Chemistry–A European Journal
Review
doi.org/10.1002/chem.202303760
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

A Powerful P–N Connection: Preparative Approaches, Reactivity, and Applications of *P*-Stereogenic Aminophosphines

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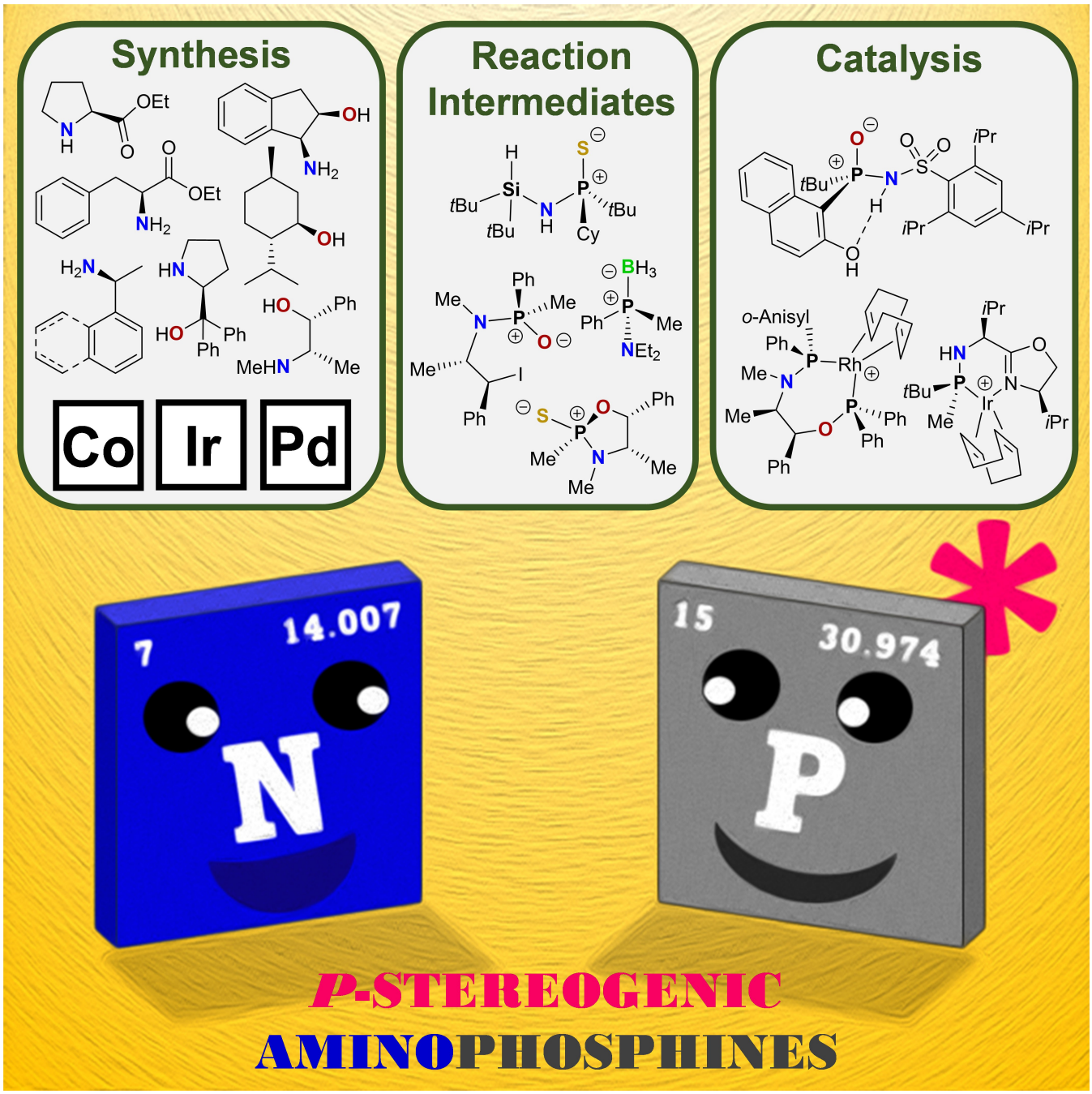

For more than five decades, *P*-stereogenic aminophosphine chalcogenides and boranes have attracted scientific attention and are still in the focus of ongoing research. In the last years, novel transition metal-based synthesis methods have been discovered, in addition to the long-known use of chiral auxiliaries. Enantiomerically pure compounds with N–P^+–X^- (X = O, S, BH_3) motifs served as valuable reactive building blocks to provide new classes of organophosphorus derivatives, thereby preserving the stereochemical information at the phosphorus atom. Over the years, intriguing applications in organocatalysis and transition metal catalysis have been reported for some representatives. Asymmetric reductions of C=C, C=N, and C=O double bonds were feasible with selected *P*-stereogenic aminophosphine oxides in the presence of hydrogen transfer reagents. *P*-stereogenic aminophosphine boranes could be easily deprotected and used as ligands for various transition metals to enable catalytic asymmetric hydrogenations of olefins and imines. This review traces the emergence of a synthetically and catalytically powerful functional compound class with phosphorus-centered chirality in its main lines, starting from classical approaches to modern synthesis methods to current applications.

1. Introduction

Organophosphorus compounds, be they phosphines[1] or phosphine chalcogenides[2], have emerged as key derivatives for a variety of reactions in modern synthetic chemistry. Their suitability as intermediates[3] and organocatalysts[1b–e,2b,c,4] renders them essential and indispensable in today's research. Likewise, they have broad applications as ligands in transition metal catalysis[1a,2a,5] and are used for hydrogenation reactions.[6] In general, P(III) organophosphorus compounds are investigated more frequently. However, a great advantage of P(V) compounds is their stability against air and moisture. Investigations of the latter compounds are therefore rising.[2c,7]

For the further development of catalysis, it is of great interest to introduce specific functional entities into the molecules, which enable them to interact with key intermediates during catalytic processes. This is feasible with heteroatomic moieties like amino groups that are capable of further functionalization[8] or that have exceptional qualities for use as synthesis intermediates and precursors.[9] The N–P^+–Ch^- (Ch = chalcogenide) motif proved to be a beneficial feature for novel ligands,[10] in catalysis,[11] and in medicinal chemistry.[12] In addition, amino- and thiophosphates have recently been proposed as plausible molecules in early Earth scenarios.[13] Especially in the context of ligand design, oxidation of P(III) compounds with selenium has many advantages, as the ^{77}Se NMR spectroscopic parameters such as the $^1J_{P-Se}$ coupling constant provide important information about the electronic nature of the new phosphines.[7c,f,g]

The possibility that both tri- and tetra-substituted phosphorus compounds can exhibit phosphorus-centered chirality is another important feature of these molecules, which is worth taking advantage of. Synthesis methods often involve the use of chiral auxiliaries, leading to diastereomeric mixtures that need to be separated.[14] A great advantage of P(III) and P(V) compounds with chloro substituents is their ability to be resolved by dynamic kinetic resolution using chiral alcohols and amines, thus leading to the enrichment of one favored stereoisomer.[15] Furthermore, the stereoselectivity of the resolution is strongly dependent on the reaction conditions, such as temperature, solvent, base, and the ratio of starting materials.[16] Highly diastereomerically pure compounds could be obtained by separation techniques like fractional crystallization or chromatography. The desired enantiomers can then be obtained by cleavage of the chiral auxiliary.[14] The first examples were already reported in the late 1960s[17] and various preparation methods for *P*-stereogenic molecules have then been developed in the following decades.[18] While many synthetic routes to all-*C*-substituted *P*-stereogenic compounds are known,[19] heteroatom-substituted analogues have so far received comparatively little attention. Applications can be found as intermediates,[20] in organocatalysis,[21] for enantioselective hydrogenations,[20e,22] and for the design of new ligands.[15a,23]

In this Review, we provide a comprehensive overview on the powerful connection between phosphorus and nitrogen under stereochemical aspects. We focus on *P*-stereogenic aminophosphine chalcogenides and boranes and provide a systematic overview of classical and modern synthetic methods and highlight perspectives for applications of these stereochemically valuable functional molecular building blocks in synthesis and asymmetric catalysis. Reports about deprotected aminophosphines for use as ligands in transition metal catalysis are included as well. Aminophosphinic compounds are also discussed in this Review, as they have provided impressive utility to the world of asymmetric organocatalysis.

2. Auxiliary-Based Approaches Towards *P*-Stereogenic Aminophosphine Chalcogenides and Boranes

The use of monodentate chiral auxiliaries is still a widely used method to introduce a stereogenic phosphorus center. For this purpose, readily available *C*-stereogenic auxiliaries are used. Due to the possibility of diastereomeric separation methods, this approach is often more reliable in terms of stereoselectivity

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than novel techniques such as the challenging organocatalyzed synthesis of single enantiomers. For example, in 2016, the preparation of *P*-stereogenic oxazaphospholidines catalyzed by tertiary amines only gave moderate enantioselectivities, possibly due to unwanted side reactions.[24] *P*-stereogenic compounds with P–N bonds are often prepared as chalcogenides or boranes and are either used directly as they are or are deprotected prior to use depending on the intended synthetic purpose. Some examples for commonly used chiral auxiliaries are shown in Figure 1.

In the late 1970s, the group of Koizumi provided a general route applying L-proline ethyl ester [(S_C)-**1**] as chiral auxiliary (Scheme 1).[25] After coupling the amino acid derivative with phenyldichlorophosphate (**2**), a diastereomeric mixture of **3** was obtained, which could be functionalized stepwise with alcohols. Anhydrous pyridine was used both as solvent and HCl scavenger. In a subsequent reaction, the remaining P–Cl bond was substituted by ethanol or *n*-butanol. At this point, the diastereomers (S_C,S_P)-**4** and (S_C,R_P)-**4** were separated by column chromatography before subjecting the individual diastereomers to further functionalization. For cleaving the P–N bond, heating at reflux under strongly acidic conditions in the respective alcohol (methanol, ethanol or *n*-propanol) was required. With this method, the optically active dialkylphenylphosphates (S_P)-**5** and (R_P)-**5** were generated with enantiomeric ratios of 97 : 3, according to the Eu(hfc)$_3$ shift method.[26] In a later publication, the substrate scope was expanded to include amino and alkyl groups instead of using only alkyloxy moieties, and sulfide-functionalized starting compounds were also introduced.[27]

A second amino acid derivative-based approach was described by Koizumi et al. using L-phenylalanine ethyl ester [(S_C)-**6**] for synthesizing the alkylphenylphosphoramidates (S_P)-**10** and (R_P)-**10** (Scheme 2).[28] Again, phenyldichlorophosphate (**2**) was the starting material of choice and was initially coupled

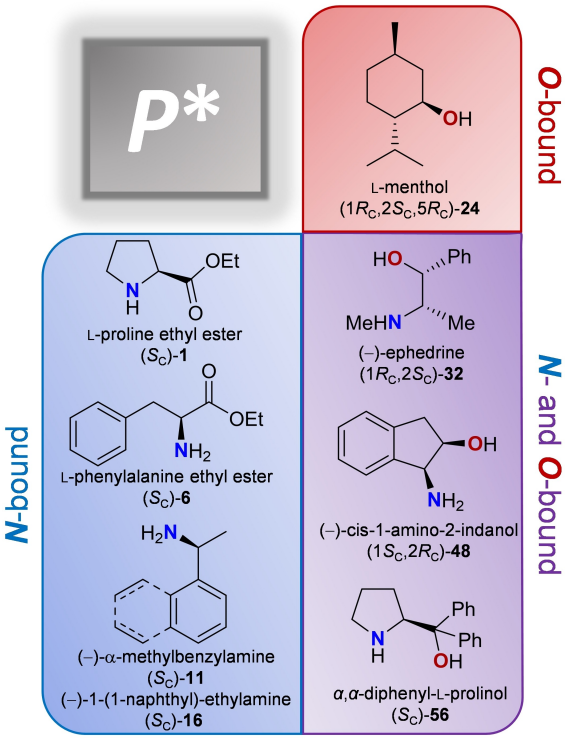

Figure 1. Commonly used *O*- and *N*-bound chiral auxiliaries.

with the amino acid derivative (S_C)-**6** in tetrahydrofuran using triethylamine as HCl scavenger. To introduce the second alkyloxy moiety, the intermediate was then reacted with either methanol or ethanol. Since separation of the resulting 1 : 1 diastereomeric mixture of **7** has failed at this point, the reaction sequence was continued by *N*-chlorination with *t*BuOCl. The *N*-chlorinated products (S_C,S_P)-**8** and (S_C,R_P)-**8** could then be

Tanja Huber was born in Ingolstadt (Germany) and studied Chemistry at the Ludwig-Maximilians-Universität München (LMU, Germany). After receiving her Bachelor's degree in 2016, she continued with her Master studies at the same university and graduated in 2018. During a research stay in the group of Professor Neil Burford at the University of Victoria (Canada) in 2016, she gained first insights into the chemistry of phosphorus compounds. In 2019, she moved to the University of Regensburg (Germany) to join the research group of Jonathan O. Bauer for her doctoral thesis about P-stereogenic aminophosphine chalcogenides and the investigation of their supramolecular aggregation behavior.

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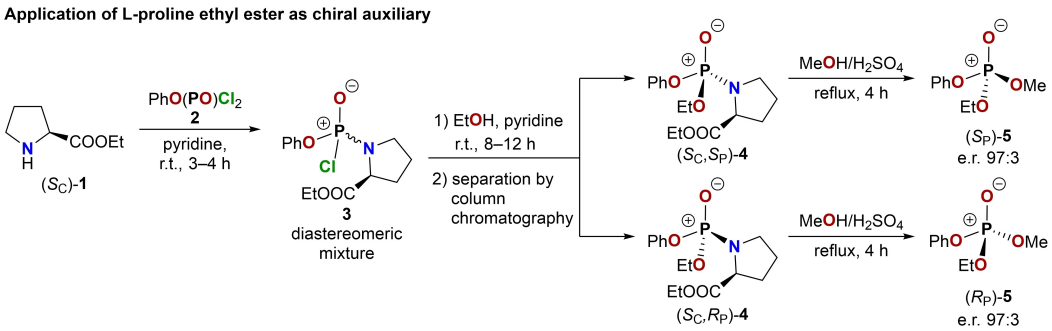
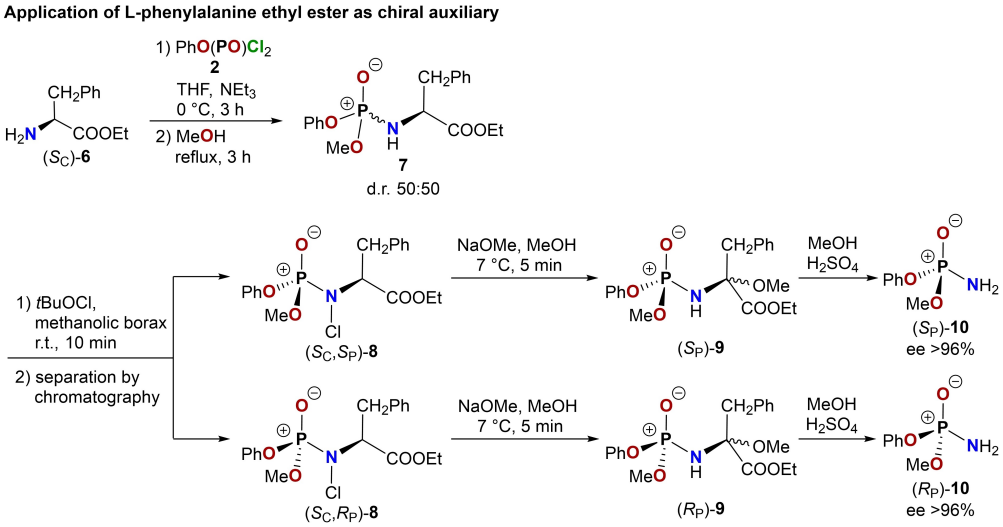


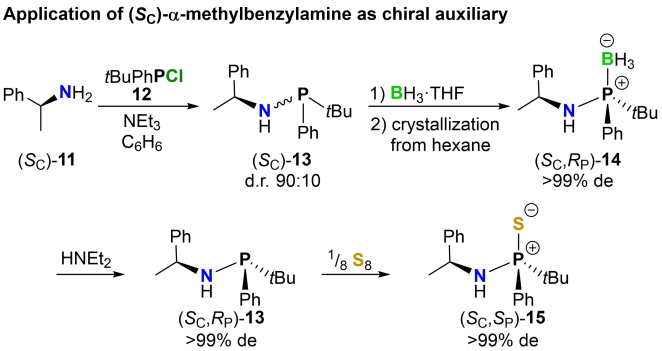
Scheme 1. Syntheses of (S_P)-**5** and (R_P)-**5** using L-proline ethyl ester [(S_C)-**1**] as chiral auxiliary, and subsequent twofold alcoholysis.[25a]



Scheme 2. Syntheses of (S_P)-**10** and (R_P)-**10** after using L-phenylalanine ethyl ester [(S_C)-**6**] as chiral auxiliary (THF = tetrahydrofuran).[28]

separated by flash chromatography and further used in their crude state. Before the chiral auxiliary could be cleaved to afford the desired phosphoramidate, the pure diastereomers had to be transformed into a species that allowed C–N bond cleavage. For this purpose, the individual diastereomers (S_C,S_P)-**8** and (S_C,R_P)-**8** were subjected to alkaline methanolation by sodium methoxide in dry methanol at 7 °C. The resulting amino acetals (S_P)-**9** and (R_P)-**9** were each formed as epimer mixtures. However, this epimerism was irrelevant, since the concerning part was meant to be cleaved from the actual product in the next step by sulfuric acid in methanol.[28] After purification by silica chromatography, the enantiomeric excesses of products (S_P)-**10** and (R_P)-**10** were determined to be over 96% by the Eu(hfc)$_3$ shift method.[26] Furthermore, the stereochemistry of acid-catalyzed alcoholysis was studied[28] and compared with previous results.[29]

Synthesis and investigation of *P*-chiral N–P$^+$–S$^-$ compounds have been rather neglected compared to the corresponding oxides. In the course of investigations by Kolodiazhnyi and co-workers in 2003,[16,30] diastereomeric *P*-chiral phosphine sulfides with (S_C)-α-methylbenzylamine [(S_C)-**11**] as the chiral auxiliary were reported, but not further considered for follow-up reactions.[16,30] Compound (S_C)-**11** was also used for providing *P*-chiral 4-nitrophenyl alkyl methylphosphonothioates.[31] In Kolodiazhnyi's multiple step preparation (Scheme 3), an unsymmetric dialkyl- or alkylaryl-chlorophosphine (**12**) was reacted with the chiral auxiliary (S_C)-**11** to afford (S_C)-**13** (d.r. 90:10), which was subsequently treated with BH$_3$·THF in order to obtain the diastereomerically pure, borane-protected product (S_C,R_P)-**14** after recrystallization from hexane. After removing the borane, the aminophosphine intermediate (S_C,R_P)-**13** was usable for



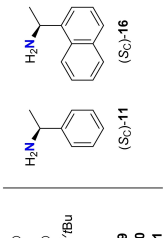
Scheme 3. Synthetic pathway towards (S_C,R_P)-**14** and (S_C,S_P)-**15** reported by Kolodiazhnyi.[16,30]

several further transformations, such as oxidation with hydrogen peroxide or elemental sulfur leading to compound (S_C,S_P)-**15**.[16,30]

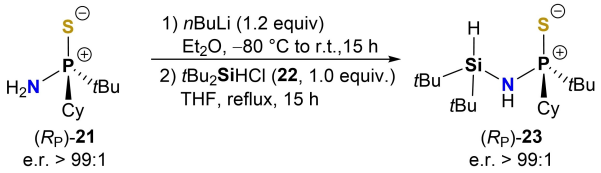
In 2010, Riera, Verdaguer, and co-workers presented a way to cleave the C–N bond of the chiral auxiliary in BH_3-protected *tert*-butylphenylaminophosphines (Table 1, entries 1 and 2).[32] In a solution of lithium in liquid ammonia, it was possible to attain the desired cleavage. However, due to the strongly reductive conditions, the phenyl substituent at the phosphorus atom underwent a Birch-type reduction when using (S_C)-α-methylbenzylamine [(S_C)-**11**] as chiral auxiliary, leading to compound (S_P)-**19** (Table 1, entry 1). This unwanted reduction could be prevented by using (S_C)-1-(1-naphthyl)-ethylamine [(S_C)-**16**] as chiral auxiliary. Thus, the desired product (R_P)-**20** could be obtained (Table 1, entry 2).[32] Inspired by those findings, Bauer and co-workers published a thorough investigation of sulfurized analogues in 2022.[33] In the case of aminophosphine sulfides, mixtures with intact and reduced phenyl substituents at the phosphorus atom were observed, no matter if (S_C)-α-methylbenzylamine [(S_C)-**11**] or (S_C)-1-(1-naphthyl)ethylamine [(S_C)-**16**] was used as chiral auxiliary. Furthermore, the molecules were not spared from P–Ph and P–S bond cleavage, which made the phenyl substituent impractical for this kind of reaction. The key to the applicability of the Li/NH_3 mixture was simply to replace the phenyl substituent by an aliphatic cyclohexyl substituent (Table 1, entry 3). The resulting cleavage product (R_P)-**21** was the first reported enantiomerically pure *P*-stereogenic primary aminophosphine sulfide. It represents a class of functionalizable precursors, which could be demonstrated by coupling it with a chlorosilane (**22**), affording compound (R_P)-**23** (Scheme 4). With that in mind, novel *P*-chiral ligands and organocatalysts might be achievable. Additionally, a new spectroscopic method for determining the enantiomeric purity of aminophosphine sulfides using the lithium salt of (*R*)-BINOL-dithiophosphoric acid as chiral shift reagent was presented and demonstrated that no racemization has occurred during the reductive elimination.[33]

A long-known[17c,18i,34] *O*-bound auxiliary-based method was applied in 2018 by Stankevič et al.,[35] when diastereomerically pure aminophosphine boranes were synthesized with L-menthol [(1R_C,2S_C,5R_C)-**24**] as chiral auxiliary and used as reactive intermediates to obtain methylphenylphosphinous acid methyl ester borane [(S_P)-**31**] (Scheme 5). After coupling of dichlorophenylphosphine (**25**) with L-menthol [(1R_C,2S_C,5R_C)-**24**] in the presence of triethylamine, compound (1R_C,2S_C,5R_C)-**26** was obtained and the remaining chloro substituent was exchanged using diethylamine (**27**), affording compound (1R_C,2S_C,5R_C)-**28**. Protection with borane enabled separation by fractional crystallization of the diastereomeric 1:1 mixture of (1R_C,2S_C,5R_C)-**29** from cyclohexane/Et_2O at −78 °C. One of the diastereomerically pure intermediates [(1R_C,2S_C,5R_C,R_P)-**29**] was then subjected to different electrophilic reagents, such as methyl iodide, after creating Birch-type reaction conditions that caused a P–O bond cleavage. Interestingly, the phenyl moiety was not affected by the strong reductive conditions as it was described by Riera and Verdaguer,[32] and by Bauer et al.[33] It is known that the outcome of Birch-type reductions of arylphosphoric acid amides is highly

Table 1. Reductive C–N bond cleavage of (S_C,R_P)-**14**[32], (S_C,R_P)-**17**,[32] and (S_C,R_P)-**18**[33] under Birch-type reaction conditions.



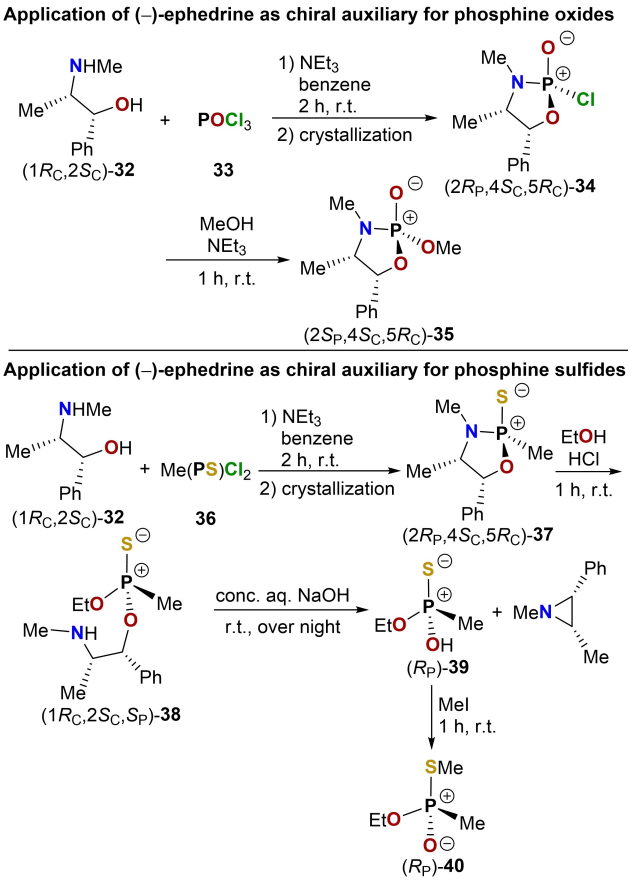
entry	t [min]	Ar	X	R^1	R^2	chiral auxiliary	starting material	product	purity of product	
1	5–10	Ph	BH_3	Ph	1-(cyclo-hexa-2,5-dien)	(S_C)-**11**	(S_C,R_P)-**14**	(S_P)-**19**	not determined	Riera and Verdaguer, **2010**
2	5–10	1-Naph	BH_3	Ph	Ph	(S_C)-**16**	(S_C,R_P)-**17**	(R_P)-**20**	99 % ee	Riera and Verdaguer, **2010**
3	2	Ph	S	Cy	Cy	(S_C)-**11**	(S_C,R_P)-**18**	(R_P)-**21**	99 % ee	Bauer, **2022**



Scheme 4. Synthesis of compound (R_P)-**23** by coupling enantiomerically pure (R_P)-**21** with an achiral chlorosilane (**22**).[33]

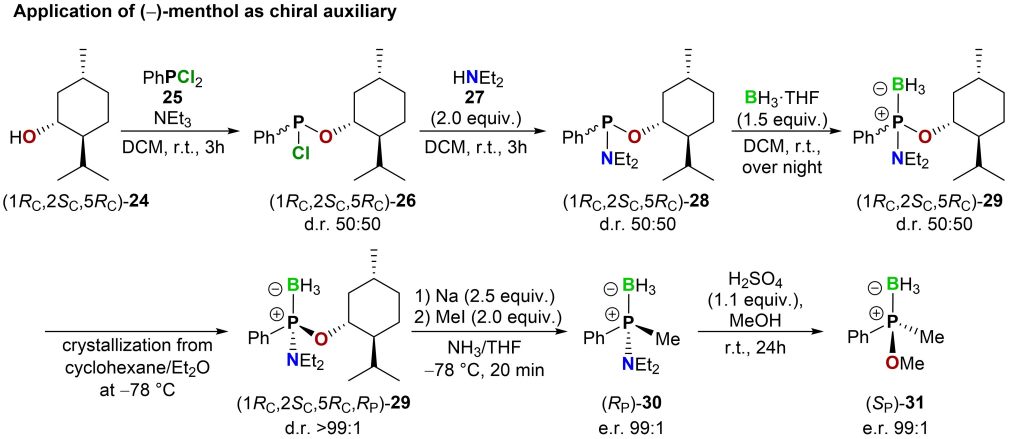
dependent on their substituents.[36] The enantiomerically pure product (R_P)-**30** could finally be transformed into a methyl ester (S_P)-**31** by stereospecific exchange of the diethylamino moiety through acidic methanolysis. The absolute configurations of all products were derived from literature precedents.[35]

Besides monodentate *N*- and *O*-bound chiral auxiliaries, also bidentate auxiliaries are part of the synthesis repertoire for providing *P*-stereogenic compounds. A prominent example is (–)-ephedrine [(1R_C,2S_C)-**32**], which was introduced by Inch[37] (Scheme 6) in the 1970s and further studied by Jugé (Scheme 7) around the turn of the millenium.[20a,b,22b,38] This auxiliary is capable of chelating a phosphorus center by forming a P–O and P–N bond in the same reaction step. Inch et al. used phosphoryl trichloride (**33**) in benzene and triethylamine as HCl scavenger to obtain a stereochemically pure, five-membered N–P(O)–O heterocycle [(2R_P,4S_C,5R_C)-**34**] after crystallization (Scheme 6, top). The remaining P–Cl bond could be subsequently functionalized when subjected to an alcohol in the presence of triethylamine, and compound (2S_P,4S_C,5R_C)-**35** was obtained. The substitution proceeded with retention of configuration.[37a,c] Chelation of monoalkyl-substituted phosphine sulfide **36** was likewise possible forming the N–P(S)–O heterocycle (2R_P,4S_C,5R_C)-**37**, which could be opened by P–N bond cleavage through acidic alcoholysis with inversion of configuration while forming compound (1R_C,2S_C,S_P)-**38** (Scheme 6, bottom). After alkaline treatment with sodium hydroxide, the non-isolated intermediate (R_P)-**39** was reacted with methyl iodide to get to (R_P)-**40**.[37b] The absolute configurations of all products were derived from literature precedents and all syntheses were described to be stereospecific.[37]

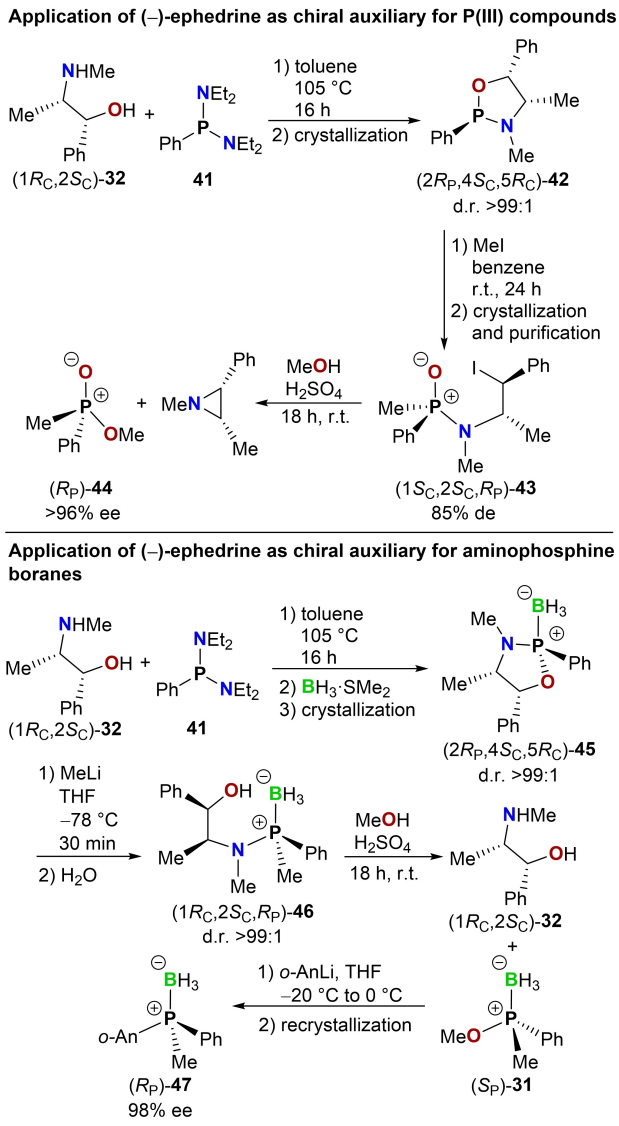


Scheme 6. Top: (–)-Ephedrine-based approach to chelate phosphoryl trichloride (**33**), and functionalization of the remaining P–Cl bond.[37a,c] Bottom: Synthesis of (R_P)-**40** after ring opening of (2R_P,4S_C,5R_C)-**37**.[37b]

Jugé and co-workers were using P(III) compounds for the reaction with (–)-ephedrine [(1R_C,2S_C)-**32**]. Instead of chloride, their starting materials (such as **41**) had diethylamine as leaving group, which worked well at high temperatures without using



Scheme 5. Synthesis towards diastereomerically pure (–)-menthol-substituted aminophosphine borane [(1R_C,2S_C,5R_C,R_P)-**29**], which can be substituted by a methyl and a methoxy entity while maintaining the stereochemical integrity at the phosphorus center (DCM = dichloromethane).[35]



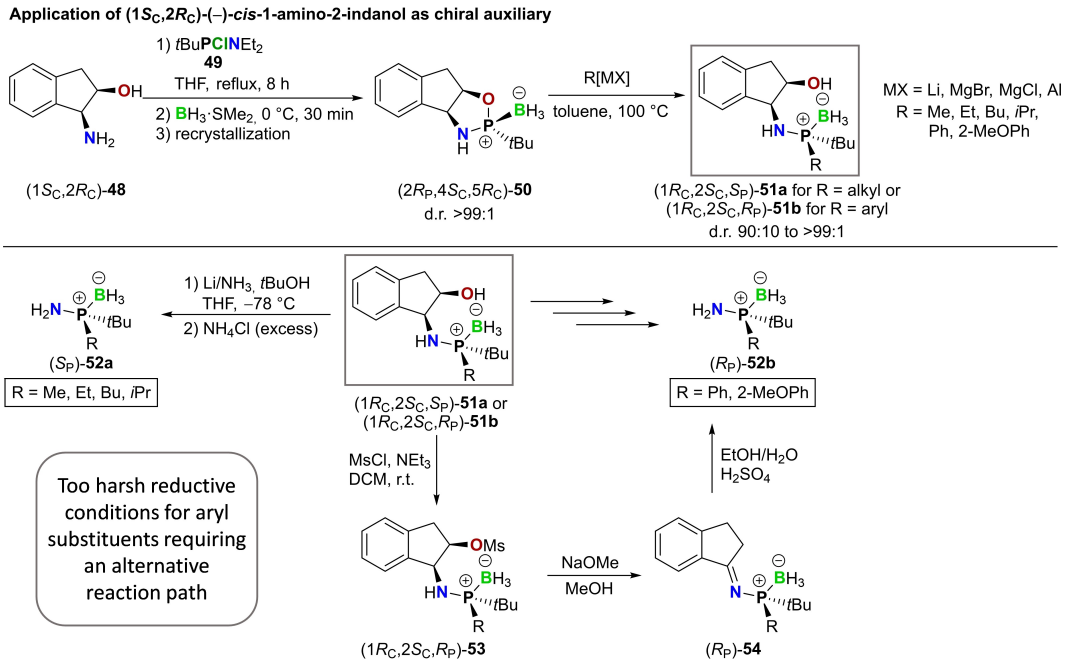
Scheme 7. Top: (–)-Ephedrine-based approach to (R_P)-**44** after Michaelis-Arbusow rearrangement and acidic methanolysis.[38a] Bottom: (–)-Ephedrine-based approach to obtain borane-protected phosphine (R_P)-**47** after four steps (*o*-An = *ortho*-anisol).[20a,b,38b]

any base (Scheme 7). The N–P(III)–O ring of ($2R_P$,$4S_C$,$5R_C$)-**42** was opened in a Michaelis-Arbusow rearrangement with retention of configuration at phosphorus through the reaction with alkyl halides such as methyl iodide. Aminophosphine oxide ($1S_C$,$2S_C$,R_P)-**43** was thereby formed with high diastereomeric excess featuring a stereogenic P(V) center. Subsequent acidic methanolysis led to cleavage of the P–N bond and afforded compound (R_P)-**44**. The alcoholysis took place with inversion of configuration (Scheme 7, top).[38a] After the reaction of (–)-ephedrine [($1R_C$,$2S_C$)-**32**] with bis(diethylamino)phenylphosphine (**41**), the phosphorus atom of the heterocycle could be protected by borane, obtaining compound ($2R_P$,$4S_C$,$5R_C$)-**45**. Reaction with methyllithium led to cleavage of the P–O bond with retention of configuration at phosphorus [($2R_P$,$4S_C$,$5R_C$)-**46**]. Acidic methanolysis led to P–N bond cleavage, which allowed (–)-ephedrine [($1R_C$,$2S_C$)-**32**] to be recovered. The methanolized phosphine borane (S_P)-**31** was obtained with inverted configuration and could be further reacted with aryl lithium compounds, again with inversion of configuration [(R_P)-**47**] (Scheme 7, bottom).[20a,b] Absolute configurations were determined by X-ray crystallography or assumed as previously reported.[20a,b,38b]

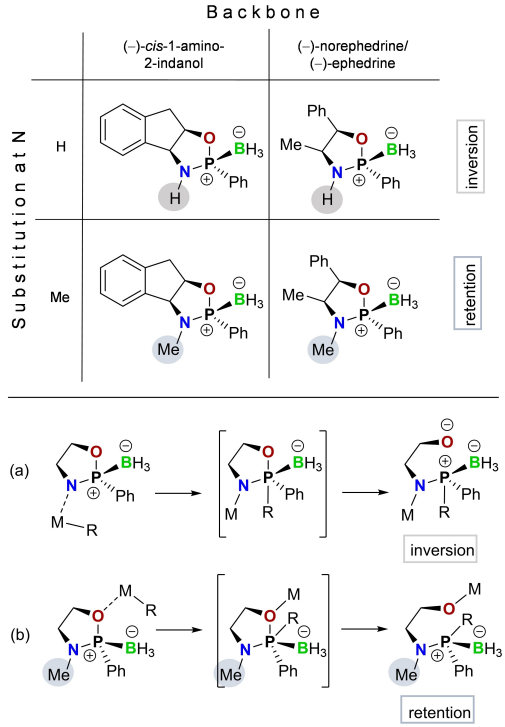
In 2011, Riera, Verdaguer, and co-workers published a method based on the (–)-ephedrine strategy, but with a variation of the backbone of the chiral auxiliary (Scheme 8, top).[20d] Using (–)-*cis*-1-amino-2-indanol [($1S_C$,$2R_C$)-**48**], a highly diastereomerically enriched product (d.r. 18:1) was obtained after reaction with *tert*-butylchlorodiethylaminophosphine (**49**) and borane dimethylsulfide complex. The pure major diastereomer ($2R_P$,$4S_C$,$5R_C$)-**50** could be obtained after recrystallization from hexane and the absolute configuration was determined by the anomalous dispersion method. The chiral auxiliary was removed in two steps. First, ring-opening with organometallic reagents led to cleavage of the P–O bond and gave ($1R_C$,$2S_C$,S_P)-**51a** (R = alkyl) or ($1R_C$,$2S_C$,R_P)-**51b** (R = aryl), while leaving the P–N bond intact. To the surprise of the authors, this happened in general with inversion of configuration for both alkyl and aryl substituents, no matter if Grignard or other organometallic reagents were used (Scheme 8, top).[20d] Previously investigated P–O bond cleavages in monocyclic 1,3,2-oxazaphospholes were reported to proceed with retention of configuration.[20b,38a,39] Excellent diastereomeric ratios were achieved using methylmagnesium bromide. Various other organometallic reagents also gave good ratios, not worse than 90:10, and the corresponding products could be purified by recrystallization from hexane or by column chromatography. In order to finally set the aminophosphine boranes (S_P)-**52a** (R = alkyl) free, the chiral auxiliary was cleaved using lithium in liquid ammonia, whereby the enantiomeric purity was completely maintained (> 99% ee). However, as also mentioned in other publications,[32,33] phenyl ring-containing substrates were reduced according to Birch reduction. The authors found a remedy for this circumstance by forming an iminophosphine after mesylation of the hydroxy group [($1R_C$,$2S_C$,R_P)-**53** (R = aryl)] and subsequent alkaline-mediated elimination towards (R_P)-**54** (R = aryl). Acidic hydrolysis afforded the corresponding aminophosphine boranes (R_P)-**52b** (R = aryl) with > 99% ee (Scheme 8, bottom).[20d]

In a follow-up publication two years later,[40] the results of a thorough investigation regarding the stereodivergent P–O ring opening were reported and an explanation of the differing stereochemical pathways of the findings of Riera and Verdaguer[20d] compared to those of Inch[39] and Jugé[20b] was given (Scheme 9, top). Three possible reasons were suggested: different substitution at phosphorus (*t*Bu vs. Ph), different substitution at nitrogen (H vs. Me) and different backbones [(–)-*cis*-1-amino-2-indanol vs. (–)-ephedrine].[40]

To find the main factor, Riera and Verdaguer additionally investigated *N*-methylated (–)-*cis*-1-amino-2-indanol and (–)-norephedrine as chiral backbones. For the reaction of the *N*,*O*-chelated phosphine boranes with organolithium compounds, the presence of an NH moiety provided inversion, while an NMe moiety provided retention at the stereogenic phosphorus atom



Scheme 8. Top: Synthesis of enantiomerically enriched and pure aminophosphine boranes ($1R_C,2S_C,S_P$)-**51 a** (R = alkyl) and ($1R_C,2S_C,R_P$)-**51 b** (R = aryl) using (–)-*cis*-1-amino-2-indanol [($1S_C,2R_C$)-**48**] as chiral auxiliary.[20d] Bottom: Differences in cleavage reactions for the substrates ($1R_C,2S_C,S_P$)-**51 a** and ($1R_C,2S_C,R_P$)-**51 b** (Ms = SO_2CH_3).[20d]



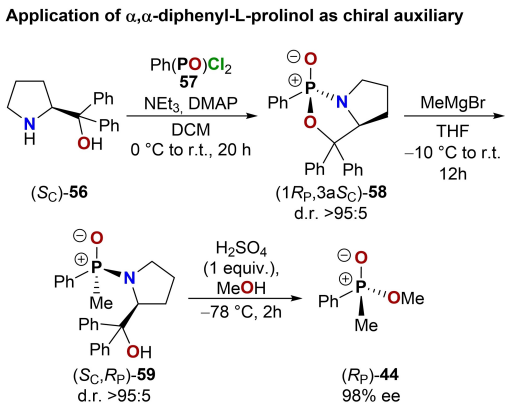
Scheme 9. Top: Overview of the different substitution patterns mentioned by Inch,[39] Jugé,[20b] Riera and Verdaguer.[20d,40] Bottom: Proposed mechanistic pathways of the reactions with NH or NMe entities.[40]

(Scheme 9, top). In case of NH, the cation of the organometallic reagent can deprotonate the nitrogen atom and the attack of R^- takes place from the backside leading to an inversion of configuration (Scheme 9, bottom, mechanism a). If the nitrogen atom is blocked by a methyl group, the cation temporarily sticks to oxygen causing R^- to attack from the frontside, which results in retention of configuration (Scheme 9, bottom, mechanism b). Proof of this hypothesis was supported by computational investigations of the mechanism. Consequently, the different reactivities of the *N*-methylated and non-*N*-methylated chiral auxiliaries can be exploited to obtain final products with both (R_P)- and (S_P)-configuration.[40]

Another approach with an *N,O*-bidentate chiral auxiliary included the application of α,α-diphenyl-L-prolinol [(S_C)-**56**].[41] Using dichlorophenylphosphine oxide (**57**) in the presence of triethylamine as HCl scavenger and DMAP as organocatalyst, the bicyclic 1,3,2-oxazaphospholidine-2-oxide intermediate ($1R_P,3aS_C$)-**58** was formed in an excellent diastereomeric ratio of >95:5 (Scheme 10). Reaction with MeMgBr resulted in the cleavage of the P–O bond and afforded (S_C,R_P)-**59**. The chiral auxiliary could be removed completely through acidic methanolysis of the P–N bond at −78 °C to form the corresponding methyl ester (R_P)-**44**. The absolute configurations were determined by single-crystal X-ray structure analysis of a follow-up product and the transformations were concluded to be inversion processes.[41b]

3. Transition Metal-Catalyzed Approaches Towards *P*-Stereogenic Aminophosphine Chalcogenides and Boranes

Along with the development of novel synthetic methods, the preparation of *P*-stereogenic compounds with P–N functions by



Scheme 10. Synthesis of diastereomerically pure α,α-diphenyl-L-prolinol-substituted aminophosphine oxide ($1R_P$,$3aS_C$)-**58**, and subsequent stereospecific methanolysis (DMAP = 4-(dimethylamino)pyridine).[41b]

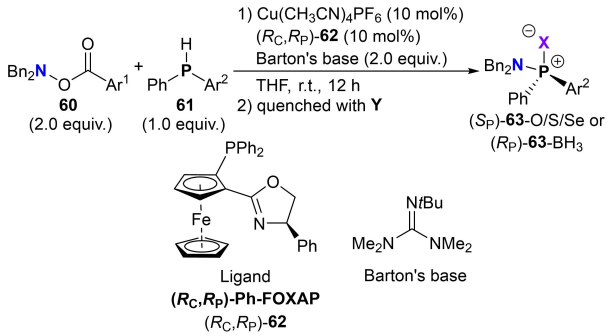
means of transition metal catalysis has been increasingly reported. Procedures for non-*P*-stereogenic or racemic compounds are also known from the literature.[42] Promising results in terms of conversion, stereoselectivity, and catalyst efficiency give reason for further innovative developments in the future.

3.1. Synthesis by Copper Catalysis

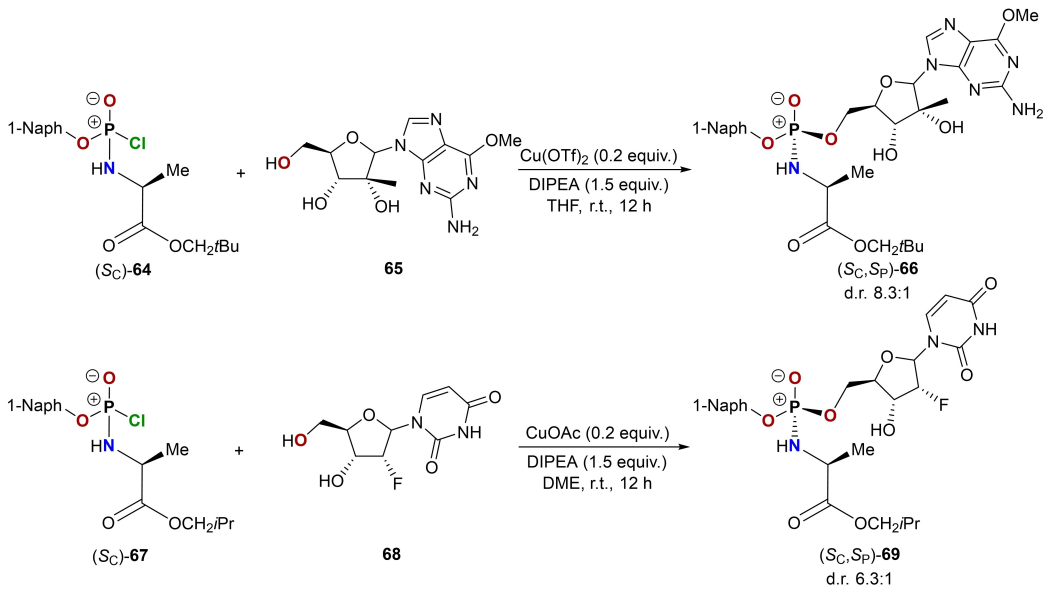
In 2022, Yin and co-workers presented a general procedure for copper(I)-catalyzed syntheses of *P*-stereogenic aminophosphine chalcogenides and boranes (Table 2).[43] The classes of coupling partners were *O*-benzoyl hydroxylamines and diarylphosphines. Several chiral ligands were tested to obtain asymmetric products with the best possible enantiomeric enrichment. The first choice fell on (R_C,R_P)-Ph-FOXAP [(R_C,R_P)-**62**], a diphenylphosphino- and 4-phenyloxazoline-substituted ferrocene derivative (Table 2). $Cu(CH_3CN)_4PF_6$ was used as catalyst in the presence of Barton's base. The P–N-coupled intermediate was then quenched with hydrogen peroxide. In this context, dibenzylaminoesters (**60**) with electron-deficient aryl groups such as 3,5-$(CF_3)_2$-C_6H_3 were found to increase both yield and stereoselectivity. The same is true for diarylphosphine substrates (**61**) with sterically hindered aryl substituents. The best result for substrates with PO entities [product (S_P)-**63**-O] in terms of enantiomeric excess (90%) was obtained with mesityl-substituted phosphines (**61**-Mes) (Table 2, entry 1), as determined by HPLC on a chiral stationary phase. The absolute configuration was determined by single-crystal X-ray structure analysis for one of the synthesized derivatives and deduced for all other obtained products. After the best conditions had been found, different reagents (sulfur, selenium, and borane-tetrahydrofuran-complex) were used instead of hydrogen peroxide for quenching the unprotected aminophosphine and afforded products (S_P)-**63**-S, (S_P)-**63**-Se, and (R_P)-**63**-BH_3 with enantiomeric excesses of 90%, 89%, and 92%, respectively (Table 2, entries 2–4).[43]

A copper-catalyzed synthesis of diastereomerically enriched *P*-stereogenic compounds containing a P–N bond was reported in 2015 through P–O bond coupling for the purpose of generating the nucleoside-based prodrugs (S_C,S_P)-**66** and (S_C,S_P)-**69** (Scheme 11). While purine-based substrates (**65**) gave the best results with copper(II) triflate (d.r. 1:8.3), the best choice for pyrimidine-based substrates (**68**) was copper(I) acetate (d.r. 1:6.3), whereby the absolute configurations were derived from comparable molecules previously reported in a patent. The respective catalytic reactions gave 35–40% conversion with *N*,*N*-diisopropylethylamine (DIPEA) as the base and tetrahydrofuran (THF) or dimethoxyethane (DME) as the solvent.[44] Strategies for several non-metal-catalyzed syntheses of nucleoside-based, *P*-stereogenic drugs, such as remdesivir [(S_C,S_P)-**74**] (Scheme 12) that was used during the COVID-19 pandemic,[45] were recently summarized in a review article.[46]

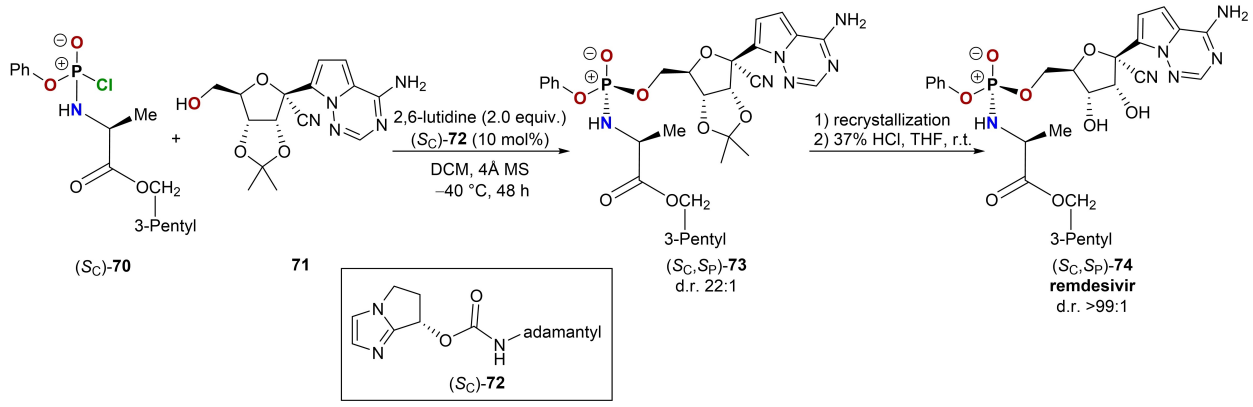
Table 2. Comparison of copper(I)-catalyzed syntheses to obtain enantiomerically enriched *N*,*N*-dibenzyl-*P*,*P*-diaryl-aminophosphine borane and chalcogenides yielding similar enantiomeric excesses.[43]



entry	Ar^1	Ar^2	Y	X	product	ee (%)
1	3,5-$(CF_3)_2$-C_6H_3	Mes	H_2O_2	**O**	(S_P)-**63**-O	90
2	3,5-$(CF_3)_2$-C_6H_3	2,6-Me_2-C_6H_3	S_8	**S**	(S_P)-**63**-S	90
3	3,5-$(CF_3)_2$-C_6H_3	2,6-Me_2-C_6H_3	**Se**	**Se**	(S_P)-**63**-Se	89
4	3,5-$(CF_3)_2$-C_6H_3	2,6-Me_2-C_6H_3	BH_3·THF	BH_3	(R_P)-**63**-BH_3	92



Scheme 11. Cu(II)- and Cu(I)-catalyzed syntheses of nucleoside-based prodrugs (S_C,S_P)-**66** and (S_C,S_P)-**69** through P–O bond coupling (DIPEA = *N*,*N*-diisopropylethylamine, DME = dimethoxyethane; stereodescriptors of compounds **65** and **68** have been omitted for clarity).[44]



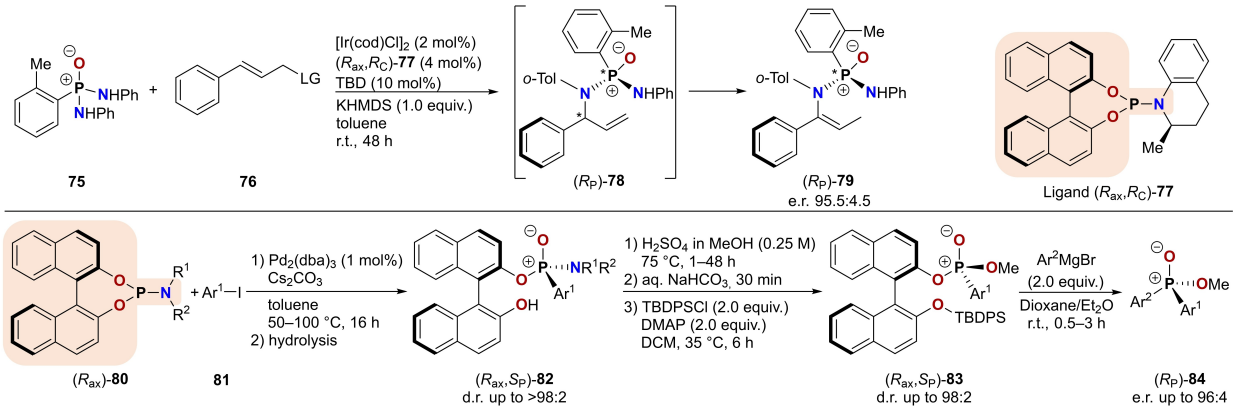
Scheme 12. Organocatalyzed synthesis of anti-COVID-19-drug remdesivir [(S_C,S_P)-**74**] through P–O bond coupling (2,6-lutidine = 2,6-dimethylpyridine; stereodescriptors of compound **71** have been omitted for clarity).[45]

Simple copper(I) and copper(II) salts have also been used for dehydrocoupling of P(O)–H bonds with primary amines. Both achiral and enantiomerically pure *P*-stereogenic H-phosphinates were applied and the coupling products showed overall good yields with 2 mol% copper(II) bromide as the catalyst in ethyl acetate. The optically pure starting materials incidentally maintained their stereochemical integrity in the product, albeit with inversion of configuration after the cross-coupling.[47]

3.2. Synthesis by Iridium Catalysis

Using $[Ir(cod)Cl]_2$ as the catalyst, an (*R*)-BINOL-based chiral ligand [(R_{ax},R_C)-**77**], and KHMDS as the base, access to *P*-chiral *N*-vinylphosphonamides such as (R_P)-**79** was opened (Scheme 13, top). The products were generated in excellent enantiomeric ratios up to 99:1 by asymmetric allylic substitution-isomerization, in which a non-chiral diaminophosphine oxide (**75**) reacted with an allylic compound such as diethyl cinnamylphosphonate (**76**). In the initial kinetically controlled reaction step, both a *C*- and a *P*-stereogenic center were each introduced by the coupling process, accompanied by a shift of the allylic double bond to the terminal position, affording compound (R_P)-**78**. However, due to thermodynamic control, the double bond is shifted back towards the C–N bond and the final product (R_P)-**79** is obtained. The absolute stereochemistry at phosphorus of the final product was determined by X-ray crystallography and deduced for all other obtained derivatives. One of the novel *N*-vinylphosphonamides was investigated for its applicability as chiral catalyst. Both iodocyclization of a phenol derivative and a reductive aldol reaction were investigated in this context.

Although they only showed enantiomeric ratios of not more than 60.5:39.5, they provide a valuable basis for further investigations regarding catalytic applications.[48]



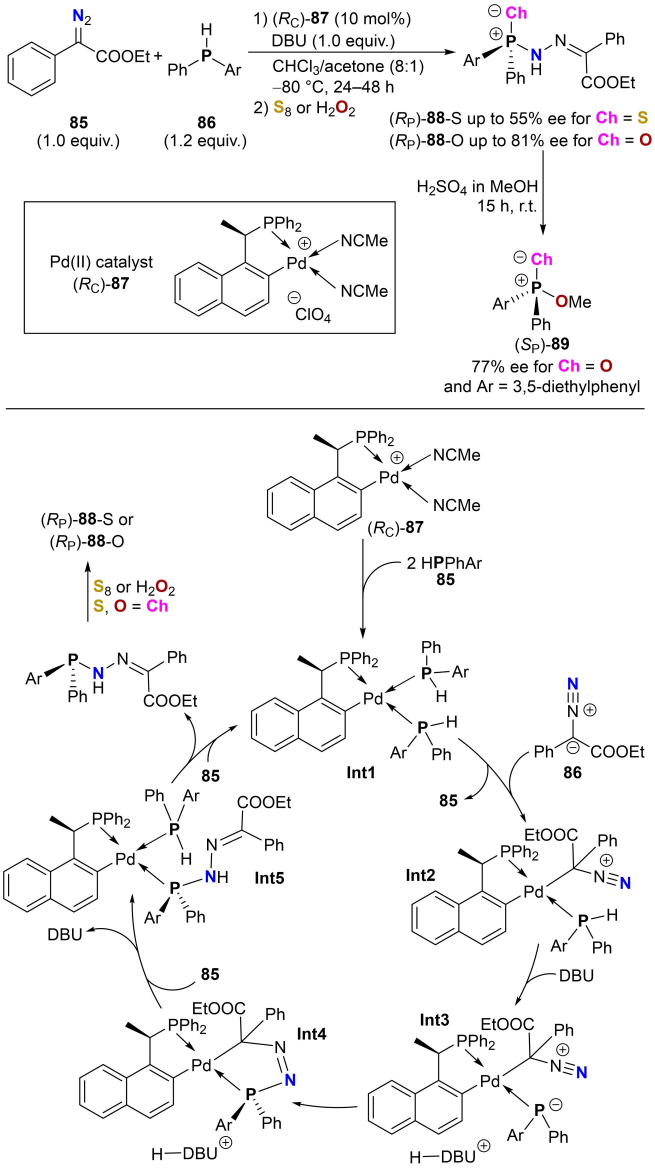
Scheme 13. Top: Iridium(I)-catalyzed synthesis of enantiomerically enriched (R_P)-**79** using the (*R*)-BINOL-based ligand (R_{ax},R_C)-**77** (LG = leaving group = OP(O)(OEt)$_2$, cod = 1,5-cyclooctadiene, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, KHMDS = potassium hexamethyldisilazane).[48] Bottom: Palladium(0)-catalyzed synthesis of enantiomerically enriched (*R*)-BINOL-substituted aminophosphine oxide (R_{ax},S_P)-**82** using derivatives of (R_{ax},R_C)-**77** as starting compounds, and subsequent reaction with acidic methanol and Grignard reagents (dba = dibenzylideneacetone, TBDPS = *tert*-butyldiphenylsilyl, DMAP = 4-dimethylaminopyridine).[49]

3.3. Synthesis by Palladium Catalysis

The scaffold of the (*R*)-BINOL-based chiral ligand used for the Ir(I)-catalyzed asymmetric allylic substitution-isomerization (see Scheme 13, top)[48] was also used as substrate in recent studies towards enantiomerically pure aminophosphine oxides like (R_{ax},S_P)-**82** (Scheme 13, bottom).[49] Using $Pd_2(dba)_3$ as catalyst and Cs_2CO_3 as base, the (*R*)-BINOL-based precursor (R_{ax})-**80** was converted with aryl iodides (**81**) in toluene at 50–100 °C for 16 h and subsequently hydrolyzed to obtain aminophosphine oxides [(R_{ax},S_P)-**82**] with diastereomeric ratios up to >98:2 and good yields (Scheme 13, bottom). Formally, this is an auxiliary-based approach using a palladium catalyst (see also chapter 2). The absolute configuration was determined by single-crystal X-ray structure analysis for one of the synthesized derivatives and deduced for all other obtained compounds. The products can be further substituted by alkoxides and Grignard reagents (Scheme 13, bottom), each with inversion of configuration, which was again confirmed by single-crystal X-ray diffraction analysis for one representative product. Furthermore, equipping the free hydroxy group of the (*R*)-BINOL fragment with a silyl protection group after methanolysis [product (R_{ax},S_P)-**83**] led to better enantiomeric ratios (up to 96:4) for product (R_P)-**84** in the Grignard reaction. Mechanistic studies revealed an oxidative addition of both precursors to the Pd(0) center and a reductive elimination upon C–P bond formation.[49] The same (*R*)-BINOL-based P(III) scaffolds also react with alkenyl halides when catalyzed by Ni(0) catalysts. Diastereomeric ratios of up to >20:1 could be obtained with 10 mol% Ni(cod)(dq) [bis(1,5-cyclooctadiene)(duroquinone) nickel(0)] in 1,2-dichloroethane at 80 °C after 12–24 h.[50]

Palladium(II)-catalyzed approach towards *P*-chiral, enantiomerically enriched phosphinic hydrazones (R_P)-**88**-S and (R_P)-**88**-O was provided in 2020 by Pullarkat, Leung, and co-workers (Scheme 14, top). The P–N–N compounds constitute a class of important intermediates for the synthesis of diarylphosphinates such as (S_P)-**89**, which can be obtained after acidic methanolysis of the phosphinic hydrazones with inversion of configuration. The modification of the Pd(II) catalysts as well as the substrates, α-diazoesters, and secondary racemic phosphines offered enantiomeric excesses up to 55% for sulfur-protected and up to 81% for oxygen-protected phosphinic hydrazones. The best results could be obtained with compounds **85** and **86** as starting materials and (R_C)-**87** as Pd(II) catalyst. The use of diazabicycloundecene (DBU) as the base in a mixture of chloroform and acetone at −80 °C turned out to be helpful for the stereochemical outcome. The proposed mechanism (Scheme 14, bottom) starts with the coordination of two secondary diarylphosphines to the Pd(II) center (**Int1**) followed by coordination of the α-carbon atom of the α-diazoester (**Int2**). Deprotonation of the phosphine (**Int3**) leads to a nucleophilic attack at the azo group forming a rigid, five-membered Pd(II) intermediate (**Int4**). Eventually, the ring is reopened (**Int5**), before the non-oxidized product is eliminated and the catalyst reoccupied.[51]

Quite an intriguing way to obtain enantiomerically enriched aminophosphine oxides [(S_P)-**93**] using Pd(II) catalysis was reported in 2015 (Scheme 15, top). Starting from racemic, diarylsubstituted aminophosphine oxide (**90**), a desymmetrizing *ortho*-C–H-arylation was carried out by the reaction with boronic ester **91** in the presence of *N*-Boc-protected amino acid (R_C)-**92** as chiral ligand (Scheme 15, top). The best results were obtained by using 10 mol% $Pd(OAc)_2$ in combination with Ag_2CO_3 as oxidant and benzoquinone as additive in dimethylformamide. Enantiomeric excesses up to 98% were achieved as determined by chiral HPLC analysis and the absolute configuration at phosphorus was assigned by single-crystal X-ray diffraction analysis.[52] In a follow-up work, the obtained products were reported to undergo *ortho*-C–N bond coupling through radical oxidation, thus yielding cyclic phosphine amides. Moreover, it could be shown in this work that the oxides could be transferred into sulfides using Lawesson's reagent.[53] In a very recently published article, the selective attachment of alkynyl bromide **95** on the *ortho*-position of a



Scheme 14. Top: Palladium(II)-catalyzed synthesis of enantiomerically enriched phosphinic hydrazones (R_P)-**88**-S and (R_P)-**88**-O and conversion into diarylphosphinates (S_P)-**89** by acidic methanolysis (DBU = diazabicycloundecene).[51] Bottom: Proposed mechanism for the reaction of α-diazoester **85** with secondary racemic phosphine **86**.[51]

phenyl ring in **94** with the lactam L-pyroglutamic acid [(S_C)-**96**] as chiral ligand was reported (Scheme 15, middle). The absolute configuration at phosphorus of product (R_P)-**97** was determined by X-ray crystallography.[54] Related with the aforementioned work,[52–54] further catalytic approaches to enantiomerically pure *P*-stereogenic compounds were investigated and recently reviewed.[55]

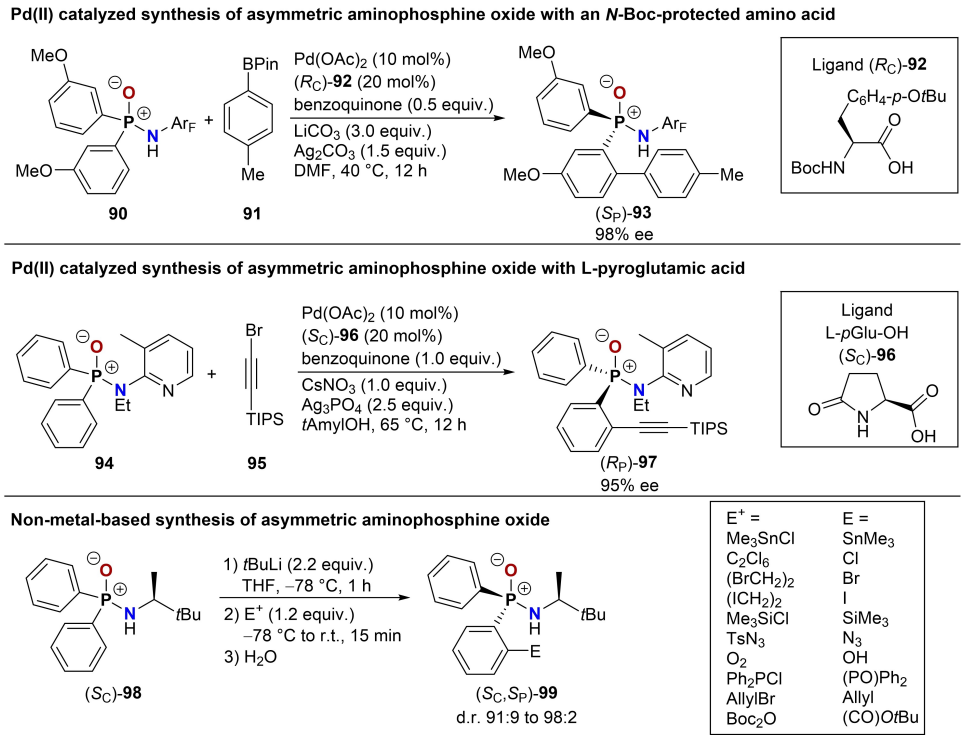
A non-metal-based, substrate-controlled desymmetrizing aryl coupling method (Scheme 15, bottom) furnished similar stereoselectivity compared to the previously described Pd(II) catalyzed syntheses.[56] Starting from a *C*-stereogenic, (S_C)-α-methylbenzylamine-substituted aminophosphine oxide [(S_C)-**98**], the electrophilic *ortho*-substitution of one of the phenyl groups was achieved by stereoselective deprotonation of one of the diastereotopic phenyl rings with *t*BuLi followed by the reaction with an electrophile (Scheme 15, bottom). Diastereomeric ratios of up to 98:2 were obtained.[56] The absolute configuration at phosphorus of products (S_C,S_P)-**99** could be revealed by X-ray structure determination of a representative derivative.[56c] The newly introduced functional unit at the *ortho*-position could then be replaced by alkyl or aryl moieties[56b] or by the 4-amino-TEMPO (4-amino-2,2,6,6-tetramethylpiperidinyloxyl) radical.[56d] Analogous asymmetric *ortho*-substitutions were reported for aminophosphazenes, which contain a P^+–N^-–COOMe instead of a P^+–O^- unit. They could be converted to the corresponding aminophosphine oxides or sulfides when subjected to phenyliso(thio)cyanate (Ph–NCO or Ph–NCS).[56a,b]

4. Applications of *P*-Stereogenic Aminophosphine Chalcogenides and Boranes

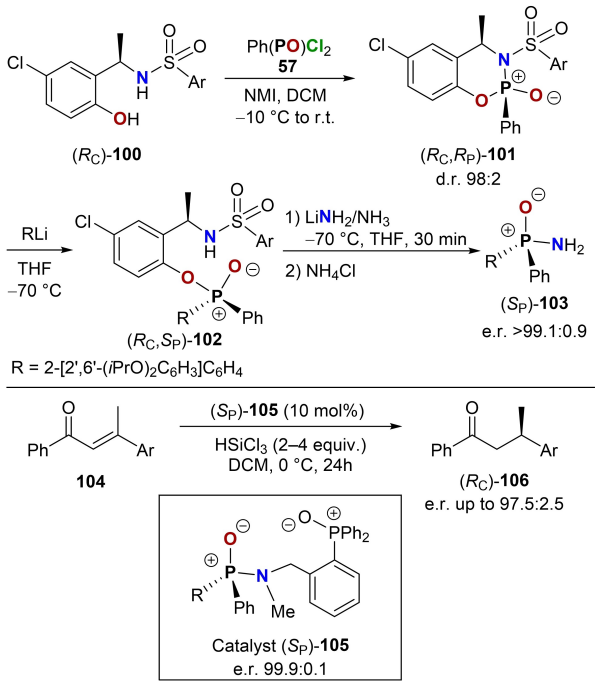
4.1. Applications of Aminophosphine Oxides as a Novel Class of Organocatalysts

Many researchers have used the work of Inch[26,37,39] and Jugé[20a,b,22b,38a] on enantiomerically pure N–P^+–O^- compounds as a starting point for their investigation of functionalized phosphorus-stereogenic compounds.

In 2015, Han et al. found an efficient way to synthesize primary aminophosphine oxides [(S_P)-**103**] with a wide range of substitution patterns (Scheme 16, top).[57] They made use of 1,3,2-benzoxazaphosphinine-2-oxide [(R_C)-**100**] as chiral intermediate for providing the phosphorus-stereogenic products (S_P)-**103** with enantiomeric purities of up to 99% after treatment with an organometallic reagent and lithium amide. Only two years later, they reported the design of efficient asymmetric Lewis base organocatalysts [(S_P)-**105**] by functionalizing the amino group with an *ortho*-phosphine oxide-substituted benzyl moiety. Excellent asymmetric induction of the *P*-stereogenic compound was proven for the reduction of chalcone derivatives **104**, forming products (R_C)-**106** with enantiomeric ratios up to 97.5:2.5 (Scheme 16, bottom).[57b] In 2019, the *P*-stereogenic aminophosphine oxides (S_P)-**103** served as precursors for Brønsted acid organocatalysts such as (R_P)-**108**. Catalytically active species of this type have been shown to be effective for certain enantioselective transformations. Through the coupling of the nitrogen atom of the *P*-stereogenic aminophosphine oxides with electron withdrawing groups such as SO_2Ar or $P(O)R_2$, the acidity of the resulting NH function could be increased, which was crucial for the reliability of this type of Brønsted acid catalysts. The substituents at the stereogenic phosphorus center can also affect the NH acidity. Reactivity as well as stereoselectivity of the catalyzed reaction can thereby be modified. The new set of *P*-stereogenic aminophosphine oxides catalyzed hydrogenations using quinoline derivatives such as **107** as substrates and Hantzsch ester as reducing agent (Scheme 17, left).[58] Analogous reactions were performed in the



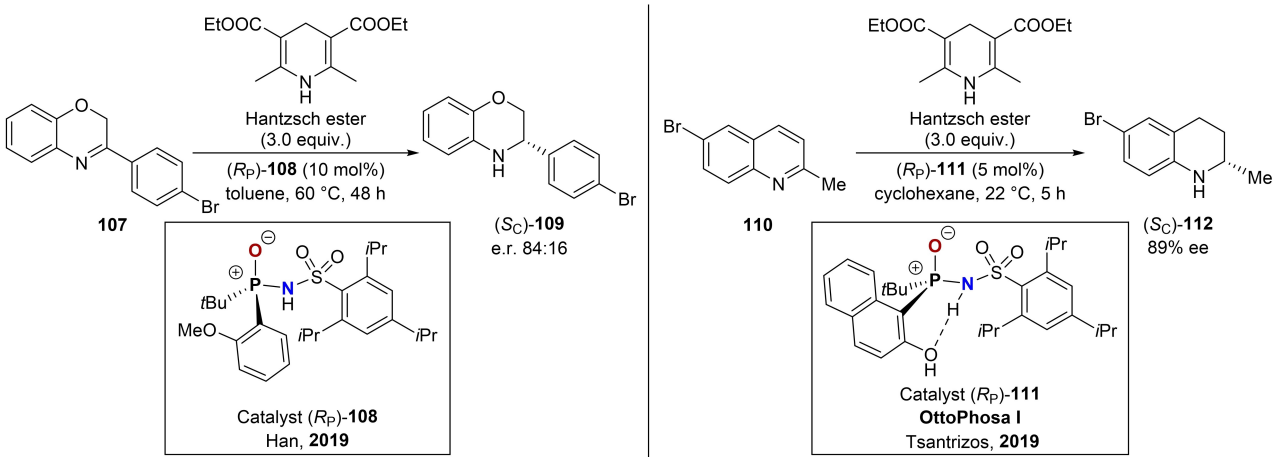
Scheme 15. Top: Palladium(II)-catalyzed synthesis of (S_P)-**93** starting from a *P*,*P*-diarylaminophosphine oxide (**90**) by selective *ortho*-arylation of one of the *P*-aryl substituents (Ar_F = 2,3,5,6-tetrafluorobenzonitrile, BPin = pinacolborane, DMF = dimethylformamide).[52] Middle: Another palladium(II)-catalyzed approach with a different chiral ligand (TIPS = triisopropylsilane, *t*AmylOH = 2-methyl-2-butanol).[54] Bottom: Non-metal-based approach.[56]



Scheme 16. Top: Highly enantioselective method for the synthesis of various *P*-stereogenic aminophosphine oxides [(S_P)-**103**] (NMI = *N*-methylimidazole).[57] Bottom: Asymmetric reduction of chalcone **104** catalyzed by the functionalized aminophosphine oxide (S_P)-**105**.[57b]

past with atropisomeric (*R*)-BINOL-phosphoric acid derivatives.[59] Full conversion could be achieved with some achiral test catalysts after 24 h. The *P*-stereogenic catalysts also gave full conversion after 24–48 h and yielded enantiomerically enriched products with enantiomeric ratios ranging from 53:47 to 84:16, strongly depending on the substituents of the catalyst, but also on the substituents of the quinoline-based substrate. Highest selectivity was observed with the sterically demanding catalyst (R_P)-**108** and with 2-aryl-substituted quinoline derivative **107**, which gave (S_C)-**109** as product.[58]

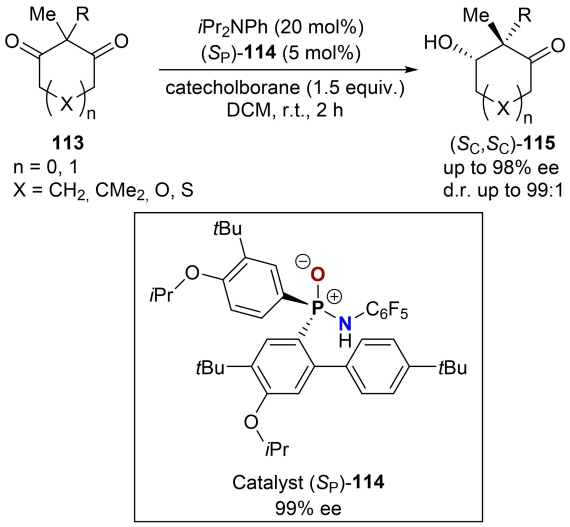
In the same year, Tsantrizos and co-workers reported similar molecular patterns for Brønsted acid organocatalysis, however, with some innovations (Scheme 17, right).[60] (R_P)-**111**, also known as OttoPhosa I, is the prototype of a *P*-stereogenic aminophosphine derivative with an electron withdrawing arylsulfonate moiety attached to the nitrogen atom and a phenolic moiety attached to the phosphorus atom. The hydroxy group of the phenolic moiety is capable of hydrogen bond formation to the NH group. This increases the acidity of the NH moiety on the one hand and stabilizes the transition state structure on the other hand, leading to an increased reaction rate and better enantioselectivities. Using a 2-methyl-substituted quinoline, enantiomeric excesses of 80–89% could be reached with OttoPhosa I [(R_P)-**111**], depending on reaction time and solvent. The best result was achieved for the conversation of compound **110** into product (S_C)-**112** using cyclohexane as solvent at 22 °C.[60] In a subsequent publication, the scope of catalysts and substrates was expanded and it was shown that such catalysts are limited in application at temperatures higher than room temperature, as they tend to racemize upon heating.[61] Nevertheless, this class of organocatalysts



Scheme 17. Left: Hydrogen transfer reaction of quinoline derivative **107** using aminophosphine oxide catalyst (R_P)-**108** without intramolecular hydrogen bond stabilization.[58] Right: Hydrogen transfer reaction of quinoline derivative **110** with hydrogen bond-stabilized OttoPhosa I [(R_P)-**111**].[60]

provided short reaction times and good enantioselectivities, which could possibly be further enhanced upon crystallization.

The previously described products of the palladium(II)-catalyzed synthesis of *ortho*-substituted, enantiomerically enriched *P*,*P*-diarylaminophosphine oxides [(S_P)-**93**, Scheme 15, top][52] were used as novel organocatalysts in the reductive desymmetrization of cyclic 2,2-disubstituted 1,3-diketones (Scheme 18). Five- and six-membered substrates of type **113** could be converted into products of type (S_C,S_C)-**115** with high to excellent enantio- and diastereoselectivities, although the reductions of six-membered derivatives turned out to be challenging in the past. After extensive investigations, the most suitable reaction conditions were found with dichloromethane as solvent, catecholborane as reducing agent, and di-*iso*-propylphenylamine as additive. The reaction was quenched with methanol and subjected to aqueous work-up.[62] The wide substrate scope, easy upscaling, and high selectivity made these findings also applicable in the synthesis of natural products.[63]



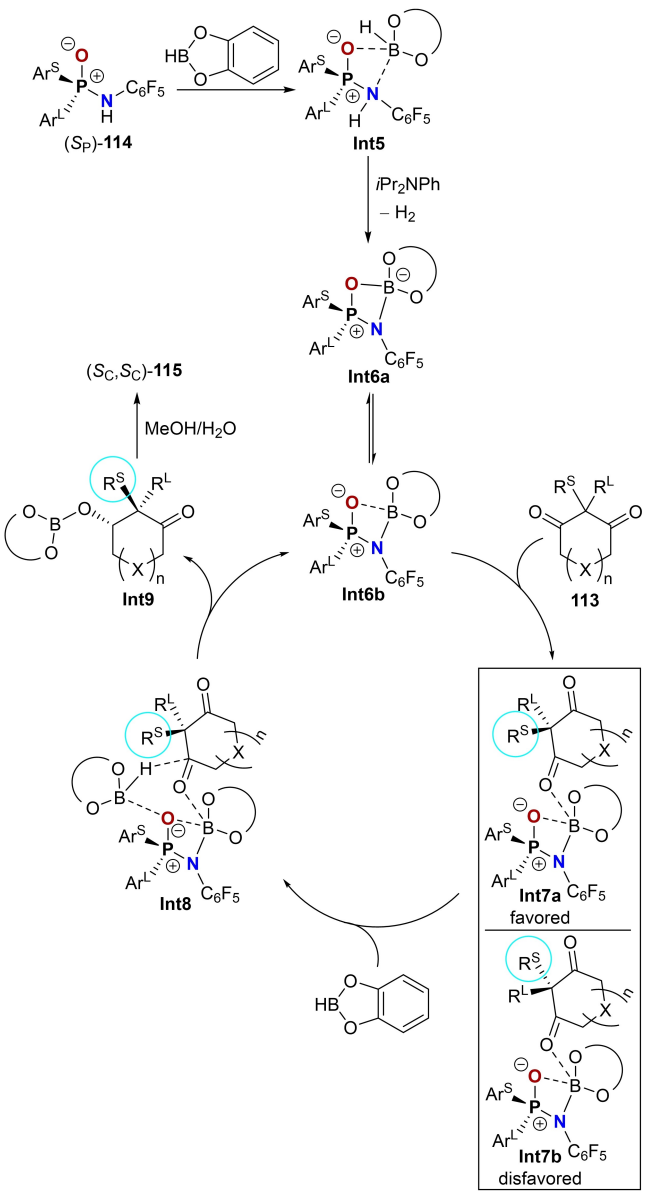
Scheme 18. Enantioselective reduction of **113** catalyzed by (S_P)-**114**.[62]

The proposed mechanism for the reduction (Scheme 19) starts with a coordination of Lewis-acidic catecholborane by the P^+–O^- unit of the catalyst (**Int5**). Following, the addition of di-(*iso*-propyl)phenylamine causes the release of one molecule dihydrogen. The resulting intermediate can either be described as a P^+–O–B^- zwitterionic structure (**Int6a**) or as a coordination complex (**Int6b**) forming an additional O···B interaction with the 1,3-diketone **113**. Due to the different substituents at the 2-position, there is a favored (**Int7a**) and a disfavored (**Int7b**) case. In the favored case, the less bulky substituent (R^S) is pointing towards the activated catalyst. A second catecholborane molecule is then coordinated by the P^+–O^- unit (**Int8**) and capable of reacting with compound **113** affording the corresponding hydroborane (**Int9**), which finally turns into the alcohol (S_C,S_C)-**115** after aqueous work-up.[62]

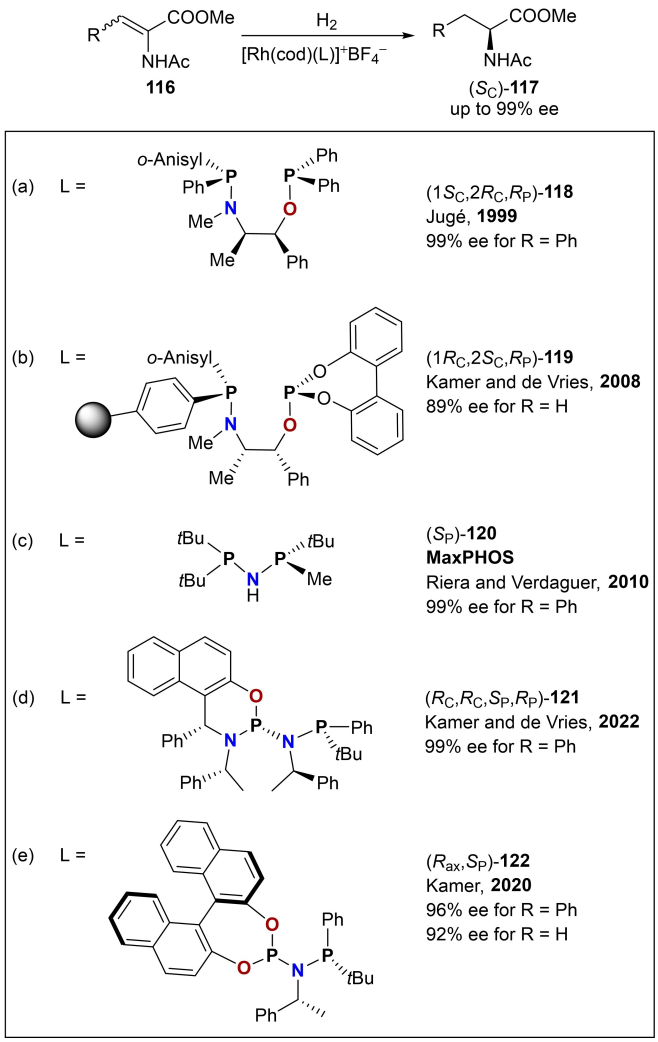
4.2. Transition Metal-Catalyzed Transformations Using *P*-Stereogenic Aminophosphine Ligands

The P(V)–N compounds (S_P)-**105**, (R_P)-**108**, (R_P)-**111**, and (S_P)-**114** containing a stereogenic phosphorus(V) center were shown to have useful properties for many synthetic applications. However, they do not represent the heteroatom-substituted phosphorus species most commonly used in catalysis. As mentioned in several publications,[16,22b,23d,32,64] BH_3 is suitable for protecting phosphorus(III) compounds without changing the oxidation state and a lot of effort has been made in the last twenty years to equip such compounds with *P*-centered chirality.

For their use as ligands in transition metal catalysis, they are deprotected again before coordinating the metal center. Since a comprehensive overview on this topic was published some time ago,[20e] we will only focus on the most groundbreaking achievements in this chapter.



Scheme 19. Proposed reaction mechanism of the enantioselective reduction of **113** catalyzed by (S_P)-**114** [R^S/Ar^S = small (aryl) rest; R^L/Ar^L = large (aryl) rest].[62]



Scheme 20. Asymmetric hydrogenation of olefins **116** with different rhodium(I) diphosphine chelate complexes reported by Jugé (a),[22b,38d] Kamer and de Vries (b[23f] and d[65]), Riera and Verdaguer (c),[32] and Kamer (e)[66] (cod = 1,5-cyclooctadiene).

4.2.1. Asymmetric Catalysis with Rhodium(I) Complexes

Jugé and co-workers reported that an ephedrine-based pathway led to chiral diphosphines such as (1S_C,2R_C,R_P)-**118**, which represent suitable ligands for rhodium(I) complexes used for homogeneous catalytic hydrogenations of compounds **116** to obtain products (S_C)-**117** (Scheme 20, a). Interestingly, the *P*-stereogenic center within the chiral molecule having multiple chirality centers was much more pivotal than the ephedrine backbone for the enantioselectivity of the catalyzed reactions. Up to 99% ee was achieved, strongly depending on the bulkiness of the aminophosphine substituents that determine the conformation of the rhodium chelate complex.[22b,38d]

Work on less traditional analogues of ephedrine-based *P*-stereogenic ligands was carried out by Kamer and de Vries[23f] using solid-phase synthesis (Scheme 20, b). The resin-bound molecules (1R_C,2S_C,R_P)-**119** were equally tested in rhodium(I)-catalyzed asymmetric hydrogenations showing an enantiomeric excess up to 89%.

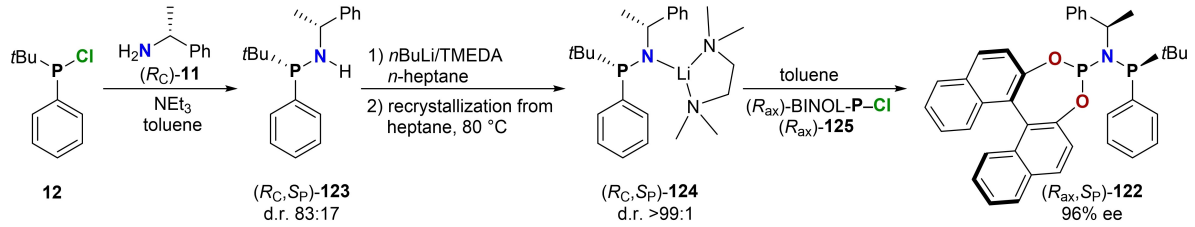
Major contributions to the development of enantiomerically pure P–BH_3-based compounds and their applications were made by Riera, Verdaguer, and co-workers (Scheme 20, c). First synthesis approaches in 2010 included the easily available chiral auxiliaries (−)-α-methylbenzylamine [(S_C)-**11**] and (−)-1-(1-naphthyl)ethylamine [(S_C)-**16**].[32] This in turn was important preparatory work for the studies on aminophosphine sulfides.[33] The primary and secondary aminophosphine boranes could be functionalized at the nitrogen atom without loss of the stereochemical information at the asymmetrically substituted phosphorus center. Carbon- as well as phosphorus-based substituents were connected to the nitrogen atom. The latter

functionalization provided aminodiphosphine (PNP) ligands such as (S_P)-**120** (also known as MaxPHOS ligand) after deprotection, which were used for rhodium(I)-catalyzed highly enantioselective hydrogenations of olefins.[32]

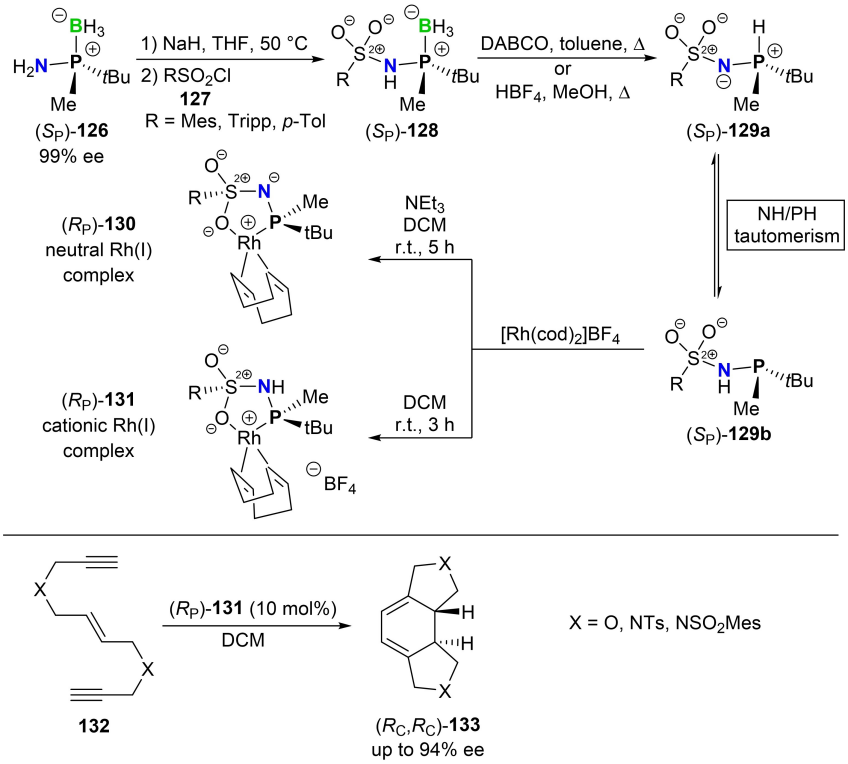
Another example of rhodium(I)-PNP-catalyzed olefin hydrogenations with excellent enantiomeric ratios of up to 99% ee was reported by Kamer and de Vries using ligand (R_C,R_C,S_P,R_P)-**121** with a Betti base backbone (Scheme 20, d).[65]

Furthermore, phosphorus-stereogenic PNP ligands based on an axially chiral BINOL backbone such as (R_{ax},S_P)-**122** were also described by Kamer (Scheme 20, e) and gave up to 96% ee in asymmetric hydrogenations of olefins **116**. The ligand preparation (Scheme 21) started with a well-known method by coupling (R_C)-**11** and phosphine **12** to give an oily product [(R_C,S_P)-**123**] with a diastereomeric ratio of 83:17. In order to achieve optical purity, the authors did not use the common route via oxidation or borane-protection of the phosphorus atom, but formed a lithium amide complex with TMEDA, which could be fractionally crystallized to obtain (R_C,S_P)-**124**. The coupling with the BINOL fragment was achieved using either (S_{ax})- or (R_{ax})-BINOL-phosphorochloridite (**125**) to obtain the PNP ligand (R_{ax},S_P)-**122**.[66]

Two years later, the groups of Riera and Verdaguer reported a new class of rhodium(I) catalysts with phosphinosulfonamide (PNSO) ligands for intramolecular cycloadditions of terminal enediynes **132** (Scheme 22).[67] The ligand preparation started from enantiomerically pure (S_P)-**126** with sodium hydride and sulfonyl chlorides **127** or *N*-phenyl-bis(trifluoromethanesulfonimide) in THF to obtain (S_P)-**128** as intermediate product in good to excellent yields. Since the goal was to generate ligands for rhodium(I), the borane entity had to be cleaved in order to release the required coordination site on the stereogenic phosphorus atom. This was achieved under basic (DABCO) or acidic (HBF_4) conditions and heating (Scheme 22, top). Surprisingly, the deprotected products were stable under air due to a simple reason: the ability for NH/PH tautomerism led to the PH form (S_P)-**129a** in most of the cases because of the relative basicity of the phosphorus atom. This



Scheme 21. Synthesis of (R_{ax})-BINOL-substituted PNP ligand (R_{ax},S_P)-**122**.[66]



Scheme 22. Top: Synthesis of PNSO ligands (S_P)-**129** showing NH/PH tautomerism, and preparation of rhodium(I)-PNSO-complexes.[67] Bottom: Rhodium(I)-catalyzed [2+2+2] intramolecular cycloaddition of enediynes **132**.[67]

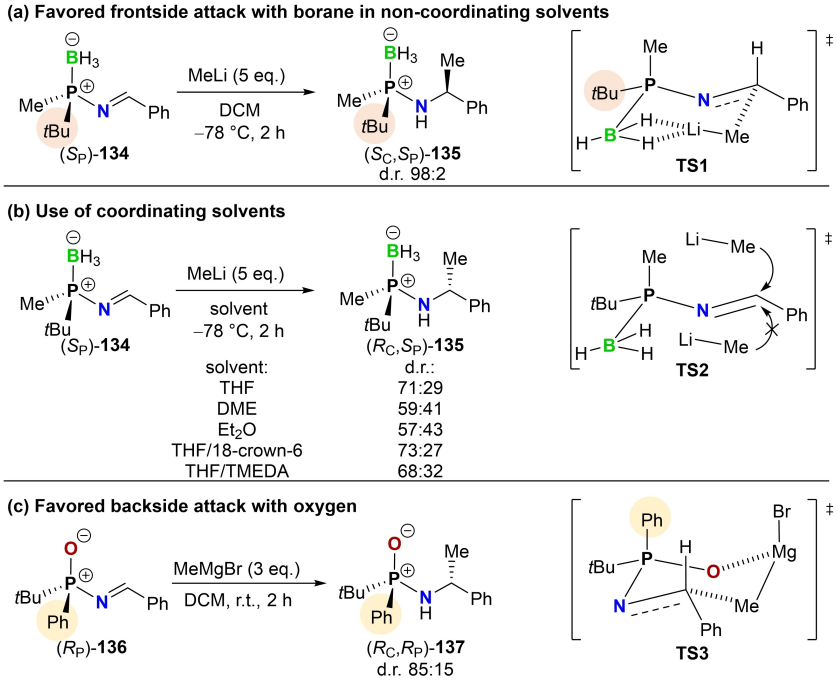
basic character is increased by electron-rich substituents on the phosphorus atom and by electron-withdrawing substituents at the nitrogen atom. A tautomeric equilibrium in general can be effectively shifted towards the P(III) state by coordinating the phosphorus lone electron pair to a metal center. It is assumed that such molecules do not lose their chiral information during this tautomeric equilibrium, as is indeed the case with the tautomerism of PH/OH compounds. Both, air-stable neutral [(R_P)-**130**] and cationic [(R_P)-**131**] rhodium(I) complexes could be synthesized. In addition to thorough structural investigations of the cationic complex,[67] the complexes were tested for the challenging[68] [2+2+2] intramolecular cycloaddition of enediynes **132**. While the neutral complexes (R_P)-**130** did not lead to any cyclization, the cationic complexes (R_P)-**131** showed remarkable conversions and enantiomeric excesses of up to 94% for products (R_C,R_C)-**133**, depending on the reaction conditions as well as the exact composition of the *O*- or *N*-tethered substrate (Scheme 22, bottom).[67]

4.2.2. Asymmetric Catalysis with Iridium(I) Complexes

In 2015, the reactivity of phosphine boranes with adjacent imine functionalities towards organometallic reagents (Scheme 23, a and b) was published by Riera and Verdaguer.[64] Borane-protected *N*-phosphonyl imines such as (S_P)-**134** were prepared in a microwave at 80 °C from enantiomerically pure (S_P)-**126** and various aldehydes. The condensation was promoted by titanium(IV) ethoxide under neat conditions.

The borane moiety proved to be an efficient directing group for the 1,2-addition of organometallic reagents to the imine double bond, leading to unequal mixtures of diastereomers (Scheme 23, a and b).[64] Such a directing behavior was previously only known for P(V) compounds[69] (Scheme 23, c) and sulfinyles[70]. Depending on the solvent, diastereomerically enriched 1,2-addition products (S_C,S_P)-**135** or (R_C,S_P)-**135** with a diastereomeric ratio of up to 98:2 could be obtained for the phosphine boranes.[64]

A crucial factor was the coordination ability of the solvents. Coordinating solvents in general provided less stereoselectivity (d.r. values between 41:59 and 27:73), whereas non-coordinating solvents such as dichloromethane gave excellent ratios. Moreover, the selectivity was reversed for the different types of solvent, which means that non-coordinating solvents preferably yielded (S_C,S_P)-**135** (Scheme 23, a) and coordinating solvents (R_C,S_P)-**135** (Scheme 23, b). The authors provided insight into the stereochemical behavior based on a structural proposal of the transition state. With non-coordinating solvents, a distorted cyclic chair conformation is favorable (**TS1**, Scheme 23, a), in which lithium is η^2-coordinated by the BH_3 directing group. This well-defined transition state structure ensures the high stereoselectivity of the 1,2-addition. Since coordinating solvents usually enclose lithium cations, the chair-shaped transition state cannot be built (**TS2**, Scheme 23, b). Not even the use of cation scavengers such as TMEDA or 18-crown-6 could prevent the lithium cations from being trapped by the coordinating solvent, resulting in poorer and reversed stereoselectivity.[64] P^+–O^- compounds build a similar chair-shaped transition state structure compared to P–BH_3 analogues (**TS3**, Scheme 23, c). However, reaction of the enantiomerically pure *P*-stereogenic *N*-phosphinoylimine (R_P)-**136** and MeMgBr in dichloromethane yielded (R_C,R_P)-**137** in a diastereomeric ratio of only 85:15,[69]



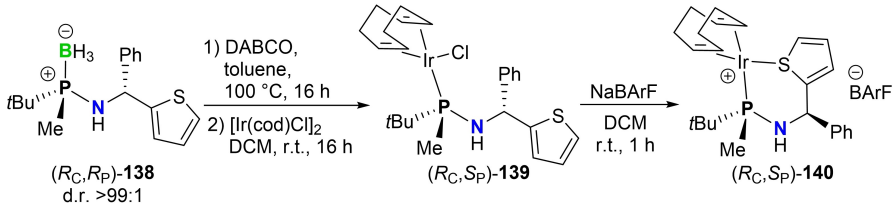
Scheme 23. Directing behavior of borane in non-coordinating solvents (a),[64] borane in coordinating solvents (b),[64] and oxygen in non-coordinating solvents (c)[69] in stereoselective 1,2-addition reactions of organometallic reagents with *N*-phosphanylimines (S_P)-**134** and (R_P)-**136** (DME = dimethoxyethane, 18-crown-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine).

emphasizing that the borane moiety is a more effective directing group than the P^{+}–O^{-} group.[64]

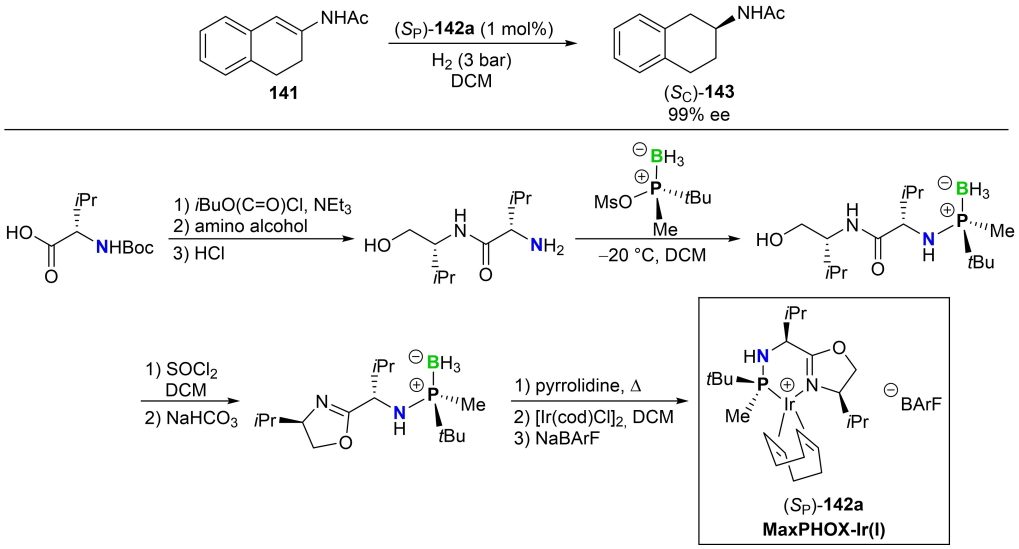
Since the main goal was to establish a new type of ligands for catalytic applications, (R_C,R_P)-**138**, which features a thiophene moiety and can be obtained in a diastereomeric ratio of <99:1, was deprotected using DABCO and coordinated to iridium(I) to get to (R_C,S_P)-**139** (Scheme 24). When treating the resulting neutral complex with NaBArF, the thiophene moiety coordinated as well, yielding the cationic, *P*,*S*-bonded bidentate Ir(I) complex (R_C,S_P)-**140**. The molecular structure of the complex salt in the crystalline state was used to determine the absolute configuration of the ligand.[64] So far, no catalytic activity was reported for exactly this type of complexes.

However, also in 2015, the same group[71] presented the MaxPHOX-Ir(I) family with characteristic *P*,*N*-bidentate phosphine-oxazoline ligands coordinating to iridium(I). (S_P)-**142 a** is a representative of this type of catalysts and is capable of highly enantioselective hydrogenation of cyclic enamides (Scheme 25, top). This way, the reduction of compound **141** could be achieved leading to product (S_C)-**143** with 99% ee, whereas only 9% ee were achieved with a Rh(I) catalyst some years earlier.[32] The ligands and their corresponding complexes were synthesized in a wide variety of different stereoisomers with various substituents starting from three simple building blocks, each containing a *C*- or *P*-stereogenic center. The synthesis is shown for one example [(S_P)-**142 a**] in Scheme 25 (bottom).[71b]

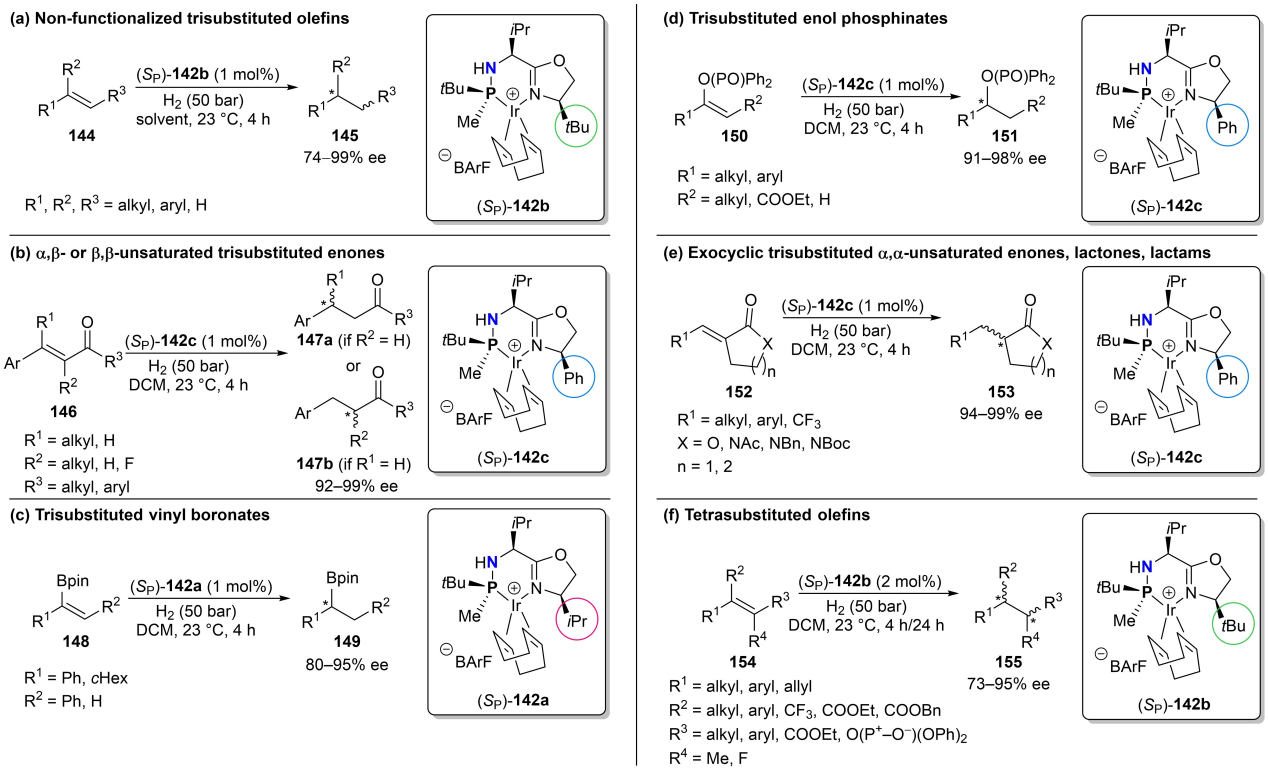
Research on the MaxPHOX–Ir(I)-complex was expanded in the following years. Just recently, numerous non-chelating di-, tri-, and tetrasubstituted olefins were reported to undergo catalytic hydrogenations with up to >99% ee. The trisubstituted alkenes were not only exclusively equipped with aryl and alkyl groups (**144**), but also contained poorly coordinating units such as enones [non-cyclic (**146**) and cyclic (**152**)], vinyl boronates (**148**), enol phosphinates (**150**), lactams (**152**), and lactones (**152**) (Scheme 26, a–e). For the tetrasubstituted species **154** it is noteworthy that even with four different substituents almost enantiomerically pure products with 95% ee could be generated (Scheme 26, f).[72] The authors thus complemented a library of olefinic substrates, which had originally begun some years earlier with a similar catalyst.[73] In general, the success of asymmetric olefin hydrogenation with excellent enantioselectivity highly depends on the substitution pattern. In Scheme 26, the various studied species and the corresponding catalysts for their hydrogenation are shown.[72] DFT calculations supported the proposal of two possible transition states during the catalytic cycle, both of which originate from an Ir(III)/Ir(V) tetrahydride intermediate. The initial hydrogen transfer from the metal center to the coordinated olefin is expected to ultimately determine the enantiose-



Scheme 24. Synthesis of a neutral *P*-monodentate [(R_C,S_P)-**139**] and a cationic *P*,*S*-bidentate [(R_C,S_P)-**140**] iridium(I) complex (cod = 1,5-cyclooctadiene, BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).[64]



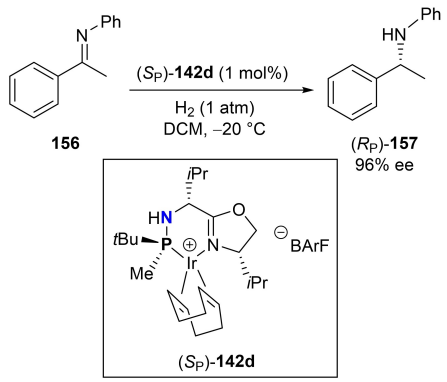
Scheme 25. Top: Highly enantioselective iridium(I)-catalyzed asymmetric hydrogenation of the cyclic enamide **141**.[71b] Bottom: Synthesis of (S_P)-**142 a**, a representative of the MaxPHOX-Ir(I) family.[71b]



Scheme 26. Overview of different MaxPHOX–Ir(I)-complexes being able to catalyze various hydrogenation reactions.[72]

lectivity, which in turn can be estimated from the relative energies of the two possible transition states. The respective pathways are either a migration-insertion mechanism (most favorable) or a σ-bond metathesis (energetically feasible according to the calculations, but not favored).[72]

In 2018, MaxPHOX–Ir(I)-mediated hydrogenation of a variety of *N*-aryl imines was achieved. Compound (R_P)-**157** could be obtained with 96% ee from **156** with (S_P)-**142d** as catalyst (Scheme 27). This was feasible at atmospheric hydrogen pressure at −20 °C. The stereochemical outcome and the catalyst activity of these reactions were strongly dependent on the substitution pattern at the phosphorus atom and also on the counterion used. Avoiding *P*-centered chirality in the catalyst or replacing the classic BArF anion with borontetrafluoride reduced both the reaction rate and stereoselectivity.[74]

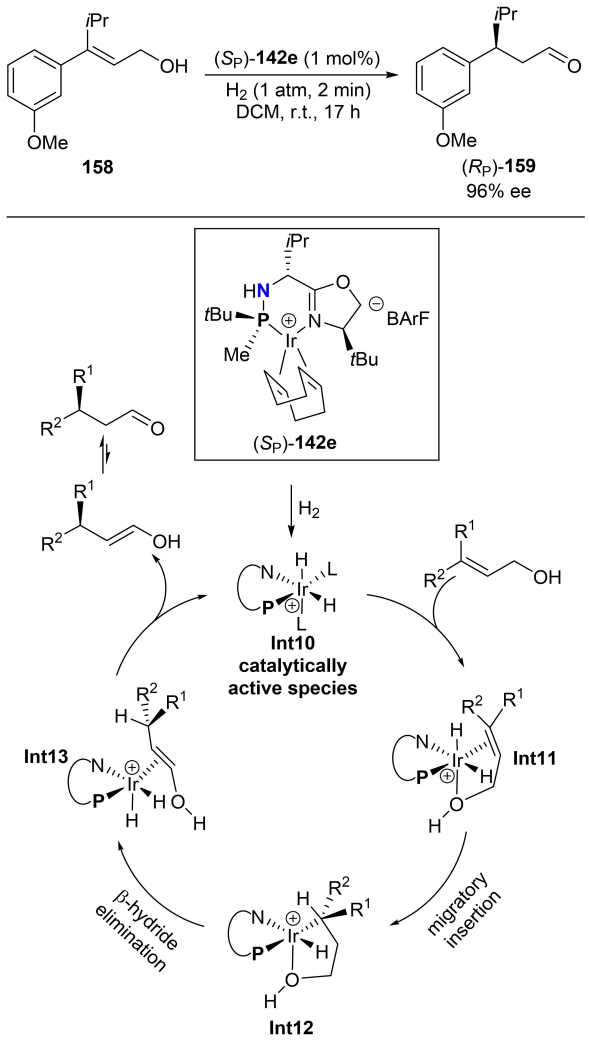


Scheme 27. MaxPHOX–Ir(I)-catalyzed asymmetric hydrogenation of *N*-aryl imine **156** (BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).[74]

A very striking feature of the MaxPHOX–Ir(I) catalysts was published in 2020 with their ability to enantioselectively isomerize primary allylic alcohols to aldehydes.[75] After studying the different derivatives of MaxPHOX–Ir(I) and various olefinic substrates, the best performing catalyst was (S_P)-**142e** and led to 96% ee for the isomerization of **158** to (R_P)-**159** (Scheme 28, top). Therefore, the dichloromethane solution containing the starting material was flooded with hydrogen for two minutes and stirred at room temperature under nitrogen atmosphere for 17 hours. The catalytic cycle (Scheme 28, bottom) is initiated by activation of (S_P)-**142e** through hydrogenation (**Int10**) and subsequent coordination of the Ir(I) center by the allylic substrate (**Int11**). A migratory insertion of the axial hydrogen atom to the substrate (**Int12**) followed by β-hydride elimination (**Int13**) led to the enol product, which now contains a stereogenic carbon atom and a C=C double bond, the latter being shifted by one position compared to the starting material. Since the enol is now capable of keto-enol tautomerism, it can be converted to the more stable aldehyde. Both the transition state and intermediate structures of the catalytic cycle are supported by DFT calculations.[76]

5. Summary and Outlook

Phosphorus-stereogenic aminophosphines were shown to provide a unique property profile for two important areas of



Scheme 28. Top: MaxPHOX–Ir(I)-catalyzed isomerization of allylic alcohol **158** to its corresponding aldehyde (R_P)-**159**.[76] Bottom: Proposed catalytic cycle of the upper reaction.[76]

catalysis, namely organocatalysis and transition metal catalysis. So far, only aminophosphine oxides have been used for organocatalytic reactions. However, the newly created access to other *P*-stereogenic aminophosphine chalcogenides opens up further areas of application in organocatalysis and may stimulate the design of new ligands for transition metal-catalyzed reactions. The ability to achieve outstanding stereoselectivities in a large number of asymmetric transition metal-catalyzed reactions is remarkable and encourages further investigation into complexes with aminophosphine-based ligands.

Synthesis methods for providing *P*-stereogenic, enantiomerically pure aminophosphine chalcogenides and boranes are extensive, ranging from the long-known and still appreciated use of chiral auxiliaries to modern techniques using transition metals such as copper, iridium, and palladium. Stereochemically pure aminophosphine chalcogenides exhibit an interesting bifunctional pattern capable of forming hydrogen bonds, which should be further investigated in terms of defined supramolecular structures with chiral information. This contribution may help researchers in the fields of ligand design, asymmetric catalysis, and chiral supramolecular chemistry to get new ideas and to focus on new building blocks whose potential is far from being exhausted.

6. Cautionary Note

Some of the presented products and intermediates might potentially be toxic due to their structural similarity to parathion, which inhibits acetylcholinesterase.[77]

Acknowledgements

This work was jointly supported by the Elite Network of Bavaria (ENB), the Bavarian State Ministry of Science and the Arts (StMWK), and the University of Regensburg (Project N-LW-NW-2016-366). Intellectual support was given by the Deutsche Forschungsgemeinschaft (DFG) through the Research Training Group "Ion Pair Effects in Molecular Reactivity" (RTG 2620, Project 426795949). Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data underlying this review article are based on the literature cited.

Keywords: aminophosphines · organocatalysis · *P*-stereogenic compounds · synthetic methods · transition metal catalysis

[1] For reviews, see: a) D. H. Valentine Jr., J. H. Hillhouse, *Synthesis* **2003**, *16*, 2437–2460; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050; c) Z. Wang, X. Xu, O. Kwon, *Chem. Soc. Rev.* **2014**, *43*, 2927–2940; d) H. Guo, Y. C. Fan, Z. Sun, Y. Wu, O. Kwon, *Chem. Rev.* **2018**, *118*, 10049–10293; e) P. Karanam, G. M. Reddy, S. R. Koppolu, W. Lin, *Tetrahedron Lett.* **2018**, *59*, 59–76.
[2] For reviews, see: a) A. Gallen, A. Riera, X. Verdaguer, A. Grabulosa, *Catal. Sci. Technol.* **2019**, *9*, 5504–5561; b) S. Kotani, M. Nakajima, *Tetrahedron Lett.* **2020**, *61*, 151421; c) M. Hayashi, *Chem. Lett.* **2021**, *50*, 1–6.
[3] M. C. Hilton, X. Zhang, B. T. Boyle, J. V. Alegre-Requena, R. S. Paton, A. McNally, *Science* **2018**, *362*, 799–804.
[4] a) M. Myers, E. F. Connor, T. Glauser, A. Möck, G. Nyce, J. L. Hedrick, *J. Polym. Sci. Part A* **2002**, *40*, 844–851; b) H. Ni, W.-L. Chan, Y. Lu, *Chem. Rev.* **2018**, *118*, 9344–9411; c) C. Xie, A. J. Smaligo, X.-R. Song, O. Kwon, *ACS Cent. Sci.* **2021**, *7*, 536–558.
[5] a) T. M. Shaikh, C.-M. Weng, F.-E. Hong, *Coord. Chem. Rev.* **2012**, *256*, 771–803; b) Y. H. Lee, B. Morandi, *Coord. Chem. Rev.* **2019**, *386*, 96–118.
[6] a) N. L. Dunn, M. Ha, A. T. Radosevich, *J. Am. Chem. Soc.* **2012**, *134*, 11330–11333; b) J. Lam, K. M. Szkop, E. Mosaferi, D. W. Stephan, *Chem. Soc. Rev.* **2019**, *48*, 3592–3612.
[7] a) C. Marquardt, O. Hegen, T. Kahoun, M. Scheer, *Chem. Eur. J.* **2017**, *23*, 4397–4404; b) M. J. Poller, T. Huber, J. Frickel, N. Burford, K. Karaghiosoff,

Phosphorus Sulfur Silicon Relat. Elem. **2019**, *194*, 513–514; c) A. Denhof, M. Olaru, E. Lork, S. Mebs, L. Chęcińska, J. Beckmann, *Eur. J. Inorg. Chem.* **2020**, 4093–4110; d) N. Fontana, N. A. Espinosa-Jalapa, M. Seidl, J. O. Bauer, *Chem. Eur. J.* **2021**, *27*, 2649–2653; e) N. Fontana, N. A. Espinosa-Jalapa, M. Seidl, J. O. Bauer, *Chem. Commun.* **2022**, *58*, 2144–2147; f) A. Falk, J. O. Bauer, *Inorg. Chem.* **2022**, *61*, 15576–15588; g) N. Fontana, J. O. Bauer, *ChemistrySelect* **2023**, *8*, e202301373.

[8] a) M. Fiorini, G. M. Giongo, *J. Mol. Catal.* **1979**, *5*, 303–310; b) B. Schmid, S. Frieß, A. Herrera, A. Linden, F. W. Heinemann, H. Locke, S. Harder, R. Dorta, *Dalton Trans.* **2016**, *45*, 12028–12040; c) C. Fliedel, A. Ghisolfi, P. Braunstein, *Chem. Rev.* **2016**, *116*, 9237–9304.

[9] a) H. R. Allcock, *Phosphorus-Nitrogen Compounds: cyclic, linear, and high polymeric systems*, Academic Press, New York, NY, USA, **1972**; b) S. Yoshida, K. Igawa, K. Tomooka, *J. Am. Chem. Soc.* **2012**, *134*, 19358–19361; c) M. A. Shameem, A. Orthaber, *Chem. Eur. J.* **2016**, *22*, 10718–10735; d) M. B. Smith, *Molecules* **2022**, *27*, 6293; e) D. Ray, S. Majee, R. N. Yadav, B. K. Banik, *Molecules* **2023**, *28*, 3524.

[10] a) Michael Witt, H. W. Roesky, *Chem. Rev.* **1994**, *94*, 1163–1181; b) P. Bhattacharyya, J. Woollins, *Polyhedron* **1995**, *14*, 3367–3388; c) C. A. Kumar, T. K. Panda, *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 1084–1101.

[11] W. Zhao, P. K. Yan, A. T. Radosevich, *J. Am. Chem. Soc.* **2015**, *137*, 616–619.

[12] J. B. Rodriguez, C. Gallo-Rodriguez, *ChemMedChem* **2019**, *14*, 190–216.

[13] a) M. Karki, C. Gibard, S. Bhowmik, R. Krishnamurthy, *Life* **2017**, *7*, 32; b) D. J. Ritson, J. Xu, J. D. Sutherland, *Synlett* **2017**, *28*, 64–67; c) C. Gibard, S. Bhowmik, M. Karki, E.-K. Kim, R. Krishnamurthy, *Nat. Chem.* **2018**, *10*, 212–217; d) C. Gibard, I. B. Gorrell, E. I. Jiménez, T. P. Kee, M. A. Pasek, R. Krishnamurthy, *Angew. Chem. Int. Ed.* **2019**, *58*, 8151–8155; *Angew. Chem.* **2019**, *131*, 8235–8239; e) D. J. Ritson, S. J. Mojzsis, J. D. Sutherland, *Nat. Geosci.* **2020**, *13*, 344–348.

[14] Y. Gnas, F. Glorius, *Synthesis* **2006**, *12*, 1899–1930.

[15] a) K. M. Pietrusiewicz, M. Zablocka, *Chem. Rev.* **1994**, *94*, 1375–1411; b) J.-F. Cavalier, F. Fotiadu, R. Verger, G. Buono, *Synlett* **1998**, 73–75; c) I. Fernández, N. Khiar, A. Roca, A. Benabra, A. Alcudia, J. Espartero, F. Alcudia, *Tetrahedron Lett.* **1999**, *40*, 2029–2032.

[16] O. I. Kolodiazhnyi, E. V. Gryshkun, N. V. Andrushko, M. Freytag, P. G. Jones, R. Schmutzler, *Tetrahedron: Asymmetry* **2003**, *14*, 181–183.

[17] a) O. Korpiun, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784–4786; b) O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4842–4846; c) T. L. Emmick, R. L. Letsinger, *J. Am. Chem. Soc.* **1968**, *90*, 3459–3465.

[18] For reviews, see: a) K. M. Pietrusiewicz, M. Zabłocka, *Chem. Rev.* **1994**, *94*, 1375–1411; b) D. Glueck, *Synlett* **2007**, *17*, 2627–2634; c) A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, *251*, 25–90; d) D. S. Glueck, *Chem. Eur. J.* **2008**, *14*, 7108–7117; e) J. S. Harvey, V. Gouverneur, *Chem. Commun.* **2010**, *46*, 7477–7485; f) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **2012**, *23*, 1–46; g) O. I. Kolodiazhnyi, *Top. Curr. Chem.* **2015**, *360*, 161–236; h) M. Dutartre, J. Bayardon, S. Jugé, *Chem. Soc. Rev.* **2016**, *45*, 5771–5794; i) S. Lemouzy, L. Giordano, D. Hérault, G. Buono, *Eur. J. Org. Chem.* **2020**, *2020*, 3351–3366; j) H. Li, L. Yin, *Chin. J. Org. Chem.* **2022**, *42*, 3183–3200; k) D. S. Glueck, *Synthesis* **2022**, *54*, 271–280.

[19] For examples, see: a) A. N. Serreqi, R. J. Kazlauskas, *J. Org. Chem.* **1994**, *59*, 7609–7615; b) A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076; c) K. Shioji, Y. Ueno, Y. Kurauchi, K. Okuma, *Tetrahedron Lett.* **2001**, *42*, 6569–6571; d) M. J. McGrath, P. O'Brien, *J. Am. Chem. Soc.* **2005**, *127*, 16378–16379; e) D. Wiktelius, M. J. Johansson, K. Luthman, N. Kann, *Org. Lett.* **2005**, *7*, 4991–4994; f) C. Genet, S. J. Canipa, P. O'Brien, S. Taylor, *J. Am. Chem. Soc.* **2006**, *128*, 9336–9337; g) N. F. Blank, K. C. McBroom, D. S. Glueck, W. S. Kassel, A. L. Rheingold, *Organometallics* **2006**, *25*, 1742–1748; h) J. J. Gammon, S. J. Canipa, P. O'Brien, B. Kelly, S. Taylor, *Chem. Commun.* **2008**, 3750–3752; i) J. J. Gammon, P. O'Brien, B. Kelly, *Org. Lett.* **2009**, *11*, 5022–5025; j) S. J. Canipa, P. O'Brien, S. Taylor, *Tetrahedron: Asymmetry* **2009**, *20*, 2407–2412; k) J. S. Harvey, S. J. Malcolmson, K. S. Dunne, S. J. Meek, A. L. Thompson, R. R. Schrock, A. H. Hoveyda, V. Gouverneur, *Angew. Chem. Int. Ed.* **2009**, *48*, 762–766; *Angew. Chem.* **2009**, *121*, 776–780; l) J. J. Gammon, V. H. Gessner, G. R. Barker, J. Granander, A. C. Whitwood, C. Strohmann, P. O'Brien, B. Kelly, *J. Am. Chem. Soc.* **2010**, *132*, 13922–13927; m) J. Granander, F. Secci, S. J. Canipa, P. O'Brien, B. Kelly, *J. Org. Chem.* **2011**, *76*, 4794–4799.

[20] a) S. Jugé, M. Stephan, J. A. Laffitte, J. P. Genet, *Tetrahedron Lett.* **1990**, *31*, 6357–6360; b) S. Jugé, M. Stephan, R. Merdès, J. P. Genet, S. Halut-Desportes, *J. Chem. Soc. Chem. Commun.* **1993**, 531–533; c) M. Stankevic, K. M. Pietrusiewicz, *J. Org. Chem.* **2007**, *72*, 816–822; d) T. León, A. Riera, X. Verdaguer, *J. Am. Chem. Soc.* **2011**, *133*, 5740–5743; e) A. Cabré, A. Riera, X. Verdaguer, *Acc. Chem. Res.* **2020**, *53*, 676–689.

[21] a) J. Holz, M.-N. Gensow, O. Zayas, A. Borner, *Curr. Org. Chem.* **2007**, *11*, 61–106; b) M. Benaglia, S. Rossi, *Org. Biomol. Chem.* **2010**, *8*, 3824–3830; c) S. Takizawa, E. Rémond, F. A. Arteaga, Y. Yoshida, V. Sridharan, J. Bayardon, S. Jugé, H. Sasai, *Chem. Commun.* **2013**, *49*, 8392–8394; d) C. E. Henry, Q. Xu, Y. C. Fan, T. J. Martin, L. Belding, T. Dudding, O. Kwon, *J. Am. Chem. Soc.* **2014**, *136*, 11890–11893; e) H. Y. Su, M. S. Taylor, *J. Org. Chem.* **2017**, *82*, 3173–3182; f) A. J. Smaligo, S. Vardhineedi, O. Kwon, *ACS Catal.* **2018**, *8*, 5188–5192; g) H. Qiu, Q. Dai, J. He, W. Li, J. Zhang, *Chem. Sci.* **2020**, *11*, 9983–9988.

[22] a) T. Imamoto, H. Tsuruta, Y. Wada, H. Masuda, K. Yamaguchi, *Tetrahedron Lett.* **1995**, *36*, 8271–8274; b) D. Moulin, C. Darcel, S. Jugé, *Tetrahedron: Asymmetry* **1999**, *10*, 4729–4743; c) A. Ohashi, S. Kikuchi, M. Yasutake, T. Imamoto, *Eur. J. Org. Chem.* **2002**, *2002*, 2535–2546; d) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; e) G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *Coord. Chem. Rev.* **2008**, *252*, 471–491; f) A. Vidal-Ferran, A. Grabulosa, X. Verdaguer, A. Riera, *in Catalytic Asymmetric Synthesis*, 4th ed. (Eds: T. Akiyama, I. Ojima), Wiley, Hoboken, NJ, USA, **2022**, Ch. 15; g) P. Rojo, A. Riera, X. Verdaguer, *Coord. Chem. Rev.* **2023**, *489*, 215192.

[23] a) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252; b) E. J. Corey, Z. Chen, G. J. Tanoury, *J. Am. Chem. Soc.* **1993**, *115*, 11000–11001; c) T. Miura, H. Yamada, S. Kikuchi, T. Imamoto, *J. Org. Chem.* **2000**, *65*, 1877–1880; d) C. Bauduin, D. Moulin, E. B. Kaloun, C. Darcel, S. Jugé, *J. Org. Chem.* **2003**, *68*, 4293–4301; e) J.-V. Naubron, L. Giordano, F. Fotiadu, T. Bürgi, N. Vanthuyne, C. Roussel, G. Buono, *J. Org. Chem.* **2006**, *71*, 5586–5593; f) R. den Heeten, B. H. G. Swennenhuis, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Angew. Chem. Int. Ed.* **2008**, *47*, 6602–6605; *Angew. Chem.* **2008**, *120*, 6704–6707; g) D. Moraleda, D. Gatineau, D. Martin, L. Giordano, G. Buono, *Chem. Commun.* **2008**, 3031–3033; h) J. Bayardon, S. Jugé, *in Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*, 1st ed. (Eds: P. C. J. Kamer, P. W. N. M. van Leeuwen), Wiley, Hoboken, NJ, USA, **2012**, Ch. 12; i) T. Imamoto, *Proc. Jpn. Acad. Ser. B* **2021**, *97*, 520–542.

[24] L. Wang, Z. Du, Q. Wu, R. Jin, Z. Bian, C. Kang, H. Guo, X. Ma, L. Gao, *Eur. J. Org. Chem.* **2016**, *2016*, 2024–2028.

[25] a) T. Koizumi, Y. Kobayashi, H. Amitani, E. Yoshii, *J. Org. Chem.* **1977**, *42*, 3459–3460; b) T. Koizumi, H. Amitani, E. Yoshii, *Synthesis* **1979**, 110–112.

[26] C. R. Hall, T. D. Inch, G. J. Lewis, R. A. Chittenden, *J. Chem. Soc. Chem. Commun.* **1975**, 720–721.

[27] T. Koizumi, H. Takagi, E. Yoshii, *Chem. Lett.* **1980**, *9*, 1403–1406.

[28] Y. Kobayashi, T. Koizumi, E. Yoshii, *Chem. Pharm. Bull.* **1979**, *27*, 1641–1650.

[29] a) T. Koizumi, Y. Kobayashi, E. Yoshii, *J. Chem. Soc. Chem. Commun.* **1974**, 678–679; b) T. Koizumi, Y. Kobayashi, E. Yoshii, *Chem. Pharm. Bull.* **1976**, *24*, 834–835.

[30] E. V. Gryshkun, N. V. Andrushko, O. I. Kolodiazhnyi, *Phosphorus Sulfur Silicon Relat. Elem.* **2004**, *179*, 1027–1046.

[31] P. M. Reddy, I. M. Kovach, *Tetrahedron Lett.* **2002**, *43*, 4063–4066.

[32] M. Revés, C. Ferrer, T. León, S. Doran, P. Etayo, A. Vidal-Ferran, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9452–9455; *Angew. Chem.* **2010**, *122*, 9642–9645.

[33] T. Huber, N. A. Espinosa-Jalapa, J. O. Bauer, *Chem. Eur. J.* **2022**, *28*, e202202608.

[34] a) W. B. Farnham, R. A. Lewis, R. K. Murray Jr., K. Mislow, *J. Am. Chem. Soc.* **1970**, *92*, 5809–5810; b) J. K. Whitesell, *Chem. Rev.* **1992**, *92*, 953–964.

[35] A. Włodarczyk, A. E. Kozioł, M. Stankevič, *Eur. J. Org. Chem.* **2018**, 1589–1600.

[36] M. Stankevič, A. Włodarczyk, D. Nieckarz, *Eur. J. Org. Chem.* **2013**, 4351–4371.

[37] a) D. B. Cooper, J. M. Harrison, T. D. Inch, *Tetrahedron Lett.* **1974**, *15*, 2697–2700; b) D. B. Cooper, C. R. Hall, T. D. Inch, *J. Chem. Soc. Chem. Commun.* **1975**, 721–723; c) D. B. Cooper, C. R. Hall, J. M. Harrison, T. D. Inch, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1969–1980.

[38] a) S. Jugé, J. P. Genet, *Tetrahedron Lett.* **1989**, *30*, 2783–2786; b) S. Jugé, M. Stephan, J. P. Genet, S. Halut-Desportes, S. Jeannin, *Acta Crystallogr.* **1990**, *C46*, 1869–1872; c) D. Moulin, S. Bago, C. Bauduin, C. Darcel, S. Jugé, *Tetrahedron: Asymmetry* **2000**, *11*, 3939–3956; d) C. Darcel, D. Moulin, J.-C. Henry, M. Lagrelette, P. Richard, P. D. Harvey, S. Jugé, *Eur. J. Org. Chem.* **2007**, 2078–2090.

[39] C. Hall, T. D. Inch, I. W. Lawston, *Tetrahedron Lett.* **1979**, *20*, 2729–2732.

[40] H. Zijlstra, T. León, A. de Cózar, C. Fonseca Guerra, D. Byrom, A. Riera, X. Verdaguer, F. M. Bickelhaupt, *J. Am. Chem. Soc.* **2013**, *135*, 4483–4491.
[41] a) L. Wang, S. Cao, Z. Du, Q. Wu, Z. Bian, C. Kang, L. Gao, J. Zhang, *RSC Adv.* **2016**, *6*, 89665–89670; b) R. Xu, Z. Gao, Y. Yu, Y. Tang, D. Tian, T. Chen, Y. Chen, G. Xu, E. Shi, W. Tang, *Chem. Commun.* **2021**, *57*, 3335–3338.
[42] a) Y. Wu, K. Chen, X. Ge, P. Ma, Z. Xu, H. Lu, G. Li, *Org. Lett.* **2020**, *22*, 6143–6149; b) C. Tan, X. Liu, H. Jia, X. Zhao, J. Chen, Z. Wang, J. Tan, *Chem. Eur. J.* **2020**, *26*, 881–887; c) Y.-Y. Zhu, Y. Niu, Y.-N. Niu, S.-D. Yang, *Org. Biomol. Chem.* **2021**, *19*, 10296–10313; d) Z. Bai, F. Song, H. Wang, W. Cheng, S. Zhu, Y. Huang, G. He, G. Chen, *CCS Chem.* **2022**, *4*, 2258–2266; e) Z. Zhang, Q. Yan, R. Gao, H. Wang, *Phosphorus Sulfur Silicon Relat. Elem.* **2023**, *198*, 789–799.
[43] Y.-B. Li, H. Tian, S. Zhang, J.-Z. Xiao, L. Yin, *Angew. Chem. Int. Ed.* **2022**, *61*, e202117760; *Angew. Chem.* **2022**, *134*, e202117760.
[44] F. Pertusati, C. McGuigan, *Chem. Commun.* **2015**, *51*, 8070–8073.
[45] M. Wang, L. Zhang, X. Huo, Z. Zhang, Q. Yuan, P. Li, J. Chen, Y. Zou, Z. Wu, W. Zhang, *Angew. Chem. Int. Ed.* **2020**, *59*, 20814–20819; *Angew. Chem.* **2020**, *132*, 21000–21005.
[46] J. Liu, H. Chen, M. Wang, W. He, J.-L. Yan, *Front. Chem.* **2023**, *11*, 1132025.
[47] Y. Zhou, J. Yang, T. Chen, S.-F. Yin, D. Han, L.-B. Han, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 400–402.
[48] X.-L. Zhang, X. Qi, Y.-X. Wu, P. Liu, Y. He, *Cell Rep. Phys. Sci.* **2021**, *2*, 100594.
[49] A. Mondal, N. O. Thiel, R. Dorel, B. L. Feringa, *Nat. Catal.* **2022**, *5*, 10–19.
[50] X.-B. Chen, D. Padín, C. N. Stindt, B. L. Feringa, *Angew. Chem. Int. Ed.* **2023**, *62*, e202307450; *Angew. Chem.* **2023**, *135*, e202307450.
[51] L. B. Balázs, Y. Huang, J. B. Khalikuzzaman, Y. Li, S. A. Pullarkat, P.-H. Leung, *J. Org. Chem.* **2020**, *85*, 14763–14771.
[52] Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao, F.-S. Han, *J. Am. Chem. Soc.* **2015**, *137*, 632–635.
[53] Y.-H. Chen, X.-L. Qin, F.-S. Han, *Chem. Commun.* **2017**, *53*, 5826–5829.
[54] T. Zhou, L.-J. Fan, Z.-J. Chen, M.-X. Jiang, P.-F. Qian, X. Hu, K. Zhang, B.-F. Shi, *Org. Lett.* **2023**, *25*, 5724–5729.
[55] P.-F. Qian, J.-Y. Li, T. Zhou, B.-F. Shi, *Synthesis* **2022**, *54*, 4784–4794.
[56] a) M. Casimiro, L. Roces, S. García-Granda, M. J. Iglesias, F. López-Ortiz, *Org. Lett.* **2013**, *15*, 2378–2381; b) M. Casimiro, G. P. Guedes, M. J. Iglesias, F. López-Ortiz, *Tetrahedron: Asymmetry* **2015**, *26*, 53–66; c) M. A. del Águila-Sánchez, Y. Navarro, J. García López, G. P. Guedes, F. López-Ortiz, *Dalton Trans.* **2016**, *45*, 2008–2022; d) Y. Navarro, G. P. Guedes, M. A. del Águila-Sánchez, M. J. Iglesias, F. Lloret, F. López-Ortiz, *Dalton Trans.* **2021**, *50*, 2585–2595.
[57] a) Z. S. Han, N. Goyal, M. A. Herbage, J. D. Sieber, B. Qu, Y. Xu, Z. Li, J. T. Reeves, J.-N. Desrosiers, S. Ma, N. Grinberg, H. Lee, H. P. R. Mangunuru, Y. Zhang, D. Krishnamurthy, B. Z. Lu, J. J. Song, G. Wang, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 2474–2477; b) Z. S. Han, L. Zhang, Y. Xu, J. D. Sieber, M. A. Marsini, Z. Li, J. T. Reeves, K. R. Fandrick, N. D. Patel, J.-N. Desrosiers, B. Qu, A. Chen, D. M. Rudzinski, L. P. Samankumara, S. Ma, N. Grinberg, F. Roschangar, N. K. Yee, G. Wang, J. J. Song, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2015**, *54*, 5474–5477; *Angew. Chem.* **2015**, *127*, 5564–5567.
[58] Z. S. Han, H. Wu, B. Qu, Y. Wang, L. Wu, L. Zhang, Y. Xu, L. Wu, Y. Zhang, H. Lee, F. Roschangar, J. J. Song, C. H. Senanayake, *Tetrahedron Lett.* **2019**, *60*, 1834–1837.
[59] M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686, *Angew. Chem.* **2006**, *118*, 3765–3768.
[60] M. Yuan, I. I. Mbaezue, Z. Zhou, F. Topic, Y. S. Tsantrizos, *Org. Biomol. Chem.* **2019**, *17*, 8690–8694.
[61] I. I. Mbaezue, F. Topic, Y. S. Tsantrizos, *Synlett* **2023**, *34*, 1709–1714.
[62] X.-L. Qin, A. Li, F.-S. Han, *J. Am. Chem. Soc.* **2021**, *143*, 2994–3002.
[63] G.-J. Wu, D.-X. Tan, F.-S. Han, *Acc. Chem. Res.* **2021**, *54*, 4354–4370.
[64] A. Flores-Gaspar, S. Orgué, A. Grabulosa, A. Riera, X. Verdaguer, *Chem. Commun.* **2015**, *51*, 1941–1944.
[65] S. Chakrabortty, K. Konieczny, B. H. Müller, A. Spannenberg, P. C. J. Kamer, J. G. de Vries, *Catal. Sci. Technol.* **2022**, *12*, 1392–1399.
[66] J.-O. Moritz, S. Chakrabortty, B. H. Müller, A. Spannenberg, P. C. J. Kamer, *J. Org. Chem.* **2020**, *85*, 14537–14544.
[67] T. León, M. Parera, A. Roglans, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2012**, *51*, 6951–6955; *Angew. Chem.* **2012**, *124*, 7057–7061.
[68] T. Shibata, K. Tsuchikama, *Org. Biomol. Chem.* **2008**, *6*, 1317–1323.
[69] a) I. Notar Francesco, A. Wagner, F. Colobert, *Chem. Commun.* **2010**, *46*, 2139–2141; b) I. Notar Francesco, C. Egloff, A. Wagner, F. Colobert, *Eur. J. Org. Chem.* **2011**, 4037–4045.
[70] a) G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914; b) D. A. Cogan, G. Liu, J. A. Ellman, *Tetrahedron* **1999**, *55*, 8883–8904; c) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740.
[71] a) S. Orgué, A. Flores-Gaspar, M. Biosca, O. Pàmies, M. Diéguez, A. Riera, X. Verdaguer, *Chem. Commun.* **2015**, *51*, 17548–17551; b) E. Salomó, S. Orgué, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2016**, *55*, 7988–7992; *Angew. Chem.* **2016**, *128*, 8120–8124.
[72] M. Biosca, P. de La Cruz-Sánchez, J. Faiges, J. Margalef, E. Salomó, A. Riera, X. Verdaguer, J. Ferré, F. Maseras, M. Besora, O. Pàmies, M. Diéguez, *ACS Catal.* **2023**, *13*, 3020–3035.
[73] M. Biosca, M. Magre, O. Pàmies, M. Diéguez, *ACS Catal.* **2018**, *8*, 10316–10320.
[74] E. Salomó, P. Rojo, P. Hernández-Lladó, A. Riera, X. Verdaguer, *J. Org. Chem.* **2018**, *83*, 4618–4627.
[75] X.-X. Zhang, Y. Zhang, L. Liao, Y. Gao, H. E. M. Su, J.-S. Yu, *ChemCatChem* **2022**, *14*, e202200126.
[76] A. Cabré, M. Garçon, A. Gallen, L. Grisoni, A. Grabulosa, X. Verdaguer, A. Riera, *ChemCatChem* **2020**, *12*, 4112–4120.
[77] F. Eyer, V. Meischner, D. Kiderlen, H. Thiermann, F. Worek, M. Haberkorn, N. Felgenhauer, T. Zilker, P. Eyer, *Toxicol. Rev.* **2003**, *22*, 143–163.

Manuscript received: November 11, 2023
Accepted manuscript online: December 6, 2023
Version of record online: ■■, ■■

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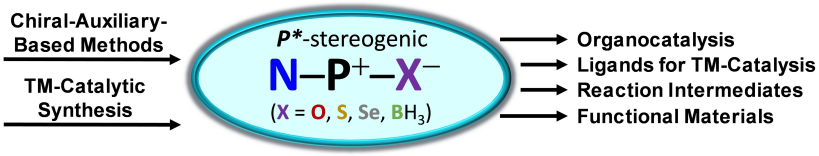

New catalytic possibilities in the synthesis of *P*-stereogenic aminophosphine chalcogenides and boranes serve as an expansion in addition to established methods based on chiral auxiliaries. Stereoselective transformations into valuable building blocks facilitate catalyst design for use in organocatalytic and transition metal-based applications. Here, we present the main achievements of the last decades regarding synthesis, stereocontrolled reactivities, and catalytic applications of *P*-stereogenic P–N-based compounds.

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