



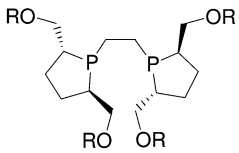
30
R = Me, Et



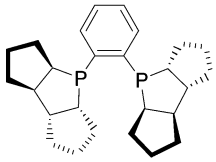
31



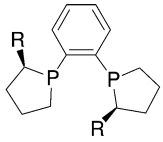
32
BASPHOS
R = H, Me, Bn, 2-THP



33
BASPHOS
R = Me, Bn



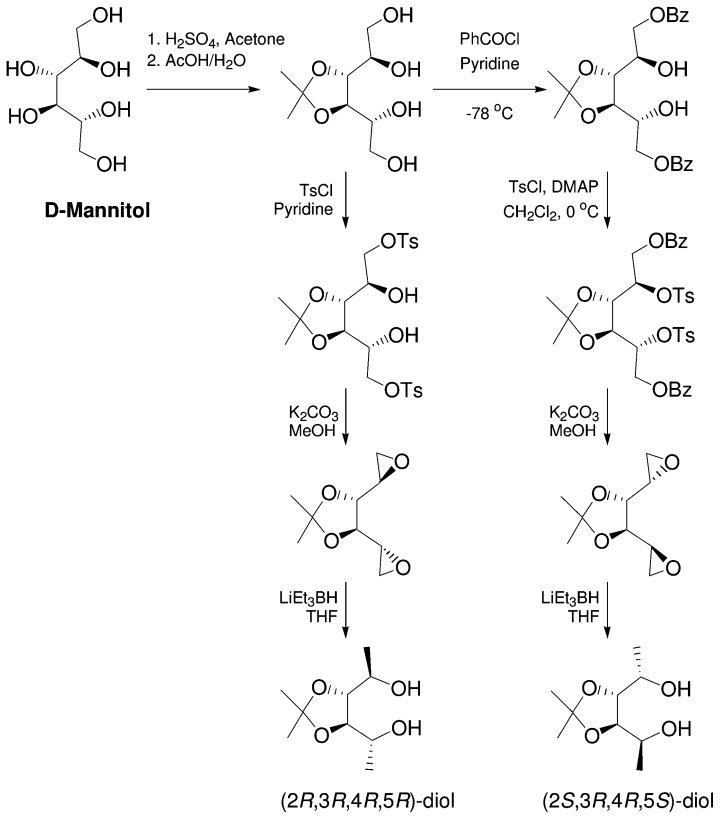
34
C5-Tricyclophos



35
R = Me, CH_2OMe, Bn

Fig. 24.5 Ligands with modifications to the phospholane substituents.

prepared *in situ* with $[Rh(COD)_2]X$ (X = BF_4, SbF_6, PF_6 and OTf) [52a, b], the isolated precatalyst, [(**24**) Rh(COD)]BF_4, was shown to be active and very selective (>90% ee) [53b]. A mannitol-derived cyclic sulfate has also been employed in the synthesis of monodentate phospholanes **28–30** [52a, b] and the ferrocenyl-based diphosphine **31** [54]. Although enantioselective hydrogenation with **28–30** has not been reported, **31** has been shown to be extremely active (TON 10000; TOF >800 h^{-1}) and selective (89.8–99.9% ee) for the Rh-catalyzed reduction of a range of functionalized olefins. By preparing a diasteromeric bisepoxide pair from D-mannitol (Scheme 24.3), RajanBabu and Yan have also accessed the dia-



Scheme 24.3 The preparation of diastereomeric diols from D-mannitol.

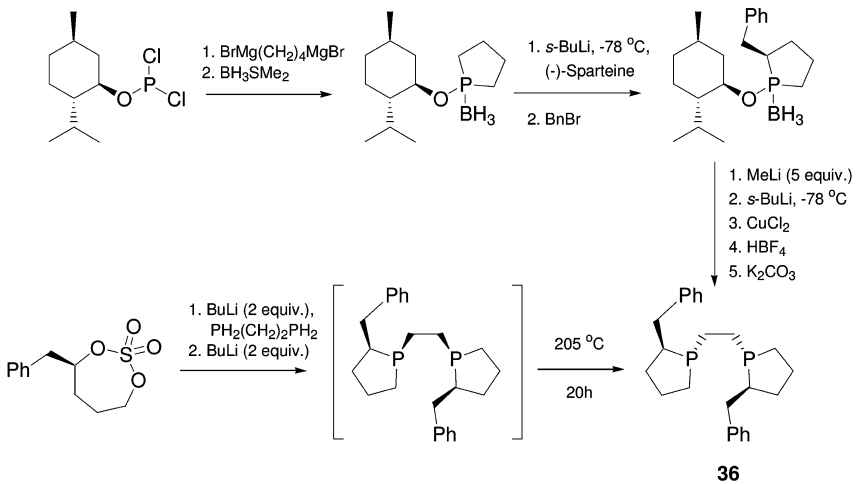
stereomeric 3,4-disubstituted phospholanes **26** and **27** [53a]. When comparing **24** (R = Me) with **26**, as expected the opposite enantiomer was obtained for the hydrogenation of methyl 2-acetamidoacrylate (MAA), but interestingly **26** gave a slight improvement on the level of selectivity [97.4% ee (*R*) versus 90.5% ee (*S*)] [53b]. Rieger et al. extended the range of substituents at the 2,5-positions of ligands **24** and **25** (R = Et, *n*-Pr, isoamyl and Bn) by means of copper-catalyzed coupling of the appropriate Grignard reagent to the mannitol-derived bisepoxide [55]. Testing this series of ligands against the hydrogenation of *α*-methylcinnamic acid and itaconic acid showed high selectivity in every case (96–99% ee).

Several methods have been described to liberate the hydroxyl groups from **24** to produce the water-soluble, tetrahydroxyl bidentate ligand **25** [52, 53b]. Water-soluble ligands are of interest due to the prospect of recycling the catalyst into an aqueous phase, ideally without loss of performance. The enantiomeric hydrogenation of itaconic acid was performed in aqueous methanol over a range of solvent compositions (MeOH: H_2O, 9:1 to 3:97), with consistently excellent levels of performance (100% conversion, 99% ee, SCR 100, 12 h) [52b]. Interest-

ingly, when applied to the reduction of MAA under comparable conditions, an increase in the percentage of water was found to have a deleterious effect on selectivity [53b]. However, at equal volumes of methanol and water, Rh complexes of **25** and analogous tetrahydroxy phospholanes could be recycled (up to five runs at SCR 100) by extracting the product into ether, with no significant losses in enantioselectivity.

Another family of mannitol-derived bisphospholanes was introduced by Holz and Börner. Removal of the hydroxy groups at the 3 and 4 positions leads to a key intermediate that ultimately produces 2,5-disubstituted phospholanes BASPHOS **32** and **33**. The water-soluble, tetrahydroxyl-substituted variant **32** (R = H) displayed excellent selectivities for the Rh-catalyzed hydrogenation of 2-acetamido acrylic acid and the corresponding methyl ester in water (99.6% and 93.6% ee, respectively) [56a]. RajanBabu and co-workers confirmed this and showed that the catalyst could be recycled up to four times, with no loss in selectivity (SCR 100) [53b]. An interesting feature of the synthesis of this ligand is the protection of the air-sensitive phosphine groups as the rhodium complex prior to liberation of the hydroxyl groups (tetrahydropyranyl group removal), saving two borane protection–deprotection steps. The corresponding 2,5-bis(alkoxymethylene)-substituted ligands **32** and **33** (R = Me, Bn) have also been tested for the Rh-catalyzed hydrogenation of *α*- and *β*-dehydroamino acid derivatives, itaconates and an unsaturated phosphonate, together with Ru-catalyzed reduction of prochiral *β*-keto esters [56b–e]. The wide range of enantioselectivities obtained (8 to 99% ee) was found to depend strongly on both the phospholane substituent and the backbone used.

A unique tricyclic bisphospholane ligand, C5-Tricyclophos (**34**), has been described in a patent by Zhang [57]. Derived from resolved bicyclopentyl-2,2′-diol (originally used in the preparation of the chiral diphosphine, BICP [58]), this li-



Scheme 24.4 Alternative syntheses of the BPE analogue **36**.

gand has shown moderate enantioselectivity for the reduction of α-acetamidocinnamate (53% ee) and MAC (78% ee). An interesting class of P-chirogenic monosubstituted phospholanes, **35** and **36**, has recently been introduced by Hoge [59]. Originally, the 1,2-ethane variant **36** was prepared using menthol as a chiral auxiliary for the directed selective benzylation of the phospholane ring and subsequent phosphorus methylation with stereochemical retention (Scheme 24.4) [59a]. Oxidative homo-coupling and deboronation completed the synthesis. A more versatile method was subsequently published, via the traditional cyclic sulfate route, for the preparation of BPE, DuPhos and monodentate analogues with alternative phospholane substituents (R = Me and CH_2OMe) [59b]. These ligands have been successfully applied to the hydrogenation of α- and β-dehydroamino acid derivatives and a pharmaceutically important precursor to Pregabalin [59a, b, d], giving results comparable to BPE and DuPhos [60, 61].

24.2.4
Other Phospholane-Containing Ligands

In addition to direct DuPhos and BPE analogues, several other ligands containing five-membered phosphacycles have been reported (Fig. 24.6). As early as 1991, non-C_2-symmetric phospholane-containing phosphines **37–39** were reported by Brunner and Limmer [7]. These were prepared by base-induced addition of the secondary phospholane to the appropriate diphenylphosphino-substituted olefin. As for the symmetrical 3,4-disubstituted bisphospholanes, enantioselectivities for the Rh-catalyzed reduction of α-acetamidocinnamate were poor.

Brown et al. [62] prepared a family of unsymmetrical diphosphine ligands **40** by the conjugate addition of racemic borane-protected *o*-anisylphenyl phosphide to diethylvinylphosphonate followed by deprotection, reduction and phospholane formation with the appropriate cyclic sulfate (2,5-hexanediol- or L-mannitol-derived). The diastereomers of the mannitol-derived phosphines could be separated chromatographically and converted to their dihydroxyl analogue, whereas the disubstituted-phospholane required medium-pressure liquid (flash) chromatography (MPLC). Rh-catalyzed hydrogenations with these ligands gave moderate enantioselectivities for several standard substrates and, whilst some significant matching and mis-matching effects were observed, the chirality of the product was determined primarily by the phospholane moiety.

Since this report, several research groups have replaced one phospholane ring of Me-DuPhos with a diaryl phosphine group. Stelzer et al. [63] described the synthesis of ligand **41** (R = Me, Ar = Ph) by treating the standard cyclic sulfate with a mixed primary-tertiary diphosphine. The ligand was purified via its dihydrochloride salt, liberating the free diphosphine quantitatively by treatment with $NaHCO_3$. Independently, Saito [64] and Pringle [65] reported the use of **41** (R = Me, Ar = Ph) in Rh-catalyzed asymmetric hydrogenation of a range of olefins, with particularly good results being obtained for prochiral enamides. Saito and co-workers made a small family of this class of ligand, UCAPs, and demonstrated that adjusting the diaryl-substituted phosphine could lead to higher se-

lectivities than Me-DuPhos for a trisubstituted enamide [64]. The structurally related P,N ligand, DuPHAMIN **42** has also been prepared by Brauer and coworkers [66]. Remarkably, large matching and mis-matching effects were observed for the Rh-catalyzed hydrogenation of MAC, with the (*R*,*R*,*R*) ligand giving complete conversion at 20 °C (96% ee), but the (*S*,*R*,*R*) ligand being inactive. Pringle also synthesized the ferrocenyl-based **43** [65], but showed this to be less efficient than the phenylene-linked analogue.

The sterically bulky and conformationally rigid bicyclic ligand PennPhos (**44**) was developed by Zhang [57, 67]. The synthesis uses chiral 1,4-cyclohexanediols, converting them to the dimesylate to enable cyclization with 1,2-diphosphinobenzene under basic conditions. This has given high selectivity in Rh-catalyzed hydrogenation of both aryl and alkyl methyl ketones [57, 67b], cyclic enol acetates [67c, d], enol ethers [67d], cyclic enamides [67d, e] and α-dehydroamino acid derivatives [57]. Under certain conditions, the selectivities obtained for cyclic enamides are superior to those achieved with Me-DuPhos, but inferior for acyclic enamides. The bulky monodentate ligand **45** has been described in a patent by Börner, but gave poor enantioselectivities for α- and β-amino acid derivates, dimethylitaconate (DMI) and itaconic acid [68].

The research group of Zhang has also introduced two rigid P-chiral bisphospholane ligands, TangPhos **46** and DuanPhos **47** (Scheme 24.5), both of which contain two chiral phosphorus centers and two chiral carbon centers. Since the synthesis of TangPhos employs an enantioselective deprotonation of 1-*t*-butylphospholane sulfide with a butyllithium–sparteine complex, only one enantiomer is readily accessible [69]. On the other hand, either enantiomer of DuanPhos can be obtained enantiomerically pure by resolution of the corresponding bisoxide with either L- or D-dibenzoyl tartaric acid [70] (Scheme 24.5). Both ligands have been found to be very efficient in the Rh-catalyzed hydrogenation of a range of olefinic substrates such as α-acetamidoacrylate derivatives, α-arylenamides [69, 70], β-acetamidoacrylates [69b, 70, 71], itaconic acids, and enol acetates [69b, 70, 72]. DuanPhos has also been reported to give high rates (TON 4500; TOF 375 h^{-1}) and excellent enantioselectivities (93–99% ee) for a range of β-secondary-amino ketone salts [73].

The 1-*t*-butylphospholane sulfide intermediate to TangPhos was also used to prepare the P,N ligands **48** by reacting the lithium complex with CO_2 and then oxazoline formation with a range of chiral amino alcohols [69b, 74]. The Ir complexes of these ligands have been successfully used in the reduction of β-methylcinnamic esters (80–99% ee) and methylstilbene derivatives (75–95% ee), a particularly challenging class of unfunctionalized olefins [4c].

The BeePHOS (**49**) and mBeePHOS (**50**) classes of ligands introduced by Saito [75] are prepared by reacting the appropriate primary phosphine with a mesylated alkylalcohol-substituted aryl halide. Although a single diastereomer is obtained, the absolute configuration is unknown. Whilst trials of Ru-catalyzed hydrogenation of MAC and methyl α-hydroxymethylacrylate were disappointing, the Rh-catalyzed reactions were more active. On the whole, selectivities were lower than those obtained with Me-DuPhos under the same conditions. Ligand

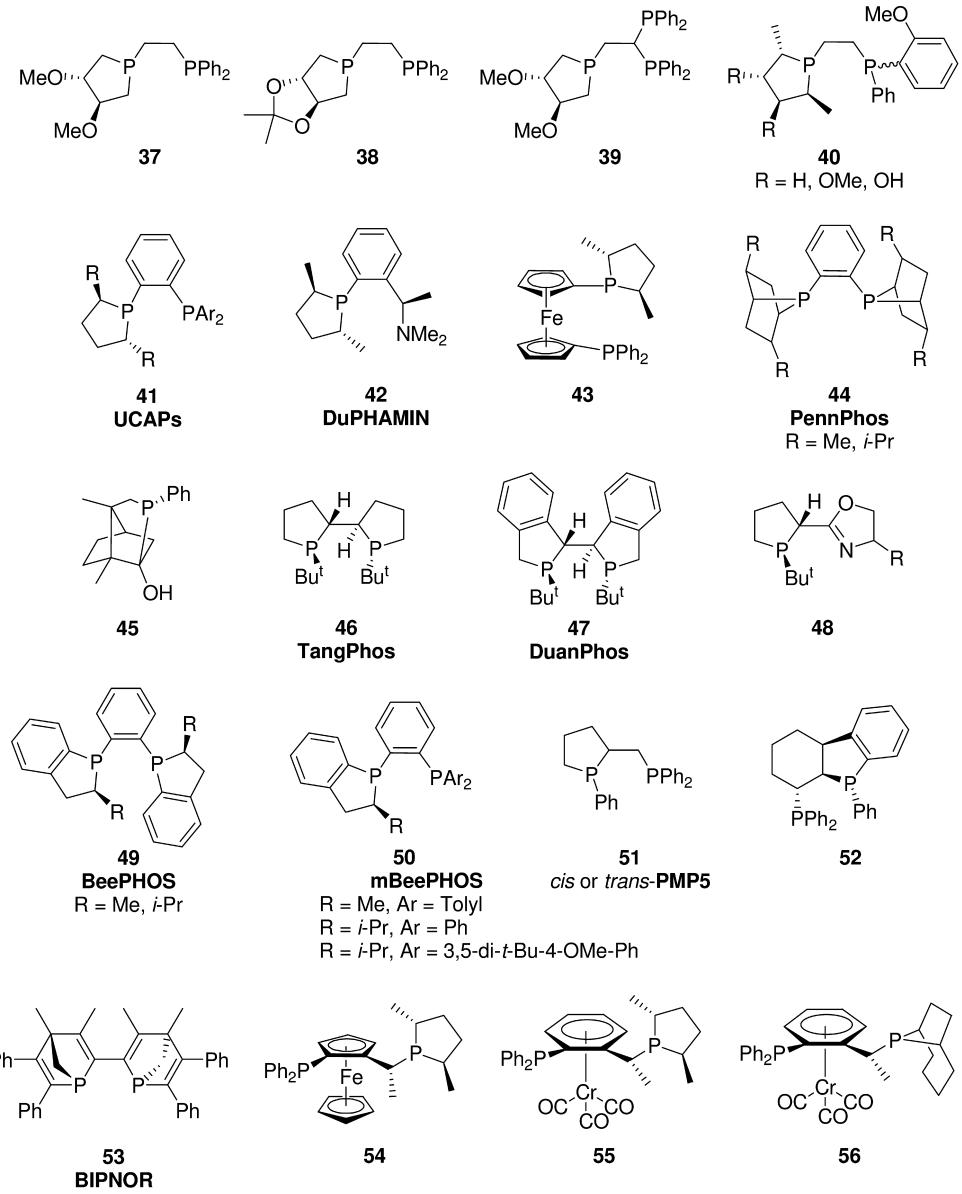
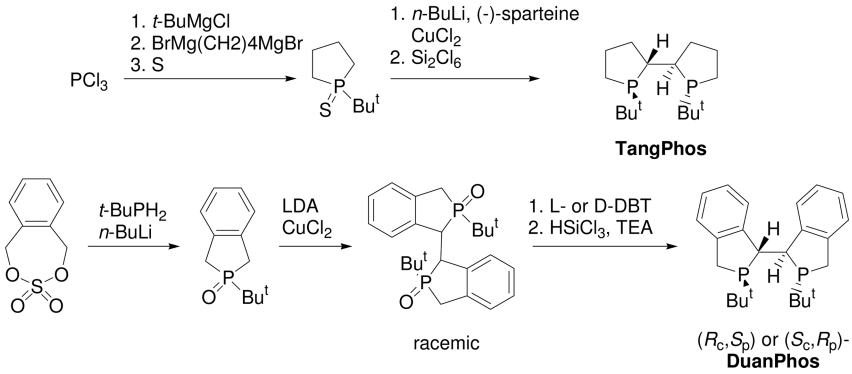


Fig. 24.6 Alternative ligands containing five-membered phosphacycles.

51 has recently appeared in separate patents from both Kobayashi and Schmid [76]. Given the name *cis* and *trans*-PMP5 by Schmid et al., the Rh complexes have been reported to be active catalysts for the reduction of several standard substrates, *α*-enol acetates and *β*-ketoacid derivatives, with variable enantioselectivities [76 b]. In general, the *cis* isomer is more selective than the *trans*.



Scheme 24.5 The syntheses of TangPhos and DuanPhos.

The rigid bicyclic diphosphine **52** was prepared by Knochel and co-workers by the radical cyclization of a bromophosphine oxide, itself obtained from a double [2,3]-sigmatropic shift of an intermediate phosphinite [77]. Unfortunately, this ligand only gave moderate enantioselectivity (21–58% ee) against standard model substrates under normal screening conditions (MeOH, room temperature, 10 atm, SCR 100). The P-chiral diphosphine BIPNOR (**53**) was synthesized by Mathey et al. via a [4 + 2] cycloaddition of tetramethyl-1,1′-bisphospholyl and tolan, the crucial intermediate arising from a double [1,5] shift of each phosphole around the ring [78]. With the phosphorus atoms being located at the bridgehead of a bicyclic system, none of the usual racemization pathways potentially observed for P-homochiral phosphines can occur (Berry pseudorotation and edge inversion). Both *meso* and *rac* diastereomers and the resulting racemic mixture are separated by chromatography of their Pd complexes. Enantioselectivities for the Rh-catalyzed hydrogenation of *α*-acetamidocinnamic acid and itaconic acid are comparable to those achieved with DuPhos-based catalysts.

The group of Salzer has recently reported phospholanes **54**–**56** based on chiral half-sandwich complexes [79]. These were obtained by treatment of the appropriately substituted complex with a secondary phospholane, itself accessed via the cyclic sulfate or dimesylate and PH_3. These were tested against a range of substrates with C=C, C=O and C=N bonds, with variable results [80].

24.2.5
Related Phosphacycle-Based Ligands

Although strictly not phospholanes, several other noteworthy P-heterocycle-containing ligands have been applied to asymmetric hydrogenation (Fig. 24.7). The first optically active phosphetanes to be used in catalysis were described by Marinetti and Ricard [81]. Although active in Pd-catalyzed hydrosilylation, these monodentate ligands (**57**) proved to be very poor for the hydrogenation of MAC [81 b, c]. More recently, Burk and co-workers [82] and the groups of Marinetti and Genêt

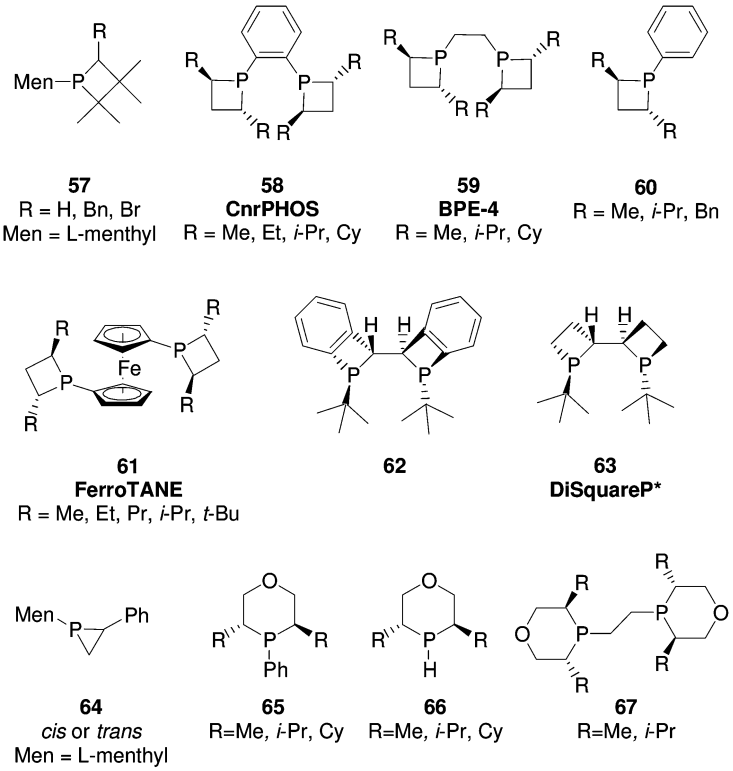


Fig. 24.7 Related P-heterocyclic ligands.

[83] have independently prepared and examined several enantiomerically pure ferrocenyl-based 2,4-disubstituted phosphetanes as ligands for asymmetric hydrogenation. These ligands were prepared from the appropriate primary phosphines and a range of chiral 2,4-diols using the traditional cyclic sulfate methodology (*vide supra*). Although not as enantioselective as their bisphospholane analogues in reducing dehydroamino acid derivatives [83 a, d], Genêt's CnrPHOS (**58**) and BPE-4 (**59**) are reported to be extremely selective in the Ru-catalyzed hydrogenation of several *β*-ketoesters (73–98% ee) [83 d, e]. Interestingly, reasonable levels of enantioselectivity were achievable with the monodentate ligands **60** against *α*-acetamidocinnamic acid (10 to 86% ee) [83 f]. The ferrocenyl-based bisphosphetanes, FerroTANE (**61**), have been shown to be exceptional for the Rh-catalyzed reduction of (*E*)-*β*-dehydroamino acids [56 c, 84] as well as a number of itaconic and succinamide derivatives [82 a, 85, 86], outperforming DuPhos in both cases. Albeit less selective, FerroTANE has also been examined for Ru-catalyzed hydrogenation of *β*-ketoesters [83 d] and Rh-catalyzed hydrogenation of *α*-dehydroamino acids [83 c], and is a precursor to the potent anticonvulsant (*S*)-Pregabalin [61].

In recent years, the research group of Imamoto has been very active in the area of C_2-symmetric P-stereogenic phosphine ligands [87]. Two such ligands,

62 and DiSquareP* **63**, were prepared using the same strategy, the key being an oxidative homocoupling of the corresponding benzophosphetene or phosphetane, respectively [87]. Both ligands have been applied to the Rh-catalyzed hydrogenation of MAC, but in particular DiSquareP* has displayed excellent activity (TON 50 000; TOF $\sim$1100 h^{-1}) and selectivity (99% ee) for this and other α-dehydroamino acid derivatives. Interestingly, **63** is also an extremely selective ligand for the reduction of α-substituted enamides, but does not perform well on either substrate class when β,β-disubstitution is present.

The three-membered phosphirane **64** was studied by Marinetti et al. for the Rh-catalyzed hydrogenation of MAA, MAC, and itaconic acid with, in general, poor enantioselectivities [88]. Since ring-opened oxidized phosphorus species were observed at the end of the reactions, some doubt was voiced as to the exact nature of the catalytic species. The oxaphosphinanes **65**, were synthesized by Helmchen via reaction of the diol ether mesylates with dilithiophenylphosphine [89]. Since these showed poor performance for the Rh-catalyzed reduction of α-dehydroamino acids and itaconate derivatives, the corresponding secondary phosphinanes **66** were prepared by cleavage of the P–Ph bond with lithium. These were then converted through to the bidentate analogue **67**. Interestingly, both **66** and **67** performed well against these standard substrates (80–98% ee), but gave the opposite sense of stereochemical induction for a number of products [89].

24.3 Enantioselective Hydrogenation of Alkenes

24.3.1 Enantioselective Hydrogenation of α-Dehydroamino Acid Derivatives

The pivotal role of natural α-amino acids among a myriad of biologically active molecules is widely appreciated, and is of particular importance in the pharmaceutical industry. Unnatural α-amino acids also have a prominent position in the development of new pharmaceutical products. It has been shown that substitution of natural α-amino acids for unnatural amino acids can often impart significant improvements in physical, chemical and biological properties such as resistance to proteolytic breakdown, stability, bioavailability, and efficacy. One of the many synthetic methods available for the production of enantiomerically enriched α-amino acids is the metal-catalyzed enantioselective reduction of α-dehydroamino acid derivatives [90].

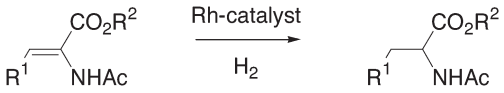
The parent DuPhos and BPE ligands exhibit excellent enantioselectivities routinely in excess of 95% with the majority of model α-dehydroamino acid substrates (Table 24.1) [4a, 8, 12, 13, 20, 90]. High molar SCRs (in the order of >1000 : 1), as well as TOFs in excess of 1000 h^{-1}, are indicative of the high catalyst activity and productivity typically found with DuPhos and BPE systems with these simple substrates. Burk reported that in the enantiomeric hydrogenation

of MAA and MAC, with alkyl-DuPhos–Rh catalysts, optimal enantioselectivity could be achieved with the *n*-Pr-DuPhos ligand over other alkyl DuPhos or BPE ligands [13]. Cationic rhodium catalysts derived from Ph-BPE, the first aryl member of the diphospholane ligand class, are reported to be significantly more reactive and selective than the analogous alkyl-BPE ligands in the hydrogenation of various model substrates [34]. Experimental and computational mechanistic studies using Me-DuPhos-Ir and Me-DuPhos–Rh respectively revealed that an "anti-lock and key" reaction pathway also operates with DuPhos; consequently, the facial selectivity of the more reactive minor diastereoisomer is the source of enantioselectivity in the final product [91–93]. A small number of experimental and theoretical investigations of the use of DuPhos–Rh catalysts in supercritical CO_2 have been reported, with some notable differences with standard substrates being observed [39, 94].

The mannitol-derived phospholane systems from Zhang, Rajanbabu and Börner (ligands **22–27**, **31–33**) have been extensively tested with model substrates. In general, these ligands have been shown to hydrogenate a similar range of simple α-dehydroamino acid substrates to DuPhos and BPE, and are able to replicate their high enantioselectivities and reactivities. Furthermore, despite the further elaboration of the phospholane ring systems of several of the mannitol ligands, the stereochemical outcome of the reported reactions is identical to that of DuPhos and BPE ligands with the same spatial arrangement. As expected, the diastereomeric hydroxylated ligands (*S*,*S*,*S*,*S*)-**25** and (*R*,*S*,*S*,*R*)-**27** gave the opposite sense of stereoinduction in the hydrogenation of MAA with ee-values of >99% (*S*) and 97% (*R*) respectively. This indicates that the spatial orientation of the 2,5-positions of the phospholane is the principal factor in defining the stereochemical outcome of MAA hydrogenation. Interestingly, the ketal variants (*S*,*S*,*S*,*S*)-**24** and (*R*,*S*,*S*,*R*)-**26** showed a more marked difference in the hydrogenation of MAA, with ee-values of 90.5% (*S*) and 97.4% (*R*), respectively [53 b]. Zhang's mannitol-derived ferrocenyl phospholane Me-f-KetalPhos system facilitates the hydrogenation of MAA in 99.4% ee [54], whereas the parent Me- and Et-5-Fc ligands achieve only 64 and 83% ee, respectively [30]. Zhang has gone on to show that the hydrogenation of an extensive range of simple aromatic, substituted aromatic and heteroaromatic β-substituted α-dehydroamino acid systems can be achieved with his mannitol-derived systems with excellent enantioselectivity, albeit it under standard screening conditions and typically with high catalyst loadings [52 b]. Börner and co-workers noted that the significant degree of structural variation possible within the BASPHOS ligand family imparts a greater degree of substrate sensitivity than their DuPhos and BPE counterparts, and thus results in more variable enantioselectivities over a wide range of simple substrates [56 b].

UlluPHOS [43, 44], catASium M [48, 95], Kephos [45, 96] and Butiphane [97] – four ligand systems which possess larger P–Rh–P bite angles than DuPhos [44, 46, 97] – all achieved enantioselectivities >95% when used in the hydrogenation of some model substrates. Much importance has been attached to P–Rh–P bite angles larger than the parent DuPhos system. It is believed that the pos-

Table 24.1 Phospholanes reported to hydrogenate model α-dehydroamino acid derivatives in >95% ee.



68 $R^1 = H$, $R^2 = Me$ **69** $R^1 = H$, $R^2 = H$
70 $R^1 = Ph$, $R^2 = Me$ **71** $R^1 = Ph$, $R^2 = H$

Substrate	Ligand	SCR	Reaction conditions [a]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
68	(*S*,*S*)-Me-DuPhos [b]	1000	MeOH, 20 °C, 2 atm, 1 h	1000	>1000	99	13, 27
68	(*S*,*S*)-Et-BPE [b]	1000	MeOH, 20 °C, 2 atm, 1 h	1000	>1000	98	13 ,27
68	(*R*,*R*)-Ph-BPE	5000	MeOH, 25 °C, 9.9 atm, 1 h	5000	–	>99	34
68	(*R*,*R*)-Me–**16**	1000	MeOH, rt, 2 atm, 1–16 h	1000	–	95	24
68	(R,S_p,S_p,R)-Bn-**35** [b]	100	MeOH, rt, 2 atm, 15 min	100	>400	98 (*S*)	59b
68	(*R*,*R*)-UlluPHOS	1000	MeOH, 27 °C, 2.8 atm, 1 h	1000	>1000	98 (*S*)	43, 44
68	(*S*,*S*,*S*,*S*)-Me-**25** [b]	100	MeOH, rt, 3 atm, 9 h	100	–	98 (*S*)	52a,b
68	(*R*,*S*,*S*,*R*)-**26**	100	MeOH, rt, 2.8 atm, 7 h [c]	–	–	97 (*R*)	53b
68	(*S*,*S*,*S*,*S*)-Me-f-Ketal-Phos	10000	THF, rt, 3 atm, 12 h	10000	833	99 (*S*)	54
68	(*R*,*R*,*S*,*S*)-DuanPhos	10000	MeOH, rt, 1.4 atm, 2 h	10000	5000	99 (*R*)	70
68	(*S*,*S*)-DiSquareP*	100	MeOH, rt, 1 atm, 1 h	100	100	99	87b
69	(*R*,*R*)-H-Ph-BASPHOS	–	H_2O	–	–	>99 (*S*)	56a
69	(R,S_p,S_p,R)-Bn-**35** [b]	100	MeOH, rt, 2 atm, 15 min	100	>400	97 (*S*)	59b
69	(*S*,*S*,*S*,*S*)-Me-**25**	100	MeOH, rt, 3 atm, 9 h	100	–	>99 (*S*)	52a,b
69	(*R*,*R*)-Me-**67**	1000	MeOH, 20 °C, 1.1 atm, 24 h	1000	–	97 (*R*)	89
70	(*R*,*R*)-Ph-BPE	3000	MeOH, 28 °C, 10 atm, 1.25 h	3000	>2400	99	34
70	(*R*,*R*)-*n*-Pr-DuPhos [b]	1000	MeOH, 20 °C, 2 atm, 1 h	1000	>1000	99	13, 27
70	(*R*,*R*)-Me–**16**	1000	MeOH, rt, 2 atm, 1–16 h	1000	–	98	24
70	(+)-*i*-Pr-BeePHOS	200	MeOH, 30 °C, 4 atm, 14–16 h	200	–	98	75
70	(*R*,*R*,*R*)-DuPHAMIN	100	Toluene, 20 °C, 5 atm, 12 h [f]	95	7.9	96	66
70	(*R*,*R*)-Me-Ph-BASPHOS [b]	100	MeOH, 25 °C, 1 atm, 15 min	100	400	99 (*S*)	56b,e

Table 24.1 (continued)

Substrate	Ligand	SCR	Reaction conditions [a]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
70	(*R*,*R*)-Bn-Et-BASPHOS	100	MeOH, 25 °C, 1 atm, 5 h	100	20	96 (*S*)	56b
70	(R,S_p,S_p,R)-Bn-**35** [b]	100	MeOH, rt, 2 atm, 15 min	100	>400	95 (*S*)	59b
70	(*R*,*R*)-*cis*-PMP5	1000	MeOH, rt, 1.5 atm, 2 h [e]	750	375	98 (*S*)	76b
70	(*S*,*S*,*S*,*S*)-Me-**25**	100	MeOH, rt, 3 atm, 12 h	100	–	>99 (*S*)	52a
70	(*S*,*S*,*S*,*S*)-Et-**25**	100	MeOH, rt, 3 atm, 12 h	100	–	>99 (*S*)	52b
70	(*S*,*S*,*S*,*S*)-*t*-Bu-Rophos **23** [b]	100	MeOH, rt, 1 atm, 2 h [d]	50	25	98 (*S*)	53b
70	(*S*,*S*,*S*,*S*)-Bn-Rophos **22**	100	MeOH, rt, 1 atm, 48 min [d]	50	63	96 (*S*)	53b
70	(*S*,*S*,*S*,*S*)-Me-f-Ketal-Phos	100	THF, rt, 1 atm, 1 h	100	–	99 (*S*)	54
70	[(*R*,*R*)-catASium M	200	THF, 25 °C, 1.5 atm, 2 h	200	100	96 (*R*)	48, 95
70	(*S*,*S*)-Me-Kephos	1000	MeOH, rt, 1 atm	1000	300	97	45, 96
70	(*R*,*R*)-Et-Butiphane	1000	MeOH, rt, 1 atm	1000	550	99	97
70	(*R*,*R*)-**14**	100	MeOH, 20 °C, 1 atm, 24 min	100	250	93 (*S*)	33
70	(*S*,*S*,*R*,*R*)-TangPhos	10000	MeOH, rt, 1.4 atm	10000	–	>99 (*R*)	69
70	(*R*,*R*,*S*,*S*)-DuanPhos	100	MeOH, rt, 1.4 atm, 12 h	100	–	99 (*R*)	70
70	(*S*,*S*)-**62**	1000	MeOH, 20 °C, 2 atm, 1 h [c]	–	–	96	87a
70	(*R*,*R*)-Me-FerroTANE	100	MeOH, 50 °C, 1 atm, 24 h [c]	–	–	96 (*R*)	83d
70	(*S*,*S*)-DiSquareP*	50000	MeOH, rt, 6 atm, 43 h	50000	1163	99	87b
71	(*R*,*R*)-Me-DuPhos	1000	EtOH, 27 °C, 2 atm, 1 h	1000	>1000	95 (*S*)	44
71	(R,S_p,S_p,R)-Bn-**35**	100	MeOH, rt, 2 atm, 15 min	100	>400	96 (*S*)	59b
71	(*R*,*R*)-UlluPHOS	1000	EtOH, 27 °C, 2 atm, 1 h	1000	>1000	99 (*S*)	43, 44
71	(*S*,*S*,*S*,*S*)-Me-**25** [b]	244	MeOH, rt, 1.3 atm, 20 h	244	–	99 (*S*)	52, 55
71	(*S*,*S*,*S*,*S*)-Et-**25**	100	MeOH, rt, 3 atm, 12 h	100	–	>99 (*S*)	52b, 55

Table 24.1 (continued)

Substrate	Ligand	SCR	Reaction conditions [a)]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
71	(*S*,*S*,*S*,*S*)-*t*-Bu-Rophos **23** [b)]	100	MeOH, rt, 1 atm, 2 h [d)]	50	26	97 (*S*)	51
71	(*S*,*S*,*R*,*R*)-TangPhos	100	MeOH, rt, 1.4 atm, 12 h [c)]	–	–	99 (*R*)	69

a) Complete conversion unless otherwise stated.
b) Similar high enantioselectivities have also been obtained with several other ligands of this class.
c) No conversion given.
d) 50% conversion.
e) 75% conversion.
f) 95% conversion.

session of a wider P–Rh–P angle places the substrate in closer proximity to the metal, resulting in a more intimate contact between the substrate and catalyst, which could impart a greater degree of selectivity. However, this potentially oversimplifies the differences in performance of certain ligands in enantioselective hydrogenations. It is likely that the outcome of enantiomeric hydrogenations is governed by a variety of stereoelectronic factors, as well as reaction parameters such as pressure, temperature, and solvent. Sannicolo et al. have studied the reaction rates of Me-DuPhos and UlluPHOS in the hydrogenation of 2-acetamidocinnamic acid under identical conditions. The resulting kinetic rate data revealed that the UlluPHOS–Rh catalyst hydrogenated the substrate more quickly than the Me-DuPhos catalyst, with $k_{\text{UlluPHOS}}/k_{\text{Me-DuPhos}} = 7.73$; this was in part attributed to the greater electron density of the thiophene-based ligand [44]. Et-Butiphane and Me-Kephos both hydrogenated MAC in high enantioselectivity, with SCRs of 1000:1; however, the respective TOFs of 550 and 300 h^{-1} were somewhat lower than the value of >2400 h^{-1} reported for the Ph-BPE ligand at a SCR of 3000:1 and with the same substrate under near-identical conditions [35, 96, 97]. Pringle's 1,2-diphospholano-cyclopentane ligand **16** can be synthesized as both λ and δ conformers, though only the δ conformer is reported to achieve high enantioselectivities [24]. The corresponding λ conformer achieves enantioselectivities approximately 20% lower than the δ conformer, indicating a strong matching/mismatching effect between the chirality of the phospholane rings and chiral backbone.

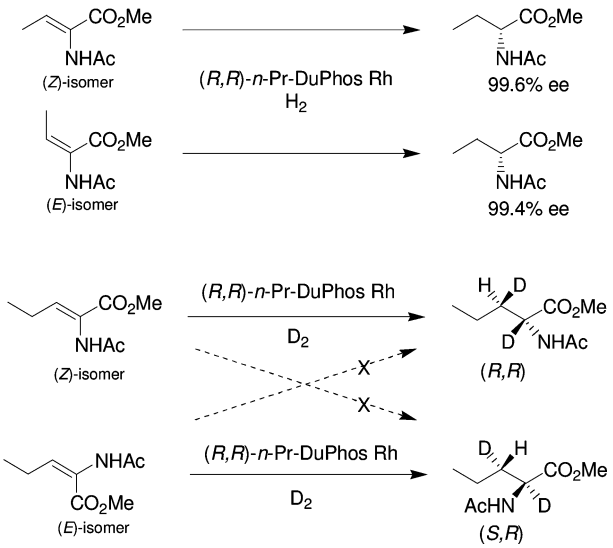
The non-*trans*-2,5-disubstituted phospholanes from Hoge (**35**), Takasago (BeePHOS family) and Zhang (TangPhos and DuanPhos) are all capable of achieving high enantioselectivities with standard α-dehydroamino acid substrates (see Table 24.1) Hoge's 1,2-phenylene system (**35**) generally gave higher enantioselectivities with model substrates than its related 1,2-ethylene system (**36**) [59c]. Takasago's BeePHOS family showed variable performance when hydrogenating MAC in that the ee-values ranged from 47 to 98% [75]. Zhang demonstrated

that both the TangPhos and DuanPhos systems are able of performing hydrogenations with high enantioselectivities at economical catalyst loadings [69, 70]. In comparison to other non-*trans*-2,5-disubstituted phospholanes, only TangPhos so far has shown broad applicability akin to DuPhos and BPE. Moreover, Hoge's mono-substituted **35** and Takasago's BeePHOS show better utility with other substrate classes.

Monophospholanes or bidentate ligands containing a single phospholane moiety have also been successfully applied in the hydrogenation of standard α-dehydroamino acid substrates, though they have not yet been shown to be useful beyond the standard substrates. Remarkably, Fiaud's monophospholane **14** achieves 93% ee with MAC, whereas the bidentate monophospholano ligands (*R,R,R*)-DuPHAMIN (**42**) [66] and (*R,R*)-*cis*-PMP5 (**51**) [76b] hydrogenate MAC in 96% and 98% ee, respectively. Unsurprisingly, the TOFs for DuPHAMIN are too low to be of industrial use. Other related bidentate-monophospholane systems (**37–41**, **43**, **52**, **54–56**) have generally been found to give moderate to low ee-values with model substrates under normal screening conditions [7, 62, 65, 75, 77, 80].

Standard α-dehydroamino acid substrates have been hydrogenated in high enantioselectivities by phosphetanes and phosphinanes. Imamoto's phosphetanes **62** and DiSquareP* (**63**) achieve excellent enantioselectivities; furthermore, DiSquareP*achieves a SCR of 50000:1 with MAC, indicating exceptional catalyst productivity and stability [87]. The ferrocenyl system (*R,R*)-Me-FerroTANE hydrogenates MAC in 96% ee [83d]. Other phosphetanes, such as Genêt's Cy-BPE-4, *i*-Pr-CnrPHOS [83a], Berens' monophosphetanes [82b] or Takasago's IPT-SEGPHOS [50] have to date been found to give only moderate enantioselectivities with model substrates. Helmchen's bidentate oxa-phosphinane **67**, remarkably hydrogenates 2-acetamidoacrylic acid in 97.4% ee, while several analogous mono-oxa-phosphinanes have demonstrated high enantioselectivity (>90% ee) in the reduction of MAC and are currently the only reported examples of chiral phosphinanes which are highly selective [89].

β-Substituted α-dehydroamino acids are frequently synthesized as mixtures of (*E*/*Z*)-isomers [90], and several studies have shown that the geometry of β-substituted α-dehydroamino acid substrates can have a profound effect on both enantioselectivity and hydrogenation rates [98]. In some exceptional cases the opposite enantiomer can be produced when hydrogenating the (*E*) or (*Z*)-olefin with a single catalyst enantiomer [99]. Burk demonstrated, in a series of experiments using *n*-Pr-DuPhos–Rh with the isomerically pure (*E*) and (*Z*)-methyl-2-acetamido-2-butenoate, that both geometrical isomers of the alkene could be hydrogenated with almost identical high enantioselectivity and the same sense of facial selectivity regardless of the alkene geometry (see Scheme 24.6). Deuterium-labeling studies of the reduction of methyl 2-acetamido-2-pentenoate showed that the origin of the DuPhos–Rh catalysts' high enantioselectivity with (*E*/*Z*)-α-dehydroamino acid mixtures was not the result of alkene isomerization [13]. Reduction of (*E*) and (*Z*)-isomers of methyl 2-acetamido-2-pentenoate with D_2 and *n*-Pr-DuPhos–Rh gave rise to diastereomerically pure isotopomers

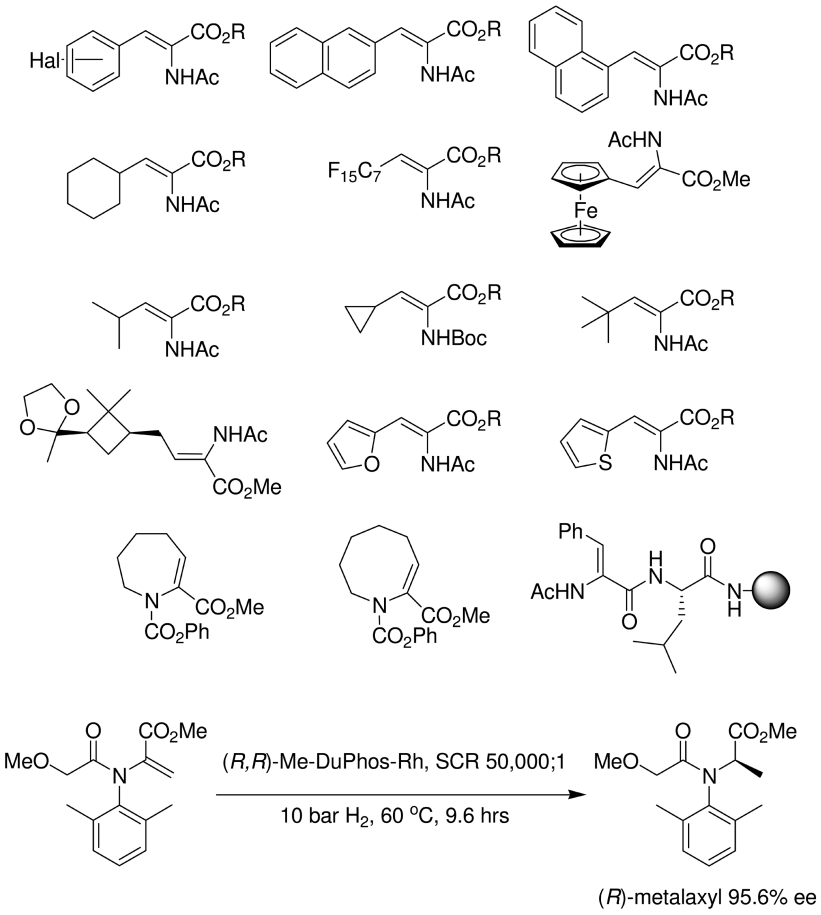


Scheme 24.6 Hydrogenation of (*E*) and (*Z*)-α-dehydroamino acid derivatives.

which, together with a 1 : 1 ratio of deuterium incorporation in the α and β-positions, excludes an (*E*/*Z*)-isomerization mechanism.

The synthetic utility of phospholane-derived catalysts has been directly extended to a broad range of simple, non-standard α-dehydroamino acid substrates, with enantioselectivities in excess of >95% ee being readily achieved [20, 100–107] (Scheme 24.7). The commercially available anti-fungicide (*R*)-metalaxyl has a MAA-related structure, and in a study by Blaser et al. conducted to assess the viability of an enantioselective hydrogenation approach to the active ingredient, the Me-DuPhos–Rh system produced the desired α-amino acid in high enantioselectivity (95.6% ee) and with extremely high productivity and activity (TON 50 000; TOF 5200 h^{-1}) [108, 109]. Some simple phenoxycarbonyl-protected cyclic α-dehydroamino acid substrates have been hydrogenated. In the case of five- and six-membered systems only low or modest enantioselectivities could be obtained, whereas seven-, eight-, nine-, thirteen-, and sixteen-atom ring systems gave 86 to 97% ee [110]. It has also been shown that even a polymer-supported dehydrophenylalanine substrate is readily hydrogenated by Me-DuPhos–Rh with high ee and de values [111].

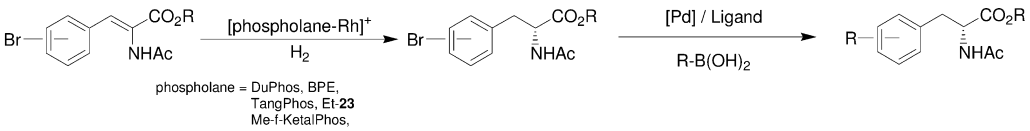
Tandem processes consisting of enantioselective hydrogenation and cross-coupling have been shown to provide a useful approach for generating a diverse range of substituted aromatic α-amino acids, the corresponding α-dehydroamino acid precursors of which are not easily prepared (Scheme 24.8). Burk and Hruby have exploited the ability of DuPhos–Rh catalysts to hydrogenate various halogen- and boronic acid-substituted β-aromatic and β-heteroaromatic α-dehydroamino acids with high enantiomeric excesses. The resulting aromatic halides or boronic acids can be coupled with a variety of vinyl, aryl, and heteroaryl-groups

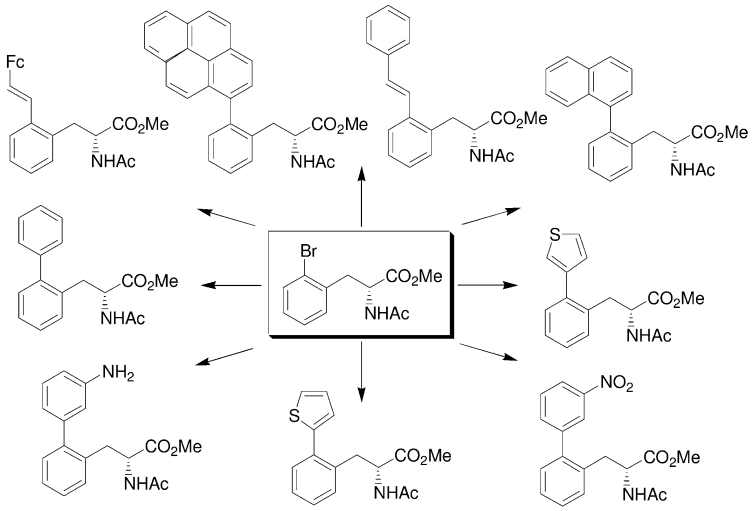


Scheme 24.7 Non-standard α-dehydroamino acid derivatives reduced by Rh-phospholane-based catalysts.

to produce a diverse range of new unnatural α-amino acids [20, 90, 100, 112–114]. Hruby has used this approach to great effect to generate a number of novel χ^2-constrained α-amino acids [112, 114].

A further key factor in the success of phospholane-derived catalysts is their ability to hydrogenate a variety of α-dehydroamino acids possessing functional groups, which in theory could either inhibit or adversely interfere with the selectivity of a hydrogenation process or, indeed, themselves be hydrogenated. These include strongly donating groups (e.g., heteroatoms, heterocycles, sulfides) or unsaturated groups (e.g., olefinic, ketonic and nitro groups). A large number of heteroaryl-α-amino acids have been prepared via asymmetric hydrogenation with chiral phospholane-modified catalysts. Zhang et al. reported that TangPhos and Et-**25** have been used in the preparation of a 2-thiophenylalanine





Scheme 24.8 Unnatural amino-acid derivatives accessed via tandem catalysis.

derivative in >99% ee at low pressure, without interference from the thiophene moiety [52b, 69a]. However, DuPhos, in particular, has been applied most extensively in this field. Simple thiophenyl [4a, 13, 20, 100, 115], furanyl [4a, 20, 100, 115], pyrroyl [115], pyrrolidyl [116], coumaryl [117] and a diverse range of tryptophanyl-α-amino acids [113, 114, 118–120] have all been synthesized with high enantioselectivities by means of enantiomeric hydrogenation of the requisite α-dehydroamino acids (see Fig. 24.8). In a number of cases, prolonged reaction times and molar catalysts loadings in the range of 1 to 3% were required to effect complete conversion. Moody generated di- and tri-peptide fragments of stephanotic acid using Et-DuPhos–Rh in the key asymmetric step [119]. In a remarkable piece of work, Carlier demonstrated that all five unnatural regioisomers of tryptophan derivatives could be accessed via enantioselective hydrogenation of the requisite α-dehydroamino acids with Et-DuPhos–Rh, and in no less than 96.7% ee in each case [118]. Substantially more complex and highly functionalized tryptophanyl-substrates have been prepared by Feldman et al. (Fig. 24.8), albeit with low enantioselectivities [121].

Pyridyl- and quinolyl-substrates are significantly more challenging to hydrogenate, due to the greater donating power of the nitrogen in these systems and, in general, modified hydrogenation protocols are necessary. A 2-quinolyl-alanine derivative was prepared by enantioselective hydrogenation with [Et-DuPhos–Rh]$^+$, in the presence of HBF_4, as the N-protonated species in 94% ee (see

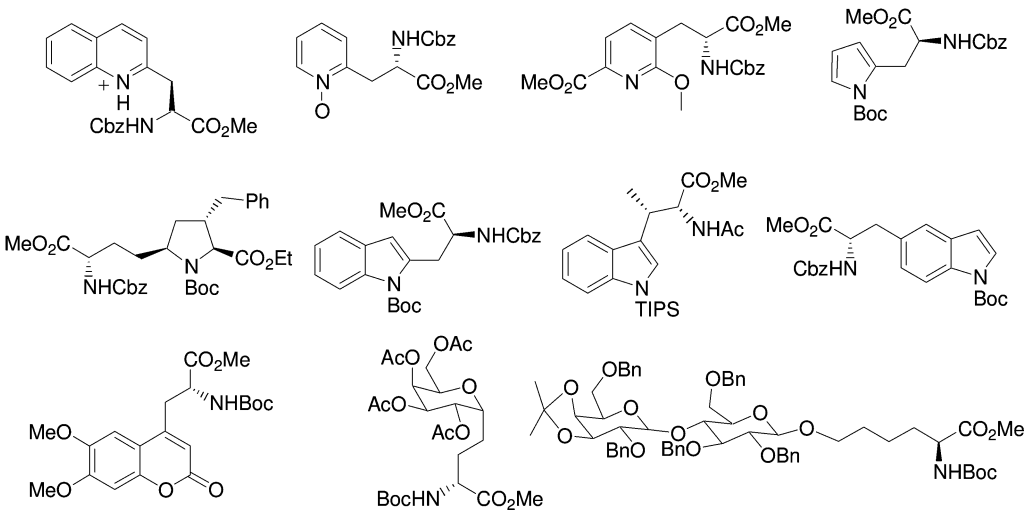


Fig. 24.8 Heteroalanines, tryptophan derivatives and glycosylated α-amino acid derivatives.

Fig. 24.8) [122]. Whilst this protocol can be used to prepare 3-pyridyl-alanine derivatives [22], the corresponding 2-pyridyl-alanine cannot be made [122]. However, Adamczyk has prepared several 2-pyridyl-alanine analogues through hydrogenation of the pyridine-*N*-oxide substrates in 80–83% ee (see Fig. 24.8) [123]. In general, only when the 2- and 6-positions of the pyridine ring are occupied can 2-, 3- or 4-pyridyl-alanine derivatives be prepared, without nitrogen modification, via hydrogenation with [phospholane–Rh]$^+$ catalysts [122–124].

Numerous examples exist of simple heteroatom-substituted substrates which have been hydrogenated by [phospholane–Rh]$^+$ including, amongst others, sulfide substrates [13,14], (*E*/*Z*)-isomers of *N*,*N*′-protected 2,3-diaminopropanoic and 2,3-diaminobutanoic acid derivatives [125], ε-NO_2-substituted α-dehydroamino acid [126], 4-piperidinylglycine precursor [127], and a ketonic substrate [14]. Heavily functionalized glycosylated α-amino acid derivatives have also been prepared using DuPhos–Rh catalysts [128]. Diastereoisomers of structurally complex and functionalized dipeptides have been prepared by Ortuño; a matching/mismatching effect is clear between the chiral substrate and the respective catalyst enantiomers, where (*R*,*R*)-Et-DuPhos–Rh gave >99% de and (*S*,*S*)-Et-DuPhos–Rh resulted in only 90% de, though the distal ketone moiety was not reduced [129].

A number of di- and tri-α-dehydroamino acid substrates have been shown to be hydrogenated in high ee and de with DuPhos–Rh catalysts, despite the potential for the initial chiral centers formed to interfere in subsequent stereodiscriminating steps [122,130] (Fig. 24.9). Interestingly, a number of these substrates are orthogonally protected at the acid or the amide functional groups, which is apparently not a barrier to high ee- and de-values [130a–d]. Hruby used this approach to synthesize a series of novel rigid dipeptide β-turn mimetics via the reduction of symmetrical di-α-dehydroamino acids [131].

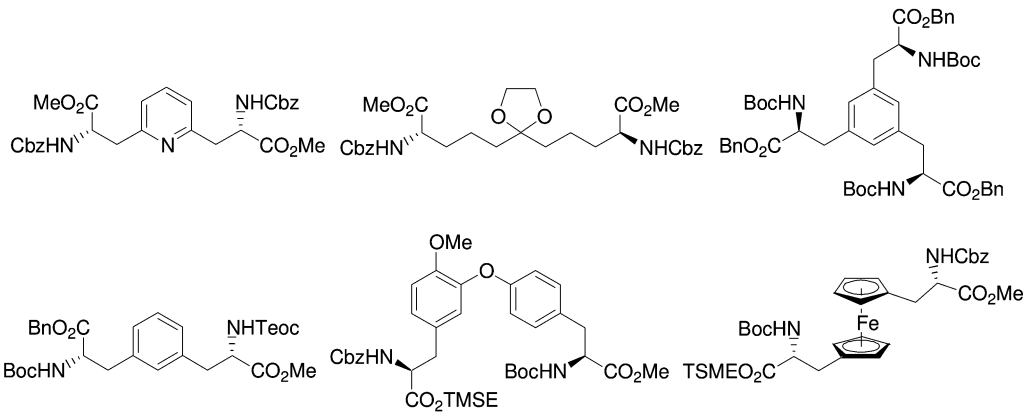
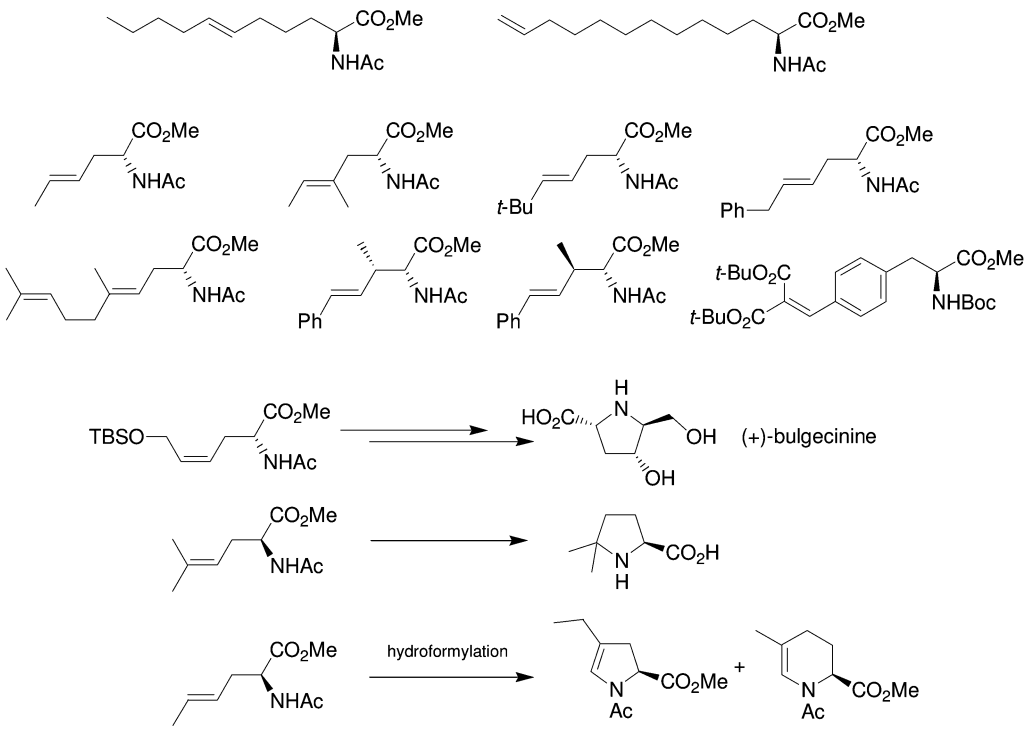


Fig. 24.9 Di and tri α-amino acid derivatives.

Phospholane-modified catalysts have shown the ability to discriminate between olefinic bonds in conjugated/nonconjugated β- and β,β-disubstituted α-didehydroamino acids, in both a highly regio- and enantioselective fashion [13, 90, 132, 133] (Scheme 24.9). The latter group involves the hydrogenation of tetrasubstituted alkenes with concomitant formation of two stereogenic centers. In general, the more reactive functionalized enamide bond is selectively reduced over simple unfunctionalized bonds. However, over-reduction can be observed, particularly when the reaction times are prolonged, as in the case of highly substituted olefins or in reactions near completion and the reduction of the distal bond becomes more favorable [132]. Over-reduction can be tempered by careful monitoring of the hydrogen uptake, solvent screening, lowering the hydrogen pressure, and reducing catalyst loadings [132, 133].

The choice of catalyst can have a significant effect on enantioselectivity and, in certain cases, the regioselectivity and activity. With nonconjugated α-didehydroamino acids, such as 2-acetamido-trideca-2,7-dienoic acid methyl ester or 2-acetamido-tetradeca-2,13-dienoic acid methyl ester, the proximal olefin is easily reduced at low catalyst loading with *n*-Pr-DuPhos–Rh in >99% ee and essentially complete regioselectivity [13]. However, in the case of conjugated α-didehydroamino acids, such as the 2-acetamido-6-(*tert*-butyl-dimethyl-silanyloxy)-hexa-2,4-dienoic acid methyl ester, the wrong choice of catalyst can lead to significant undesired over-reduction. 2-Acetamido-6-(*tert*-butyl-dimethyl-silanyloxy)-hexa-2,4-dienoic acid methyl ester can be hydrogenated in high ee and regioselectivity with Et-DuPhos–Rh (>99% ee and <0.5% over-reduction), whereas *i*-Pr-DuPhos–Rh gives only 87.8% ee and demonstrated little or no regioselectivity [133]. It has generally been observed that the DuPhos– and BPE–Rh systems can reduce tri-substituted $\alpha,\beta,\gamma.\delta$-didehydroamino acids with a remarkable degree of chemoselectivity in all but a few cases studied. Where the distal C=C bond is also activated to a certain extent, as in the case of styryl-dienamides, the degree of over-reduction is routinely <2%.



Scheme 24.9 Unsaturated α-amino acid derivatives prepared via chemoselective asymmetric hydrogenation.

In cases where the proximal double bond is highly substituted, such as tetrasubstituted α-didehydroamino acids, selective reduction of the proximal double bond becomes increasingly difficult. Burk found, with a series of β,β-disubstituted $\alpha,\beta,\gamma,\delta$-didehydroamino acids, that only the smaller, sterically less-congested catalysts Me-BPE–Rh and Me-DuPhos–Rh were able to achieve high reactivity and selectivities [132]. The overall lower reactivity of these highly substituted systems generally requires higher catalyst loadings and more forcing conditions to achieve high or full conversions. In many cases complete conversion could not be achieved, and over-reduction approached 10%. Reduction of the (2*Z*,4*E*)-isomers in comparison to the (2*E*,4*E*)-dienamides has also been studied; unsurprisingly, the (2*Z*,4*E*)-isomer is more readily reduced in contrast to the (2*E*,4*E*)-dienamides.

The reduction of dienamides with [phospholane–Rh]$^+$ catalysts has been applied in the synthesis of a number of biologically interesting targets (Scheme 24.9). Burk and co-workers synthesized (+)-bulgecinine from 2-acetamido-6-(*tert*-butyl-dimethyl-silanyloxy)-hexa-2,4-dienoic acid methyl ester utilizing [(*R*,*R*)-Et-DuPhos–Rh]$^+$ [133], while Boehringer Ingelheim used (*R*,*R*,*S*,*S*)-TangPhos–Rh and (*S*,*S*)-Et-DuPhos–Rh to generate key intermediates in protease inhibitors [134], and 5,5-dimethylproline has been generated using (*S*,*S*)-Et-DuPhos–Rh

[135]. Garbay reported the chemoselective reduction of a α-dehydrophenylalanine substrate bearing a *p*-acrylate moiety [105]. Robinson et al. have also used a tandem, one-pot asymmetric hydrogenation-hydroformylation-cyclization approach to generate six- to eight-membered cyclic α-amino acids [136].

The enantioselective hydrogenation of β,β-disubstituted α-dehydroamino acids by means of [diphosphine-Metal]$^+$ catalysts is challenging in terms of enantioselectivity, chemoselectivity (*vide supra*), and reactivity. Few ligand systems have been tested with β,β-disubstituted substrates, and the reported results indicate that variable ee-values and high catalyst loadings are commonplace for many of the [diphosphine-Metal]$^+$ systems with tetrasubstituted olefins [137]. However, DuPhos and BPE catalysts demonstrate the capacity to consistently hydrogenate a wide range of β,β-disubstituted α-dehydroamino acid substrates with excellent ee-values and industrially applicable loadings [14, 20, 39, 90, 125, 138] (Fig. 24.10). Furthermore, the ability to hydrogenate (*E*) or (*Z*) α-dehydroamino acids with high enantioselectivity means that, with dissimilar substituents, two stereogenic centers can be created with high enantio- and diastereoselectivity when the (*E*) and (*Z*) α-dehydroamino acid is hydrogenated with both catalyst enantiomers.

In the majority of cases reported, optimal stereoselectivity and reactivity in sterically congested tetrasubstituted alkenes can be achieved with sterically less cumbersome Me-DuPhos and Me-BPE ligands. This is most graphically highlighted with the model substrate 2-acetamido-3-methyl-but-2-enoic acid methyl ester, where both Me-BPE and Me-DuPhos–Rh catalysts hydrogenate the substrate in >95% ee, whereas Et-DuPhos achieves 74% ee, *n*-Pr-DuPhos 45% ee, and *i*-Pr-DuPhos merely 14% ee [14]. This trend has been found over a broad range of substrates [14, 132], although there are some exceptional cases where Et-DuPhos–Rh achieves high enantio- and diastereoselectivity [39, 138]. Burk also made the observation that benzene was the optimal solvent for the majority of cases, however supercritical CO_2 ($scCO_2$) has also been shown to be a suitable medium for the enantioselective hydrogenation of β,β-disubstituted α-dehydroamino acids [39]. Zhang's phospholane catalyst Me-f-KetalPhos–Rh hydrogenated the model substrate 2-acetamido-3-methyl-but-2-enoic acid methyl

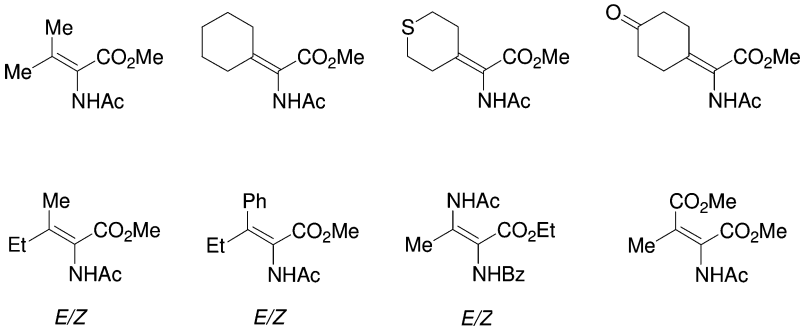


Fig. 24.10 β,β-disubstituted α-dehydroamino acid derivatives.

ester in 87.3% ee, whereas the phosphetanes DiSquareP* [87b], *i*-Pr-CnrPHOS, and Cy-BPE-4 [83a] have been shown to give only low to moderate ee-values with a few model substrates. (*S*,*S*)-*i*-Pr-CnrPHOS–Rh demonstrated a remarkable inversion of facial selectivity with 2-acetamido-3-phenyl-but-2-enoic acid methyl ester, giving the (2*S*,3*R*)-product in 38% ee at 10 bar H_2 and the (2*R*,3*S*)-isomer in 80% ee at 100 bar H_2.

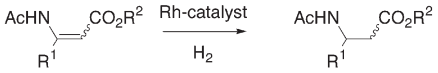
Several biologically interesting targets have been synthesized via phospholane–Rh catalyzed hydrogenation of *β*,*β*-disubstituted *α*-dehydroamino acid substrates, including all four diastereoisomers of *N*,*N*′-protected 2,3-diaminobutanoic acid derivatives [125] (*vide supra*), a 4-piperidinylglycine derivative used as metalloproteinase and thrombin inhibitors (*vide supra*) [127a], as well as a sterically congested *β*-methyltryptophan derivative [120].

24.3.2
Enantioselective Hydrogenation of *β*-Dehydroamino Acid Derivatives

Enantiomerically pure *β*-amino acids and their derivatives are an important class of compounds due to of their use as chiral building blocks in the synthesis of both biologically active molecules [139] and novel peptidomimetics [140]. Their incorporation is partly a result of the unusual secondary structures they can create, and also because they are frequently resistant to proteolysis. Currently, the principal methods used for their preparation involve chiral auxiliaries in stoichiometric reactions and to a lesser extent enantioselective catalysis [141]. One of the most promising and industrially viable methodologies involves the enantiomeric hydrogenation of an appropriate *β*-dehydroamino acid derivative with a homogeneous metal catalyst [142]. Owing to its simplicity, this approach has seen rapid development in recent years, with the most successful catalysts typically being Rh and Ru complexes containing phosphorus-based ligands, including several diphospholanes. The most selective examples (>95% ee), achieved with the most commonly used *β*-dehydroamino acid-derived substrates (R^1 = Me or Ph), are collected in Table 24.2, together with several results useful for comparison purposes.

As can be seen from Table 24.2, these rhodium catalysts are in general extremely active under very mild reaction conditions (H_2 pressure 1–20 atm, room temperature), albeit at catalyst loadings typical of screening studies (SCR 100). Although rare exceptions are known [143], the hydrogenation of (*E*)-*β*-dehydroamino acid esters generally proceeds with considerably higher enantioselectivity than the corresponding (*Z*)-isomers. It is worth mentioning, however, that Rh-TangPhos is reported to perform remarkably well against either stereoisomer [69b, 71]. This is important since in the synthesis of dehydroamino acids, the (*E*/*Z*)-isomeric mixtures obtained can be difficult to separate, especially in the case of *β*-aryl substitution [71, 143, 148]. Furthermore, the (*Z*)-isomer is predominantly formed due to stabilizing hydrogen bonds [149]. Whether or not this additional bonding retards coordination to the metal center and concomitantly lowers selectivity is arguable, especially in protic media. However, use of the

Table 24.2 Phospholanes reported to hydrogenate model β-dehydroamino acid derivatives in >95% ee.



72 R^1 = Me, R^2 = Et
73 R^1 = Me, R^2 = Me
74 R^1 = Ph, R^2 = Et
75 R^1 = Ph, R^2 = Me

Substrate	Ligand	SCR	Reaction conditions [a]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
(*E*)-**72**	(*R,R*)-Me-DuPhos	100	Toluene, rt, 2.7 atm, 24 h [c]	100	–	99	143
(*Z*)-**72**	(*R,R*)-Me-DuPhos	100	Toluene, rt, 20 atm, 24 h [c]	100	–	88	143
(*E*)-**72**	(*S,S*)-Et-DuPhos	100	THF, 25 °C, 2 atm, 1 h [c]	100	–	99	144
(*Z*)-**72**	(*S,S*)-Et-DuPhos	100	THF, 25 °C, 2 atm, 1 h [c]	100	–	89	144
(*E*)-**72**	(*R,R*)-*i*-Pr-DuPhos	100	TFE, rt, 9.7 atm, <2 min	100	>3000	99	145
(Z)-**72**	(*R,R*)-*i*-Pr-DuPhos	100	TFE, rt, 9.7 atm, <2 min	100	>3000	92	145
(*E/Z*)-**72**	(*R,R*)-*i*-Pr-DuPhos	1000	TFE, rt, 9.7 atm, 40 min	1000	1500	95	145
(*E*)-**72**	(*R,R*)-Et-BPE	100	THF, 40 °C, 2 atm, 1 h [c]	100	–	99	144
(*Z*)-**72**	(*R,R*)-Et-BPE	100	THF, 40 °C, 2 atm, 1 h [c]	100	–	90	144
(*E*)-**72**	(*R,R,S,S*)-DuanPhos	100	MeOH, rt, 1.4 atm [b]	–	–	99 (*R*)	70
(*Z*)-**72**	(*R,R,S,S*)-DuanPhos	100	MeOH, rt, 1.4 atm [b]	–	–	97 (*R*)	70
(*E*)-**73**	(*R,R*)-Me-DuPhos	100	Toluene, rt, 2.7 atm, 24 h [c]	100	–	99	143
(*Z*)-**73**	(*R,R*)-Me-DuPhos	100	Toluene, rt, 2.7 atm, 24 h [c]	100	–	64	143
(*E*)-**73**	(*S,S*)-Me-DuPhos	100	MeOH, 25 °C, 1 atm, 1 h [c]	100	–	98	146a
(*Z*)-**73**	(*S,S*)-Me-DuPhos	100	MeOH, 25 °C, 1 atm, 1 h [c]	100	–	88	146a
(*E*)-**73**	(*S,S*)-Et-DuPhos	100	MeOH, 25 °C, 1 atm [b]	100	–	98	146
(*Z*)-**73**	(*S,S*)-Et-DuPhos	100	MeOH, 25 °C, 1 atm [b]	100	–	88	146
(*E/Z*)-**73**	(*S,S*)-Et-DuPhos	100	MeOH, 25 °C, 1 atm [b]	100	–	92	146
(*E*)-**73**	(*R,R*)-Et-DuPhos	100	THF, 40 °C, 2 atm, 1 h [c]	100	–	95	144
(*Z*)-**73**	(*R,R*)-Et-DuPhos	100	THF, 40 °C, 2 atm, 1 h [c]	100	–	86	144

Table 24.2 (continued)

Substrate	Ligand	SCR	Reaction conditions [a]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
(*E*)-**73**	(*R*,*R*)-Et-BPE	100	THF, 40 °C, 2 atm, 1 h [c]	100	–	98	144
(*Z*)-**73**	(*R*,*R*)-Et-BPE	100	THF, 40 °C, 2 atm, 1 h [c]	100	–	82	144
(*E*)-**73**	(*R*,*R*)-Me-Ph-BASPHOS	100	MeOH, 25 °C, 1 atm [b]	100	–	99 (*S*)	56b
(*Z*)-**73**	(*R*,*R*)-Me-Ph-BASPHOS	100	MeOH, 25 °C, 1 atm [b]	100	–	70 (*S*)	56b
(*E*)-**73**	(S,R_p,S,R_p)-**36**	100	THF, rt, 1.4 atm, 5 min	100	1200	96 (*R*)	59c
(*Z*)-**73**	(S,R_p,S,R_p)-**36**	100	THF, rt, 1.4 atm, 45 min	100	133	89 (*R*)	59c
(*E*)-**73**	(R,S_p,S_p,R)-**35**	100	THF, rt, 1.4 atm, 15 min	100	400	96 (*S*)	59c
(*Z*)-**73**	(R,S_p,S_p,R)-**35**	100	THF, rt, 1.4 atm, 1 h 15 min	100	80	83 (*S*)	59c
(*E*)-**73**	(*R*,*R*)-catASium M	100	MeOH, 25 °C, 1 atm, 3 h [c]	100	–	98 (*R*)	95
(*Z*)-**73**	(*R*,*R*)-catASium M	100	MeOH, 25 °C, 1 atm, 3 h [c]	100	–	83 (*R*)	95
(*E*)-**73**	(*R*,*R*)-Et-FerroTANE	100	MeOH, 25 °C, 1 atm [b]	100	–	99 (*S*)	56d, 147
(*Z*)-**73**	(*R*,*R*)-Et-FerroTANE	100	MeOH, 25 °C, 1 atm [b]	100	–	28 (*S*)	56d, 147
(*E*)-**73**	(*S*,*S*,*R*,*R*)-TangPhos	200	THF, rt, 1.4 atm, 24 h [c]	200	–	>99	69b, 71
(*Z*)-**73**	(*S*,*S*,*R*,*R*)-TangPhos	200	THF, rt, 1.4 atm, 24 h [c]	200	–	99	69b, 71
(*E*/*Z*)-**73**	(*S*,*S*,*R*,*R*)-TangPhos	200	THF, rt, 1.4 atm, 24 h [c]	200	–	>99	69b, 71
(*Z*)-**73**	(*S*)-Me-Butiphane	200	MeOH, 25 °C, 5 atm [b]	200	–	98	42
(*E*)-**74**	(*R*,*R*)-Et-FerroTANE	100	MeOH, 25 °C, 1 atm [b]	100	–	99 (*S*)	56d, 147
(*E*)-**75**	(*R*,*R*)-Et-FerroTANE	100	MeOH, 25 °C, 1 atm [b]	100	–	99 (*S*)	56d, 147
(*E*/*Z*)-**75**	(*S*,*S*,*R*,*R*)-TangPhos	200	THF, rt, 1.4 atm, 24 h [c]	–	–	94 (*S*)	69b, 71

a) Complete conversion unless otherwise stated.
b) No reaction time given.
c) No conversion given

strongly polar solvent 2,2,2-trifluoroethanol (TFE) had a beneficial effect on enantioselectivities when a Rh-*i*-Pr-DuPhos catalyst was applied [145]. Limited solvent studies have been performed with a number of phospholane-based ligand systems [65, 71, 143, 146a], but in general alcoholic solvents are the most suitable, together with tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2).

Several accounts have described (*Z*)-dehydroamino acid esters as being less active than the corresponding (*E*)-isomer [59c, 143–145]. In fact, Bruneau and Demonchaux reported that when reduction of an (*E/Z*)-mixture of **73** with Rh-Et-DuPhos in THF was not complete, only unreacted (*Z*)-**73** was detected. These findings conflict, however, with results obtained in MeOH [56d], where the ligand structure was also found to be significant to the relative reactivity of each stereoisomer. As for *α*-dehydroamino acid derivatives, preformed metal–diphosphine complexes generally perform in superior fashion to those prepared *in situ* [56d].

Zhang et al. reported that for Rh-catalyzed enantiomeric hydrogenation with either BICP or Me-DuPhos, the (*Z*)-isomers were generally less reactive, and required higher pressures for complete conversion [143]. Enantioselectivities for the (*E*)-isomer were shown to be unaffected by increased pressure. On the other hand, Heller and co-workers showed that operating at low hydrogen pressures in a polar solvent had a significantly beneficial effect on enantioselectivities when hydrogenating (*Z*)-**73** with [Et-DuPhos Rh(COD)]BF_4 (e.g., 35% ee at 45 atm and 87% ee at 1 atm), albeit at the expense of reaction rates [146a]. This was also found to be the case with several other ligand systems [56d]. In light of these findings, a tentative mechanistic concept has been proposed which provides evidence that the reaction proceeds via an "unsaturated route" with the prochiral olefin coordinating to the metal center prior to oxidative addition of hydrogen [150].

In general, the same sense of chiral induction is obtained with either geometrical stereoisomer, which facilitates the use of (*E/Z*)-isomeric mixtures. An exception to this was recently reported by Heller and Börner [56d]. Remarkably, hydrogenation of methyl (*Z*)-*β*-acetylamino pentenoate with [(*S,S*)-Et-DuPhosRh(COD)]BF_4 at 1 bar gave the (*R*)-enantiomer of product in 31% ee, whereas the same reaction at 30 bar resulted in an inversion of configuration and the (*S*)-product in 77% ee.

The effects of temperature on enantioselectivities have been examined using a Rh-Et-DuPhos catalyst in both MeOH [56d] and THF [144]. With *β*-dehydroamino acid derivative **73** in MeOH, an increase in temperature was found to have a slight beneficial effect for both (*E*) and (*Z*)-isomers over a 70 °C range, with maximum values being observed between 0 °C and 25 °C. In THF, however, the effect is much more pronounced, especially for the (*Z*)-isomer which varies in selectivity from 65% ee at 10 °C to 86% ee at 25 °C. Interestingly, when substrate **72** was reduced with a Rh-Et-BPE catalyst in THF, this temperature dependence on enantioselectivity for the (*Z*)-isomer was most apparent, the selectivities varying from 43% ee (10 °C) to 90% ee (40 °C). Examination of these results also seemed to indicate that the hydrogenation of *β*-dehydroamino acid derivatives follows an unsaturated pathway (*vide supra*) [144].

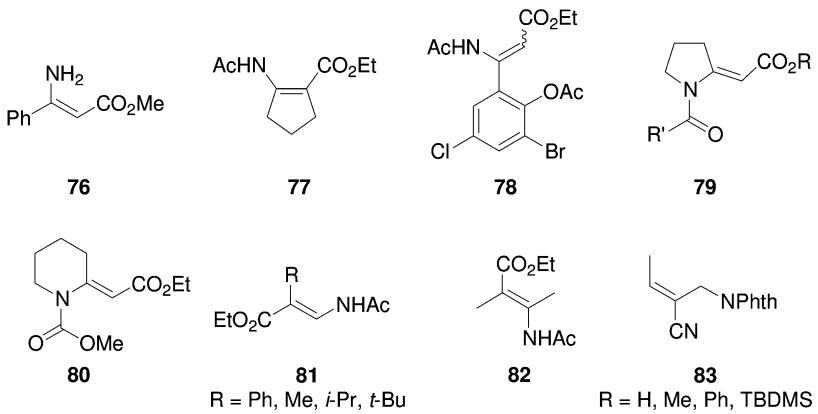


Fig. 24.11 Unusual β-dehydroamino acid derivatives to have been reduced with phospholane-based catalysts.

Several phospholane-based ligands have shown a wide substrate scope beyond the standard examples represented in Table 24.2. Both Et-FerroTANE **61** [147] and TangPhos **46** [69b, 71] have been successfully applied to a diverse range of methyl and ethyl β-aryl-dehydroamino acids containing various aromatic substituents, whilst catASium M **20a** [95] has been used for the reduction of numerous β-alkyl-dehydroamino acid esters.

In addition to the standard substrates described above, the enantioselective hydrogenations of several other β-dehydroamino acid derivatives using phospholane-based or related ligands are worthy of note (Fig. 24.11). Using TFE as solvent, a screen of commercially available catalysts showed that the unprotected β-dehydroamino acid ester (*Z*)-**76** could be partially reduced (77% conversion) in 88% ee with [(*R*,*R*)-Et-FerroTANE Rh(COD)]BF_4, but ultimately, an *in-situ*-prepared Rh-Josiphos-type catalyst gave superior results [151]. Interestingly, preliminary deuterium-labeling studies suggested that the hydrogenation of (*Z*)-**76** proceeds through the imine tautomer in an analogous fashion to β-ketoester hydrogenations. Enantioselective reduction of the tetrasubstituted cyclic β-dehydroamino acid ester (*E*)-**77** was recently reported by Zhang et al., and although both *in-situ*-prepared Ru catalysts of Me-DuPhos and TangPhos were found to give complete conversion (SCR 20) in moderate enantioselectivities (71% ee and 57% ee, respectively), atropisomeric biaryl-based ligands were more selective (e.g., C2- to C5-TunePhos all gave 99% ee) [152].

As one of several routes investigated for the preparation of a key intermediate for a $\alpha_v\beta_3$ integrin antagonist, the enantiomeric hydrogenation of olefin **78** was examined [153]. Despite investigating several different catalysts under multiple reaction conditions on various derivatives of **78**, a viable method was not forthcoming. The best result obtained was 70% ee with [(*S*,*S*)-Et-DuPhos Rh(COD)]OTf in CH_2Cl_2 at 5 atm H_2. Lee and co-workers examined the enantioselective synthesis of homoproline derivatives via Rh-catalyzed reduction of the cyclic substrate (*E*)-**79**

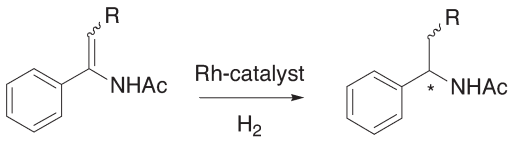
with a range of different ligands [154]. Although, (*R*,*R*)-Me-DuPhos was the most selective (>99% ee (*R*)), the conversion was only 37%. The chiral bidentate phosphine Me-BDMI proved to be the overall ligand of choice. Reduction of the structurally related *β*-dehydroamino acid ester (*E*)-**80** was recently described in a patent by Solvay, with [(*R*,*R*)-Me-DuPhos Rh(COD)]OTf giving complete conversion to the (*R*)-product in 95.5% ee (5 atm H_2, 25 °C, SCR 100) [155].

Finally, an interesting variation on the standard substitution pattern shown above is the regioisomeric β^2-amino acids, the substituent being *α* to the carboxylic functionality. Two approaches for their synthesis, which adopts enantiomeric hydrogenation with a phospholane-based ligand, have been described. Robinson, Jackson and colleagues reported the preparation of a range of substrates of type (*E*)-**81** and subsequent Rh-catalyzed enantioselective hydrogenation with either Me or Et-DuPhos and Me-BPE. Through modification of the amide group, the ligand and the solvent, moderate enantioselectivities up to 67% ee where attainable [156]. The *α*,*β*-disubstituted *β*-dehydroamino acid ester (*E*)-**82** was also examined with BPE and DuPhos catalyst systems; Rh-Me-BPE was the most selective, giving complete conversion in 65% ee over 72 h in benzene (4 atm, room temperature). An alternative approach to β^2-amino acids was also explored through the reduction of *α*,*β*-unsaturated nitriles **83**, again using Rh-Me-BPE or Rh-Et-DuPhos catalysts (up to 48% ee), and the amino acids being obtained after hydrolysis and phthalimide deprotection [157]. Conversion of the nitrile to the corresponding methyl ester and switching to a Ru-BINAP-based system increased the enantioselectivities to 84% ee.

24.3.3 Enantioselective Hydrogenation of Enamides

Chiral amines constitute an important class of compounds that have been extensively employed as resolving agents, chiral auxiliaries, and pharmaceutical intermediates. Traditionally, classical resolution or biocatalysis have been typically chosen as the preferred methods for industrial manufacturing, though the enantioselective hydrogenation of enamides or imines (*vide infra*) has recently received much attention, with several phospholane-based ligands proving to be applicable. Table 24.3 details the most selective phospholanes (≥95% ee) to have been used in the Rh-catalyzed hydrogenation of frequently used simple enamides, namely *N*-(1-phenyl-vinyl)-acetamide **84** and *N*-(1-phenyl-propenyl)-acetamide **85**. In general, the conditions employed are mild, with high reactivities being observed at low temperatures and pressures. For example, TONs as high as 5000 to 10 000 have been achieved with Ph-BPE **15** [34] or the P-chiral phospholane, TangPhos **46** [69]. In the case of the *β*-branched enamide **85**, (*S*,*S*,*R*,*R*)-DiSquareP* **63** has been reported to be extremely selective for reduction of the (*E*)-isomer (>99% ee), but with the enantioselectivity being much lower for the corresponding (*Z*)-isomer (37% ee) [87b]. However, this is not the case for the diphospholanes BPE and TangPhos, with excellent levels of selectivity being obtained even when an (*E*/*Z*)-isomeric mixture is applied.

Table 24.3 Phospholanes reported to hydrogenate model enamide substrates in >95% ee.



84 R = H
85 R = Me

Substrate	Ligand	SCR	Reaction conditions [a)]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
84	(*S,S,R,R*)-DiSquareP*	100	MeOH, rt, 1 atm, 1 h	100	>100	>99 (*R*)	87b
84	(*S,S,S,S*)-Et-**16**	100	MeOH, rt, 10 atm, 24 h	100	–	96 (*S*)	52b, c
84	(*R,R*)-Me-Ph-UCAP	100	MeOH, rt, 5 atm, 3 h	100	>33	94 (*R*)	65, 67
84	(*S,S,R,R*)-TangPhos	10000	MeOH, rt, 1.4 atm [d)]	10000	–	99 (*R*)	69
84	(*R,R,S,S*)-DuanPhos	100	MeOH, rt, 1.4 atm [d)]	10000	–	>99 (*R*)	70
84	(*R,R*)-Ph-BPE	5000	MeOH, 25 °C, 10 atm [d]	5000	–	99	34
84	(*R,R*)-Me-BPE	500	MeOH, 22 °C, 4 atm, 15 h	500	>33	95	17
(*E*)-**85**	(*S,S,R,R*)-DiSquareP*	100	MeOH, rt, 1 atm, 1 h	100	>100	>99 (*R*)	87b
(*Z*)-**85**	(*S,S,R,R*)-DiSquareP*	100	MeOH, rt, 2 atm, 1 h	100	>100	37 (*R*)	87b
(*Z*)-**85** [c)]	(*S,S*)-Me-DTBM-UCAP	500	MeOH, 30 °C, 4 atm, 15 h	500	>33	99 (*S*)	64
(*E/Z*)-**85**	(*S,S,R,R*)-TangPhos	100	MeOH, rt, 1.4 atm, 12 h	100	–	98 (*R*)	69
(*E/Z*)-**85**	(*R,R*)-Me-BPE	100	MeOH, rt, 1.4 atm, 12 h	100	–	95 (*R*)	17

a) Complete conversion unless otherwise stated.
b) Similar high enantioselectivities have also been obtained with several other ligands of this class.
c) *N*-benzoyl instead of *N*-acetyl.
d) No reaction time given.

In addition to these simple model substrates, several phospholane-containing ligands have shown broad functional group tolerance when applied to the Rh-catalyzed hydrogenation of aromatically substituted α-arylenamides. Burk et al. reported the use of DuPhos and BPE ligands for the reduction of α-arylenamides containing alkyl, halogen, thio, alkoxy, aromatic, and heteroaromatic substituents, commenting that the enantioselectivities tended to increase with decreasing steric demand of the phospholane moiety at the 2,5-positions [17]. This was later extended to include esters, ketones and cyano groups, showing that these systems are also chemoselective [35]. Similar levels of tolerance have been demonstrated, with several phospholanic ligands originating from the group of Zhang, including the tetrahydroxy diphosphine **25** (R = Me) [52b, 53b], TangPhos [69] and, to a lesser

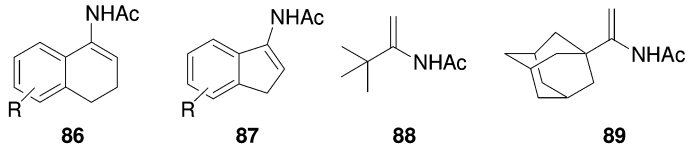


Fig. 24.12 General enamide classes to have been reduced with phospholane-based catalysts.

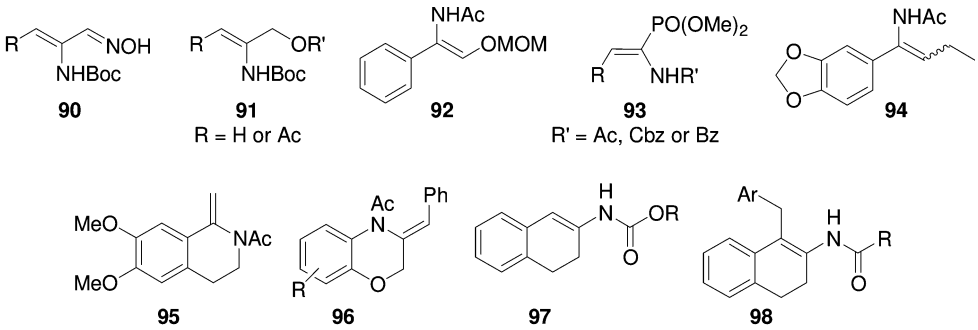


Fig. 24.13 Unusual enamides to have been reduced with phospholane-based catalysts.

extent, DuanPhos [70]. The effective hydrogenation of (*Z*)-**85** and the *N*-benzoyl analogue were independently reported by Pringle [65] and Saito [64] respectively, using a range of unsymmetrical diphosphines, UCAPs **41**.

Both (*S,S*)-Me-BPE [19] and (*R,S,R,S*)-Me-PennPhos **44** [67d,e] have been successfully applied to the Rh-catalyzed hydrogenation of a range of cyclic enamides derived from α-tetralones and α-indolones (**86** and **87**). Under mild conditions, both ligands achieved good to excellent enantioselectivities (71–99% ee), with PennPhos giving reasonable levels of catalyst reactivity (TON up to 2000; TOF $\sim 100\ h^{-1}$), even for tetra-substituted enamides. Interestingly, PennPhos gives lower selectivities for acyclic enamides when compared to BPE catalysts, whereas BPE requires lower temperatures to attain high enantioselectivities with cyclic enamides (e.g., 71% ee at 20 °C and 92% ee at 0 °C for unsubstituted **86**).

Alkyl enamides, such as *N*-(1-*tert*-butyl-vinyl)-acetamide **88** and *N*-(1-adamantyl-vinyl)-acetamide **89**, can also be hydrogenated in high enantioselectivity (>99% ee) and activity (TON 5000; TOF $>625\ h^{-1}$) with Rh-Me-DuPhos [19]. Remarkably, these bulky alkyl enamides are reduced with the opposite sense of induction, a phenomenon also observed when the bisphospholane DiSquareP* **63** was applied [87b]. A computational modeling study by Landis and Feldgus suggested that the reduction of α-alkyl and α-arylenamides involves different coordination pathways [93, 158].

In addition to standard cyclic and acyclic enamides, the effective hydrogenation of several more unusual enamides has been reported (Fig. 24.13). A concise method for the synthesis of chiral β-amino alcohols, amino oximes and chiral 1,2-diamines has been described by Burk et al. via the enantioselective hydroge-

nation of **90** or **91** using Rh catalysts of Me or Et-DuPhos [18]. In general, the enantioselectivities were high (91–99% ee), with reactions proceeding smoothly to completion within 12 h at SCR 1000. Zhang and co-workers have reported the hydrogenation of a series of MOM-protected *β*-hydroxy-*α*-arylenamides **92** as a mixture of (*E*/*Z*) isomers [159]. Although BICP–Rh and Me-DuPhos–Rh complexes were both found to be excellent catalysts for this transformation (90–99% ee), Rh-Me-DuPhos displayed higher enantioselectivity over a broader substrate range. Ultimately, the products could be converted to chiral *α*-arylglycinols by *O*-MOM and *N*-acetyl deprotection under acidic conditions. By screening a range of diphosphines, including five phospholane-based ligands, Pagenkopf et al. extended the scope of this reaction to include *o*-alkoxy-substituted enamides [160]. Me-BPE and Me-DuPhos were found to be the most selective ligands (92–98% ee), with better results being achieved with the isolated [(P-P) Rh COD]OTf precatalysts over *in-situ* preparation. The size of the *o*-substituent was not found to have any significant effect on selectivity.

By using a Rh-catalyst containing a ligand from either the DuPhos or BPE family, Burk and co-workers successfully hydrogenated a range of phosphonated enamides **93** (R′ = Ac or Cbz) in moderate to high enantioselectivities (57–95% ee), with aryl-substituted examples giving lower selectivity than alkyl analogues [161]. In contrast to the reduction of several other substrate classes with Rh-DuPhos or Rh-BPE complexes [12, 13, 15, 18, 21], a strong dependence on olefin geometry was observed, with (*E*)-isomers being significantly more selective. Börner and Holz also reported the Rh-catalyzed reduction of a phosphonated enamide **93** (R = Ph, R′ = Bz) with two DuPhos/BPE type ligand systems, Rophos (**22** and **23**) [51a] and BASPHOS (**32** and **33**) [56e]. Although enantioselectivities with Rophos were generally higher than with BASPHOS (up to 99% ee versus 79% ee), activities were slightly lower (TOF 6 h^{-1} versus 25 h^{-1}). The enantioselective hydrogenation of enamide **94** using [(*R*,*R*)-Me-DuPhos Rh(COD)]BF_4 was reported by Storace et al. [162]. This intermediate to the leukocyte elastase inhibitor, DMP 777, was prepared quantitatively in 96.5% ee at SCR 1800 under mild conditions (2 atm, room temperature) in MeOH. Although a single crystallization afforded the optically pure amide in 86% yield and >99% ee, ultimately enantiomeric hydrogenation was not chosen as the preferred method for manufacturing.

As well as endo-cyclic enamides (*vide supra*), phospholane-based Rh catalysts have also been applied to the enantiomeric reduction of exo-cyclic enamides. Zhang reported TangPhos to hydrogenate **95** in 97% ee [69], while Zhou showed Me-DuPhos to be extremely efficient for a broad range of substituted dihydrobenzoxazines **96** (92–99% ee) [163]. Finally, the hydrogenation of a series of trisubstituted ene carbamates **97** and tetrasubstituted enamides **98** was found to be catalyzed by Ru complexes of either Me-DuPhos and Me-BPE [164]. The catalysts were formed *in situ* by reacting the diphosphine with [Ru(COD)(methallyl)$_2$] in the presence of HBF_4 or triflic acid. Notably, the use of atropisomeric ligands, BINAP and BIPHEMP, led to no activity and similarly, hydrogenation did not occur with the more commonly used [(diphosphine)Rh(COD)]BF_4 precatalysts.

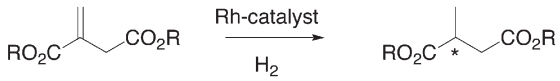
24.3.4
Enantioselective Hydrogenation of Unsaturated Acid and Ester Derivatives

The enantioselective hydrogenation of *α,β*- or *β,γ*-unsaturated acid derivatives and ester substrates including itaconic acids, acrylic acid derivatives, butenolides, and dehydrojasmonates, is a practical and efficient methodology for accessing, amongst others, chiral acids, chiral *α*-hydroxy acids, chiral lactones and chiral amides. These are of particular importance across the pharmaceutical and the "flavors and fragrances" industries.

The enantioselective hydrogenation of itaconic acid derivatives in particular has received much interest; one area of significance is the generation of succinate compounds for use as peptidomimetics [82a]. As indicated in Table 24.4, a variety of phospholanes are suitable ligands for hydrogenating the commonly used model substrates, itaconic acid and its dimethyl ester (DMI), with high enantioselectivities. Moreover, phosphetanes and phosphinanes have demonstrated high enantioselectivities with both substrates. In several cases exceptionally high catalyst activity has been demonstrated; Ph-BPE and catASium M are reported to hydrogenate DMI with TOFs of 60 000 and 40 000 h^{-1}, respectively [34, 47]. Although high enantioselectivities are also reported for the parent itaconic acid substrate, catalyst activities are substantially lower with this substrate in comparison to DMI. Surprisingly, the parent Me-DuPhos ligand is neither particularly selective nor active with the diacid [44], and a number of ligands are reported with superior selectivity and activity. BASPHOS ligands have demonstrated a significant degree of substrate sensitivity with DMI and itaconic acid; enantioselectivities ranging from 8.1% to 97.9% are reported for (*R,R*)-Me-Et-BASPHOS (**33**) and (*R,R*)-Me-Ph-BASPHOS (**32**), respectively [56b]. Pressure and solvent effects have been observed in the hydrogenation of DMI using a catASium M ligand, where higher pressures (7.9 atm) and CH_2Cl_2 as solvent gave superior results [46–48]. Itaconic acid has been hydrogenated by **25** in various MeOH/H_2O mixtures, ranging from 9 : 1 to 3 : 97, without variance or loss of enantioselectivity. The three-carbon bridged tridentate ligand (*S,S*)-Me-**11** hydrogenated DMI in 94% ee, albeit with protracted reaction times, whereas the related bidentate ligand (*R,R*)-Me-**7** surprisingly gave only 78% ee [11]. Remarkably, Corma et al. have reported the first use Me-DuPhos-based Pt and Au catalysts for the reduction of simple itaconic acid derivatives in high enantioselectivity (3 to 95% ee) and extremely high rates (TOF up to 10 200 h^{-1}) [166]. Unfortunately, these high activities were achieved at the expense of selectivity.

β-Substituted and *β,β*-disubstituted itaconic acid substrates, generated via the Stobbe condensation and resulting in mono 1-esters, provide a more structurally diverse and challenging set of substrates. Currently, only DuPhos, BPE and – to a lesser extent TangPhos and catASium M – have been shown to achieve high enantioselectivities across this broad range of itaconate substrates (Fig. 24.14). The (*E*/*Z*)-mixtures typically formed in Stobbe condensations can be tolerated by phospholane-based catalysts without loss of performance [21, 72]. Performing itaconate hydrogenations at temperatures of around 0 °C has been found to be

Table 24.4 Phospholanes reported to hydrogenate model itaconic acid substrates in >95% ee.



99 R = Me
100 R = H

Substrate	Ligand	SCR	Reaction conditions [a]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
99	(*S*,*S*)-Et-DuPhos	1000	MeOH, 20 °C, 5.4 atm, 2.8 h	1000	– [b]	>97 (*R*)	21
99	(*R*,*R*)-Et-BPE	1000	MeOH, 20 °C, 5.4 atm, 1 h	1000	1000	97 (*R*)	34
99	(*R*,*R*)-Ph-BPE	10000	MeOH, 28 °C, 9.9 atm, 10 min	10000	60000	99 (*R*)	34
99	(*R*,*R*)-Me-Ph-BASPHOS	100	MeOH, 28 °C, 1 atm, 3 h	100	33.3	97 (*R*)	56b
99	(*R*,*R*)-UlluPHOS	1000	MeOH, 27 °C, 2 atm, 2.8 h	1000	–	>99 (*S*)	44
99	(*R*,*R*)-Me-DuPhos	1000	MeOH, 27 °C, 2 atm, 2.8 h	1000	–	>99 (*S*)	44
99	(*S*,*S*,*S*,*S*)-*t*-Bu-**23**	100	MeOH, rt, 1 atm, 8 min	50 [c]	375	99 (*R*)	51
99	(*S*,*S*,*S*,*S*)-Bn-**22**	100	MeOH, rt, 1 atm, 28 min	50 [c]	107	98 (*R*)	51
99	catASium M	– [a]	CH_2Cl_2, 25 °C, 7.9 atm, 15 min	10000	40000	99	47
99	(*S*,*S*,*R*,*R*)-TangPhos	5000	THF, rt, 1.4 atm	5000	– [b]	99 (*S*)	72
99	(*R*,*R*,*S*,*S*)-DuanPhos	100	THF, rt, 1.4 atm	–	– [b]	99 (*S*)	70
99	(*Rp*,*Rc*,*R*,*R*)-**54**	100	MeOH, 25 °C, 1 atm, 1 h	100	100	>99 (*S*)	80
99	(*R*,*R*)-Et-FerroTANE	200	MeOH, 25 °C, 5.4 atm, 1 h	200	>200	98 (*S*)	82, 83
99	(*S*,*S*)-*n*-Pr-FerroTANE	200	MeOH, 20 °C, 5.4 atm, 1 h	200	>200	97 (*R*)	82, 83
100	(*S*,*S*)-Et-DuPhos	100	MeOH, rt, 17.8 atm, 2 h	95 [d]	47.5	96 (*R*)	165
100	(*R*,*R*)-Me-Ph-BASPHOS	100	MeOH, 25 °C, 1 atm, 20 min	100	300	97 (*R*)	56b
100	(*R*,*R*)-*cis*-PMP5	1000	MeOH, rt, 1.5 atm, 2 h	998 [c]	499	97 (*R*)	76b
100	(*S*,*S*,*S*,*S*)-Me-**25**	192	MeOH, rt, 1.3 atm, 20 h	192	–	>99 (*R*)	55
100	(*S*,*S*,*S*,*S*)-Bn-**23**	100	MeOH, rt, 1 atm, 24 min	50	125	98 (*R*)	51
100	(*S*,*S*,*S*,*S*)- Bn-**22**	100	MeOH, rt, 1 atm, 10 min	50	300	98 (*R*)	51
100	(*S*,*S*,*S*,*S*)-**31**	100	MeOH, rt, 5.4 atm, 12 h	100	8.3	>99 (*R*)	54

Table 24.4 (continued)

Substrate	Ligand	SCR	Reaction conditions [a)]	TON	TOF [h^{-1}]	% ee (config.)	Reference(s)
100	catASium M	–[a)]	MeOH, 25 °C, 3.9 atm, 3 h	500	–[b)]	97	47
100	(*S,S,R,R*)-TangPhos	200	THF, rt, 1.4 atm	–	–[b)]	99 (*S*)	72
100	(*R,R*)-*ent*-Cy-**66**	500	*i*-PrOH, 20 °C, 1 atm, 24 h	–	–[b)]	96 (*S*)	89

a) No catalyst loading given.
b) Insufficient data on loading, time or yield to calculate TOF.
c) Reaction not gone to completion.

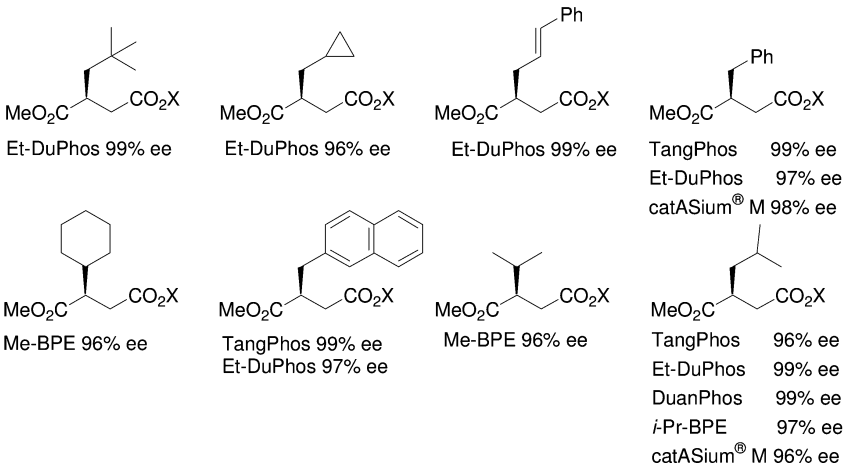


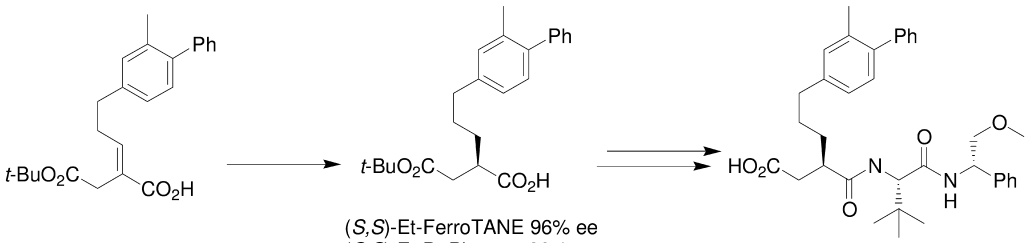
Fig. 24.14 Succinic acid derivatives produced by phospholane–Rh-catalyzed hydrogenation (X=H, Na or R_3NH).

beneficial in terms of enantioselectivity. The nature of the secondary binding group can play a critical role in terms of reaction rates and enantioselectivity with this substrate class; the hydrogenation of 2-isopropylidenesuccinic acid 1-methyl ester with (*R,R*)-Me-BPE at SCR 300:1 gave only 33% conversion and 88% ee, whereas the *tert*-butylamine salt of the acid gave complete conversion at SCR 500:1 with 95% ee under comparable conditions [167]. The use of a salt form is reported to enhance both reactivity and selectivity, enabling industrially viable catalyst loadings of SCR >4000:1 to be readily achieved [21]. Amine and alkali metal salts of itaconic acid are generally employed, though optimal results seem to be best achieved with preformed and purified amine salts [168]. The enhanced performance of the itaconate acid salts is possibly a result of both the enhanced binding ability of the carboxylate group and higher substrate purity.

β,β-Disubstituted itaconic acid substrates require higher catalyst loadings and hydrogen pressures to achieve reasonable reaction rates, which is unsurprising given the level of steric congestion around the olefinic bond. The most effective hydrogenation was attained when using the sterically less cumbersome Me-BPE ligand; indeed, when used in conjunction with substrates as the amine salt, enantioselectivities of 96% could be realized [21].

Inverse itaconate derivatives (4-itaconic acid derivatives) have been studied to a lesser extent than the 1-itaconic acid derivatives. In the limited number of reported hydrogenations of itaconic acid 4-esters, the parent DuPhos ligands have performed poorly with model substrates. For example, in the hydrogenation of itaconic acid 4-methyl ester in MeOH, both Me- and Et-DuPhos gave less than 3% yield and poor to moderate ee-values (41 to 74%) [82c]. However, catASium M is reported to achieve 99% ee and a TOF of 8000 h^{-1} in CH_2Cl_2 with itaconic acid 4-methyl ester [47]. The related Me- and Et-5-Fc ferrocenyl phospholanes hydrogenate itaconic acid 4-methyl ester with complete conversion at SCR 2000:1, though the enantioselectivities remain low at <45% [82c]. FerroTANE based catalysts reduce itaconic acid 4-methyl ester and 2-pentylidene-succinic acid 4-methyl ester in >94% ee at SCRs of between 1000:1 and 2000:1 [82c]. Moreover, a series of 2-alkylsuccinic acids 4-*tert*-butyl ester targets have been generated in high ee using Et-FerroTANE and Et-DuPhos. This approach has been used in synthesizing the MMP-3 inhibitor UK-370,106 101 [169] (Scheme 24.10).

Inverse amido-itaconates also proved to be challenging substrates for phospholane-based catalysts, and only limited success has been achieved to date. 2-Methylenesuccinamic acid (**102**) has been reported to be reduced by Et-DuPhos–Rh in 96% ee at SCR 100 000:1, with an average TOF of 13 000 h^{-1}. The removal of a trace chloride-containing contaminant was found to be crucial in obtaining high enantioselectivities and reaction rates [85]. An isoquinuclidine containing inverse amido-itaconate **103**, which is currently being evaluated in preparations for the treatment of diabetes, has been prepared using Rh-Et-DuPhos in 98.7% ee [170]. Whilst phospholane systems have achieved only moderate success in this substrate class, the FerroTANE family of ligands has been reported broadly to outperform all ligand classes, with superior enantioselectivities

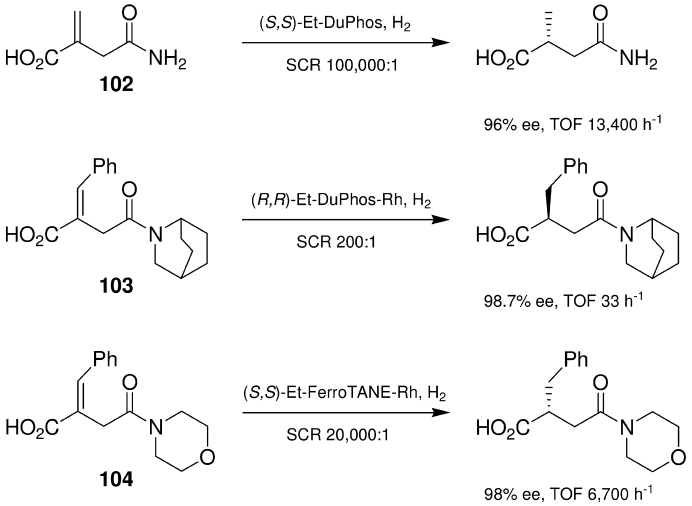


101
UK-370,106

Scheme 24.10 Inverse itaconate approach to a protease inhibitor.

and industrially viable catalyst activities. Burk tested an array of inverse amido-itaconates (e.g., **104**) where both the amide fragment and *β*-substitution on the olefin were varied, and found most enantioselectivities to be >95% with TOFs in the range of 1000 to 6000 h^{-1} when Et-FerroTANE was used as the chiral ligand [82 a, c].

Although the efficient enantioselective reduction of *α,β*-unsaturated acids and lactones is typically achieved using ruthenium-biaryldiphosphine-based catalysts [2], several reports have been made of phospholane-ruthenium, -rhodium and -iridium systems that perform this hydrogenation with comparably high enantioselectivities. Burk has reported that the ubiquitous model substrate for Ru-biaryl-phosphine catalysts, tiglic acid, can been reduced with up to 94% ee with a Ru-*i*-Pr-DuPhos catalyst [27, 171 a, 172 a]. However, the array of substrate structures reported for this class is diverse and bears little similarity to the model substrates (Fig. 24.15). Simple acrylic acid derivatives such as methyl *α*-hydroxymethacrylate and 2-[[(phenylmethoxy)amino]methyl]-2-hexenoic acid methyl ester **105** have been hydrogenated by both Me-DuPhos and TangPhos–Rh catalysts in 90% and 96–98% ee [75, 173]. (*E*)-*β*-methylcinnamates **106** have been reduced using Zhang's mixed phospholane-oxazoline catalyst Ir-**48**, giving results comparable to Pfaltz's established iridium phosphonite-oxazoline systems [74]. Trisubstituted aryl/heteroaryl-sulfonylated acrylic acid derivatives (e.g., **107**) have been hydrogenated in remarkably high enantioselectivities with Me-DuPhos–Rh [174]. A challenging *α*-(*γ*-amino)-*β*-imidazolyl-acrylic acid substrate **108** was reduced using *i*-Pr-5-Fc–Rh in the presence of quinidine to give the target product in high ee using a combined enantioselective hydrogen/classical resolution approach [175]. A series of diastereomeric scaffolds (e.g., **109**) were synthesized from functionalized chiral



Scheme 24.11 Enantioselective reduction of inverse amido-itaconates.

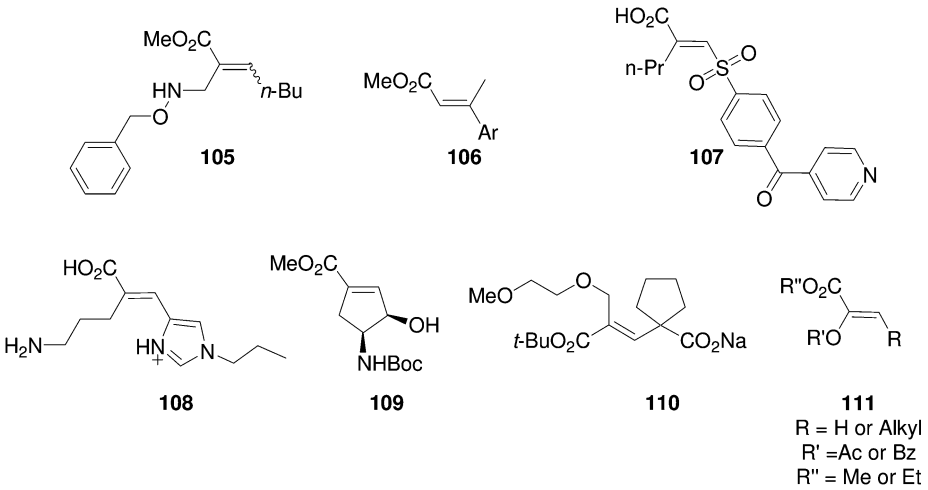
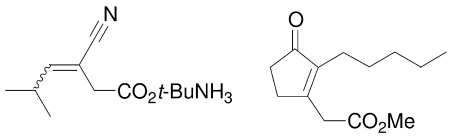


Fig. 24.15 Diverse α,β-unsaturated acid derivatives reduced with phospholane catalysts.

cyclopentene rings bearing an acrylate substructure, while facial selectivity could be controlled via the judicious use of DuPhos or BPE–Rh catalysts or Crabtree's catalyst [176]. Sterically congested α,β-unsaturated lactone substrates (butenolides) bearing potentially inhibiting heterocycles have been hydrogenated with Me-DuPhos–Rh in 80% ee [177]. A key glutarate component **110** in the atrial natriuretic factor (ANF) potentiator Candoxatril has been synthesized in high ee using both a MeDuPhos–Rh and Ph-BPE–Rh catalyst [34, 178]. The use of a Rh-phospholane catalyst circumvented the problem of the generation of unreactive enol ethers as side products, which was a major issue when Ru-BINAP was used [178]. A Penn-Phos–Ru species reduced 3-(*p*-fluorobenzylidene) valerolactam in 70% ee, a target molecule for producing 3-alkylpiperidines as pharmacophores; however, BDPP-Ir was found to be a better system for reducing the *exo*-cyclic olefin [179].

A wide range of α-(acetyloxy)- and α-(benzoyloxy)acrylates **111**, with both alkyl and aryl β-substituents, have been successfully hydrogenated with cationic Rh-DuPhos complexes [180]. In particular, the reduction could be performed on an (*E*/*Z*)-isomeric mixture, with selectivities generally being greater than 97% ee. A brief solvent study showed MeOH, *i*-PrOH, or CH_2Cl_2 to be the best solvents in terms of both catalyst activity and selectivity, and benzene to inhibit the reaction by formation of a stable adduct. Increased hydrogen pressure had a negligible influence on selectivity. Ultimately, the hydrogenation products were converted to enantiomerically enriched α-hydroxy esters and 1,2-diols, without any loss in optical purity. An example of a (*Z*)-α-(phenoxy)-β-alkyl-acrylate has been reported to have been reduced in 86 and 89% ee using Et-FerroTANE–Ru and *i*-Pr-DuPhos–Ru catalysts; Me-f-KetalPhos–Ru, whilst catalytically active, produced an essentially racemic product, and a SynPhos–Ru catalyst proved to be the optimal catalyst screened [181].



112 113

Fig. 24.16 β,γ-unsaturated acids reduced with MeDuPhos–Rh and Ru catalysts.

The hydrogenation of a β,γ-unsaturated acid **112** has been key to the enantioselective synthesis of a potent anticonvulsant (*S*)-(+)-3-aminomethyl-5 methylhexanoic acid, Pregabalin [60, 61] (see Fig. 24.16). (*E*/*Z*)-mixtures of three possible precursors were examined for reactivity and selectivity. The ester substrate was found to be not particularly useful in terms of both reactivity and selectivity towards a number of DuPhos, BPE and FerroTANE catalysts; remarkably, using (*R*,*R*)-Me-DuPhos at room temperature or at 55 °C resulted in a reversal of facial selectivity, albeit with modest enantioselectivities in each case. The *t*-$BuNH_3^+$ and K^+ salts of the acid were found to be superior in both reactivity and enantioselectivity, and whilst both salts performed comparably well, the hydrogenation was optimized using the *t*-$BuNH_3^+$ salt as a result of substrate quality concerns [60]. An optimized procedure using (*R*,*R*)-Me-DuPhos–Rh has been used at the kilogram scale to give the desired product in 97.7% ee at SCR 2700 : 1 and 4.4 atm. Hoge's C_1-symmetric phospholanes (**35** and **36**) are also selective towards this substrate: at low pressure (2 atm) and SCR 100 : 1, **35** was moderately more selective than **36**, giving 96% and 92% ee, respectively. Hoge demonstrated with **36** that high enantioselectivities at lower catalyst loadings could only be achieved with a concomitant increase in H_2 pressure; subsequently, 97% ee could be achieved at 13.5 atm [59a, b, d]. Jasmonoid compounds have indicated numerous phtyobiological activities and olfactory properties, the *cis*-jasmonate compounds being of particular interest to the perfume industry (Fig. 24.16). Direct reduction of the olefinic double bond of dehydrojasmonate **113** via *syn*-addition of H_2 is the most direct route to the *cis*-isomers. However, traditional cationic Rh-phospholanes are not electrophilic enough to hydrogenate the tetrasubstituted double bond. Bergens developed a more electrophilic, coordinatively unsaturated 16-electron cationic ruthenium-hydride-phosphine system that was not only capable of hydrogenating the double bond but, when modified with Me-DuPhos and provided with enantiomeric excesses up to 60% and a >99 : 1 *cis*/*trans* ratio, furnished the desired enantiomerically enriched *cis*-isomer. However, a Josiphos variant operated with better enantioselectivity [182]. It is not clear whether the pendant ester group plays a secondary binding role during the hydrogenation.

24.3.5
Enantioselective Hydrogenation of Unsaturated Alcohol Derivatives

One method of accessing chiral alcohols is through the enantioselective hydrogenation of the corresponding enol acetates. Despite this substrate class having similar structures to enamides, far fewer successful examples of this reaction

have been reported. It has been argued that this may be in part due to the enol acetate having a weaker binding acyl group than the analogous enamide [4c]. Notwithstanding this, Burk was successful in hydrogenating a range of simple α-substituted enol acetates **114** in good to excellent enantioselectivities (89–99% ee) with either Rh-DuPhos or Rh-BPE catalysts [12]. High enantioselectivities have also been obtained when applying Rh-Me-DuPhos for the reduction of 1-alkenyl or 1-alkynyl enol acetates, **115** and **116** [183]. In the case of **116**, the triple bond is reduced to a double bond with (*Z*)-configuration after reduction of the enol acetate. Interestingly, the judicious choice of **115** or **116** as substrate allows access to either (*E*) or (*Z*)-α,β-unsaturated acetates. The analogous saturated straight-chain derivatives were found to hydrogenate smoothly, but with only moderate selectivity (64–77% ee). [Me-DuPhos Rh(COD)]OTf has also been reported to catalyze the hydrogenation of 2-acetyloxy-1,1,1-trifluorododec-2-ene in 92% ee, but higher selectivities were obtained with Ru-based catalysts of atropisomeric biaryl ligands, BINAP and BIPHEMP.

Burk et al. also showed the Rh-complexes of Me and Et-DuPhos to be effective catalysts for the enantioselective reduction of several phosphonated enol acetates of type **117** (86–96% ee with TOF $\sim 10\ h^{-1}$ at 25 °C, 4 atm), providing an efficient route to enantiomerically enriched alkyl-substituted α-hydroxy phosphonites [161]. Remarkably, these catalysts were inactive against an aryl-substituted analogue, and although partial conversion could be obtained with Me-BPE, both the selectivity and reactivity were much lower (70% ee, TOF $1.5\ h^{-1}$). Recently, the research group of Zhang has reported several phospholane-based ligands to be effective for the Rh-catalyzed reduction of acyclic, α-aryl substituted enol esters of type **118** (PennPhos [67c,d], TangPhos [69b, 72], DuanPhos [70] and **48** (R = Me) [52b]). In general, high to excellent enantioselectivities are achieved (81–99% ee) under mild reaction conditions, albeit at high catalyst loadings (SCR 100). The *in-situ*-prepared Rh-PennPhos catalyst [67c,d] has also been applied to the reduction of five- and six-membered cyclic enol acetates, **119** and **120**, derived from substituted 1-indanone and 1-tetralone, respectively.

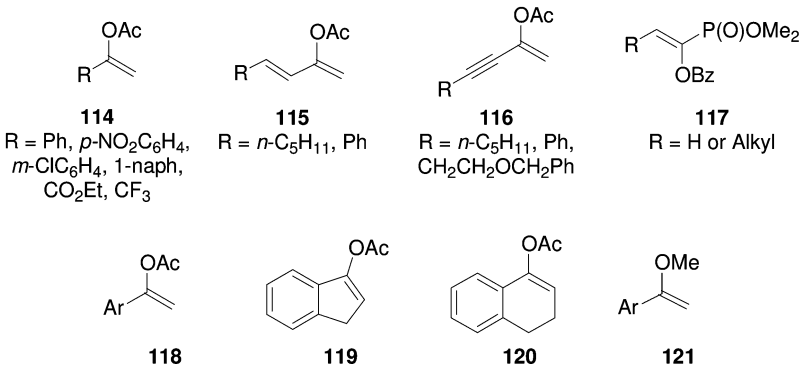
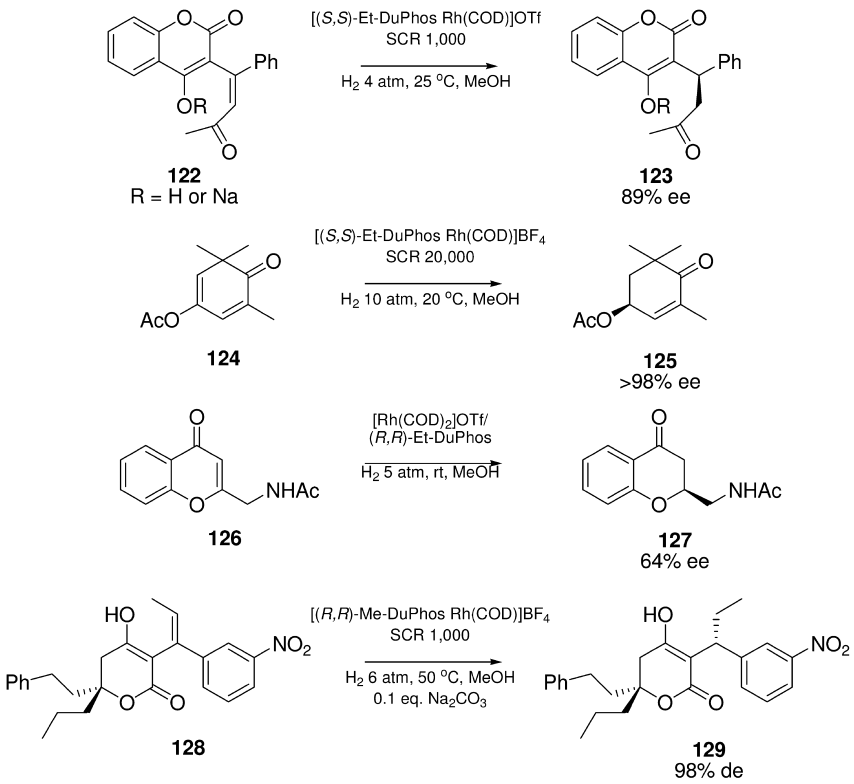


Fig. 24.17 Unsaturated alcohol derivatives to have been reduced by phospholane ligands.



Scheme 24.12 Several pharmaceutically active compounds to have been synthesized via Rh-phospholane-mediated asymmetric hydrogenation.

Catalyst performance was far superior to the corresponding BINAP or Me-DuPhos systems, with both conversions and selectivities being higher. The hydrogenation of enol ethers using Rh-PennPhos catalysts has been reported in a patent by Zhang [67 d]. Under mild conditions, high enantioselectivities were obtained (73–94% ee) for 1-aryl-1-methoxy-ethene derivatives **121**, compared to Me-DuPhos (40–73% ee) and BINAP (46–48% ee).

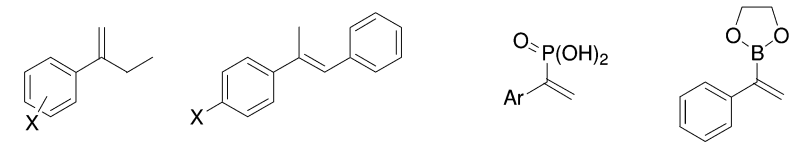
The enantioselective reduction of unsaturated alcohol derivatives has been applied to the synthesis of several biologically active compounds (Scheme 24.12). Warfarin (**123**, R = H) is an important anticoagulant that is normally prescribed as the racemate, despite the enantiomers having dissimilar pharmacological profiles. One of the earliest reported uses of DuPhos was in the development of a chiral switch for this bioactive molecule, facilitating the preparation of (*R*)- and (*S*)-warfarin [184]. Although attempted reduction of the parent hydroxycoumarin **122** (R = H) led to formation of an unreactive cyclic hemiketal, hydrogenation of the sodium salt proceeded smoothly with Rh-Et-DuPhos in 86–89% ee.

Hoffman la Roche have reported the synthesis of an intermediate to zeaxanthin via the enantioselective reduction of cyclic enolacetate **124** [185]. Using a Rh-Et-DuPhos catalyst, excellent levels of selectivity (98% ee) could be obtained at extremely low catalyst loadings (TON 20 000; TOF 5000 h^{-1}). Chroman derivatives, such as **127**, have been reported by Merck to affect the central nervous system [186]. As part of a wide ligand screen, an *in-situ*-prepared Rh-Et-DuPhos complex has been reported to be amongst the most selective for the preparation of **127**, albeit in 64% ee. Finally, an enantioselective approach to **129**, a key intermediate to the HIV protease inhibitor tipranavir (PNU-140710), was developed by Chirotech for Pharmacia & Upjohn [187]. The use of [(*R,R*)-Me-DuPhos–Rh(COD)]BF_4 and Na_2CO_3 as a co-catalyst gave quantitative conversion in 93% de (SCR 1000, 6 atm, 50–60 °C). Once again, (*E/Z*)-mixtures could be tolerated together with high chemoselectivity with regards to over-reduction of the nitro functional group. Both UlluPHOS **18** [43, 44] and catASium M **20a** (A = O, R = Me) [188] have also been applied to this reaction.

24.3.6
Enantioselective Hydrogenation of Miscellaneous C=C Bonds

Through continued exploration of the applicability of enantiomeric hydrogenation, phospholane-based catalysts have been reported to be efficient for the reduction of several atypical olefinic substrates (Fig. 24.18).

Due to the lack of an ordered chelate complex provided by the substrate containing a secondary binding site, the enantioselective reduction of unfunctionalized olefins remains a challenging area where only limited success has been achieved. Noyori et al. reported Me-DuPhos–Ru catalysts to be effective for the hydrogenation of *α*-ethylstyrenes **130** [189]. By activating the precatalyst with an alkoxide base in 2-propanol, respectable enantioselectivities (71–89% ee) and activity (TON up to 2600; TOF 160 h^{-1}) could be obtained under mild reaction conditions. Using the cationic iridium complexes of a class of phospholane-oxazoline ligands, **48**, Zhang and co-workers successfully reduced methylstilbene derivatives **131** in 75–91% ee [74]. These selectivities are comparable to those obtained with the best ligand systems for this substrate class [4b,c, 190]. Although outperformed by biaryl-based ligands such as BINAP, Me-DuPhos has



130 X = H, *p*-Me, *p*-F, *p*-Cl, *p*-Br, *p*-CF_3, *m*-Cl, *m*-Br, *o*-Br

131 X = H, OMe, Cl

132 Ar = Ph, *p*-Me-C_6H_4, 1-Np, *p*-Cl-C_6H_4

133

Fig. 24.18 Unusual olefins to have been reduced with phospholane-based catalysts.

also shown to be active in the Ru-catalyzed reduction of α-aryl-substituted ethylphosphonates **132** (16–37% ee) [191] and ethanediol 1-phenylethenylboronic ester **133** (42% ee) [192].

24.4 Enantioselective Hydrogenation of C=O and C=N Bonds

24.4.1 Enantioselective Hydrogenation of Ketones

The enantioselective hydrogenation of ketones using Rh or Ru diphosphine catalysts is the most efficient method for the synthesis of chiral alcohols. Although in general, atropisomeric biaryl-based chiral ligands have proven to be the most versatile for this substrate class [2, 4b,c], significant success has been achieved with phospholane-containing systems (Fig. 24.19). As early as 1991, Burk et al. reported the use of Rh-phospholane **7** catalysts for the reduction of methyl acetoacetate [11], albeit with poor enantioselectivity (20–27% ee). Switching to a Ru-based precatalyst greatly enhanced both the activities and selectivities obtained [172], with [*i*-Pr-BPE $RuBr_2$] being found to be broadly effective for a range of β-keto esters **134** (76–99% ee, TON 500, TOF >15 h^{-1}) at low hydrogen pressures [172a]. Interestingly, amongst other applications, this was used for the preparation of enantiomerically pure 1,4-dicyclohexyl-1,4-butanediol and, ultimately, the synthesis of a new phospholane ligand, Cy-BPE; a rare case of "ligand self-generation". In general, the DuPhos class of phospholanes (and analogues [43, 44]) shows much lower activities for the reduction of β-keto esters than the more basic BPE ligands, with higher pressures, temperatures and reaction times being required [193]. Despite these harsher conditions, excellent enantioselectivities (96–99% ee) were obtained for the reduction of **134** (R = Me or $MeO_2C(CH_2)_2$, R′ = Me or Et) with the tetramethoxy ligand, BASPHOS **32** (R = Me) [56b].

The groups of Marinetti and Genêt have shown that several bisphosphetane-derived ligands (**58**, **59**, **61**) form effective Ru-based catalysts for the hydrogena-

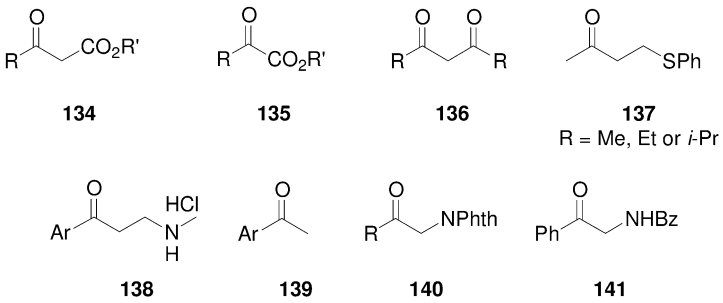


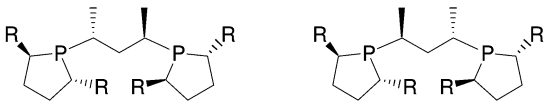
Fig. 24.19 General ketone classes to have been reduced with phospholane-based catalysts.

tion of β-keto esters, but once again, higher temperatures and pressures were generally required for reasonable activity [83 b–e]. Overall, moderate to high enantioselectivities were observed, with the bulkier 2,4-disubstituted phosphetanes (*i*-Pr > Et > Me) being more selective [83 d, e]. The bisphosphetanes CnrPHOS **58** (R = *i*-Pr or Cy) have also been applied to the Ru-catalyzed enantiomeric reduction of α-keto ester **135** (R = Ph, R′ = Et), β-diketones **136**, and β-thioketone **137**. In the case of substrates **135** and **136**, excellent selectivities were observed (98% and 97% ee, respectively), despite the high temperatures employed, with **136** also being obtained with high diastereoselectivity (94%). Cy-BPE-4 **59** has also been shown to be extremely selective for the Ru-catalyzed reduction of β-diketone **136** (R = Me), giving 98% ee and 95% de [83 b].

One application of phospholane-containing ligands for the enantiomeric reduction of a ketone recently appeared in a patent application from Lonza [194]. In the presence of NaOMe, both Me-DuPhos and Me-KetalPhos (**24**) gave reasonable selectivities (71.3% and 79.8% ee, respectively) for the Rh-catalyzed reduction of a β-amino ketone **138** (Ar = 2-thienyl), an intermediate for the pharmaceutically active drug duloxetine. Zhang and co-workers have also demonstrated the use of Rh-DuanPhos (**47**) for the reduction of a range of β-secondary-amino ketone hydrochlorides, including precursors to the drugs (*S*)-fluoxetine and (*S*)-duloxetine [73]. In general, remarkably high enantioselectivities were obtained (93–99% ee) with high TONs (> 4500) and TOF (375 h^{-1}) when using the secondary amino group, whilst the corresponding tertiary amine was unreactive.

The Rh-catalyzed hydrogenation of methyl pyruvate, **135** (R,R′ = Me), was studied by Burk et al. with bisphospholanes containing a chiral backbone, **6** and **7** (Fig. 24.20). Significant matching and mismatching effects were observed (43% versus 75% ee), with the matched system being ligand **7** [29]. Genêt also studied the reduction of α-keto esters, showing Me-DuPhos to form an effective Ru-catalyst when tested against **135** (R = Ph, R′ = Me) (80% ee) [172 b].

As for unfunctionalized olefinic substrates, the enantioselective hydrogenation of unfunctionalized ketones is considerably more challenging due to the absence of a secondary chelating moiety. Undoubtedly, until now the catalyst of choice for this substrate class is the *trans*-[$RuCl_2$(diphosphine)(diamine)] catalyst developed by Noyori [195], with numerous examples being reported with high enantioselectivities (> 95% ee) and activities (TON up to 2 400 000; TOF 259 000 h^{-1}) [196]. Although far less active (TOF < 50 h^{-1}), Zhang has reported significant selectivities with a Rh-PennPhos (**44**) system [57, 67 b]. When com-



6 R = Me, Et, i-Pr **7** R = Me, Et, i-Pr

Fig. 24.20 Matching and mismatching bisphospholanes.

bined with either 2,6-lutidine or KBr additives, moderate to high enantioselectivities (55–99% ee) are achieved for a range of simple ketones, including dialkyl-substituted ketones (up to 92% ee), a class against which the Noyori system is much less effective. A ruthenium complex of the P-chiral diphosphine BIPNOR (**53**) has also been reported to reduce unfunctionalized ketones of class **139** with moderate enantioselectivity (57–81% ee) [78b,d].

Finally, the group of Zhou has recently published the first Pd-catalyzed enantiomeric reduction of ketones using Me-DuPhos [197]. By performing the reaction in TFE, a series of *α*-phthalimido ketones **140** were reduced in high yield and 75–92% ee, albeit at high catalyst loadings (SCR 50), reaction times (12 h) and pressures (13.7 atm). This procedure was extended to include ketones **134** (R = Ph, R′ = Et), **139** (Ar = Ph), and **141**.

24.4.2
Enantioselective Hydrogenation of Imines and C=N–X Bonds

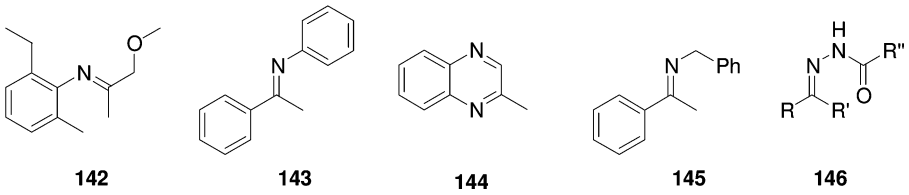
Enantiomerically pure amines are extremely important building blocks for biologically active molecules, and whilst numerous methods are available for their preparation, the catalytic enantioselective hydrogenation of a C=N bond potentially offers a cheap and industrially viable process. The multi-ton synthesis of (*S*)-metolachlor fully demonstrates this [108]. Although phospholane-based ligands have not proven to be the ligands of choice for this substrate class, several examples of their effective use have been reported.

Indeed, the imine intermediate **142** in the synthesis of metolachlor has been reduced in 97% ee using an iridium complex of the phospholane-containing ligand **55** [80].

A *trans*-[$RuCl_2$(diphosphine)(1,2-diamine)] complex with (*R,R*)-Et-DuPhos and (*R,R*)-1,2-diaminocyclohexane as the ligand combination has been found to be effective for the hydrogenation of imine **143**, with up to 94% ee being obtained under the standard basic conditions employed for this catalytic system [198]. Unfortunately, the optimum combination of chiral diphosphine and diamine was found to be substrate-dependent, with only 40% ee being obtained for 2-methylquinoxaline **144** with Et-DuPhos.

Corma et al. have recently demonstrated the hydrogenation of **145** using a binuclear gold complex of (*R,R*)-Me-DuPhos [166]. Reasonable rates were observed (TOF 1005 h^{-1}), with the enantioselectivity being higher (75% ee) than that obtained with Pt- and Ir-based catalysts (15% ee in each case).

Burk et al. showed the enantioselective hydrogenation of a broad range of *N*-acylhydrazones **146** to occur readily with [Et-DuPhos Rh(COD)]OTf [14]. The reaction was found to be extremely chemoselective, with little or no reduction of alkenes, alkynes, ketones, aldehydes, esters, nitriles, imines, carbon-halogen, or nitro groups occurring. Excellent enantioselectivities were achieved (88–97% ee) at reasonable rates (TOF up to 500 h^{-1}) under very mild conditions (4 bar H_2, 20 °C). The products from these reactions could be easily converted into chiral amines or *α*-amino acids by cleavage of the N–N bond with samarium diiodide.



142 143 144 145 146

Fig. 24.21 C=N bonds to have been reduced with phospholane-based catalysts.

24.5 Concluding Remarks

Since the breakthrough introduction of the DuPhos and BPE family of ligands by Burk, the use of phospholanes in asymmetric hydrogenation has witnessed an explosion of interest, with many new and imaginative analogues emerging. This intense activity has extended the applicability of this important class of ligands beyond the standard substrates and towards the synthesis of a diverse range of chiral intermediates. This in turn has led to the realization of their commercial potential with multi-kilogram catalyst sales and applications on the industrial scale. We are only now beginning to witness the true synthetic utility of this technology and, with its increased adoption, it is anticipated that many more large-scale applications will be reported in the future.

Abbreviations

ANF	atrial natriuretic factor
BPE	1,2-bis(trans-2,5-dialkylphospholano)ethane
COD	1,5-cyclooctadiene
de	diastereomeric excess
DMI	dimethylitaconate
DuPhos	1,2-bis(trans-2,5-dialkylphospholano)benzene
ee	enantiomeric excess
LC	liquid chromatography
MAA	methyl 2-acetamidoacrylate
MAC	(*Z*)-methyl-2-acetamidocinnamate
MPLC	medium-pressure liquid (flash) chromatography
NBD	norbornadiene
SCR	substrate:catalyst ratio
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TOF	turnover frequency
TON	turnover number

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