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Tetrahedron: *Asymmetry* 15 (2004) 2123–2137

Tetrahedron: *Asymmetry*

TETRAHEDRON: ASYMMETRY REPORT NUMBER 67

Recent developments in chiral phospholane chemistry

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Received 4 May 2004; accepted 9 June 2004

Abstract—Phospholanes have attracted considerable attention as ligands for asymmetric catalysis. The DuPHOS family of ligands reported by Burk et al. in 1991 has found considerable success as ligands for asymmetric hydrogenations. An overview of recent synthetic approaches to chiral phospholanes is presented. Also included are some of the more recent applications of phospholanes in asymmetric catalysis.

Contents

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doi:10.1016/j.tetasy.2004.06.025

1. Introduction

As the demand for new, highly selective routes to chiral materials grows, so does the urgency of creating new routes to novel chiral phosphines. How will this need be fulfilled? Two overlapping approaches are currently being pursued. The first approach emphasizes the discovery of novel ligand structures that bear little resemblance to existing structures. In principle the discovery of such new structures can result from computer-aided searches[1,2] or high throughput syntheses and screening.[3–7] At present there are few good examples of a purely computational design of a new ligand set for asymmetric catalysis, although this may change due to recent developments in computer-based ligand construction. Generation of large combinatorial libraries of phosphines with subsequent screening for catalysis has demonstrated success.[8–17] One difficulty in applying this approach to phosphine synthesis is that common routes (such as the reaction of phosphorus halides with organolithium or Grignard reagents) to chiral phosphines are not compatible with combinatorial methods and the presence of diverse functional groups. Another problem is more general to combinatorial methods. In order to maximize the chance of success, the number of different structural permutations required for thorough screening is large leading to high capital costs for advanced machinery as well as a large time commitment.

An alternative approach to fulfilling the need for more effective chiral phosphines involves permutations of 'privileged' structures.[18] Privileged structures are those, which yield high selectivity in a broad range of applications. Examples of privileged phosphine structures include BINAP-like phosphines and phospholanes. Phospholanes, which are the focus of this article, are five-membered rings containing phosphorus. For the purpose of this review, the phospholane term will be further limited to reference only to chiral tertiary phosphines with three P–C bonds.

The chiral, C_2-symmetric phospholanes developed by Burk et al. at Du Pont have been widely used as ligands in transition metal catalyzed reactions, particularly Rh-catalyzed hydrogenations (Scheme 1). Hydrogenations of *N*-acetyl-α-enamides, *N*-acylhydrazones, *N*-Boc-α-enamides, β-amino alcohols, α- and β-hydroxy esters and itaconic acid have been achieved with very high enantioselectivity.[19,20] The success of the DuPHOS ligand class is linked to the rigid, chiral environment created by substituents at the 2,5-positions of the five-membered ring.[21–23] Quadrant models qualitatively depict the steric environment around the catalyst (Fig. 1). Two of the four R groups on the DuPHOS structure point towards the open metal coordination site and are thought to exert enantioselective forces on the reaction pathway through steric interactions.

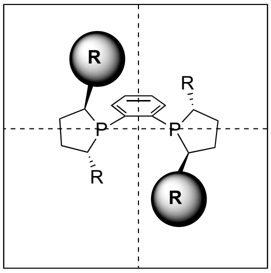
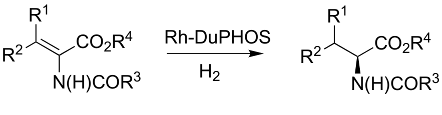


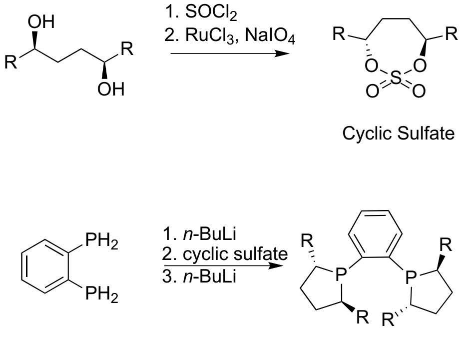
Figure 1. Quadrant model of DuPHOS.

Considering the broad range of transformations catalyzed by phosphines and their metal complexes, difficulties in a priori prediction of enantioselectivity or its sense are not surprising, even with rigid ligands and well-defined structures. As pointed out by Knowles at the dawning of effective enantioselective, catalytic hydrogenations: 'Since achieving 95% ee only involves energy differences of about 2 kcal, which is not more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict what kind of ligand structures will be effective.'[24] While the power of computational methods continues to advance at a rapid rate, it is still unreasonable to expect such methods to be able to predict enantioselectivity for a particular substrate/ligand combination. A further complicating factor with a priori prediction of enantioselectivities concerns the nature of the enantiodetermining step (which may or may not be rate determining): rarely is the enantiodetermining step well established and even more rarely are adequate transition state models available. As a result, most effort has been directed towards the syntheses of new variants of the DuPHOS ligand and empirical testing of selectivity.

The traditional route to chiral phospholanes is shown in Scheme 2. Chiral 1,4-diols are first converted to the cyclic sulfate by reaction with thionyl chloride to form a cyclic sulfite. The sulfite is then oxidized by ruthenium chloride and sodium periodate to the cyclic sulfate. Reaction with 2 equiv of *n*-BuLi and a primary phosphine provides the phospholane with net inversion of stereochemistry. The chiral 1,4-diols were initially



Scheme 1. Hydrogenation of α-enamides.



Scheme 2. DuPHOS synthesis.

synthesized through Kolbe coupling and as a result a few 1,4-diols were applied to the synthesis of phospholanes (R = Me, Et, *i*-Pr).[25] Phospholanes could then be converted to lithium phosphides by the reaction of lithium metal with phenyl phospholanes; this route was initially applied to access bisphosphines.[25,26] This method was soon discarded for a simpler route involving primary bisphosphines (Scheme 2)[27] and also because the lithium phosphide approach appeared to suffer from formation of P–P coupled products as well as racemization at the C2 and C5 positions.[28] Although this limited range of bisphosphines (including DuPHOS and BPE) has proven highly successful primarily for asymmetric hydrogenations, the potential for further development in phospholane synthesis and application to catalysis remains. This review summarizes some of the recent developments in phospholane chemistry since the original work by Burk et al. with a focus on new synthetic approaches to phospholane synthesis (Fig. 2).

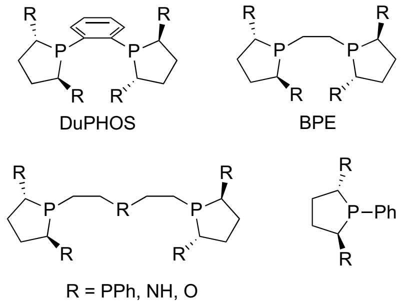


Figure 2. Original mono- and bisphospholanes.

2. Synthesis of new phospholanes

2.1. New primary phosphines

A straightforward method of generating new phospholanes involves the synthesis of new primary phosphines. Theoretically any primary phosphine, which tolerates the conditions of phospholane synthesis, can be used. Varying the ligand backbone of a primary bisphosphine enables access to a range of phospholane bite angles. This objective has motivated several research groups to explore new structures in an attempt to improve the chemistry of DuPHOS.

Ferrocene **1**,[29] xanthene **2** and phenoxathiin **3**[30,31] have been used as backbones to synthesize primary bisphosphines (Fig. 3). Routes to primary phosphines take advantage of the inherent selectivity of the precursors to form specific dilithiated structures. Reaction between the dilithiated species and diethylchlorophosphonite followed by reduction with lithium aluminium hydride (LAH) forms the primary phosphines (LAH reductions of phosphonate esters have been improved by the addition of an equivalent of TMSCl).[32] Berens recently found that *N*,*N*-dialkyl-aminophosphines can act as directing groups for the lithiation reaction and has reported several structures based upon the benzo[*b*]thiophene backbone **4**.[33]

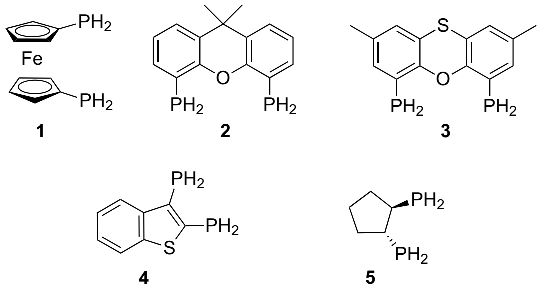


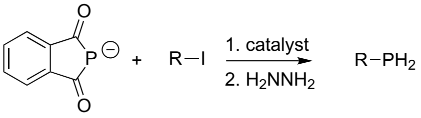
Figure 3. Primary bisphosphines.

Primary phosphine *trans*-1,2 diphosphinocyclopentane **5** is one of the few literature examples of a chiral primary bisphosphine.[34,35] It can be resolved by fractional crystallization of diisopropyl tartrate dioxaphospholane. Pringle et al. successfully applied this chiral phosphine to the synthesis of matched and mismatched phospholanes.[21] The 2,5-dimethyl phospholanes bridged by the *trans*-1,2 cyclopentane was applied to the hydrogenation of methyl-(*Z*)-2-acetamidocinnamate and provided products with 77% and 98% ee depending on the chirality of the cyclopentane backbone with the chirality at the 2,5-positions determining the product stereochemistry. Under identical conditions Me-BPE yielded the product with 85% ee.

The main bottleneck in the development of new phospholanes from primary phosphines is the synthesis. Primary phosphines are expensive and have limited commercial availability. Common syntheses of primary phosphines involve LAH reduction of phosphonites or phosphinites, which is complicated on large scales. Novel primary phosphines via LAH reduction requires access to the corresponding phosphonites and phosphinites. Buchwald et al. have recently demonstrated a promising Cu-catalyzed route to aryl phosphonates from aryl halides.[36] Preliminary results have shown that phosphonites generated by this method can be reduced to the primary phosphines with LAH.[37]

While this route appears to be convenient for the synthesis of phosphonites, a preferable approach would be to eliminate the need for an LAH reduction step. One approach to primary phosphines has been applied to the synthesis of a ferrocenyl phosphine.[38,39] Tris(hydroxymethyl)phosphine can be reacted with the ferrocenylmethyl ammonium salt $FcCH_2NMe_3^+I^-$ to give $FcCH_2P(CH_2OH)_2$. This can be converted to the primary phosphine by the addition of sodium metabisulfate (to abstract formaldehyde). This method can presumably be applied to the synthesis of other primary phosphines.

O'Brien et al. have disclosed the synthesis of phthaloyl phosphide, which can serve as a convenient primary phosphine precursor.[40] The benefit of this reagent is that a primary phosphine can be generated by treatment with hydrazine. The phosphide can then be used as a nucleophile and be coupled to aryl or alkyl halides with a suitable catalyst (Scheme 3).[41] The primary drawback is that the synthesis of phthaloyl phosphide requires PH_3.

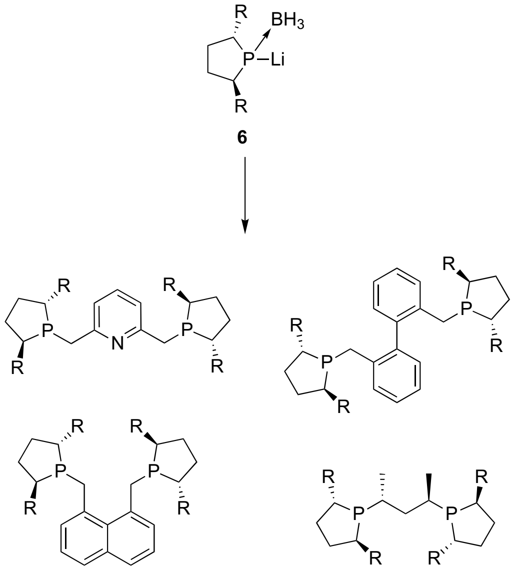


Scheme 3. Potential route to primary phosphines.

2.2. Modification of a secondary phospholane

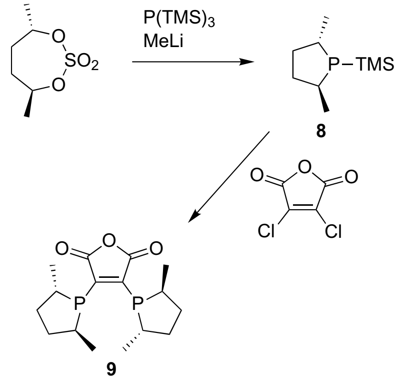
Secondary phospholanes are an attractive intermediate for the development of new phospholanes. Although Burk has reported the synthesis of the lithium salt of phospholane, the previously mentioned problems with epimerization and P–P coupling have prompted the development of other routes. Difficulties associated with simple phosphide salts include high sensitivity to moisture and oxygen. Morimoto et al. reported that the phospholane borane complex can be reacted with lithium metal to form a more stable form of the lithium salt **6**.[42]

Burk et al. has also used the borane-protected lithium phosphide to generate phospholane **7** with a chiral backbone (Scheme 4).[28] It was found that there is a significant match/mismatch effect in hydrogenation reactions of enamides and methyl pyruvate. However the chirality of the final product is still determined by the chirality at the 2,5-positions on the phospholane.



Scheme 4. Bisphospholanes derived from the phospholane salt.

A drawback to the use of borane-protected lithium salts is that the vicinal bisphosphine syntheses apparently fail.[43] Presumably, this is a result of steric congestion. Another route to an easily derivatized phospholane is through the use of the TMS-protected secondary phospholane. Burk et al. originally disclosed the synthesis of the TMS phospholane **8** but reported that the bond was not susceptible to nucleophilic cleavage.[28] The phospholane was unreactive with BuLi while TMS–P bond could not be cleaved with excess methanol. Recently, Holz et al. reported the preparation of TMS-protected secondary phospholane through a more convenient route (Scheme 5).[43] This phospholane can be reacted with 2,3-dichloromaleic anhydride to form bisphosphine **9** (MalPHOS). Hydrogenations of (*Z*)-β-acylamido acrylates using MalPHOS as the ligand gave improved selectivity over Me-DuPHOS.



Scheme 5. Synthesis of MalPHOS.

2.3. Functionalized primary phosphines

Recent ligand developments demonstrate that electronically and sterically asymmetric chelates positively affect selectivities.[44–47] Several groups have explored the synthesis of phospholane-containing ligands, which contain either another phosphine or heteroatom (e.g., S, O or N). The most common synthetic approach to mixed ligands containing phospholanes is the development of primary phosphines with another functionality already attached. This requires that the functionality is stable to the reduction conditions used to make the primary phosphine (e.g., LAH reduction), as well as be stable under the conditions required to synthesize the phospholane.

Carmichael et al. reported the synthesis of a bisphosphine **10** containing a phospholane and a P-chiral moiety.[48] The bisphosphine is generated by the addition of the borane-protected P-chiral phosphide to diethylvinylphosphonate followed by reduction. After conversion to phospholane, the P-chiral diastereomers are separated by MPLC. Hydrogenations with these ligands yield moderate enantioselectivities with several substrates. The chirality of the product is determined primarily by the phospholane, but there is a significant matching effect involving the chirality of the P-chiral moiety (Fig. 4).

Since this initial report, Stelzer et al. have reported the development of a series of mixed phosphines including the primary–tertiary arylphosphine **11**.[49] The key step in the synthesis is the Pd-catalyzed coupling of diphenylphosphine and *ortho*-bromoiodobenzene. The *ortho*-bromide is then lithiated with butyl lithium followed by reaction with bis(dimethylamino)chlorophosphine. This intermediate can then be reduced to the primary

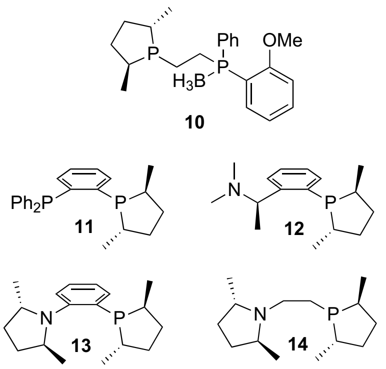
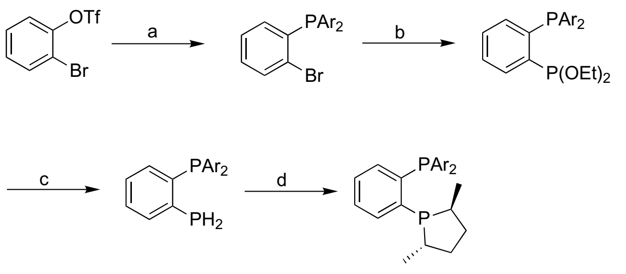


Figure 4. Mixed phospholanes.

phosphine. Saito et al. have recently used a similar approach to generate a small array of C_1-symmetric bisphosphines (Scheme 6).[50] This collection of ligands was used in the Rh-catalyzed hydrogenation of (*Z*)-*N*-benzoy-1-phenylpropenamine and in one case (Ar = 1-naphthyl) the enantioselectivity obtained matched Me-DuPHOS (95% ee).



Scheme 6. Reagents and conditions: (a) (i) $Ar_2P(O)H$, $Pd_2(dba)_3$, dppp, DIEA, tol., reflux, (ii) $HSiCl_3$, $PhNMe_2$, tol., reflux; (b) (i) *n*-BuLi, THF, −78 °C, (ii) $(EtO)_2PCl$; (c) LAH, TMSCl, THF; (d) (i) *n*-BuLi, THF, 0 °C, (ii) (2*R*,5*R*)-2,5-hexanediol cyclic sulfate, (iii) *n*-BuLi, 0 °C to rt.

Phosphorus-heteroatom chelates demonstrate useful reactivity and selectivity for metal catalyzed reactions.[45–47,51,52] A tertiary nitrogen was initially incorporated into a phospholane through the reaction of the phospholane lithium salt with bis(2-chloroethyl)trimethylsilylamine (Fig. 2).[26] A common approach to mixed chelates with phospholanes is to synthesize a primary phosphine with a tertiary heteroatom present. RajanBabu et al. reported the benefit of incorporating a labile group into a phospholane.[53] Following the same general procedure (converting the appropriate aryl bromide into the primary phosphine and reacting this with the cyclic sulfate) they synthesized monophospholanes for use as ligands in hydrovinylation (Fig. 5). It was postulated that the hemilabile groups coordinate to the metal and play an essential role in the reaction. Recently, this work has been extended to include acetals such as **15**.[54] These phospholanes have been applied as ligands in the hydrovinylation of arenes and provide products with high selectivity (88% ee for styrene).

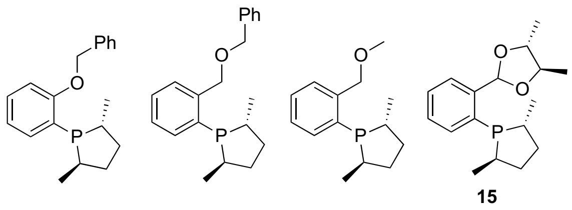


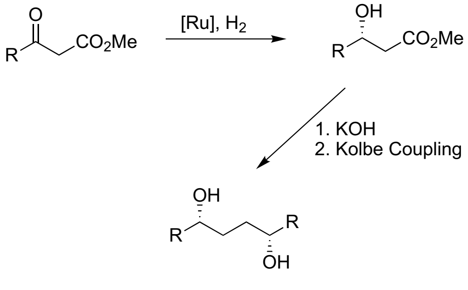
Figure 5.

Brauer et al. used the presence of the nitrogen functionality to direct the lithiation of the *ortho*-CH bond in the formation of the phospholane-nitrogen ligand **12**.[55] A chiral match/mismatch effect in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate (96% vs 60% ee) resulted. This influence of the matching chirality also appears to affect the reactivity of the catalysts. The hydrogenation reaction with the (*R*,*R*,*R*) ligand proceeds at 20 °C but exhibits no reaction with the (*S*,*R*,*R*) ligand.

Moberg et al. used a similar approach to explore the role of steric symmetry in the asymmetric allylic alkylation reaction.[56] Pseudo C_2-symmetric ligands can be produced from 2-bromoaniline by first reacting the primary amine with the (*S*,*S*)-2,5-hexandiol cyclic sulfate (by analogy with the corresponding phospholane synthesis) to form the pyrrolidine. The resulting aryl bromide can be readily converted to primary phosphines **13**. Ligand **14** was synthesized in a similar manner from (2-aminoethyl)phosphonic acid diethyl ester.

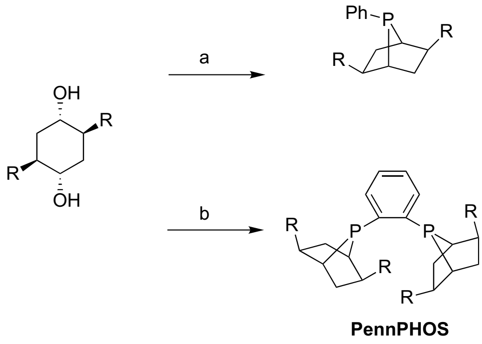
2.4. New resolved diols

An alternative strategy for the generation of new phospholanes is the creation of new diol starting materials. Since their initial reports, Burk et al. have reported the synthesis of new phospholanes based on chiral 1,4-diols (R = *n*-propyl, cyclohexyl) obtained through the route shown in Scheme 7.[57,58] The Cy-BPE phospholane has been applied to rhodium-catalyzed hydrogenation of β-keto esters. Hydrogenations with Cy-BPE as the ligand produce (*S*)-methyl 3-cyclohexyl-3-hydroxypropionate in 98% ee. This product can be converted into the chiral 1,4-diol used to make Cy-BPE.[58]



Scheme 7. General synthesis of chiral diols.

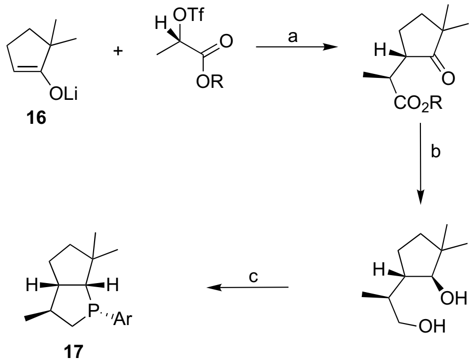
Zhang et al. have developed a new bicyclic ligand system by using previously reported chiral 1,4-cyclohexanediols (Scheme 8).[59–62] The PennPHOS ligands exhibit high



Scheme 8. Reagents and conditions: (a) (i) MsCl, Et_3N, DCM, (ii) Li_2PPh, THF; (b) (i) MsCl, Et_3N, DCM, (ii) 1,2-bis(phosphino)benzene, NaH, HMPA, THF.

selectivity as ligands in the hydrogenation of aryl and alkyl methyl ketones and cyclic enamides. The selectivity of the reactions with cyclic enamides are much higher compared to Me-DuPHOS under the conditions tested. However, acylic enamides are hydrogenated with poorer selectivity using PennPHOS when compared to using DuPHOS as the ligand.

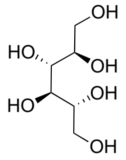
Another significant use of new chiral diols was in the development of the PBO catalyst system. Vedejs and Daugulis, while developing a new phosphine-based acylation catalyst, created new bicyclic phosphabicyclo-[3.3.0]octanes (PBO). The key step in the synthesis of the chiral phospholane is the diastereoselective alkylation of **16** with methoxyethoxyethyl lactate triflate, which provides the desired diastereomer in a 9:1 ratio.[63] The resulting PBO catalyst **17** is highly effective in the kinetic resolutions of several secondary alcohols (Scheme 9).



Scheme 9. Reagents and conditions: (a) −55 °C, 24 h; (b) LAH; (c) (i) $SOCl_2$, (ii) $RuCl_3$, $NaIO_4$, (iii) $ArPH_2$, (iv) *n*-BuLi.

2.5. Resolved diols from the chiral pool

Prior to the disclosure of the DuPHOS ligands, Brunner and Sevi reported the synthesis of phospholanes derived from tartaric acid.[64] Unfortunately, these ligands provide very poor selectivities for asymmetric hydrogenations, presumably because they lack steric bulk or chirality at the 2,5-positions. Although this type of phospholane is not successful, the concept of using materials from the 'chiral pool' as starting materials for phospholanes continues to be an attractive approach to further ligand development. The functional groups present in the chiral starting materials provide additional advantages. Inclusion of functional groups into chiral phosphines is highly desirable for further functionalization and there are many synthetic approaches towards their incorporation into phosphines.[65] Functional groups in a ligand structure may allow beneficial secondary interactions in a catalytic reaction.[66,67]



D-Mannitol

Carbohydrate chemistry is a mature, well-developed field and provides well-developed protection strategies for the synthesis of mannitol derivatives. Several research groups realized the potential of mannitol as a chiral precursor for phospholanes and have reported their syntheses. Börner et al. reported one of the first phospholane syntheses based on mannitol.[68] The key step is the use of orthogonal protecting groups that take advantage of the difference in reactivity between a primary and secondary hydroxyl group.[69] Another feature of this route, which makes the synthesis of phospholanes possible, is the stability of the protecting group to the conditions required to make the phospholane ring. Bisphosphine **19** (RoPHOS) synthesized from the reaction between the diol and bisphosphinoethane was applied to the asymmetric hydrogenation of a range of functionalized olefins with high selectivity. The research groups of RajanBabu, Brown and Zhang also reported the synthesis of mannitol-derived phospholanes containing ether functionalities.[48,70,71] Their routes, also based upon previous work with mannitol[72] use the *iso*-propylidene protecting group (Fig. 6). Zhang et al. applied this diol to the synthesis of bisphospholane **20** with a ferrocene backbone.[73] Rhodium-catalyzed hydrogenations with this ligand provide selectivities comparable to other C_2-symmetric ferrocenyl bisphosphine ligands.

The use of dianhydromannitol **18** as a source of a 1,4-diol also has been reported. Yan and RajanBabu have used the synthetic routes available to synthesize both the (2*R*,3*R*,4*R*,5*R*) and (2*S*,3*R*,4*R*,5*S*) diastereomers of the 3,4-functionalized phospholanes (Scheme 10).[71] The epoxides can be reduced with superhydride or LAH to give the 1,4-diols. The authors speculated that the epoxides could also be further derivatized through ring opening reactions with copper. This route has recently been applied by Rieger et al. to generate several structural variants of this phospholane.[74] The epoxide is synthesized by a previously reported procedure[75] and the dianhydro mannitol is converted to the diol by copper-catalyzed coupling with a Grignard. The use of an epoxide intermediate allows for the generation of a wide range of structures from a single intermediate.

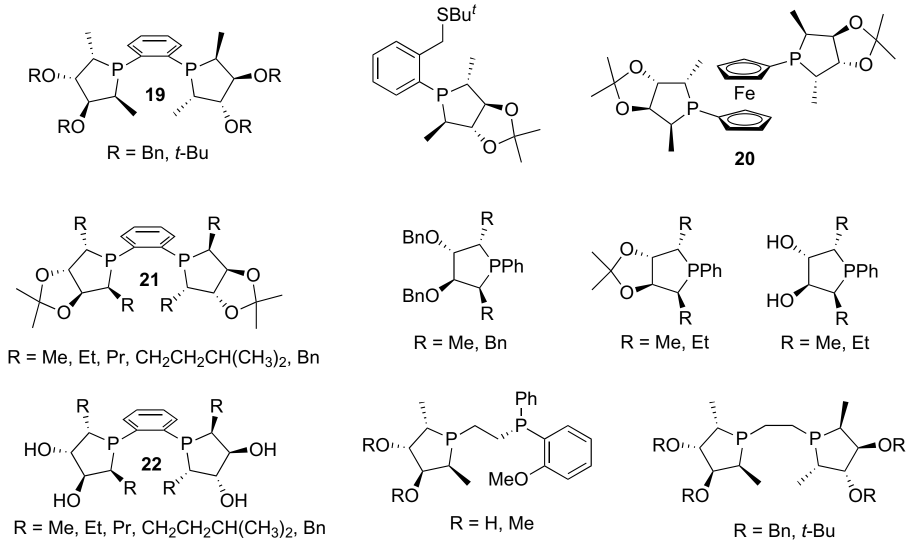
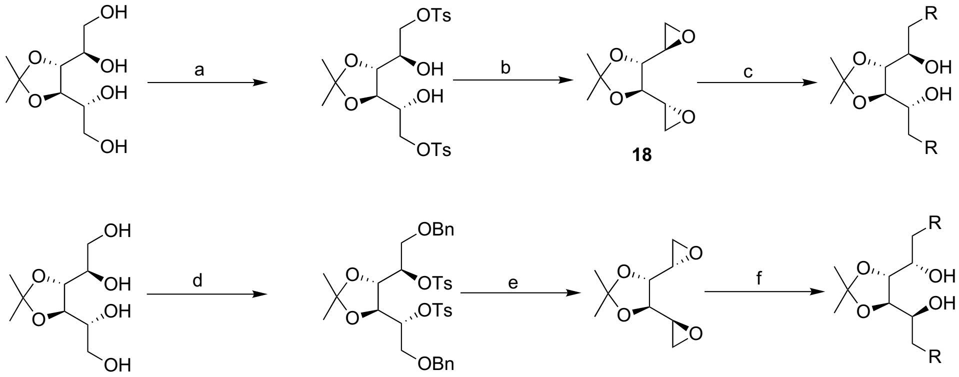


Figure 6. Examples of 3,4-functionalized phospholanes.



Scheme 10. Reagents and conditions: (a) TsCl, pyr; (b) MeOH, K_2CO_3; (c) CuBr, RMgBr, −40 °C or if R = H: $LiEt_3BH$, THF; (d) (i) PhCOCl, pyr, −80 °C, (ii) TsCl, NEt_3, DMAP; (e) MeOH, K_2CO_3; (f) CuBr, RMgBr, −40 °C or if R = H: $LiEt_3BH$, THF.

The bisphospholanes derived from the diols were tested as ligands in the hydrogenation of α-(acetamido)cinnamic acid and itaconic acid with yields of the product of up to 99% ee.

Dihydroxy phospholanes, such as **22**, can be synthesized readily from the *iso*-propylidene **21** by treatment with an acid. Zhang et al. have reported the synthesis of analogous bisphospholanes with dihydroxyl groups.[70,76] The tetrahydroxyl phospholane is water soluble and hydrogenations of itaconic acid can be carried out in a water/methanol mixture (97:3) with 100% conversion and 99% ee. RajanBabu et al. also reported that the tetrahydroxy phospholanes can be used as ligands in the hydrogenation of methyl acetamidoacrylate in water/methanol mixtures.[77] The selectivity of the hydrogenation is highly dependent on the amount of water in the reactions. Higher percentages of water lead to a decrease in the reaction selectivity. RajanBabu et al. have demonstrated that the catalyst can be recycled by extracting the product into ether.

While the addition of functional groups to the 3,4-positions on the phospholane has led to new structures, the work of Brunner and Sevi demonstrated that the inclusion of functionality at the 3,4-position has little influence on catalyst selectivity.[64] If the goal of a new phospholane synthesis is to maximize the interactions between the new structural moieties and the chiral pocket of a transition metal catalyst, the most meaningful changes in a phospholane should take place at the 2,5-position. In 1999, Börner et al. developed a class of phospholanes (BASPHOS, **23**) derived from mannitol with functionality at the 2,5-positions.[78] Mannitol was converted to 3,4-dideoxy-D-threo-hexitol by a known procedure. During the phosphine cyclization step, the hydroxyls are protected as tetrahydropyranyl (THP)-acetals. After synthesis, the THP protecting group is removed with HBF_4. The authors conclude that the isolation of the phospholane is more convenient if the hydroxyl deprotection is effected as the Rh-bisphosphine complex. Essentially, the rhodium acts as a protecting group for the phosphorus. The Rh complex is water soluble and hydrogenates 2-acetamido acrylic acid with 99.6% ee in aqueous conditions. RajanBabu et al. also reported the hydrogenation of methyl acetamidoacrylate in water with 99% ee using the same ligand.[77] They found that the catalyst can be recycled up to four times with no loss in selectivity. When the tetrahydroxy phospholane was applied to the hydrogenation of unsaturated amino acid derivatives in methanol, significantly lowered selectivities were found compared to the benzyl and methyl ether derivatives of BASPHOS.[79] Significantly, it was found that the identity of the functionalized substituents at the 2,5-position has a profound effect on the selectivity of the reaction. This indicates that the changes in the ligand structure impact the chiral pocket in the hydrogenation reaction. This introduces the potential for ligand tuning to possibly improve selectivities in reactions where the DuPHOS ligands give poor performance (Fig. 7).

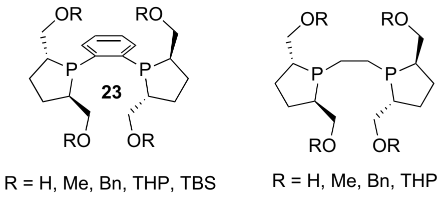


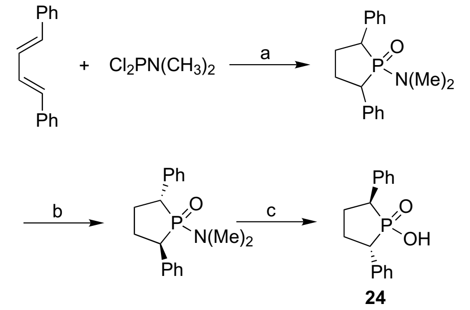
Figure 7. 2,5-Functionalized phospholanes.

2.6. Alternative approaches to phospholanes

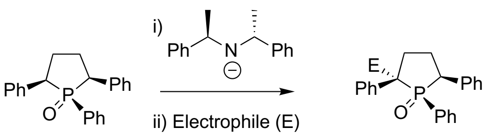
There have been several approaches reported for the synthesis of phospholanes that are distinct from the Burk route. While the Burk route is well-developed and has been extensively applied to the synthesis of phospholanes, some drawbacks make the development of new routes attractive. The primary drawback to the Burk method is the difficulty in introducing functional groups onto the phospholane ring. The use of thionyl chloride, a strong oxidant and butyl lithium limits the functional groups that can be included in the synthesis. Additionally, 2,5-diarylphospholanes cannot be synthesized by this method as the aryl cyclic sulfate tends to undergo elimination reactions under basic conditions.[80]

In 1991, Fiaud and Legros reported the synthesis of 1,2,5-triphenylphospholane from the known (*E*,*E*)-triphenylphospholane oxide.[81] They found that the C_s-symmetric *meso* product could be racemized to the racemic product (*pseudo*-C_2 symmetry) by the addition of methyl lithium as catalyst. The racemic product is reduced to the tertiary phosphine with LAH. Unfortunately, the racemic product can only be resolved with chiral LC. Several years later, an alternative approach was devised using (*N*,*N*-diisopropylamino)dichlorophosphine to generate the phospholanic acid **24** (Scheme 11). The acid can be resolved by crystallization of the quinine salt.[80,82] The phospholanic acid can be converted into either a tertiary monophosphine[80,82] or bisphosphine.[83]

Simpkins et al. have also used the readily available 1,2,5-triphenylphospholane oxide as a starting material for the generation of chiral phosphines.[84,85] They found that the deprotonation of the α-carbon on the ring with a chiral base at −100 °C followed by reaction with an electrophile provides the product with up to 90% ee (Scheme 12). The phosphine oxide can be reduced to the phosphine by reduction with a combination of trichlorosilane–pyridine in benzene.

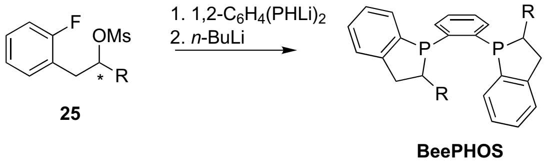


Scheme 11. Reagents and conditions: (a) (i) $AlCl_3$, −10 °C, (ii) $NaHCO_3$, EDTA, 0 °C, (iii) 5% Pd/C, H_2; (b) MeONa, MeOH; (c) (i) HCl, MeOH, (ii) quinine, recryst.



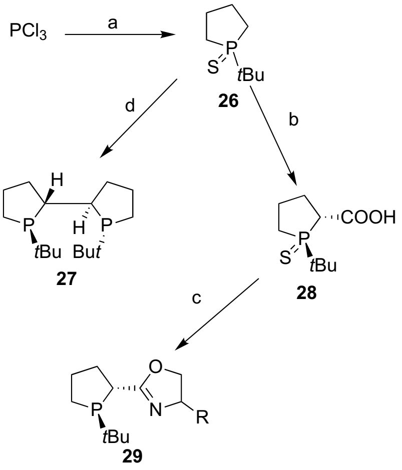
Scheme 12. Chiral desymmetrization of phospholane.

Another route to a chiral phospholane involves a diol and an aryl halide to form the phospholane (Scheme 13). The reaction between **25** and 1,2-bis(phosphino)benzene in the presence of butyl lithium affords the BeePHOS structure (the absolute configuration at the stereogenic carbon is unknown).[86] Rhodium-catalyzed hydrogenations of methyl *N*-acetamidocinnamate proceeds with 98% ee using ligand *i*-PrBeePHOS, which matches results obtained with Me-DuPHOS. Conversely, selectivities for the hydrogenation of methyl α-hydroxymethylacrylate with BeePHOS ligands were all lower compared to Me-DuPHOS.



Scheme 13. BeePHOS synthesis.

Tang and Zhang reported the synthesis of phospholane sulfide **26** through the stepwise reaction of PCl_3 with *t*-BuMgCl, $ClMg(CH_2)_4MgCl$ and sulfur (Scheme 14).[87,88] Chirality is introduced by selective deprotonation with a butyl lithium–sparteine complex followed by either a copper-mediated coupling to form the bisphosphine **27** or reaction with carbon dioxide to generate the chiral phosphine **28**. The carboxylic acid can be



Scheme 14. Reagents and conditions: (a) *t*-BuMgCl, $BrMg(CH_2)_4MgBr$, S; (b) *n*-BuLi, (−)-sparteine, CO_2, −78 °C; (c) (i) $NH_2CH(R)CH_2OH$, EDC, HOBt, 70 °C, (ii) MsCl, (iii) Raney Ni; (d) (i) *n*-BuLi, (−)-sparteine, $CuCl_2$, (ii) Si_2Cl_6.

converted to oxazoline **29** using established procedures. The carboxylic acid phospholane structure was also reported in a patent by Kobayashi.[89] The phospholane was converted to a bisphosphine by a standard procedure (Fig. 8).

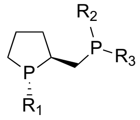
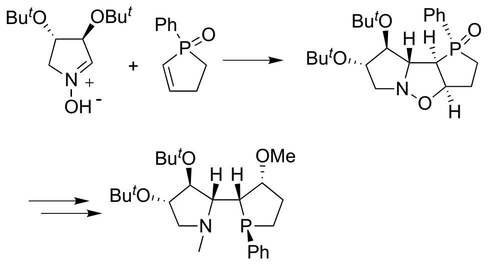


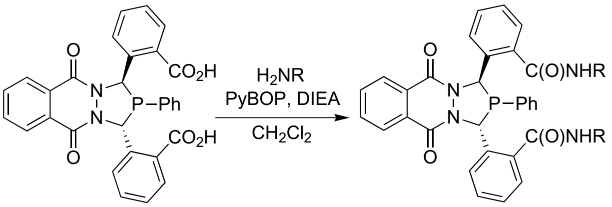
Figure 8. Kobayashi bisphosphine.

A similar phospholane was reported by Bianchini et al. in 1995.[90] The phospholane is obtained from the isoxazolidine,[91] which is the main product in the cycloaddition of a nitrone and phosphole (Scheme 15).

Another route to functionalized phospholanes has been reported by Landis and co-workers.[92,93] They reported the synthesis of 3,4-diazaphospholanes by a Mannich-like condensation reaction between an azine (synthesized from an aldehyde and hydrazine), a primary phosphine and an acid chloride (see Scheme 16). The use of 2-carboxybenzaldehyde enables the inclusion of a carboxylic acid into the structure and facilitates the complete resolution of each enantiomer through crystallization with chiral methylbenzylamine. The carboxylic acid can be functionalized further using amino acid coupling chemistry or through conversion to an oxazoline (Scheme 17). The primary advantage of this route is that one resolved structure can be readily converted into a large array of different structures.

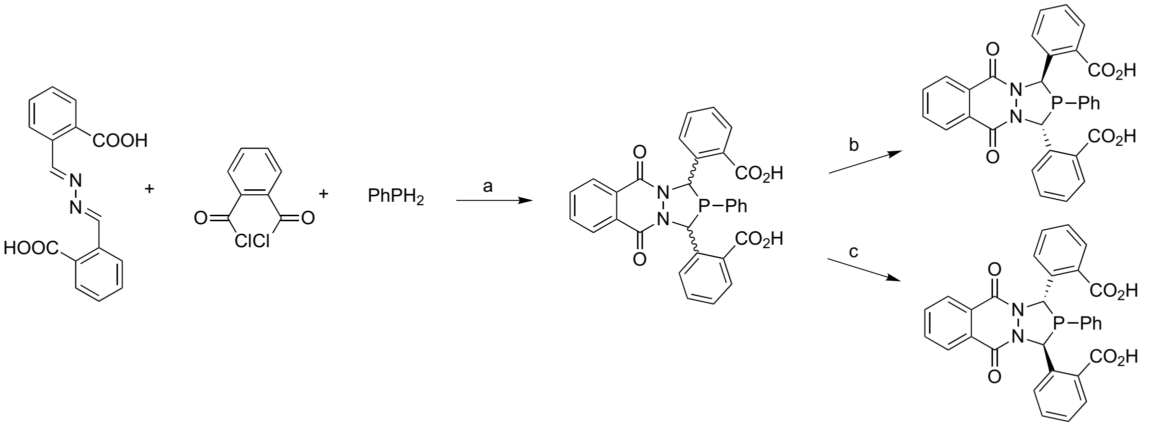


Scheme 15. Synthetic route to the Bianchini phospholane.



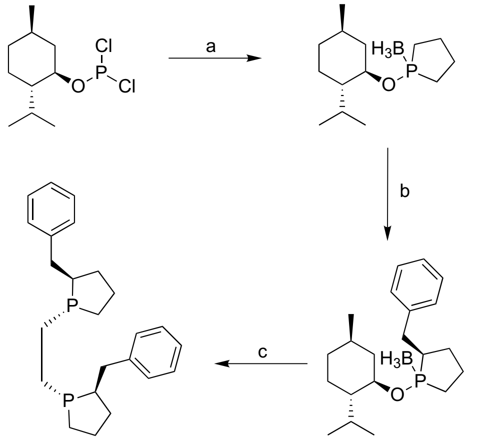
Scheme 17. Derivatization of 3,4-diazaphospholanes.

Recently, Hoge developed an interesting variant on the DuPHOS structure. Based on the quadrant model of hydrogenation reactions, he reasoned that steric bulk is unnecessary at both the 2 and 5 positions of the phospholane (see Fig. 1).[94] According to Hoge, the presence of substituents pointing away from the catalyst centre may lead to decreased selectivity in hydrogenations.



Scheme 16. Reagents and conditions: (a) (i) THF, (ii) 10% aq K_2CO_3, (iii) 3 M HCl; (b) (i) (*S*)-α-methylbenzylamine, THF, (ii) 10% aq K_2CO_3, (iii) 3 M HCl; (c) (i) (*R*)-α-methylbenzylamine, THF, (ii) 10% aq K_2CO_3, (iii) 3 M HCl.

He hypothesized that by removing these substituents leads to a larger difference in the sterics of the quadrant, leading to a greater difference in the diastereomeric transition states in the hydrogenation reaction. A summary of the synthesis is presented in Scheme 18. Key to the synthesis is the use of menthol as a removable source of the chirality for the selective methylation of the α-carbons followed by methylation of the phosphorus with methyl lithium with retention of stereochemistry (it is interesting to compare this to the result reported by Fiaud and Legros that 1,2,5-triphenylphospholane racemizes with a catalytic amount of methyl lithium present).[81] Application of the resulting bisphospholane was applied to the Rh-catalyzed hydrogenation of acetamidoacrylic acid derivatives. Selectivities with this ligand are comparable to those obtained previously with BPE. The Hoge ligands were also applied to the hydrogenation of precursors to the pharmaceutical pregabalin and could provide the product in up to 97% ee.



Scheme 18. Reagents and conditions: (a) (i) $BrMg(CH_2)_4MgBr$, (ii) BH_3; (b) (i) *s*-BuLi, (−)-sparteine, −78 °C, (ii) BnBr; (c) (i) 5 equiv MeLi, (ii) *s*-BuLi, −78 °C, (iii) $CuCl_2$, (iv) HBF_4, (v) K_2CO_3.

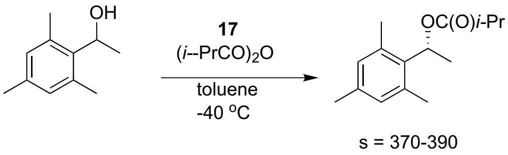
A potential route to chiral phospholanes has recently been explored by Marks et al.[95] Lanthanocene complexes affect the intramolecular hydrophosphination of phosphinoalkenes to form phosphorus containing heterocycles. This approach has been applied to the synthesis of racemic 2,5-dimethylphospholanes. While the generated structures are not chiral, presumably this route can become enantioselective through the development of a chiral catalyst.

3. Asymmetric catalysis with phospholanes

In light of the success of the DuPHOS ligands and the prior history of successful asymmetric catalysts, asymmetric hydrogenation is the primary benchmark for testing most new chiral phosphines. Due to several comprehensive reviews, which have recently been published on hydrogenations,[19,20,96] we focus on the applications of phospholanes towards other asymmetric catalytic transformations.

3.1. Acylation

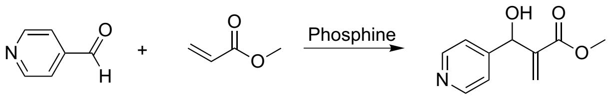
Alkyl phosphines are electron rich and consequently have been applied as nucleophilic catalysts. In 1993, Vedejs and Diver reported the use of tributylphosphine as an acylation catalyst similar in reactivity to DMAP.[97] The use of the Burk monophospholane enables the acylation of several alcohols with moderate enantioselectivity at 10% conversion, but with relatively poor reactivity.[98] Vedejs postulated that a reduction in the steric bulk around the phosphorus lone pair would improve the reactivity of the phospholane. The PBO catalyst system developed by Vedejs exhibited very efficient kinetic resolutions of alcohols in the acylation with $(i\text{-PrCO})_2O$.[63,99–102] Particularly high selectivities can be achieved with aryl alkyl carbinols (Scheme 19). Allylic alcohols also are resolved with moderate to good selectivities depending on the steric bulk and conformational flexibility of the alcohol.[103]



Scheme 19. Alcohol kinetic resolution.

3.2. Baylis–Hillman reaction

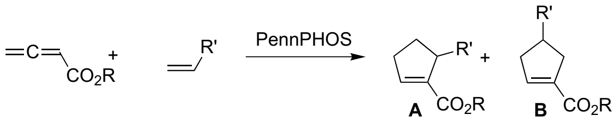
Another transformation catalyzed by phosphines is the Baylis–Hillman reaction.[104] The Baylis–Hillman reaction involves the addition of an electrophile, such as an aldehyde, to an activated olefin in the presence of a tertiary amine or phosphine. Hydroxy monophospholane **22** was applied to the Baylis–Hillman reaction (Scheme 20) to provide the product with low enantioselectivity (17% ee).[76] However, it was noted that the tetrahydroxy phospholane enhances the rate of the reaction to a significant extent when compared to the analagous *iso*-propylidene protected phospholane **21**.



Scheme 20. Baylis–Hillman reaction.

3.3. Phosphine catalyzed cycloadditions

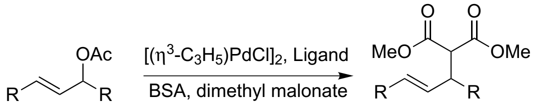
Recent work has demonstrated that phosphines catalyze [3+2] cycloadditions. Zhang et al. successfully applied the PennPHOS ligand to the [3+2] annulation reaction (Scheme 21).[105] The reaction is highly regioselective and the **A** regioisomer formed with 81% ee in benzene at room temperature (R = Et, R′ = CO_2Et).



Scheme 21. [3+2] Cycloaddition.

3.4. Allylic alkylation

Numerous research groups have applied phospholanes as ligands for transition metal catalysts of allylic alkylation reactions (Scheme 22). There are many variants of the allyl substitution reaction, however only three test substrates (diphenylallyl acetate, dimethylallyl acetate and cyclohexenyl allyl acetate) are commonly used to gauge new ligands. A wide range of phospholane structures have been applied to Mo, Pd, Rh and Ir catalyzed allylic alkylations including P–P and P–N mixed ligands. Examples of selectivities for several different ligands are presented in Figure 9.[31,56,61,81,93,106,107]



Scheme 22. Allylic alkylation reaction.

The most common test substrate for allylic alkylation is 1,3-diphenylallyl acetate (R = Ph). However, this is not a particularly demanding substrate as many ligands provide the product in >97% ee.[108] In general, the chirality of the phospholane appears to determine the absolute configuration of the product when mixed ligands are used. Phospholanes have been successfully applied to more challenging substrates such as 1,3-dimethylallyl acetate (R = Me) and 1-cyclohex-2-enyl acetate. Landis and Clark reported that the mixed phospholane-amide **30** could be used in the allylic alkylation of 1,3-dimethylallyl acetate in up to 92% ee, which matches the highest reported selectivity to date. Osborn et al. reported that cyclohexenyl acetate undergoes allylic alkylation with the DuXantPHOS ligand **31** in up to 87% ee (at 20 °C), which is amongst the highest values reported for that substrate.

3.5. Copolymerization

Me-DuPHOS has been applied to the Pd-catalyzed copolymerization of α-olefins and carbon monoxide.[109] Jiang and Sen reported that copolymerization reactions

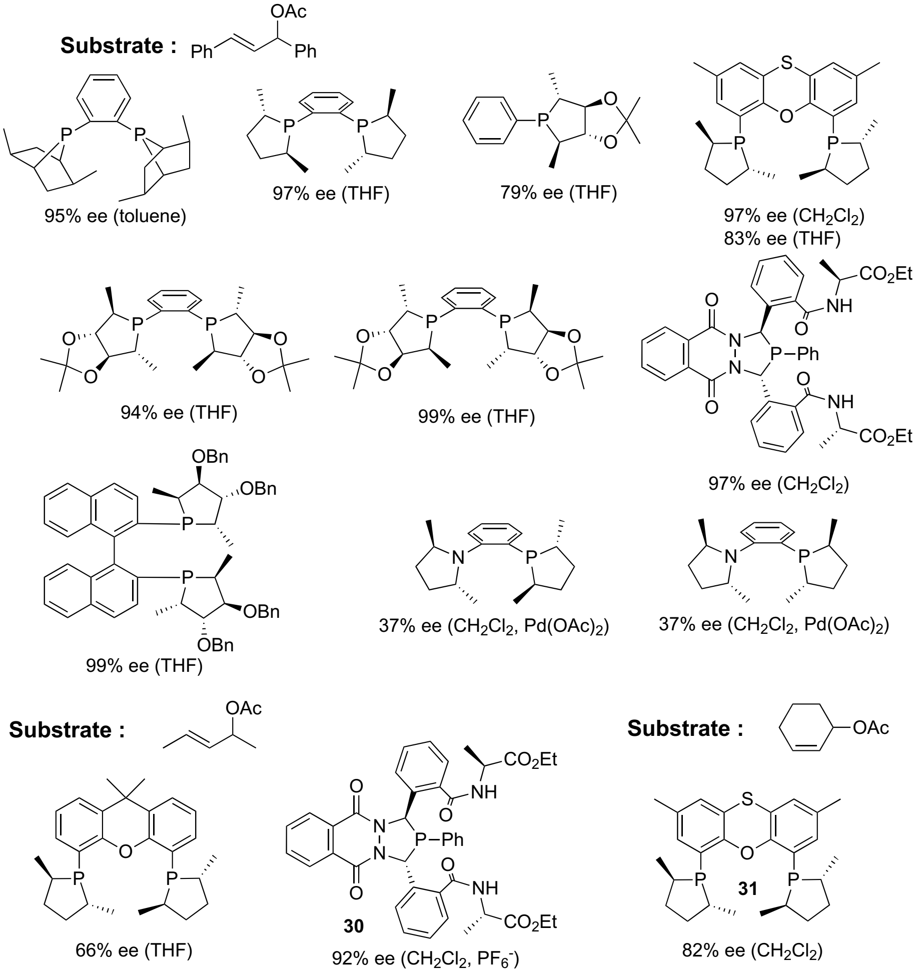
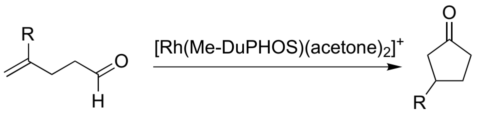


Figure 9. Ligands for allylic alkylation.

of propylene and CO with [Pd(Me-DuPHOS)-$(CH_3CN)_2](BF_4)_2$ provides isotactic mixtures of the 1,4-ketal and spiroketal units with greater than 90% enantioselectivity. Additionally, polymerization of 2-butene and carbon monoxide can be accomplished with a palladium–DuPHOS catalyst to give an isotactic poly(1,5-ketone). A significant advantage of late transition metal catalysts for alkene/CO copolymerizations is its tolerance to functional groups. However, the inclusion of functional groups on the alkene monomer commonly leads to decreased reactivity, particularly when the functional groups are located near the olefin. This presumably results from coordination of the functional group to the metal centre. The use of DuPHOS as the ligand appears to allow functional groups to be placed closer to the olefin functionality than with other ligands, presumably because the steric bulk of the phospholane hinders functional group coordination.[110] Copolymerization reactions with carbon monoxide have been extended to create polymers with amide, carbamate, hydroxyl and carboxylate olefins, as well as vinyl epoxides and fluoroalkenes.[110–113]

3.6. Hydroacylation

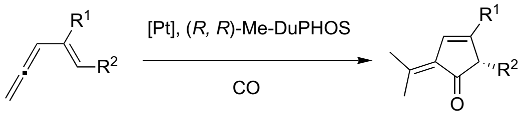
The asymmetric intramolecular hydroacylation of 4-substituted pent-4-enals has been developed using a Rh–BINAP catalyst.[114] Bosnich et al. have found that Me-DuPHOS provides products for this class of substrates in greater than 90% ee with high turnover frequency (Scheme 23).[115] When R is either a primary or secondary group, selectivities are low.



Scheme 23. Hydroacylation.

3.7. Cycloaddition with CO

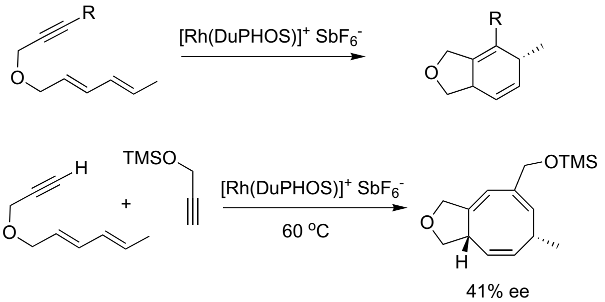
Murakami et al. have applied the DuPHOS ligand to the [4+1] cycloaddition of vinylallenes with carbon monoxide (Scheme 24).[116,117] (*R*,*R*)-Me-DuPHOS and (*R*,*R*)-Et-DuPHOS were evaluated for selectivity with a couple of substrates and it was found that the Et-DuPHOS–Pt complexes catalyzed the reaction with slightly better selectivity (4–10% ee difference).[117] In all cases tested, DuPHOS provided the product with moderate to good enantioselectivity (64–79% ee). It was also observed that the inclusion of an ester at the R^1 position led to highly selective products in the cycloaddition (>90% ee).



Scheme 24. Cycloaddition with CO.

3.8. Cycloisomerization

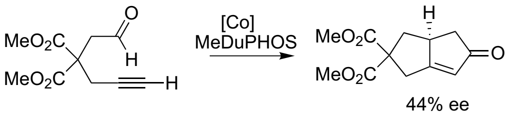
Phospholanes have also been used as ligands for metal catalyzed [4+2] cycloisomerizations. Gilbertson et al. reported that a Rh–DuPHOS complex catalyzes the cycloisomerization of dienynes with up to 95% ee.[118] Reactions with Me-DuPHOS give higher selectivity than the ligands BINAP, ChiraPHOS and DIOP under the same conditions. It was found during this study that a significant amount of the dimer formed from the insertion of another equivalent of the alkyne. As a result, this reaction has been extended to a [4+2+2] cyclization involving a dieneyne and an alkyne. Unfortunately, enantioselectivity in these reactions was low (Scheme 25).[119]



Scheme 25. Cycloisomerization.

3.9. Pauson Khand reaction

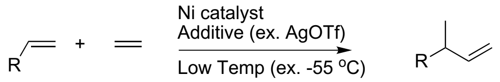
The Pauson Khand reaction is a well known route in the synthesis of 2-cyclopentenones (Scheme 26). An asymmetric route has recently been reported in which a small array of phosphines were screened for selectivity.[120] Me-DuPHOS metal complexes catalyze the reaction with moderate selectivity, but are out performed by BINAP. However, Me-DuPHOS does provide much higher selectivity for this reaction than DIOP, ferrocenyl phosphines and binaphthyl diamine.



Scheme 26. Pauson Khand reaction.

3.10. Hydrovinylation

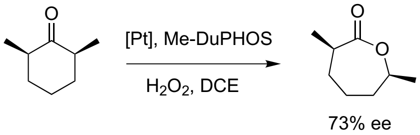
Asymmetric hydrovinylation of olefins is a potentially potent method for C–C bond formation (Scheme 27).[121] In particular, hydrovinylation of vinylarenes is a particularly attractive target, as the chiral products are relevant starting materials for pharmaceuticals. The phospholane structures in Figure 5 have shown promise as a ligand in the Ni-catalyzed hydrovinylation of 2-methoxy-6-vinylnaphthalene. However the reaction has only moderate selectivity (up to 50% ee) and it is quite sensitive to additives.[53,122] The reaction is also highly sensitive to the steric bulk at the 2,5-positions on the phospholane. Changing the group at the 2,5-position from a methyl to an ethyl group leads to an improvement in the selectivity in the hydrovinylation of styrene (67% vs 50% ee), but the use of an *iso*-propyl group leads to an inactive catalyst.[121] This compares to the best reported enantioselectivity reported to date of 93% ee.[123] Phospholane acetals, such as **15**, have recently been shown to exhibit high selectivities (88% ee for styrene) and appear to have promise as ligands for further development.[54]



Scheme 27. Hydrovinylation.

3.11. Baeyer–Villiger oxidation

An interesting application of the DuPHOS ligand concerns the Pt-catalyzed Baeyer–Villiger reaction (Scheme 28).[124] The oxidation of *meso*-cyclohexanones occurs in the presence of a Pt–DuPHOS catalyst with 35% hydrogen peroxide as the oxidant.[125] The reaction provides the product with 73% ee, which is roughly identical to results using BINAP as the ligand. Results with both of these bisphosphines give significantly higher selectivities than other bisphosphines tested.



Scheme 28. Baeyer–Villiger oxidation.

4. Future directions

The Burk route to chiral phospholanes has been successfully applied to the synthesis of a wide range of phospholanes. Although some examples of DuPHOS variants exhibit enhanced selectivities, the DuPHOS phospholanes remain the ligand of choice for new asymmetric reactions. Improving the selectivity of phospholane-based ligands will require more dramatic changes from the DuPHOS structure.

In order to maximize the chances of success for a new phospholane, a greater diversity of structures and functional groups is required. Thus, phospholanes that can be extended combinatorially, especially with inclusion of a large variety of functional groups, are attractive targets. Several recent reports mark progress towards this goal. The recent reports of inclusion of a carboxylic acid functionality into phospholane structures have the potential for further development (Schemes 14 and 16). Clark and Landis have demonstrated that amino acid chemistry can be readily applied to phospholane structures containing a carboxylic acid functionality to create an easily accessible, extensible collection of structures (Scheme 17). Correspondingly, the 2,5-hydroxyl functionalized phospholanes, such as **23**, hold potential as starting points for large arrays of ligands.

Another avenue for further development is the application of phospholanes as ligands in the catalysis of non-hydrogenation reactions. Phospholanes are excellent ligands for hydrogenation catalysts; it is likely that phospholanes will be effective in many other catalytic transformations, such as hydroformylation. The catalytic transformations reviewed herein demonstrate the widening range of reactions for which phospholanes are effective ligands or catalysts by themselves. Although selectivities for these reactions are often not very high, it must be noted that a broad range of phospholanes have not been tested for these transformations. As Vedejs et al. have demonstrated with their development of a highly selective catalyst for the kinetic resolution of aryl and allyl alcohols, varying the structure of the phospholane to match the unique demand of a particular substrate can lead to highly selective catalysts.

5. Conclusion

Phospholanes, along with the BINAP and chiral ferrocenyl phosphines, continue to define the state-of-the-art in ligands for asymmetric catalysis. Future work will certainly include faster and more flexible syntheses of these important structures. As a result, one is virtually certain to see chiral phospholane ligands continue to play leading roles in the rapidly expanding applications of asymmetric catalysis to organic transformations.

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