UNIWERSYTET MARII CURIE-SKŁODOWSKIEJ
W LUBLINIE

Wydział Chemii

Instytut Nauk Chemicznych

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A combination of C-P cross-coupling between >P(O)H compounds and cycloalkenyl electrophiles, and asymmetric conjugate addition as a source of chiral 1,2-functionalized cyclohexanes for applications in organic synthesis

Rozprawa doktorska
wykonana w Katedrze Chemii Organicznej
pod kierunkiem dra hab. inż. Marka Stankeviča

Lublin 2023

I dedicate this work to my mother

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This Ph.D. project was funded by the grant of Polish Ministry of Science and Higher Eduction "Diamentowy Grant 2018", project no. DI 2017 012247.

Parts of the results presented in this thesis were published in the following publication: "Copper-Catalyzed C-P Cross-Coupling of (Cyclo)alkenyl/Aryl Bromides and Secondary Phosphine Oxides with in situ Halogen Exchange", P. Woźnicki, M. Stankevič, *Eur. J. Org. Chem.* **2021**, 3484–3491.

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1. Introduction

The preparation of enantiopure compounds has been one of the greatest challenges of organic synthesis since its inception as a discipline of chemistry. The importance of techniques leading to enantiopure compounds is best reflected in the pharmaceutical industry.[1] All chiral drugs of natural origin are used as single enantiomers. This is due to stereospecificity of biochemical reactions producing natural compounds. On the other hand synthetic chiral drugs may be used as racemic mixtures or single enantiomers. Stereoisomers of chiral drugs are typically characterized by different pharmacological properties including different affinity to receptors and different susceptibility to metabolism. This is the consequence of the chiral nature of protein-building α-aminoacids and, what follows, specific spatial requirements of receptor clefts for binding of ligands. The desired pharmacological action is typically exerted primarily or completely by a single stereoisomer, while other stereoisomers may possess the same qualitative effect but different in potency, be inactive, or be active at other targets. As such these isomers may contribute negatively to the adverse effect profile of a racemic drug and in some cases confer serious toxicity. Sometimes enantiomers can have different but in both cases desirable effects (dextromethorphan – an antitussive, levomethorphan – an opioid analgesic). The extent to which stereoisomers differ in effects depends on the numbers of chiral centres and their location in the structure of a drug molecule relative to the points of attachment to a receptor. Although single isomer formulations appear to be universally superior to racemic drugs in terms of efficacy and safety when only one isomer has the favourable properties, the preparation of enantiopure drugs is associated with additional costs in time and material resources, thus the benefit of using a single isomer drug should be weighed against the economical feasibility of the whole manufacturing and testing process.[1]

There are three main approaches to obtaining enantiopure compounds[1b]:

1) resolution of enantiomers,
2) stereospecific transformation of a compound of natural origin (*chiral pool synthesis*),
3) stereoselective synthesis.

Resolution of enantiomers is typically performed by the formation of diastereomeric derivatives followed by fractional crystallization or separation by a chromatographic method,[1e] alternatively enantiomers can be separated on a chromatographic column with a

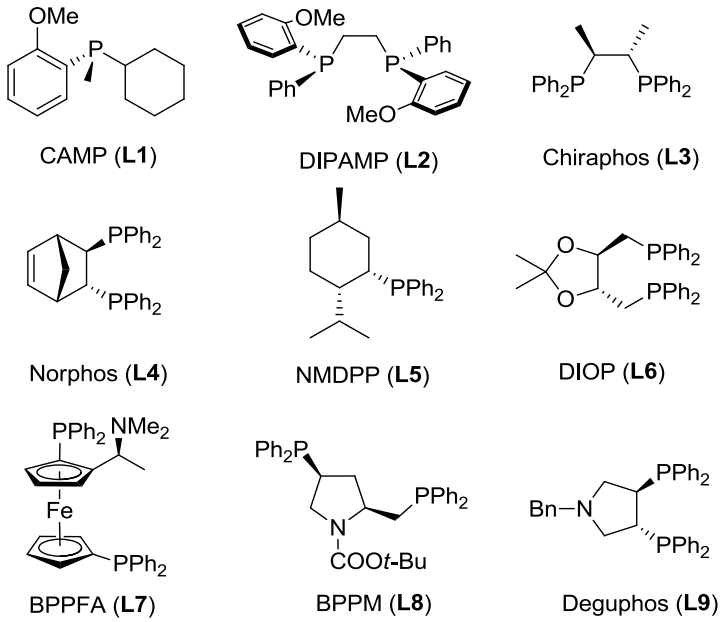
chiral stationary phase. *Chiral pool synthesis* uses natural chiral compounds as substrates and subjects them to stereospecific reactions. Stereoselective synthesis focuses on the selective transformation of a prochiral substrate into an enantioenriched chiral product. The preferential formation of a single stereoisomer takes place as a result of stereochemical induction due to the presence of a chiral fragment in the substrate, reagent, catalyst or solvent. The chiral fragment may be present in the substrate of natural or semi-synthetic origin (*chiral pool*), temporarily introduced into the structure of the substrate as a *chiral auxiliary*, or be present in the promoter/catalyst which forms a chiral intermediate or transition state with the substrate. Stereoselective catalysis is by far the most versatile approach due to the requirement of only a small quantity of a stereoinducing factor.[2a]

Stereoselective catalysis can be divided into metal catalysis, organocatalysis, and biocatalysis. Of these, asymmetric metal catalysis, and especially transition metal catalysis, covers the broadest scope of organic transformations.[2a,e] As the d orbitals of transition metals can hold up to 10 electrons, transition metals of different groups can access different ranges of oxidation states, with the s and p orbitals taking part in bonding, transition metals can accommodate multiple ligands with up to 18 electrons in the valence shell. The electronic and steric properties of transition metal complexes are heavily influenced by the bonded ligands and chiral ligands are the source of chirality in chiral metal catalysts. As such, finding the right catalyst for a given transformation is in large part dependent on finding the right ligand.[2b,c]

Trivalent organophosphorus compounds are the biggest group of ligands for transition metals, owing to their σ-donating and π-accepting properties, they form relatively strong coordinating bonds with transition metals as opposed to more labile amines.[2d] The asymmetric transition metal catalysis started in late 1960's with the first publications on Rh-catalyzed asymmetric hydrogenation of olefins. The discovery of this reaction was strongly related to the advances in the synthesis of *P*-chiral organophosphorus compounds. Because of the higher barrier to pyramidal inversion of tertiary phosphines, they have higher configurational stability compared with amines.[3] Tertiary phosphines were considered as the first chiral ligands due to the close proximity of a chiral centre to a metal atom in a complex. The early experiments of Knowles[4a] and Horner[4b] in 1968 with optically enriched methyl(phenyl)*n*-propylphosphine proved that the concept of a stereoselective hydrogenation with a Rh catalyst possessing a chiral phosphine ligand was viable. Atropic acid, α-ethylstyrene and α-methoxystyrene were hydrogenated providing the products with 4-15%

ee.[4] The low enantioselectivity observed meant that the ligand design was a non-trivial process. In the following years several research groups reported on both *P*-chiral and *C*-chiral mono- and diphosphine ligands which showed remarkable efficiency in asymmetric hydrogenation (Figure 1).[5-13] These early ligands, however, had a narrow scope typically limited to *Z* isomers of α-acylaminocinnamic acid derivatives (dehydrophenylalanine derivatives), and their efficacy was highly dependent on the substitution of the phenyl ring and the acyl group at the nitrogen atom in the substrate.

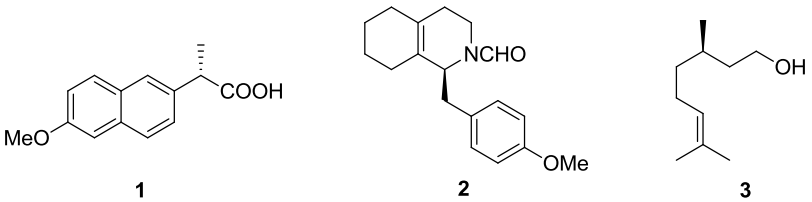
Figure 1



The research conducted in 1970-1980's culminated in the discovery of superior ligands with a much better efficiency – BINAP, DuPhos and Josiphos. Noyori discovered that Ru/BINAP catalysts offered much wider scope in asymmetric hydrogenation expanding the reaction to α,β-unsaturated carboxylic acids,[14a] enamides,[14b] and allylic alcohols[14c] (Figure 2), as well as functionalized ketones[14d,e] (Scheme 1), all of which, until then, had remained elusive substrates under Rh catalysis. Industrially, Ru/BINAP catalysts have been used in the synthesis of non-steroid anti-inflammatory drugs such as naproxen[14a,15] and ibuprofen,[15] the synthesis of a precursor to dextromethorphan, an antitussive,[16] the hydrogenation of geraniol to obtain both citronellol enantiomers in pure form,[14c,17,18] and the synthesis of chiral building blocks which were then transformed into antibiotics (carbapenems, levofloxacin)[18] and ligands containing 2,5-disubstituted phospholane motif.[20] For simple ketones lacking additional coordinating groups Ru catalysts possessing BINAP analogues and diamine ligands were developed.[21] The Rh/(*S*)-BINAP complex was also found to catalyze isomerisation of

N,*N*-diethylgeranylamine, a key step in the industrial synthesis of L-menthol,[19] and isomerisation of *N*,*N*-diethyl-6,7,10,11-tetrahydrofarnesylamine, an intermediate step en route to α-tocopherol.[22] Based on the success of BINAP numerous atropisomeric phosphine ligands were reported, including BINAP analogues with substituted phenyl groups at phosphorus (Tol-BINAP, Xyl-BINAP, DTB-BINAP, DTBM-BINAP) and biaryl diphosphines in which the naphthalene moiety was replaced with another bicyclic moiety – benzodioxole (SEGPHOS), benzodioxane (SYNPHOS), tetrahydronaphthalene (H_8-BINAP) – or substituted phenyl moieties (BIPHEMP, MeO-BIPHEP, C_n-TunaPhos). BINAP and its derivatives are currently one of the most widely employed ligand families and have shown high efficacy in many stereoselective reactions.[23]

Figure 2



1
(*S*)-naproxen
Ru/(*S*)-BINAP
97% ee

2
dextromethorphan precursor
Ru/(*S*)-Tol-BINAP
97% ee

3
(*R*)-citronellol
Ru/(*S*)-BINAP
98% ee

DuPhos (**L12**) and BPE (**L13**) ligands reported in early 1990's by Burk *et al.* further increased the level of stereoselectivity of dehydroaminoacid derivative hydrogenation under Rh catalysis and are the ligands of choice for this purpose.[20,24] They also expanded the scope of olefins, C=O and C=N compounds.[17,24] Interestingly, these ligands were derived from β-ketoesters which were stereoselectively reduced using Ru/BINAP catalysis *en route* to chiral 1,4-diols which are precursors to cyclic sulfonates used to form a phospholane ring with a primary phosphine. Following the success of DuPhos ligands, more highly efficient ligands possessing two *P*-heterocyclic rings joined by the 1,2-phenylene motif were synthesized such as TangPhos, DuanPhos, PennPhos, and BenzP*.[24]

In 1994 Togni *et al.* reported on the synthesis of Josiphos which was obtained from PPFA[25] – the ligand previously prepared by Kumada *et al.* through diastereoselective lithiation of Ugi's amine[26] (*vide infra*, Scheme 2). Initially, Josiphos showed high efficacy in Rh-catalyzed hydrogenation of dehydroaminoacid esters, diethyl itaconate, and ethyl acetoacetate, Rh-catalyzed hydroboration of styrene, and Pd-catalyzed allylic substitution.[25] Many analogues with different combinations of substituents at the phosphorus atoms have

been synthesized since then and a few of them have a broad application in asymmetric metal catalysis (Figure 3).[27,28] The most notable industrial application is the asymmetric imine hydrogenation in the synthesis of (*S*)-metolachlor, a synthetic herbicide, with the Ir/Xyliphos catalyst.[29] It is the biggest known operating enantioselective reaction and the ligand has been prepared on the scale of hundred kilograms. Also, the Ru/Josiphos catalyst is used in the asymmetric hydrogenation of methyl jasmonate,[30] and the Rh/PPF-*t*-Bu catalyst is used in the asymmetric olefin hydrogenation process leading to a biotin precursor.[31] Following the success of Josiphos, chiral ferrocenylphosphine ligands with different substitution patterns were synthesized such as Taniaphos, Walphos, Mandyphos, BoPhoz, Pigiphos, and TRAP.[32]

Scheme 1

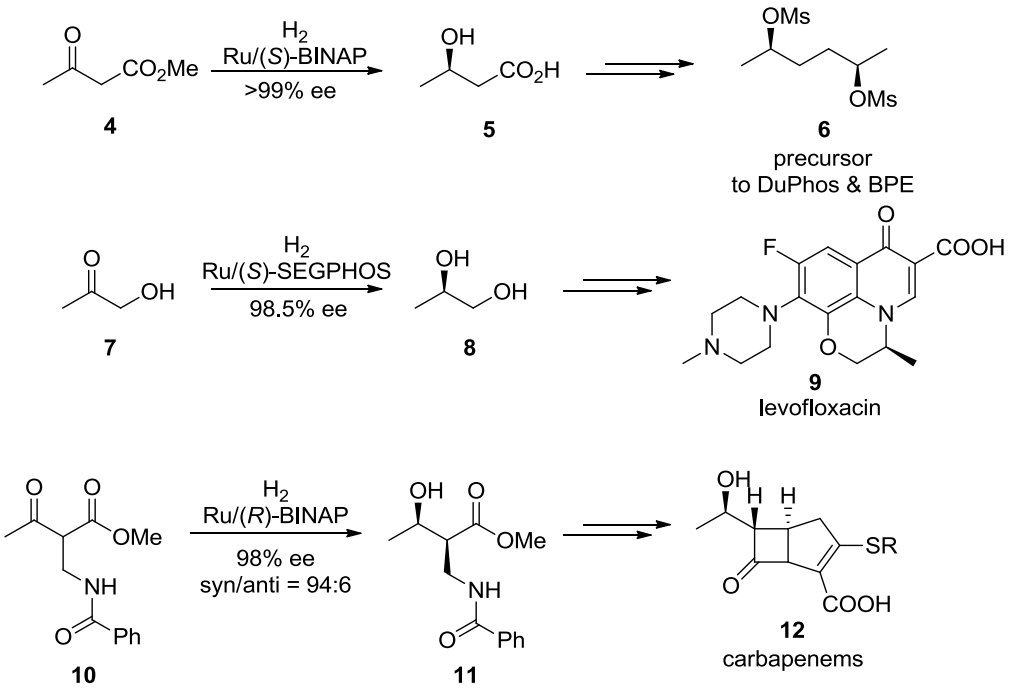
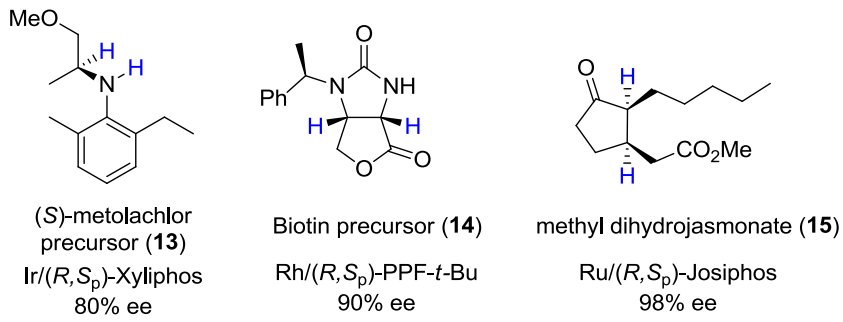
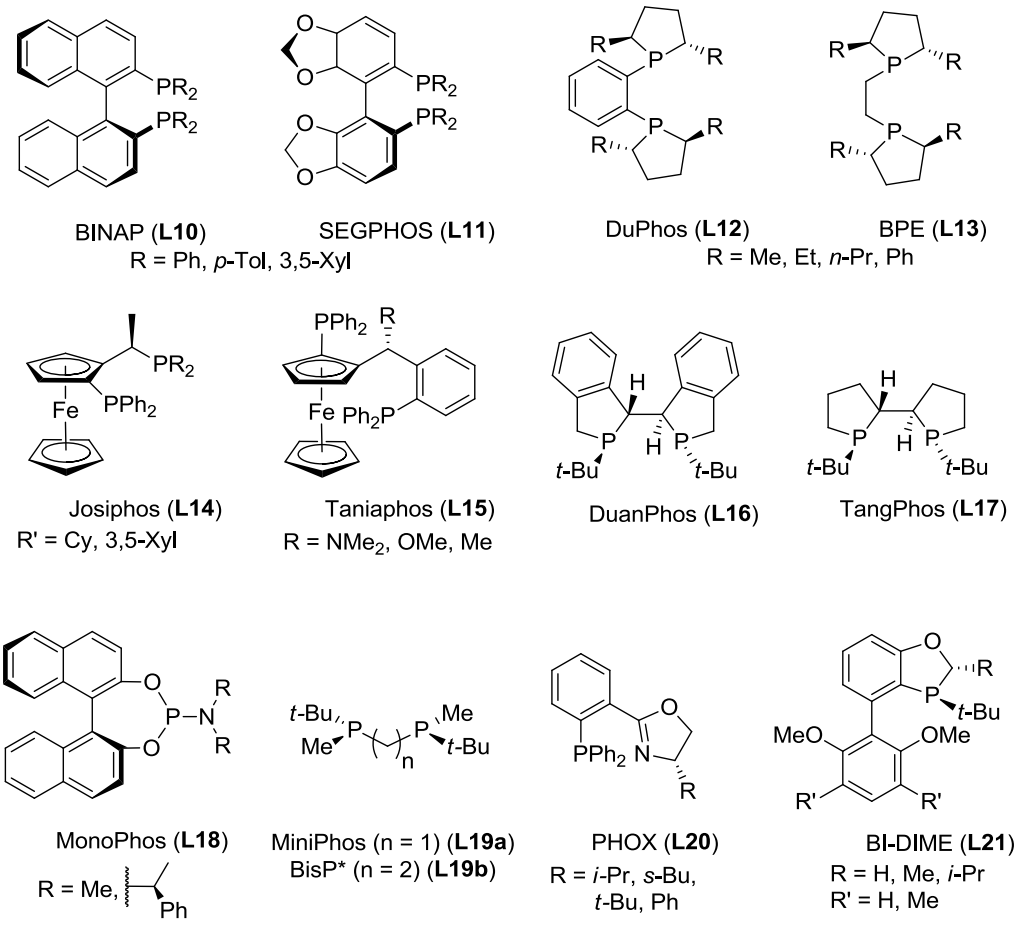


Figure 3

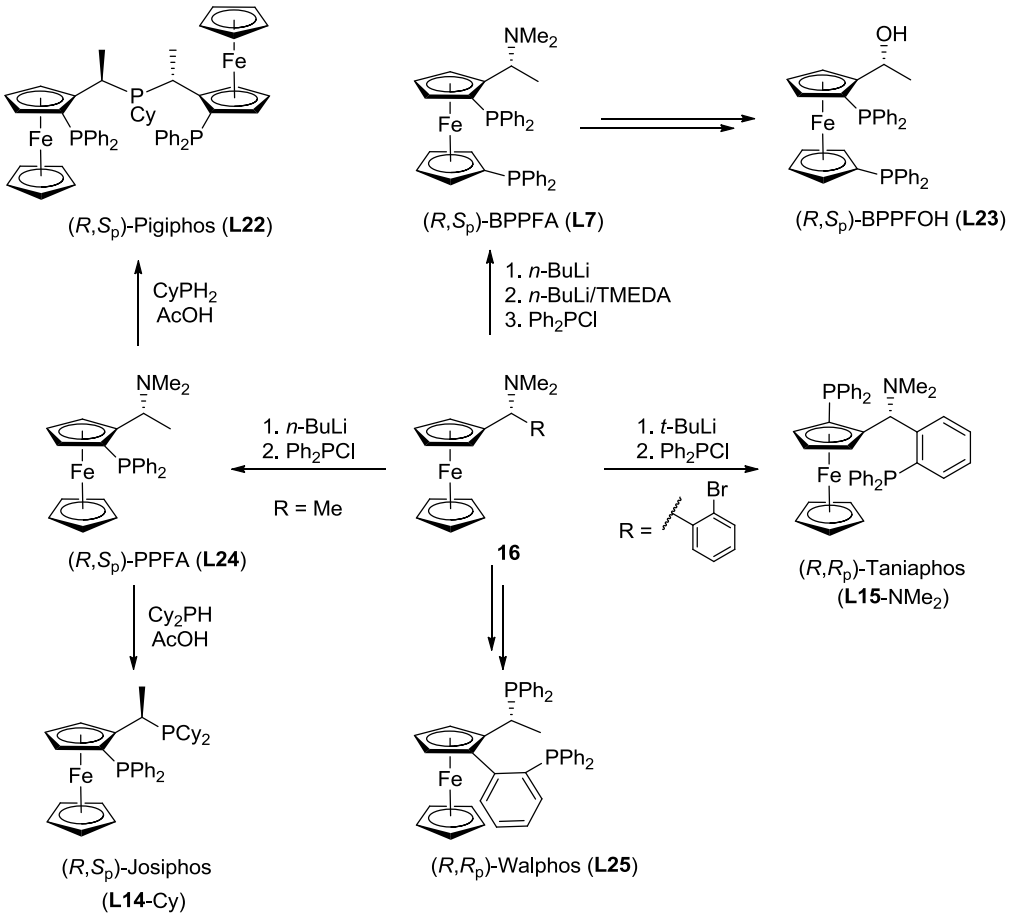


Huge commercial success of BINAP, DuPhos, Josiphos and their analogues greatly influenced the design of new ligands and shaped the requirements for them to be adopted by the chemical industry. The most commercially successful chiral ligands have a wide scope of applications in organic synthesis, forming complexes with different transition metals that can catalyze mechanistically distinct reactions. Ligands with such qualities are called privileged ligands, the term coined by Jacobsen.[33] Figure 4 showcases several families of commercialized privileged ligands. The optimization of a catalytic reaction includes fine-tuning of the catalyst properties which is done by making small changes to the ligand structure such as exchanging or introducing functional groups. For this reason a common feature of privileged ligands is a modifiable scaffold, i.e. it should be possible to change the electronic and steric properties of the ligand by using a different reagent at some point in the synthesis or following a different pathway from a common intermediate. The synthesis of a successful chiral ligand should be concise and use relatively cheap and abundant starting materials as the costs rise exponentially during scaling up from a lab scale to an industrial process. The protocol should also avoid resolution steps.

Figure 4



Scheme 2



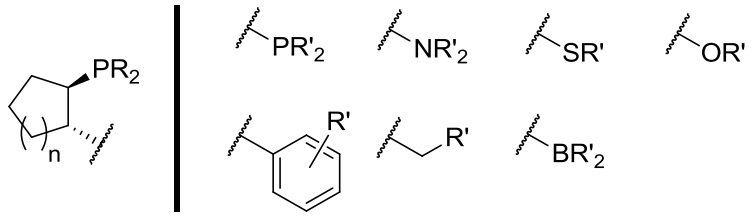
A good example of a privileged ligand family are ferrocenylphosphines which possess both the central and planar chirality. The two-step synthesis of Josiphos from Ugi's amine[34] is highly modular allowing to install two different phosphino groups onto the Cp ring and the alkyl side chain.[35] In fact, as the lithiation of Ugi's amine and the nucleophilic substitution of the dimethylamino group are both highly stereoselective, Ugi's amine and analogous aminoalkylferrocenes serve as convenient intermediates for the synthesis of a variety of ferrocenylphosphine ligands with different substitution patterns, including BPPFA (**L7**) and BPPFOH (**L23**), Taniaphos (**L15**-NMe_2), Walphos (**L25**), and Pigiphos (**L22**) (Scheme 2).[27,28,35]

Despite the availability of a large number of ligands for different applications, there is still high interest in developing new ligands with tunable structure both for general and specific applications. Unfortunately, the process of ligand design is not fully rational. The structures of the very first ligands found to be suitable for asymmetric hydrogenation have been found by chance and intuition rather than as a result of a rational design process.

Nonetheless, there are several useful concepts and parameters describing electronic and steric effects of ligands (ligand field theory, Pearson acid base concept, σ-donor, π-donor, π-acceptor, cone angle, bite angle, percent buried volume), and these can be used to rationalize ligand properties required for specific reactions, especially when a mechanism is known.[2c,2f,36]

The majority of the first successful chiral ligands were bidentate diphosphines with C_2 symmetry and this theme has been present in the following decades in the ligand design leading up to BINAP and DuPhos. While C_2 symmetry reduces the number of possible arrangements of the substrate and catalyst that could lead to a decrease in enantioselectivity, and hence simplifies the design process, it is not, however, a prerequisite for an effective chiral ligand.[36] In fact, certain reactions benefit from a non-symmetric ligand with two coordinating groups differing in electronic and steric properties. As early as in 1986 Achiwa *et al.* reported that the BPPM analogue with one of the PPh_2 groups changed to PCy_2 (BCPM) was superior in terms of both activity and stereoselectivity in Rh-catalyzed hydrogenation of ketopantolactone, and its design was rationalized through mechanistic consideration of the reaction.[37] Similarly PHOX (phosphinooxazoline) ligands which are mixed *P*,*N*-ligands were successfully developed for Pd-catalyzed allylic substitution based on the rationale that a bidentate ligand with two different coordinating groups would differentiate two termini of the Pd-allyl intermediate through stronger *trans* effect, and differentiate two faces of the intermediate as a result of the chiral centre in the ligand, providing both high regio- and stereoselectivity.[38] Later PHOX ligands were also found to form highly active Ir catalysts, akin to non-chiral Crabtree's catalyst, for asymmetric hydrogenation of non-functionalized tri- and tetrasubstituted olefins which are unreactive under Rh and Ru catalysis.[36,39]

Figure 5



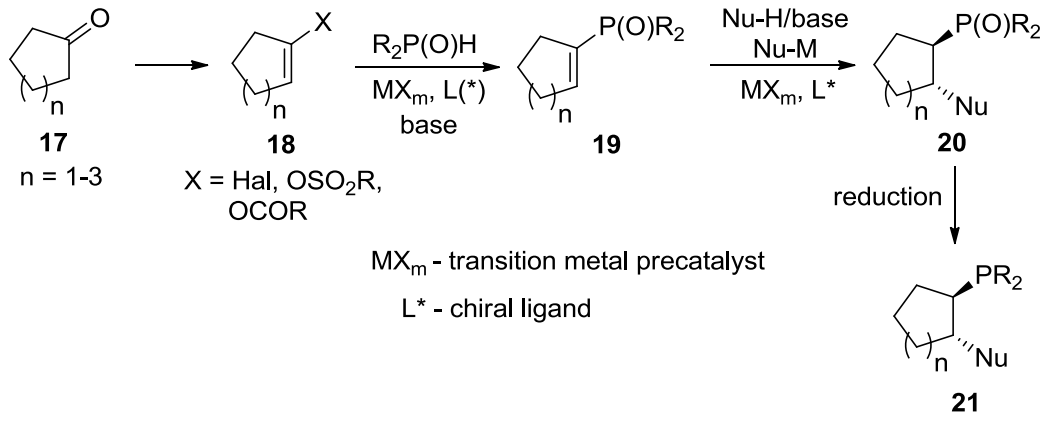
Among a great number of chiral phosphines that have been used as chiral ligands in asymmetric catalysis, phosphines based on the *trans*-1,2-cycloalkylene scaffold, with a phosphino group at C1 and another functional group at C2, appear to be an interesting target for a modular synthesis (Figure 5). *Trans*-1,2-bis(phosphino)cycloalkanes have been known

since the 1980s, however, so far their utility as ligands has been shown only in a limited number of reactions and the last article on their use was published in 2004. On the other hand 2-(diphenylphosphino)cyclohexylamine analogues have been shown to act as efficient organocatalysts and ligands in a number of publications in the late 2000s and throughout the 2010s. The great potential of the *trans*-1,2-cyclohexylene scaffold for stereoinduction has also been extensively demonstrated with *trans*-1,2-diaminocyclohexane derivatives,[40] including (1) salen ligands (Katsuki-Jacobsen epoxidation),[40a,c] (2) Trost ligands (Tsuji-Trost reaction),[40a,d] (3) *N,N'*-bis(sulfonyl) analogues (asymmetric addition of organozinc reagents to carbonyl compounds),[40b] and (4) *N,N,N',N'*-tetraalkyl diamines (asymmetric lithiation).[40e] The research into the application of *trans*-1,2-bis(phosphino)cycloalkanes and 2-substituted 1-phosphinocycloalkanes has been much more limited so far possibly due to the lack of a viable general synthetic pathway granting access to a wide spectrum of analogues.

2. Aim of the thesis

The aim of this thesis was to study the viability of developing a four-step synthesis of 2-substituted 1-phosphinocycloalkanes (Scheme 3). The proposed method starts from cycloalkanones (**17**), which are readily available commercially in bulk quantities, and the first step is the transformation into cycloalkenyl (pseudo)halides using previously reported methods.[41-42] The key part of the synthesis is the sequence of two reactions catalyzed by a transition metal complex – C-P cross-coupling between cycloalkenyl electrophiles (**18**) and secondary phosphine oxides to obtain cycloalkenylphosphine oxides (**19**), and asymmetric conjugate addition of various carbon and heteroatom nucleophiles to the cross-coupling products. These two catalytic steps would ideally be done using catalysts based on cheaper and more abundant first-row transition metals such as copper, nickel, or cobalt rather than more expensive and scarce palladium or rhodium. As both C-P cross-coupling[158,203] and addition to electron-deficient olefins[244] have been done under copper and nickel catalysis, it might be possible to devise a one-pot procedure with the two reactions being catalyzed by one catalyst or two different catalysts. The final step would be the reduction of tertiary phosphine oxides into the corresponding phosphines.

Scheme 3



Regarding the feasibility of the approach, the first and last steps of the proposed method are well known. Methods to transform cycloalkanones into the corresponding chloro-,[41a] bromo-,[41b,c] and iodocycloalkenes[41d-f] as well as carboxylic,[42a] sulfonyl,[78,229,230] and phosphinoyl[42b] esters have been described before. The reduction of tertiary phosphine oxides possessing different substituents into tertiary phosphines has been accomplished using different reducing agents.[43] C-P cross-coupling reaction has been known since 1980's and its

current state-of-the-art includes procedures for a wide scope of substrates using palladium, copper, and nickel catalysis,[158,203] although most protocols focus on aryl coupling partners and methods employing cycloalkenyl electrophiles are more rare and typically use Pd catalysts.[78,164b,174,226-233] In contrast, asymmetric conjugate addition to α,β-unsaturated organophosphorus compounds has not been researched as extensively, as of August 2022 there have been only seven scientific articles published in this field and cycloalkenylphosphine derivatives have not been reported as substrates so far.[235-240,242]

Considering the research goal and the current state-of-the-art in the field of the key reactions, I set out to accomplish the following objectives as part of my Ph.D. thesis:

1) development of a procedure for C-P cross-coupling between cycloalkenyl electrophiles and secondary phosphine oxides by screening cycloalkenyl halides and cycloalkenyl esters as electrophiles under copper and nickel catalysis;
2) development of a procedure for metal-catalyzed asymmetric conjugate addition of phosphorus nucleophiles to cycloalkenylphosphine derivatives;
3) development of a procedure for metal-catalyzed asymmetric conjugate addition of organomagnesium and/or organozinc reagents to cycloalkenylphosphine derivatives;
4) extension of the asymmetric conjugate addition reactions to acylic alkenylphosphine derivatives.

3. Literature

3.1. C2-functionalized 1-phosphinocycloalkanes

Two groups of chiral phosphine ligands based on the *trans*-1,2-cycloalkylene scaffold have been reported in the literature (**Figure 6**):

- *trans*-1,2-bis(phosphino)cycloalkanes,
- 2-(phosphino)cycloalkylamine derivatives.

Aside from those, structurally related bicyclic ligands have also been reported. This group features two subgroups:

- *P*,*P*-ligands prepared through Diels-Alder reactions of *trans*-1,2-bis(diphenylphosphino)ethylene: Norphos, Renorphos, Phellanphos and Nopaphos, and several Norphos derivatives,
- *P*,*P*- and *P*,*N*-ligands derived from (+)-camphor and (+)-nopinone.

Figure 6

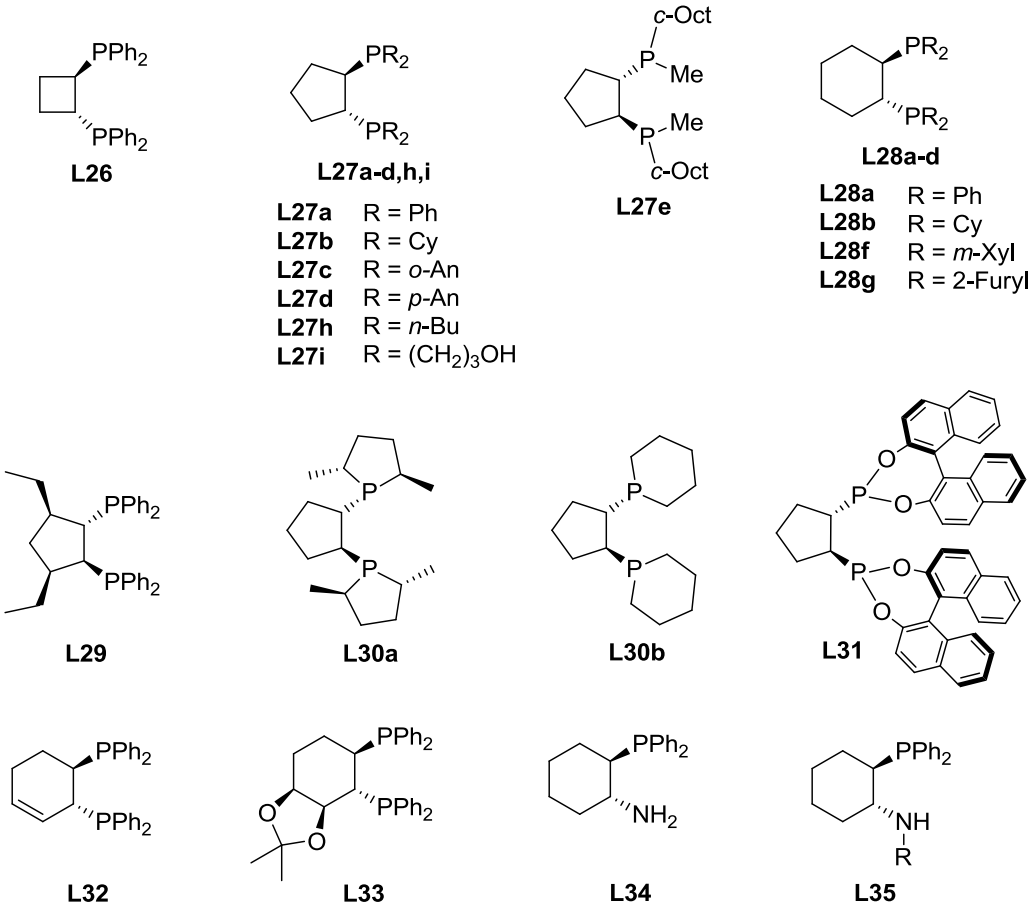
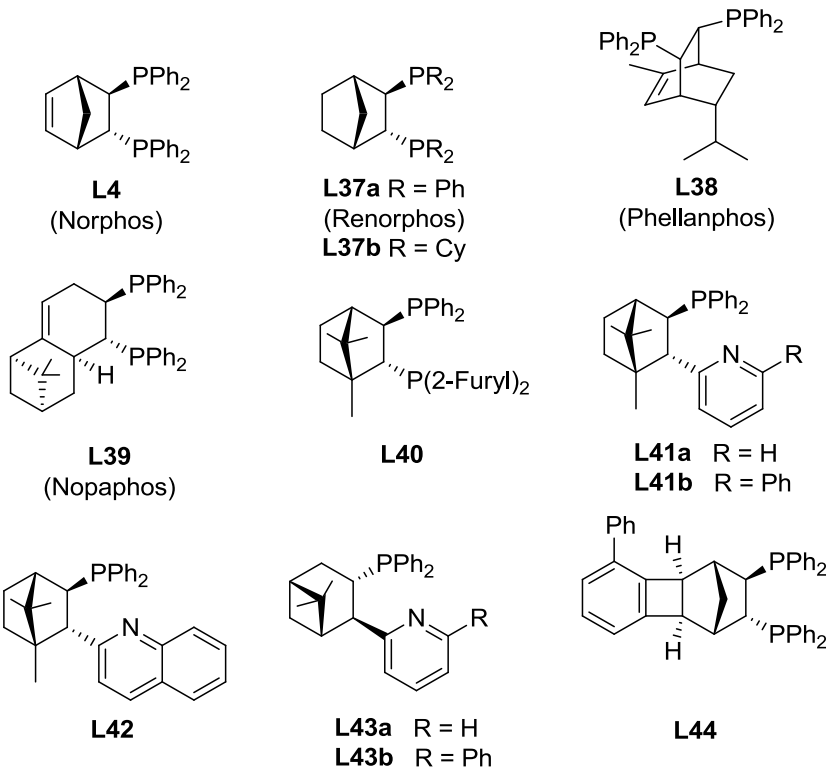
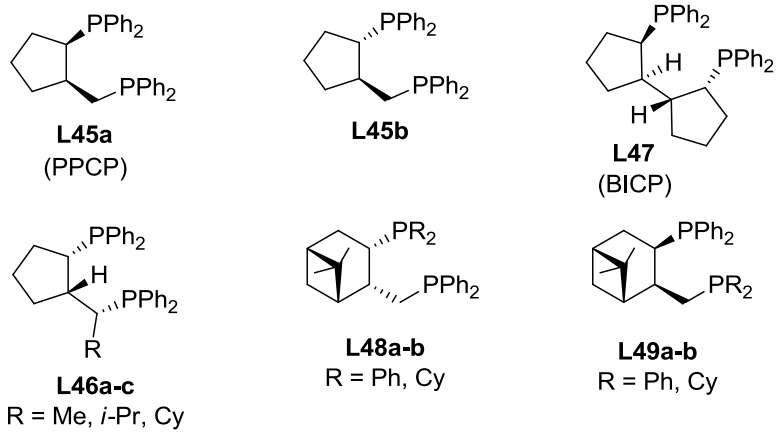


Figure 7



Several related phosphine ligands with *cis*-1,2-cycloalkylene scaffold have also been reported (Figure 8). These ligands feature a phosphinoalkyl or phosphinocycloalkyl group at C2. The progenitor of this class is PPCP (**L45a**) which has been shown to induce high enantioselectivity in Rh-catalyzed hydrogenation of dehydrophenylalanine and dehydroalanine, the *cis* configuration was crucial for high stereoselectivity and its epimer **L45b** performed poorly. Knochel *et al.* reported on the analogues of PCPP (L46). Conceptually related ligands include Zhang's BICP (**L47**) and Knochel's bicyclic ligands (**L48**, **L49**).

Figure 8



Bis(phosphino)cycloalkanes do not possess common names although different names have been used by different authors. In this dissertation I propose a naming convention for simple bis(phosphino)cycloalkanes extended from α,ω-bis(phosphino)alkanes (dppm, dppe, dppp, dppb, dpppent, dpph) in such a way that the substituents at the phosphorus atoms are represented by the first three or four letters in the same manner as for its non-cyclic analogues (dpp – diphenylphosphino, dcyp – dicyclohexylphosphino, dcpp – dicyclopentylphosphino, dipp – diisopropylphosphino etc.) and the last two letters represent the cycloalkane ring in the following manner (cb – cyclobutane, cp –cyclopentane, cy – cyclohexane, ch – cycloheptane).

3.1.1. Application of C2-functionalized cycloalkylphosphines

3.1.1.1. Monocyclic bis(phosphino)cycloalkanes

The monocyclic cycloalkane-based diphosphines have been primarily tested and proven effective as chiral ligands for Rh-catalyzed asymmetric hydrogenation of dehydroaminoacid derivatives. They were not, however, as thoroughly tested in other catalytic reactions as their bicyclic counterpart Norphos or non-cyclic counterparts, ChiraPhos, ProPhos, or BPE, and the hydrogenation reactions in which they were used as ligands were typically limited to *N*-acetyldehydrophenylalanine and *N*-acetyldehydroalanine. Other reactions in which bis(phosphino)cycloalkanes were used as ligands include Rh-catalyzed hydroboration of styrenes, Rh-catalyzed C=N hydrogenation, Ru-catalyzed C=O hydrogenation, Ni-catalyzed cross-coupling of chiral secondary alkylmagnesium halides, Ni-catalyzed allylic substitution with organomagnesium compounds, and cross-coupling of 1-bromo-2-methylnaphthalene with 1-(bromomagnesio)-2-methylnaphthalene.

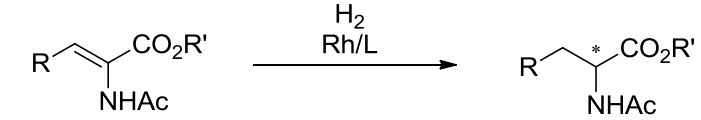
In 1983 Green *et al.* were the first to report on the application of enatiopure **L27a** (DPPCP) in asymmetric catalysis.[44] It was tested in Rh-catalyzed hydrogenation of *N*-benzoyldehydrophenylalanine and its methyl ester, and the optical purity was reported to be "100±2%". In 1986 Brown and Maddox compared the effectiveness of enantiopure DPPCP (**L27a**) and DPPCY (**L28a**), obtained *in situ* via stereoselective displacement in a chiral Ir-enamide complex, in Rh-catalyzed hydrogenation of *N*-acetyldehydrophenylalanine methyl ester.[45] Diphosphine ligands obtained in a reaction with dextro- and levorotatory Ir-enamide complexes were tested. In this reaction DPPCP (**L27a**) performed slightly better (90% ee (*S*), 91% ee (*R*)) than ChiraPhos (**L3**; 87% ee (*S*), 89.5% ee (*R*)) while DPPCY (**L28a**) was noticeably inferior (81% ee (*S*), 79% ee (*R*)). In a different study by the group of Dahlenburg, isolated enantiopure DPPCP (**L27a**) was found to be similarly effective for the same substrate

and even more effective for the corresponding aminoacid, it was also found to give high ee values for the hydrogenation of *N*-acetyldehydroalanine and its methyl ester (Scheme 4, Table 2, Entries 5-6).[46,47] Analogues with cyclohexyl (**L27b**), *n*-butyl (**L27h**), and 3-hydroxypropyl (**L27i**) substituents at the phosphorus atoms performed considerably worse in the hydrogenation of *N*-acetyldehydrophenylalanine, providing rather low ee values (Table, 2, Entries 7-9), and bis(phosphorinane) **L30b** gave a very poor result (Table 2, Entry 19).[50] Two more ligands with the cyclopentane core possessing additional chirality elements were tested, the BINOLate analogue **L31** possessing axial chirality and the cyclooctyl(methyl)phosphino analogue **L27e** possessing chiral phosphorus atoms (Table 2, Entries 10-13, 20-23).[46,47] In both cases two pairs of diastereomers were tried and the matched and mismatched combinations of configurations were thus found. The matched **L31** and **L27e** were moderately effective in the hydrogenation of *N*-acetyldehydrophenylalanine and its methyl ester providing the saturated acid with 73-78% ee and the saturated ester with 85-86% ee. For the analogous reactions of dehydroalanine derivatives **L31** and **L27e** gave comparable results to DPPCP with **L31** performing slightly better and **L27e** slightly worse. It is worth noting, however, that in the case of the bis(phosphonite) ligands **L31** the major factor determining the sense of the optical induction is the configuration of the axially chiral BINOLate moiety rather than the configuration of the cyclopentane ring as ligands with (*R*)-BINOLate fragments led to the products with the (*S*)-configuration regardless of the configuration of the cyclopentane.[47]

In 2000 Fernandez *et al.* reported on the synthesis and application of the *trans*-1,2-cyclopentylene analogue (**L30a**) of DuPhos and BPE in the stereoselective hydrogenation of two dehydroaminoacid methyl esters.[48] They predicted that the cyclopentane core would add enough rigidity to the ligand structure so that after forming a complex with Rh(I) it would not undergo interconversion between the two diastereomeric chelate conformers (Figure 9). Indeed, the ligand with the matched configuration (*S,S,R,R*)-**L30a** was superior to (*R,R*)-BPE, and (*R,R,R,R)*-**L30a** with the mismatched configuration was inferior (Table 2, Entries 16-18). More recently, Pietrusiewicz *et al.* tested an analogue (**L29**) of DPPCP possessing two ethyl substituents at C3 and C5 in the cyclopentane backbone, obtained through ring-opening metathesis of Norphos dioxide and subsequent reduction.[49] In the hydrogenation of *N*-acetyldehydrophenylalanine and *N*-acetyldehydroalanine **L29** performed comparably to the previously reported DPPCP, however, the hydrogenation was done at the hydrogen pressure of 5 bar and 20 bar, respectively (Table 2, Entry 14). In comparison, Norphos (**L4**) performed

equally well in the hydrogenation of *N*-acetyldehydrophenylalanine at 5 bar but provided poor stereoselectivity in the hydrogenation of *N*-acetyldehydroalanine at 20 bar (Table 2, Entry 15). Thus **L29** may be more suitable for hydrogenation of less reactive substrates that require higher hydrogen pressure.

Scheme 4



22a (R = Ph, R' = H)
22b (R = Ph, R' = Me)
22c (R = H, R' = H)
22d (R = H, R' = Me)

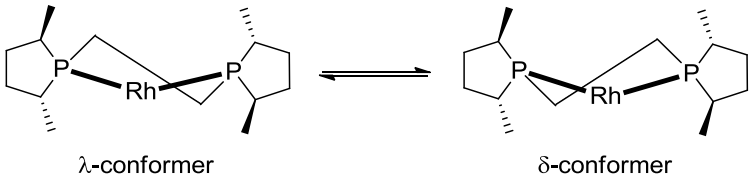
23a (R = Ph, R' = H)
23b (R = Ph, R' = Me)
23c (R = H, R' = H)
23d (R = H, R' = Me)

Table 2

Entry	Ligand	Product, ee (%)				Ref.
		23a	**23b**	**23c**	**23d**	
1	(*S*,*S*)-Norphos	95	-	90	-	
2	(*R*,*R*)-Renorphos	95	-	95	-	
3	(*S*,*S*)-Phellanphos	95	-	95	-	
4	(*R*,*R*)-Nopaphos	80	-	81	-	
5[e]	(*R*,*R*)-**L27a**	95	91	92	86	*46,47*
6[e]	(*S*,*S*)-**L27a**	93	91	91	85	*46,47*
7[a]	(*S*,*S*)-**L27b**	41	-	-	-	*50*
8[a]	(*S*,*S*)-**L27h**	43	-	-	-	*50*
9[a]	(*S*,*S*)-**L27i**	55	-	-	-	*50*
10[e]	(*R*,*R*,R_P)-**L27e**	28	34	23	28	*46,47*
11[e]	(*S*,*S*,S_P)-**L27e**	26	35	21	29	*46,47*
12[e]	(*R*,*R*,S_P)-**L27e**	73	86	90	83	*46,47*
13[e]	(*S*,*S*,R_P)-**L27e**	74	86	90	82	*46,47*
14	(*S*,*S*,*R*,*S*)-**L29**	95[c]	81[c]	90[d]	-	*49*
15	(*S*,*S*)-Norphos	95[c]	83[c]	33[d]	-	*49*
16[b]	(*S*,*S*,*R*,*R*)-**L30a**	-	98	-	95	*48*
17[b]	(*R*,*R*,*R*,*R*)-**L30a**	-	77	-	73	*48*
18[b]	(*R*,*R*)-Me-BPE	-	85	-	91	*48*
19[a]	(*S*,*S*)-**L30b**	6	-	-	-	*50*
20[e]	(*R*,*R*,*R*,*R*)-**L31**	77	85	92	86	*46,47*
21[e]	(*S*,*S*,*S*,*S*)-**L31**	78	85	96	89	*46,47*
22[e]	(*R*,*R*,*S*,*S*)-**L31**	20	36	27	39	*46,47*
23[e]	(*S*,*S*,*R*,*R*)-**L31**	24	36	28	31	*46,47*

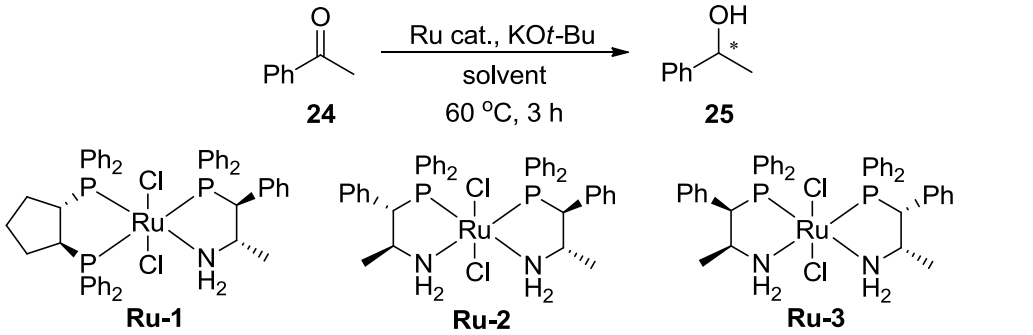
a) H_2 pressure was 1.1 atm.; b) H_2 pressure was 2 atm.; c) H_2 pressure was 5 atm.; d) H_2 pressure was 10 atm.; e) H_2 pressure not given.

Figure 9



In 2008 Dahlenburg tested DPPCP (**L27a**) in Ru complexes possessing an additional *P*,*N*-ligand molecule in direct hydrogenation and transfer hydrogenation of acetophenone, and compared this complex with Ru complexes possessing two same *P*,*N*-ligands with (*S*,*S*)- or (*S*,*R*)-configuration each.[51] In both reactions the mixed Ru complex was superior, nonetheless, the enantioselectivies obtained were moderate and far below the most efficient Ru(diphosphine)(diamine) catalysts for direct and transfer hydrogenation of unfunctionalized ketones.[21,52]

Scheme 5



direct hydrogenation (Ru cat. (0.01 mol%), KO*t*-Bu (1 mol%), 20 bar H_2, *i*-PrOH)

>99%, 67% ee | >99%, 29% ee | 50%, 5% ee

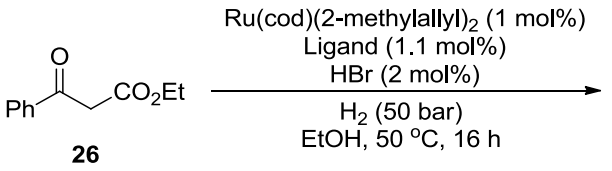
transfer hydrogenation (Ru cat. (0.5 mol%), KO*t*-Bu (2.5 mol%), *i*-PrOH/benzene 1:1)

64%, 59% ee[a] | 97%, 10% ee | 82%, 12% ee

[a] Ru cat. (0.05 mol%), KOt-Bu (0.25 mol%)

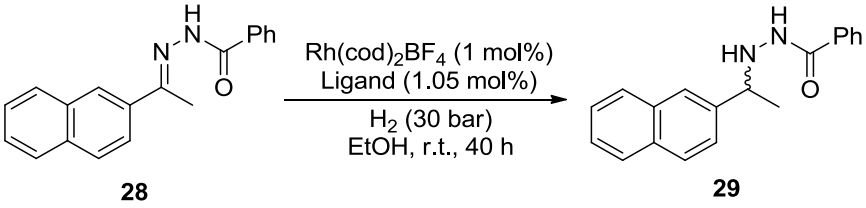
Cyclohexane-based diphosphine ligands were earlier tested in Ru-catalyzed asymmetric hydrogenation of ethyl 3-oxo-3-phenylpropanoate **26** (Scheme 6) and Rh-catalyzed hydrogenation of *N*-benzoylhydrazone **28** (Scheme 7).[53] Moderate enantioselectivity was observed for the hydrogenation of **26** and the ligand **L33** gave the best yield and ee. For the hydrogenation of **28** the ligand **L32** was the best but still provided only moderate ee.

Scheme 6



Ligand	Yield (%)	ee (%)
L28a	88	65
L28f	55	68
L32	52	68
L33	93	75

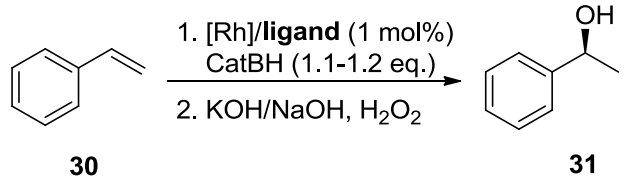
Scheme 7



Ligand	Yield (%)	ee (%)
L28f	61	23
L32	100	61
L33	49	36

An interesting application of DCYPCY (**L28b**), also reported by the group of Knochel, is Rh-catalyzed hydroboration of styrenes.[54] The reaction has been known to be problematic in terms of stereoselectivity and DCYPCY is among the few ligands that provide products of high optical purity.[55] For the reaction of unsubstituted styrene bis(phosphino)cyclohexanes with different substituents at the phosphorus atoms were tested (**L28a**,**b**,**f**,**g**) as well as the bicyclic ligand **L40**; the reaction with DCYPCY (**L28b**) as the ligand was the most stereoselective (**Scheme 8**). The Rh/DCYPCY catalyst catalyzed hydroboration of *meta*- and *para*-substituted styrenes with 58-93% ee, while **L28g** was superior for *ortho*-substituted styrenes (77-82% ee).

Scheme 8

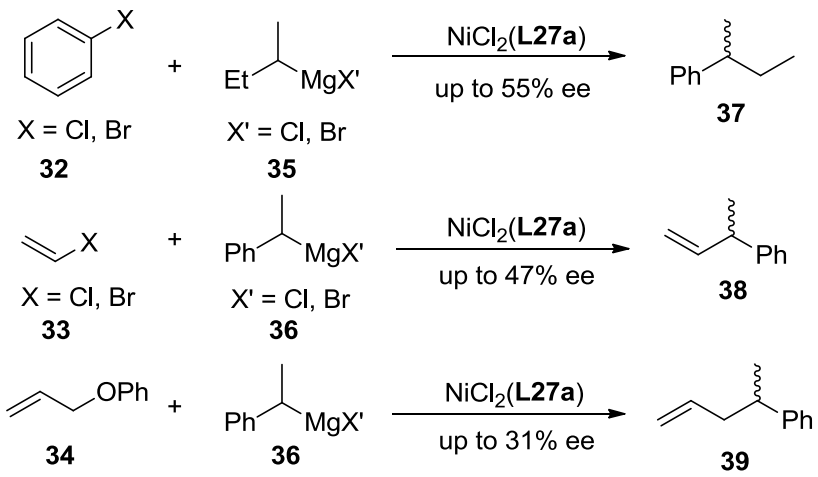


Ligand	ee (%), conf.
L28a	8 (*S*)
L28b	65 (*R*)
L28f	65 (*S*)
L28g	92 (*S*)
L32	8 (*R*)
L33	15 (*R*)
L40	61 (*S*)

Consiglio and Indolese used DPPCP (**L27a**) in Ni-catalyzed cross-coupling between chiral racemic secondary alkylmagnesium halides and phenyl, vinyl, and allyl electrophiles (**Scheme 9**).[56] Grignard reagents derived from alkyl chlorides and bromides were tested in combinations with phenyl and vinyl chlorides and bromides, in all cases different yields and stereoselectivies were observed for different combinations with no clear trend observed. For

the cross-coupling between *sec*-butyl Grignard reagent and phenyl halide, the highest stereoselectivity was obtained for a combination of *sec*-butylmagnesium bromide and bromobenzene (55% ee). On the other hand, in the reaction with vinyl halide the best combination consisted of methylbenzylmagnesium chloride and vinyl chloride (47% ee). For all reactions the *p*-anisyl analogue **L27b** was also tested as the ligand, but in all cases its use was associated with much lower stereoselectivity and heavily decreased reactivity in some cases. **L27a** was also superior to Chiraphos and Prophos, nonetheless, the enantioselectivities obtained with **L27a** were moderately low.

Scheme 9

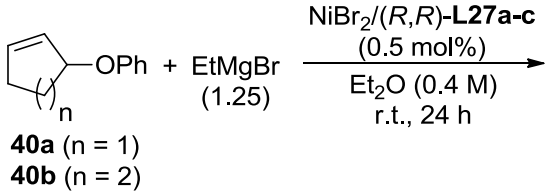


Consiglio and Indolese also tested DPPCP (**L27a**) and its *o*- and *p*-anisyl analogues (**L27b** and **L27c**) in the allylic substitution of cyclic allyl phenyl ethers **40a-b** by EtMgBr under Ni catalysis (**Scheme 10**).[57] **L27a** was again the most efficient leading to the products **41a** and **41b** with 83% and 75% ee respectively. Enantioselectivity of the reaction with **L27b** was comparable, however, the reactions with both **L27b** and **L27c** were sluggish and did not reach completion. Among other ligands tested BIPHEMP was superior providing **41a** and **41b** with 94% and 83% ee, respectively. MeO-BIPHEP and BINAP ligands were comparable to **L27a** in both cases, however, the reactions with BINAP afforded the products with lower yields (67% and 11% respectively). The reaction was later tested with MeMgBr, *n*-PrMgBr, *i*-PrMgBr, however, the yields and enantioselectivies were poor to moderate, similar results were obtained when BIPHEMP was used as the ligand.[58]

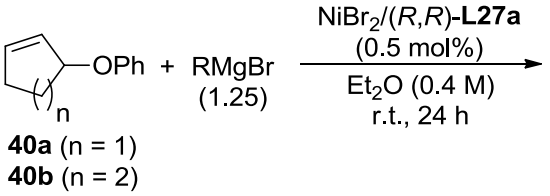
Pavlov *et al.* tested the Ni/DPPCP catalyst in asymmetric allylic substitution of crotyl alcohol derivatives **42a-d** with PhMgBr (**Scheme 11**).[59] Moderately low to moderate enantioselectivities were obtained. Aside from crotyl alcohol, for all substrates the reaction

led to a mixture of the chiral γ-substituted product **38** and the non-chiral α-substituted product **43**. The highest regio- and stereoselectivity was observed for crotyl trimethylsilyl ether (**42d**).

Scheme 10

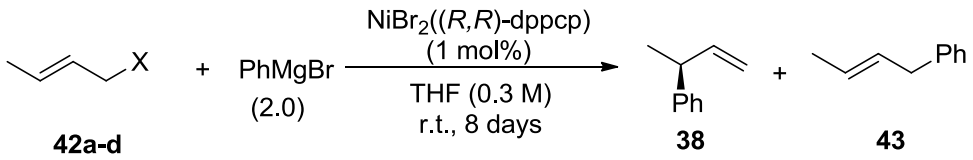


Ligand	Yield (ee) [%]	
	41a	**41b**
L27a	91 (83)	99 (75)
L27b	40 (83)	7 (69)
L27c	8 (40)	40 (2)



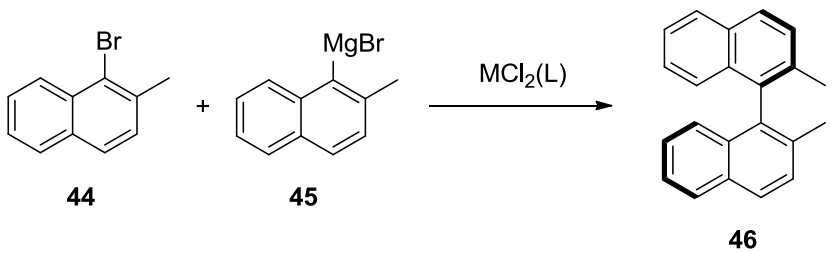
RMgX	Yield (ee) [%]	
	41a	**41b**
MeMgBr	12 (41)	6 (10)
EtMgBr	91 (83)	99 (75)
n-PrMgBr	80 (71)	17 (28)
i-PrMgBr	3 (33)	1 (8)

Scheme 11



X	Yield (%)	ee (%)	**36/43**
OH	10	41	100 : 0
OPh	40	53	53 : 48
OC(O)OEt	45	52	49 : 51
$OSiMe_3$	80	67	66 : 34

Scheme 12



$NiCl_2$(**L27b**)	47%	26% ee
$NiCl_2$(**L30b**)	10%	
$PdCl_2$(**L27b**)	0%	
$PdCl_2$(**L30b**)	17%	

DCYPCP (**L27b**) was also tested by Dahlenburg and Kurth in Ni- and Pd-catalyzed atroposelective cross-coupling of 1-bromo-2-methylnaphthalene with 1-(bromomagnesio)-2-methylnaphthalene, however with a rather poor result.[60] The reaction was found to be exceptionally sluggish and in the best case with the Ni catalyst it took 28 days to reach 47% conversion which translated into 10% isolated yield with 26% ee (Scheme 12).

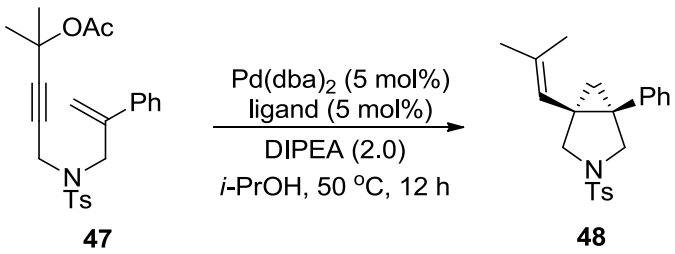
Overall extra rigidity of bis(phosphino)cycloalkanes in comparison to Chiraphos and BPE seems to play to their strength. Nonetheless, this area has severe limitations: there was only one study with a direct comparison between bis(phosphino)cyclopentane and cyclohexane, mostly cyclopentane ligands were tested, and ligands with a seven-membered scaffold ring or bigger have not been reported so far. Few reactions other than asymmetric hydrogenation were tested using bis(phosphino)cycloalkanes.

3.1.1.2. Bicyclic bis(phosphino)cycloalkanes

Historically, among bis(phosphino)cycloalkanes the bridged bicyclic diphosphine ligands Norphos (**L4**)[61] and Phellanphos (**L38**)[62] were the first to be reported on in 1979 by Brunner and Pieronczyk, and Kagan *et al.* respectively, differing in the date of manuscript submission by only one week. These ligands were found be highly effective for asymmetric hydrogenation of dehydroaminoacid derivatives (*vide supra*, Table 2, Entries 1 & 3) and were available through a short synthesis. Norphos was obtained through Diels-Alder reaction between *trans*-1,2-bis(diphenylphosphinoyl)ethylene and cyclopentadiene, resolution of enantiomers with dibenzoyltartaric acid, and reduction to the free diphosphine.[61] The double bond in Rh/Norphos complex was found to be reduced *in situ* under the hydrogenation conditions to give Rh/Renorphos complex, and thus Renorphos (**L37a**) can be used as an equally effective ligand to form catalysts *in situ* (*vide supra*, Table 2, Entry 2), although its preparation involves an additional step compared to Norphos.[63] Phellanphos (**L38**) was synthesized through Diels-Alder reaction of *trans*-1,2-bis(diphenylthiophosphinoyl)ethylene and (-)-α-phellandrene followed by reduction of the diphosphine disulfide.[62] A related bicyclic ligand Nopaphos (**L39**) was obtained in an analogous manner by Kagan starting from (+)-nopadiene, however, it was substantially inferior to Norphos and Phellanphos in asymmetric hydrogenation of *N*-acetyldehydrophenylalanine and *N*-acetyldehydroalanine (*vide supra*, Table 2, Entry 4).[64] Norphos was the only ligand from the bicyclic group that gained interest in the community and was later subjected to numerous stereoselective reactions, however, it did not prove to be a ligand of general utility. It provided good results in Pd-catalyzed enyne bicyclization (Scheme 13),[65] Rh-catalyzed Diels-Alder reaction of methacrolein and cyclopentadiene (Scheme 14),[66] and Ru-catalyzed hydrogenation of β,γ-unsaturated carboxylic acid (Scheme 15),[67] however, in the third study Mandyphos was a superior ligand. Moderate stereoselectivies were observed for Ni-catalyzed cross-coupling between secondary alkyl Grignard reagents and phenyl or vinyl halides (Scheme 16),[68] and for Pd-catalyzed allylic alkylation with sodium dimethyl malonate (Scheme 17).[69] Norphos

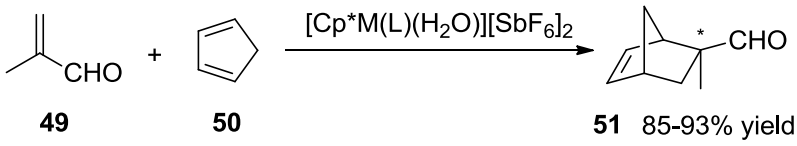
was also tested in numerous catalytic reactions producing poor stereoselectivities including C=N hydrogenation,[70] C=N and C=O hydrosilylation,[71] Baeyer-Villiger oxidation,[72] conjugate addition of Et_2Zn to cyclic enones,[73] allylic alkylation,[74] and intramolecular Pd-catalyzed Heck hydroalkenylation.[75]

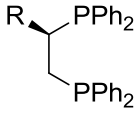
Scheme 13



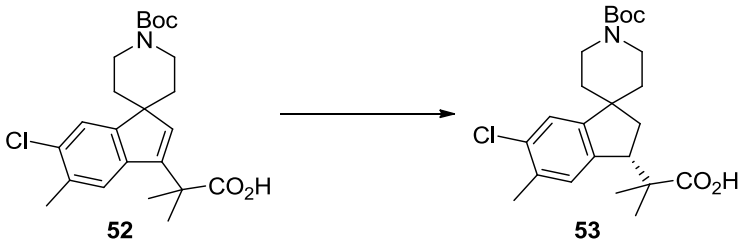
Ligand	Yield	ee
Chiraphos (**L3**)	44%	89%
Norphos (**L4**)	78%	97%
BINAP (**L9**-Ph)	14%	-55%
Me-BPE (**L12**-Me)	0%	-
Me-DuPhos (**L11**-Me)	0%	-

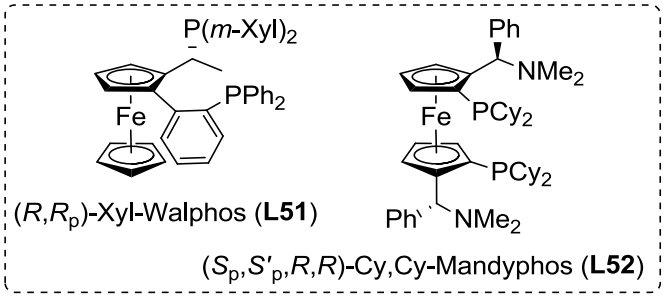
Scheme 14



Ligand			ee (%)	
			M = Rh	M = Ir
	**L50a**	R = Ph	79	80
	L50b	R = Bn	79	89
	L50c	R = *i*-Pr	70	74
	L50d	R = Cy	88	96
L50a-d	**L4**	Norphos	93	96

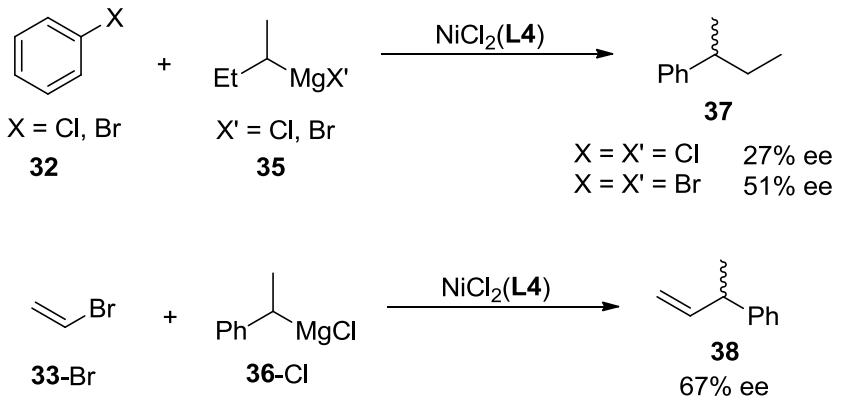
Scheme 15



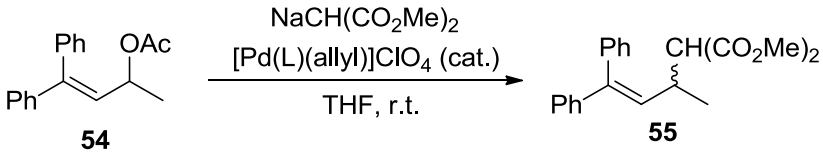


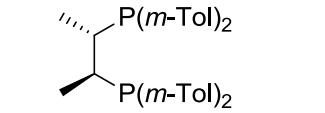
Catalyst	Yield (%)	ee (%)
Rh/**L51**	92	85
Ru/**L51**	100	14
Ru/**L52**	100	95
Ru/(*S*)-Norphos	100	88

Scheme 16



Scheme 17



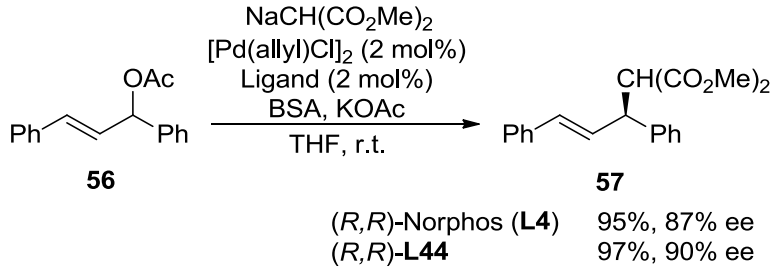


(*S,S*)-Metachiraphos (**L53**)

Ligand	ee (%)
(*R,R*)-DIPAMP (**L2**)	1
(*S,S*)-Chiraphos (**L3**)	65
(*S,S*)-Metachiraphos (**L53**)	72
(*S,S*)-Norphos (**L4**)	76

Although the method to prepare Norphos allows for the preparation of both enantiomers, access to analogues with different substituents at the phosphorus atoms is not convenient as it requires the preparation of corresponding bis(phosphinoyl)ethylenes, and as such, Norphos analogues have not been described in the literature. On the other hand several analogues made by double bond functionalization of Norphos dioxide have been reported. These include 6-hydroxy-Norphos by Kagan *et al.* which was used in Rh-catalyzed hydrogenation of *N*-acetyldehydrophenylalanine and provided the product with 98% ee,[76] and Catellani-type cycloarylation analogues reported by Pietrusiewicz *et al.*[77] out of which one diphosphine (**L44**) was obtained from the corresponding dioxide and tested in allylic alkylation proving to be slightly better than Norphos (Scheme 18). Nevertheless, such slight improvements over the original ligand do not seem to warrant the additional synthetic steps.

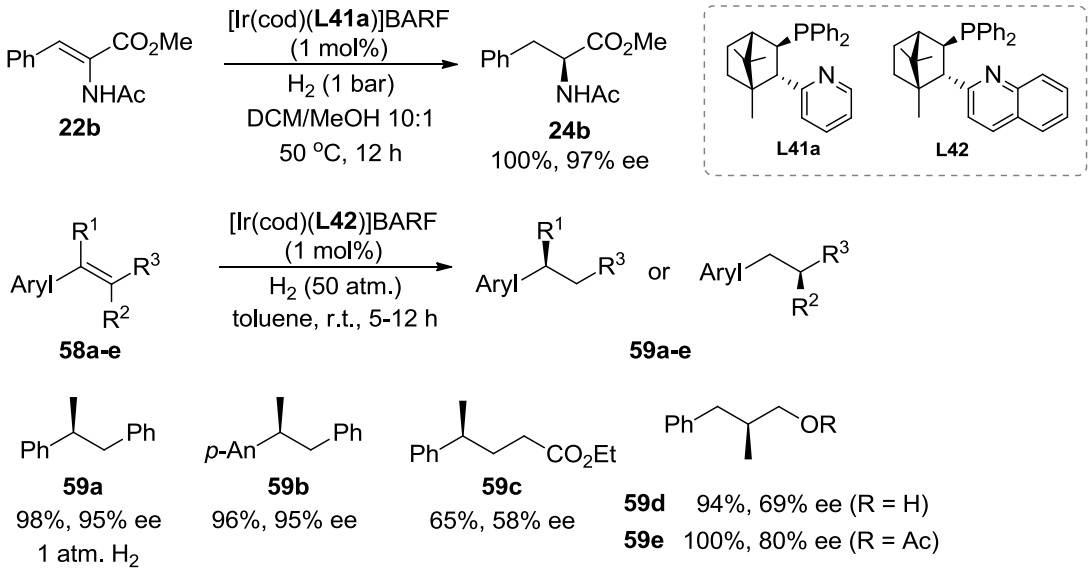
Scheme 18



3.1.1.3. Bicyclic 2-(heteroaryl)cycloalkylphosphines

Following his work on monocyclic bis(phosphino)cyclohexanes, Knochel *et al.* reported on the synthesis of bicyclic 2-(heteroaryl)cycloalkylphosphines **L41**-**L43** (*vide supra*, Figure 7) and their application in Ir-catalyzed asymmetric hydrogenation of trisubstituted olefins with and without coordinating groups (Scheme 19).[78] The Ir/**L41a** complex catalyzed hydrogenation of *N*-acetyldehydrophenylalanine methyl ester with 97% ee. The enantioselectivies of the hydrogenation of unfunctionalized olefins **58a** and **58b** using the Ir/**L42** complex were remarkably high and are only surpassed by certain phosphine-oxazoline *P*,*N*-ligands.[79] However, the same catalyst induced only moderate stereoselectivity in the hydrogenation of the olefins **58c-e** with hydroxyl, acetoxy or ethoxycarbonyl groups.

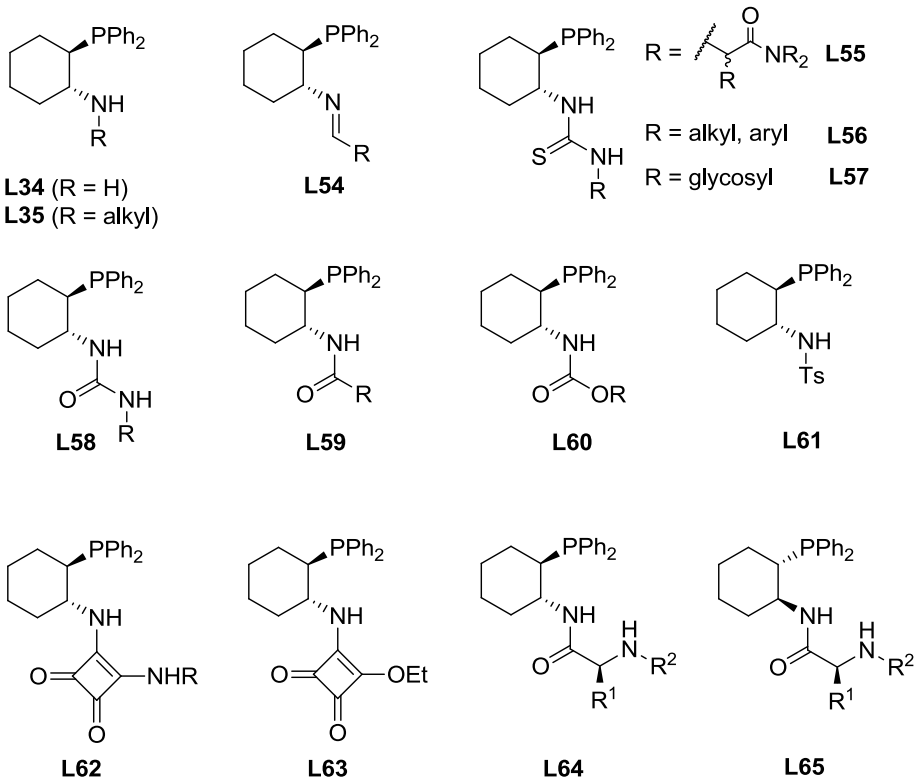
Scheme 19



3.1.1.4. Monocyclic 2-(phosphino)cyclohexylamines and derivatives

The application of *trans*-2-(phosphino)cyclohexylamines and derivatives in asymmetric catalysis as ligands or organocatalysts is a relatively new area of study that started at the beginning of the 21st century. The progenitor, phosphine-amine (**L34**), is not a good chiral ligand or organocatalyst itself.[82,97,106,111,113,115,117,118] On the other hand, it serves as a convenient precursor for numerous derivatives with the functionalized amino group that have been found to be highly effective in certain organocatalytic and transition-metal catalyzed reactions (Figure 10), particularly thiourea[86-110] (**L55-L57**), squaramide[95,97,101-103,105-109] (**L62**, **L63**), and α-aminoamide derivatives[103-105,108,109,111-118] (**L64**, **L65**). Other derivatives synthesized and tested include imines[82,111,113-118] (**L54**), ureas[100] (**L58**), amides[95,102,103,105-109,111-118] (**L59**), carbamates[109,114,116] (**L60**), sulfonamide[109] (**L61**), and secondary amines[117,118] (**L35**). No cycloalkane ring homologues have been tested.

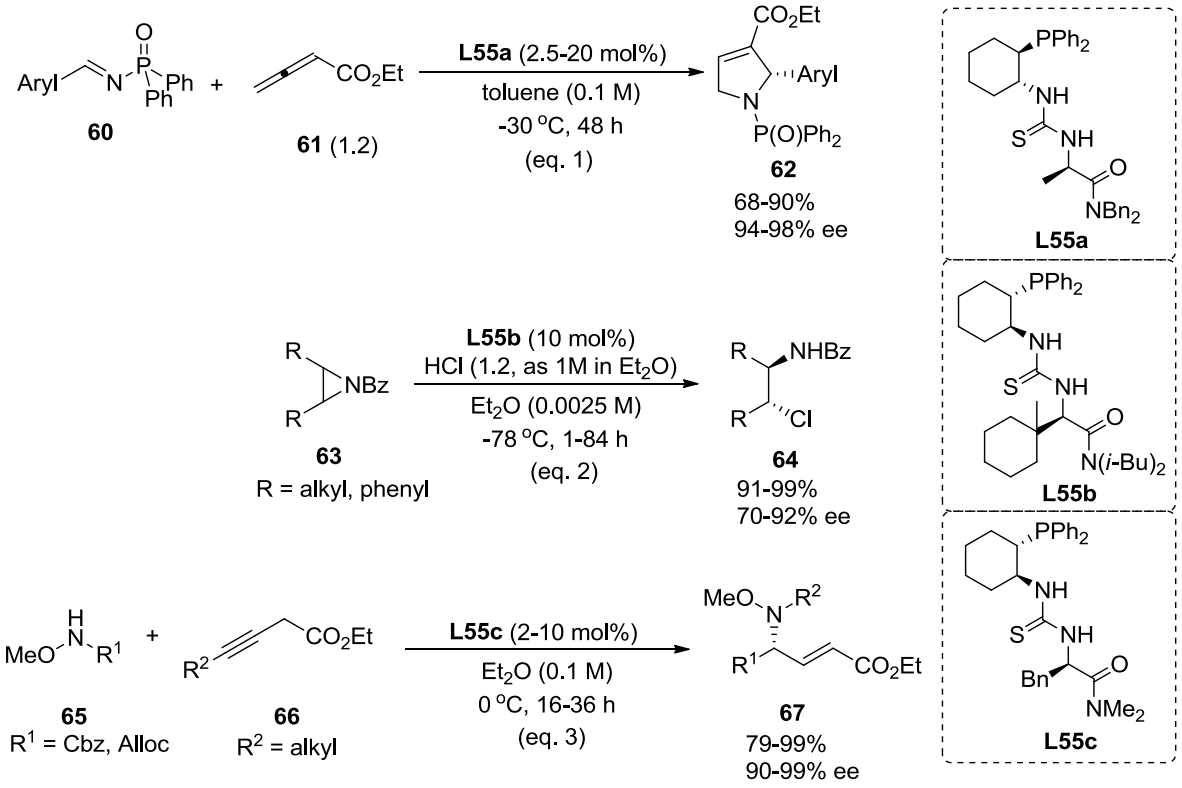
Figure 10



The first method of preparation of enantiopure *trans*-2-(diphenylphosphino)cyclohexylamine was described in 2002 by Yudin *et al.*[80] It was followed up in 2004 by a publication from the same research group on the application of the iminophosphine derivative (**L54a**, R = Ph) in Pd-catalyzed allylic substitution[81,82] and then in

2008 by two papers from two research groups on the application of thiourea derivatives as organocatalysts. Fang and Jacobsen reported on [3+2]-cycloaddition between allenoate and *N*-phosphinoylimine[86] (Scheme 20, eq. 1) and Wu *et al.* reported on Morita-Baylis-Hilman reaction between aromatic aldehydes and methyl vinyl ketone[89] (Scheme 21, eq. 1).

Scheme 20



In the following years Jacobsen also published papers on HCl addition to aziridines[87] and hydroamination of allenyl and propargyl esters[88] (Scheme 20, eq. 2-3). In his studies Jacobsen used amidothiourea organocatalysts **L55a-c** in which the amidoamino and 2-(diphenylphosphino)cycloalkylamino fragments were joined together by thiocarbonyl group into the thiourea structure.[86-88]

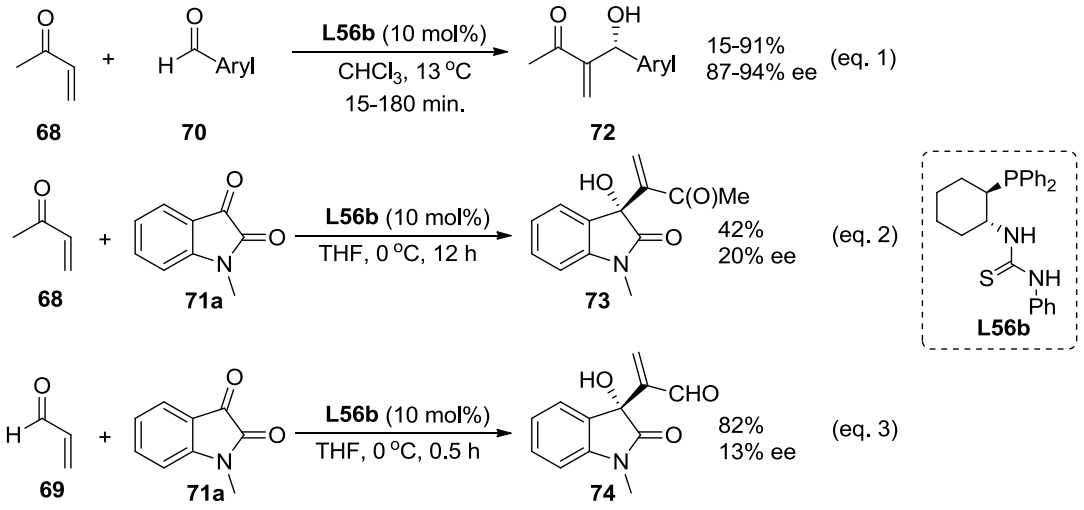
Between 2008 and 2018 Wu went on to publish over 20 papers on organocatalytic and copper-catalyzed reactions utilizing *trans*-2-(phosphino)cyclohexylamine derivatives. Organocatalytic reactions included Morita-Baylis-Hilman (MBH) reactions,[88-101] allylic substitution in MBH carboxylates/carbonates,[106,107] aza-Diels-Alder reaction,[108] rhodanine addition to allenoate,[109] and silylcyanide addition to carbonyl.[105] On top of that several research groups contributed a smaller number of papers to the field. Chen *et al.* contributed two publications on organocatalytic addition to cyanochalcones[104] and unsaturated

dinitriles,[110] and Ramasastry *et al.* contributed three papers on intramolecular MBH reactions.[97-99] Porwański *et al.* published three papers in which four phosphine-ureas derived from mono- and disaccharides were tested in MBH reaction and aza-Henry reaction.[119-121] Guo *et al.* reported on cycloaddition of a cyclic sulfamate derivative,[122,123] while Zhang *et al.*[124] and Sasai *et al.*[125] reported on two distinct spiroannulations. Most recently Lin *et al.* used a cyclic *P*,*N*-ligand in cycloaddition of chromones and MBH carbonates.[126]

3.1.1.4.1. Organocatalytic reactions

In 2008 Wu *et al.* described the use of a phosphinocyclohexyl thiourea **L56b** as an effective organocatalyst in MBH reaction between methyl vinyl ketone and aromatic aldehydes[89] (Scheme 21, eq. 1) which proved vastly superior to previous catalytic systems. A few years later, however, this organocatalyst proved poor for the reactions of methyl vinyl ketone and acrolein with *N*-methylisatin.[100]

Scheme 21

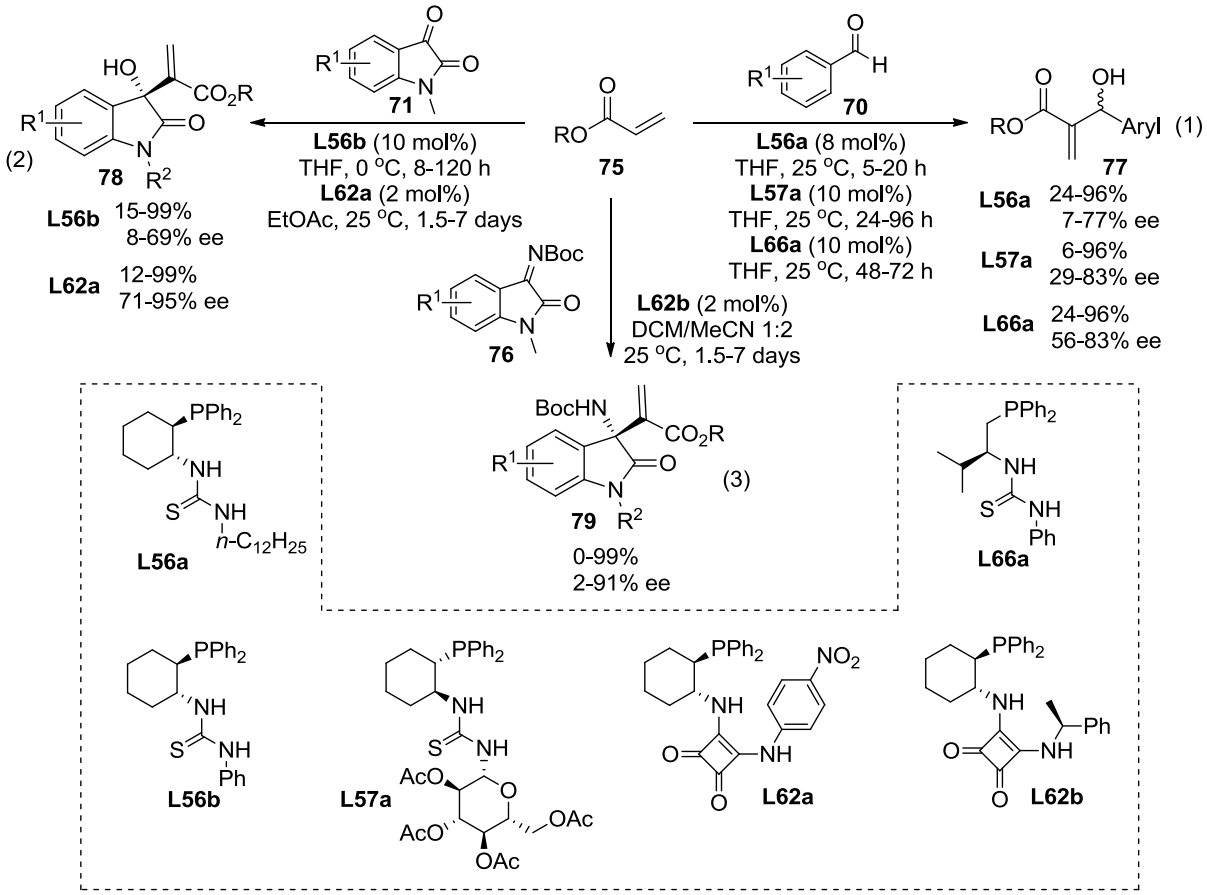


In the following years the group released several publications on MBH of acrylic esters with aromatic aldehydes. Phosphinothiourea **L56b** turned out less effective at stereoinduction, several analogues were tested with **L56a** giving the best balance of enantioselectivity and yield (Scheme 22, eq. 1).[90] A related non-cyclic valine-derived phosphinothiourea **L66a** was found to be more efficient.[91] Superior results were later obtained with phosphinocyclohexyl glycosyl thiourea **L57a** derived from D-glucose, however, the enantioselectivity still did not match that of the reaction of methyl vinyl ketone.[92] In all cases ethyl and *n*-butyl esters were optimal with 2-nitrobenzaldehyde producing the lowest ee values among aromatic aldehydes. With all three phosphinothioureas 1-naphthyl esters led to

low yield and low ee, phenyl esters were tested with **L66a** and **L57a** and were problematic in both cases, *tert*-butyl esters gave good ee but lower yields with **L56a** and **L66a** than *n*-butyl esters, and with **L57a** it gave low ee and low yield.

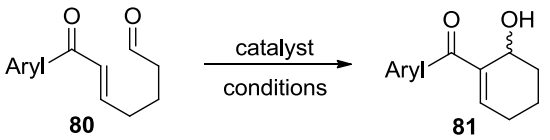
Phosphinothiourea **L56b** was also used in MBH reaction between acrylate esters and isatin derivatives[100] and **L56a** was tested in a reaction with isatin ketimine derivatives.[102] However, both compounds produced rather low ee values. Much better results were obtained with phosphinosquaramide organocatalysts **L62a**[101] and **L62b**,[102] respectively (Scheme 22, eq. 2 and 3).

Scheme 22



Related phosphinothioureas **L56c** and **L66b** were found to be the best among cyclic[93] and acyclic[94] organocatalysts for intramolecular MBH reaction of **80** (Scheme 23). In this case the cyclic analogue proved to be superior producing higher ee and requiring lower catalyst loading. Even better catalysts proved to be mannose-derived phosphinoglycosyl thiourea **L57b**[96] and squaramide ester derivative **L63**[95] with the latter being the best overall which is reflected in the results for the most problematic 2-bromo substrate **80**.

Scheme 23



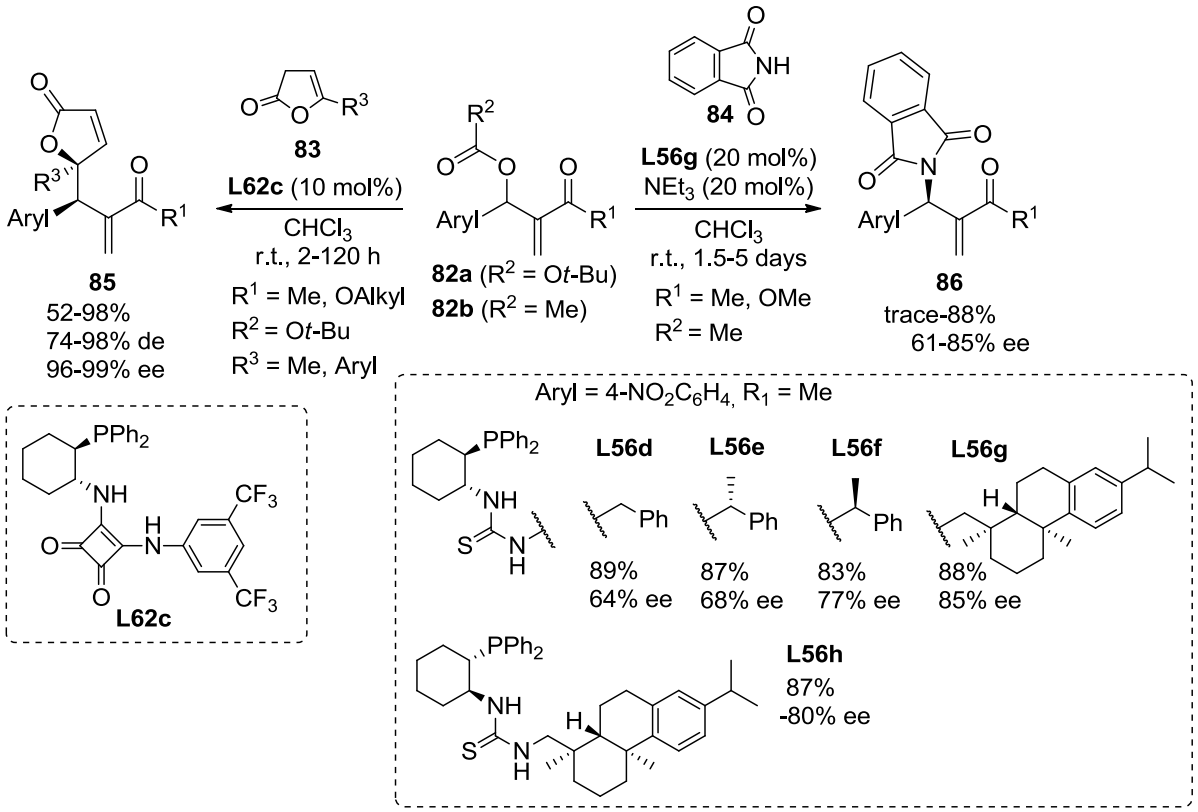
	L56c	L66b	L63	L57b
	5 mol% *t*-BuOH (0.1 M) r.t., 1.5-7 days	10 mol% DCM (0.2 M) r.t., 12-48 h	3 mol% EtOH (0.2 M) r.t., 1.5-7 days	2 mol% *t*-BuOH (0.1 M) r.t., 2-6 days
	63-98% 16-98% ee	63-100% 5-84% ee	64-99% 80-93% ee	86-99% 23-99% ee
Aryl = 2-BrC_6H_4	97% 16% ee	100% 5% ee	78% 80% ee	96% 29% ee

Squaramide **L62c** was used in allylic substitution of MBH Boc-carbonate **82a** with butenolides **83** and gave products **85** with generally good diastereoselectivity and high enantiopurity of the major diastereomer (Scheme 24).[106] In allylic amination of MBH acetate **82b** a series of phosphinothioureas were tested including **L56a-f**, however, moderate results were obtained at best.[107] In the series of *N*-benzyl phosphinothioureas **L56d-f** the addition of an α-methyl group onto the *N*-benzyl group and generation of a new chiral centre increased the ee value from 64% to 77% ee, **L56e**, the epimer of **L56f**, gave the product **86a** with the same configuration but lower enantiomeric excess (68% ee). Stereoselectivity was further increased to 85% ee by using phosphinothiourea **L56g** derived from dehydroabietic acid. When the epimer **L56h** was used, the product with the opposite configuration was obtained with slightly lower 80% ee, thus the configuration at C1 and C2 in the cyclohexane ring is the deciding factor in the mode of stereoinduction.[107]

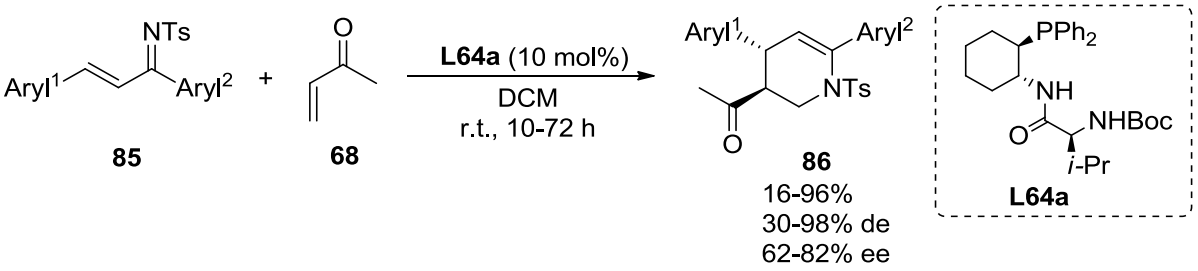
Wu *et al.* also described the use of phosphine-ureas derived from aminoacids **L64a** and **L64b** in aza-Diels Alder reaction between α,β-unsaturated *N*-tosylimines **85** and methyl vinyl ketone **68** (Scheme 25),[108] and Rauhut-Currier-type addition of methyl vinyl ketone to *para*-quinone methides **87** (Scheme 26),[104] respectively. Phosphine-carbamate **L60a** was found to be the best organocatalyst for the addition of rhodanines (**89**) to allenoate esters (**90**) after an extensive screening in which a series of thioureas, amides, aminoamides, carbamates, squaramides, and sulfonamide **L61** were tested and proven inferior (Scheme 27).[109] In the

cyanosilylation of dialkoxyketones (**92**) galactose-derived phosphine-thiourea **L57c** produced the highest enantioselectivity (Scheme 28).[105] The configuration at C1 and C2 in the cyclohexane ring was again found to determine the configuration of the major enantiomer, however, the glycosyl group and its matching with the cyclohexane configuration was crucial for high stereoselectivity, in the case of the C1,C2-epimer of **L57c** racemic product **93a** (R^1 = 4-chloro) was obtained.[105]

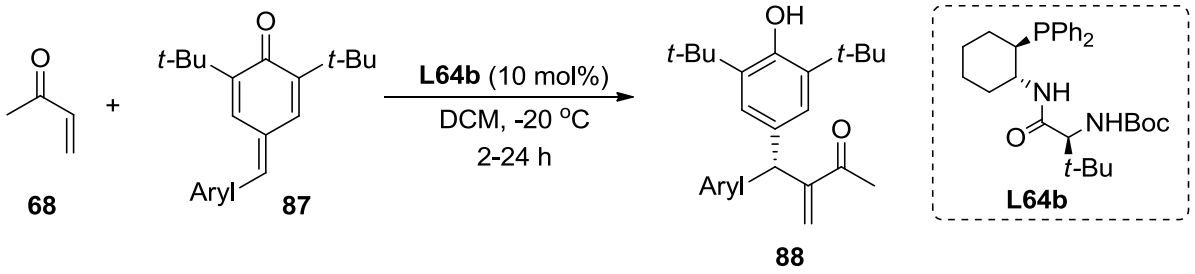
Scheme 24



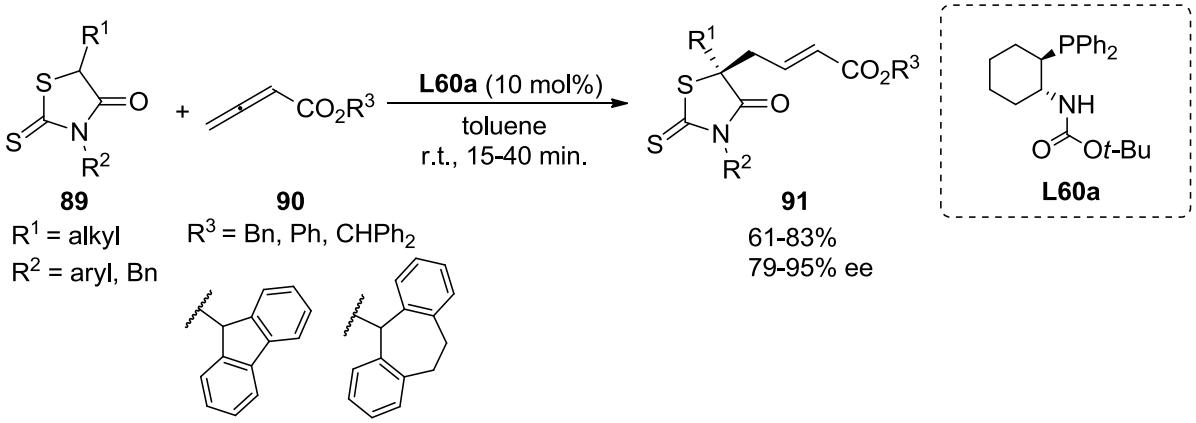
Scheme 25



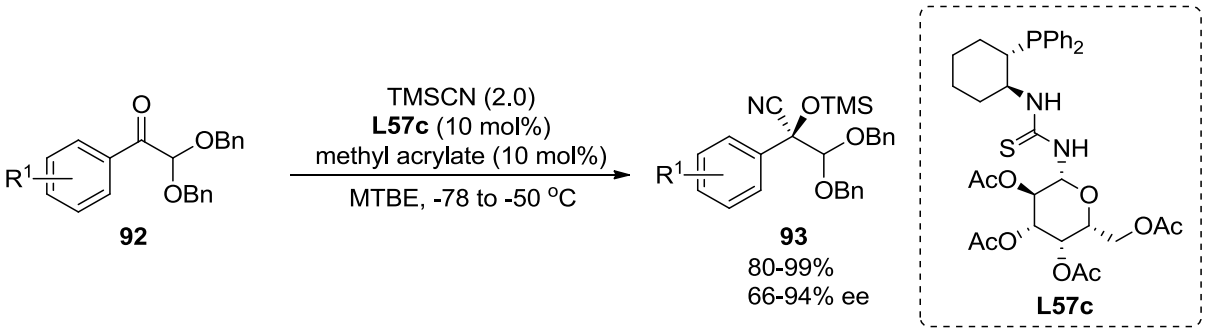
Scheme 26



Scheme 27

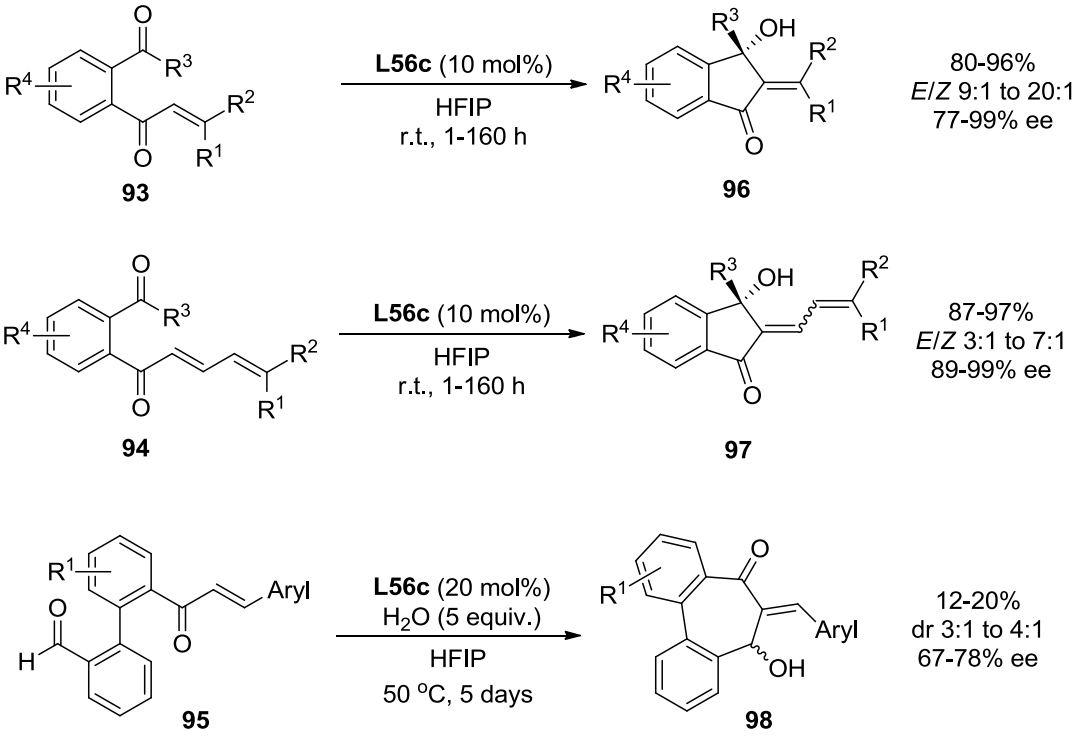


Scheme 28

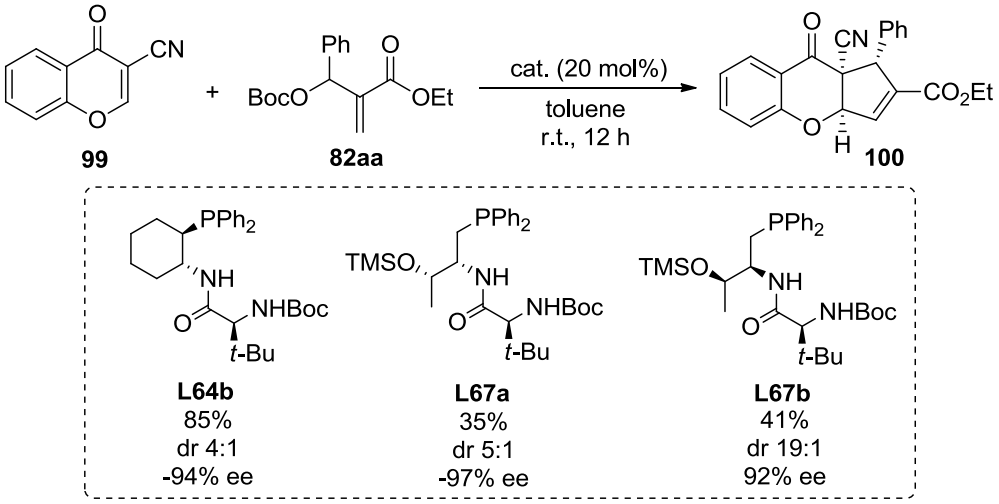


Ramasastry *et al.* used the phosphine-thiourea **L56c** in three intramolecular MBH reactions with moderate to very good enantioselectivity (Scheme 29).[97-99] Lin *et al.* tested the aminoamide **L64b** in a cycloaddition of chromone (**99**) and MBH carbonate (**82aa**) obtaining high enantioselectivity but only moderate diastereoselectivity. The acyclic analogue **L67b** provided high diastereoselectivity, however, at the cost of substantial yield decrease and slight decrease in enantioselectivity. The epimer **L67a** offered the best enantioselectivity but the reaction suffered from the low yield and low diastereoselectivity (Scheme 30), thus **L67b** was chosen for the substrate scope study.[126]

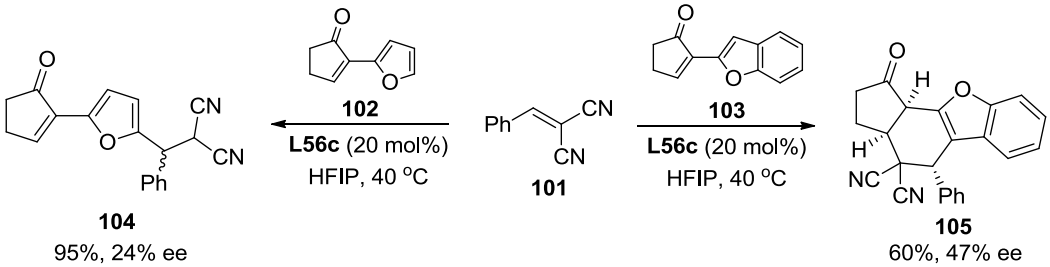
Scheme 29



Scheme 30

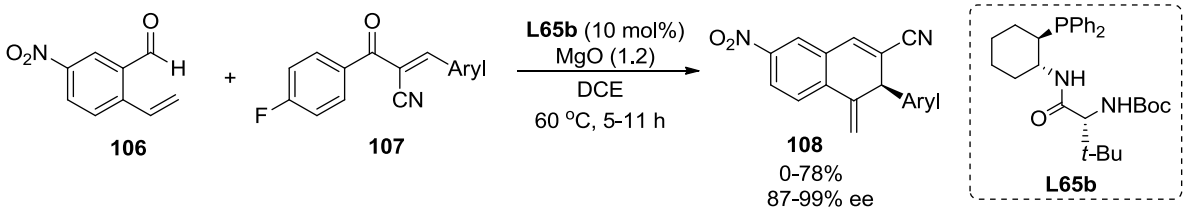


Scheme 31

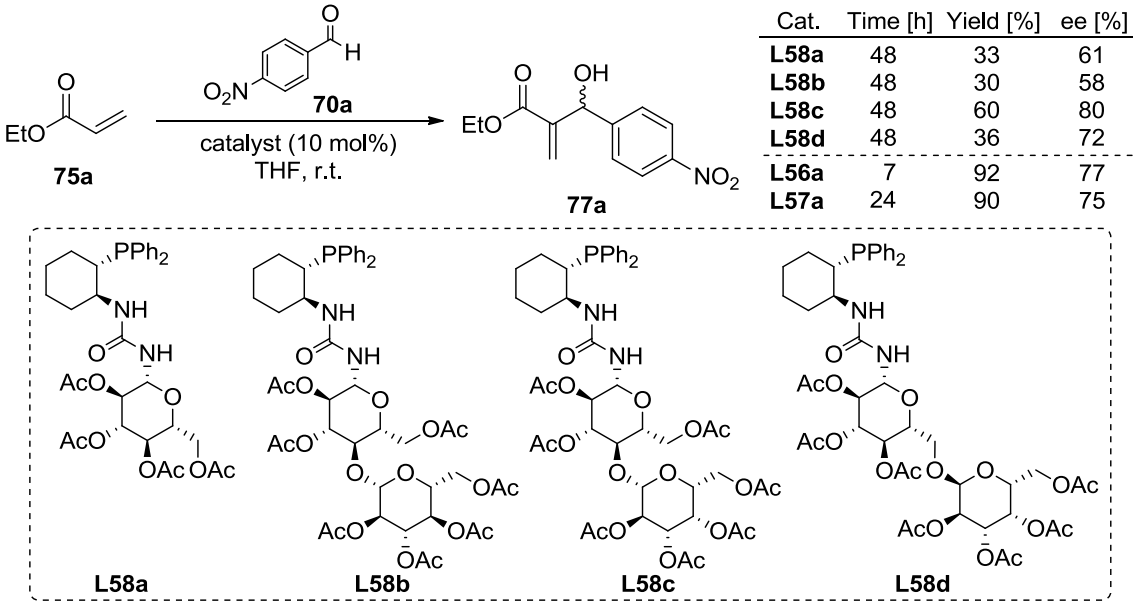


Chen *et al.* used thiourea **L56c** in the Friedel-Crafts reaction of α-furan-2-yl and α-benzofuran-2-yl cyclopent-2-enones **102** and **103** with unsaturated dinitrile **101**, but obtained only low stereoselectivity (Scheme 31).[110] On the other hand, the aminoamide **L65b** prepared from (*R*)-*tert*-leucine was found to provide high enantioselectivity in a cascade initiated by Rauhut-Currier reaction between 2-formyl-4-nitrostyrene **106** and chalcone derivative **107** (Scheme 32).[104]

Scheme 32



Scheme 33



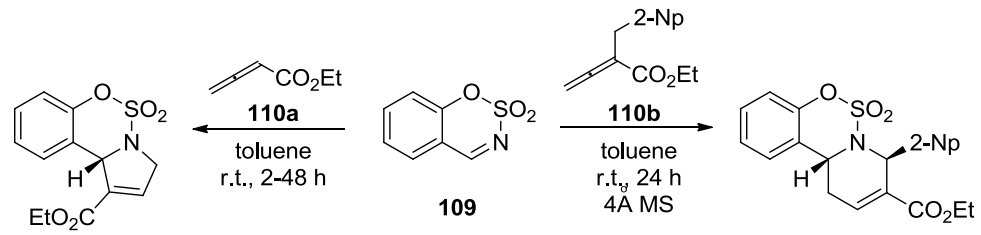
Cat.	Time [h]	Yield [%]	ee [%]
L58a	48	33	61
L58b	48	30	58
L58c	48	60	80
L58d	48	36	72
L56a	7	92	77
L57a	24	90	75

Porwański *et al.* prepared four phosphine-ureas with *N*-glycosyl groups derived from glucose, cellobiose, lactose, and melibiose (**L58a-d**).[119-121] These were tested in MBH reaction of ethyl acrylate and *p*-nitrobenzaldehyde (Scheme 33), the phosphine-urea derived from lactose (**L58c**) gave the product with slightly higher ee (80% ee) compared to previously tested thioureas **L56a** and **L57a**, however, at the expense of lower yield. **L57a** and **L58a** are the glucose-derived thiourea and urea analogues, respectively, in this particular reaction the latter was inferior.[120] Phosphine-ureas **L58b-d** were also tested in aza-Henry reaction between

nitromethane and benzaldehyde *N*-tosylaldimine but in all cases racemic products were obtained (0-4% ee).[120,121]

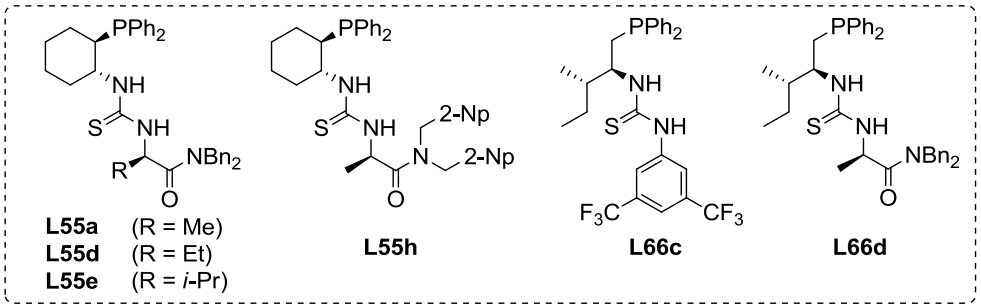
Guo *et al.* tested the amidothiourea **L55a**, developed by Jacobsen, and several analogues in [3+2]- and [4+2]-cycloaddition reactions of a cyclic sulfamate derivative (Scheme 34).[122,123] Zhang *et al.* tested phosphine-thiourea **L56c** in spiroannulation between a cyclobut-2-enone derivative and unsaturated nitrile and obtained moderate enantioselectivity, the best organocatalyst turned out be the acyclic analogue **L66b** (Scheme 35).[124] Sasai *et al.* reported on spiroannulation of a tryptamine derivative and carbonylalkyne and tested **L61** as one of the catalysts but obtained racemic product, the acyclic analogue **L68a** was much more efficient (Scheme 36).[125]

Scheme 34

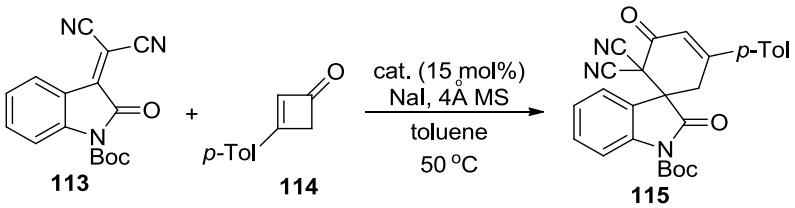


Cat.	Yield [%]	ee [%]
L55a	86	38
L55d	93	27
L55e	74	4
L55h	92	-8
L66c	70	45

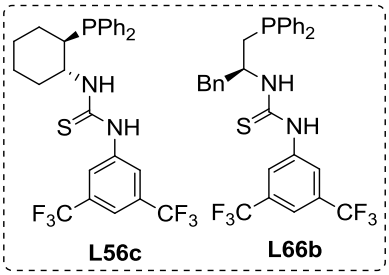
Cat.	Yield [%]	ee [%]	dr
L55a	25	-39	4:1
L66c	70	90	>20:1
L66d	81	99	>20:1



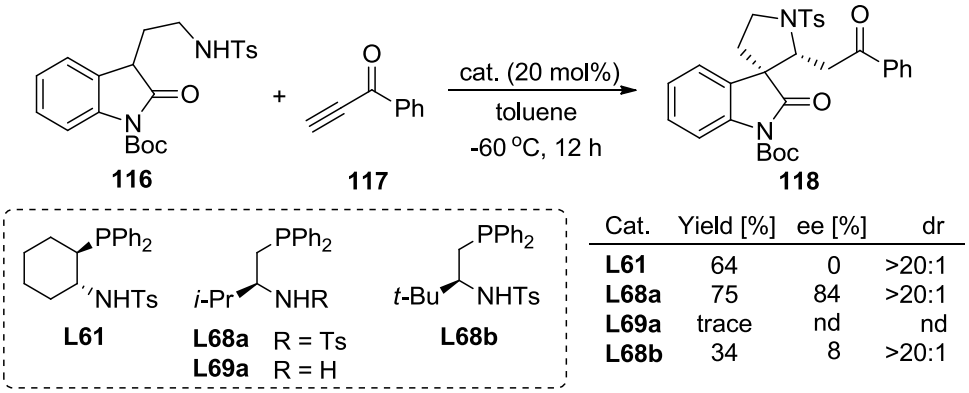
Scheme 35



Cat.	time [h]	Yield [%]	ee [%]
L56c	26	92	-73
L66b	12	97	85



Scheme 36



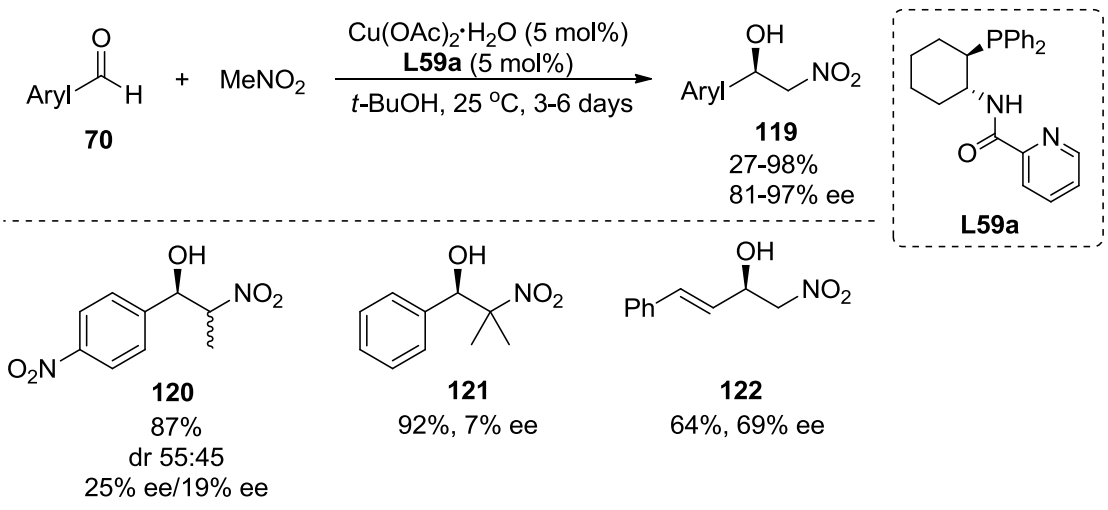
Cat.	Yield [%]	ee [%]	dr
L61	64	0	>20:1
L68a	75	84	>20:1
L69a	trace	nd	nd
L68b	34	8	>20:1

3.1.1.4.2. Transition metal-catalyzed reactions

Apart from organocatalytic reactions, 2-(diphenylphosphino)cyclohexylamine derivatives have also been successfully employed in several addition and conjugate addition reactions catalyzed by copper complexes.[111-118] All the publications in this field have come from the group of Wu and have been published in the recent years (2016-2019). The ligands used all fall into the subfamily of tridentate phosphine-aminoamide *P*,*N*,*N*-ligands (**L59a**, **L64**, **L65**).

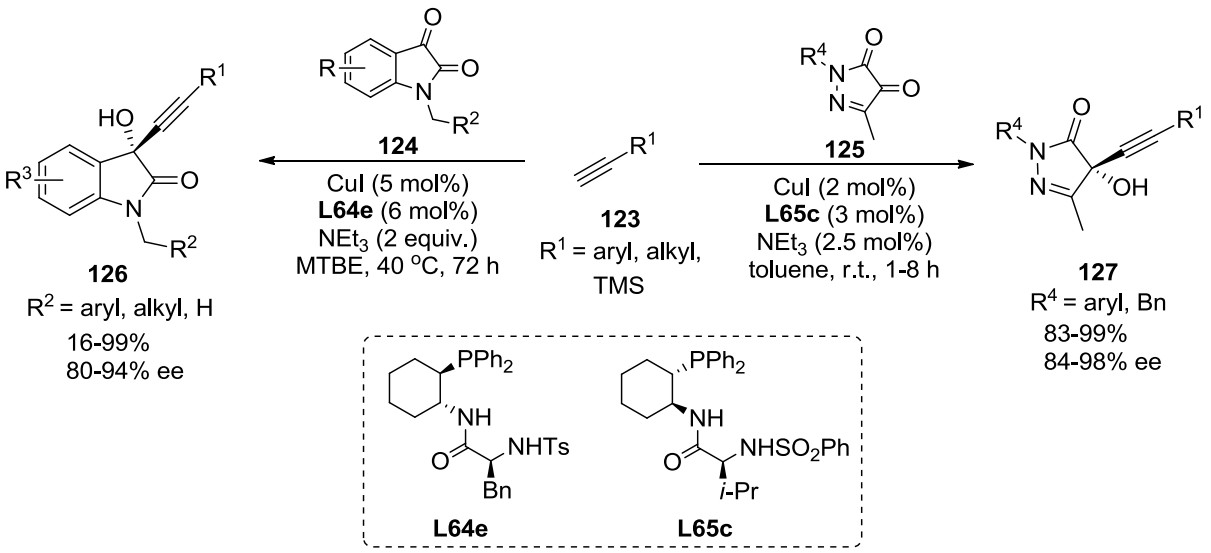
In 2016 Wu *et al.* described asymmetric Henry reaction using the phosphine-picolinamide derivative **L59a** as the ligand (Scheme 37).[111] Good to very good enantioselectivity was obtained for *ortho*-, *meta*- and *para*-substituted benzaldehydes, moderate enantioselectivity was observed for cinnamaldehyde. The reaction was limited to nitromethane, poor results were obtained for nitroethane and 2-nitropropane.

Scheme 37

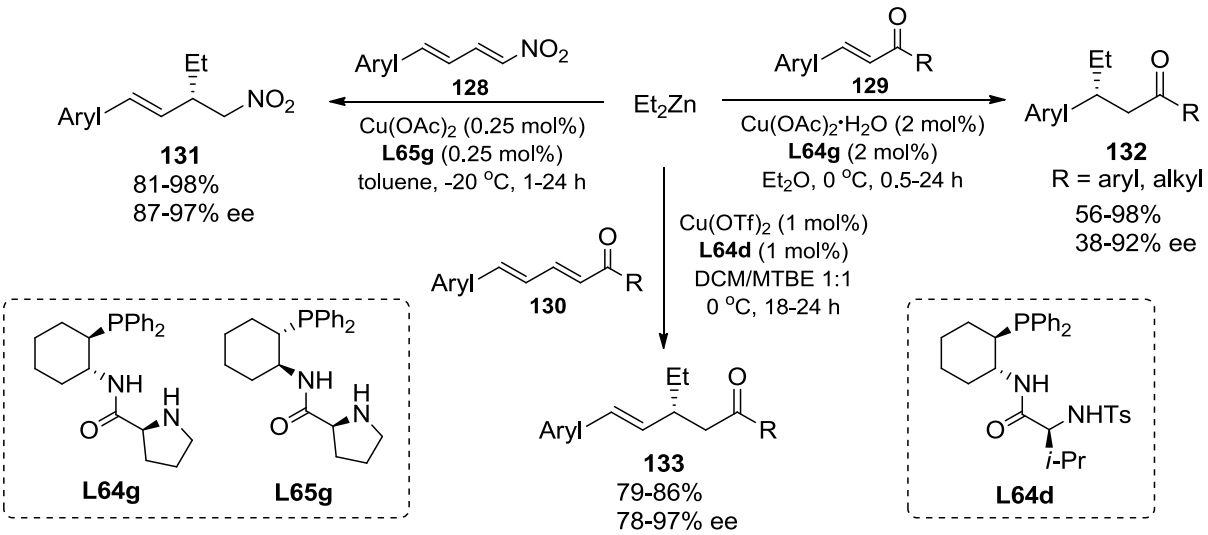


Phosphine-aminoamide ligands **L64e** and **L65c** were found to be highly effective for the addition of terminal alkynes to isatins[112] and pyrazole-4,5-diones[114] (Scheme 38). Copper complexes with the ligands **L64g** and **L65g** derived from L-proline were found to catalyze the conjugate addition reactions of Et_2Zn to δ-arylnitrodienes **128**[118] and enones **129**,[117] respectively, while the ligand **L64d** was superior for dienones **130**[117] (Scheme 39).

Scheme 38



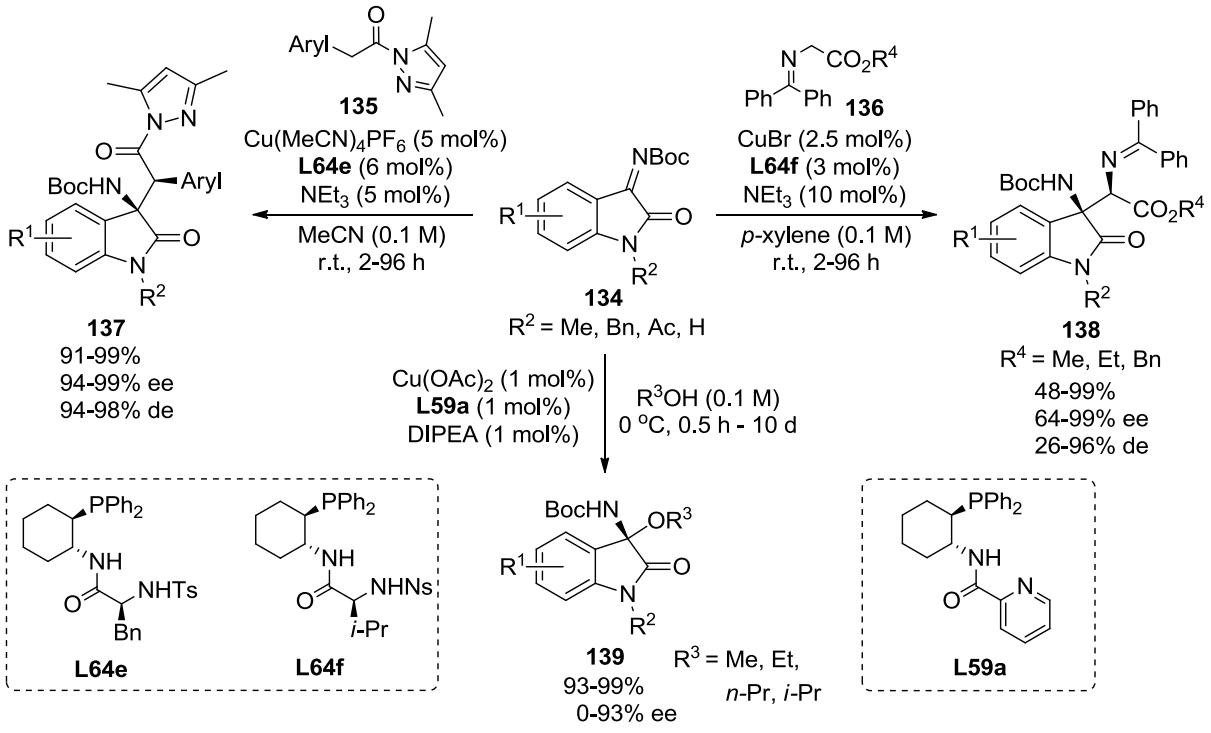
Scheme 39



Carbon nucleophiles, *N*-acylpyrazoles **135**[115] and glycine Schiff bases **136**,[113] and alcohols[116] were found to undergo addition to *N*-Boc isatin ketimines **134** under copper

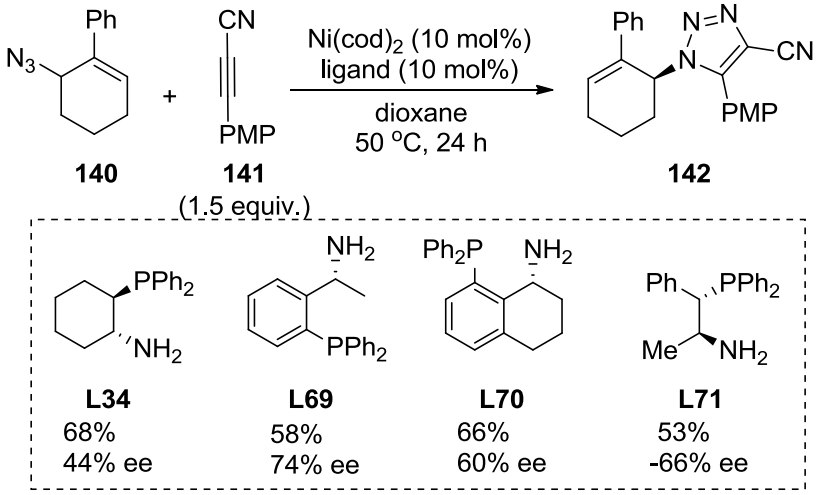
catalysis with phosphine-aminoamide ligands (Scheme 40). In the case of *N*-acylpyrazole (**135**), the copper source was very important for optimal yield and stereoselectivity. The reaction featured very good scope of the substrates, high yield, de and ee for isatin ketimines with different substituents at C5, C6 and C7 and different aryl groups in the nucleophile.[115] In the case of glycine Schiff bases (**136**), the copper source was not particularly important, several Cu(I) salts performed equally well with respect to yield, diastereo- and enantioselectivity, whereas Cu(II) salts were inferior yielding products with lower diastereoselectivity or not catalyzing the reaction at all. Several groups of solvents performed similarly but aromatics were generally marginally better than acyclic ethers.[113] Alcohol addition reactions had very high yields, however, the enantioselectivity varied greatly depending on the substituents at the aromatic ring of isatin ketimine, *N*-substituent, and the alcohol used (MeOH > EtOH, *n*-PrOH >> *i*-PrOH). The copper source was crucial for high enantioselectivity. Alcohols were essentially used as solvents which had primarily a positive effect on the rate of the reaction but also on the enantioselectivity. DCM and MeCN were found to be slightly inferior solvents in the optimization study. The reaction failed with benzyl mercaptan producing the product with only 7% ee.[116]

Scheme 40



The primary amine/phosphine **L34** was tested in five out of the eight publications on copper catalysis and in all cases it exerted no to very little stereoinduction, and most reactions employing it as the ligand also suffered from moderate to serious yield decrease.[111,113,115,117,118] **L34** was also tested by Topczewski *et al.* in Ni-catalyzed alkyne-azide cycloaddition (Scheme 41). The reaction proceeded only with phosphine/primary amine ligands **L34** and **L69**-**L71**, however, **L34** was the worst one with respect to enantioselectivity and **L69** gave the best result.[127]

Scheme 41



3.1.1.5. *Cis*-1-phosphino-2-phosphinoalkylcycloalkanes

Building on the ligand design concept of non-symmetric phosphino groups in bidentate ligands proposed by Achiwa during his studies on BPPM analogues,[37] Inoguchi and Achiwa reported in 1991 on (diphenylphosphino)cyclopentanes possessing diphenylphosphinomethyl group at C2 with *cis* and *trans* configuration (**L45a**,**b**).[128] These ligands were prepared as rigid analogues of BDPP (**L72**) in order to lock their rhodium complexes in the skew and chair conformations. BDPP had been developed by Bosnich *et al.* in 1981 and had shown a generally high level of stereoinduction in Rh-catalyzed hydrogenation of dehydroaminoacid derivatives[129] (*vide infra*, Scheme 43, Table 4, Entry 1) but also performed much better than previously reported ligands in the hydrogenation of acetophenone, the corresponding *N*-benzylimine, and α-ethylstyrene.[130] However, the stereoselectivity of Rh-catalyzed C=O and C=N hydrogenation[131] and Pt-catalyzed styrene hydroformylation[132] was found to be highly dependent on the solvent and reaction temperature. This effect was not observed in the hydrogenation of dehydroaminoacids which

has been explained by the higher ring flexibility of the Rh(BDPP)(substrate) complexes with substrates possessing less functional groups and the equilibrium shifting from the chiral skew conformation to the achiral chair conformation.[131] Achiwa predicted that the skew and chair conformations would be preferred for the rigidified *cis* and *trans* ligands **L45a** and **L45b**, respectively.[128] When the hydrogenation of *N*-acetyldehydrophenylalanine was carried out at 5 atm. of hydrogen (Scheme 42, Table 3), the *cis* ligand **L45a** was vastly superior to BDPP and its 4-methoxy-3,5-dimethylphenyl analogue (**L73**), maintaining full conversion and high enantioselectivity of 92% ee even at 0.005 mol% catalyst loading (Table 3, Entries 5-7) while both BDPP and **L73** showed lower ee at 0.1 mol% loading (Table 3, Entries 1 & 3) and after going down to 0.01 mol% loading experienced substantial decreases in the conversion and enantioselectivity (Table 3, Entries 2 & 4). On the other hand, the *trans* ligand **L45b** led to very low stereoselectivity even at 0.1 mol% loading (Table 3, Entry 9).

Scheme 42

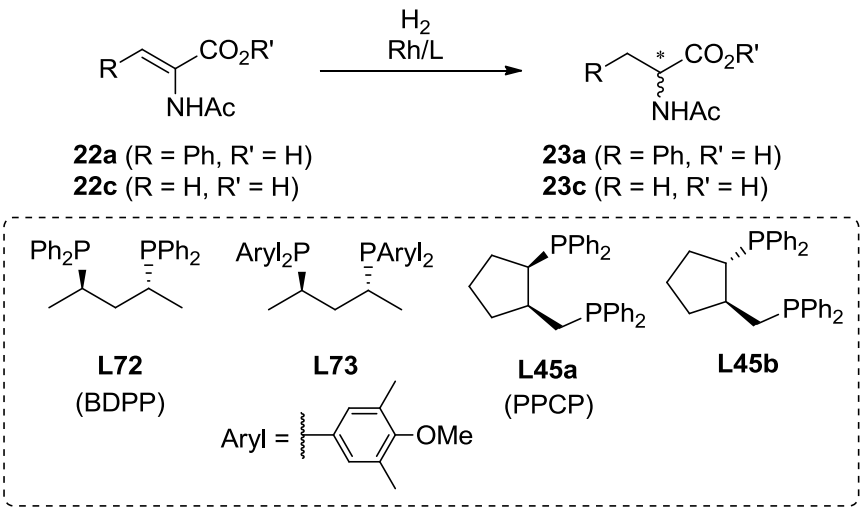


Table 3

Entry	Ligand	S.M.	Cat. loading [mol%]	Conv. [%]	ee [%]
1	**L72**	**22a**	0.1	100	62
2			0.01	10	-
3	**L73**	**22a**	0.1	100	81
4			0.01	76	54
5	**L45a**	**22a**	0.1	100	96
6			0.01	100	94
7			0.005	100	92
8		**22c**	0.1	100	87
9	**L45b**	**22a**	0.1	100	20

In 1997 Zhang *et al.* reported on the synthesis and application of a structurally related ligand – BICP (**L47**) which possesses two 2-(diphenylphosphino)cyclopentane rings joined together via 1,1'-single bond linker.[133] The $Rh(cod)_2BF_4$/BICP catalytic system gave high enantioselectivity in the asymmetric hydrogenation of a series of dehydroaminoacid derivatives (Scheme 43, Table 4, Entry 8). The cationic rhodium source as well as 50 mol% of triethylamine additive were crucial for high stereoselectivity.[133] The Ir/BICP complex was highly effective for the hydrogenation of imines.[134]

Scheme 43

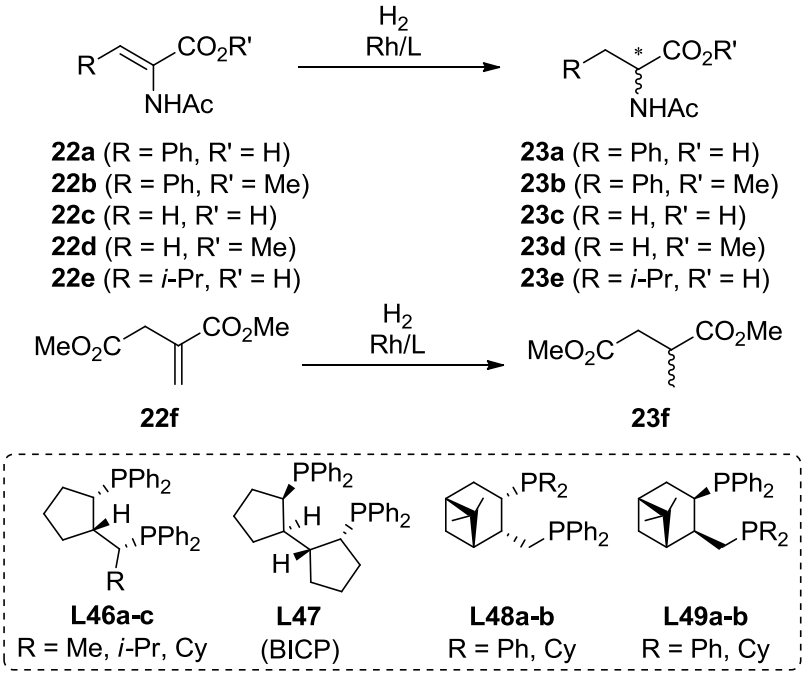


Table 4

Entry	Ligand	Product, ee (%)					
		23a	**23b**	**23c**	**23d**	**23e**	**23f**
1	**L72** (BDPP)	93[a], 62[b]	72[a]	98[a]	-	23[a]	-
2	**L73**	81[b]	-	-	-	-	-
3	**L45a** (PPCP)	96[b]	94[a]	87[b]	-	-	-
4	**L45b**	20[b]	-	-	-	-	-
5[a]	**L46a**	-	78	-	63	-	14
6[a]	**L46b**	-	31	-	34	-	19
7[a]	**L46c**	-	10	-	10	-	8
8[a]	**L47** (BICP)	97	-	98	-	93	-
9[a]	**L48a**	-	84	-	60	-	18
10[a]	**L48b**	-	51	-	79	-	17
11[a]	**L49a**	-	78	-	61	-	81
12[a]	**L49b**	-	46	-	7	-	54

a) H_2 pressure was 1 atm.; b) H_2 pressure was 5 atm.

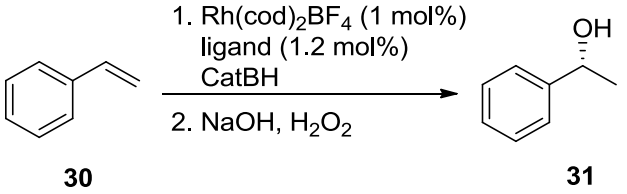
Gavryushin and Knochel synthesized several PPCP analogues with an additional chiral centre in the phosphinomethyl side chain (**L46a-c**)[136] and bicyclic analogues possessing a pinane scaffold and phosphino groups located *anti* and *syn* to the dimethylmethylene bridge (**L48a-b** and **L49a-b**).[135,136] These compounds were tested as ligands in several transition metal-catalyzed reactions.

In the hydrogenation of dehydrophenylalanine methyl ester **22b** both monocyclic (**L46a-c**) and bicyclic (**L48a-b**, **L49a-b**) analogues all proved to be inferior to PPCP (Scheme 43, Table 4, Entries 3, 5-7, 9-12).[135,136] Among the monocyclic ligands **L46a** with the α-methyl side chain performed the best and stereoselectivity decreased in the series with increasing steric bulk at the α position. The same trend was observed for dehydroalanine methyl ester **22d** and for all three ligands the stereoselectivity was similar to that of the phenylalanine derivative. All three ligands were also tested in the hydrogenation of dimethyl itaconate **22f** but performed rather poorly (Table 4, Entries 5-7). No comparable reaction with PPCP was done for **22d** and **22f**. Among the bicyclic ligands no single ligand proved to be general (Table 4, Entries 9-12), for **22b** the best ligand was the exo bis(diphenylphoshino) ligand **L48a**. Bis(diphenylphoshino) ligands were noticeably better than ligands with two different phosphino groups, and exo ligands were slightly better then endo ligands. For **22d** bis(diphenylphosphino) exo (**L48a**) and endo (**L49a**) ligands were comparable, however, the mixed exo ligand (**L48b**) was much better than the mixed endo ligand (**L49b**) and it was the best ligand for this substrate. For the hydrogenation of dimethyl itaconate (**22f**), the endo ligand **L49a** was the best followed by the mixed endo ligand **L49b**, whereas the ligands **L48a**,**b** both led to very low stereoselectivity.

The monocyclic ligands **L46a-c** and the bicyclic ligands **L48a** and **L49a** were also tested in Rh-catalyzed hydroboration of styrene (Scheme 44) and Rh-catalyzed conjugate addition of phenylboronic acid to cyclohexenone (Scheme 45).[136] In hydroboration the ligand **L46c**, the bulkiest among monocyclics, was the best but the ee was only 80% which was inferior to DCYPCY (**L28b**), previously reported by the group of Knochel.[54] The reactions employing the pinane-based ligands **L48a** and **L49a** afforded racemic product. All catalysts prepared from **L46a-c**, **L48a** or **L49a** were also less active than the Rh/DCYPCY catalyst (Rh/**L28b**), the yields of the hydroboration were 55-69% (at -20 to 0 ^{o}C) vs. 85% with DCYPCY (at -35 ^{o}C). In the case of the conjugate addition to cyclohexenone the ligands

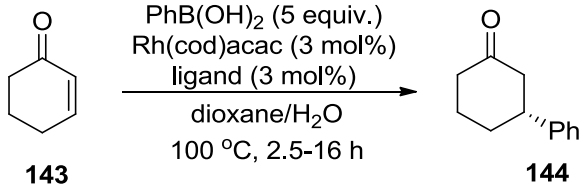
L46a-c were all superior to PPCP (**L45**) and the methyl-substituted **L46a** was the best, little or no stereoselectivity was observed with **L49a** and **L48a**, respectively. Selected ligands of the type **L46** and **L48**/**L49** were also tested in Rh-catalyzed hydrogenation of acetophenone *N*-benzoylhydrazone, Ru-catalyzed hydrogenation of ethyl benzoylacetate, and Pd-catalyzed allylic substitution of 1,3-diphenylallyl acetate with dimethyl malonate. In all of these reactions the tested ligands performed poorly with stereoselectivity below 37% ee.

Scheme 44



Ligand	yield (%)	ee (%)	temp.
L46a	65	57	-10 °C
L46b	65	73	-20 °C
L46c	69	80	-10 °C
L48a	55	0	0 °C
L49a	67	0	0 °C

Scheme 45



Ligand	ee (%)
L45	31
L46a	88
L46b	57
L46c	68
L48a	0
L49a	8

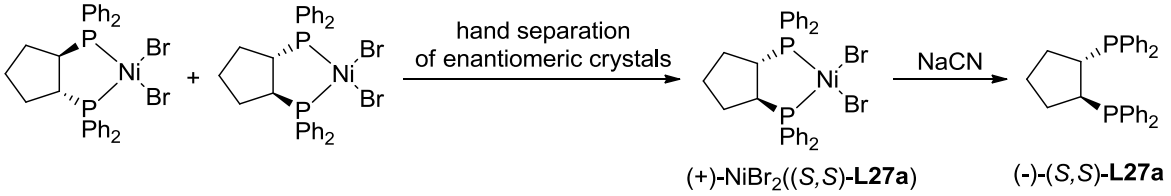
3.1.2. Preparation of C2-functionalized cycloalkylphosphines

3.1.2.1. Introduction

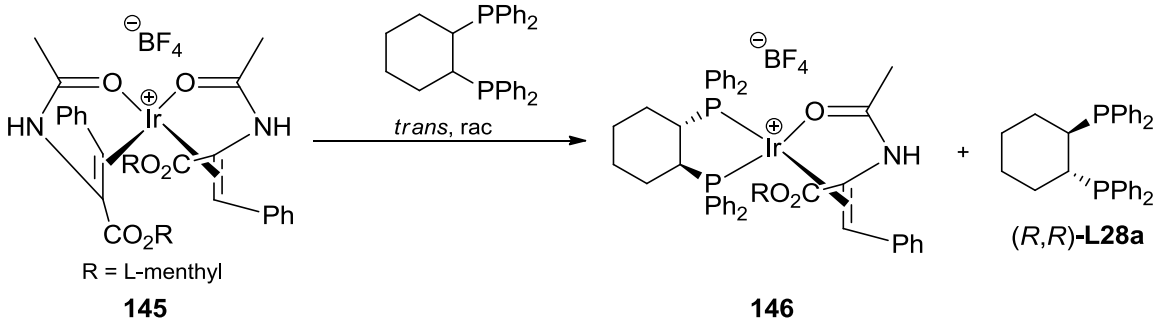
The first *trans*-1,2-cycloalkylene diphosphine to be reported was 1,2-bis(diphenylphosphino)cyclopentane (**L27a**) and its preparation was described in 1983 by Green *et al.*[44] The racemic diphosphine was used to make $NiBr_2$(**L27a**) complex which upon recrystallization from dichloromethane underwent resolution to form conglomerates of enantiopure crystals that could be separated by hand (Scheme 46). The enantiopure diphosphine was released from the complex by the treatment with NaCN. This method was later used in 1993 by Pavlov *et al.* to obtain enantiopure $NiBr_2$(**L27a**) which was tested in allylic substitution reactions.[59] However, the generality and scalability of this approach is unknown and as noted by Consiglio and Indolese, it was impractical to obtain large amounts of the ligand using this method.[56]

In 1986 Brown and Maddox described a stereoselective substitution reaction at the chiral iridium-bis(enamide) complex by chiral diphosphines Chiraphos (**L3**), DPPCP (**L27a**) and DPPCY (**L28a**) based on kinetic resolution (Scheme 47).[45] The iridium complex reacted selectively with one enantiomer of a diphosphine leaving the other enantiomer uncomplexed in the solution. To this solution a rhodium precatalyst was added to form the complex with the free diphosphine enantiomer and this complex was then tested in asymmetric hydrogenation of dehydroaminoacid derivatives. The applicability of this method to other cyclic diphosphines is unknown. Two different sets of conditions were required to resolve **L27a** and **L28a**, excess iridium bis(enamide) complex was necessary, and no control reactions with isolated enantiopure **L27a** and **L28a** were performed. As the unreacted starting iridium bis(enamide) and the formed iridium diphosphine complexes both remain in the solution, they are a potential interference if one desired to use the free diphosphine enantiomer to test a catalytic reaction different from the asymmetric hydrogenation used in the study. Thus, this method has very limited utility. Nonetheless, the works of Green *et al.* and Brown and Maddox sparked the interest in cycloalkylene diphosphines as ligands and warranted further effort to invent better and more general methods for their preparation.

Scheme 46



Scheme 47



The methods of the preparation of enantiopure C2-functionalized cycloalkylphosphines can be classified as one of the three types with each type featuring a different key step in which an enantiopure phosphine derivative is obtained:

1) type 1 includes resolution of diastereomers of an organophosphorus compound,
2) type 2 includes a stereospecific reaction of an enantiopure substrate with a phosphorus reagent,
3) type 3 includes a stereoselective reaction of a phosphorus nucleophile at a prochiral substrate.

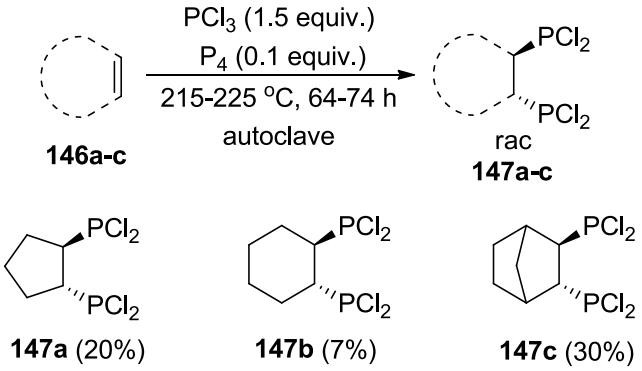
3.1.2.2. Preparation of racemic compounds

Resolution techniques require a racemic mixture of a phosphine derivative to be resolved, thus a reliable method to obtain a racemate is equally important as the resolution itself. Five distinct methods for the preparation of racemic 1,2-cycloalkylene diphosphines have been reported with a varying degree of generality.

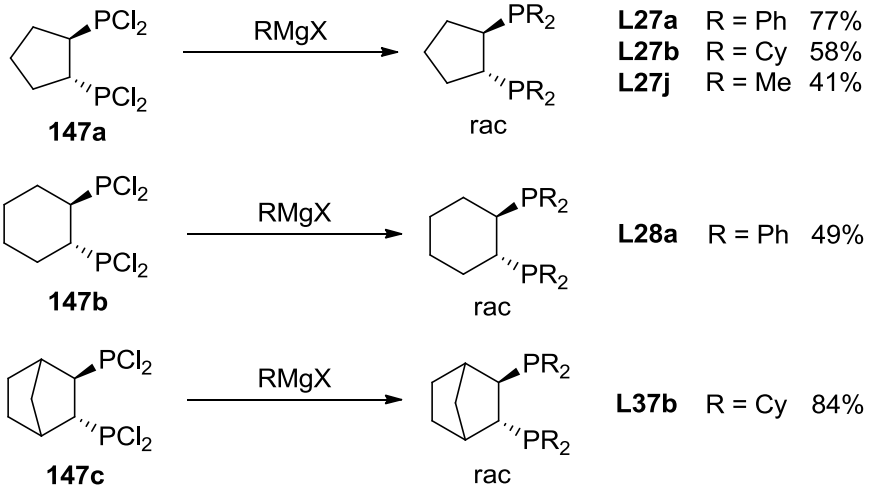
In 1983 Green *et al.* reported obtaining DPPCP (**L27a**) from the bis(dichlorophosphino)cyclopentane **147a**.[44] This compound was prepared from cyclopentene and PCl_3 in the presence of a catalytic amount of white phosphorus in an autoclave at 215 ^oC (Scheme 48). This method was an adaptation of a similar reaction between ethylene and PCl_3 leading to 1,2-bis(dichlorophosphino)ethane.[137] In the patent application from 1984, Green extended this method to the higher homologue **147b** starting from cyclohexene.[44b] The mechanism of the reaction is unknown, however, assuming 1:2 cycloalkene/PCl_3 stoiochiometry and PCl_3 as the limiting reagent in these reactions the isolated yields of **147a** and **147b** were 20% and 7%, respectively. Saare and Dahlenburg later used this method with norbornene and obtained the bicyclic bis(dichlorophosphine) **147c**.[138] The reactions were carried out at the scale of 1.98–2.65 mol of cycloalkene. A disadvantage of this method is the requirement of highly toxic white phosphorus and manipulation of sensitive P-Cl compounds. An alternative method employing milder conditions was reported in 1993 by Drieß and Haiber, when cyclohexene was reacted with P_2Cl_4 at room temperature for 10 days, **147b** was isolated in 50% yield after distillation.[139] However, P_2Cl_4 is a very unstable compound and must be generated *in situ* by co-condensation of copper and PCl_3 at -196 ^oC and thawing the mixture. For this reason the reaction requires a rather complex apparatus which renders the procedure cumbersome.

Bis(dichlorophosphino)cycloalkanes **147a-c** are versatile precursors to other cycloalkylene organophosphorus compounds and were reacted with Grignard reagents to obtain the corresponding bis(phosphines) in moderate to good yields (Scheme 49).[44b,138]

Scheme 48

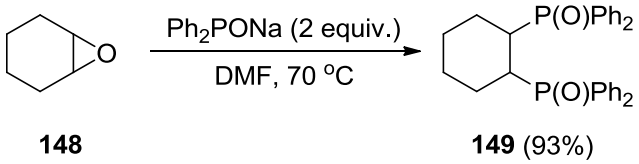


Scheme 49



Also in 1983 Wife *et al.* reported on the high-yielding preparation of bis(diphenylphosphinoyl)cyclohexane (**149**) from 1,2-epoxycyclohexane (**148**) and 2 equiv. of sodium diphenylphosphinite generated *in situ* by deprotonation of diphenylphosphine oxide with sodium hydride (Scheme 50).[140]

Scheme 50

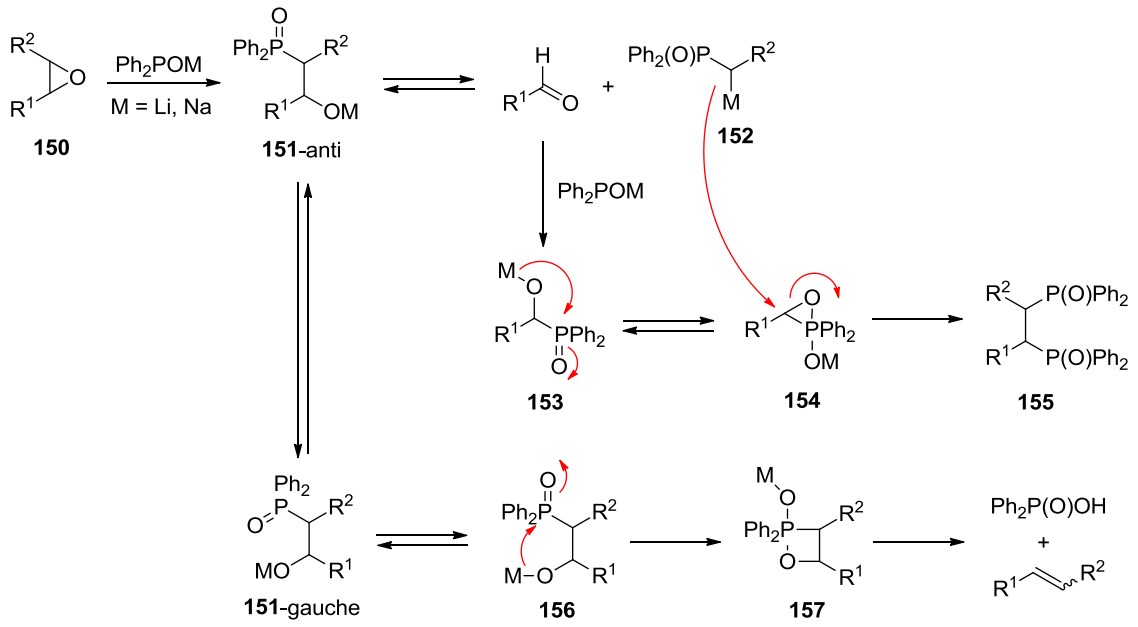


The reaction is formally a double substitution at the epoxide. However, the diphosphine dioxide product was only observed with ethylene oxide and 1,2-epoxycyclohexane while vicinally disubstituted acyclic oxiranes such as 2,3-epoxybutane led

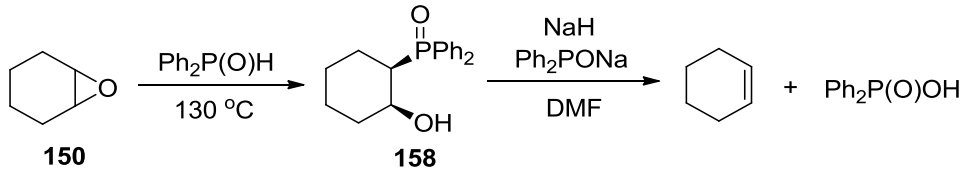
to the formation of diphenylphosphinic acid.[140] Based on probing the reaction before completion and running control reactions the authors proposed a diverging mechanism explaining the behaviour of different oxiranes (Scheme 51).[141]

The first equivalent of Ph_2POM undergoes *anti*-addition to an epoxide to give **151**-anti. The intermediate undergoes a retro-aldol-type fragmentation to form an aldehyde and α-metallated alkyldiphenylphosphine oxide **152**. The proposal of this fragmentation is based on the presence of a substantial amount of $Ph_2P(O)Me$ and an equal amount of an unidentified compound in the quenched aliquots of ongoing reactions with simple oxiranes. The second equivalent of Ph_2POM undergoes addition to the formed aldehyde to form the adduct **153** which is in equilibrium with the cyclic form **154**. The latter reacts with the α-metallated phosphine oxide **152** to give the diphosphine dioxide product **155**. Alternatively, for acyclic epoxides the mechanism can diverge after the first addition to the epoxide, **151**-anti undergoes conformation change to **151**-gauche which then follows the mechanism of Wittig-Horner reaction. This pathway is not possible with 1,2-epoxycyclohexane as there is no free rotation around the C1-C2 bond. However, when diphenylphosphine oxide was reacted with excess 1,2-epoxycyclohexane neat at 130 ^{o}C, a small amount of the adduct **158** was obtained, and this compound produced cyclohexene when subjected to NaH and Ph_2PONa in DMF, even at room temperature (Scheme 52).

Scheme 51

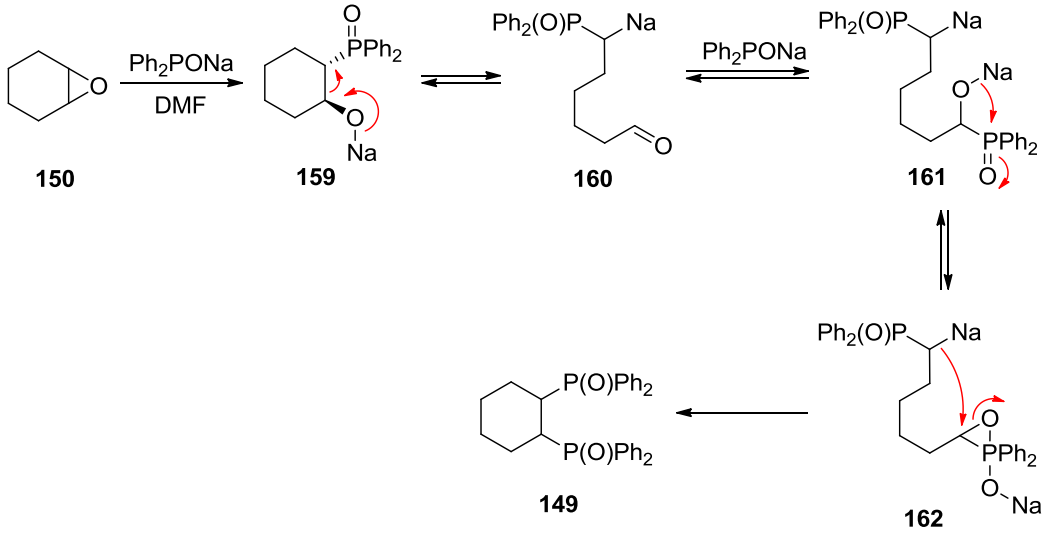


Scheme 52



Unfortunately, the configuration of the diphosphine dioxide **149** was not reported or discussed, there was also no analytical data available in the paper for any of the products, and the proposed mechanism does not exclude the formation of the *cis* or *trans* isomer or a mixture of both (Scheme 53).

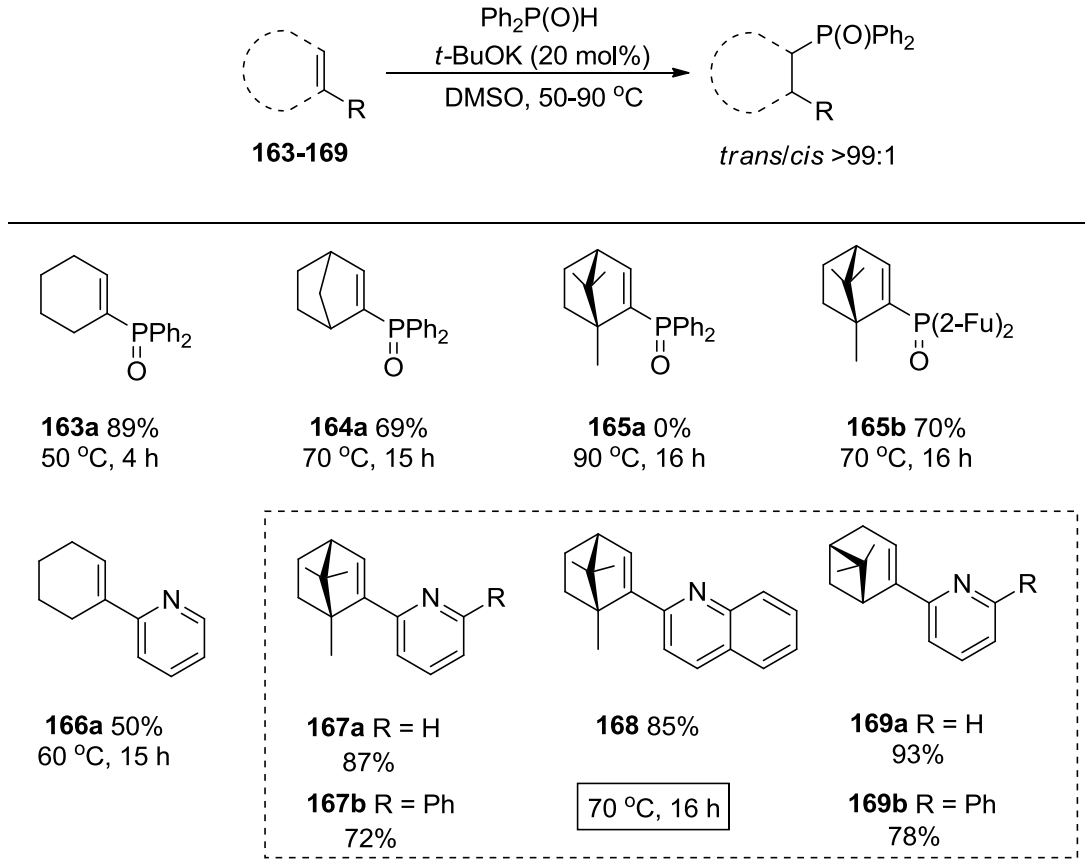
Scheme 53



The third method for the preparation of racemic 1,2-cycloalkylene diphosphine derivatives was published by Knochel *et al.* in 2002.[142] It involves the conjugate addition reaction of diphenylphosphine oxide to cycloalkenylphosphine oxide in the presence of potassium *tert*-butoxide in DMSO (Scheme 54). The reaction produces exclusively the *trans* isomer and also works with 2-pyridyl or 2-quinolyl as activating groups for the olefin. It is especially useful with bicyclic substrates derived from the chiral pool such as camphor and nopinone due to its high diastereoselectivity and it was used in the synthesis of the ligands **L40**-**L43** (*vide supra*, Figure 7).[78] All the cycloalkenylphosphine oxide substrates for this reaction were presumably prepared by the Pd-catalyzed cross-coupling between cycloalkenyl triflates and secondary phosphine oxides, although the procedure and analytical data were

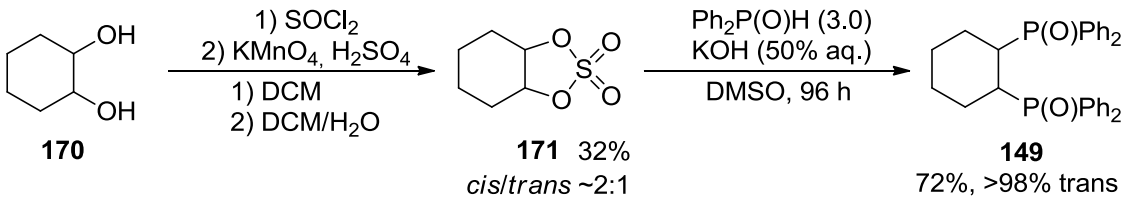
only reported for **165b**. Compounds **167-169** were prepared analogously by the Pd-catalyzed Negishi cross-coupling with 2-pyridyl- or 2-quinolylzinc bromides.

Scheme 54



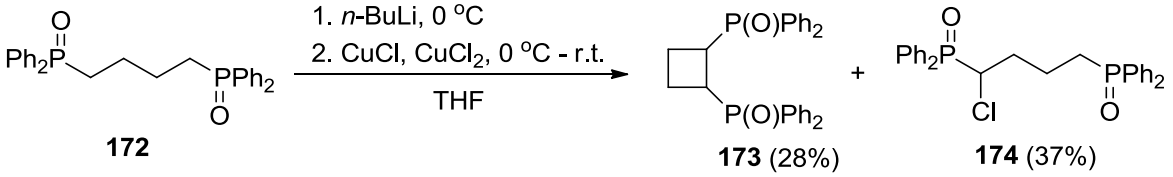
1,2-Bis(diphenylphosphinoyl)cyclohexane **149** can also be synthesized through double nucleophilic substitution of the cyclic sulfate **171** by diphenylphosphine oxide in the presence of aqueous KOH in DMSO as the solvent (Scheme 55).[143]

Scheme 55



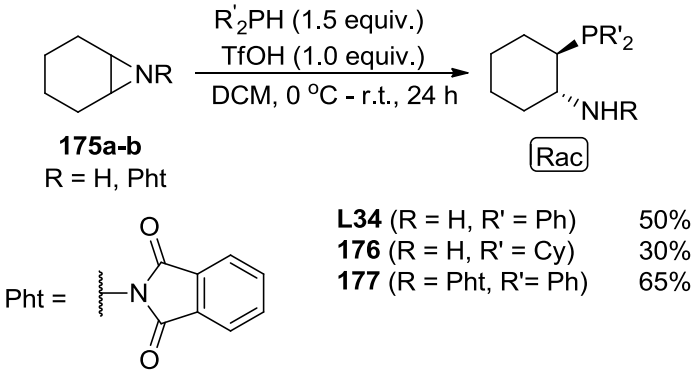
Minami *et al.* prepared 1,2-bis(diphenylphosphinoyl)cyclobutane (**173**) via copper-mediated oxidative cyclization of α,α'-dilithiated 1,2-bis(diphenylphosphinoyl)butane (Scheme 56).[144]

Scheme 56



Apart from diphosphine derivatives, *trans*-2-(phosphino)cyclohexylamine derivatives were synthesized in racemic form by Yudin *et al.* via ring-opening nucleophilic addition of secondary phosphines Ph_2PH and Cy_2PH to aziridine **175a** and its *N*-phthalimidoyl analogue **175b** (Scheme 57).[80] *Trans* products were obtained exclusively with low to moderate yields (30-65%) and triflic acid was crucial as the activating agent.

Scheme 57



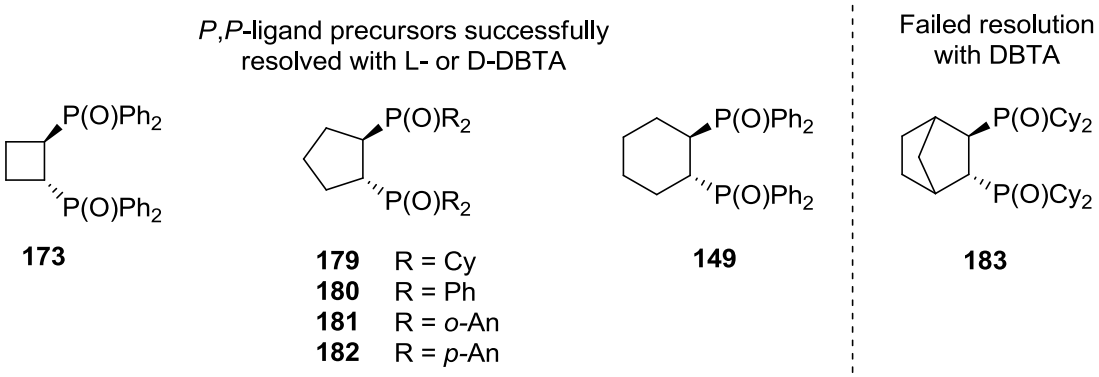
3.1.2.3. Preparation of enantiopure compounds by diastereomer resolution

Resolution of diastereomers by fractional crystallization is the oldest approach used in organophosphorus chemistry for the preparation of enantiopure chiral organophosphorus compounds[145,146] and has been used in the preparation of many breakthrough ligands, including Norphos,[61] BisP*[147a] and BINAP.[147b] However, development of a resolution protocol is a complex process requiring finding a set of an optimal derivatizing agent, solvent or solvent mixture, and conditions. The protocols for resolution are typically tailored for a single compound as even small changes in the structure of a compound to be resolved can render the method ineffective. For these reasons more and more work is devoted to developing more robust asymmetric catalytic methods to obtain chiral ligands. In order to be amenable to resolution a chiral organophosphorus compound must possess a functionality that allows for transformation to a diastereomeric derivative from which the enantiopure compound can be recovered quantitatively after resolution. Resolvable organophosphorus

derivatives primarily include molecular complexes of secondary or tertiary phosphine oxides or diphosphine dioxides with moderate or weak organic acids,[148] phosphonium salts with a chiral counteranion,[149] coordination complexes of mono- or diphosphines with chiral transition metal complexes,[147] and menthyl esters of phosphinic acids and other compounds with P-OMenthyl moiety.[150]

Resolution methods for the preparation of enantiopure C2-functionalized cycloalkylphosphines include primarily resolution of racemates of diphosphine dioxides by the formation of diastereomeric molecular complexes with *O,O*'-dibenzoyltartaric acid (DBTA) and fractional crystallization (Figure 11). A typical procedure consists of the formation of the molecular complex, precipitation of the less soluble diastereomer, and liberation of the diphosphine dioxide from the complex by treatment with an aqueous base solution. The free diphosphine is then obtained through reduction of the diphosphine dioxide. The precipitate is typically only enriched in one of the diastereomers and thus repetition of the resolution on the enriched sample or recrystallization of the enriched molecular complex is necessary to obtain the pure diastereomer. The mother liquor contains the more soluble diastereomer in excess and after solvent evaporation this mixture of diastereomers can be treated in the same way as the precipitate to recover the starting material which can then be used in a resolution with the other enantiomer of DBTA to obtain the other enantiomer of the diphosphine dioxide.

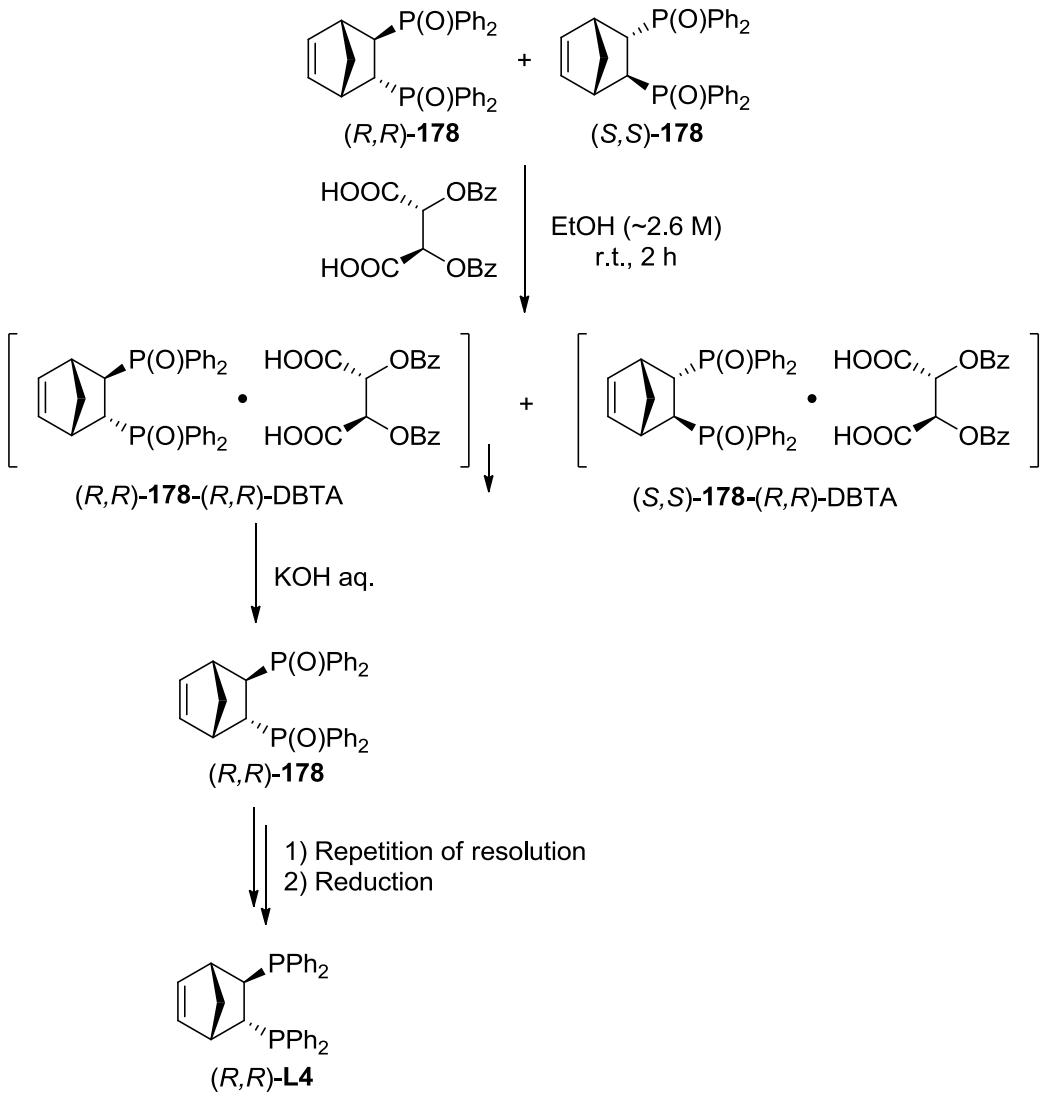
Figure 11



This approach was first reported in 1979 by Brunner and Pieronczyk to resolve Norphos dioxide (**178**) with L-DBTA.[61a] Scheme 58 illustrates the original procedure which required repetition of the resolution. An updated procedure was published by Brunner *et al.* in 2008.[151] Its advantage was a single resolution step in $CHCl_3$/EtOAc two-solvent system followed by recrystallization from hot MeOH. An analogous procedure employing L-DBTA

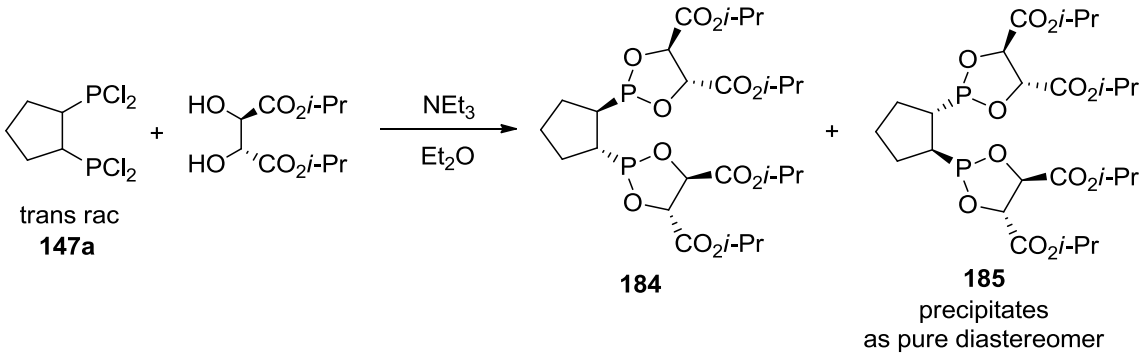
was used by Minami *et al.* to resolve bis(diphenylphosphinoyl)cyclobutane (**173**). Here, the resolution had to be performed four times on the consecutively enriched samples to obtain the enantiopure diphosphine dioxide.[144] Saare and Dahlenburg resolved bis(dicyclohexylphosphinoyl)cyclopentane (**179**) using D-DBTA, the precipitate enriched in the (*S*,*S*)-**179**/D-DBTA diastereomer was recrystallized once from THF/pentane to give the pure diastereomer.[138] Consiglio and Indolese also resolved the phenyl, *o*-anisyl, and *p*-anisyl analogues (**180**-**182**),[56] and resolution of bis(diphenylphosphinoyl)cyclohexane **149** with D-DBTA was reported in the Jaekel's and Paciello's patent.[143] However, an analogous resolution of the norbornane-2,3-diyl analogue **183** failed with both L- and D-DBTA, similarly, no meaningful enrichment was observed with (+)-camphorsulfonic acid in the complex crystallized from solvents of different polarity.[138]

Scheme 58



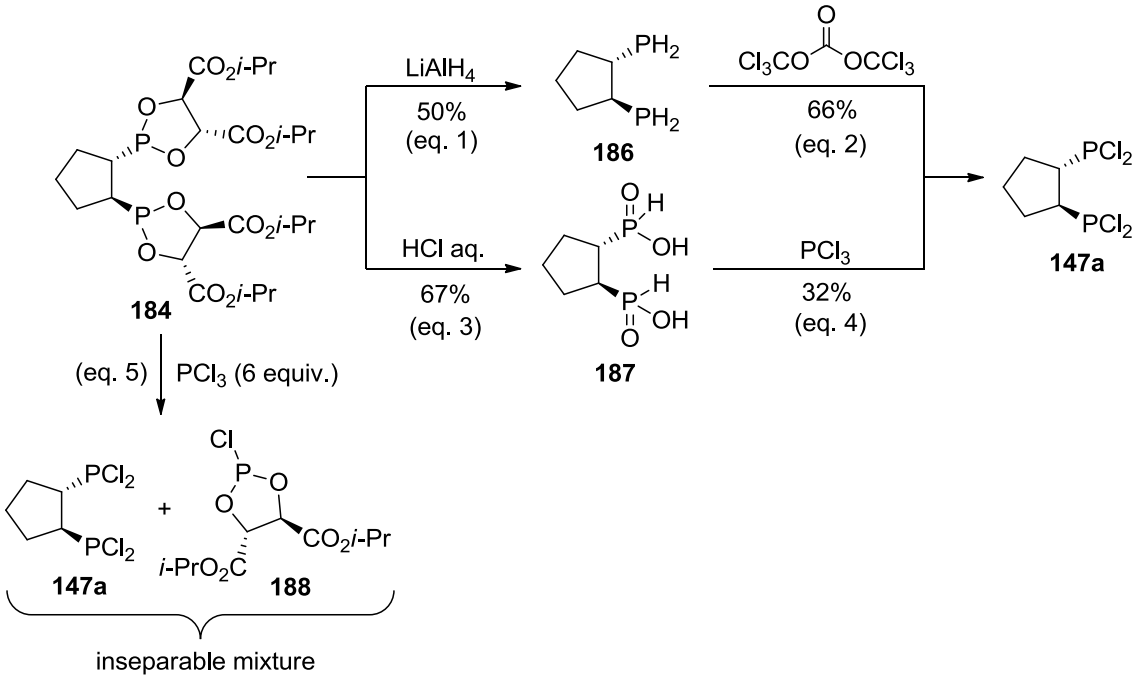
Dahlenberg *et al.* used a different resolution approach to enantiopure cyclopentane-based *P*,*P*-ligands installing a temporary chiral auxiliary at the phosphorus atoms (Scheme 59).[152] Racemic *trans*-1,2-bis(dichlorophosphino)cyclopentane (**147a**) was reacted with diisopropyl tartrate in diethyl ether to form a pair of bis(phosphonite) diastereomers **184** and **185**, and the latter precipitated from the reaction mixture as a pure diastereomer. Bis(phosphonite) **185** is a precursor to the more synthetically useful bis(primary phosphine) **186** and bis(dichlorophosphine) **147a** (Scheme 60). Bis(phosphine) **186** was obtained directly from **185** in a reaction with $LiAlH_4$ and upon the reaction with triphosgene it was converted to enantiopure bis(dichlorophosphine) **147a** (Scheme 60, eq. 1-2). A direct reaction between bis(phosphonite) **185** and PCl_3 led to an inseparable mixture of **147a** and chlorophosphite **188** (Scheme 60, eq. 5).[152] An alternative pathway from **183** to **147a**, devised by Brunner *et al.*, consisted of acidic hydrolysis of **185** yielding bis(phosphonous acid) **187** followed by a reaction with PCl_3 to give **147a** (Scheme 60, eq. 3-4).[153]

Scheme 59

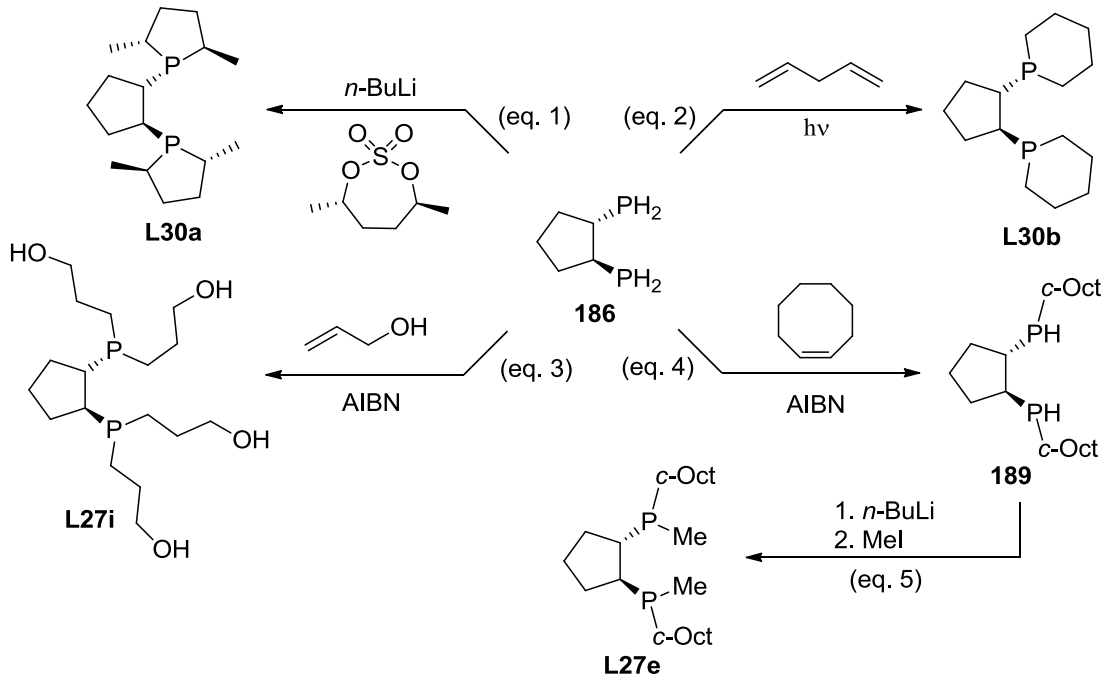


Together, bis(phosphine) **186** and bis(dichlorophosphine) **147a** are complementary precursors to a variety of trivalent organophosphorus compounds acting as reagents with (pro)nucleophilic and electrophilic phosphorus atoms, respectively (Schemes 61 and 62). Bis(phosphine) **186** was used to obtain the bis(phospholane) ligand **L30a** through P-H deprotonative lithiation and nucleophilic substitution with the cyclic sulfone derived from enantiopure hexane-2,5-diol (Scheme 61, eq. 1).[48] It also reacted with olefins in radical additions initiated by light or a radical initiator (Scheme 61, eq. 2-4). In the reaction with cyclooctene, bis(secondary phosphine) **189** was obtained which was subsequently deprotonated with *n*-BuLi and subjected to methylation with MeI to give **L27e** as a mixture of diastereomers.[50]

Scheme 60



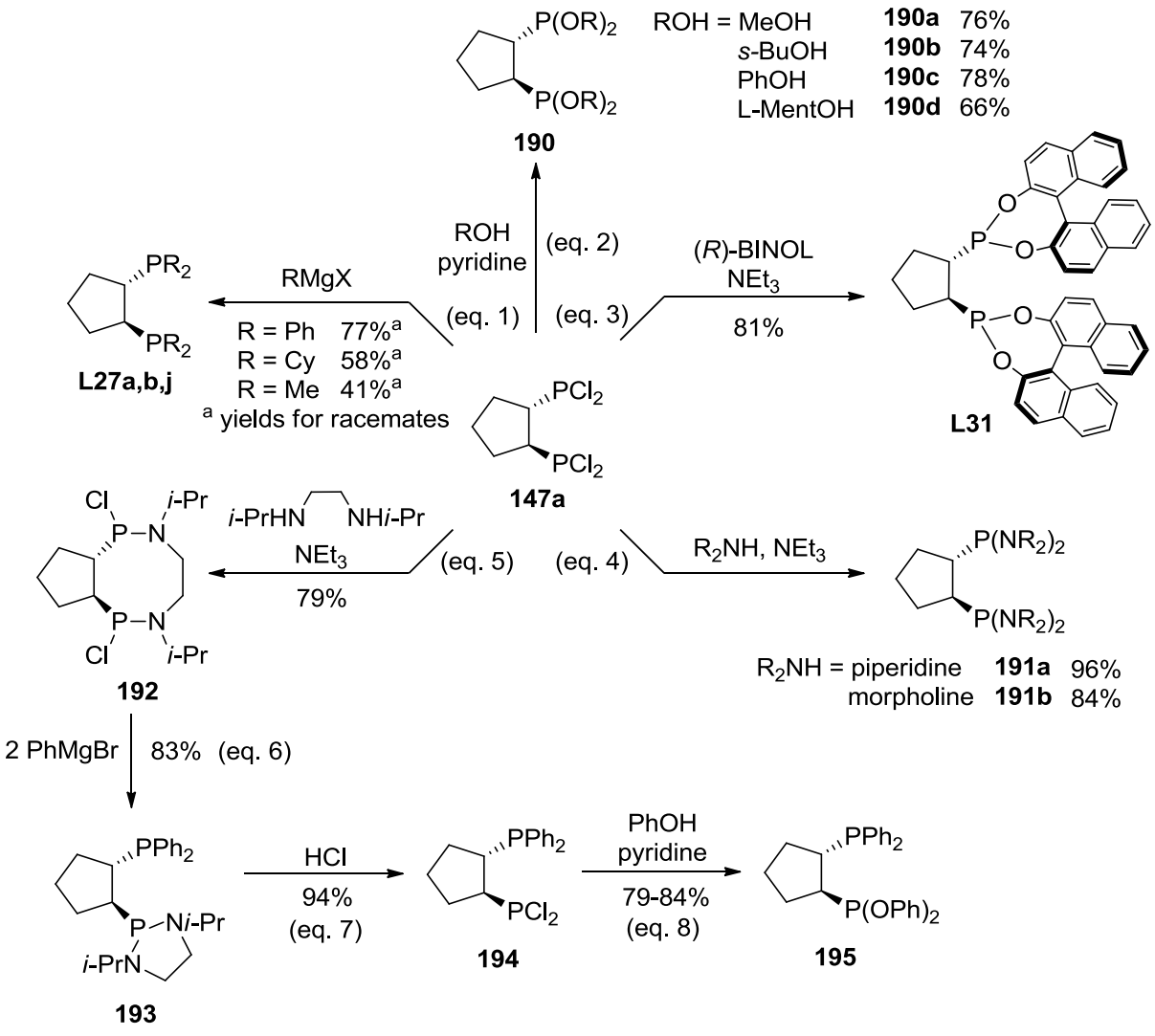
Scheme 61



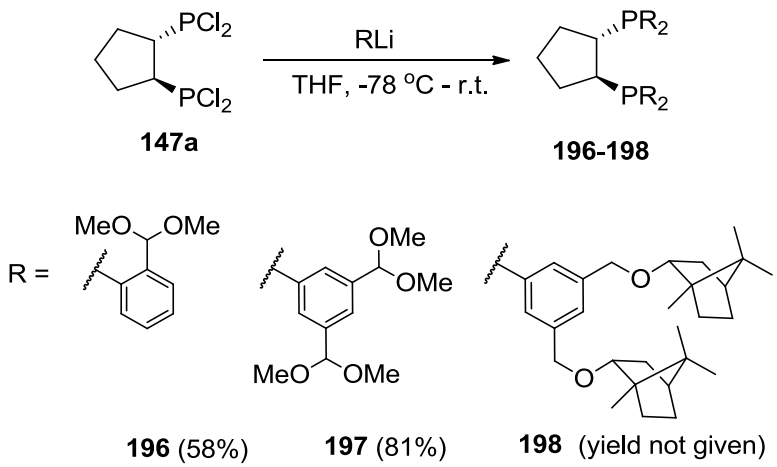
Bis(dichlorophosphine) **147a** has been shown to react with Grignard reagents (Scheme 62, eq. 1)[44b,138] and aryllithium reagents (Scheme 63)[153] with moderate to good yields. The use of more bulky organometallics was associated with lower yields. Bis(diarylphosphines) **196**-**197** possessing formyl groups protected as dimethyl acetals were

used as precursors to the corresponding imines derived from chiral amines or aminoalcohols.[153] Bis(phosphonites) **190a-d** were obtained in good yields in reactions with alcohols and pyridine (Scheme 62, eq. 2).[154,155] The BINOL derived ligand **L31**[154] and bis(diaminophosphines) **191a-b**[154,155] were obtained in a similar manner with NEt_3 as the base (Scheme 62, eq. 3-4). An interesting application of **147a** is the preparation of homochiral bis(phosphines). In the reaction with *N,N'*-diisopropylethylenediamine bis(dichlorophosphine) **186** formed the bicyclic dichlorodiphosphine **192**. This compound, when subjected to a reaction with two equivalents of PhMgBr, gave the dissymmetric product **193** in which the diazaphospholane moiety could be transformed into the more synthetically useful dichloride **194**. The phosphine-phosphonite **195** was obtained from **194** using phenol and pyridine (Scheme 62, eq. 5-8).[156]

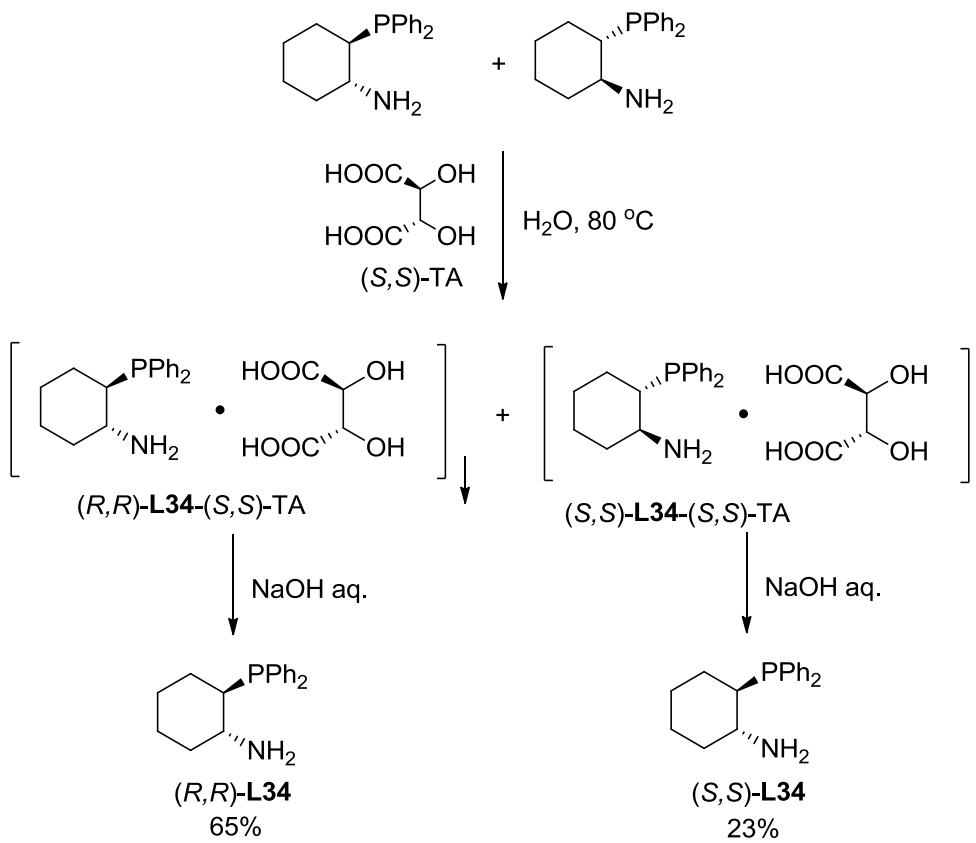
Scheme 62



Scheme 63



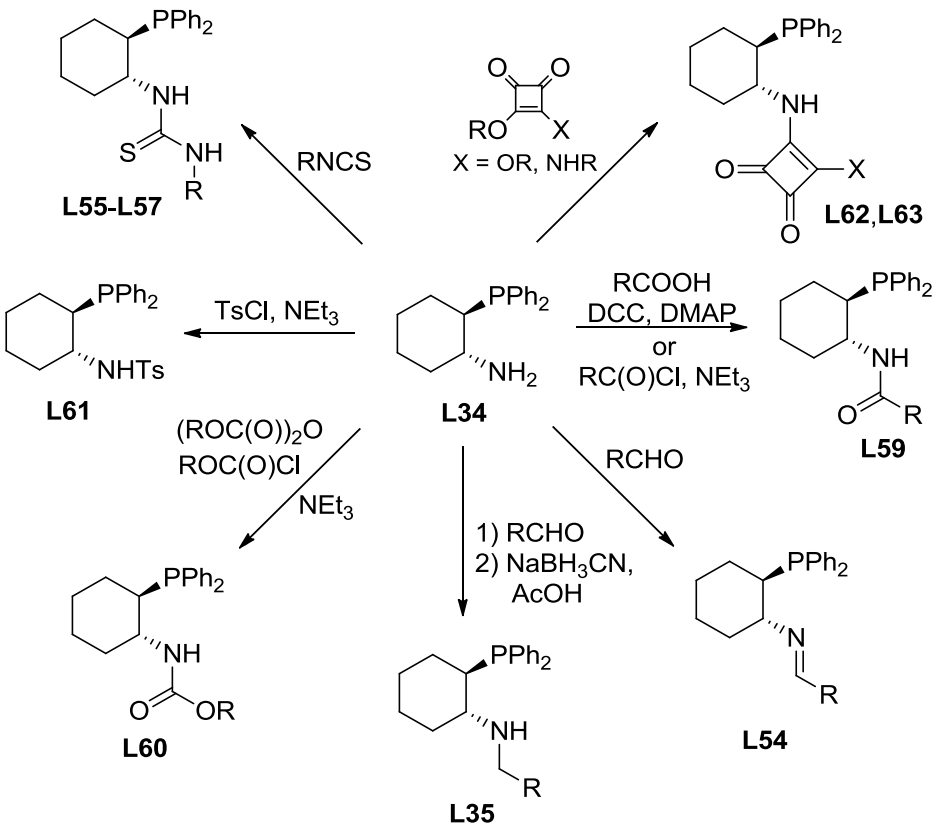
Scheme 64



Yudin *et al.* resolved 2-(diphenylphosphino)cyclohexylamine (**L34**) through its D-tartrate salts by fractional crystallization from water (Scheme 64).[80] The less soluble diastereomer (*R*,*R*)-**L34**-(*S*,*S*)-TA was obtained after two recrystallizations of the precipitate and the free phosphine-amine (*R*,*R*)-**L34** was obtained in 65% yield and >99% ee after treatment with aqueous NaOH solution and extraction with dichloromethane. The more

soluble diastereomer (*S*,*S*)-**L34**-(*S*,*S*)-TA was obtained from the mother liquor after the addition of 5 equiv. of D-tartaric acid and recrystallization of the precipitate from 95% ethanol, and the free phosphine-amine (*S*,*S*)-**L34** was obtained in 21% yield, >99% ee. This has been the primarily method used to obtain **L34** as a universal precursor to a variety of derivatives: thioureas from isothiocyanates,[86,90] squaramides from squarate esters,[95] amides from carboxylic acids,[111] amides from acyl chlorides,[108] imines from aldehydes[111] and secondary amines after imine reduction,[118] carbamates from dicarbonates or acyl chlorides,[109] and *p*-toluenesulfonamide from tosyl chloride[109] (Scheme 65).

Scheme 65



3.1.2.4. Preparation of enantiopure compounds by a stereospecific reaction

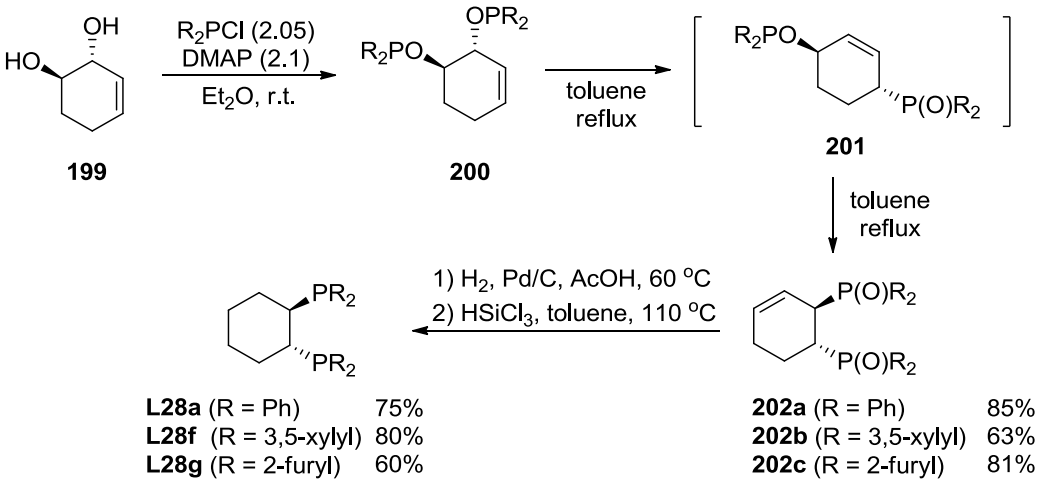
Three types of stereospecific reactions employed to install phosphino groups *en route* to enantiopure *P*,*P*- or *P*,*N*-ligands based on the 1,2-cycloalkylene scaffold have been reported:

1) thermal rearrangement of allyl phosphinites to allylphosphine oxides,[54]
2) nucleophilic substitution on an enantiopure alkyl electrophile by a phosphorus nucleophile,

3) addition to enantiopure electron-deficient bicyclic olefins derived from natural compounds.

Several of the early ligands (NMDPP,[9] Chiraphos,[7a] Prophos,[7b] DIOP,[10] Phellanphos,[64] Nopaphos[64]) were derived from natural compounds or their derivatives. This is a viable approach provided that the precursor is available at a low cost. However, enantiopure precursors can also be obtained synthetically. This approach was taken by Knochel *et al.* who reported on the preparation of bis(phosphino)cyclohexanes (**L28**) from enantiopure cyclohexenediol **199** using thermal rearrangement of cyclic allyl phosphinites to allylphosphine oxides which proceeded stereospecifically.[53,54] The reaction was used to convert the enantiopure cyclohexenediol **199** to the diphosphine dioxide **202** via the formation of the allylic phosphinite **200** in the first step and double rearrangement leading to **202** via the intermediate **201** (Scheme 66). After hydrogenation and phosphine oxide reduction the ligands **L28a**,**f**,**g** were obtained. Alternatively, **202a** could be transformed into **L28b** through the hydrogenation of *P*-phenyl substituents to *P*-cyclohexyl using H_2 and Raney Ni followed by the reduction with trichlorosilane (Scheme 67, eq. 1). **202a** was also transformed into **L32** by a direct reduction (Scheme 67, eq. 2) and into **L33** via Os-catalyzed olefin dihydroxylation, phosphine oxide reduction, and finally ketal formation with 2,2-dimethoxypropane (Scheme 67, eq. 3).[53,54]

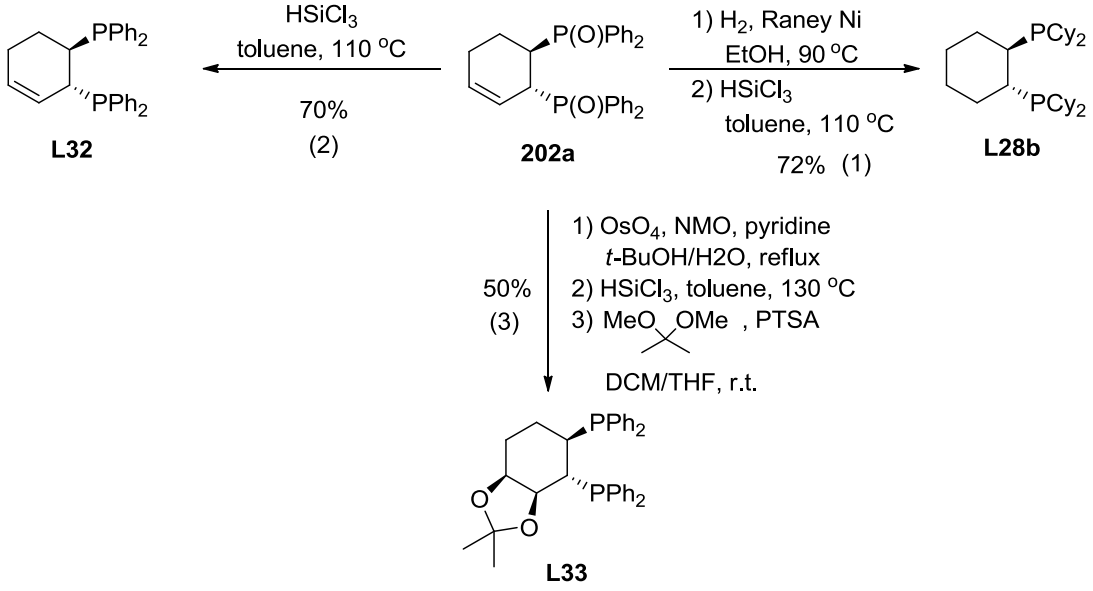
Scheme 66



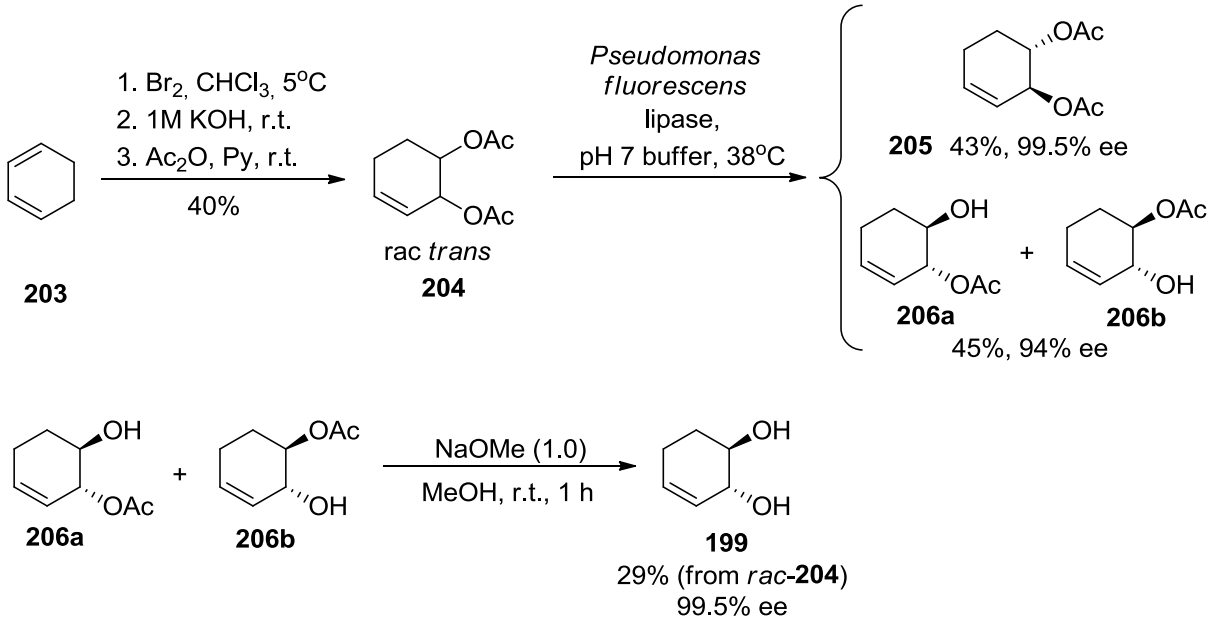
The Knochel's method allows for the synthesis of type **L28** ligands in 4 steps: 1) bis(phosphinite) formation, 2) thermal rearrangement, 3) double bond reduction, 4) diphosphine dioxide reduction, with steps 1-2 done in a one-pot approach. However, the diol **199** is not available commercially and had to be prepared from cyclohexa-1,3-diene **203** in 5

steps as shown in Scheme 68. First, the racemic *trans*-diacetate **204** was obtained by bromine addition and subsequent nucleophilic substitution with hydroxide, finally the diol was esterified with acetic anhydride. **204** was resolved by stereoselective hydrolysis using lipase from *Pseudomonas fluorescens*, the (*S*,*S*)-isomer remained unchanged and the (*R*,*R*)-isomer was converted to a mixture of mono-hydroxy cyclohexenes **206a** and **206b**. The diacetate **205** was separated and both fractions were hydrolyzed to obtain both enantiomers of the diol **199**.

Scheme 67

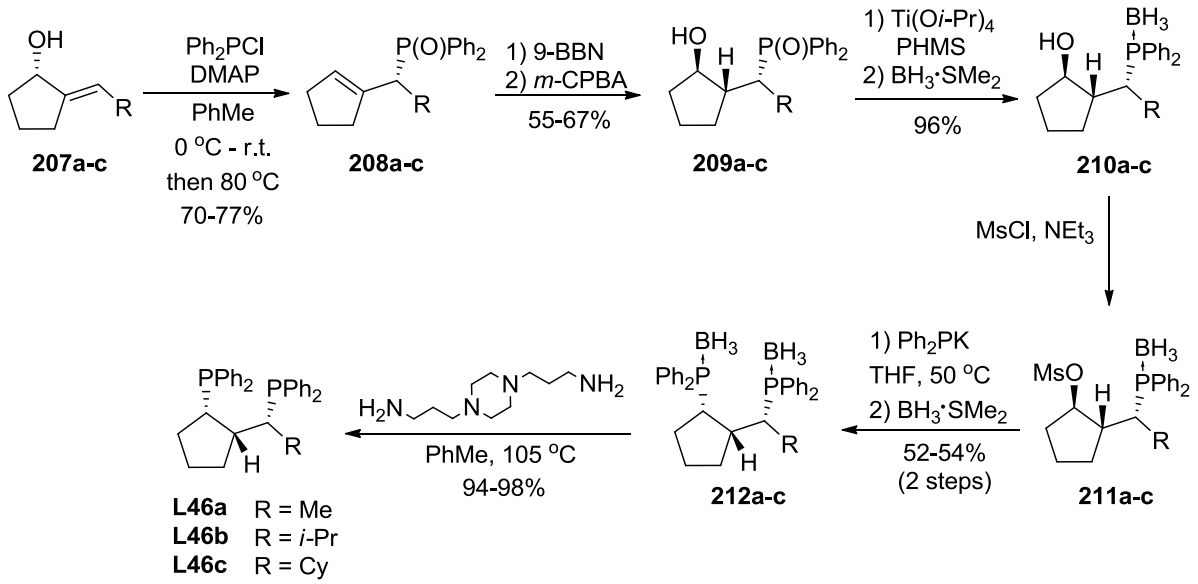


Scheme 68



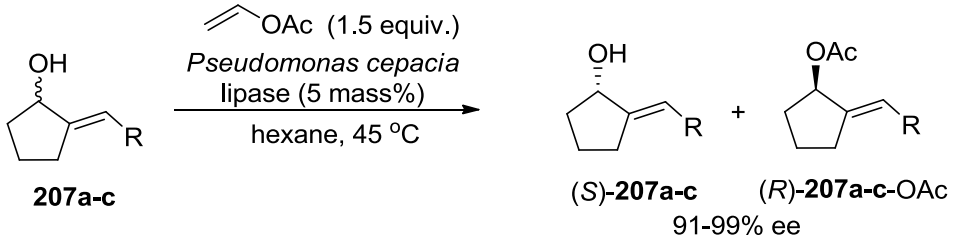
The PPCP analogues **L46a-c** were also prepared by Gavryushin and Knochel taking advantage of the stereospecific thermal rearrangement of allyl phosphinites obtained from the secondary alcohols **207a-c** (Scheme 69).[136] The allylphosphine oxides **208a-c** were then transformed in five steps into the exocyclic phosphine-boranes **211a-c** possessing a mesyloxy group on the cyclopentane ring to set up a nucleophilic substitution with Ph_2PK followed by protection to give diphosphine-diboranes **212a-c** which were eventually deprotected to yield **L46a-c**. The part involving phosphine oxide **209a-c** reduction and phosphine protection with borane to **210a-c** was necessary as the phosphine oxide analogue of **211a-c** decomposed in a reaction with Ph_2PK.

Scheme 69



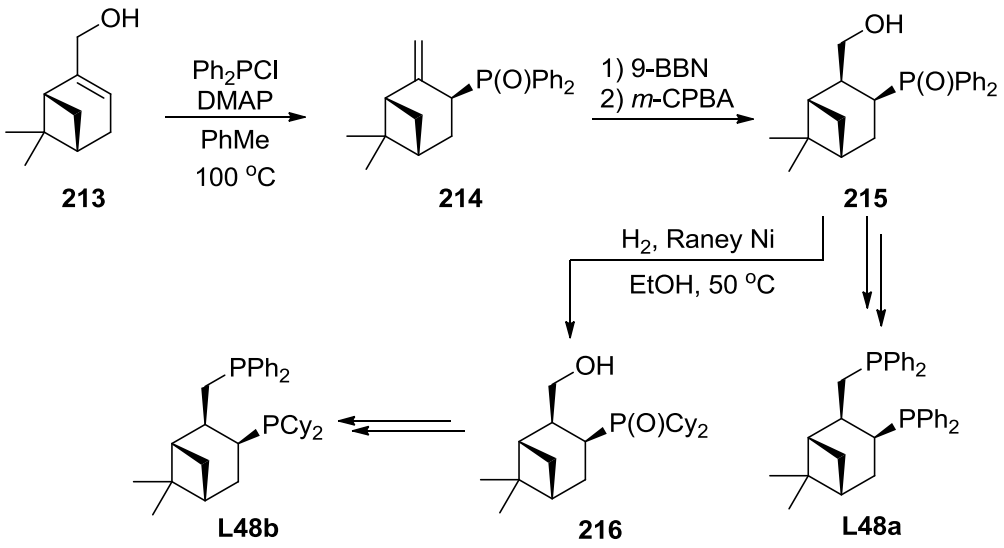
The racemic allylic alcohols **207a-c** were obtained in two steps from cyclopentanone through condensation with an aldehyde and carbonyl group reduction. The racemates were resolved into enantiomers by the enzyme-catalyzed acylation (Scheme 70).[136]

Scheme 70

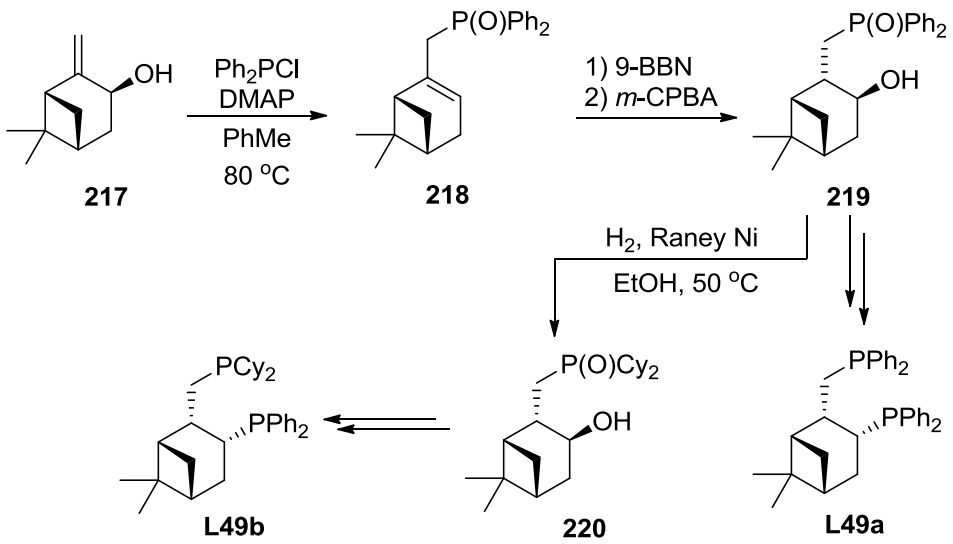


The bicyclic ligands **L48a** and **L48b** were obtained in the same sequence of reactions as **L46a-c** but starting from naturally occurring bicyclic allylic alcohols (-)-myrtenol **213** and (-)-*trans*-pinocarveol **217**, respectively (Scheme 71 and 72).[135,136] The steric hindrance of the dimethylmethylene bridge determined the direction of the nucleophilic attack of the -$OPPh_2$ moiety at the olefin in the rearrangement step and then determined the face of the olefin which reacted with 9-BBN in the hydroboration step. Ligands **L49a** and **L49b** possessing dicyclohexylphosphino groups were prepared from the intermediate alcohols **215** and **219** by the reduction of *P*-phenyl groups using H_2/Raney Ni catalytic system to give **216** and **220** which were then treated in the same manner as their diphenylphosphino counterparts.

Scheme 71

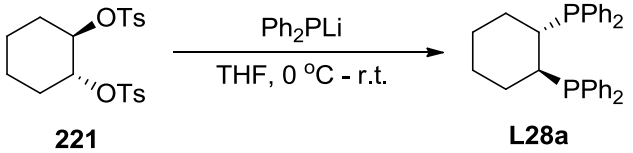


Scheme 72



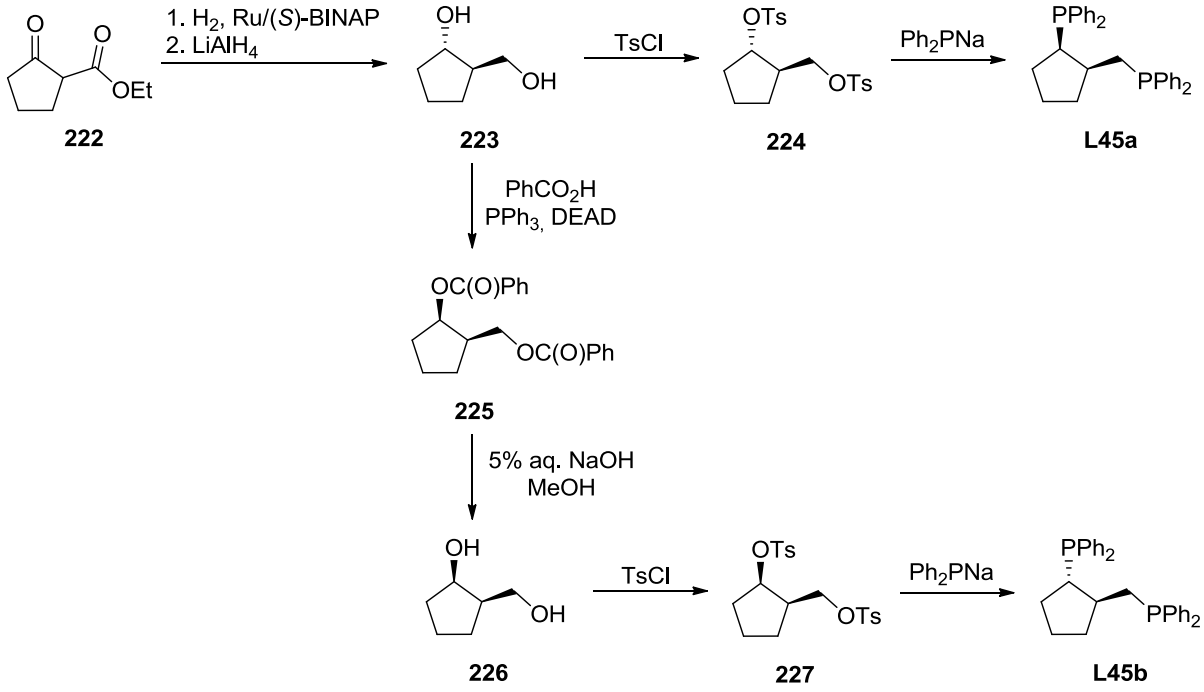
Stereospecific nucleophilic substitution of sulfonate groups by lithium diphenylphosphide was first used by Bosnich *et al.* to prepare Chiraphos and later Prophos.[7] This approach was also reported for the preparation of DPPCY (**L28a**) from (1*R*,2*R*)-*trans*-cyclohexane-1,2-diol ditosylate **221** (Scheme 73)[157] and PPCP (**L45a**) as well its *trans*-epimer (**L45b**) from diols **223** and **226** which were derived from the cyclic ketoester **222** (Scheme 74).[128] The compound **223** was obtained from **222** by Ru/BINAP-catalyzed ketone hydrogenation followed by the ester reduction with LAH, the *cis*-diol **226** was obtained from **223** in two steps using Mitsunobu reaction to invert the configuration at C1 and hydrolysis of the diester **225**.

Scheme 73



221 **L28a**

Scheme 74



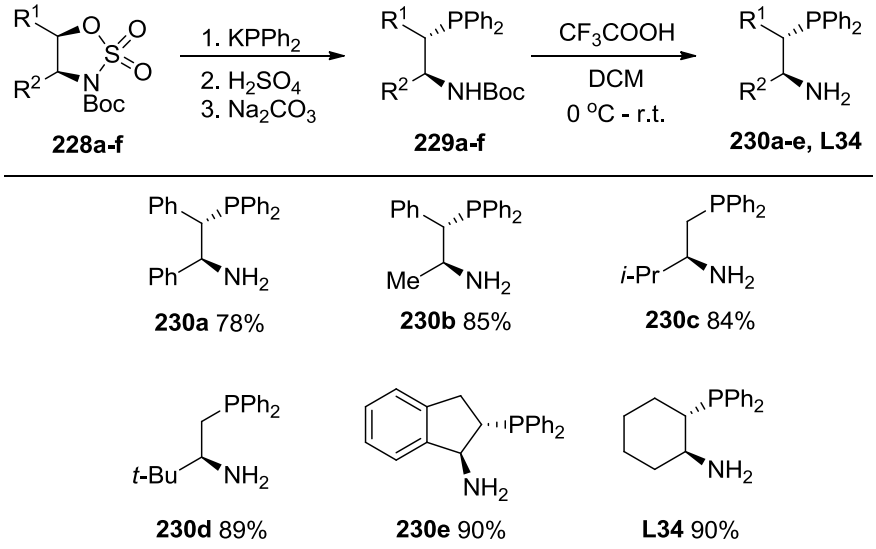
222 **223** **224** **L45a**

225

226 **227** **L45b**

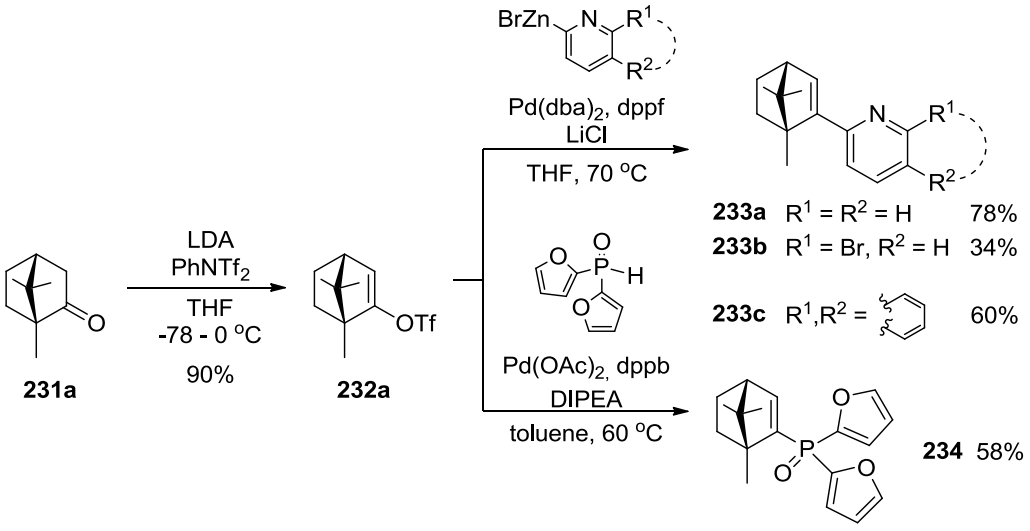
Guo *et al.* described a stereospecific ring-opening substitution of cyclic *N*-Boc sulfamidates **228a-f** derived from chiral aminoalcohols by potassium diphenylphosphide. After deprotection of the amine in **229a-f** both acyclic and cyclic aminophosphines **230a-e** and **L34** were obtained in good to very good yields (Scheme 75).[83]

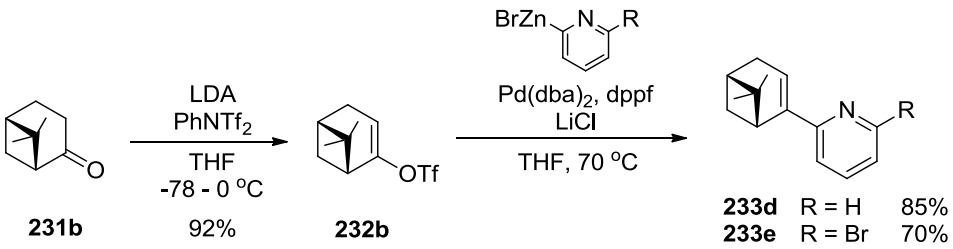
Scheme 75



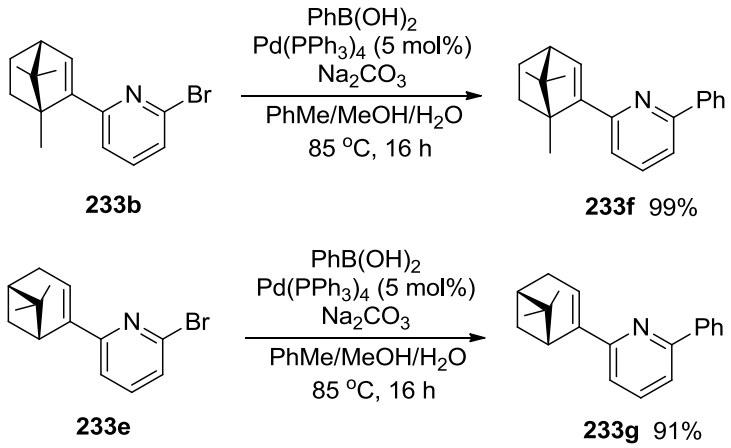
The bicyclic *P*,*P*- and *P*,*N*-ligands **L40**-**L43** reported by Bunlaksananusorn and Knochel were synthesized from electron-deficient olefins **233** and **234** derived from (+)-camphor or (+)-nopinone.[78] First, the bicyclic ketones **231a** and **231b** were transformed into the corresponding enol triflates **232a** and **232b**. These were then subjected to the Pd-catalyzed Negishi cross-coupling with 2-pyridyl- or 2-quinolylzinc bromides to obtain the 2-substituted pyridines **233a**,**b**,**d**,**e** or quinoline **233c**, or Pd-catalyzed C-P cross-coupling with di(2-furyl)phosphine oxide to obtain the cycloalkenylphosphine oxide **234** (Scheme 76). The precursors **233f** and **233g** to the ligands **L41b** and **L43b** possessing the 6-phenylpyridine moiety were obtained by the Pd-catalyzed Suzuki-Miyaura cross-coupling between the 6-bromopyridine intermediates **233b** and **233e** and phenylboronic acid (Scheme 77).

Scheme 76



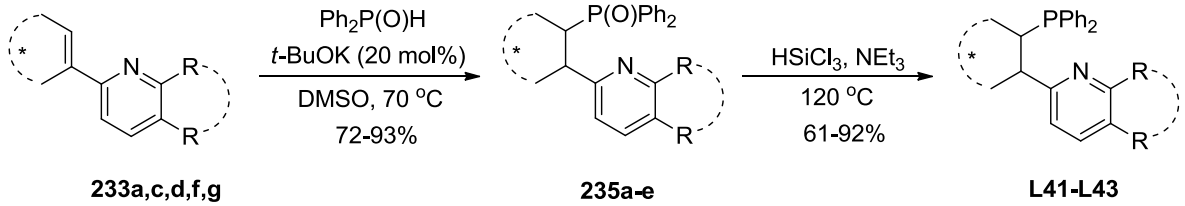


Scheme 77

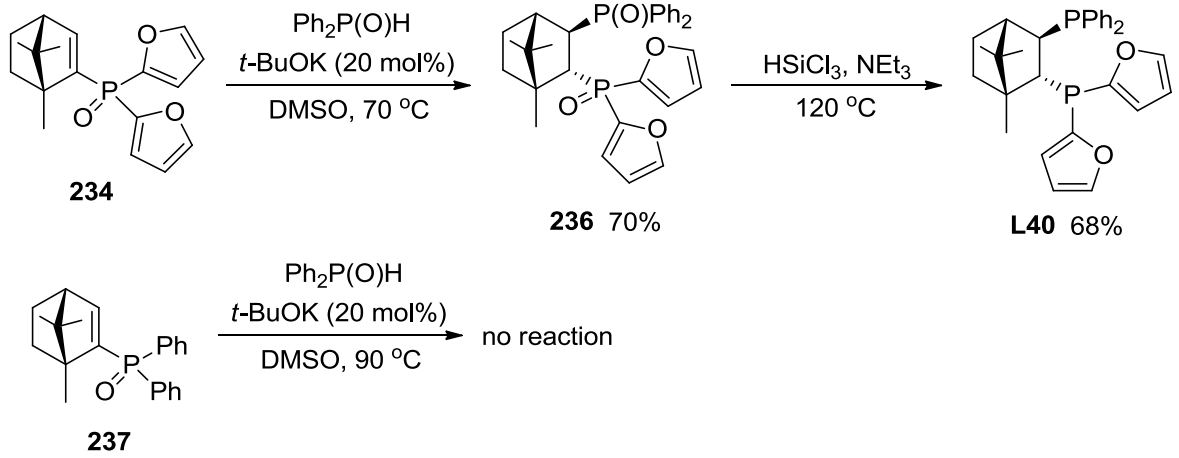


Finally, the cycloalkenyl heteroarenes **233a**,**c**,**d**,**f**,**g** were reacted with diphenylphosphine oxide in the presence of catalytic potassium *tert*-butoxide in DMSO to give phosphine oxides **235a-e** as single diastereomers which after reduction with trichlorosilane yielded the ligands **L41**-**L43** (Scheme 78). The attempted addition reaction of diphenylphosphine oxide to cycloalkenyl(diphenyl)phosphine oxide **234** failed even at a higher temperature of 90 °C, on the other hand the cycloalkenylphosphine oxide **234** possessing smaller 2-furyl substituents at the phosphorus atom reacted satisfactorily to give the diphosphine dioxide **236** in 70% yield, the latter being reduced to **L40** in an analogous manner to *P*,*N*-ligand precursors (Scheme 79).

Scheme 78



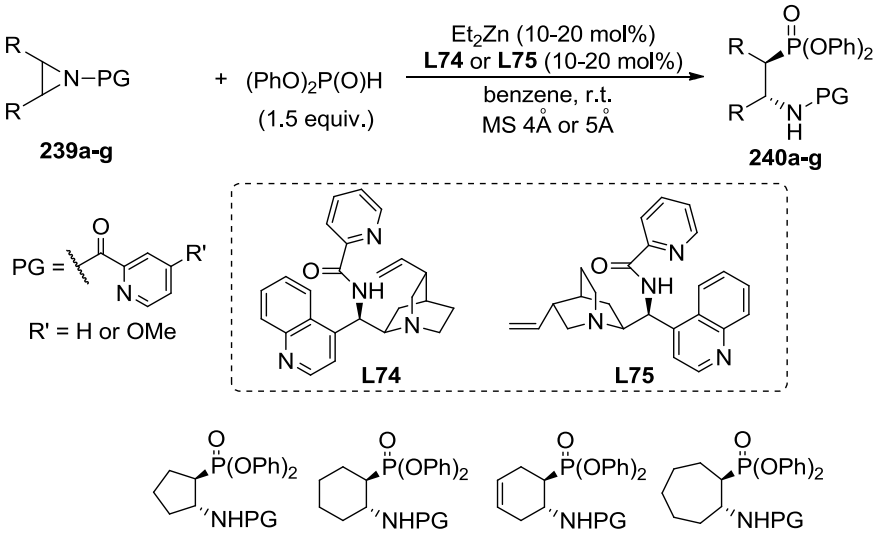
Scheme 79



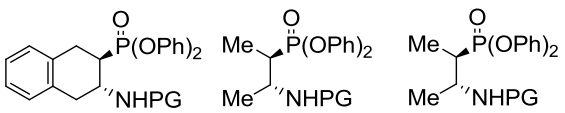
3.1.2.5. Preparation of enantiopure compounds by a stereoselective catalytic reaction

So far only two stereoselective catalytic reactions for the synthesis of C2-functionalized cycloalkylphosphines have been reported, both were devised to access 2-(phosphino)cycloalkylamines.

Scheme 80



ligand	240a	240b	240c	240d
L74	78%, 97% ee	84%, 99% ee	81%, 99% ee	19%, 90% ee
L75	85%, 96% ee	80%, 98% ee	81%, 99% ee	

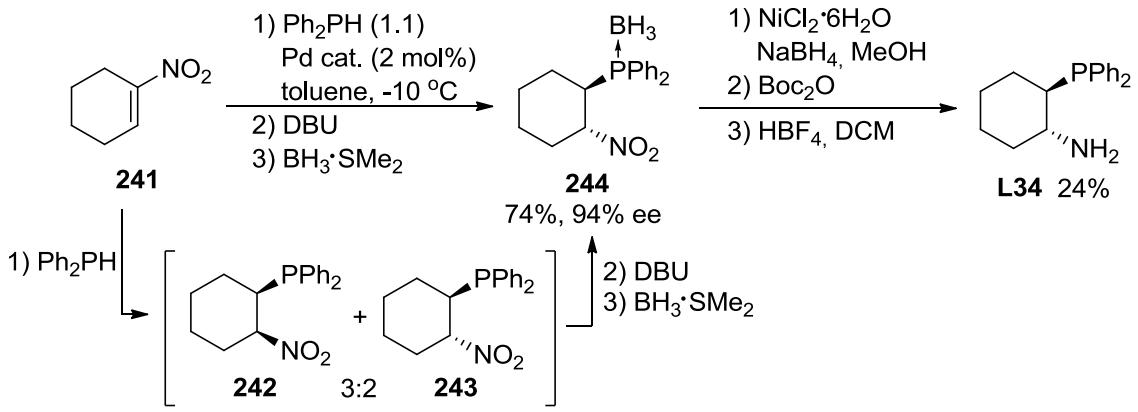


ligand	240e	240f	240g
L74	81%, 98% ee	90%, 99% ee	80%, 95% ee
L75	76%, 98% ee	80%, 97% ee	83%, 95% ee

In 2012 Nakamura *et al.* reported on the asymmetric addition of diphenyl phosphite to activated cyclic and acyclic aziridines **239a-g** catalyzed by Et_2Zn/cinchona alkaloid derivative **L74**/**L75** catalysts (Scheme 80).[84] Ligands **L74** and **L75** were derived from *epi*-cinchonine and *epi*-cinchonidine, respectively, and, despite not being enantiomers, they could be used complementarily to provide products with the (*S*,*S*) or (*R*,*R*)-configuration, respectively, with only small differences in the yield and enantioselectivity. Good yields and very good ee were observed for cyclic aziridines **239a-c**,**e**, whereas **239d** was an exception giving the product with low yield and somewhat lower ee.

Also in 2012, Duan *et al.* reported on the Pd-catalyzed stereoselective addition of diphenylphosphine to nitroalkenes including nitrocyclohexene **241** (Scheme 81).[85] Interestingly, in the case of **241** the reaction gave a 3:2 mixture of *cis* and *trans* isomers **242** and **243**. The *cis* isomer was isomerized by DBU and after protection with borane the phosphine-borane **244** was obtained in74% yield and 94% ee. It was transformed into **L34** in three steps in 24% yield.

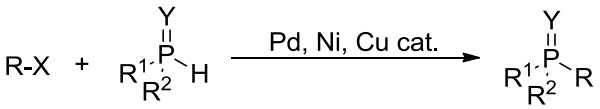
Scheme 81



3.2. C-P cross-coupling

C-P cross-coupling, also commonly referred to as Hirao cross-coupling, is a transition metal-catalyzed cross-coupling reaction between a phosphorus (pro)nucleophile and an aryl/alkenyl/alkynyl electrophile (Scheme 82). Originally developed by Hirao in early 1980's under palladium catalysis, since then the reaction has been improved by tailoring the catalytic system to specific groups of substrates, lowering the catalyst loading, and extending the pool of phosphorus and aryl/alkenyl coupling partners. With the renaissance of interest in cheaper transition metals at the turn of the century, protocols employing copper and nickel catalysts have also been developed and although they typically lack the generality of the palladium-catalyzed reactions, their cost-efficiency and complementariness to palladium often makes them the method of choice for reactive substrates. C-P cross-coupling is one of the most versatile C(sp^2)-P bond-forming reactions, complementary to nucleophilic substitution at electrophilic phosphorus with organometallics, and still remains an active field of research. Several reviews and book chapters have been published covering the broad subject of C-P cross-coupling.[158,203] This chapter discusses the progress made in the field of C-P cross-coupling since its development and the current state-of-the-art. However, it is specifically aimed to focus on the protocols that have been tested for the cross-coupling of phosphorus nucleophiles with cycloalkenyl electrophiles.

Scheme 82



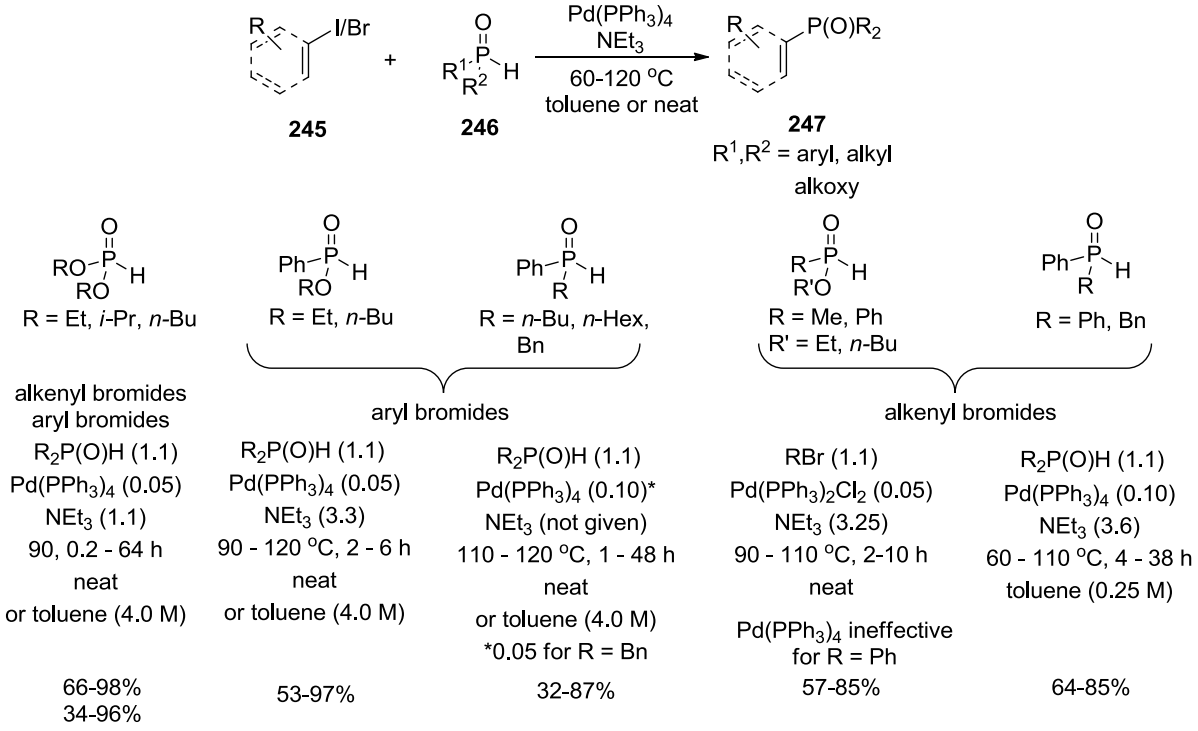
R = aryl, alkenyl
X = I, Br, Cl, CN
OSO_2R, OC(O)R
R^1, R^2 = aryl, alkyl, alkoxy
Y = O, BH_3, lone pair

The C-P cross-coupling reaction was first reported by Hirao *et al.* for dialkyl *H*-phosphonates and alkenyl bromides or aryl bromides,[159] and then expanded in the following years to *H*-phosphinates and secondary phosphine oxides in the works of Xu *et al.* (Scheme 83).[160] The original Hirao protocol employed $Pd(PPh_3)_4$ as the precatalyst and triethylamine as the base and the reactions were typically carried out with a slight excess of phosphonates (10-20%), neat or in the case of solid aryl bromides with a small volume of toluene added. Xu noted that for the reactions of *n*-butyl and *n*-hexyl(phenyl)phosphine oxides 10 mol% of

$Pd(PPh_3)_4$ was required and speculated that this was due to the disproportionation of secondary phosphine oxides to the corresponding secondary phosphines and phosphinic acids.[160b] Also, in the cross-coupling of *H*-phosphinates with alkenyl bromides it was found that $Pd(PPh_3)_4$ was ineffective for alkyl phenylphosphinates and $Pd(PPh_3)_2Cl_2$ was required.[160d]

Regarding the scope of electrophiles, among aromatic compounds, aryl bromides were primarily studied and the only aryl iodide tested was iodobenzene. No meaningful difference in the yield was noted between bromobenzene and iodobenzene. The scope of the reaction was broad and included *ortho*- and *para*-substituted bromoarenes with electron-donating and electron-withdrawing substituents as well as 3-bromopyridine and 2-bromothiophene. Among alkenyl halides only alkenyl bromides were tested and these included α-bromo- and β-bromostyrenes, *E*- and *Z*-bromopropenes, 1-bromo-2-methylprop-1-ene, and methyl 3-bromomethacrylate.

Scheme 83



3.2.1. Pd-catalyzed C-P cross-coupling

The Hirao's protocol, unmodified or with slight modifications, has been shown to work for different combinations of coupling partners, including reactions of:

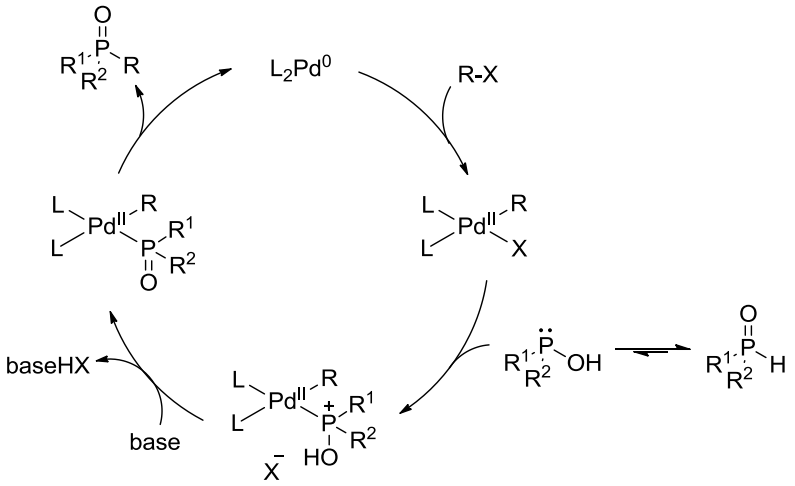
- secondary phosphine oxides with aryl iodides/bromides,[160b,c;170,178]
- dialkyl *H*-phosphonates with aryl iodides/bromides,[158] aryl chlorides/triflates,[164c] alkenyl triflates,[174] and aryl mesylates/tosylates,[176]
- alkyl alkyl/aryl-*H*-phosphinates with aryl iodides/bromides[160a,d;164d,e] and alkenyl triflates,[232,233]
- secondary phosphine-boranes and phosphinite-boranes with aryl iodides[162] and aryl/alkenyl triflates/tosylates,[227-229]
- secondary phosphines with aryl iodides/bromides/chlorides,[177]
- hypophosphorous acid or anilinium hypophosphite and aryl iodides/bromides/triflates.[164a,b]

Typical alterations to the original protocol include the introduction of a solvent (from non-polar aromatics such as toluene and benzene, through ethereal solvents such as THF and dioxane, to dipolar aprotic solvents such as acetonitrile, DMF and DMSO) and change of the base to DIPEA, DABCO, *N*-methylmorpholine, propylene oxide, K_2CO_3 or Cs_2CO_3.[158] Despite the applicability to a variety of coupling partners, $Pd(PPh_3)_4$ has been found to be inferior to catalysts generated from a Pd(II) source and bidentate diphosphine ligands in terms of scope and activity.[158]

Mechanistically, Pd-catalyzed C-P cross-coupling works in an analogous manner to other carbon-heteroatom cross-coupling reactions with the catalytic cycle starting with Pd^0 and the cycle steps are: 1) oxidative addition to aryl/alkenyl (pseudo)halide, base-assisted ligand exchange consisting of 2) halide displacement by the P(III) form of the phosphorus coupling partner and 3) deprotonation by the weak base, and finally 4) reductive elimination (Scheme 84).[179] Thus, some limitations of the reaction are the consequence of the difficulty of the formation of L_2Pd^0 complex and its reactivity towards aryl/alkenyl (pseudo)halides. The general order of organic halide reactivity in the oxidative addition is: iodides > bromides > chlorides, and electron-deficient substrates are more reactive. The ligand exchange starts with the coordination of the P(III) form to the metal center and thus the equilibrium between the P(III) and P(V) tautomers plays an extremely important role as well.[179a] The reactions of *H*-phosphonates and *H*-phosphinates are often complicated by the *P*-oxidation to the corresponding phosphonic and phosphinic acids via the P(III) form and *O*-dealkylation.[164c-e] Among secondary phosphine oxides and *H*-phosphinates, substrates possessing *P*-alkyl substituents are generally less efficient.[164d,164e,169] The electronic effect of the aryl ligand on the reductive elimination step has been found to be opposite for *H*-phosphonates and

secondary phosphines. In the case of *H*-phosphonates electron-rich aryl groups increase the rate of reductive elimination,[180] contrary to cross-coupling of secondary phosphines,[181] amines,[182] alcohols,[182] and thiols[182] for which reductive elimination is faster with electron-withdrawing aryl groups. Reductive elimination is also accelerated by diphosphine ligands with a large bite angle[180] and the addition of ionic additives, especially acetate, increases the rate of the ligand exchange step.[179b]

Scheme 84



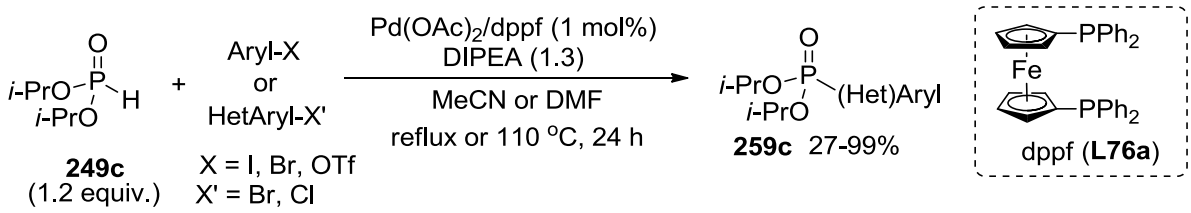
The research in the field of C-P cross-coupling has been focused on solving the problems with the reactivity of certain groups of organophosphorus compounds, extending aryl/alkenyl coupling partners to less reactive chlorides and sulfonates, lowering the catalyst loading, lowering the reaction temperature, and finding cheaper and greener catalysts.

Montchamp *et al.* reported on an updated protocol for the cross-coupling of diisopropyl phosphonate with aryl and heteroaryl (pseudo)halides using $Pd(OAc)_2$/dppf as the precatalyst at 1 mol% loading.[164c] Diisopropyl phosphonate rather than diethyl phosphonate and DIPEA instead of triethylamine were used to limit undesired *O*-dealkylation. Most reactions worked well in acetonitrile but some required DMF (Scheme 85).

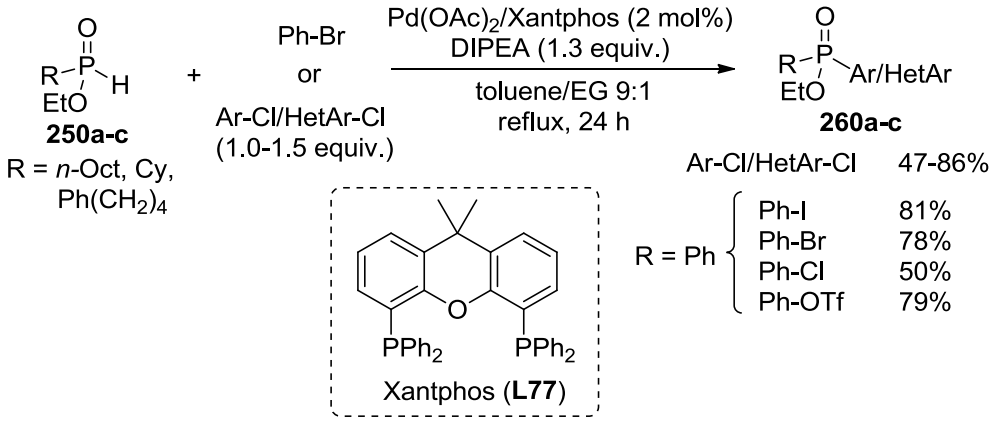
H-phosphinates are a difficult class of substrates due to an unfavourable equilibrium between the P(V) and P(III) forms, and alkyl alkyl-*H*-phosphinates are particularly problematic as the *P*-alkyl substituent further destabilizes the P(III) form. A reaction between ethyl *n*-octylphosphinate and bromobenzene with the Pd/dppf catalyst gave only low yields below 30% regardless of the solvent used. Montchamp *et al.* discovered that ethylene glycol as a co-solvent additive dramatically increased the yield of the cross-coupling, the effect was

the most pronounced with toluene but was also large for polar solvents.[160d,e] The best combination of the ligand and solvent/additive was the Pd/Xantphos catalyst in toluene/EG 9:1 and Pd/dppf in toluene/dimethoxyethane (DME) 9:1. The Pd/Xantphos catalytic system was found to work in the cross-coupling of ethyl alkylphosphinates with aryl and heteroaryl chlorides although the yields were mostly moderate (Scheme 86). With ethyl phenylphosphinate, iodobenzene, bromobenzene and phenyl triflate all gave similar results and chlorobenzene was less efficient. The authors speculated that the additive promotes the equilibrium shift to the P(III) form and/or stabilizes the Pd catalyst, the same positive effect was earlier noticed in Pd-catalyzed hydrophosphinylation.[165]

Scheme 85



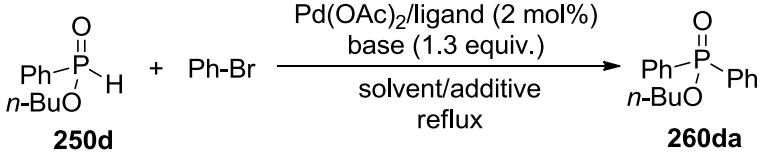
Scheme 86



Arylphosphinates are slightly more reactive than alkylphosphinates as the *P*-aryl substituent has a stabilizing effect on the P(III) form. The additives did not show as much of a positive effect on the reaction of *n*-butyl phenylphosphinate with bromobenzene. Nonetheless, with the Pd/Xantphos catalyst the yield in the presence of 10% EG was still higher than in the absence of it.[164d] The reactivity of the system heavily depended on the right combination of the ligand, solvent and additive. With the Pd/xantphos in toluene/EG 9:1 pyridine was the optimal base, on the other hand, the Pd/dppf worked better with propylene oxide in toluene/DME 9:1. Both catalysts could be used as effectively with DIPEA as the base when

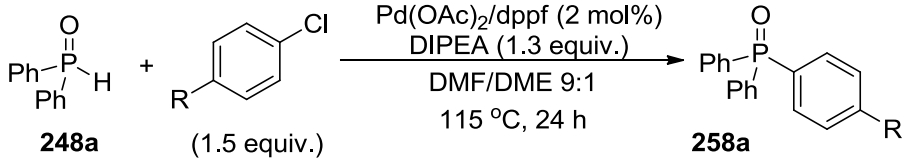
DME was the only solvent (Scheme 87). The Pd/dppf catalytic system was also found to catalyze the cross-coupling of activated aryl chlorides with diphenylphosphine oxide, with chlorobenzene the yield was acceptable only when 3.0 equiv. of the chloride were used (Scheme 88).[164d]

Scheme 87



Ligand	Solvent/additive	Base	Yield
Xantphos (**L77**)	PhMe	DIPEA	70%
	PhMe/EG 9:1	DIPEA	80%
	PhMe/EG 9:1	pyridine	92%
	DME	DIPEA	94%
dppf (**L76a**)	PhMe/DME 9:1	pyridine	30%
	PhMe/DME 9:1	propylene oxide	96%
	DME	DIPEA	92%

Scheme 88



	Isol. yield
R = H	36%[a], 78%[b]
R = CN	96%
R = CF_3	93%
R = CO_2Et	96%

[a] ^{31}P NMR yield

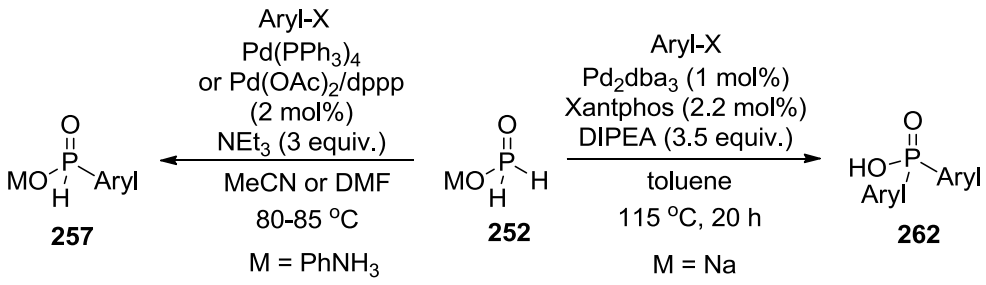
[b] 3.0 equiv. PhCl

Another problematic phosphorus compound in the cross-coupling is hypophosphorous acid due to its strong reducing properties and thermal instability towards decomposition to phosphine and phosphorous acid. It requires strictly inert and anhydrous conditions and does not tolerate heating.[164a] It is available commercially only as a 50% aq. solution that requires water evaporation.[173,174] Schwabacher *et al.* developed a protocol for the cross-coupling of methyl hypophosphite generated *in situ* from hypophosphorous acid and excess trimethyl orthoformate which stabilizes the hypophosphite ester in solution, otherwise

it is unstable and decomposes even at 0 °C.[163] However, this approach only partially circumvents the problems associated with the use of hypophosphorous acid.

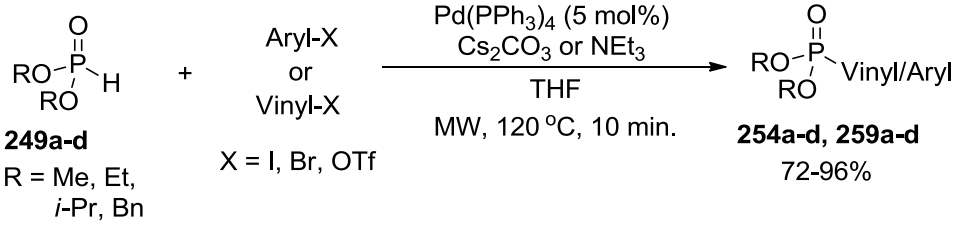
More elegant solutions became available from the groups of Montchamp and Deelman (Scheme 89). Montchamp discovered that anilinium hypophosphite is a convenient surrogate for hypophosphorous acid as it is a cheap, non-hygroscopic solid with a high melting point and reacts with aryl iodides, bromides, and triflates with the $Pd(PPh_3)_4$ precatalyst, and with $Pd(OAc)_2$/dppp it reacts with alkenyl bromides and triflates, and 4-chlorobenzonitrile.[164a,b] More recently Deelman *et al.* showed that sodium hypophosphite monohydrate was a convenient coupling partner under the Pd/Xantphos catalysis to make diarylphosphinic acids.[166]

Scheme 89



Kalek and Stawiński introduced microwave heating as a way to increase the rate of C-P cross-coupling. Dialkyl *H*-phosphonates were coupled with aryl/alkenyl iodides, bromides and triflates using $Pd(PPh_3)_4$ and Cs_2CO_3 or NEt_3 as the base, and microwave heating for 10 min. at 120 °C (Scheme 90).[167] Similarly, anilinium hypophosphite could be coupled in high yields with aryl iodides and bromides affording monoaryl- or diarylphosphinic acids with the Pd/Xantphos catalyst at a loading as low as 0.1 mol% and in short reaction times (10-15 min.).[168]

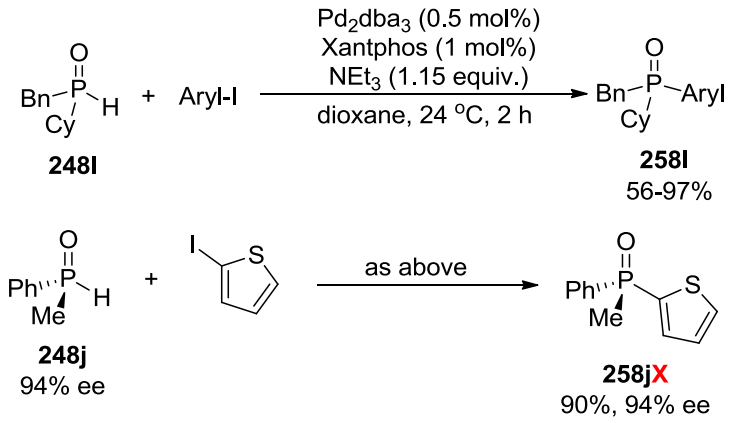
Scheme 90



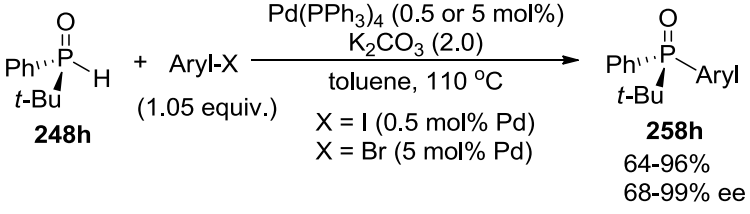
Bloomfield and Herzon discovered that the Pd/Xantphos complex generated from Pd_2dba_3 and the ligand was a highly active catalyst for the cross-coupling of secondary phosphine oxides and aryl iodides at room temperature (Scheme 91).[169] The reaction afforded high yields of the products even for dialkylphosphine oxides. In the model reaction of dimethylphosphine oxide and iodobenzene the ligands Xantphos, dppf, BINAP, and Josiphos gave the product in 97%, 85%, 2% and 0%, respectively. The reaction of enantiopure methyl(phenyl)phosphine oxide with 2-iodothiophene proceeded with complete stereoretention.

As early as 1986 Xu *et al.* discovered that the Pd-catalyzed C-P cross-coupling was stereoretentive for enantiopure isopropyl methylphosphinate with respect to the configuration at the phosphorus atom and the compound could be reacted with aryl and alkenyl bromides to give products with >97% ee.[161] In 2018 Chrzanowski *et al.* reported that $Pd(PPh_3)_4$ in the presence of K_2CO_3 as the base was a highly effective catalyst for the reactions of enantiopure *tert*-butyl(phenyl)phosphine oxide with a series of functionalized (hetero)aryl iodides and bromides affording products with moderate to excellent enantioselectivity. The catalyst loading was 0.5 mol% and 5.0 mol% for aryl iodides and bromides, respectively (Scheme 92).[170]

Scheme 91

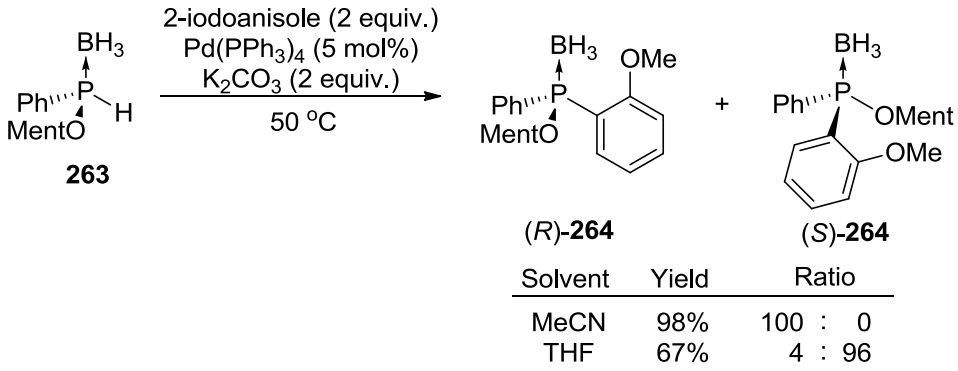


Scheme 92

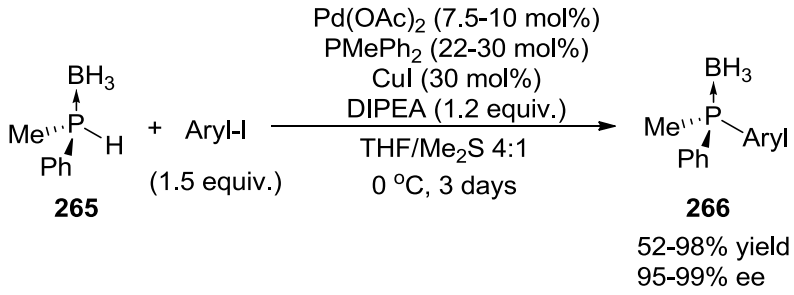


Imamoto *et al.* discovered that enantiopure menthyl phenyl-*H*-phosphinite-borane[162a] and *tert*-butyl(aryl)phosphine-boranes[162b,c] could be coupled stereoselectively with retention or inversion of the configuration at the phosphorus atom depending on the solvent used (Scheme 93). When K_2CO_3 was used as the base, complete retention was observed in acetonitrile, less polar solvents such as THF, dioxane, and toluene were associated with inversion and the selectivity was the highest in THF. Interestingly, when Ag_2CO_3 was used as the base, stereoretention was observed even in THF and toluene. The lowest operating temperature in the Imamoto's protocol was 50 ^oC. Livinghouse et al. found that the reaction temperature for secondary phosphine-boranes could be lowered to 0 ^oC by introducing a Cu(I) co-catalyst and the reactions proceeded with excellent stereoretention (Scheme 94).[171]

Scheme 93



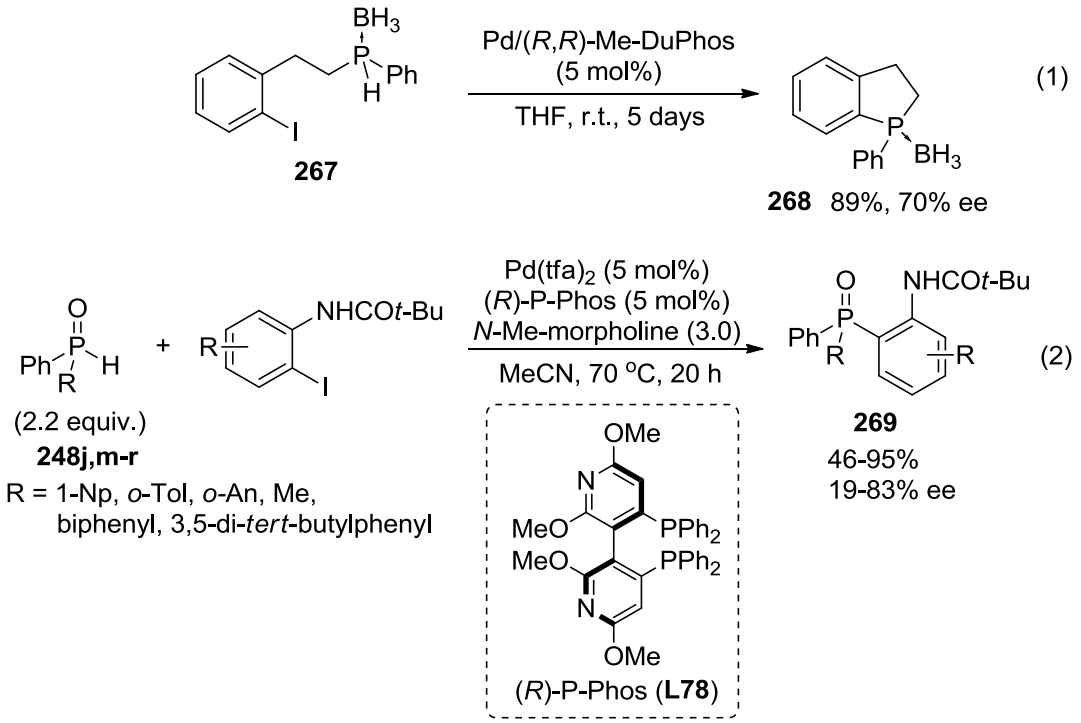
Scheme 94



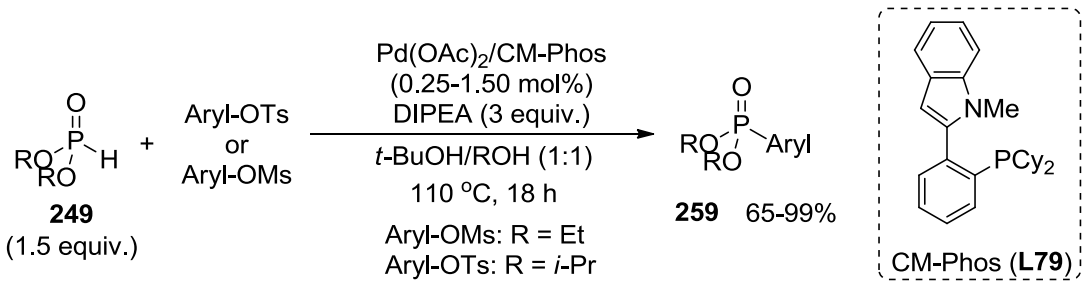
Stereoselective C-P cross-coupling reactions of racemic organophosphorus reagents are rare. Glueck *et al.* carried out cross-coupling of racemic secondary methylphosphines possessing bulky aryl or menthyl substituents with aryl (pseudo)halides.[172a] Aryl iodides were the most effective, however, the stereoselectivity of the reaction varied greatly (7-91% ee) and was highly dependent on the aryl iodide with electron-rich substrates producing higher ee and

electron-poor substrates producing lower ee relative to iodobenzene. The authors also reported on the intramolecular variant using the secondary phosphine-borane possessing 2-iodophenethyl substituent (Scheme 95, eq. 1) or the corresponding secondary phosphine obtaining the products with 70% ee and 63% ee, respectively.[172b] Cai *et al.* developed a kinetic resolution protocol for reactions of phenyl(aryl)- and phenyl(methyl)phosphine oxides with 2-iodo-*N*-pivaloylanilines, poor to moderately good enantioselectivty was observed (Scheme 95, eq. 2).[175]

Scheme 95



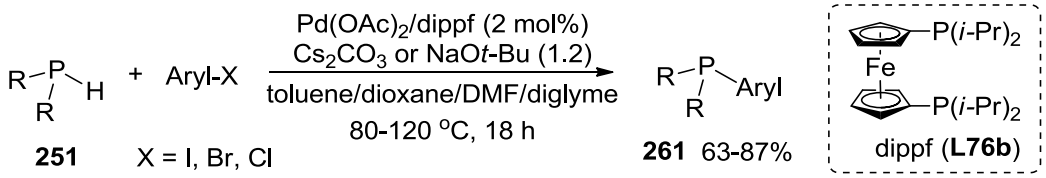
Scheme 96



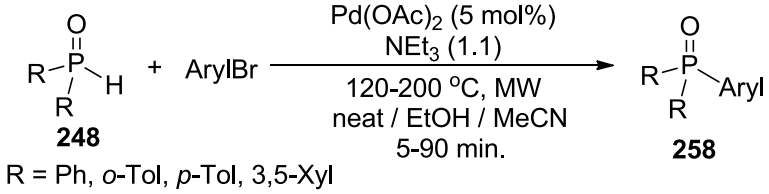
By using a more sophisiticated ligand, Kwong *et al.* extended the cross-coupling of *H*-phosphonates to aryl tosylates and mesylates (Scheme 96).[176] Buchwald *et al.* reported that the less popular Pd/dippf catalyst was effective in the cross-coupling of secondary phosphines

with aryl halides (Scheme 97).[177] Keglevich *et al.* found that *H*-phosphonates, *H*-phosphinates and secondary phosphine oxides can be coupled with bromobenzene without an external ligand, participating in the reaction as the reducing agent for Pd(II) and the ligand for Pd(0) (Scheme 98).[178]

Scheme 97



Scheme 98

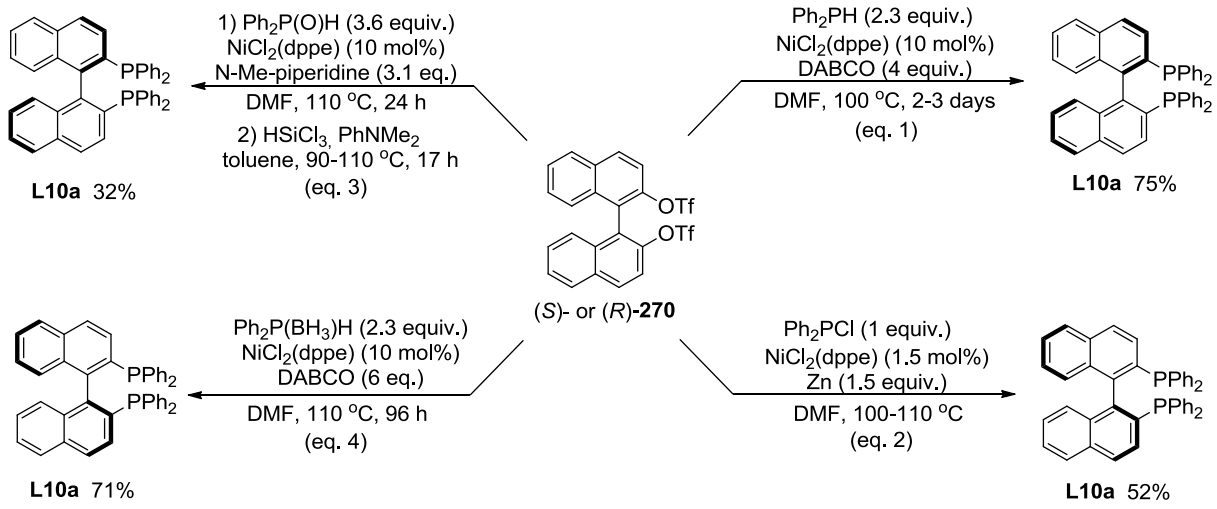


3.2.2. Ni-catalyzed C-P cross-coupling

Ni-catalyzed C-P cross-coupling was first reported in 1994 by Cai *et al.*[183] In an attempt to synthesize (*R*)-BINAP via cross-coupling of enantiopure (*R*)-BINOL ditriflate and diphenylphosphine, the $Pd(OAc)_2$/dppb catalyst failed to give any product. On the other hand a series of Ni(II) complexes proved to be successful at the task with $NiCl_2$(dppe) being the best (Scheme 99, eq. 1). A few years later Laneman *et al.* reported on the cross-coupling of aryl and alkenyl triflates and bromides with chlorodiphenylphosphine. The reaction was carried out in the presence of zinc which played a dual role reducing the Ni(II) precatalyst to the active form and reducing chlorophosphine to (diphenylphosphino)zinc chloride Ph_2PZnCl. The method was applied to (*S*)-BINOL ditriflate and (*S*)-BINAP was obtained in 52% yield (Scheme 99, eq. 2).[184] In an alternative approach developed by N. Sayo *et al.* (*R*)-BINOL ditrifilate was reacted with diphenylphosphine oxide under nickel catalysis which led to a mixture of diphosphine and monophosphine-monooxide which was then reduced using trichlorosilane (Scheme 99, eq. 3).[185] In all cases the reactions afforded the products with no loss of optical purity. However, from the perspective of the chemical industry the first two reactions are problematic due to the implemention of highly sensitive and toxic organophosphorus substrates, and a serious disadvantage of the third method is the reduction

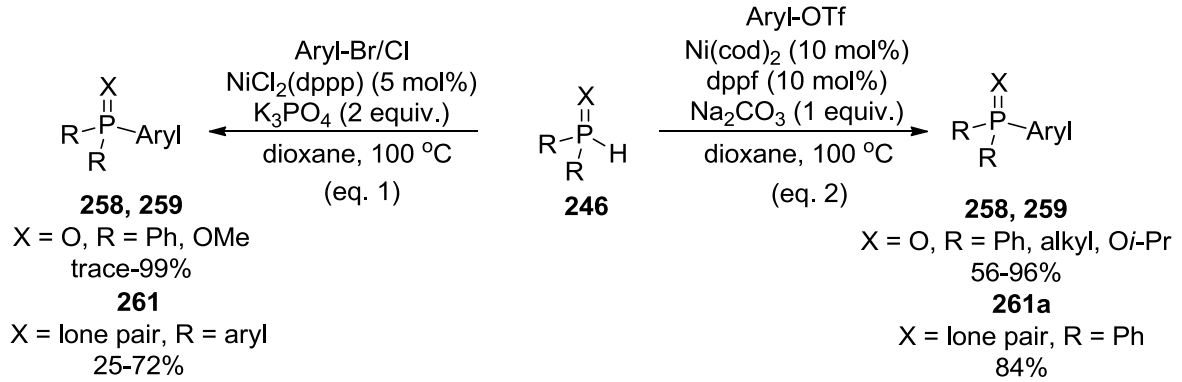
step. To overcome these problems a protocol employing secondary phosphine-boranes as substrates and affording diphosphines as products was developed at Takeda (Scheme 99, eq. 4).[186]

Scheme 99



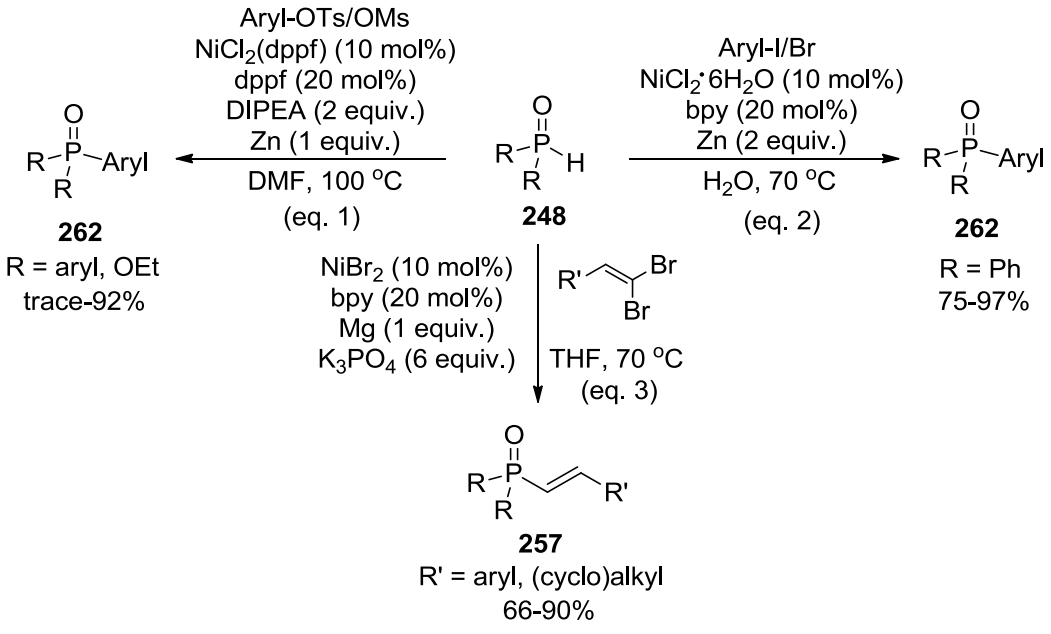
Nickel catalysis primarily excels at the C-P cross-coupling of less active substrates such as aryl chlorides,[187,188] phenol-derived C-O electrophiles such as sulfonates,[189,190] carboxylates,[192] carbamates,[192] carbonates,[192b] and nitriles.[193,194] However, protocols of general utility for aryl bromides[188] and aryl triflates[189] have also been reported (Scheme 100). $NiCl_2$(dppp) was found to be an efficient catalyst for the reactions of diphenylphosphine oxide, dimethyl phosphonate, and diphenylphosphine with aryl bromides and chlorides (Scheme 100, eq. 1).[188] Aryl triflates were coupled with diphenyl-, phenyl(alkyl), dialkylphosphine oxides, diisopropyl phosphonates and diphenylphosphine using the $Ni(cod)_2$/dppf catalytic system (Scheme 100, eq. 2).[189]

Scheme 100



The mechanism of Ni-catalyzed C-P cross-coupling has not been studied as extensively as its Pd-catalyzed counterpart. Mechanisms involving the Ni(0)/Ni(II) catalytic cycle analogous to Pd-catalyzed reactions have been proposed,[188,194,196] however, few publications included experimental data as evidence.[200] In 1980 Balthazor and Grabiak reported on Ni-catalyzed Arbuzov-type reaction between $P(OEt)_3$ and aryl iodides, and showed that $NiCl_2$ was reduced in the presence of excess triethyl phosphate to $Ni^0[P(OEt)_3]_4$. This compound functioned as an effective catalyst for the cross-coupling of $P(OEt)_3$ with aryl iodides, however, as with $NiCl_2$ a very high temperature of 130-140 ^oC was required.[201] Han *et al.* proposed that in the $NiCl_2$(dppp)-catalyzed cross-coupling the bidentate ligand facilitated the reduction of Ni(II) to Ni(0) by the *H*-phosphonate or secondary phosphine oxide. This was based on the observation of solubilisation of the nickel precatalyst and yellow colour of the obtained solution upon the addition of a $R_2P(O)H$ compound, and XPS analysis of the formed species.[188] Gao *et al.* carried out calculations supporting the Ni(0)/Ni(II) catalytic cycle for the cross-coupling of β-bromostyrene and diphenylphosphine oxide.[196]

Scheme 101

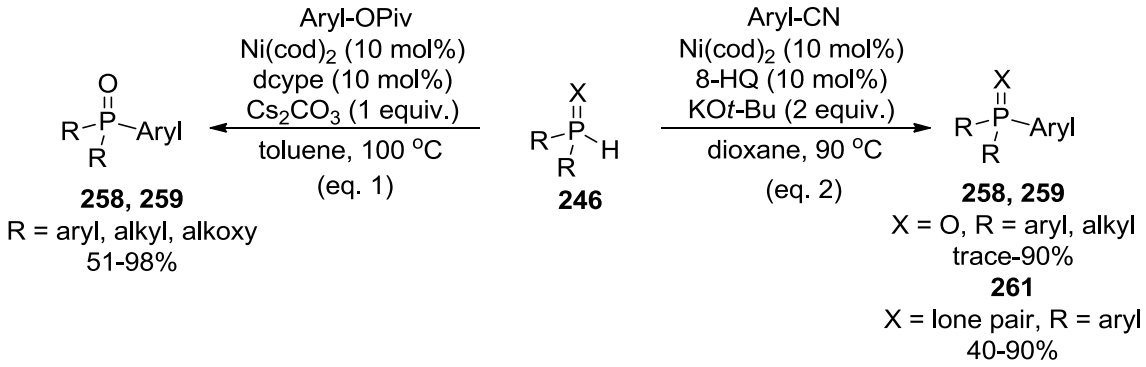


A common disadvantage of a number of Ni-catalyzed protocols is the requirement of an external reducing agent, such as zinc[190,191] or magnesium,[196] to reduce Ni(II) to Ni(0) *in situ*. The Zhang's protocol for the coupling of aryl tosylates and mesylates required both an external reducing agent and excess ligand despite using preformed $NiCl_2$(dppf) as the precatalyst (Scheme 101, eq. 1).[190] The Tang's protocol for aryl iodides and bromides[191] and

Gao's protocol for dibromoalkenes[196] both used a Ni(II) salt as a precatalyst in the presence of bipyridine as the ligand and a metal reducing agent (Scheme 101, eq. 2-3). Recently Keglevich *et al.* performed calculations of the ligand-free $NiCl_2$-catalyzed cross-coupling between diphenylphosphine oxide or diethyl phosphite with bromobenzene which pointed to a Ni(II)/Ni(IV) catalytic cycle with prohibitively high energetic barrier found for Ni(II) reduction by $R_2P(O)H$ compounds.[199]

The protocols employing $Ni(cod)_2$ are more robust as they only require a stoichiometric amount of a ligand to form the Ni(0) catalyst. Catalysts generated *in situ* from $Ni(cod)_2$ and DCYPE or 8-hydroxyquinoline (8-HQ) were effectively used for the C-P cross-coupling with aryl pivalates[192] and aryl nitriles,[193] respectively (Scheme 102). However, $Ni(cod)_2$ is a rather unstable complex sensitive to air, water, light and heat, and requires storage in the freezer and manipulation under strictly inert and anhydrous conditions. No stereoselective reactions of racemic organophosphorus substrates have been reported so far under Ni catalysis, however, the cross-coupling of optically pure menthyl phenylphosphinate and 4-bromobenzene was shown to be stereoretentive with the Tang's protocol.[191] Yang *et al.* showed that the cross-coupling of 2-naphthyl cyanide and enantioenriched phenyl(methyl)phosphine oxide proceeded with a small erosion of ee in the product (84% to 76% ee) but it required the chiral $NiCl_2$/(*R*)-BINAP precatalyst, complete racemisation was observed with $NiCl_2(PPh_3)_2$ and no reaction took place with (*S*)-BINAP.[194]

Scheme 102

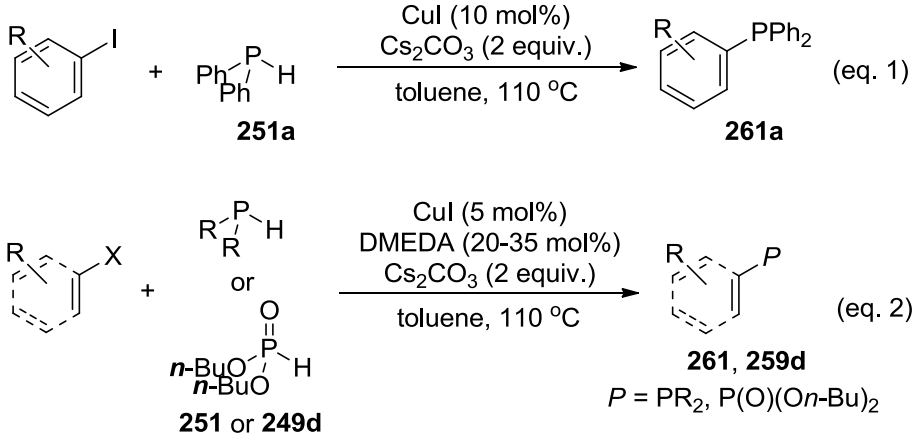


A common trend present in the field of Ni catalysis is the utilization of photoredox catalysis. In the presence of photoredox catalysts Ni-catalyzed C-P cross-coupling reactions take place under milder conditions, usually at room temperature. The reported photoredox catalysts include $[Ru(bpy)_3Cl_2]\cdot 6H_2O$,[193a,b] cadmium sulfide,[193c] and thioxanthen-9-one.[193d]

3.2.3. Cu-catalyzed C-P cross-coupling

Cu-catalyzed C-P cross-coupling is a cost-efficient alternative to the Pd-catalyzed counterpart.[158e,203] The most commonly used precatalyst is copper(I) iodide, a non-hygroscopic and air-stable salt. The ligands are usually mono- or diamines, including DMEDA,[170,204,206,210,215] L-proline,[208] pipecolinic acid,[208] *N*-methylpyrrolidine-2-carboxamide,[209] pyrrolidine-2-phosphonic acid phenyl monoester (PPAPM),[207] phenanthroline,[211,216,220a] α-phenylethylamine,[170,212], bis-2,6-(methylaminomethyl)pyridine[214], and most recently picolinamides.[217] These ligands are cheaper than phosphine ligands employed in Pd-catalyzed reactions. For some substrates good results are also obtained under ligand-free conditions, however, none of these reactions are truly ligand-free as Cu(I) precatalysts are complexed by organophosphorus reagents or amine bases.[205,213,220c,221] Although amine bases were used in several protocols, typically inorganic bases are used, most often alkali metal carbonates. Many groups of organophosphorus substrates have been used in Cu-catalyzed C-P cross-coupling including secondary phosphines,[204-206,214] secondary phosphine oxides,[207-210,212,215,217] secondary phosphine-boranes,[216] *H*-phosphonates,[204,207-209,211,213,217] *H*-phosphinates,[207,208,213] and ammonium hypophosphite.[207,208] On the other hand, the scope of coupling partners for phosphinoyl substrates is generally limited to aryl iodides and electron-deficient aryl bromides such as 2-bromopyridine[212] or bromoarenes with a coordinating group at the *ortho* position.[210] A single example of a cross-coupling between diisopropyl phosphite and electron-deficient bromoarene – 4-bromoacetophenone – was also reported under cobalt/copper co-catalysis.[221] The recent Ma's catalytic system using CuI/picolinamide is an exception and works with unactivated aryl bromides.[217] An alternative approach of pre-reacting an aryl iodide with potassium iodide was used by Fu *et al.*[207,208] Other electrophilic coupling partners include alkenyl halides,[204] dienyl bromides,[215] and alkynyl bromides.[216] Three protocols for decarboxylative Cu-catalyzed cross-coupling were also reported, including alkenylation with substituted cinnamic acids[220a] and alkenylation[220c] or alkynylation [220b] with arylpropiolic acids. The reactions are typically carried out at an elevated temperature of 80-120 ^{o}C with the exception of protocols employing much more reactive aryliodonium salts as coupling partners which are reactive even at room temperature.[218,219] Two reviews focusing on the Cu-catalyzed C-P cross-coupling have been published recently.[158e,203]

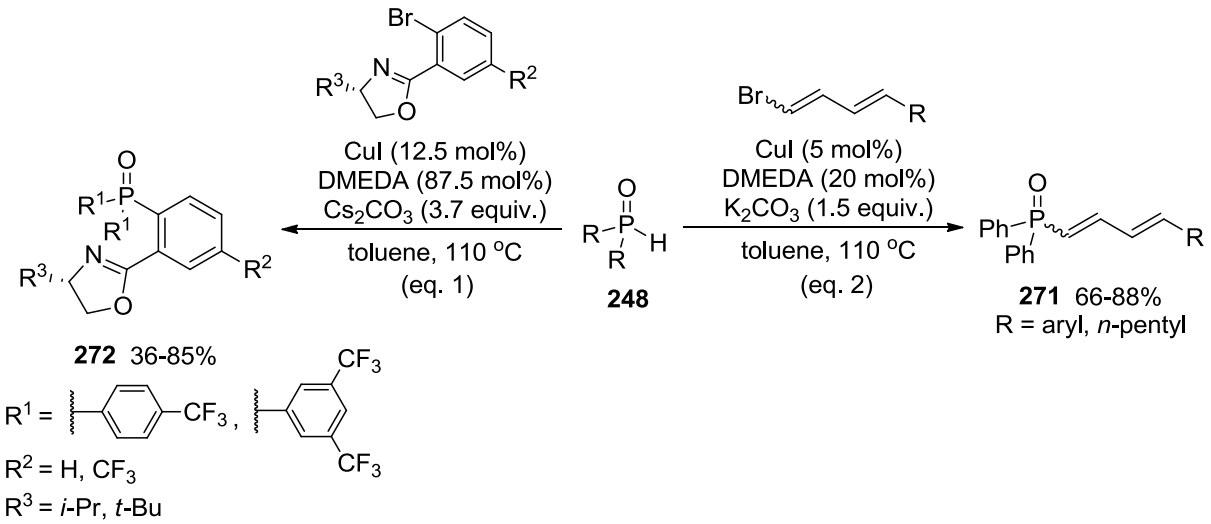
Scheme 103



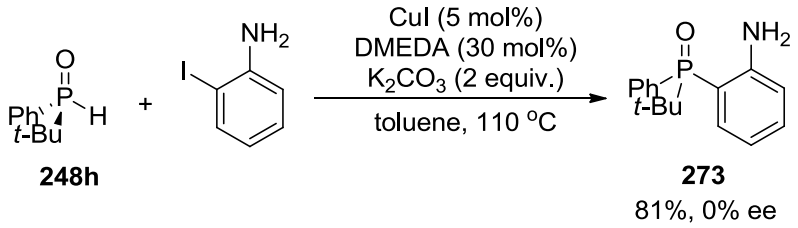
The Hirao cross-coupling was first described under copper catalysis in 2003 independently by Venkataraman[205] and Buchwald.[204] The Venkataraman's protocol employed CuI as the precatalyst for the coupling of diphenylphosphine with aryl iodides and used no external ligand (Scheme 103, eq. 1). The Buchwald's catalytic system consisted of CuI and excess DMEDA as the ligand. It was originally reported for the reactions of secondary diaryl and dialkylphosphines, and dibutyl phosphonate (Scheme 103, eq. 2). Apart from the reactions of diphenylphosphine with methyl 4-bromobenzoate and 2-iododec-1-ene, secondary phosphines were coupled with aryl iodides and dibutyl phosphonate was coupled with aryl iodides and alkenyl bromides or iodides. Good yields were observed for all the reactions, aryl iodides tolerated methoxy, amino, phenyl, and ethyl substituents at the *ortho* position without a reduction in the yield, and alkenyl iodides afforded products with slightly lower yields than alkenyl bromides.

The Cu/DMEDA catalytic system has also later been used by Stoltz *et al.* for the coupling of secondary phosphines and secondary phosphine oxides with 2-(2-bromophenyl)oxazolines,[206,210] and by Gaumont *et al.* for the coupling of diphenylphosphine oxide with dienyl bromides (Scheme 104).[215] It is arguably the most general among copper-based systems for C-P cross-coupling, however, some phosphorus substrates of interest have not been tested with DMEDA. There has been no thorough study on the utility of DMEDA in the cross-coupling of secondary phosphine oxides with aryl iodides or aryl bromides with no directing/activating groups, a single reaction with enantiopure phenyl(*tert*-butyl)phosphine oxide was reported by Chrzanowski *et al.* (Scheme 105),[170] and no cross-coupling of *H*-phosphinates was reported with DMEDA.

Scheme 104



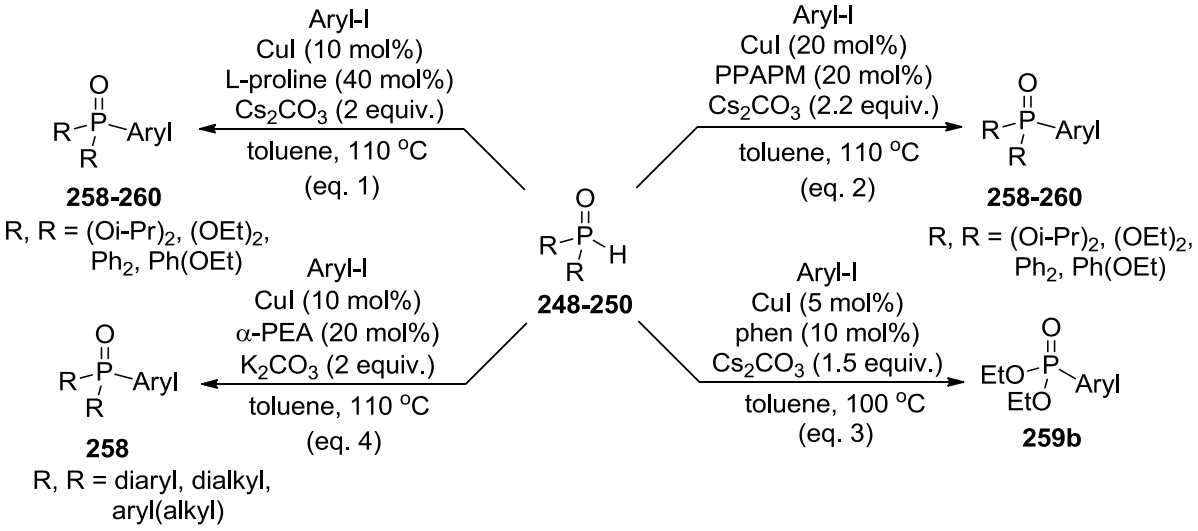
Scheme 105



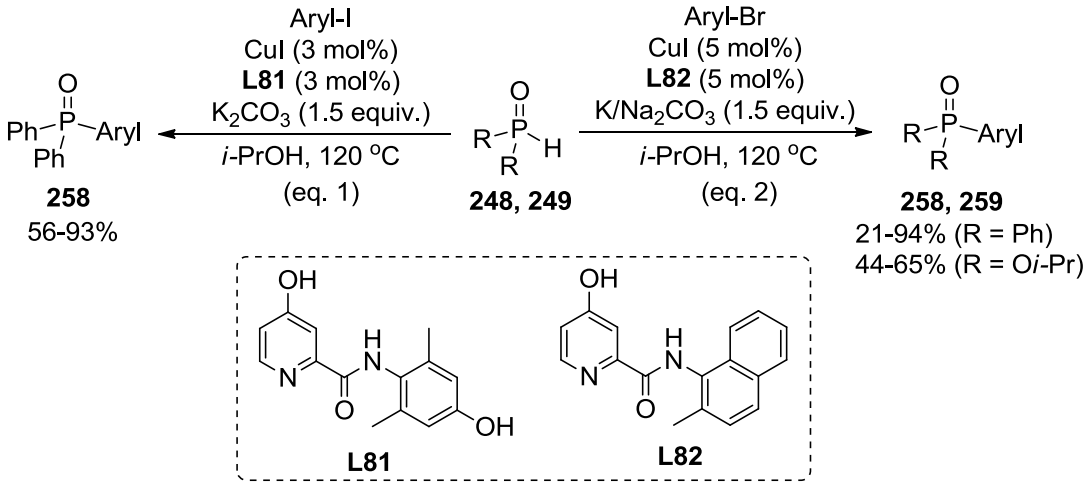
Several other ligands have been reported to work well in Cu-catalyzed Hirao and for selected applications they may offer some advantages over DMEDA. The drawbacks of DMEDA are its relatively high price compared to other amine and diamine ligands and the requirement of a large three- to seven-fold excess relative to copper, the latter, however, is also true for the majority of ligands used in Cu-catalyzed C-P cross-coupling. In 2006 Fu *et al.* reported that L-proline and pipecolinic acid were effective ligands for the cross-coupling of diisopropyl and diethyl phosphonate, ethyl phenylphosphinate, diphenylphosphine oxide, and ammonium hypophosphite under slightly different conditions with DMF as the solvent and DMAP as the base (Scheme 106, eq. 1).[208] The same group in the same year also reported on the use of pyrrolidine-2-phosphonic acid phenyl monoester (PPAPM) as the ligand with a similar scope and efficiency to L-proline (Scheme 106, eq. 2).[207] In 2008, they reported on the superiority of *N*-methylprolinamide for the cross-coupling of secondary phosphine oxides with *ortho*-bromoanilides, however, a very high amount of CuI (30 mol%) and the ligand (100 mol%) were used.[209] Karlstedt and Beletskaya found that phenanthroline was an effective ligand for the cross-coupling of diethyl phosphonate, the reaction featured a relatively low loading of 5 and 10 mol% of CuI and phenanthroline, respectively (Scheme

106, eq. 3).[211] Stankevič and Włodarczyk developed a protocol for the cross-coupling of secondary phosphine oxides with aryl iodides featuring 10 mol% of CuI and (*S*)-α-phenethylamine as the ligand, at the loading of 20 mol% corresponding to a stoichiometric amount for a monodentate ligand it was found to be superior to 10 mol% of DMEDA or phenanthroline and 20 mol% of L-proline or picolinic acid (Scheme 106, eq. 4).[212]

Scheme 106



Scheme 107

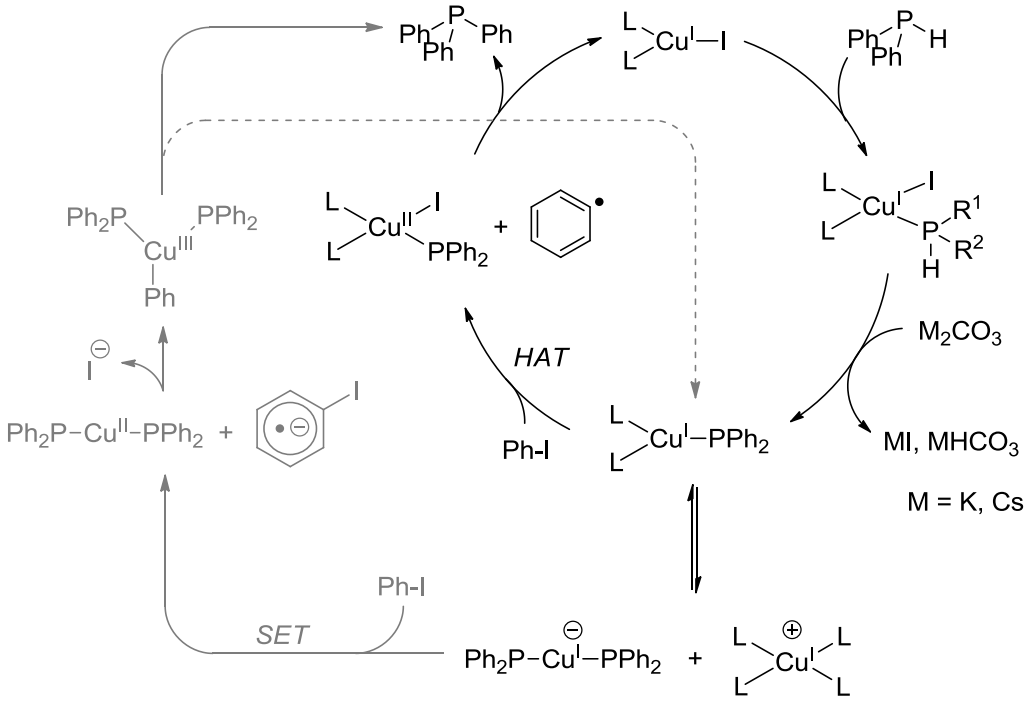


Most recently, in 2021, Ma *et al.* reported on picolinamide ligands which form highly active copper complexes that can catalyze the cross-coupling of diarylphosphine oxides and diisopropyl phosphonate with aryl bromides and iodides at a low catalyst loading of 3-5 mol% without the need for excess ligand (Scheme 107).[217]

The mechanism of Cu-catalyzed C-P cross-coupling has not been studied as extensively as the related C-N, C-O, and C-S cross-coupling and thus putative mechanisms have been proposed by analogy with the more studied systems. As of January 2023, there have been only two publications dealing with the topic. Zhang *et al.* carried out a theoretical study on the mechanism of C-P cross-coupling between diphenylphosphine and iodobenzene using CuI/EDA, CuI/phen or "ligandless" CuI as catalysts in toluene or DMSO as solvents.[222] Keglevich *et al.* used calculations to determine the mechanism of cross-coupling between diphenylphosphine oxide and iodo- or bromobenzene in the presence of catalytic CuI and NEt_3 as the base, in the absence of external ligands.[223] It should be noted that the ligandless reactions are not truly ligand-free as secondary phosphines and phosphinoyl substrates via their P(III) form act as effective ligands for Cu(I). Secondary phosphine oxides and *H*-phosphonates have been known to act as ligands for late transition metals and some of their complexes were found to be efficient catalysts for various transformations.[224]

The first step in the catalytic cycle is the coordination of the phosphorus reagent to Cu(I), then the P-H or P-OH moiety is deprotonated by a weak base and the halide is displaced. The phosphinoyl or phosphidocopper(I) complex then reacts with the aryl/alkenyl halide. Different mechanisms have been invoked for this step in the analogous carbon-heteroatom cross-coupling including: two-electron oxidative addition, single-electron transfer (SET), and halogen-atom transfer (HAT).[225] According to the two computational studies different mechanisms operate depending on the organophosphorus substrate, the ligand, and the solvent polarity. Zhang *et al.* calculated that HAT was the operating mechanism for all reactions of diphenylphosphine in toluene regardless of the ligand, while in DMSO an equilibrium between the neutral $L_2Cu\text{-}PPh_2$ and the anionic $[Cu(PPh_2)]^-$ species was predicted for diamine ligands, and the anionic species could react via the SET mechanism (Scheme 108).[222] Keglevich *et al.* found computationally that in the "ligand-free" cross-coupling between diphenylphosphine oxide and bromobenzene the most probable species participating in the oxidative addition to aryl halide are $Ph_2PO\text{-}Cu(NEt_3)$ and $Ph_2PO\text{-}Cu(P(OH)Ph_2)$. They also found experimentally that the cross-coupling worked best when 1.0 equiv. of $Ph_2P(O)H$ was used, whereas using the secondary phosphine oxide in excess was associated with decreased yields. On the other hand, excess NEt_3 was beneficial for the reaction. Combining this observation with the calculations, the authors proposed that in the presence of excess $Ph_2P(O)H$, the formation of the catalytically inactive tetraligated Cu(I) complex was favourable and excess NEt_3 could prevent that by competing for coordination sites at Cu(I).[223]

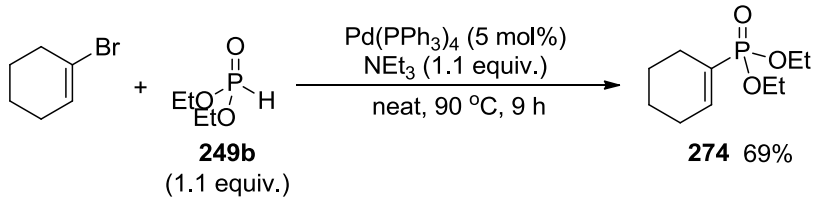
Scheme 108



3.2.4. C-P cross-coupling of cycloalkenyl electrophiles

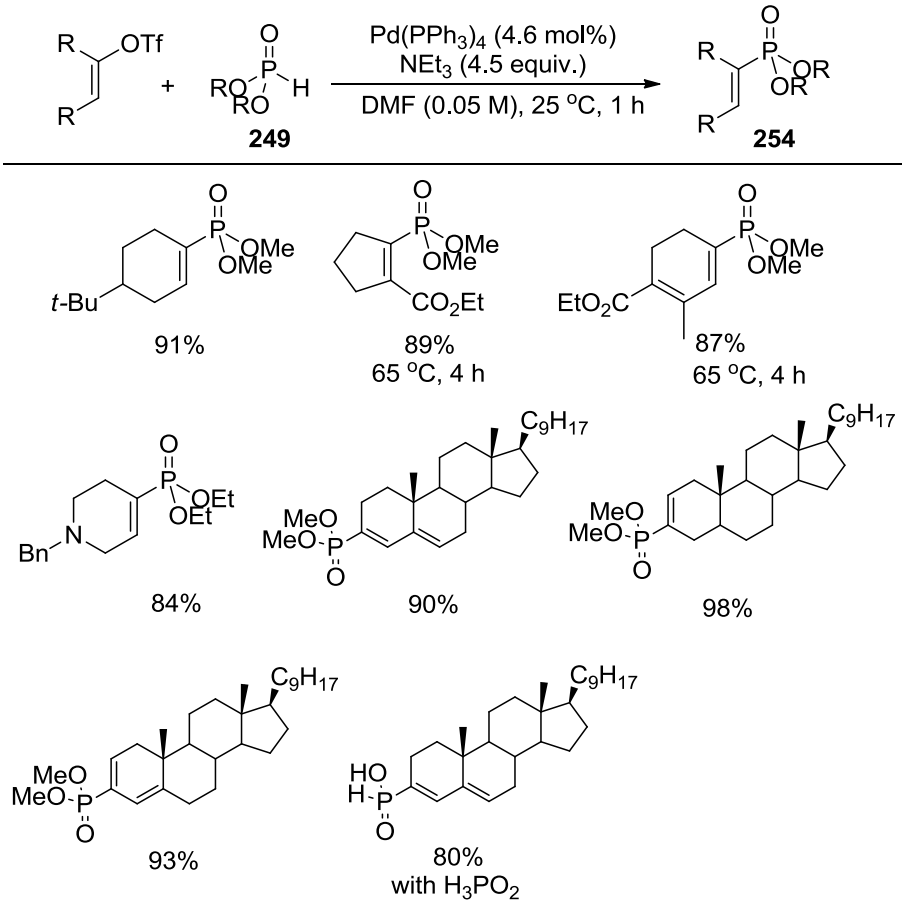
C-P cross-coupling with cycloalkenyl electrophiles is rare and mostly limited to Pd-catalyzed processes. Hirao *et al.* reported in their original paper the reaction between diethyl phosphonate and 1-bromocyclohexene and isolated the product with 69% yield (Scheme 109).[159a,c]

Scheme 109



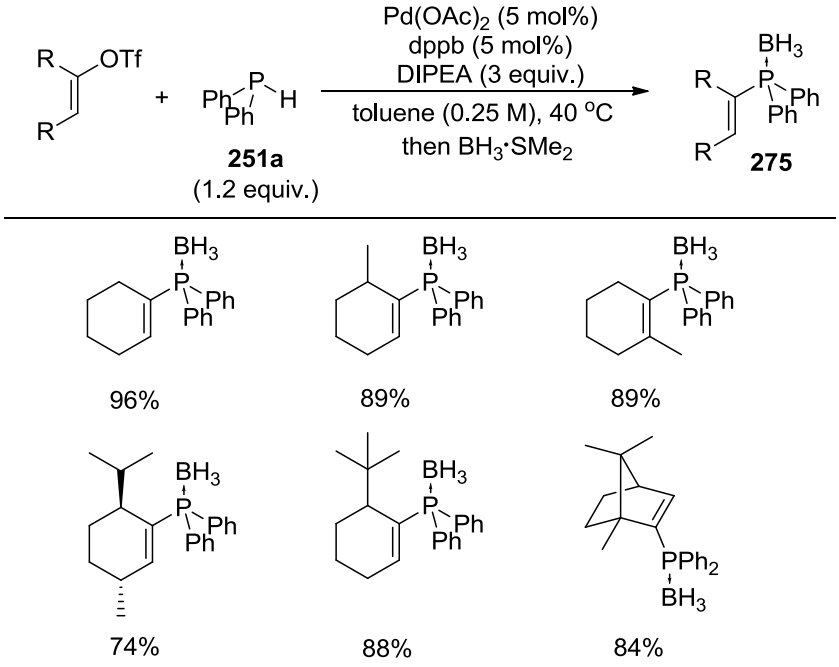
Holt and Erb used a modified Hirao's protocol for the coupling of dimethyl phosphonate with enol triflates, the reactions were carried out in DMF at room temperature with good to very good yields (Scheme 110).[174] *H*-phosphinates were also coupled with cycloalkenyl triflates using $Pd(PPh_3)_4$ as the catalyst.[232,233]

Scheme 110

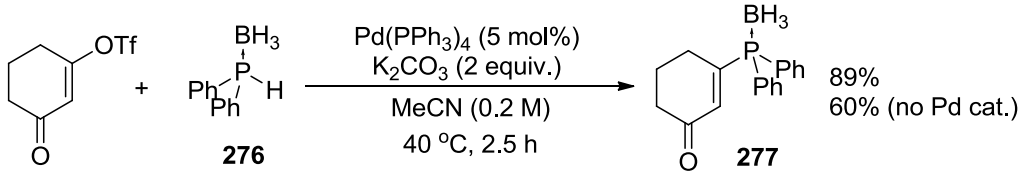


Gilbertson *et al.* coupled diphenylphosphine with unsubstituted and substituted cyclohexenyl triflates and camphor enol triflate using the Pd/dppb catalyst. The tertiary phosphine products were protected with borane-dimethyl sulfide complex before isolation (Scheme 111).[226] Lipshutz *et al.* did a direct cross-coupling between diphenylphosphine-borane and 3-oxocyclohexenyl triflate with $Pd(PPh_3)_4$ as the catalyst. Interestingly, the reaction also worked without the Pd catalyst, however, the yield was lower (Scheme 112).[227] Both reactions were carried out at a relatively low temperature of 40 °C. Gaumont *et al.* carried out a more thorough scope screening for the cross-coupling of secondary phosphine-boranes and cycloalkenyl triflates under $PdCl_2$(dppp) catalysis in DMSO at 60 or 80 °C (Scheme 113).[228] The same catalytic system turned out to work also for cycloalkenyl tosylates albeit at a higher temperature of 80 or 110 °C (Scheme 114).[229] Shorter reaction times were attained by using microwave heating.

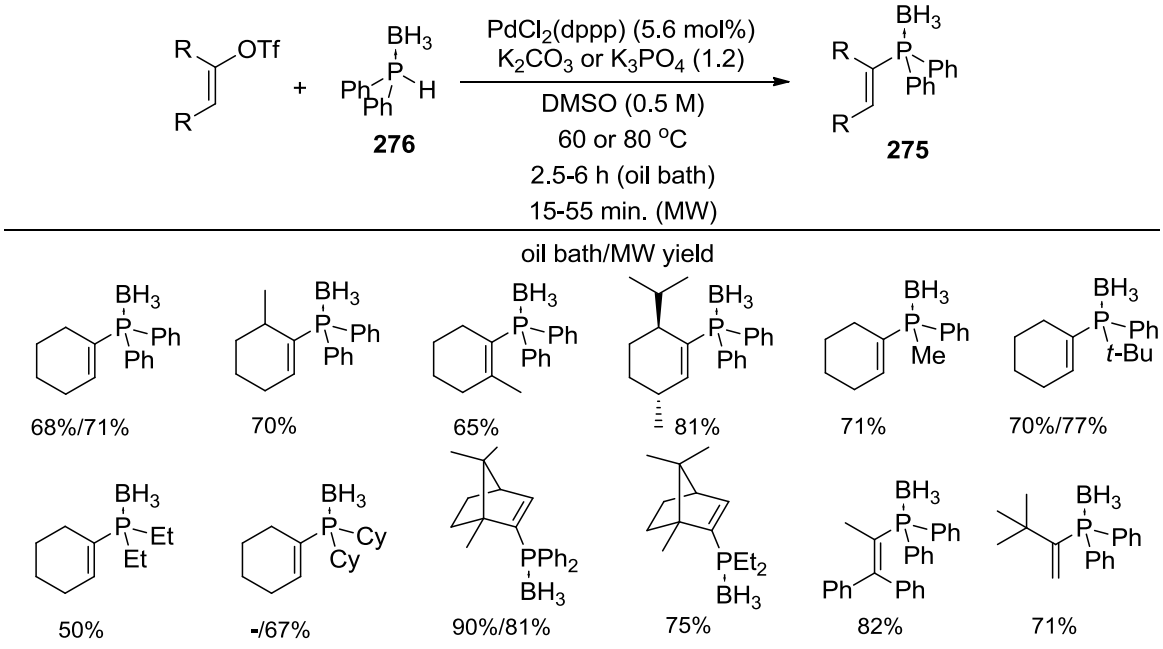
Scheme 111



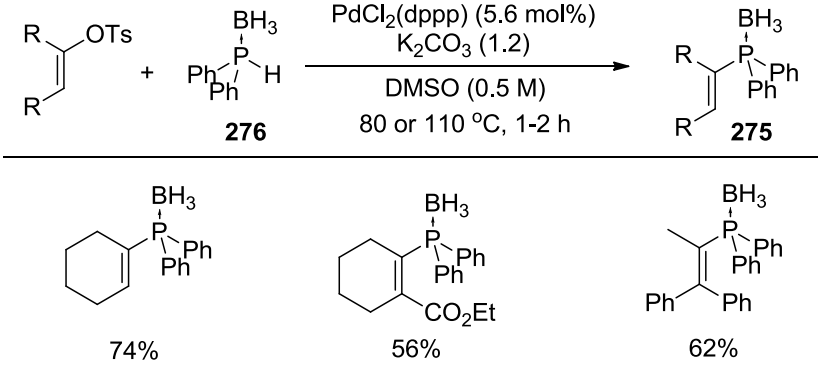
Scheme 112



Scheme 113

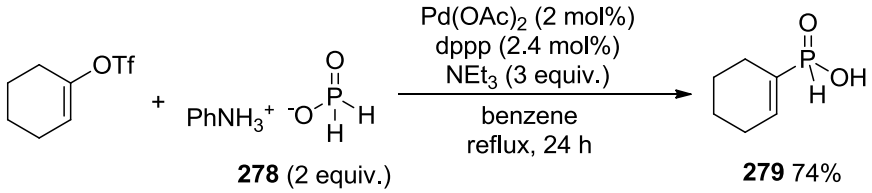


Scheme 114

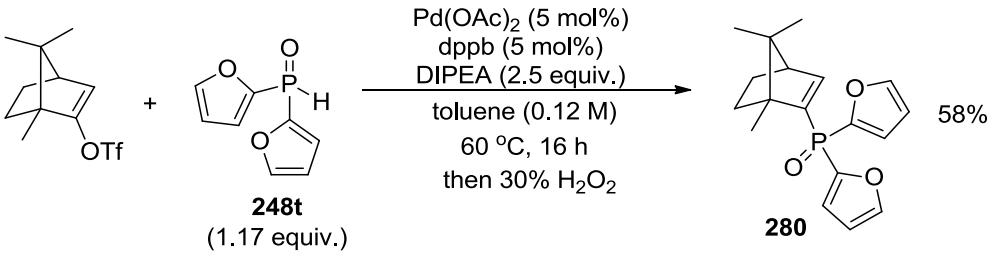


Montchamp *et al.* tested their catalytic system for anilinium hypophosphite with cyclohexenyl triflate and obtained cyclohex-1-enylphosphinic acid in 74% yield (Scheme 115).[164b] Knochel *et al.* prepared the substrate for conjugate addition by the coupling of camphor enol triflate with di(2-furyl)phosphine oxide using the Pd/dppb catalyst (Scheme 116).[78]

Scheme 115



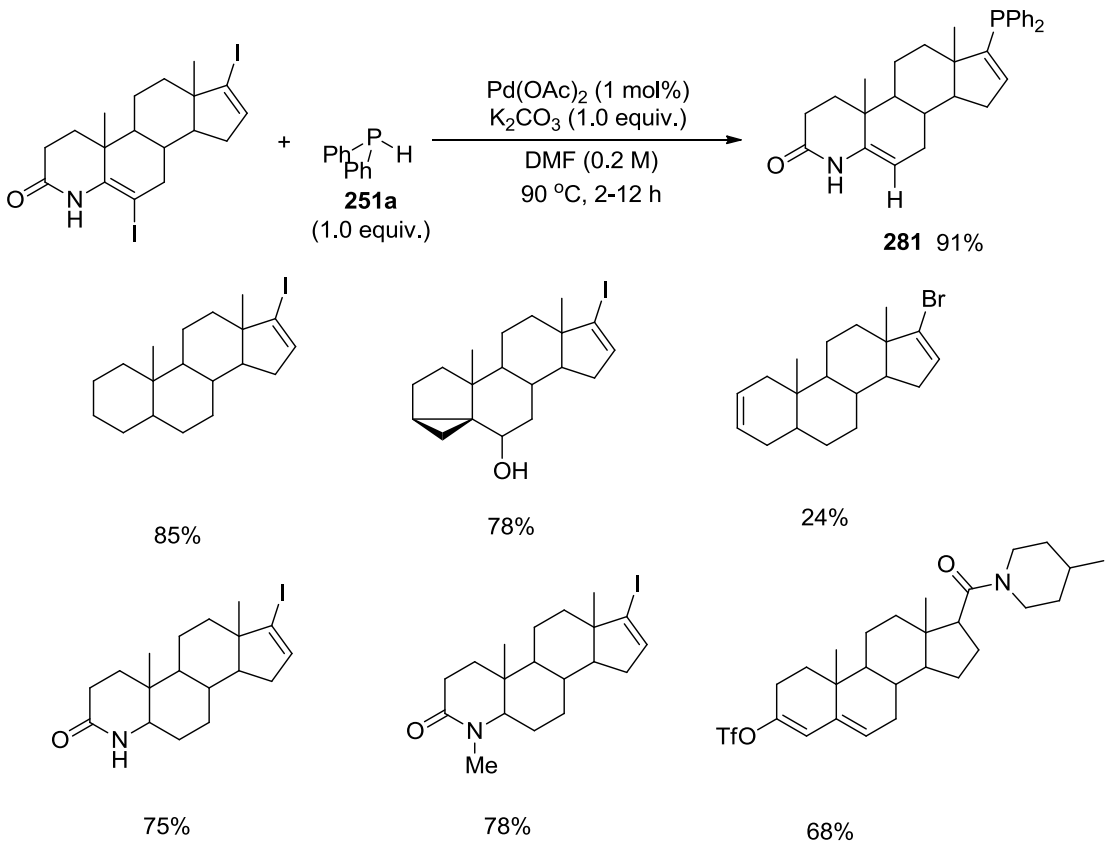
Scheme 116



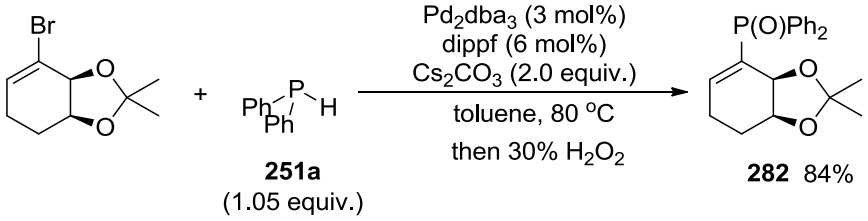
Halocycloalkenes were used less frequently. Skoda-Földes reported on the cross-coupling of diphenylphosphine with cycloalkenyl iodides derived from cholestane in 68-85% isolated yield, a single reaction with a bromocycloalkene yielded the product in 24% yield (Scheme 117).[230] The reactions were done using $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base, triethylamine was ineffective. Boyd *et al.* performed a cross-coupling reaction between

a bromocycloalkene and diphenylphosphine using the Pd/dippf catalyst, and the product was oxidized to the corresponding phosphine oxide (Scheme 118).

Scheme 117



Scheme 118

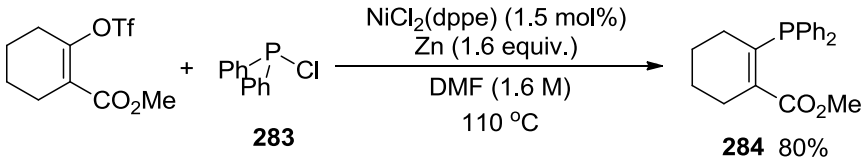


Two Ni-catalyzed protocols were used to obtain cycloalkenylphosphine derivatives. In 1997, Laneman *et al.* described C-P cross-coupling between chlorodiphenylphosphine and C(sp^2)-bromides and triflates in the presence of $NiCl_2$(dppe) and zinc dust to obtain tertiary phosphines. A single reaction with 2-methoxycarbonylcyclohex-1-enyl triflate afforded the product in 80% yield (Scheme 119).[184a] Recently, in 2017, Yu *et al.* reported on a photoredox/Ni-catalyzed cross-coupling of cycloalkenyl tosylates with diethyl phosphonate.

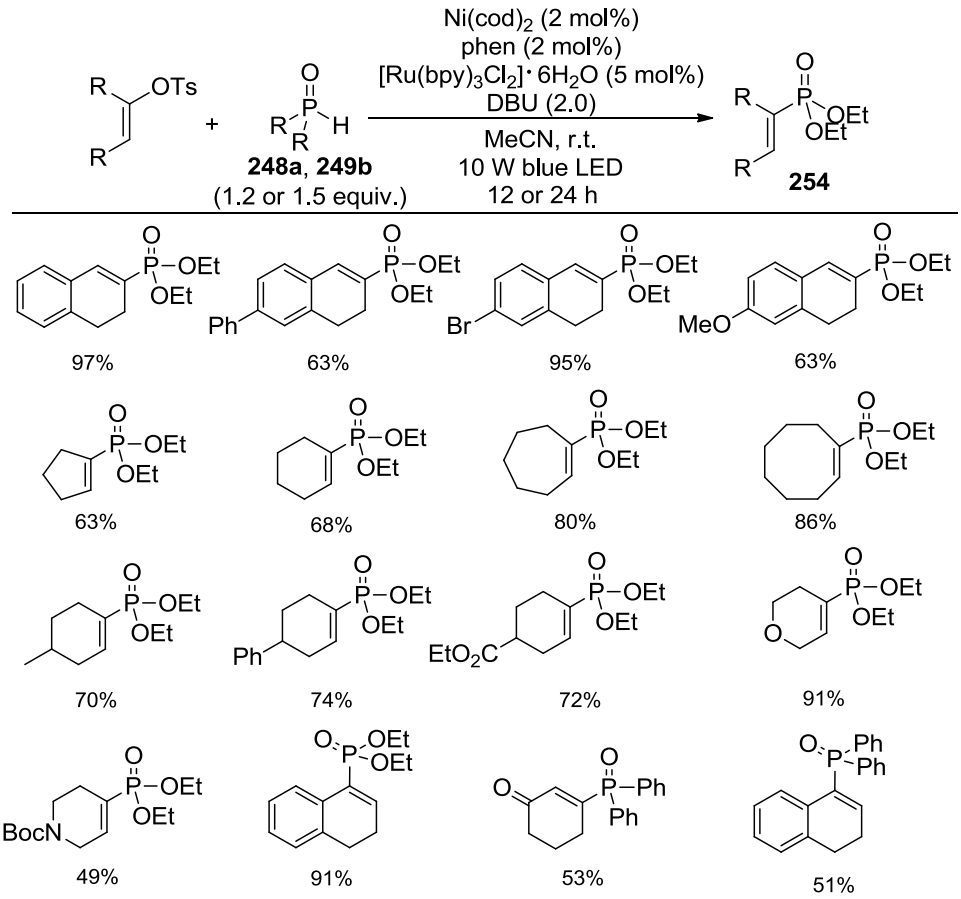
A thorough scope screening was done and products were obtained in moderate to very good yields, two reactions of diphenylphosphine oxide with moderate yields were also reported (Scheme 120).[202b]

No cross-coupling reactions with cycloalkenyl electrophiles have been reported under copper catalysis and the two protocols for Ni-catalyzed cross-coupling cover a limited scope of organophosphorus and cycloalkenyl substrates.

Scheme 119



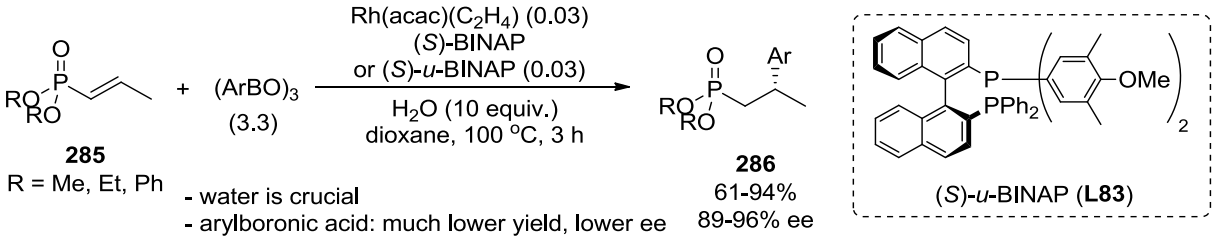
Scheme 120



3.3. Asymmetric metal-catalyzed conjugate addition to alkenylphosphine derivatives

At the beginning of this Ph.D. project in September 2018, there were only four publications dealing with stereoselective conjugate addition to alkenylphosphine derivatives, none included cycloalkenylphosphorus compounds. Following the discovery of Rh-catalyzed conjugate addition to enones in 1997 and its asymmetric variant a year later,[234] in 1999 Hayashi *et al.* reported on Rh-catalyzed conjugate addition of arylboroxines to alkenylphosphonates (Scheme 121).[235] The reaction gave moderate (for electron-poor arylboroxines) to good yields (for phenyl and electron-rich arylboroxines) with high stereoselectivity, however, the scope of alkenylphosphonates was very narrow including only acyclic linear olefins. The utilization of arylboroxines as the nucleophiles was crucial as the analogous arylboronic acids gave products with lower ee values and much lower yield. In all cases (*S*)-BINAP could be used as the ligand, in a couple of reactions for which (*S*)-*u*-BINAP was also tested, it provided marginally better results than the parent ligand.

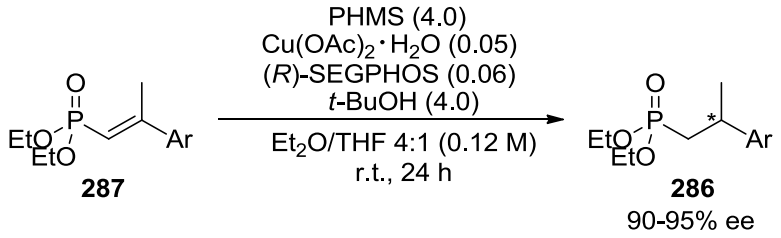
Scheme 121



In the following decade the conjugate addition to alkenylphosphorus compounds became a dormant subfield while the reaction was being developed mostly for α,β-unsaturated carbonyl compounds and various organometallic compounds under Rh, Cu, Pd and to a lesser extent Ni catalysis.[244] In 2009, Zheng *et al.* reported on Cu-catalyzed conjugate reduction of diethyl alkenylphosphonates with polymethylhydrosiloxane (PMHS) as the hydride source (Scheme 122).[236] The authors tested several atropisomeric diphosphine ligands and SEGPHOS was the only one giving satisfying yields. The source of copper had negligible impact on stereoselectivity, but $Cu(OAc)_2 \cdot H_2O$ gave the best yield. The reaction was stereoselective in toluene, THF and Et_2O, but a mixture of Et_2O/THF 4:1 provided the highest yield. *t*-BuOH additive increased the rate of the reaction as the proton source. The scope of the reaction was mostly limited to β-aryl *E*-olefins, changing the aryl group to phenylethyl

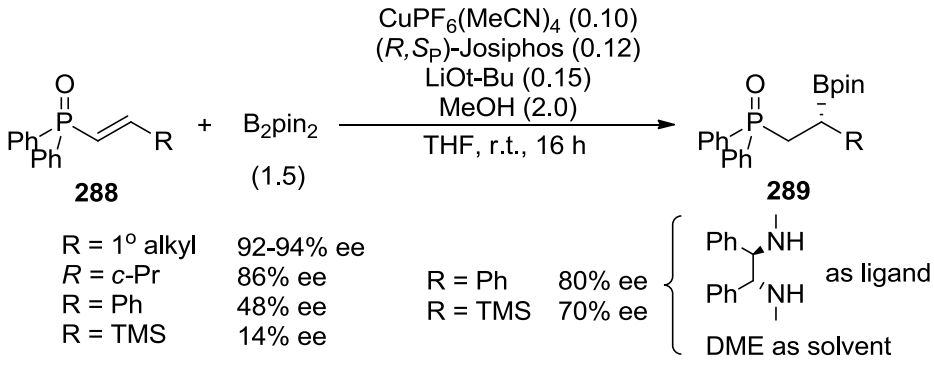
decreased the stereoselectivity in both *E* and *Z*-olefins, while changing the β-methyl to ethyl or *n*-propyl had no impact on the stereoselectity but drastically decreased the yield.

Scheme 122



In 2015, Feringa *et al.* published a paper on Cu-catalyzed conjugate boronation of alkenyl(diphenyl)phosphine oxides (Scheme 123).[237] By employing the Cu/Josiphos catalyst prepared *in situ* the group was able to obtain a series of phosphine oxide boronates with 92-96% ee for the products with *n*-alkyl group at the β position. The stereoselectivity was slightly lower for the cyclopropyl analogue and it was poor for β-phenyl and β-trimethylsilyl analogues. For the latter two, a significant improvement was achieved by employing *N,N'*-dimethyl-1,2-diphenylethylenediamine as the ligand and DME as the solvent. This modified protocol was, however, inferior for the model substrate oct-1-en-1-yl(diphenyl)phosphine oxide. MeOH additive increased the rate of the reaction substantially. Also, the catalyst loading of 10 mol% was important as at the lower loading of 5 mol% the yields were inconsistent.

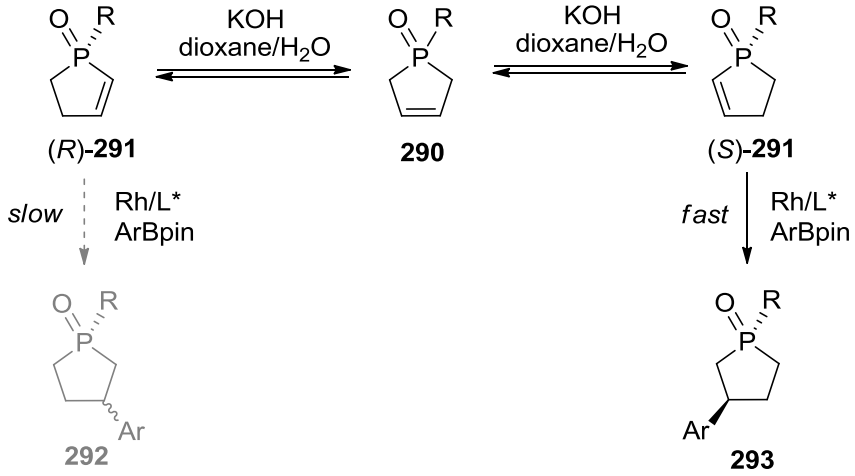
Scheme 123



In 2017, Lim and Hayashi published a paper on asymmetric Rh-catalyzed conjugate arylation of 2-phospholene oxides which were generated under the reaction conditions from the corresponding 3-phospholene oxides through base-promoted isomerization (Scheme 124).[238] In the reaction dynamic kinetic resolution of 2-phospholene oxide enantiomers takes

place because in the conjugate addition step the (*S*)-**2a** isomer reacts much faster than the (*R*)-**2a** isomer, and as (*S*)-**2a** is removed from the system by being used up in the arylation, the unreacted (*R*)-**2a** undergoes racemisation and equilibrates with (*S*)-**2a** through **1a**, therefore the reaction could be carried out with the same outcome using *rac*-**2a** instead of **1a**.

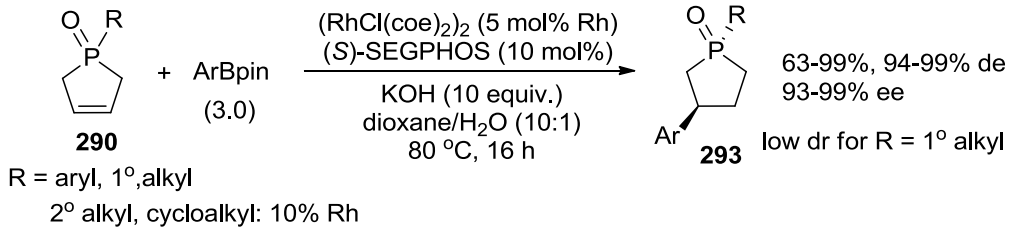
Scheme 124



The reaction required (*R*)-SEGPHOS as the ligand for high stereoselectivity, other ligands in the study included (*R*)-BINAP and (*R*)-DTBM-SEGPHOS, and two chiral diene ligands (*S,S*)-Fc-tfb and (*R,R*)-Ph-bod, however, all of them provided the product with much lower enantiopurity. The ligand had to be used at 2 equiv. relative to the Rh precatalyst to ensure both complete substrate conversion and high enantioselectivity. During the optimization study, both $PhB(OH)_2$ and $PhBF_3K$ led to the same degree of enantio- and diastereoselectivity, however, they provided the product with a lower yield than PhBpin. The reaction temperature was a crucial factor, the optimal yield and stereoselectivity was obtained at 80 ^oC. At 60 ^oC the conversion was much lower albeit with superior enantio- and diastereoselectivity, and at 100 ^oC both the conversion and stereoselectivity decreased substantially. The reaction had a wide scope of substrates among both phospholene oxides and arylboronates. Both electron-rich and electron-poor aryl groups were tolerated in both substrates, however, substrates with *ortho*-substituted aryl groups were not tested. The presence of isopropyl and cyclohexyl groups at the phosphorus atom led to lower yields (71% and 63% respectively) and required higher catalyst loading of 10 mol% Rh. Cyclohexenylboronate also required a higher loading of 7 mol% Rh. In all cases high enantioselectivity and diastereoselectivity was achieved (Scheme 125). Regarding the limitations of the reactions, *tert*-butylphospholene oxide was poorly reactive with only 7%

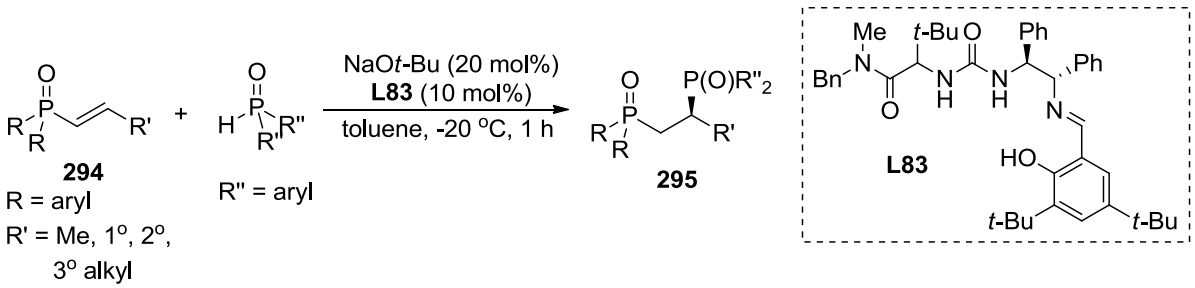
yield, while *n*-hexylphospholene oxide led to decreased enantioselectivity (90% ee) and rather poor diastereoselectivity (64% de).

Scheme 125



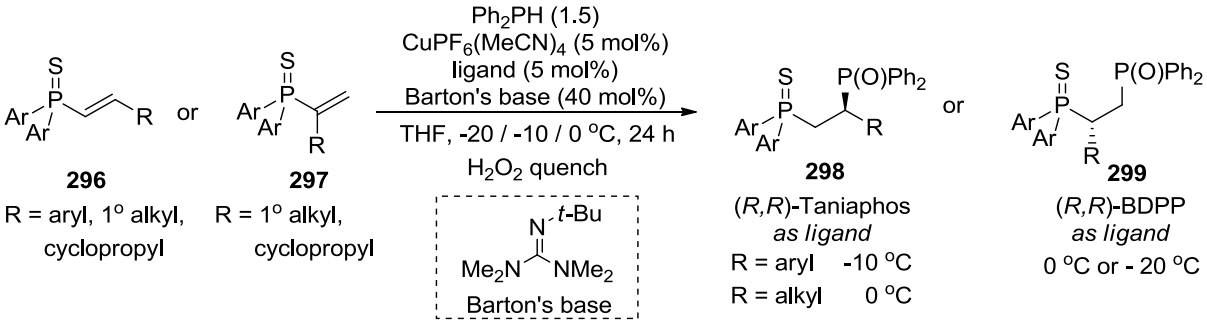
Since September 2018, there have been three papers published on stereoselective metal-catalyzed conjugate addition to alkenylphosphorus derivatives, all of which used phosphorus nucleophiles. In 2020 Kondoh *et al.* described conjugate addition of secondary phosphine oxides to alkenyl(diaryl)phosphine oxides catalyzed by NaO*t*-Bu/chiral ureate (Scheme 126).[239] The reaction required a lowered temperature (-20 °C) and a non-coordinating solvent for high stereoselectivity, toluene gave the best results, while THF, EtOAc, and DMF were all inferior. The reaction was only moderately stereoselective for diphenylphosphine oxide and required *m*-tolyl or 3,5-dimethylphenyl substituents at the phosphorus atom for high stereoselectivity. On the other hand di-*o*-tolyl and dicyclohexylphosphine oxides were unreactive. The reaction provided the adducts of bis(3,5-dimethylphenyl)phosphine oxide and alkenyl(diphenyl)phosphine oxides possessing 1° alkyl or cycloalkyl group at the β position with 87-96% ee; the presence of β-*tert*-butyl group led to very low stereoselectivity. The electronic and steric properties of the phosphinoyl group in the electrophile were also important. Both *p*-trifluoromethylphenyl and *p*-tolyl substituted 2-cyclohexylvinyl(diaryl)phosphine oxides reacted with high stereoselectivity, however, the *p*-tolyl analogue required longer reaction time, the bis(3,5-dimethylphenyl) analogue was unreactive.

Scheme 126



Also in 2020, Lin *et al.* reported on Cu-catalyzed asymmetric conjugate addition of secondary phosphines to acyclic alkenylphosphine sulfides.[240] By using the *in situ* prepared catalyst Cu/(R,R_P)Taniaphos and Barton's base, the group was able to carry out the addition of Ph_2PH to a series of β-substituted vinyl(diaryl)phosphine sulfides and obtain the products with 84-97% ee after oxidation with H_2O_2. The optimal temperature was -10 ^oC for β-aryl electrophiles and for β-alkyl electrophiles the reactions were conducted at 0 ^oC. A wide range of substrates was tested possessing at the β position *p*- or *m*-substituted phenyl, heteroaryl, and alkyl groups with terminal -SPh, -N(Me)Ts, -OBn, and -CH=CH_2 moieties. The conjugate addition was equally effective for α-alkyl vinylphosphine sulfides, however, for this group of substrates (*R,R*)-BDPP turned out to be the optimal ligand along with the lower temperature of -20 ^oC (Scheme 127). At the α position, alkyl chains with different functionalities were well tolerated, including terminal -Cl, -CN, -OBz, and -SPh. In both α- and β-substituted vinylphosphine sulfides a range of aryl groups were tolerated in the thiophosphinoyl group. α-Arylvinylphosphine sulfides were not tested as they could not be obtained from the corresponding phosphine oxides by the thionation method employing Lawesson's reagent reported earlier by the authors.[241] It is also worth noting that the reaction did not work for β-styrenyl(diphenyl)phosphine oxide either with diphenylphosphine or diphenylphosphine oxide as the nucleophile and the authors speculated that the thiophosphinoyl group was a better coordinating group for a Cu(I) centre due to a "soft-soft" interaction.

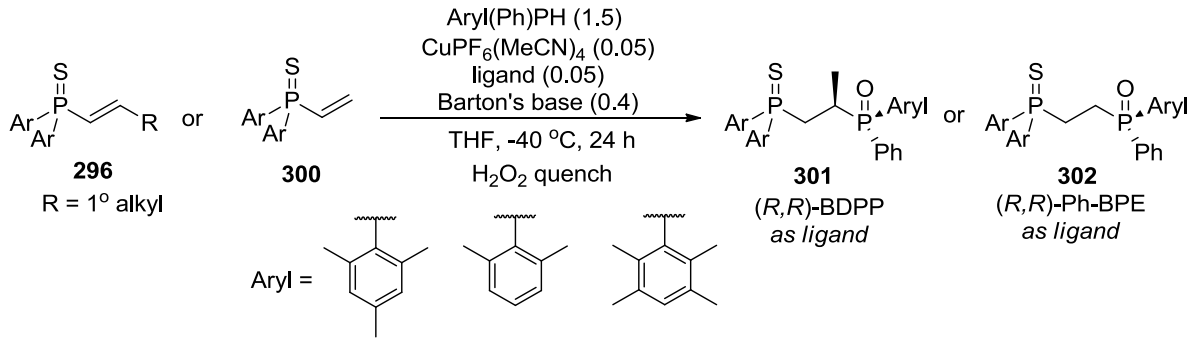
Scheme 127



Dynamic kinetic resolution of chiral racemic aryl(phenyl)phosphine combined with conjugate addition to vinyl(diphenyl)phosphine sulfide was also possible. For the reaction of mesityl(phenyl)phosphine catalysts generated from $CuPF_6(MeCN)_4$ and a variety of diphosphine ligands gave full conversion even at -40 ^oC. However, only (*R,R*)-BDPP and (*R,R*)-Ph-BPE ligands conferred high stereoselectivity and the latter used at -40 ^oC was the most effective. For oct-1-en-1-yl(diphenyl)phosphine sulfide (*R,R*)-BDPP was the only ligand

giving moderately high enantioselectivity at room temperature, however, virtually no diastereoselectivity was observed. The reaction required 0 ^{o}C or lower for >20:1 diastereomer ratio and the optimal yield and enantioselectivity was observed at -40 ^{o}C (Scheme 128).

Scheme 128



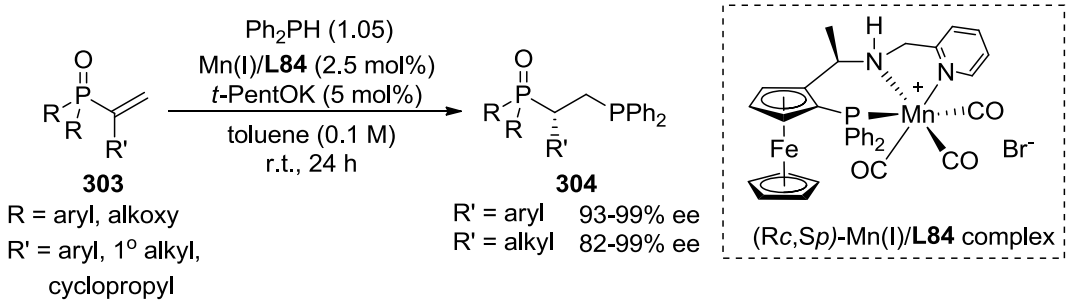
Three analogues of ProPhos with phenyl, *p*-fluorophenyl and 2-naphthyl groups at the α position were prepared from the conjugate addition adducts via three-step transformation including phosphine sulfide to phosphine oxide swap, one-pot reduction of the diphosphine dioxide and protection with borane, and finally borane deprotection. These ligands were tested in Rh-catalyzed asymmetric hydrogenation of *N*-acetyldehydrophenylalanine methyl ester and the 2-naphthyl analogue provided the reduced product with 87% ee at 0 ^{o}C and 3 atm. of H_2. This is somewhat comparable to the ee values obtained in asymmetric hydrogenation of analogous dehydroaminoacid derivatives catalyzed by Rh/(*R*)-ProPhos.[7b]

A different pattern of reactivity was reported in 2022 under Mn(I) catalysis by Ge and Harutyunyan.[242] A combination of a complex of Mn(I)/chiral tridentate ferrocenylphosphine *P*,*N*,*N*-ligand (**L84**) and *t*-PentOK as the base catalyzed the conjugate addition of diphenylphosphine to α-aryl and α-alkyl vinyl(diaryl)phosphine oxides (Scheme 129). Electrophiles with a variety of *m*- and *p*-substituted aryl, 2-naphthyl, 3-pyridyl and 2-thienyl groups at the α position all provided the products with high ee values of 93-99%. Dimethyl, diethyl, and dibenzyl α-styrenylphosphonates gave products with slightly lower ee values (89-91% ee) and ethyl phenyl(α-styrenyl)phosphinate gave a 1:1 mixture of two diastereomers with 99% ee and 80% ee, respectively.

The reaction worked with a low 2.5 mol% Mn(I)/5.0 mol% base loading and, remarkably, the catalyst loading could be further decreased to 0.5 mol% Mn(I) for a 1.0 g scale reaction run for 48 h. Various solvents were tested in the model reaction, toluene was

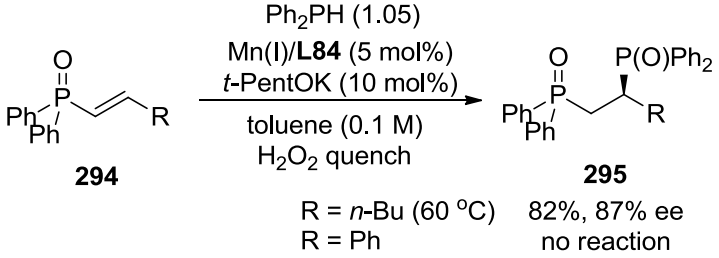
the most effective and marginally better than THF and dioxane regarding stereoselectivity, *i*-PrOH gave incomplete conversion and slightly lower ee while MeOH gave poor stereoselectivity. Among secondary phosphines tested, only Ph_2PH and *p*-Tol_2PH led to products with high yields and high ee values, whereas *p*-An_2PH gave low ee, and more sterically hindered electron-rich phosphines *o*-Tol_2PH, Cy_2PH as well as electron-deficient phosphines (p-CF_3-C_6H_4)$_2$PH and (3,5-di-CF_3-C_6H_3)$_2$PH did not react at all.

Scheme 129

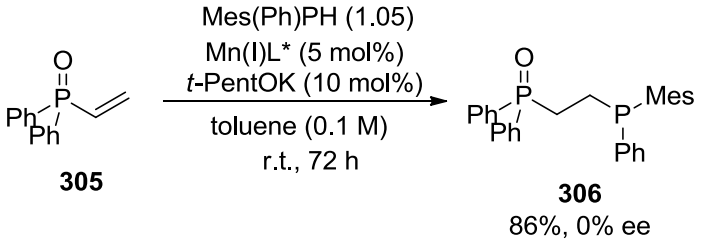


In the case of α-alkyl analogues the stereoselectivity was similarly high, although higher catalyst loading (5 mol% Mn(I)/10 mol% base) and longer reaction times (3-5 days) were required. Hydroxyethyl group decreased both the yield and enantioselectivity, however, chloropropyl and cyanoethyl groups had no impact. The reaction of β-styrenyl(diphenyl)phosphine oxide showed no conversion at all, however, the reaction did work for hex-1-en-1-yl(diphenyl)phosphine oxide at 5 mol% Mn(I) loading and 60 °C albeit with slightly lower enantioselectivity (Scheme 130). Unlike the Lin's protocol, this protocol was not stereoselective when chiral racemic mesityl(phenyl)phosphine was used as the nucleophile with vinyl(diphenyl)phosphine oxide (Scheme 131).

Scheme 130

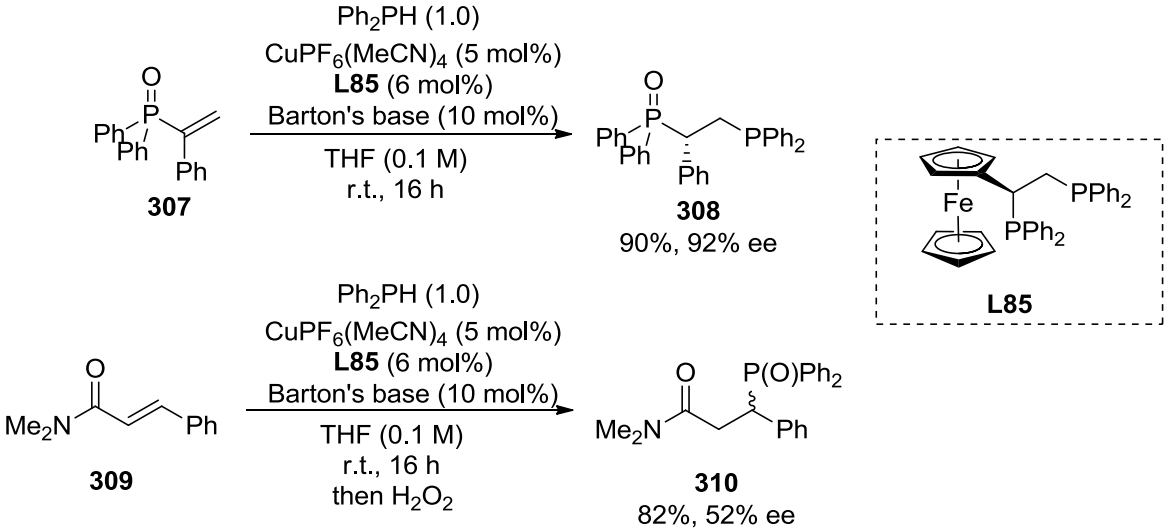


Scheme 131



The authors also showed that some of the products of their Mn-catalyzed conjugate addition could be used as precursors for diphosphine ligands. One of them, the α-ferrocenyl ProPhos analogue, which had been prepared by the one-pot conjugate addition/reduction/protection with borane followed by borane deprotection, was shown to be a highly effective ligand in Cu-catalyzed conjugate addition of Ph_2PH to α-styrenyl(diphenyl)phosphine oxide under the modified Lin's protocol conditions (Scheme 132). It was, however, much less effective in the conjugate addition to α,β-unsaturated amide than Taniaphos which was used in the original protocol.[243]

Scheme 132



The Lin's protocol has been the most robust to date regarding the scope and low 5 mol% Cu(I) loading. One limitation of the method is the requirement of alkenylphosphine sulfides as electrophiles which adds one step in the preparation of substrates. The Harutyunyan's protocol complements the Lin's protocol regarding the electrophile scope, and both protocols cover a wide range of α- and β-substituted vinylphosphine derivatives. A major

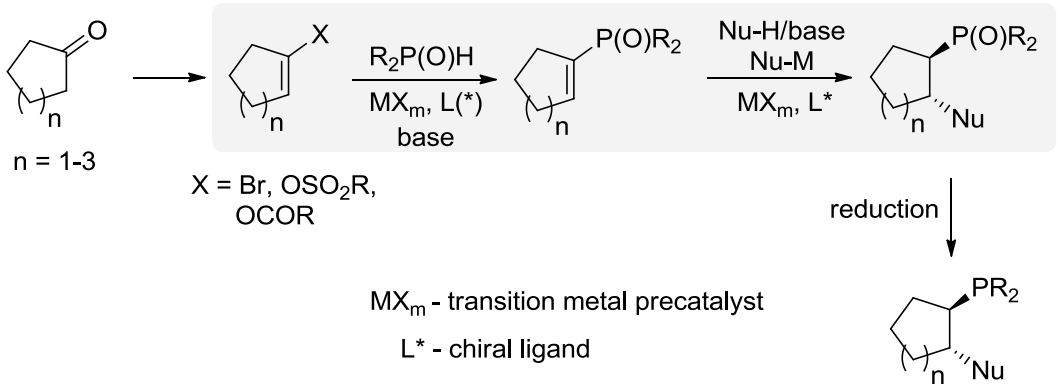
limitation of both methods is that all conjugate addition reactions were set up inside a glovebox under argon atmosphere.

In summary, the area of asymmetric metal-catalyzed conjugate addition to α,β-unsaturated organophosphorus compounds has seen great progress in the last several years, especially under copper catalysis. The scope of the nucleophiles, however, still remains fairly limited. Under copper catalysis it is now possible to install unhindered diarylphosphino and pinacolboranato groups at the β position. Carbon nucleophiles have only been used under rhodium catalysis so far and are limited to arylboronic acid derivatives.

4. Own research

As outlined in Chapter 2, the aim of this Ph.D. project was to study the viability of a synthetic pathway to 2-substituted 1-phosphinocycloalkanes starting from cycloalkanones and utilizing the combination of C-P cross-coupling of cycloalkenyl electrophiles and asymmetric conjugate addition to the cross-coupling products as the key sequence (Scheme 1). Parts of the results in this chapter have been published in a scientific paper (Cu-catalyzed C-P cross-coupling, base-catalyzed/base-promoted conjugate addition of diphenylphosphine oxide).[246] Schemes, figures, tables, and compounds are numbered anew in the following chapter.

Scheme 1



4.1. C-P cross-coupling of cycloalkenyl electrophiles and >P(O)H compounds

The first step was the identification of the most suitable protocol for the cross-coupling of cycloalkenyl electrophiles and secondary phosphine oxides to obtain tertiary cycloalkenylphosphine oxides. Copper and nickel catalysts were chosen for testing due to their cost-efficiency and diphenylphosphine oxide was chosen as the model secondary phosphine oxide. Four reactions were run under nickel catalysis with cyclohex-1-en-1-yl triflate or 1-bromocyclohexene, using $Ni(cod)_2$ as the precatalyst and three diphosphine ligands previously reported in the literature to work in analogous cross-coupling reactions with aryl coupling partners (Scheme 2, Table 1). The yields were modest in all cases. Aside from the desired product, the corresponding phosphine was formed in 2-29%. Its formation was the most prominent with the use of DCYPE or DPPP, however, the reactions with these ligands also provided higher combined yields of the phosphine oxide and phosphine. Further experiments were abandoned in favour of copper catalysis (*vide infra*).

Scheme 2

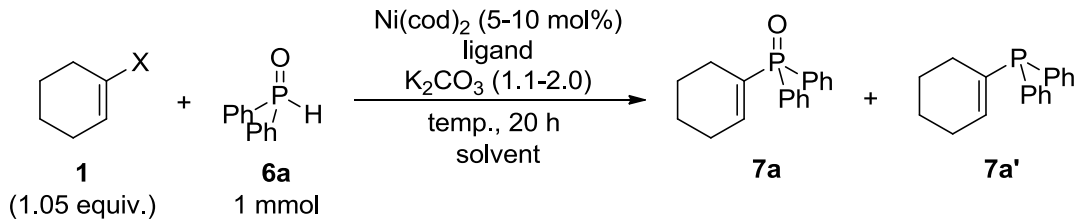
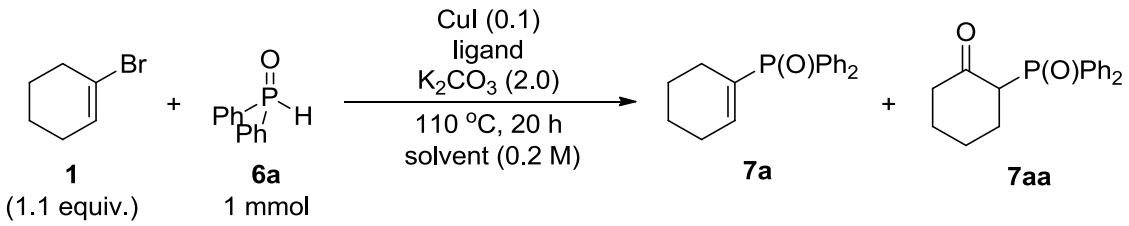


Table 1

Entry	X	$Ni(cod)_2$ [equiv.]	Ligand [equiv.]	K_2CO_3 [equiv.]	Conditions	Conv. [%]	
						PO	P
1	OTf	0.10	dppf (0.10)	1.1	dioxane (0.2 M), 95 °C	49	2
2	OTf	0.10	dcype (0.10)	1.1	dioxane (0.2 M), 95 °C	55	29
3	OTf	0.10	dcype (0.10)	2.0	toluene (0.2 M), 110 °C	51	19
4	Br	0.05	dppp (0.06)	2.0	toluene (0.1 M), 110 °C	56	17

Concurrently, the reaction was tested under copper catalysis with 1-bromocyclohexene (**1**) and diphenylphosphine oxide (**6a**) as cross-coupling partners, 10 mol% of copper(I) iodide as the precatalyst, a series of amine, phosphine and NHC ligands, potassium carbonate as the base, in toluene as the solvent (Scheme 3, Table 2). The experiments were carried out in flame-dried screw-top vials under argon atmosphere at 110 °C. Relative to copper, the amount of the ligands was typically one equivalent for bidentate ligands (10 mol%) and two equivalents of monodentate ligands (20 mol%). The exceptions were L-proline and phenanthroline which were used at 20 mol%, and TMEDA which was used at 20 mol% along with 5 mol% CuI. The reactions with L-proline, phenanthroline, (*S*)-α-phenethylamine, TMEDA and TMCyDA all gave <5% of the product (Table 5, Entries 1-5). *T*rans-cyclohexane-1,2-diamine (CyDA) and *N*,*N'*-dimethylethylenediamine (DMEDA) provided the product in 13% and 15% yield, respectively (Entries 6-7), and both triphenylphosphine and bis(dicyclohexylphosphino)ethane (dcype) were inferior (Entries 8-9). The reactions with SIMes and SIPr appeared promising due to higher conversions, however, aside from the desired cross-coupling product **7a** substantial amounts of **7a'** were obtained (Entries 10-11). In the case of SIMes, the ^{31}P NMR spectrum of the post-reaction solution did not show a peak for **7aa**, yet after filtration the ratio of **7a**/**7aa** was 5:1. The reactions with SIMes in dioxane and DMF gave inferior results (Entries 12-13).

Scheme 3



1 (1.1 equiv.) + **6a** 1 mmol → **7a** + **7aa**

Table 2

Entry	Ligand [equiv.]	Solvent	Conv. 7a/7aa [%][a]
1	**L-proline** (0.2)	toluene	<5
2	**phen** (0.2)	toluene	<5
3	**(*S*)-α-PEA** (0.2)	toluene	<5
4[b]	**TMEDA** (0.2)	toluene	<5
5	**TMCyDA** (0.1)	toluene	<5
6	**CyDA** (0.1)	toluene	13
7	**DMEDA** (0.1)	toluene	15
8	**PPh_3** (0.2)	toluene	6
9	**dcype** (0.1)	toluene	5 / 6
10	**SIMes·HCl** (0.12)	toluene	50
11	**SIPr·HCl** (0.12)	toluene	31 / 19
12	**SIMes·HCl** (0.12)	dioxane	21
13	**SIMes·HCl** (0.12)	DMF	8

a) The conversion based on the ^{31}P NMR spectrum of the post-reaction mixture; b) CuI (0.05) was used.

Based on the initial results obtained for the model cross-coupling reaction, DMEDA was chosen as the ligand for further optimization (Scheme 4, Table 3). Firstly, four reactions with an increasing amount of the ligand were carried out (Entries 1-4). Up to 30 mol% of DMEDA, the yield increased with increasing loading, reaching 51%, however, at 40 mol% the yield dropped to 25%. Thus the optimization was continued using 10 mol% of CuI and 30 mol% of DMEDA. Next, two reactions with 25% and 50% excess of diphenylphosphine oxide were run. Unfortunately, the yield decreased drastically and it was lower with the higher excess (Entries 5-6). On the other hand, satisfying yields of 78% and 73% were obtained by using 2.0 equiv. of bromocyclohexene in toluene and dioxane, respectively. Inexplicably, with 1.5 equiv. of the bromide, the reactions in toluene produced inferior results to the reaction with a near-stoichiometric ratio (Entry 7). The yield in dioxane was higher but still inferior to the best conditions (Entry 11). Interestingly, the order of the addition of the

substrates was crucial for high yield. Good yields were obtained when bromocyclohexene was added first to the solution of CuI/DMEDA followed by diphenylphosphine oxide. When this order was reversed, the yields were much lower both in toluene and dioxane (Entries 9-10).

Scheme 4

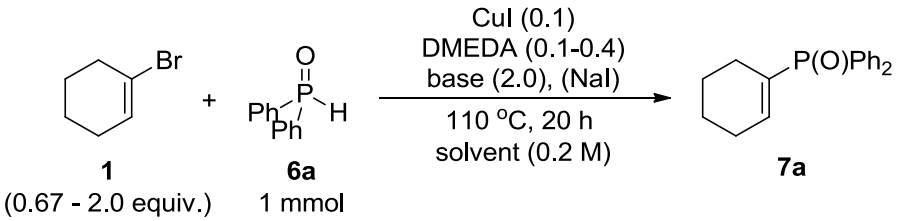


Table 2

Entry	DMEDA [equiv.]	Base	Additive	RBr/NuH ratio	Solvent	Conversion (Yield) [%]
1	0.1	K_2CO_3	-	1.1	toluene	15
2	0.2	K_2CO_3	-	1.1	toluene	45
3	0.3	K_2CO_3	-	1.1	toluene	51 (50)
4	0.4	K_2CO_3	-	1.1	toluene	25
5	0.3	K_2CO_3	-	0.8	toluene	24
6	0.3	K_2CO_3	-	0.67	toluene	11
7	0.3	K_2CO_3	-	1.5	toluene	39, 42
8	0.3	K_2CO_3	-	2.0	toluene	87 (78)
9[b]	0.3	K_2CO_3	-	2.0	toluene	33
10[b]	0.3	K_2CO_3	-	1.1	dioxane	12
11[c]	0.3	K_2CO_3	-	1.5	dioxane	70
12[a,c]	0.3	K_2CO_3	-	2.0	dioxane	84 (73)
13	0.3	K_2CO_3	NaI (1.5)	1.1	dioxane	85 (76)
14[b]	0.3	K_2CO_3	NaI (2.0)	1.1	dioxane	80 (73)
15[b]	0.3	K_2CO_3	NaI (2.6)	1.3	dioxane	57
16	0.3	Cs_2CO_3	NaI (1.5)	1.1	dioxane	12, 99 (91)[d]

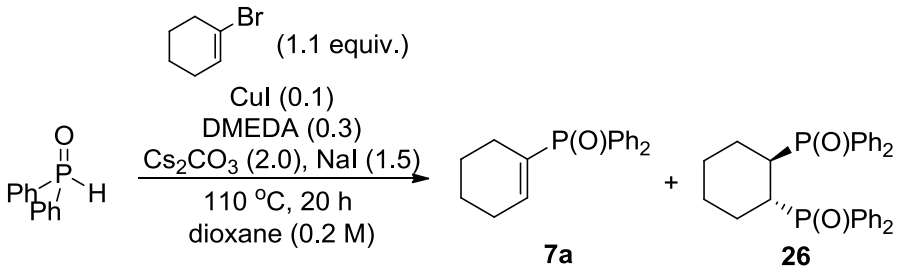
a) 2 mmol scale; b) inverse addition of reagents to CuI/DMEDA; c) 0.4 M concentration; d) 5 mmol scale.

Despite satisfying yields, the requirement of a huge excess of the bromide was a serious drawback of the protocol, considering the atom efficiency and viability of a one-pot tandem reaction. Small amounts of 1-iodocyclohexene were isolated in the first fraction after column chromatography along with unreacted 1-bromocyclohexene, which meant that halogen exchange must have taken place to an extent. This finding led to an idea that it might be possible to carry out a tandem halogen exchange/cross-coupling reaction, forming *in situ*

the presumably more reactive cyclohexenyl iodide. Halogen exchange was also desirable as opposed to using 1-iodocyclohexene directly, as the iodide turned out to be a very unstable liquid darkening significantly during the purification process, and thus was inconvenient as a substrate. While 1-bromocyclohexene itself also becomes discoloured if stored at room temperature, it can be isolated as a colourless liquid if care is taken to restrict oxygen and light access during work-up and purification, and it is stable at least for 6 months when stored in an amber bottle at 4 ^{o}C under argon.

Previously, Fu et al. performed halogen exchange of bromobenzene and *p*-bromotoluene in the presence of CuI/L-proline or CuI/PPAPM catalyst and potassium iodide prior to adding dialkyl phosphite which increased the overall reaction time to 48-60 h.[207,208] Klapars and Buchwald reported on Cu-catalyzed bromine/iodine exchange of aryl bromides using a CuI/DMCyDA catalytic system and under similar conditions to Cu-catalyzed cross-coupling C-P cross-coupling.[245] Nonetheless, concurrent tandem halogen exchange/C-P cross-coupling has not been previously reported. Thus, the model reaction was run under the previously optimized conditions in dioxane, with 1.1. equiv. of 1-bromocyclohexene and 1.5 equiv. of sodium iodide. The reaction was successful and the yield of the product was comparable to the reaction with excess bromide and no iodide additive (Table 3, Entry 13). Also, the reaction with sodium iodide was not sensitive to the order of the addition of the substrates (Entry 14), however, higher excess of the iodide salt was detrimental to the yield (Entry 15). The yield of the cross-coupling could be further increased to 91% with Cs_2CO_3 as the base when the reaction was run at 5 mmol scale, on the other hand, when it was run with 1 mmol of $Ph_2P(O)H$, the yield was only 12%.

Scheme 5



scale	7a	26
0.5 mmol	15%	12%
1.0 mmol	12%	46%
5.0 mmol	91%	<1%
5.7 mmol	86%	<1%
10.0 mmol	83%, 86%	<1%

The reaction turned out to be highly sensitive to scale with Cs_2CO_3 during the kinetic study (*vide infra*, section 4.1.2.). Good yields were obtained at the scale of 5.0 mmol or higher (83-91%), whereas poor conversion was observed at the scale of 1 mmol or lower along with substantial amounts of the conjugate addition product, diphosphine dioxide **26** (Scheme 5). Also, the high temperature of 110 ^oC as well as CuI as the precatalyst were both required for the reaction to work, as two control reactions, one with CuI at 80 ^oC and the other with $Cu(OTf)_2$ at 110 ^oC, only afforded traces of products. The impact of the base was then tested for 1-bromocyclopentene and 1-bromocycloheptene (Scheme 6, Table 3). The former behaved similarly to its higher homologue and reacted well with K_2CO_3 but poorly with Cs_2CO_3. On the other hand, 1-bromocycloheptene gave high yields of the product with both bases, with Cs_2CO_3 performing slightly better.

Scheme 6

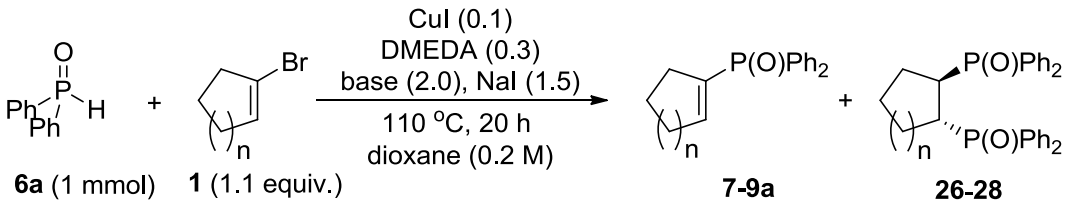
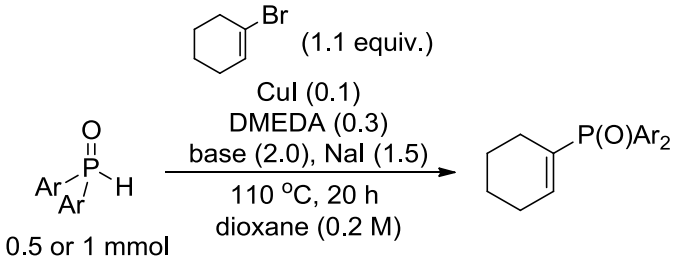


Table 3

Entry	n	Yield 7-9/26-28 [%]	
		K_2CO_3	Cs_2CO_3
1	1	84 / <1	2 / 17
2	2	76 / <1	12 / 46
3	3	88 / <1	92 / <1

Subsequently, the cross-coupling of di(*p*-tolyl), di(*o*-tolyl) and dicyclohexylphosphine oxides (**6b**, **6c**, **6g**) with 1-bromocyclohexene was carried out at 1 mmol scale using both bases (Scheme 7). K_2CO_3 turned out be a poor base, providing a satisfying yield (68%) only for the di(*p*-tolyl) analogue **7c**. The reactions with more hindered phosphine oxides were less efficient, with a markedly decreased yield for di(*o*-tolyl) analogue **7b** (41%) and very low yield for dicyclohexyl analogue **7g** (10%). Superior yields were obtained for these three phosphine oxides with Cs_2CO_3 as the base, and, interestingly, they were not sensitive to the low scale unlike the case of diphenylphosphine oxide.

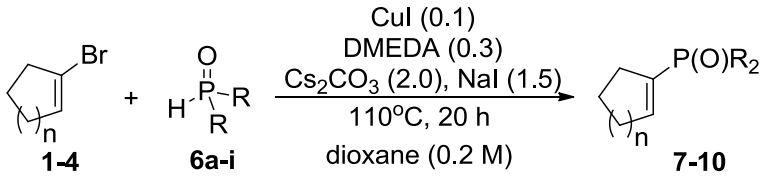
Scheme 7

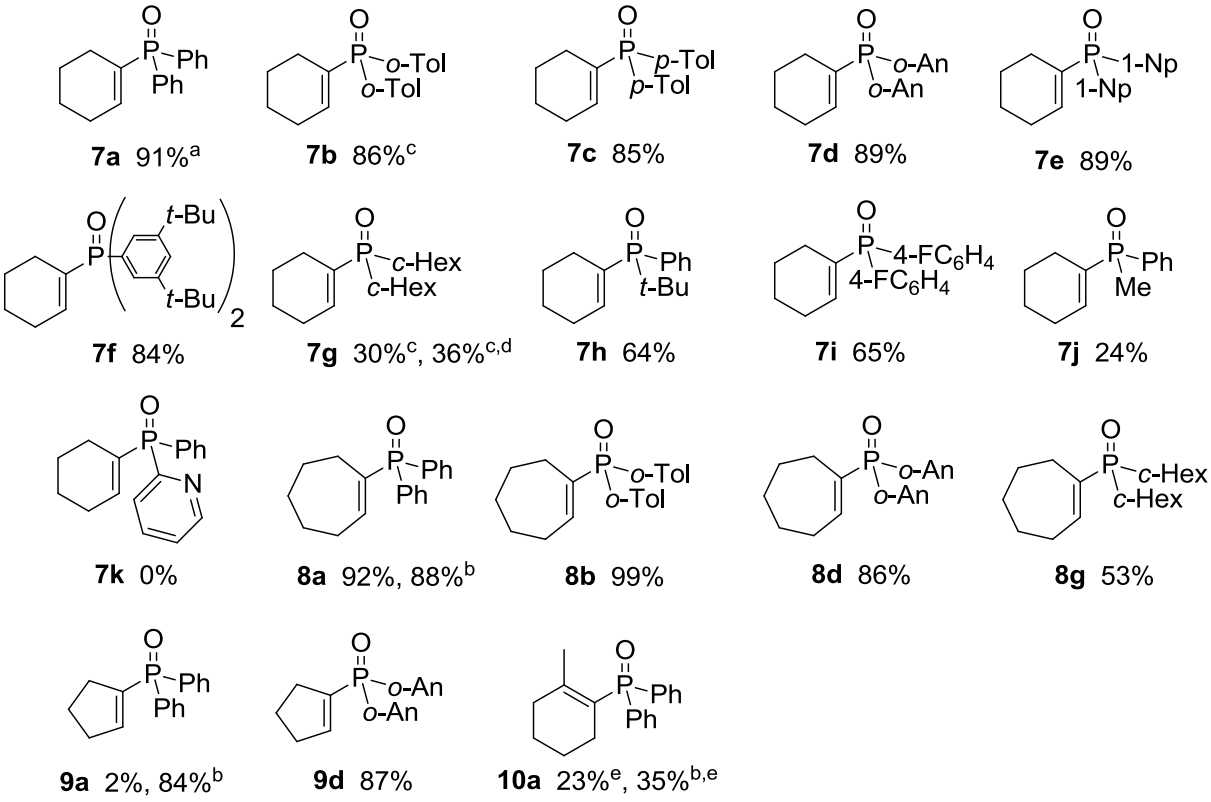


Ar	K_2CO_3	Cs_2CO_3
Ph	76%	12%, 91%[a]
p-Tol	68%	85%
o-Tol	41%	86%
Cy	10%	30%

[a] 5 mmol scale

Scheme 8





Isolated yields are given; a) the reaction run at 5 mmol scale; b) K_2CO_3 as the base; c) the reaction run at 0.5 mmol; d) DMCyDA was used as the ligand; e) a 62:38 mixture of 2-methyl- and 6-methyl-1-bromocyclohexenes was used, 6-methyl analogue was obtained as the minor product in 6% with both K_2CO_3 and Cs_2CO_3.

In the next step, the scope of the tandem halogen exchange/C-P cross-coupling was tested (Scheme 8). The reaction worked well with a series of diarylphosphine oxides **6b-f** possessing electron-donating substituents at the phosphorus atom (85-89% yield) regardless

of steric hindrance. Lower but still moderately good yields were obtained for bis(4-fluorophenyl)phosphine oxide **6i** (65%) and phenyl(*tert*-butyl)phosphine oxide **6h** (64%). Low yields were obtained for dicyclohexyl and methyl(phenyl)phosphine oxides **6g** and **6i** (24-36%), whereas phenyl(2-pyridyl)phosphine oxide **6k** was unreactive. 1-Bromocyclopentene and 1-bromocycloheptene were equally viable substrates for the reaction providing similar yields to 1-bromocyclohexene in the reactions with diarylphosphine oxides. In the reaction with dicyclohexylphosphine oxide, however, 1-bromocycloheptene proved to be more reactive providing the product **8g** with 53% yield. The reaction did not work well with diphenylphosphine oxide and a mixture of 2-methyl- and 6-methyl-1-bromocyclohexenes, affording 23% of the major product **10a** with Cs_2CO_3 and 35% with K_2CO_3.

Further optimization of the cross-coupling of dicyclohexylphosphine oxide was undertaken due to the low yields (Scheme 9, Table 4). The reaction had been first tested with 2 equiv. of 1-bromocyclohexene using DMEDA (30 mol%) or SIMes (11 mol%) as the ligand, K_2CO_3 as the base, in the absence of NaI additive (Entries 1-2). The experiment with DMEDA afforded no product at all while the reaction with SIMes provided a comparable yield to the reaction with NaI (Entry 3). The tandem reaction was also carried out with triphenylphosphine as the ligand but to no avail (Entry 4). The reaction with Cs_2CO_3 and NaI was a major improvement affording the product in 30% isolated yield (Entry 5), and thus, further experiments were focused on fine-tuning the reaction. Increasing the amount of 1-bromocyclohexene to 2 equiv. along with increasing the amount of NaI to 2.7 equiv. resulted in no conversion (Entry 6). On the other hand, a slight increase of the yield to 36% was achieved by using *N*,*N'*-dimethylcyclohexane-1,2-diamine (DMCyDA), the cyclic analogue of DMEDA, as the ligand. (Entry 7). Several bases were subsequently tested. Stronger alkoxide and hydroxide bases were inferior not only to Cs_2CO_3 but also to K_2CO_3, affording traces of the product (Entries 8-9). Deprotonation of the secondary phosphine oxide with NaH directly before the reaction was also ineffective (Entry 10). K_3PO_4 was more effective but still considerably worse than Cs_2CO_3 (Entry 11).

Scheme 9

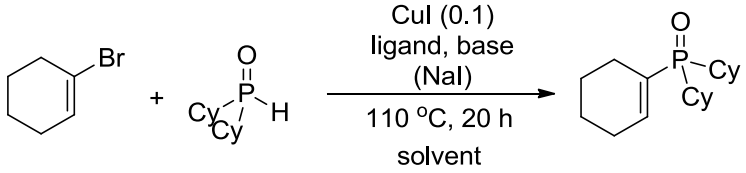
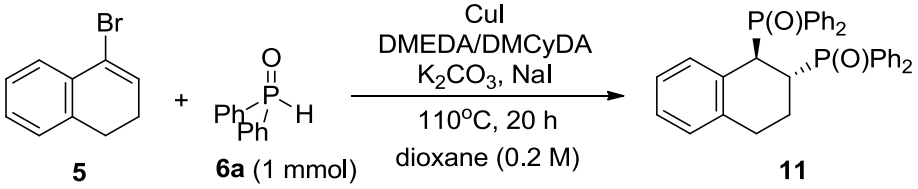


Table 4

Entry	R-Br [equiv.]	Ligand	NaI [equiv.]	Base [equiv.]	Solvent	Conv. (Yield) [%]
1	2.0	**DMEDA** (0.3)	-	K_2CO_3 (2.0)	toluene	<5
2	2.0	**SIMes-HCl** (0.11)	-	K_2CO_3 (2.0)	toluene	14
3	1.1	**DMEDA** (0.3)	1.5	K_2CO_3 (2.0)	dioxane	10
4	1.1	**PPh_3** (0.4)	1.5	K_2CO_3 (2.0)	dioxane	0
5	1.1	**DMEDA** (0.3)	1.5	Cs_2CO_3 (2.0)	dioxane	47 (30)
6	2.0	**DMEDA** (0.3)	2.7	Cs_2CO_3 (2.0)	dioxane	0
7	1.1	**DMCyDA** (0.3)	1.5	Cs_2CO_3 (2.0)	dioxane	51 (36)
8	1.1	**DMEDA** (0.3)	1.5	LiO*t*-Bu (1.5)	dioxane	0
9	1.1	**DMCyDA** (0.3)	1.5	$CsOH·H_2O$ (2.0)	dioxane	2
10	1.1	**DMCyDA** (0.3)	1.5	NaH (1.0)	dioxane	0
11	1.1	**DMCyDA** (0.3)	1.5	K_3PO_4 (2.0)	dioxane	18

The halogen exchange/cross-coupling protocol turned out to be unsuitable for an activated bromoolefin, 1-bromotetrahydronaphthalene (**5**). The procedure yielded the diphosphine dioxide **11** as the major product, most likely as a result of the conjugate addition of diphenylphopshine oxide to the cross-coupling product taking place more rapidly than the coupling itself (Scheme 10, Table 5).

Scheme 10



5 **6a** (1 mmol) **11**

Table 5

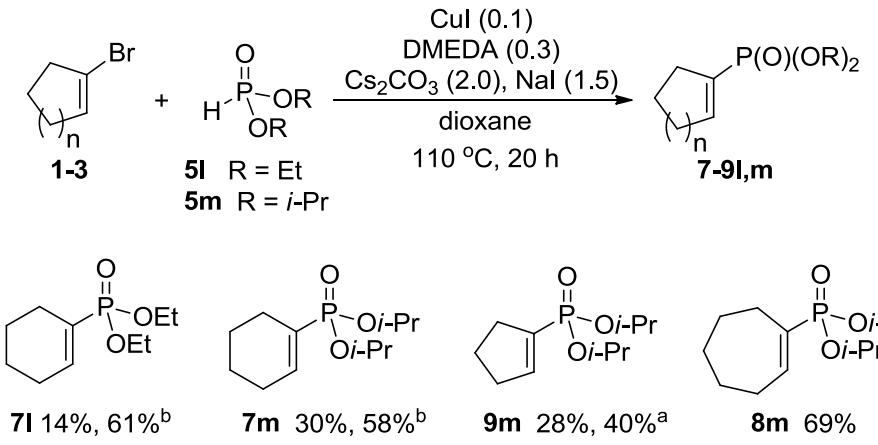
Entry	CuI [mmol]	Ligand [mmol]	R-Br [mmol]	NaI [mmol]	Base [equiv.]	Conv. (Yield) [%]	SPO conv. [%]
1	0.1	0.3	1.1	1.5	K_2CO_3 (2.0)	61 (45)	74
2[a]	0.1	0.3	1.5	1.5	K_2CO_3 (2.0)	40	48
3	0.05	0.15	0.5	0.75	K_2CO_3 (1.5)	16	21
4[b]	0.05	0.15	0.5	0.75	K_2CO_3 (1.5)	16	20
5	0.1	0.3	0.5	0.75	Cs_2CO_3 (1.5)	17	63
a) DMCyDA was used as the ligand, b) MeOH (0.5 mmol) was added							

The cross-coupling product was observed only in trace amounts in the mixed fraction with other minor products. The highest yield of **11** was obtained under the previously optimized conditions, with K_2CO_3 as the base. Attempts to increase the yield of this product either by using the bromide in excess (Table 5, Entry 2) or by using 2 equivalents of

diphenylphosphine oxide (Entry 3) were unsuccessful. In the case of the latter the addition of MeOH as the proton source had no effect on the yield compared to the reaction without it (Entry 4). Similarly, changing the base to Cs_2CO_3 and using the catalyst at a higher loading gave a comparable yield despite higher conversion of diphenylphosphine oxide (Entry 5).

The protocol was also tested with diethyl and diisopropyl phosphites but did not prove general (Scheme 11). The reaction of diethyl phosphite with 1-bromocyclohexene afforded the product with a poor yield of 14%. Diisopropyl phosphite was more effective, however, a moderately good yield was obtained only in the reaction with 1-bromocycloheptene. In the case of 1-bromocyclopentene, a better yield was obtained by changing the base to K_2CO_3 (40%). However, the protocol with 2 equivalents of the bromide and without NaI appears to be superior for H-phosphonates, as in the reaction of 1-bromocyclohexene it provided the product **7k** with 58% yield.

Scheme 11



Isolated yields are given; a) K_2CO_3 was used as the base; b) the reaction was carried out in toluene using 2.0 equiv. of the bromide, K_2CO_3 as the base and no NaI additive.

4.1.1. Cross-coupling with acyclic alkenyl and aryl bromides

Due to the lack of available protocols for *P*-alkenylation of secondary phosphine oxides with acyclic bromoalkenes under copper catalysis, the presented Cu-catalyzed halogen exchange/C-P cross-coupling was tested in a series of reactions of diphenylphosphine oxide with four bromoalkenes with a varying degree of substitution (Scheme 12, Table 6). In the case of less substituted bromoolefins, considerable amounts of conjugate addition products were obtained. The reactions of 2-bromopropene and *trans*-1-bromopropene afforded

alkenylphosphine oxides **12** and **13** in 44% and 68%, respectively, along with diphosphine dioxide **16** in 40% and 30%, respectively. Higher yields of the cross-coupling products were obtained with the more hindered bromoolefins possessing two β-methyl substituents – 1-bromo-2-methylprop-1-ene and 2-bromo-3-methylbut-2-ene. In the case of the former, aside from the coupling product **14** (85%), small amounts of the isomerized allylphosphine oxide **14a** and the conjugate addition product **17** were also formed. The reaction of the latter afforded exclusively the cross-coupling product **15** albeit in a slightly reduced yield of 75%. All the reactions were carried out using K_2CO_3 as the base, and they were not compatible with Cs_2CO_3. With the caesium base, the reactions of 2-bromopropene and 1-bromo-2-methylprop-1-ene afforded diphosphine dioxides **16** and **17** in 27% and 14%, respectively, with no detectable levels of the alkenylphosphine oxides.

Scheme 12

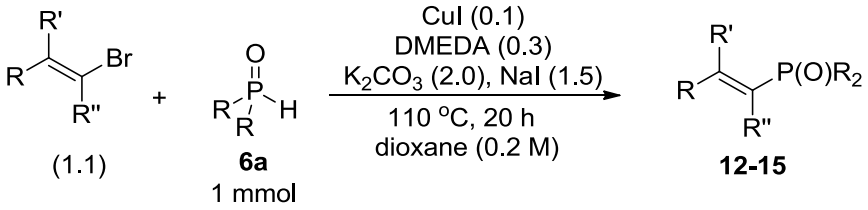
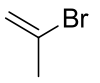
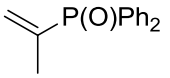
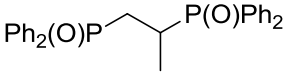
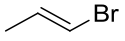
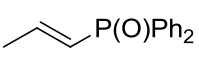
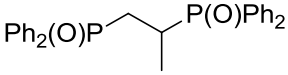
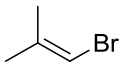
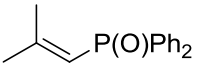
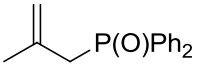
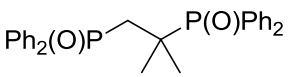
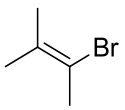
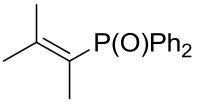


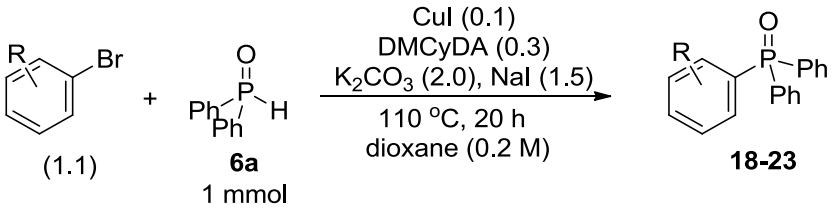
Table 6

Entry	Bromoalkene	Products[a]
1		 **12** 47% (44%)  **16** 48% (40%)
2		 **13** 70% (68%)  **16** 30%
3		 **14** 89% (85%)  **14a** 5% (4%)  **17** 5%
4		 **15** 94% (75%)

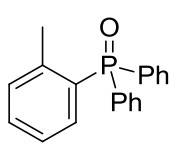
a) Conversions based on ^{31}P NMR spectra of post-reaction mixtures, isolated yields are given in parentheses

At the time of publishing the paper on the presented method, there have been no protocols available for the coupling of secondary phosphine oxides with unactivated aryl bromides under copper catalysis. Thus, diphenylphosphine oxide was reacted with six aryl bromides under the optimized conditions albeit with DMCyDA as the ligand (Scheme 13). This change was dictated by a slightly higher yield of the cross-coupling of *o*-bromotoluene with the cyclic analogue of DMEDA (15% vs. 10%). As with acyclic bromoalkenes, it was crucial to use K_2CO_3 as the base, as with Cs_2CO_3 no cross-coupling products were obtained. The reaction was sensitive to steric hindrance in the aryl coupling partner as exemplified by the low yields of the *o*-tolyl and 1-naphthylphosphine oxides **18** and **19**, 14% and 34%, respectively. On the other hand, electron density of the aryl ring had a small impact, as both 3-bromotoluene and 1-bromo-4-trifluoromethylbenzene gave moderately good yields of the products **20** (69%) and **21** (72%). Interestingly, the reactions of *o*-bromoanisole and *o*-bromoaniline afforded the products **22** and **23** with considerably higher yields than *o*-bromotoluene, this can be attributed to the ability of methoxy and amino groups to coordinate to copper.

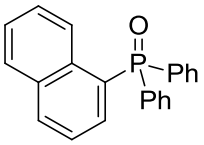
Scheme 13



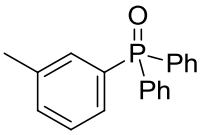
Products[a]



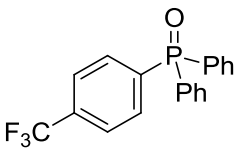
18 15% (14%)
10%[b]



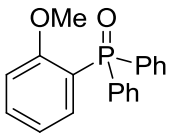
19 37% (34%)



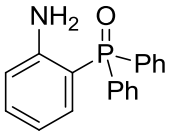
20 77% (69%)



21 88% (72%)



22 82% (71%)



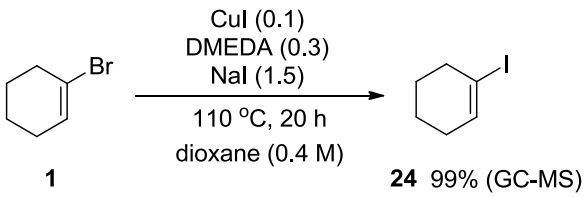
23 51% (43%)

a) Conversions based on ^{31}P NMR spectra of post-reaction mixtures, isolated yields are given in parentheses; b) DMEDA (30 mol%) was used as the ligand

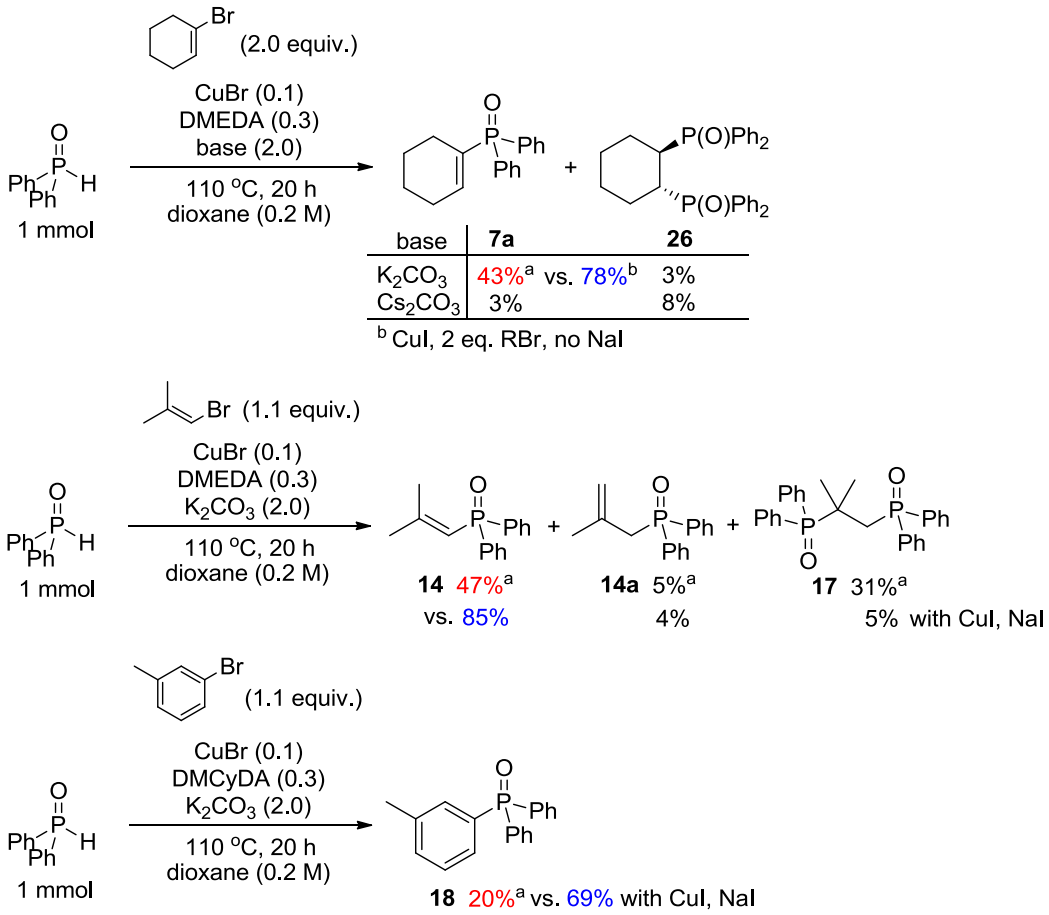
4.1.2. The role of sodium iodide additive

In order to gain more insight into the role of sodium iodide as an additive, I carried out several control reactions. First, a halogen exchange reaction with 1-bromocyclohexene under the cross-coupling conditions has been run, without secondary phosphine oxide and base (Scheme 14). Full conversion to the corresponding iodide (**24**) was observed by GC-MS after 20 hours. Next, the cross-coupling reactions of diphenylphosphine oxide with 1-bromocyclohexene, 1-bromo-2-methylpropene, and 3-bromotoluene using CuBr as the precatalyst rather than CuI and without NaI has been carried out (Scheme 15).

Scheme 14



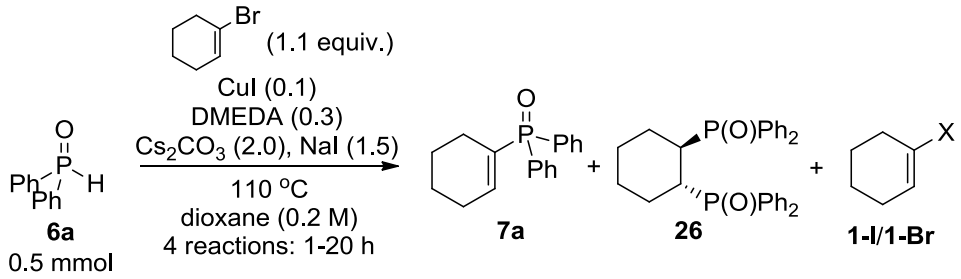
Scheme 15[a]



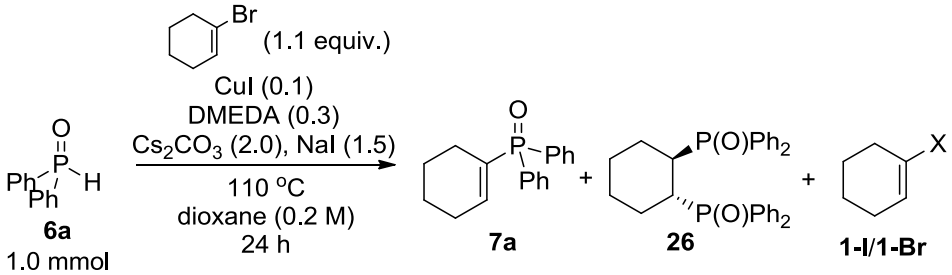
a) Yields calculated from ^{1}H NMR spectra of post-reaction mixtures against mesitylene as an internal standard

In all cases the cross-coupling did take place albeit with much inferior yields in comparison with the reactions with CuI as the precatalyst, with or without NaI. In the case of 1-bromocyclohexene, the reaction with 2.0 equiv. of the bromide afforded the product **7a** in 43% yield. This is much lower than 78% obtained under the same conditions with CuI. Similarly, in the case of 1-bromo-2-methylpropene, the yield with CuBr was only 47% compared to 85% with CuI and NaI. Aside from that, a significant amount of the conjugate addition product **17** was formed (37%). The reaction with 3-bromotoluene also suffered from a serious yield decrease from 69% with CuI and NaI to 20% with CuBr.

Scheme 16



time	**7a** [%]	**26** [%]	Br/I
1 h	13	0	3 : 97
2 h	11	5	<1 : 99
3 h	7	8	<1 : 99
20 h	15	12	not detected



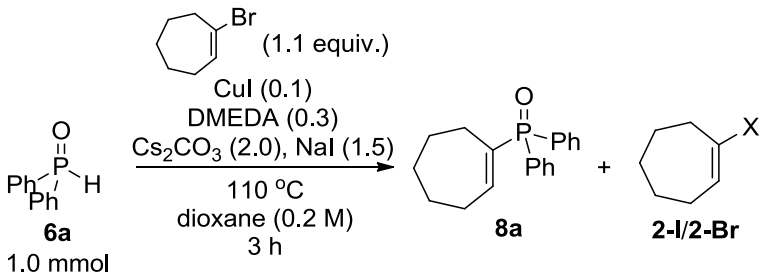
time	**7a** [%]	**26** [%]	Br/I
1 h	0	0	4 : 96
2 h	29	0	
3 h	25	6	
4 h	23	14	
5 h	23	22	
24 h	12	46	not detected

Finally, a kinetic study of the tandem halogen exchange/C-P cross-coupling between diphenylphosphine oxide and 1-bromocyclohexene has been performed (Scheme 16). First, four reactions were set up under the optimized conditions with Cs_2CO_3 as the base and they were stopped after 1, 2, 3 and 20 hours, respectively. The experiment revealed that the halogen exchange was very fast and nearly full conversion was observed already after 1 hour, however, the cross-coupling proceeded poorly. After 1 hour, 14% conversion to **7a** was

observed, and the reactions quenched after 2, 3, and 20 hours showed a slow steady formation of **26**. Over the period from the 1st hour mark to the 3rd hour mark there was no new formation of **7a** and it was only being used up in the conjugate addition. However, from the 3rd hour to the 20th hour mark, the conversion to **7a** increased by about 7%. The experiment was repeated at the 1.0 mmol scale, however, a single reaction was set up and sampled after 1, 2, 3, 4, 5, and 24 hours. Generally, the progress and outcome were similar, with the fast halogen exchange and an initial spike in the conversion to **7a** from the 1st hour mark to the 2nd hour mark followed by a slow steady formation of **26** but no new formation of **7a** until the 4th hour mark, and a second smaller spike by 5% over the period between the 4th hour and 5th hour mark. The biggest difference between the 0.5 and 1.0 mmol experiments was the final overall conversion at 27% and 58%, respectively.

These results suggest that the catalyzed cross-coupling becomes inhibited after the reaction reaches a certain level of conversion, while unreacted $Ph_2P(O)H$ is slowly undergoing conjugate addition to the already formed **7a**. The inhibition of the reaction may be explained by the formation of inactive copper(I) complexes with multiple $Ph_2P(O)H/Ph_2POH$ ligands. It is unclear, however, why this would happen with Cs_2CO_3 but not with K_2CO_3, and at the scale of 1 mmol and below but not at 5 mmol and above. One explanation may be that proportionally more water enters the reaction vessel at the lower scale and in combination with Cs_2CO_3 promotes deprotonation of $Ph_2P(O)H$ to form Ph_2POCs, which at a high enough concentration may push the equilibrium towards catalytically inactive copper species. The diphosphine dioxide **26** that is being formed possibly also impacts the equilibria between different copper species by acting as a bidentate ligand competing with DMEDA and $Ph_2P(O)H$.

Scheme 17

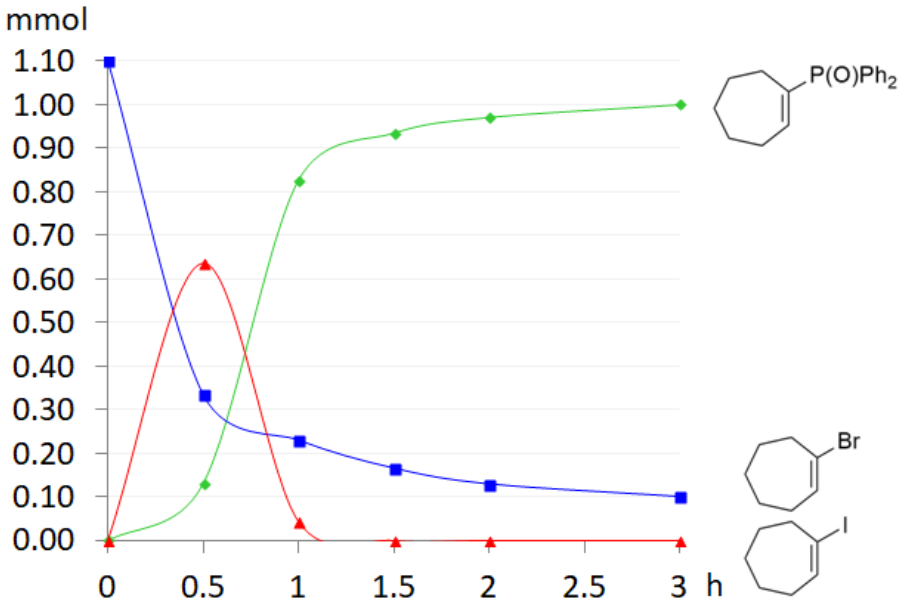


time	**8a** [%]	Br/I
0.5 h	13	34 : 66
1.0 h	83	84 : 16
1.5 h	93	100 : 0
2.0 h	97	100 : 0
2.5 h	-	100 : 0
3.0 h	100	100 : 0

Considering the reaction with 1-bromocyclohexene and Cs_2CO_3 cannot be seen as representative of the halogen exchange/cross-coupling, the kinetic study was performed with

1-bromocycloheptene instead. This was done by setting up the reaction under the optimized conditions at the 1 mmol scale, withdrawing a sample every 30 minutes, and analysing it by ^{31}P NMR spectroscopy and GC-MS (Scheme 17, Figure 1). The experiment revealed that the halogen exchange was initially much faster than the cross-coupling, however, both reactions took place concurrently. The reaction had two apparent phases. During the first 30 minutes, fast halogen exchange led to a build-up of 1-iodocyclohexene, while the cross-coupling proceeded only slowly. After the first 30 minutes, the rate of the cross-coupling increased substantially and it reached full conversion after 3 hours. At the same time the rate of the halogen exchange decreased substantially as a result of copper entering the cross-coupling cycle, and the iodoolefin formed in the halogen exchange between the 0.5 and 3.0 hour marks was immediately consumed in the cross-coupling cycle. However, the involvement of 1-bromocycloheptene as a coupling partner in the late stage of the reaction cannot be ruled out. At endpoint there was only unreacted 1-bromocycloheptene in the post-reaction mixture and no 1-iodocycloheptene was present.

Figure 1

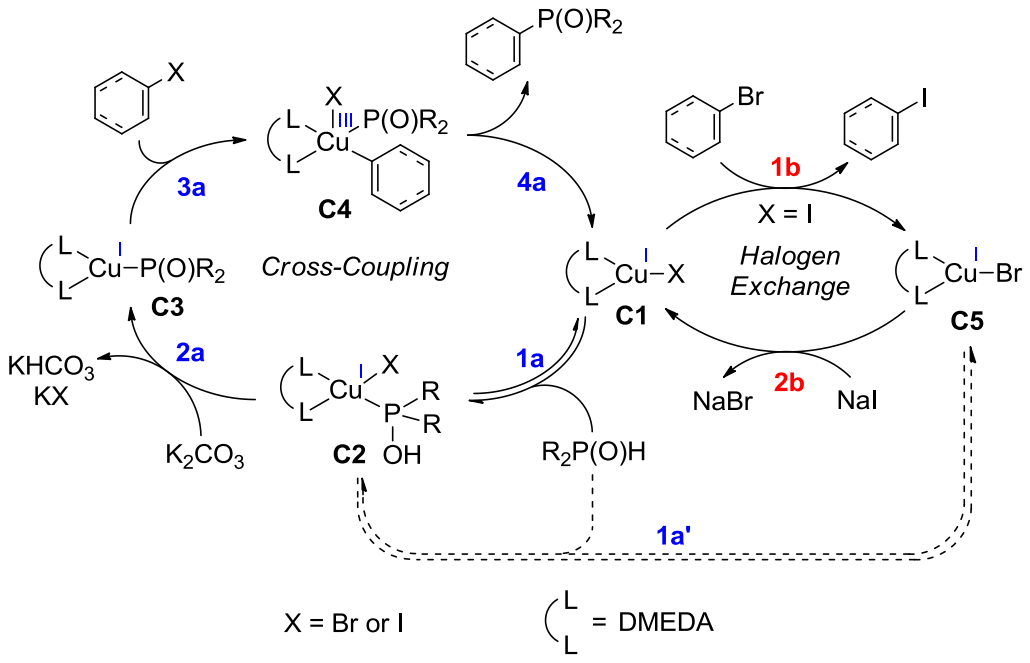


Based on the obtained results and previous studies published in the literature,[222,223] the dual catalytic cycle for the copper-catalyzed tandem halogen exchange/C-P cross-coupling is proposed as depicted in Scheme 18. The complex **C1**, readily formed from CuI and DMEDA or DMCyDA, acts as a catalyst for both the halogen exchange and cross-coupling. In the halogen exchange cycle, it reacts with an organic bromide to form the corresponding

iodide and the copper(I) bromide complex **C5** (**1b**) which is then transformed back to **C1** in a reaction with NaI additive (**2b**). Alternatively, **C5** can enter the cross-coupling cycle directly via **1a'** (predominant in the absence of NaI additive). In the cross-coupling cycle, the first step is the coordination of a secondary phosphine oxide to form the tetraligated complex **C2** (**1a**). This is followed by base-assisted substitution of the halide to form the complex **C3** with concomitant release of bicarbonate and halide salts (**2a**). Then **C3** undergoes oxidative addition to (cyclo)alkenyl or aryl halide to form the Cu(III) complex **C4** (**3a**). Reductive elimination from **C4** reinstates the catalyst **C1** and releases the cross-coupling product (**4a**).

The positive effect of excess diamine in relation to copper and the detrimental effect of excess $Ph_2P(O)H$ observed in the optimization study both suggest that the in-cycle copper species are in equilibrium with catalytically inactive species akin to bis(amidate)- and bis(imidate)cuprates, reported to be much less active than neutral monoamidate/monoimidate complexes in copper-catalyzed C-N cross-coupling.[247]

Scheme 18



The control reactions with CuBr as the precatalyst (*vide supra*, Scheme 15) prove that the organic bromides can participate in the cross-coupling on their own, however, the cross-coupling was much more effective when CuI was used, with or without NaI additive. In both cases, the efficiency of the cross-coupling is increased indirectly by increasing the efficiency of the halogen exchange and formation of the more reactive organic iodides. The rate of the halogen exchange is increased in the presence of NaI additive

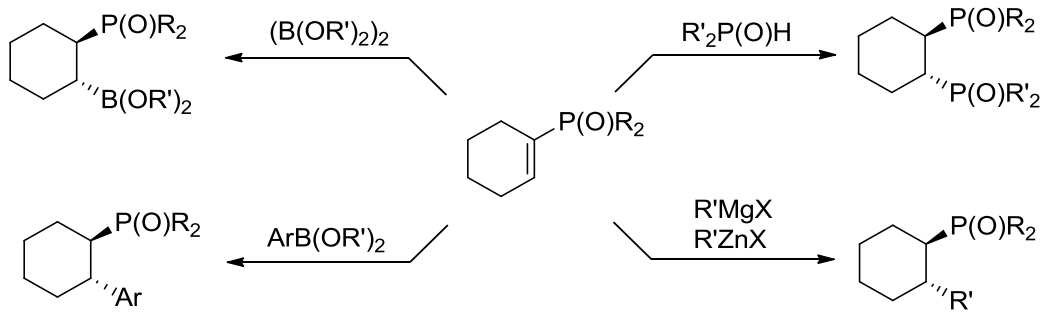
because it promotes the restoration of the catalyst **C1** from **C5** (**2b**) over the complexation of **C5** by the secondary phosphine oxide (**1a'**). NaI may also react with copper(I) halide complexes to form dihalocuprates which may act as an off-cycle reservoir of copper, preventing it from becoming inactivated by the complexation with multiple $Ph_2P(O)H/Ph_2POH$ ligands. Nevertheless, too much NaI has a negative effect on the reaction yield (*vide supra*, Table 2, Entries 14-15 and Table 4, Entries 5-6).

On the other hand, in the absence of NaI additive, the rate of the halogen exchange is increased by using excess organic bromide which promotes the step **1b** over **1a**. Then **C5** enters the cross-coupling cycle via **1a'**. Step **2b** is likely much less relevant in this case, as KI or CsI can only form at the expense of **C1** entering the cross-coupling cycle and undergoing the base-assisted substitution of the iodide (**2a**). The steps **1a** and **1a'** are reversible, however, **2a** is not. Assuming a non-significant reactivity of an organic bromide relative to the analogous iodide, in the absence of NaI additive, the rate of the halogen exchange (**1b**) must be equal or faster than the combined rate of **1a** and **2a**, otherwise the reaction will eventually stall because all the available copper will end up as the complex **C3** with no organic iodide available to complete the cycle.

4.2. Conjugate addition to cycloalkenylphosphine derivatives

The second part of this Ph.D project was devoted to the development of asymmetric catalytic conjugate addition to cycloalkenylphosphine derivatives. It was further divided into four subparts dealing with different nucleophiles (Scheme 19).

Scheme 19



4.2.1. Conjugate addition of diphenylphosphine oxide

The research on the asymmetric conjugate addition to cycloalkenylphosphine derivatives was started with the model conjugate addition reaction between cyclohexenyl(diphenyl)phosphine oxide (**7a**) and diphenylphosphine oxide using copper catalysts formed *in situ* from copper precatalysts and non-chiral diamine or diphosphine ligands to test the viability of the approach (Scheme 20, Table 7). Under the conditions similar to the cross-coupling reaction using CuI/DMEDA and K_2CO_3 no product was formed (Entry 1). On the other hand, when the *in situ* formed CuI/dppp complex (10 mol%) was combined with LiO*t*-Bu (20 mol%), the conjugate addition product was isolated in 70% yield. However, two control reactions with same amount of the alkoxide and without the copper complex afforded the product with a higher yield, the reaction in dioxane was marginally more effective (Entry 10-11). This suggested that in the presence of a Cu(I) complex the reaction may not be catalyzed by metal. Indeed, when an equimolar amount of a copper precatalyst and *tert*-butoxide were stirred at r.t. for 15 min. to form a copper(I) *tert*-butoxide complex, prior to adding the remaining reagents, the reaction did not work (Entries 3-8). Similarly, the reaction with $NiCl_2/AgBF_4$, 2,2'-bipyridine and 2 equiv. of Cs_2CO_3 afforded the product with a much lower yield (Entry 9) than the control reaction in the absence of the metal salts and the ligand (Entry 13). Bipyridine was excluded as the catalyst (Entry 12).

Scheme 20

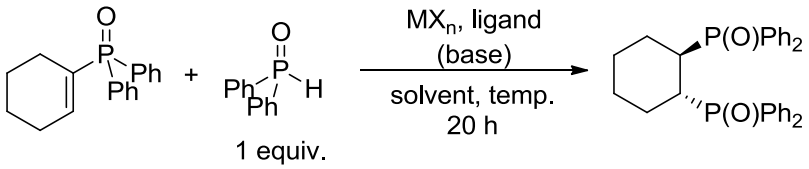
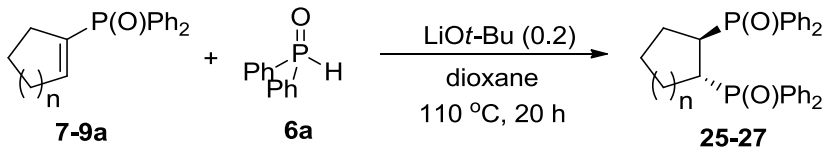


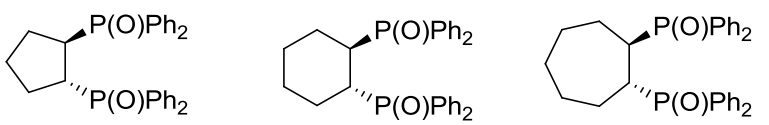
Table 7

Entry	Precatalyst [equiv.]	Ligand [equiv.]	Base/additive [equiv.]	Solvent	Isol. yield [%]
1	CuI (0.1)	DMEDA (0.2)	K_2CO_3 (1.2)	PhMe, 110 °C	<5
2	CuI (0.1)	dppp (0.1)	LiO*t*-Bu (0.2)	PhMe, 110 °C	70
3	$CuPF_6(MeCN)_4$ (0.1)	dppbz (0.12)	LiO*t*-Bu (0.14)	PhMe, r.t.	<5
4[a]	$CuPF_6(MeCN)_4$ (0.1)	dppbz (0.12)	LiO*t*-Bu (0.1)	PhMe, 110 °C	<5
5[a]	$CuPF_6(MeCN)_4$ (0.1)	MonoPhos (0.1)	LiO*t*-Bu (0.1)	PhMe, 110 °C	<5
6[a]	$CuPF_6(MeCN)_4$ (0.1)	MonoPhos (0.2)	LiO*t*-Bu (0.1)	PhMe, 110 °C	<5
7[a]	$CuPF_6(MeCN)_4$ (0.1)	MonoPhos (0.2)	KO*t*-Bu (0.1), $ZnCl_2$ (1.5)	PhMe, 110 °C	<5
8[a]	CuI (0.1)	TMEDA (0.1)	LiO*t*-Bu (0.1)	THF, 50 °C	<5
9	$NiCl_2$ (0.1)/$AgBF_4$ (0.2)	bpy (0.2)	Cs_2CO_3 (2.0)	dioxane, 110 °C	53
10	-	-	LiO*t*-Bu (0.2)	PhMe, 110 °C	85
11	-	-	LiO*t*-Bu (0.2)	dioxane, 110 °C	87
12	-	-	bpy (0.2)	dioxane, 110 °C	<5
13[b]	-	-	Cs_2CO_3 (2.0)	dioxane, 110 °C	97
a) Cu(I) salt and metal *tert*-butoxide were pre-stirred at r.t. for 15 min.; b) 1.1 equiv. of $Ph_2P(O)H$					

The conjugate addition reaction with catalytic LiO*t*-Bu was also run with cyclopent-1-en-1-yl (**9a**) and cyclohept-1-en-1-yl(diphenyl)phosphine oxides (**8a**) and yielded the expected products in equally high yields (Scheme 21). The diphosphine dioxides could be conveniently purified by recrystallization from DCM/EtOAc.

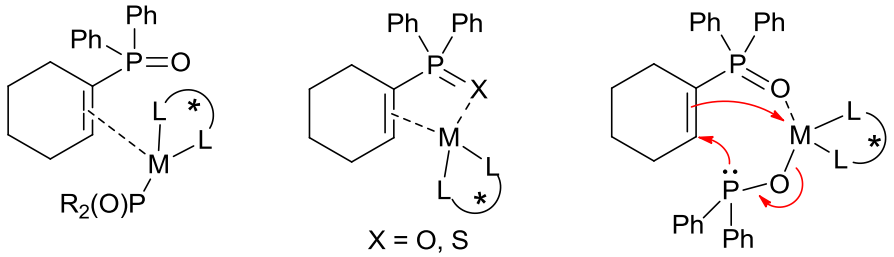
Scheme 21





a) yields based on ^{31}P NMR spectrum of post-work-up mixture; b) yields from a single crop of recrystallization.

Figure 2



soft metal olefin activation | soft metal P=X/olefin activation | hard metal P=O activation

The failed attempts with copper and nickel complexes forced me to rethink the approach to the asymmetric conjugate addition. The initial idea was that the activation of the double bond towards nucleophilic attack and stereodifferenation of the two faces of the olefin was contigent upon the monodentate coordination of the double bond (Figure 2, left drawing) or bidentate coordination of the double bond and phosphinoyl group to the chiral soft metal complex (Figure 2, central drawing). However, the results obtained so far suggested that the simple base-catalyzed addition was favoured, and the presence of a transition metal complex actually decreased the yield. Thus, I opted to test a series of harder metal precatalysts (Scheme 22, Table 8) which would *in situ* deprotonate the secondary phosphine oxide and form a chiral metal phosphinite complex acting as a Lewis acid catalyst. The olefin would coordinate to this complex exclusively via the phosphinoyl group and the phosphinite would directly attack the double bond via its lone pair (Figure 2, right drawing).

First, a stoichiometric mixture of diphenylphosphine oxide and cyclohexenylphosphine oxide **7a** was stirred in the presence of LiO*t*-Bu and (+)-sparteine at 50 ^{o}C in toluene. The reaction proceeded with a nearly full conversion of the substrates, however, a nearly 1:1 mixture of the racemic *trans*- and achiral *cis*-cyclohexanes was formed (Table 8, Entry 1). The reactions with triisobutylaluminium afforded only traces of the product, even after heating for 3 days (Table 8, Entries 2-3). A combination of *t*-BuMgCl and (*R*,*R*)-TMCyDA was more effective, affording 39% conversion after 20 h at room temperature, after another 20 h the conversion increased to 50% (Table 8, Entry 4). The substrates were also allowed to react in the presence of catalytic LiO*t*-Bu and Ti(O*i*-Pr)$_2$-(*R*,*R*)-TADDOLate, this experiment, however, yielded mostly the *cis*-product with little *trans*-product (Table 8, Entry 5).

Scheme 22

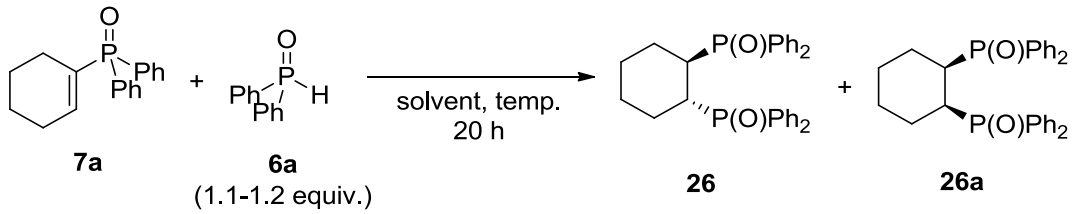


Table 8

Entry	Precatalyst [equiv.]	Additive [equiv.]	Solvent	Conv. (Yield) [%]	ee [%]
1	LiO*t*-Bu (0.2), (+)-sparteine (0.2)	-	PhMe, 50 °C, 20 h	47 (44)[a]	<5
2	Al(*i*-Bu)$_3$ (0.2) L-menthol (0.6)	-	THF, 25 °C, 72 h	7	n.d.
3	Al(*i*-Bu)$_3$ (0.1), (*R*,*R*)-TADDOL (0.1)	-	THF, 25 °C, 20 h	<5[b]	n.d.
4	*t*-BuMgCl (0.2), (*R*,*R*)-TMCyDA (0.2)	-	THF, 25 °C, 20 h	39, 50[c]	<5
5	Ti(O*i*-Pr)$_4$ (0.1), (*R*,*R*)-TADDOL (0.1)	LiO*t*-Bu (0.13)	THF, 25 °C, 20 h	10[d]	n.d.
6	*t*-BuMgCl (0.2), (*R*,*R*)-TMCyDA (0.2)	-	THF, 40 °C, 20 h	32	n.d.
7	*t*-BuMgCl (0.2), (*R*,*R*)-TMCyDA (0.2)	*i*-PrOH (0.4)	THF, 25 °C, 20 h	17	n.d.
8	Me_2Zn (0.1), (*R*)-prolinol (0.1)	-	PhMe, 25 °C, 20 h	2	n.d.
9	Me_2Zn (0.1), (*R*)-prolinol (0.1)	-	PhMe, 50 °C, 72 h	28 (15)	<5

a) the isolated yield of the *cis*-product was 53% yield; b) after 20 h at 25 °C the reaction was stirred at 50 °C for 72 h but no product formed; c) after 40 h; d) the NMR yield of the *cis*-product was 70% yield

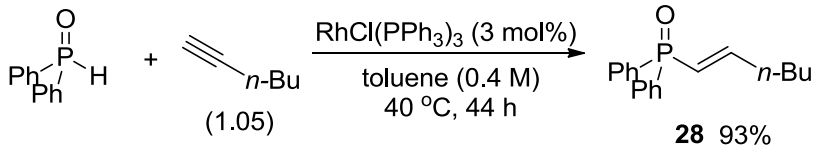
As the reaction with *t*-BuMgCl/(*R*,*R*)-TMCyDA was the most promising, two further experiments were carried out to increase the yield by increasing the temperature to 40 °C or adding *i*-PrOH as a catalytic proton source (Table 8, Entries 6-7). Both reactions, however, produced an inferior result. In another attempt, Me_2Zn pre-stirred with (*R*)-prolinol was used a catalyst in toluene (Table 8, Entries 8-9). A low yield of the product was obtained after 3 days at 50 °C, with no stereoselectivity at all. The low yields and the formation of the *cis*-product in some of the reactions discouraged me from pursuing this pathway with more stereodifferentiating ligands as I anticipated even lower reactivity with those due to more steric bulk.

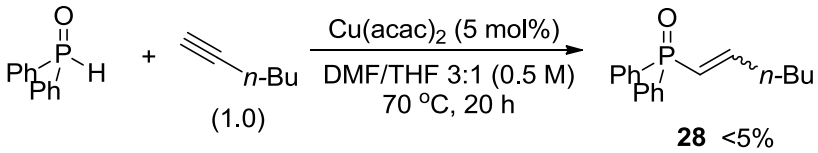
4.2.2. Conjugate addition of diphenylphosphine

During the project, in 2021, a protocol for asymmetric Cu-catalyzed conjugate addition of secondary phosphines to acyclic alkenylphosphine sulfides was published by Yin et al. I decided to test if that method was applicable to cycloalkenyl substrates. First, cyclohex-1-en-1-yl(diphenyl)phosphine sulfide **29** was prepared in a very good yield from the corresponding phosphine oxide **7a** in the reaction with 2.0 equiv. of phosphorus(V) pentasulfide. In an analogous way, the acyclic analogue, hex-1-en-1-yl(diphenyl)phosphine sulfide **30** was prepared from the corresponding phosphine oxide **28** (Scheme 24), which in

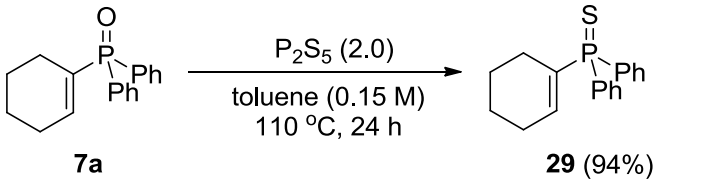
turn was prepared through Rh-catalyzed hydrophosphination from diphenylphosphine oxide and hex-1-yne. It is woth noting that I have also tried the Cu-catalyzed hydrophosphination protocol reported by Beletskaya, however, in my case it did not provide the desired product in any appreciable yields (Scheme 23). The thionation with P_2S_5 appears to be more convenient than the protocol with Lawesson's reagent reported by Yin et al. In the case of the former, the conversion of the substrates is full and the purification includes either destruction of excess P_2S_5 by an aqueous base followed by extraction or direct filtration of the reaction mixture through a silica plug.

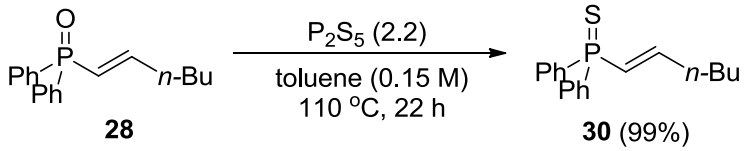
Scheme 23





Scheme 24

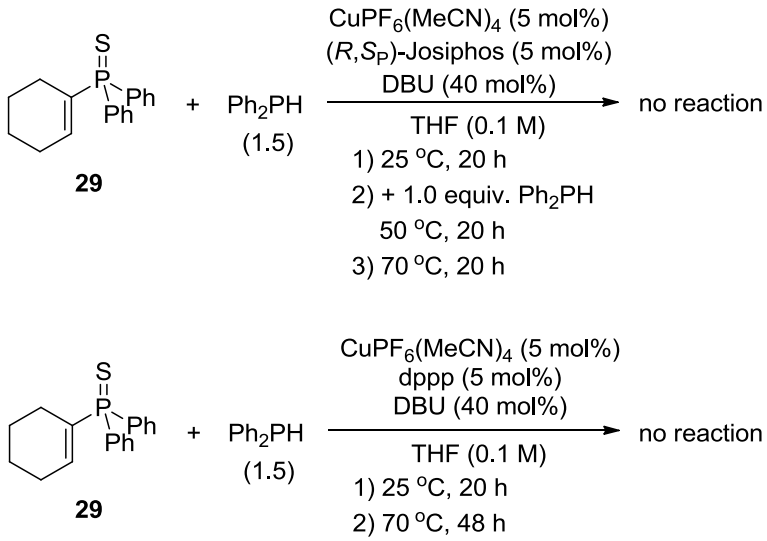




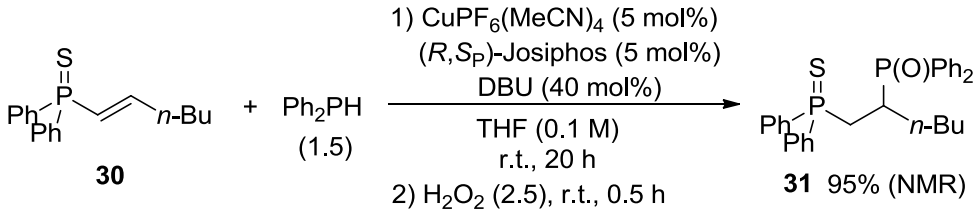
Cyclohexenylphosphine sulfide **29** was then allowed to react with diphenylphosphine, using a slightly modified Yin's catalytic system using Josiphos instead of Taniaphos, and DBU instead of Barton's base (Scheme 25). Unfortunately, the method did not extend to the cyclic substrates. No product was detected after 20 h at room temperature. An extra equivalent of diphenylphosphine was then added, and the reaction was stirred at 50 ^{o}C for another 20 h, and then at 70 ^{o}C for 20 more hours. No reaction was detected at any

point. In another experiment an achiral ligand DPPP was used but the reaction failed both at room temperature and at 70 °C as well. As the original protocol included reaction setup inside a glovebox, I run the reaction with the acyclic substrate using the same reactions conditions with Josiphos as the ligand to test if setting up the reaction on a Schlenk line could be detrimental. In this case, however, a nearly full conversion of the starting material was observed and the yield of the product was 95% by NMR spectroscopy (Scheme 26).

Scheme 25



Scheme 26



4.2.3. Conjugate boronation

Another conjugate addition reaction to the acyclic alkenylphosphine derivatives that was reported to work under copper catalysis is conjugate boronation with bis(pinacolato)diboron. I tested the method under the reported conditions with cyclohexenylphosphine oxide **7a**, however, no conversion was observed (Scheme 27, Table 9, Entry 1). Changes to the procedure such as increasing the reaction temperature to 60 °C, changing the solvent to isopropanol, or changing the ligand to Me-DuPhos or DPhEDA all failed to provide any product (Table 9, Entries 2-5).

Scheme 27

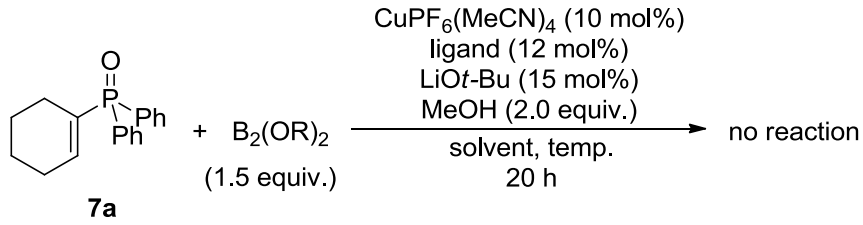


Table 9

Entry	$B_2(OR)_2$	Ligand	Conditions	Conv. [%]
1	B_2pin_2	(R,S_P)-Josiphos	THF, 25 °C	0
2	B_2pin_2	(R,S_P)-Josiphos	THF, 60 °C	0
3[a,b]	B_2pin_2	(R,S_P)-Josiphos	*i*-PrOH, 25 °C	0
4[b]	B_2pin_2	(*S*,*S*)-Me-DuPhos	THF, 25 °C	0
5[b]	B_2pin_2	(*R*,*R*)-DPhEDA	THF, 25 °C	0
6	B_2neop_2	(R,S_P)-Josiphos	THF, 60 °C	0
a) no MeOH was added; b) 1.1 equiv. of LiO*t*-Bu				

4.2.4. Conjugate addition of organomagnesium and organozinc reagents

4.2.4.1. Cu-catalyzed conjugate addition

In the next part of the project, I attempted to install an aryl group at the β position in cyclohex-1-en-1-ylphosphine oxide **7a** in a conjugate addition reaction with an aryl organometallic. I began investigations with a set of reactions with *o*-anisyl and *p*-tolylmagnesium bromides under copper catalysis in THF (Scheme 28, Table 10). Unexpectedly, the first three reactions with *o*-AnMgBr afforded two major products, the double bond isomerization product **32** and the bicyclic product **33** in nearly equal molar parts, regardless of the ligand used (Table 10, Entries 1-3).

Scheme 28

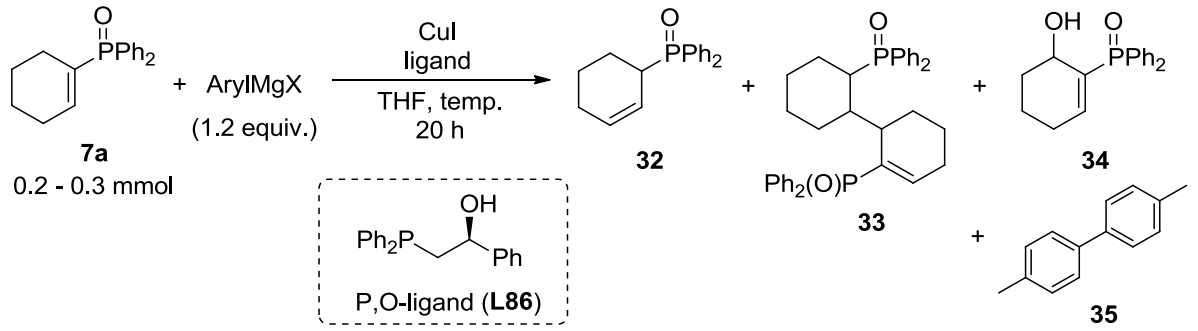


Table 10

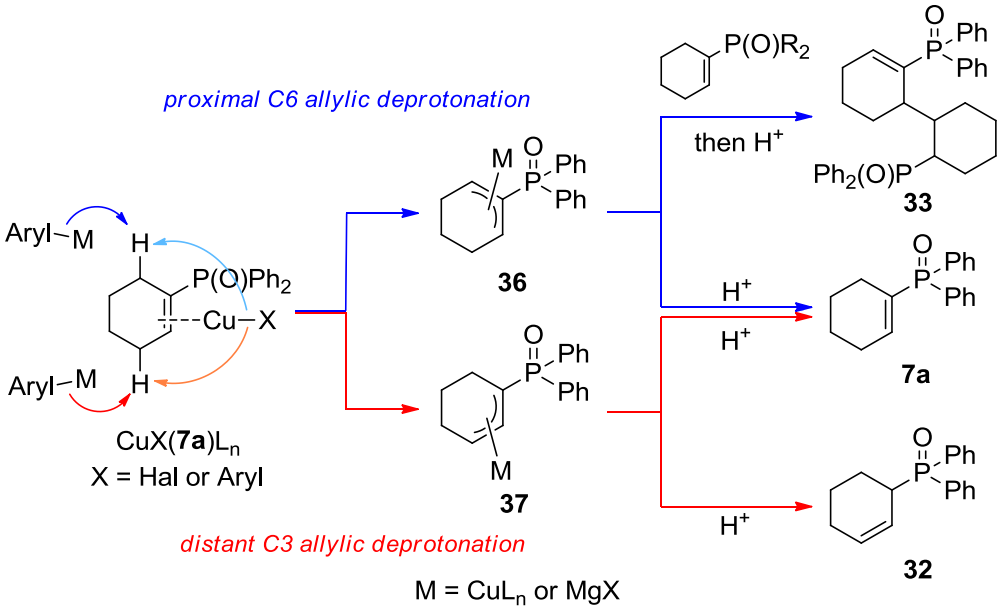
Entry	ArMgBr	CuI [equiv.]	Ligand [equiv.]	Temp.	Conv. [%]			
					32	**33**	**34**	**35**
1	*o*-AnMgBr	0.05	dppp (0.05)	25 °C	27	40	-	<5
2	*o*-AnMgBr	0.10	TMEDA (0.20)	25 °C	22	42	-	<5
3	*o*-AnMgBr	0.10	SIMes·HCl (0.11)	25 °C	23	42	-	<5
4	*p*-TolMgBr	0.05	(R,S_P)-Josiphos (0.06)	25 °C	18	43	-	12
5	*p*-TolMgBr	0.05	**L86** (0.12)	25 °C	19	38	-	9
6[a]	*p*-TolMgBr	0.10	TMEDA (0.20)	25 °C	-	-	-	16
7[b]	*p*-TolMgBr	0.10	TMEDA (0.20)	25 °C	-	-	6	48
8[b]	*p*-TolMgBr	0.10	TMEDA (0.20)	50 °C	54	18	9	6
9	*p*-TolMgBr	0.10	(*R*)-BINAP (0.11)	25 °C	-	-	11	61
10	*p*-TolMgBr	0.10	(*S*)-MonoPhos (0.20)	-50 °C	-	-	-	11
a) TMSCl (1.0 equiv.) was added; b) LiOMe (1.0 equiv.) was added								

At this point the Grignard reagent was changed to *p*-TolMgBr to limit the steric and coordination effects in the nucleophile. However, the reactions with Josiphos and **L86** both afforded the isomerized product **32** and the diphosphine dioxide **33** in a similar ratio to that observed in the reactions with *o*-AnMgBr, and no desired product (Table 10, Entries 4-5). Small amounts of the homocoupling product, 4,4'-dimethylbiphenyl, were also formed in these reactions. Next, I ran two reactions using CuI/TMEDA with an additive, TMSCl or LiOMe. Interestingly, these reactions showed barely any conversion of the organophosphorus substrate (Table 10, Entries 6-7), the latter, however, afforded a small amount of the allylic alcohol **34** and a considerable amount of the homocoupling product. Moreover, when the reaction with LiOMe was carried out at 50 °C, the major product was **32**, whereas **33** formed in a much lower amount along with traces of **34** (Table 10, Entry 8). The only ligand that did not lead to the formation of **32** and **33** at room temperature was BINAP, however, a considerable amount of the homocoupling product was formed along with 11% of **34** (Table 10, Entry 9). A single experiment with CuI/(*S*)-MonoPhos at -50 °C was unfruitful (Table 10, Entry 10).

The formation of the products **32** and **33** can be explained by copper-mediated deprotonative metalation of the proximal C6 and distant C3 allylic positions in the substrate **7a** (Scheme 29). This leads to two regioisomeric allylmetal intermediates **36** and **37**. Upon quenching the reaction mixture, the C3-metalated intermediate **37** can form the isomerized product **32** via protonation at C1, or re-form the substrate **7a** via protonation at C3 (Scheme 29, bottom pathway). The diphosphine dioxide **33** must have formed as a result of the addition of the C6-metalated intermediate **36** to the unreacted substrate **7a**, however, **36** can also re-form the substrate upon protonation (Scheme 29, top pathway). A control reaction in the

absence of the copper catalyst did not afford any products and only unreacted substrate was recovered.

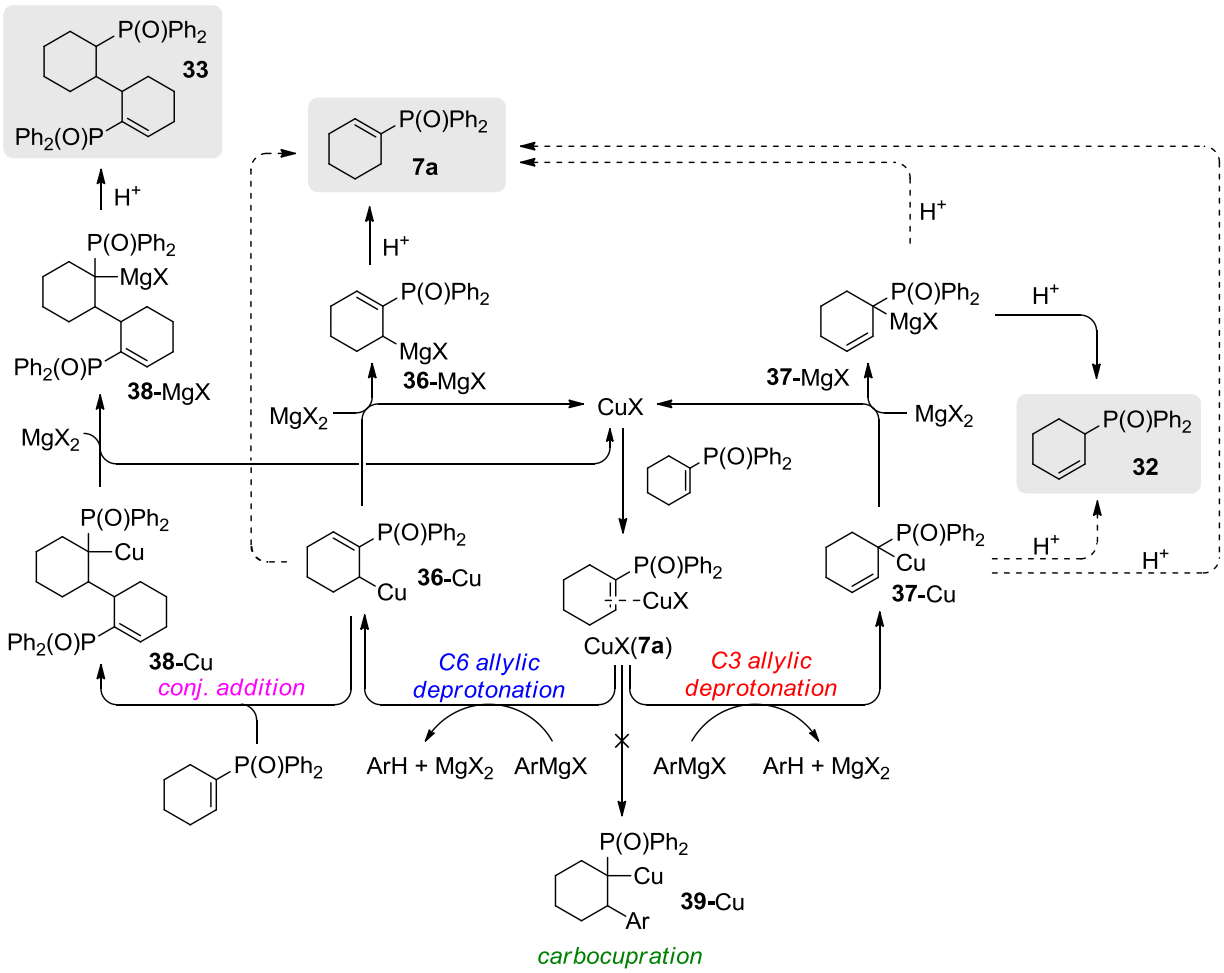
Scheme 29



Considering the yields of **32** and **33** in the reactions from Entries 1-5 in Table 10, which were 18-27% and 38-42%, respectively, it is evident that both allylic metalation of **7a** and conjugate addition of C6-metalated intermediate **36** to **7a** were catalytic in copper. The proposed catalytic cycle illustrating the pathways leading to **32** and **33** is depicted on Scheme 30. The first step in the catalytic cycle is the coordination of the olefin **7a** to the copper species "CuX" to form the complex CuX(**7a**), where X may be a halogen atom or an aryl group, ancilliary ligands are omitted for clarity. Next, CuX(**7a**) is deprotonated at the C6 and C3 allylic positions to generate organocopper intermediates **36**-Cu and **37**-Cu, respectively. The latter undergoes transmetalation with MgX_2 (or ArMgX) to form the corresponding allylic Grignard reagent **37**-MgX, and reinstate the catalyst "CuX". Upon quenching the reaction, **37**-MgX gets protonated at C1 to form the isomerized substrate **32** but it may also be protonated at C3 and re-form the substrate **7a**. On the other hand, **36**-Cu undergoes addition to unreacted **7a** forming the cuprated diphosphine dioxide **38**-Cu, which after transmetalation to **38**-MgX and protonation leads to the diphosphine dioxide **33**. In an analogous way to **37**-Cu, **36**-Cu can also undergo transmetalation to **36**-MgX and after protonation re-form the substrate **7a**. The inverse transmetalation from organocopper intermediates 36-Cu, 37-Cu and

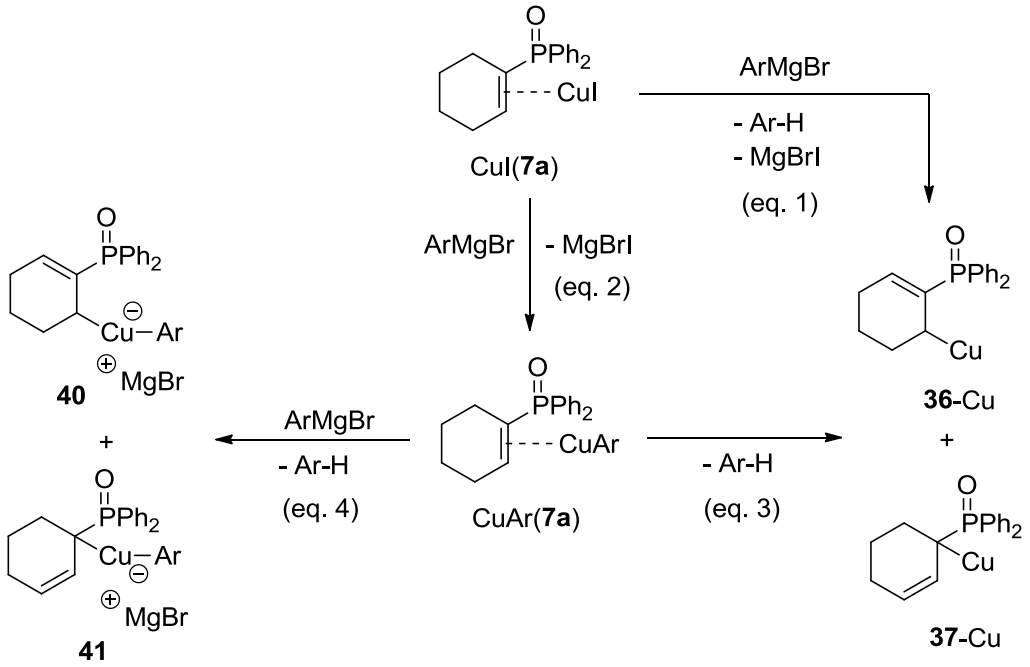
38-Cu to the corresponding organomagnesium compounds is required for a completion of the catalytic cycle. The desired carbocupration leading to **39**-Cu was not observed.

Scheme 30



Regarding the allylic metalation step and the identity of the "CuX" species, Scheme 31 depicts three possible pathways. The copper(I) complex of the substrate, CuI(**7a**), may be deprotonated directly by arylmagnesium halide (Scheme 163, eq. 1). However, if transmetalation to arylcopper(I) (Scheme 163, eq. 2) is faster than deprotonation, two alternative mechanisms involving CuAr(**7a**) can be envisioned. The metalation can take place via intramolecular deprotonative cupration (Scheme 163, eq. 3) or deprotonation by arylmagnesium halide (eq. 4). The first mechanism would generate the allylcopper intermediates **36**-Cu and **37**-Cu, whereas the second mechanism would generate the mixed allyl(aryl)cuprates **40** and **41**. These cuprates would follow analogous steps in the catalytic cycle as their monoaryl counterparts.

Scheme 31



Using (*R*)-BINAP as the ligand, I continued experimenting with the conjugate addition of *p*-TolMgBr (Scheme 32, Table 11) by changing the solvent to toluene (Entry 2), adding 6 equiv. of *N*-methylpyrrolidone (Entry 3), or using $Cu(OTf)_2$ in place of CuI (Entry 4). Nevertheless, these modifications did not bring about the desired transformation. In all cases small amounts of the allylic alcohol **34** were formed (5-11%), however, the addition of NMP suppressed homocoupling, in the other three reactions the yield of 4,4'-dimethylbiphenyl was at a similar level (61-69%). Subsequently, I ran the reactions with cyclohex-1-en-1-yldi-*o*-anisylphosphine oxide **7d** and cyclohex-1-en-1-yldiphenylphosphine sulfide **29** in order to see if *ortho*-methoxy or thiophosphinoyl group could act as more efficient directing groups for the copper catalyst (Table 11, Entries 5-6). Nevertheless, neither of the reactions produced the desired product.

Scheme 32

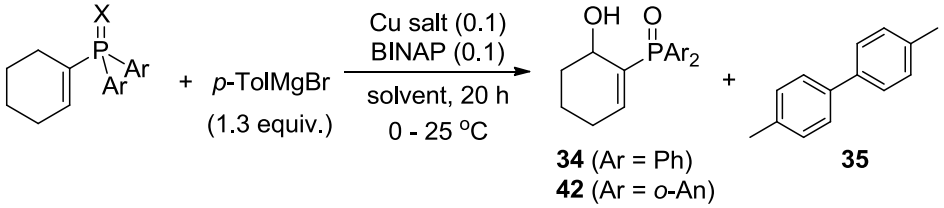


Table 11

Entry	Substrate	Cu salt	Additive	Solvent	Conv. [%]	
					34/42	35
1	**7a** (Ar = Ph, X = O)	CuI	-	THF	11	61
2	**7a** (Ar = Ph, X = O)	CuI	-	PhMe	8	64
3	**7a** (Ar = Ph, X = O)	CuI	NMP (6 eq.)	THF	5	0
4	**7a** (Ar = Ph, X = O)	$Cu(OTf)_2$	-	THF	7	69
5	**7d** (Ar = *o*-An, X = O)	CuI	-	THF	7	51
6	**29** (Ar = Ph, X = S)	CuI	-	THF	-	59

The reactions with aryl Grignard reagents did not produce the desired product and afforded undesired products as a result of homocoupling and deprotonation of the allylic positions. Hence, I turned the attention to organozinc reagents which are less basic and can be used in more polar solvents (Scheme 33, Table 12).

Scheme 33

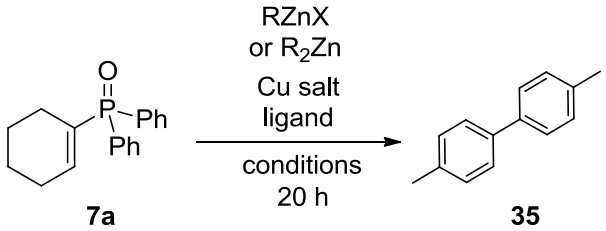


Table 12

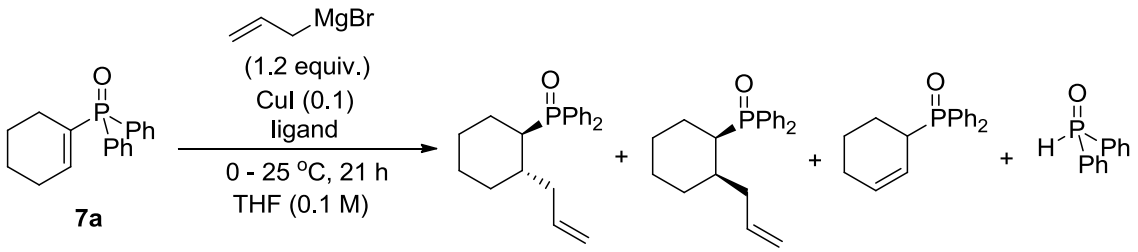
Entry	ArM	Cu salt	Ligand	Solvent	35 [%]
1[a]	*p*-TolZnCl (1.2)	CuI (0.10)	TMEDA (0.20)	THF, 25 °C	4
2[a]	*p*-TolZnCl (1.2)	CuI (0.10)	TMEDA (0.20)	THF, 60 °C	8
3[a]	*p*-TolZnCl (1.2)	CuI (0.05)	(*R*)-BINAP (0.06)	THF, 25 °C	5
4[a]	*p*-TolZnCl (1.2)	$Cu(OTf)_2$ (0.10)	(*R*)-BINAP (0.11)	DMF, 60 °C	nd
5[b]	*p*-Tol_2Zn (3.0)	CuI (0.10)	(*S*)-MonoPhos (0.20)	PhMe/THF, 60 °C	24
6	Et_2Zn (3.0)	CuI (0.10)	(*S*)-MonoPhos (0.20)	PhMe, 60 °C	nd
7[c]	$Ph_2P(O)CH_2ZnX$ (1.2)	CuI (0.05)	(*R*)-BINAP (0.06)	THF, 25 °C	<5
a) *p*-TolZnCl was prepared by transmetalation between *p*-TolMgBr and $ZnCl_2$ (1:1); b) *p*-Tol_2Zn was prepared by transmetalation between *p*-TolMgBr and $ZnCl_2$ (2:1); c) X = Cl·LiCl, the organozinc reagent was prepared by deprotonation of $Ph_2P(O)Me$ with *t*-BuLi followed by transmetalation with $ZnCl_2$					

I began the study with the reaction between the phosphine oxide **7a** and *p*-TolZnCl, using catalytic CuI/TMEDA. After running overnight at room temperature, the reaction showed no conversion of the phosphine oxide and only traces of the homocoupling (Table 12, Entry 1). Thus, the reaction was repeated at 60 °C, but it also failed (Table 12, Entry 2). A similar result was obtained with (*R*)-BINAP as the ligand, both the reaction in THF at room temperature and the reaction in DMF at 60 °C, with $Cu(OTf)_2$ as the precatalyst, failed to give

the desired product (Table 12, Entries 3-4). The two experiments with *p*-Tol_2Zn and Et_2Zn using CuI/(*S*)-MonoPhos in toluene at 60 °C also failed (Table 12, Entries 5-6). In the last reaction, I used the diphenylphosphinoylmethylzinc reagent, generated *in situ* via deprotonation of the corresponding phosphine oxide with *t*-BuLi and transmetalation with $ZnCl_2$. As in all previous experiments, the reaction did not work (Table 12, Entry 7).

Considering all the results of the conjugate addition of organometallics presented so far, the only nucleophile that has successfully undergone an addition to cyclohexenylphosphine oxide **7a** was the cyclic allylic organometallic **36** generated through deprotonation of **7a** at the C6 allylic position. Thus, I wondered if the reaction would work with allylmagnesium bromide used in place of *p*-TolMgBr. Indeed, with CuI/TMEDA (10/20 mol%) as the catalyst, the conjugate addition took place, however, both the *trans* and *cis* isomers **43** and **44** were formed at the ratio of 1:0.75 (Scheme 34). Almost full conversion of **7a** was observed, yet the conjugate addition products accounted for only 54%, the major product was the *trans* isomer (31%). Aside from the expected adduct **43**, three other products were identified – the cis isomer **44** (23%), the isomerized substrate **32** (25%), and diphenylphosphine oxide (6%). Unfortunately, **43** and **44** could not be separated using column chromatography. The reaction with BINAP in place of TMEDA was cleaner, however, the conversion to **43** and **44** was considerably lower at 17% and 11%, respectively.

Scheme 34

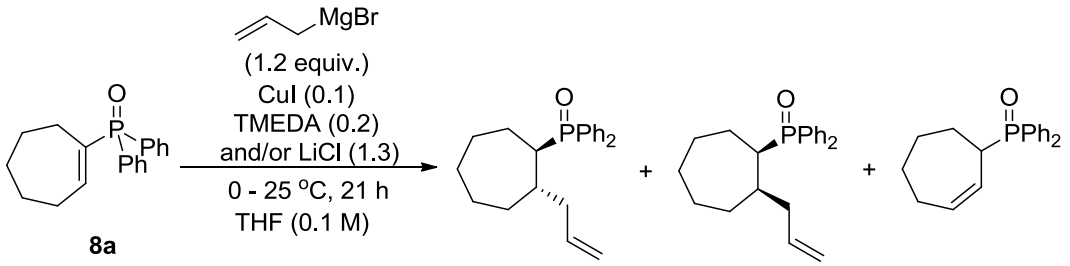


	43	44	32	6a
TMEDA (0.2)	31% (25%)	23% (19%)	25%	6%
(*R*)-BINAP (0.1)	17%	11%	<5%	-

The formation of the *cis* product was somewhat unexpected. To test if the *trans*/*cis* selectivity could depend on the size of the cycloalkane scaffold, I carried out a reaction between the cycloheptene analogue **8a** and allylmagnesium bromide in the presence of CuI/TMEDA. The reaction afforded a mixture of the conjugate addition products **45** and **46**, and the isomerized substrate **47** (Scheme 35). The major product was the *trans* isomer **45**

(46%) and only small amounts of the isomer **46** (6%) were observed, however, the reaction suffered from high isomerization of the substrate to **47** (40%). By adding 1.3 equiv. of LiCl, I was able to increase the conversion to the desired product to 58% and decrease the extent of substrate isomerization (25%) at the cost of slightly increased formation of the *cis* isomer (12%). The best yield (63%) and overall selectivity towards **45** were obtained under ligandless conditions with CuI and LiCl, the conversion to **46** was only 10% and only traces of **47** were detected.

Scheme 35



Entry	Additive(s)	**45**	**46**	**47**
1	TMEDA	46%	6%	40%
2	TMEDA + LiCl	58% (47%)	12% (9%)	25% (22%)
3	LiCl	63%	10%	2%

Conversion by ^{31}P NMR is given; isolated yields are in parentheses.

4.2.4.2. Ni-catalyzed conjugate addition

After the failure of conjugate addition of arylmagnesium and arylzinc reagents under copper catalysis, I turned the attention to nickel catalysis. I chose cyclohexenylphosphine oxide **7a** and *p*-TolMgBr as model substrates, and $NiCl_2$(dme) as the precatalyst. The screening reactions were carried out under the conditions depicted in Scheme 36 with a set of mono- and diphosphine or bis(oxazoline) ligands. Contrary to the study with copper catalysts, the reactions under nickel catalysis did afford the desired conjugate addition product, however, both the *trans*-isomer **48** and *cis*-isomer **49** were formed (Scheme 36, Table 13). The majority of ligands led to the formation of nearly equal amounts of the two compounds with the exception of (*S*)-*i*-Pr-BOX and (*R*)-BINAP in THF, which led to the preferential formation of the *cis*-isomer **49** (Table 13, Entries 4 and 6), and (*S*)-*i*-Pr-PyBOX, which slightly preferred the formation of the *trans*-isomer **48**. The least effective ligands overall were triphenylphosphine and DPPP (Table 13, Entries 1-2), whereas (*R*,S_P)-Josiphos and (*R*,R_P)-Taniaphos were the most effective ones (Table 13, Entries 8-11). In the case of (*R*,S_P)-Josiphos, the reaction was slightly more effective in toluene than in THF (Entries 8-10).

However, in the case of (*R*)-BINAP, the reaction worked in THF but afforded no product in toluene (Table 13, Entries 6-7). In all the reactions homocoupling was a considerable side reaction with 23-41% yield of 4,4'-dimethylbiphenyl (**35**). Nonetheless, there was virtually no difference between toluene distilled from a deep purple solution of sodium/benzophenone dianion and the same solvent additionally degassed directly prior to setting up the reaction by the freeze-pump-thaw method (Table 13, Entries 8-9).

Scheme 36

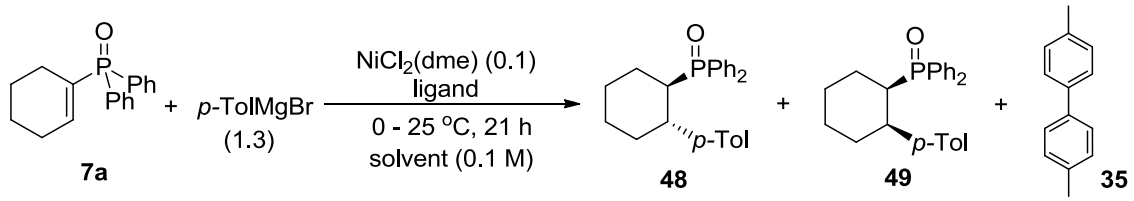


Table 13

Entry	Ligand	Solvent	Conv. [%]		
			48	**49**	**35**
1	PPh_3 (0.21)	THF	6	7	34
2	dppp (0.11)	THF	<5	<5	34
3	dcype (0.11)	THF	11	11	23
4	(*S*)-*i*-Pr-BOX (0.11)	THF	9	18	41
5	(*S*)-*i*-Pr-PyBOX (0.11)	THF	14	12	33
6	(*R*)-BINAP (0.11)	THF	10	17	33
7	(*R*)-BINAP (0.11)	PhMe[a]	0	0	35
8	(R,S_P)-Josiphos (0.11)	PhMe	16	22	34
9	(R,S_P)-Josiphos (0.11)	PhMe[a]	16	16	34
10	(R,S_P)-Josiphos (0.11)	THF	16	16	25
11	(R,R_P)-Taniaphos (0.11)	THF	19	18	27
a) the solvent was degassed by freeze-that-pump prior to the reaction					

4.2.5. Conjugate addition of phenylboronic acid and its esters

Another class of organometallics tested as potential nucleophiles in the conjugate addition reaction to cyclohexenylphosphine oxide **7a** were phenylboronic acid and its 1,3-propylene glycol and neopentyl glycol esters (Scheme 37, Table 14). The reactions were carried out using copper(I) precatalysts, diphosphine, diamine or NHC ligands, catalytic or excess base, with or without a proton source, in solvents of varying polarity at elevated temperature of 100-140 ^oC (Table 14, Entries 1-11). Unfortunately, no reaction afforded the desired product. The only product formed in some of the reactions was the isomerized substrate **32**. Its formation was mainly associated with the use of dipolar aprotic solvents, DMSO and DMF (Table 14, Entries 2, 9-11), although small amounts of it were also observed

in a single reaction in dioxane (Table 14, Entry 1). Aside from copper catalysts, *in situ* formed cobalt and palladium catalysts were used in two experiments, both of them were unsuccessful (Table 14, Entries 12-13).

Scheme 37

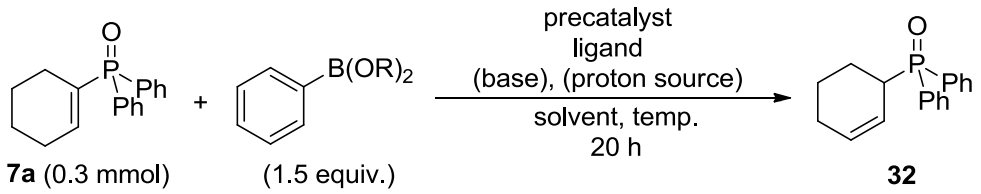


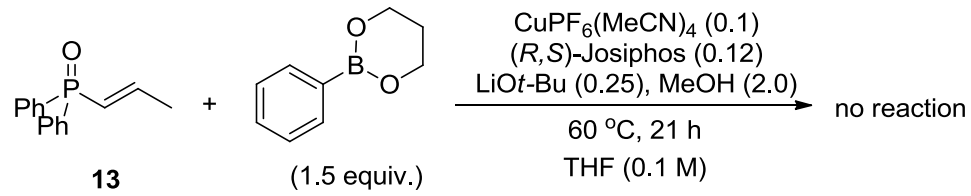
Table 14

Entry	-B(OR)$_2$	Precatalyst	Ligand	Base	Conditions	32 [%]
1[a]	B(OH)$_2$	$CuPF_6(MeCN)_4$ (0.1)	dppp (0.1)	KO*t*-Bu (2.0)	dioxane, 110 ^oC	4
2	B(OH)$_2$	$CuPF_6(MeCN)_4$ (0.1)	dppp (0.1)	KO*t*-Bu (2.0)	DMSO, 110 ^oC	9
3	B(OH)$_2$	$CuPF_6(MeCN)_4$ (0.1)	(*R*)-BINAP (0.1)	KO*t*-Bu (2.0)	*t*-AmOH, 110 ^oC	0
4[a]	B(OH)$_2$	CuCl (0.1)	SIMes·HCl (0.12)	KO*t*-Bu (0.25)	PhMe, 110 ^oC	0
5	Bpg	CuCl (0.1)	SIMes·HCl (0.12)	LiO*t*-Bu (0.25)	PhMe, 110 ^oC	0
6	Bpg	CuCl (0.1)	dcype (0.1)	LiO*t*-Bu (0.17)	PhMe, 110 ^oC	0
7	Bpg	$CuPF_6(MeCN)_4$ (0.1)	DMCyDA (0.2)	NaOAc (3.0)	dioxane, 100 ^oC	0
8[c]	Bpg	$CuPF_6(MeCN)_4$ (0.1)	dppp (0.12)	NaOAc (4.0)	dioxane, 100 ^oC	0
9[d]	Bneop	CuI (0.1)	phen (0.1)	K_3PO_4 (2.0)	DMF, 140 ^oC	11
10[d]	Bneop	CuI (0.1)	phen (0.1)	CsF (2.0)	DMF, 140 ^oC	11
11[d]	Bneop	CuI (0.1)	P(4-$FC_6H_4)_3$ (0.2)	CsF (2.0)	DMF, 140 ^oC	11
12[b]	Bpg	$CoCl_2$ (0.1)	DMCyDA (0.11)	LiOMe (1.5)	DMF, 60 ^oC	0
13[a]	Bneop	$Pd(tfa)_2$ (0.05)	(*S,S*)-Me-DuPhos (0.06)	KO*t*-Bu (2.0)	THF, 50 ^oC	0

a) MeOH (2.0 equiv.) was used as the proton source; b) MeOH (1.5 equiv.) was used as the proton source; c) $HBF_4{\cdot}OEt_2$ (2.0 equiv.) was used to form AcOH as the proton source; d) *t*-AmOH (2.4 equiv.) was used as the proton source

A single experiment set up with acyclic alkenylphosphine oxide **13** and 1,3-propylene glycol ester of phenylboronic acid, using Cu/Josiphos as the catalyst, at 60 ^oC, also failed (Scheme 38).

Scheme 38

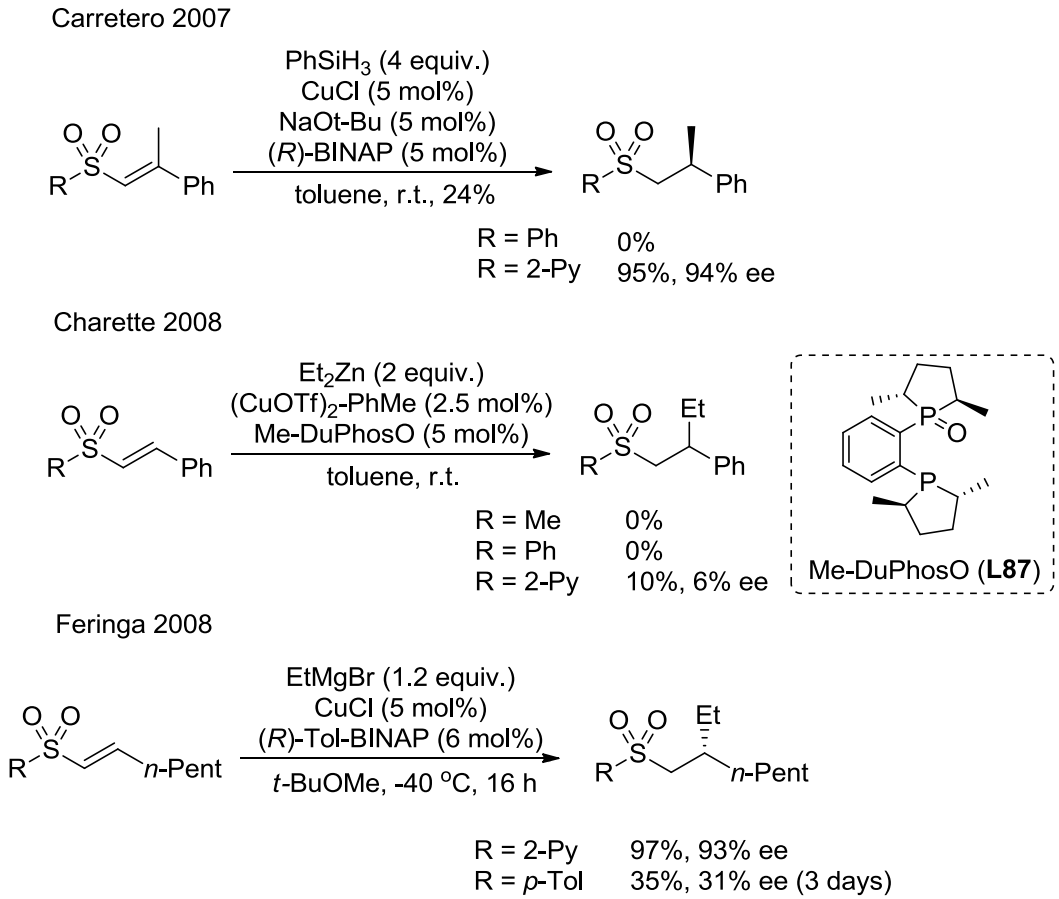


4.2.6. Attempted preparation of cyclohex-1-en-1-yl(phenyl)(2-pyridyl)phosphine oxide

As in the study of the addition of diphenylphosphine oxide, the lack of success in the conjugate addition of aryl organometallics prompted me to reconsider the model of the substrate activation through complexation of the transition metal centre by either the double

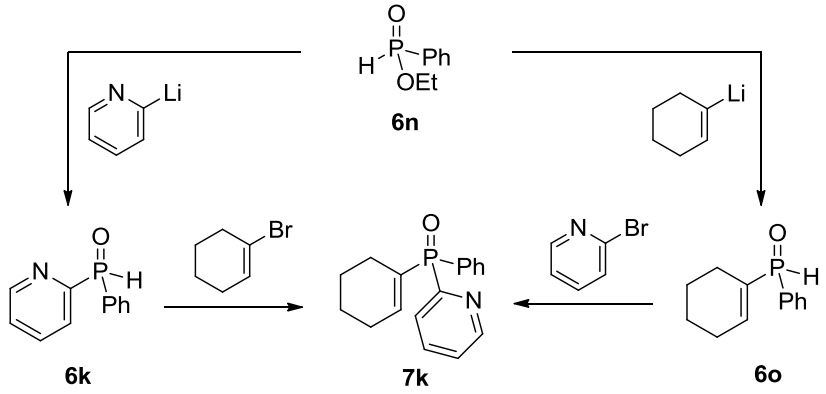
bond alone or both the double bond and the phosphinoyl group. The closest analogy in the literature to the studied reaction is the asymmetric Cu-catalyzed conjugate addition of organomagnesium and organozinc reagents to alkenylsulfones,[248] reported by the groups of Charette and Feringa. In all three publications, the substrate scope was limited to acyclic alkenyl(2-pyridyl)sulfone and the 2-pyridyl group at sulfur was crucial for reactivity (Scheme 39, eq. 2-3). The 2-pyridyl group is most likely involved in the chelation-assisted activation of the substrate. Its positive effect was first reported by Carretero et al. in Rh-catalyzed conjugate addition of phenylboronic acid to alkenylsulfones,[249a] and later the presence of the 2-pyridyl group at sulfur was found to be necessary in the case of Cu-catalyzed conjugate reduction with $PhSiH_3$ (Scheme 39, eq. 1).[249b] Charette et al. compared the reactivity of the methyl, phenyl and 2-pyridylsulfones but only under unoptimized conditions adapted from a previous study (Scheme 39, eq. 2).[248a] Feringa et al. tested *p*-tolyl(hept-1-en-1-yl)sulfone under the optimized conditions for the conjugate addition of EtMgBr and observed much lower yield and enantioselectivity than with the 2-pyridyl analogue (Scheme 39, eq. 3).[248b]

Scheme 39

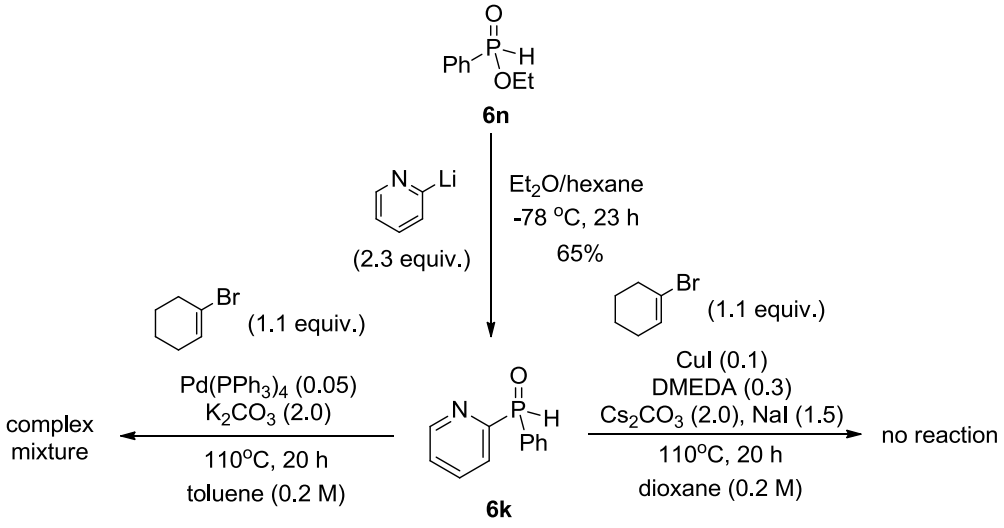


I decided to try to synthesize cyclohex-1-en-1-yl(phenyl)(pyridin-2-yl)phosphine oxide (**7k**) and then test it in conjugate addition reactions with organomagnesium and organozinc reagents. Retrosynthetic analysis revealed two pathways to **7k** starting from ethyl phenylphosphinate (**6n**), differing in the order of installing the 2-pyridyl and cyclohex-1-en-1-yl groups at the phosphorus atom (Scheme 40). The left pathway starts with the nucleophilic substitution with 2-pyridyllithium to give phenyl(2-pyridyl)phosphine oxide (**6k**). The second step is C-P cross-coupling with 1-bromocyclohexene. The right pathway features the nucleophilic substitution with cyclohex-1-en-1-yllithium to give cyclohex-1-en-1-yl(phenyl)phosphine oxide which is then subjected to cross-coupling with 2-bromopyridine. I chose the left pathway as the more convenient one due to the availability of a protocol in the literature for the preparation of **6k**[250] and previously reported tandem halogen exchange/cross-coupling protocol for bromocycloalkenes. The right pathway, on the other hand, features the synthesis of a yet not reported secondary cycloalkenylphosphine oxide (**6o**).

Scheme 40



Scheme 41



Phenyl(2-pyridyl)phosphine oxide (**6k**) was prepared in 65% from ethyl phenylphosphinate and 2-pyridyllithium according to a previously reported method.[250] However, disappointingly, it failed to react with 1-bromocyclohexene using the developed protocol for Cu-catalyzed halogen exchange/C-P cross-coupling (Scheme 41, bottom right). Notably, the ^{1}H NMR analysis of the post-reaction mixture revealed that there was no 1-iodocyclohexene formed. Presumably, the complexation of CuI by phenyl(2-pyridyl)phosphine oxide shut down the halogen exchange. An attempt with $Pd(PPh_3)_4$ was also unsuccessful, as it afforded a complex mixture of products.

This turn of events forced me to take up the right pathway from Scheme 173. I began investigating the preparation of cyclohex-1-en-1-yl(phenyl)phosphine oxide (**6o**) with the reaction between ethyl phenylphosphinate and cyclohex-1-en-1-yllithium (**50**), generated *in situ* from 1-bromocyclohexene and *t*-BuLi (Scheme 42, Table 15). However, after several attemps with varying conditions for the bromine/lithium exchange and nucleophilic substitution, it became apparent that the reaction was plagued with multiple side products and was highly sensitive to the conditions of the two steps. When the lithiation was performed at -78 ^{o}C for 30 min. and the substitution was carried out from -78 ^{o}C to r.t., the yield by ^{31}P NMR was 78%, however, the product was isolated with only 42% yield in an impure form (Table 15, Entry 1). Notably, extending the duration of the exchange by 30-45 min. at -40 ^{o}C led to very different results. When ethyl phenylphosphinate was added to the organolithium solution at -40 ^{o}C and then allowed to warm to r.t., the reaction was much less clean with only 37% of the desired product by NMR (Table 15, Entry 2). However, when the substitution was done at -78 ^{o}C overnight, unexpectedly, the experiment cleanly afforded two products – the secondary phosphine oxide **6o** and dicyclohex-1-en-1-yl(phenyl)phosphine oxide **51,** the former, however, was only isolated as a mixture with unreacted *H*-phosphinate (Table 15, Entry 3). Carrying out the lithiation in a more polar environment (pentane/Et_2O 1:7) and then running substitution from -78 ^{o}C to r.t. gave another unexpected result with the selectivity shifted towards **51** and only traces of **6o** (Table 15, Entry 4). In Entries 2-4 a slight deficit of *t*-BuLi was used relative to *tert*-butyl bromide formed in the exchange step. Interestingly, in all three reactions there was some unreacted 1-bromocyclohexene left. Finally, I carried out two reactions with the bromine/lithium exchange conditions adapted from Bailey et al. (Table 15, Entries 5-6).[251] The exchange was performed at 0 ^{o}C in hexane with 6 equiv. of THF, which at the concentration of 0.2 M corresponds to the hexane/THF ratio of 9:1. The substitution was then carried out either from 0 ^{o}C to r.t. or at -78 ^{o}C. In both

cases the conversion calculated from ^{31}P NMR spectra of the post-reaction mixtures and isolated yields were similar to the very first reaction in pentane/diethyl ether. In both cases, the product was isolated in mixed fractions with impurities. I also ran the substitution reaction using cyclohexenylmagnesium bromide lithium chloride complex, prepared from 1-bromocyclohexene, magnesium, and lithium chloride (Scheme 43); the attempted bromine/magnesium exchange using *i*-PrMgCl·LiCl at r.t. overnight was unsuccessful. The end result was comparable to the best conditions with cyclohexenyllithium, and the product was isolated in 30% yield. Unfortunately, due to the presence of multiple minor impurities isolation of the pure compound was not achieved. However, the product of the reaction with the Turbo Grignard reagent was isolated in the purest state (~90%).

Scheme 42

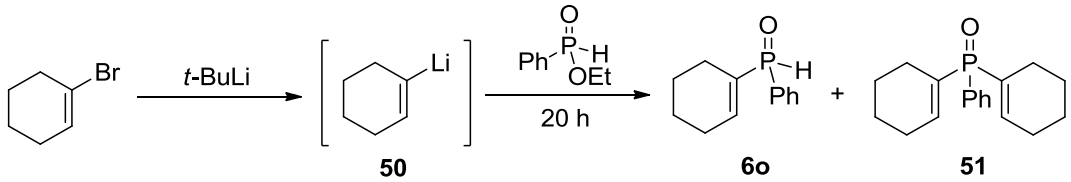
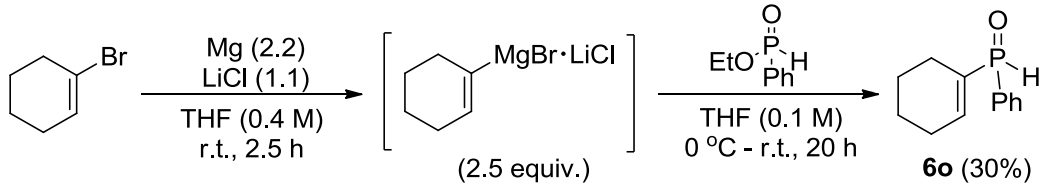


Table 15

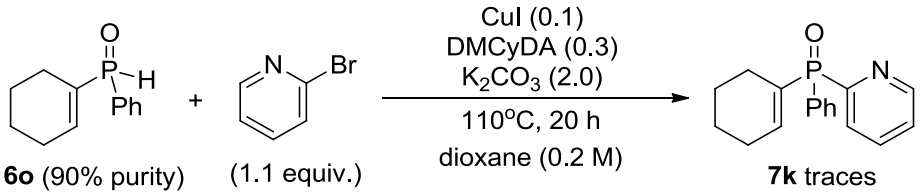
No.	*t*-BuLi [equiv.]	Br/Li exchange conditions		50 [equiv.]	Temp.	6o/51 [%][e]
1	2.0	-78°C, 30 min.	pentane/Et_2O 1:1 (0.4 M)[a]	2.2	-78 °C - r.t.	78 (42)/0
2	1.93	-78°C, 30 min. to -40°C, 45 min.	pentane/Et_2O 1:1 (0.4 M)[b]	2.3	-40 °C - r.t.	37/0
3	1.93	-78°C, 30 min. to -40°C, 30 min.	pentane/Et_2O 1:1 (0.4 M)[b]	2.3	-78 °C	44 (38)/ 42 (40)
4	1.97	-78°C, 30 min.	pentane/Et_2O 1:7 (0.1 M)[c]	2.15	-78 °C - r.t.	0/52
5	2.1	0°C, 30 min.	hexane/THF 9:1 (0.2 M)[d]	2.3	0°C - r.t.	72 (33)/0
6	2.1	0°C, 30 min.	hexane/THF 9:1 (0.2 M)[d]	2.4	-78 °C	78 (36)/0
The solvent composition during the nucleophilic substitution step: a) pentane/Et_2O 1:1.5 (0.14 M), b) pentane/Et_2O 1:1.9 (0.15 M), c) pentane/Et_2O 1:9 (0.04 M), d) hexane/THF 4:1 (0.1 M); e) the yields are calculated from ^{31}P NMR spectra, isolated yields are given in parentheses.						

Scheme 43



The sample of cyclohexenyl(phenyl)phosphine oxide (**6o**) isolated from the reaction with the Turbo Grignard reagent was subsequently reacted with 2-bromopyridine under the optimized cross-coupling conditions for aryl bromides, but without sodium iodide additive. The secondary phosphine oxide **6o** and 2-bromopyridine were both fully consumed in the reaction, but only traces of the cross-coupling product and 2,2'-oxydipyridine were detected by GC-MS (Scheme 44).

Scheme 44



5. Summary

The aim of this thesis was to evaluate the possibility of using a sequence of C-P cross-coupling between secondary phosphine oxides and cycloalkenyl electrophiles, and asymmetric conjugate addition to cycloalkenylphosphine oxides. C-P cross-coupling is a well developed reaction with available protocols under palladium, nickel, and copper catalysis. However, the protocols available for *P*-cycloalkenylation were mostly limited to Pd catalysis with the two protocols under Ni catalysis covering a limited scope of substrates. On the other hand, asymmetric transition metal-catalyzed conjugate addition to alkenylphosphine derivatives is still in its infancy and all available protocols are limited to acyclic alkenylphosphine derivatives.

The primary outcome of the project has been the development of Cu-catalyzed tandem halogen exchange/C-P cross-coupling between bromocycloalkenes and secondary phosphine oxides using a modified Buchwald's catalytic system utilizing CuI as the precatalyst, DMEDA or DMCyDA as the ligand, in the presence of Cs_2CO_3 or K_2CO_3 as the base, and NaI as the halogen exchange promoter. The iodide salt additive was crucial for achieving high yields at a near stoichiometric ratio of substrates, otherwise, in its absence high excess of a bromocycloalkene is required. A short mechanistic study revealed that NaI additive acts as an indirect promoter of the cross-coupling reaction by increasing the rate of the halogen exchange transforming the organic bromide to the corresponding iodide which is

more reactive as a coupling partner. The developed protocol has also been shown to have a limited applicability to acyclic bromoalkenes and bromoarenes, complementing Rh-catalyzed alkyne hydrophosphinylation and Cu-catalyzed cross-coupling of aryl iodides as a method for *P*-alkenylation and *P*-arylation.

In the second part of the project, I attempted to find the catalyst and conditions for the conjugate addition of several carbon and heteroatom nucleophiles to cyclohex-1-en-1-yl(diphenyl)phosphine oxide, including diphenylphosphine oxide and diphenylphosphine, bis(pinacolato) and bis(neopentyl glycolato)diboron, organomagnesium and organozinc reagents, and phenylboronic acid and its esters. In the case of diphenylphosphine oxide, higher yields of the product were obtained in the control reactions with LiO*t*-Bu or Cs_2CO_3 base alone. With Cu catalysts, when LiO*t*-Bu was used in excess relative to Cu, the product was formed in a decreased yield. However, when only as much LiO*t*-Bu was used as needed to form CuO*t*-Bu, the reaction did not work at all. A similar behaviour was noted with a nickel catalyst. This suggests that copper and nickel only formed unreactive complexes with diphenylphosphine oxide. Thus the concept of using catalytic magnesium or zinc base in the presence of a chiral ligand appears promising, however, I was not successful in obtaining high enough yields to warrant further research into the stereoselective reaction. In the case of diphenylphosphine and bis(pinacolato)diboron, I was unsuccessful in applying the recently reported protocols for their conjugate addition to acyclic alkenylphosphine derivatives under copper catalysis. The reactions failed both under the reported conditions and at elevated temperatures. A series of reactions with phenylboronic acid and its esters did not provide the desired product either.

The reactions with arylmagnesium reagents under Cu catalysis did not afford the desired adducts but instead unexpectedly led to metalation of both allylic positions in the phosphorus substrate. The intermediate metalated at the proximal allylic position underwent conjugate addition to the unreacted substrate, the second major product was the cyclic allylphosphine oxide formed via double bond isomerization. Both allylic metalation and conjugate addition were found to be Cu-catalyzed and transmetalation from organocopper to organomagnesium was a necessary step for the catalytic cycle to complete. The reactions with the corresponding arylzinc reagents did not afford any products. The addition of unsubstituted allylmagnesium bromide was more effective, however, afforded an inseparable mixture of the *trans* and *cis* products. In the case of cyclohept-1-en-1-yl(diphenyl)phosphine oxide, the oveall yield and selectivity were better, however, the most optimal conditions were ligand-

free. On the other hand, under Ni catalysis *p*-tolylmagnesium bromide did undergo conjugate addition to cyclohex-1-en-1-yl(diphenyl)phosphine oxide. However, regardless of the ligand used, both *trans* and *cis* isomers were formed and the overall yield did not exceed 38%. Overall, Cu-catalyzed conjugate addition of allylmagnesium bromide and Ni-catalyzed conjugate addition of *p*-tolylmagnesium bromide were the two most promising reactions, and the results should direct future efforts to optimize the reactions.

As related conjugate addition reactions to alkenylsulfones greatly benefited from the 2-pyridyl group at sulfur, in the last part of the project, I attempted to prepare cyclohex-1-en-1-yl(phenyl)(pyridin-2-yl)phosphine oxide and test it in the conjugate addition reactions. Unfortunately, the preparation of the substrate via C-P cross-coupling was unsuccessful with both phenyl(pyridin-2-yl)phosphine oxide and cyclohexenyl(phenyl)phosphine oxide. The latter secondary phosphine oxide was also problematic to prepare in the pure form. Unexpectedly, under certain conditions di(cyclohex-1-en-1-yl)phenylphosphine oxide was also formed.

6. Experimental

All reactions were performed under argon atmosphere using Schlenk techniques. Only dry solvents were used and the glassware was heated under vacuum prior to use. Toluene was dried with sodium/benzophenone, distilled and stored over 3Å molecular sieves. Tetrahydrofuran was distilled from sodium/benzophenone prior to use. Anhydrous dioxane was purchased from Sigma-Aldrich and used without purification. Dichloromethane was dried and distilled from P_4O_{10} prior to use. Solvents for chromatography and extraction were commercially available and used as received.

Cycloalkanones, bromine, triphenyl phosphite and triethylamine for the synthesis of bromocycloalkenes were commercially available and used as received. Di(*o*-tolyl)phosphine oxide[251], di(*p*-tolyl)phosphine oxide[251], di(*o*-anisyl)phosphine oxide[251], di(naphthalen-1-yl)phosphine oxide[252], bis(3,5-di-*tert*-butylphenyl)phosphine oxide[253], dicyclohexylphosphine oxide[251], *tert*-butyl(phenyl)phosphine oxide[254], bis(4-fluorophenyl)phosphine oxide[251], diethyl phosphite[255], 1-bromocyclohexene[41b], 1-bromocycloheptene[41c], 1-bromocyclopentene[41c], a mixture of 1-bromo-2-methylcyclohex-1-ene and 1-bromo-6-methylcyclohex-1-ene[41b], and 4-bromo-1,2-dihydronaphthalene[41b] were synthesized according to the literature procedures. Transition metal (pre)catalysts (copper(I) iodide (99%), copper(I) bromide (99.99%), copper(I) chloride (99.99%), tetrakis(acetonitrile)copper(I) hexafluorophosphate (97%), copper(II) triflate (98%), nickel(II) chloride ethylene glycol dimethyl ether complex (98%), and bis(1,5-cyclooctadiene)nickel(0), tris(triphenylphosphine)rhodium(I) chloride, and tetrakis(triphenylphosphine)palladium(0)) were purchased from Sigma-Aldrich. All the reagents and ligands used were commercially available and used as received unless stated otherwise. (*R*,*R*)-Cyclohexane-1,2-diamine ((*R*,*R*)-CyDA) was obtained from a commercial mixture of *cis*- and *trans*-1,2-diaminocyclohexane according to the literature procedure.[256]

The NMR spectra were recorded with 500 MHz spectrometer in $CDCl_3$ as a solvent at room temperature. Chemical shifts (δ) are given in ppm. ^{1}H NMR and ^{13}C NMR shifts are reported relative to residual $CHCl_3$ (δ 7.27 ppm and δ 77.0 ppm respectively) and ^{31}P NMR shifts are reported relative to 85% H_3PO_4 as an external standard. The following abbreviations are used in reporting NMR data: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (*J*) are in Hz. High-resolution mass spectrometry analyses were obtained using LCMS IT-TOF spectrometer. Mass spectra were recorded with GC-MS spectrometer working in electron ionization (EI) mode, and GC was recorded using the

following parameters: pressure, 65.0 kPa; total flow, 33.9 mL/min; column flow, 1.00 mL/min; linear velocity, 36.8 cm/s; split, 30; temperature program: for all compounds except those stated below (program A) 80 ^{o}C, hold 1 min, 80-300 ^{o}C/25 ^{o}C/min, hold 1 min; 300-340 ^{o}C/18 ^{o}C/min, hold 2 min; total 15 min; for compounds **7d**, **8d**, **9d**, **20, 22**, **23**, **48**, **49** (program B) 80 ^{o}C, hold 1 min, 80-290 ^{o}C/15 ^{o}C/min, hold 3 min; 290-320 ^{o}C/11 ^{o}C/min, hold 4.73 min; total 25 min; for compound **7e** (program C) 80 ^{o}C, hold 1 min, 80-300 ^{o}C/11 ^{o}C/min, hold 5 min; 300-340 ^{o}C/10 ^{o}C/min, hold 6.67 min; total 35 min. Thin layer chromatography (TLC) was performed with pre-coated silica gel plates and visualized by potassium permanganate ($KMnO_4$) stain or UV light. The reaction mixtures were purified by column chromatography over silica gel (40–63 μm particle size) unless stated otherwise. Melting points were determined in a capillary tube and are uncorrected.

6.1. Preparation of bromocycloalkenes from cycloalkanones

1-Bromocyclohexene (1). In a moisture and oxygen-free two-necked round-bottom flask (250 mL) equipped with magnetic stirrer and argon inlet triphenyl phosphite (9.25 mL, 35.0 mmol) was dissolved in DCM (100 mL). The solution was cooled to −60^{o}C and then bromine (2 mL, 38.5 mmol) was added producing an orange transparent solution. After stirring for 10 min. at −60^{o}C, cyclohexanone (3.3 mL, 32.0 mmol) was added at the same temperature followed by triethylamine (5.85 mL, 42 mmol) (slight fuming was observed). After stirring for 5 min. the cooling bath was removed, the argon inlet was replaced with a balloon filled with argon and the mixture was stirred for 20 h. Then a condenser was fitted to the flask, the mixture was heated to reflux, the balloon was removed and replaced with a tube at the top of the condenser to expel HBr gas. After refluxing for 2 h, the solvent was evaporated on a water pump, the remaining dark brown sludge was diluted with pentane (20 mL) and the mixture was poured into a fritted glass funnel charged with about 40 g of silica gel. The product was eluted with pentane (150-200 mL), the solvent was then evaporated on a rotary evaporator under argon atmosphere with the water bath covered with aluminum foil yielding 1-bromocycloalkene as a colorless oil that was immediately transferred to a dark glass bottle and stored under argon at 5 ^{o}C. Yield 71% (m = 3.66 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59-1.64 (m, 2H), 1.71-1.77 (m, 2H), 2.05-2.11 (m, 2H), 2.40-2.45 (m, 2H), 6.03-6.06 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1, 24.5, 27.4, 35.1, 122.3, 128.8. GC t_R = 4.62 min; GC-MS (EI, 70 eV) *m/z* = 163 (10), 161 [M] (10), 81 (100), 79 (20), 53 (14). Analytical data are in accordance with the literature.[41b]

1-Bromocycloheptene (2). The compound was obtained in an analogous way to 1-bromocyclohexene from triphenyl phosphite (9.25 mL, 35.0 mmol), bromine (2 mL, 38.5 mmol), cycloheptanone (3.8 mL, 32.0 mmol) and triethylamine (5.85 mL, 42.0 mmol) as a mixture with 1,1-dibromocycloheptane in a 10:1 ratio (m = 4.30 g). The mixture was dissolved in THF (7 mL) in a flame-dried screw-top vial filled with argon, KOH was added (0.56 g, 10.0 mmol, 5 eq. in relation to the dibromide) and then MeOH (0.5 mL) was poured in. The mixture was stirred at 65^{o}C overnight. After cooling to room temperature the mixture was diluted with Et_2O (10 mL), stirred for 5 min., then filtered through cotton wool and the solids were washed with 3x10 mL Et_2O. The combined organic fractions were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude yellow oil was purified on a short chromatographic column (12 g of 40-63 μm silica gel) using pentane as eluent yielding 3.29 g (59%) of 1-bromocycloheptene as a colorless oil which was immediately transferred to a dark glass bottle and stored under argon at 5 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55-1.60 (m, 2H), 1.60-1.66 (m, 2H), 1.69-1.75 (m, 2H), 2.06-2.11 (m, 2H), 2.67-2.71 (m, 2H), 6.19-6.23 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.2, 26.4, 29.2, 30.6, 40.6, 126.2, 133.4. Analytical data are in accordance with the literature.[41c]

1-Bromocyclopentene (3). The compound was obtained in an analogous way to 1-bromocyclohexene from triphenyl phosphite (9.25 mL, 35.0 mmol), bromine (2 mL, 38.5 mmol), cyclopentanone (2.8 mL, 32.0 mmol) and triethylamine (5.85 mL, 42.0 mmol) as a mixture with 1,1-dibromocyclopentane in a 4:1 ratio (m = 3.19 g). The mixture was dissolved in THF (8 mL) in a flame-dried screw-top vial filled with argon, KOH was added (1.05 g, 18.8 mmol, 5 eq. in relation to the dibromide) and then MeOH (1 mL) was poured in. The mixture was stirred at 65^{o}C overnight. After cooling to room temperature the mixture was diluted with Et_2O (10 mL), stirred for 5 min., and then filtered through cotton wool, the solids were washed with 3x10 mL Et_2O. The two-phase filtrate was dried with $MgSO_4$ and then filtered through a pad of Celite. The solvents were evaporated under reduced pressure and crude yellow oil was purified on a short chromatographic column (12 g of 40-63 μm silica gel) using pentane as eluent yielding 1.36 g (29%) of 1-bromocyclopentene as a colorless oil which was immediately transferred to a dark glass bottle and stored under argon at 5 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95-2.03 (m, 2H), 2.30-2.36 (m, 2H), 2.55-2.62 (m, 2H), 5.84 (quint, J = 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.2, 32.3, 39.5, 120.8, 131.1. Analytical data are in accordance with the literature.[41c]

1-Bromo-2-methylcyclohex-1-ene (4) & 1-bromo-6-methylcyclohex-1-ene (4a). The compounds were obtained as a 62:38 mixture in an analogous way to 1-bromocyclohexene from triphenyl phosphite (9.25 mL, 35.0 mmol), bromine (2 mL, 38.5 mmol), 2-methylcyclohexanone (3.9 mL, 32.0 mmol) and triethylamine (5.85 mL, 42.0 mmol) as a colorless oil that was immediately transferred to a dark glass bottle and stored under argon at 5 ^{o}C. Overall yield: 81% (m = 4.57 g). **1-Bromo-2-methylcyclohex-1-ene:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62-1.72 (m, 4H), 1.78-1.82 (m, 3H), 2.07-2.11 (m, 2H), 2.42-2.51 (m, 2H); **1-bromo-6-methylcyclohex-1-ene:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, J_{H-H} = 6.9 Hz, 3H), 1.50-1.62 (m, 3H), 1.86-1.94 (m, 1H), 2.02 (m, 2H), 2.42-2.51 (m, 1H), 6.04 (td, J_{H-H} = 4.1 Hz, J_{H-H} = 1.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.8, 20.4, 22.7, 23.3, 24.9, 27.8, 31.9, 32.7, 36.4, 37.6, 118.6, 129.1, 129.5, 132.1. Analytical data are in accordance with the literature.[41b]

1-Bromodialin (5). The compound was obtained in an analogous way to 1-bromocyclohexene from triphenyl phosphite (4.70 mL, 17.87 mmol), bromine (1.00 mL, 19.42 mmol), 1-tetralone (2.15 mL, 16.16 mmol) and triethylamine (3 mL, 21.52 mmol) as a yellow oil that was immediately transferred to a dark glass bottle and stored under argon at 5 ^{o}C. Yield: 62% (m = 2.09 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35-2.41 (m, 2H), 2.83-2.88 (m, 2H), 6.45 (t, J_{H-H} = 4.7 Hz, 1H), 7.09-7.12 (m, 1H), 7.18-7.22 (m, 1H), 7.23-7.27 (m, 1H), 7.54-7.57 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.4, 27.6, 121.4, 126.5, 126.8, 127.2, 128.2, 130.7, 133.0, 136.3. Analytical data are in accordance with the literature.[41b]

6.2. Preparation of secondary phosphine oxides and *H*-phosphonates

Diphenylphosphine oxide (6a). In a moisture and oxygen-free two-necked round-bottom flask (100 mL) equipped with magnetic stirrer and argon inlet chlorodiphenylphosphine (12.29 g, 10 mL, 55.7 mmol) was dissolved in DCM (40 mL). The solution was cooled to 0 ^{o}C and degassed water (1.5 mL, 83.5 mmol) was added, the cooling bath was then removed and the mixture was stirred for 20 h. Then water (5 mL) was added slowly followed by 1 M aq. NaOH solution (20 mL) and the mixture was stirred for 10 min. The organic phase was separated, diluted with DCM (20 mL), and washed with 1 M aq. NaOH solution (2x20 mL), water (1x20 mL), and sat. aq. NaCl solution (1x20 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated on a rotary evaporator under argon atmosphere. The liquid obtained was left under argon atmosphere for crystallization over 2 days. The colorless crystals were then dried from remaining DCM under vacuum affording 10.18 g (90%) of the

title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.54 (m, 4H), 7.56-7.62 (m, 2H), 7.68-7.75 (m, 4H), 8.09 (d, J_{P-H} = 480.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.9 (d, J_{P-C} = 12.7 Hz), 130.7 (d, J_{P-C} = 10.9 Hz), 131.3 (d, J_{P-C} = 101.7 Hz), 132.6 (d, J_{P-C} = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 21.62. Analytical data are in accordance with the literature.[257]

Diisopropyl phosphonate (6m). In an oxygen and moisture-free one-necked round-bottom flask (50 mL) equipped with magnetic stirrer and inert gas inlet, triisopropyl phosphite (10 mL, 8.44 g, 40.5 mmol) was dissolved in THF (15 mL). After cooling the solution in an ice bath degassed distilled water was added (0.73 mL, 40.5 mmol) and the mixture was stirred at room temperature. After 24 h ^{31}P NMR experiment revealed incomplete conversion of the substrate, another equivalent of water was added (0.73 mL, 40.5 mmol) and the mixture was stirred for further 24 h. Then the solvent was evaporated under reduced pressure and the residue was dried by azeotropic distillation with 10 mL of toluene. The crude oil was purified by Kugelrohr distillation (65-68 ^{o}C/4 mmHg) yielding diisopropyl phosphite as a colorless oil (6.42 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (dd, J_1 = 6.0 Hz, J_2 = 3.2 Hz, 12H), 4.68-4.78 (m, 2H), 6.85 (d, J = 687.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.9 (dd, J_1 = 25.4 Hz, J_2 = 4.5 Hz), 70.8 (d, J = 6.4 Hz); ^{31}P NMR (202 MHz, CDCl3) δ 4.47. Analytical data are in accordance with the literature.[272]

Cyclohex-1-enyl(phenyl)phosphine oxide (6o). In a dry Schlenk flask (25 mL) equipped with magnetic stirrer and inert gas inlet, magnesium turnings (0.135 g, 5.55 mmol) and iodine (0.5 mol%) were heated and dry stirred for 15 min., then the flask was evacuated to remove excess iodine and backfilled with argon. Afterwards, LiCl (0.117 g, 2.77 mmol) was added, the flask was evacuated once more, heated under vacuum to dry LiCl and backfilled with argon. In a separate dry flask filled with argon, 1-bromocyclohexene (0.405 g, 2.52 mmol) was dissolved in THF (3 mL). 0.3 mL of the solution was added to Mg and LiCl, and the reaction flask was heated gently to start the reaction. After 5 min. the remaining bromoalkene solution was diluted with THF (3 mL) and the diluted solution was added all at once to the reaction flask. The reaction mixture was stirred at room temperature for 2.5 h to obtain a grey solution of cyclohex-1-en-1-ylmagnesium bromide lithium chloride complex. The Turbo Grignard reagent solution was transferred to a new Schlenk flask (50 mL) without unreacted magnesium, the flask was cooled to 0 ^{o}C and a solution of ethyl phenylphosphinate (0.15 mL, 0.99 mmol) in THF (3 mL) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched with 1.0 M aqueous HCl solution (10 mL), diluted with distilled water (5 mL) and EtOAc (10 mL). The aqueous phase was

extracted with EtOAc (3x10 mL). The combined organic fractions were dried with $MgSO_4$ and the solvents were evaporated on a rotovap under argon. The crude mixture was purified by flash chromatography under argon using hexane/MTBE/MeOH (8:4:1) as the eluent, affording the product in ~90% purity (0.073 g, 30% yield). R_f = 0.25 (Hexane/MTBE/MeOH 8:4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55-1.75 (m, 4H), 1.93-2.03 (m, 1H), 2.05-2.16 (m, 1H), 2.22-2.30 (m, 2H), 6.76 (dm, J_{P-H} = 23.6 Hz, 1H), 7.48 (d, J_{P-H} = 475.1 Hz, 1H), 7.48-7.54 (m, 2H), 7.55-7.60 (m, 1H), 7.66-7.73 (m, 2H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.29; GC t_R = 9.09 min.; GC-MS (EI, 70 eV) *m/z* = 206 [M] (100), 205 (37), 191 (42), 127 (15), 125 (32), 81 (38), 80 (17), 79 (75), 78 (12), 77 (32), 53 (17), 51 (17), 47 (31).

6.3. Procedures for C-P cross-coupling reactions

General procedure for the copper-catalyzed halogen exchange/cross-coupling between (cyclo)alkenyl/aryl bromides and $R_2P(O)H$ compounds. Into a flame-dried 10 mL screw-top vial filled with argon CuI (0.019 g, 0.10 mmol) was flushed with dioxane or toluene (2 mL). Then DMEDA (32 μL, 0.30 mmol) or DMCyDA (47 μL, 0.30 mmol) was added and the mixture was stirred vigorously for 1 min. until a colorless to pale green/pale blue clear solution of the catalyst was obtained. Then (cyclo)alkenyl or aryl bromide (1.10-2.00 mmol) was added (some cycloalkenyl and alkenyl bromides produced immediate colour change to blue or green-blue and turbidity or fine precipitate), the mixture was stirred for 0.5 min. followed by the addition of NaI (0.225 g, 1.50 mmol) and Cs_2CO_3 (0.652 g, 2.00 mmol) or K_2CO_3 (0.276 g, 2.00 mmol), after stirring for 0.5 min. $R_2P(O)H$ (1.00 mmol) was added neat as a solid or as a liquid and the walls of the vial were rinsed with the same solvent (3 mL). The vial was then placed into a heating block pre-heated to 110 ^oC and the mixture was stirred for 20 h (the mixture turned colorless after several minutes; in case of dialkyl phosphites after around 30 min. red-purple precipitate formed). After cooling to room temperature a sample was taken for NMR analysis of the post-reaction mixture. The contents of the vial were filtered through a Celite pad which was then washed with DCM (8x5 mL). The solvents were evaporated under reduced pressure and the crude product was purified using column chromatography with hexane/MTBE/*i*-PrOH 6:3:1/8:3:1/10:3:1/12:3:1, hexane/MTBE/MeOH 6:3:1, hexane/EtOAc/MeOH 6:3:1, EtOAc/MeOH 30:1, MTBE/EtOAc/MeOH 7:7:1/6:6:1 or hexane/EtOAc 1:1/1:2 as eluent.

Cyclohex-1-en-1-yldiphenylphosphine oxide (7a). This compound was prepared according to the general procedure on a 5 mmol scale in a 50 mL Schlenk flask using 25 mL of dioxane

from 1-bromocyclohexene (0.886 g, 5.50 mmol) and diphenylphosphine oxide (1.010 g, 5.00 mmol) using CuI (0.095 g, 0.50 mmol), DMEDA (160 μL, 1.50 mmol), Cs_2CO_3 (3.460 g, 10.00 mmol), NaI (1.120 g, 7.50 mmol) as a white solid, yield: 1.280 g (91%); R_f = 0.48 (Hexane/EtOAc/MeOH 6:3:1); m.p. 117.9-118.9 ^oC (lit. 118-120 ^oC[259]); ^1H NMR (500 MHz, $CDCl_3$) δ 1.62-1.73 (m, 4H), 2.15-2.25 (m, 4H), 6.40 (dm, J_{P-H} = 20.5 Hz, 1H), 7.43-7.50 (m, 4H), 7.50-7.56 (m, 2H), 7.66-7.73 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 22.1 (d, J_{P-C} = 8.2 Hz), 24.5 (d, J_{P-C} = 9.1 Hz), 26.4 (d, J_{P-C} = 14.5 Hz), 128.4 (d, J_{P-C} = 11.8 Hz), 131.62 (d, J_{P-C} = 101.7 Hz), 131.64 (d, J_{P-C} = 2.7 Hz), 131.8 (d, J_{P-C} = 99.9 Hz), 131.9 (d, J_{P-C} = 10.0 Hz), 143.3 (d, J_{P-C} = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 30.44. GC t_R = 11.60 min; GC-MS (EI, 70 eV) *m/z* = 283 (18), 282 [M] (100), 281 (91), 202 (13), 201 (29), 183 (16), 125 (11), 79 (12), 77 (29), 51 (21), 47 (27). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}OP$ 283.1246, found 283.1238. Analytical data are in accordance with the literature.[258,259]

Cyclohex-1-en-1-yldiphenylphosphine (7a'). Isolated as a minor product in Ni-catalyzed cross-coupling reactions. ^1H NMR (500 MHz, $CDCl_3$) δ 1.60-1.70 (m, 4H), 1.95-2.01 (m, 2H), 2.14-2.21 (m, 2H), 6.05 (dm, J_{P-H} = 14.8 Hz, 1H), 7.30-7.41 (m, 10H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 0.51. Analytical data are in accordance with the literature.[273]

2-(Diphenylphosphinoyl)cyclohexanone (7aa). This compound was prepared according to the general procedure from diphenylphosphine oxide (0.211 g, 1.04 mmol), cyclohex-1-en-1-yl tosylate (0.266 g, 1.05 mmol), CuI (0.020 g, 0.11 mmol), TMEDA (16 μL, 0.11 mmol), and K_2CO_3 (0.291 g, 2.10 mmol) as a yellowish white solid, yield: 0.138 g (88% purity by ^{31}P NMR, 38% yield). R_f = 0.40 ($CHCl_3$/MeOH 50:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.63-1.90 (m, 3H), 2.01-2.24 (m, 2H), 2.27-2.38 (m, 1H), 2.39-2.47 (m, 1H), 2.71-2.81 (m, 1H), 3.49-3.57 (m, 1H), 7.4-7.61 (m, 6H), 7.79-7.86 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.6 (d, J_{P-C} = 2.7 Hz), 26.9, 28.1 (d, J_{P-C} = 3.6 Hz), 43.0, 52.5 (d, J_{P-C} = 59.0 Hz), 128.5 (d, J_{P-C} = 11.8 Hz), 128.8 (d, J_{P-C} = 11.8 Hz), 131.1 (d, J_{P-C} = 9.2 Hz), 131.2 (d, J_{P-C} = 99.9 Hz), 131.3 (d, J_{P-C} = 10.0 Hz), 131.76, 131.84, 131.5 (d, J_{P-C} = 2.7 Hz), 131.98 (d, J_{P-C} = 2.7 Hz), 207.5 (d, J_{P-C} = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 30.95.

Cyclohex-1-en-1-yldi(*o*-tolyl)phosphine oxide (7b). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.089 g, 0.55 mmol) and di(*o*-tolyl)phosphine oxide (0.116 g, 0.50 mmol) using CuI (0.0095 g, 0.05 mmol), DMEDA (16 μL, 0.15 mmol), Cs_2CO_3 (0.326 g, 1.00 mmol), NaI (0.112 g, 0.75 mmol), as a white solid, yield: 0.133 g (86%); R_f = 0.64 (Hexane/MTBE/*i*-PrOH 8:3:1); m.p. 96.5-98.0 ^oC; ^1H NMR

(500 MHz, $CDCl_3$) δ 1.67-1.77 (m, 4H), 2.14-2.20 (m, 2H), 2.21-2.27 (m, 2H), 2.55 (s, 6H), 6.38 (dm, $J_{P\text{-}H}$ = 20.5 Hz, 1H), 7.15-7.26 (m, 4H), 7.26-7.31 (m, 2H), 7.38-7.44 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 21.7 (d, $J_{P\text{-}C}$ = 4.5 Hz), 22.3 (d, $J_{P\text{-}C}$ = 8.2 Hz), 25.3 (d, $J_{P\text{-}C}$ = 9.1 Hz), 26.5 (d, $J_{P\text{-}C}$ =14.5 Hz), 125.2 (d, $J_{P\text{-}C}$ = 12.7 Hz), 130.2 (d, $J_{P\text{-}C}$ = 99.9 Hz), 131.53 (d, $J_{P\text{-}C}$ = 1.8 Hz), 131.58 (d, $J_{P\text{-}C}$ = 99.0 Hz), 131.8 (d, $J_{P\text{-}C}$ = 10.0 Hz), 132.5 (d, $J_{P\text{-}C}$ = 12.7 Hz), 142.7 (d, $J_{P\text{-}C}$ = 8.2 Hz), 143.3 (d, $J_{P\text{-}C}$ = 7.3 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 36.07. GC t_R = 11.71 min; GC-MS (EI, 70 eV) *m/z* = 311 (16), 310 [M] (77), 309 (51), 296 (22), 295 (100), 281 (26), 268 (26), 267 (40), 253 (12), 215 (16), 214 (48), 213 (19), 212 (12), 196 (11), 166 (10), 165 (20), 128 (10), 115 (10), 109 (10), 91 (42), 79 (13), 77 (14), 65 (26), 53 (14), 47 (19). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}OP$ 311.1559, found 311.1563.

Cyclohex-1-en-1-yldi(*p*-tolyl)phosphine oxide (7c). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.177 g, 1.10 mmol) and di(*p*-tolyl)phosphine oxide (0.229 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a colorless thick oil, yield: 0.264 g (85%); R_f = 0.59 (Hexane/MTBE/*i*-PrOH 6:3:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.61-1.71 (m, 4H), 2.13-2.23 (m, 4H), 2.40 (s, 6H), 6.37 (dm, $J_{P\text{-}H}$ = 20.2 Hz, 1H), 7.23-7.29 (m, 4H), 7.53-7.60 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.52, 21.56, 22.1 (d, $J_{P\text{-}C}$ = 8.2 Hz), 24.5 (d, $J_{P\text{-}C}$ = 10.0 Hz), 26.3 (d, $J_{P\text{-}C}$ = 14.5 Hz), 128.4 (d, $J_{P\text{-}C}$ = 103.5 Hz), 129.1 (d, $J_{P\text{-}C}$ = 11.8 Hz), 131.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 132.1 (d, $J_{P\text{-}C}$ = 99.9 Hz), 141.9 (d, $J_{P\text{-}C}$ = 2.7 Hz), 142.8 (d, $J_{P\text{-}C}$ = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 30.67. GC t_R = 12.61 min; GC-MS (EI, 70 eV) *m/z* = 311 (20), 310 [M] (100), 309 (96), 229 (20), 213 (12), 91 (24), 65 (17), 47 (14). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}NaOP$ 333.1379, found 333.1372.

Cyclohex-1-en-1-yldi(*o*-anisyl)phosphine oxide (7d). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.177 g, 1.10 mmol) and di(*o*-anisyl)phosphine oxide (0.263 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.305 g (89%); R_f = 0.30 (EtOAc/MTBE/MeOH 7:7:1); m.p. 156.5-158.0 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 1.61-1.69 (m, 4H), 2.11-2.24 (m, 4H), 3.65 (s, 6H), 6.69 (dm, $J_{P\text{-}H}$ = 20.8 Hz, 1H), 6.87-6.92 (m, 2H), 6.99-7.04 (m, 2H), 7.44-7.49 (m, 2H), 7.58-7.65 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 22.5 (d, $J_{P\text{-}C}$ = 9.1 Hz), 24.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 26.4 (d, $J_{P\text{-}C}$ = 15.4 Hz), 55.3, 110.8 (d, $J_{P\text{-}C}$ = 6.4 Hz), 120.5 (d, $J_{P\text{-}C}$ = 11.8 Hz), 121.1 (d, $J_{P\text{-}C}$ = 104.4 Hz), 132.4 (d, $J_{P\text{-}C}$ = 104.4 Hz), 134.0 (d, $J_{P\text{-}C}$ = 8.2 Hz), 141.0 (d, $J_{P\text{-}C}$ = 7.3 Hz), 161.1 (d, $J_{P\text{-}$

$_C$ = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.22. GC t_R = 18.63 min; GC-MS (EI, 70 eV) *m/z* = 342 [M] (15), 341 (12), 325 (26), 312 (24), 311 (100), 248 (23), 247 (11), 221 (20), 215 (24), 213 (12), 199 (16), 183 (10), 155 (12), 141 (13), 139 (11), 137 (16), 121 (41), 109 (12), 108 (16), 107 (19), 91 (42), 79 (20), 77 (37), 65 (11), 53 (15), 51 (13), 47 (19). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{23}NaO_3P$ 365.1277, found 365.1287.

Cyclohex-1-en-1-yldi(1-naphthyl)phosphine oxide (7e). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.177 g, 1.10 mmol) and di(1-naphthyl)phosphine oxide (0.302 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.341 g (89%); R_f = 0.44 (Hexane/MTBE/*i*-PrOH 10:3:1); m.p. 199.9-200.5 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65-1.77 (m, 4H), 2.19-2.26 (m, 4H), 6.55 (dm, J_{P-H} = 20.8 Hz, 1H), 7.36-7.42 (m, 2H), 7.45-7.57 (m, 6H), 7.88-7.94 (m, 2H), 7.98-8.04 (m, 2H), 8.82-8.87 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 22.3 (d, J_{P-C} = 8.2 Hz), 25.4 (d, J_{P-C} = 9.1 Hz), 26.5 (d, J_{P-C} = 14.5 Hz), 124.3 (d, J_{P-C} = 14.5 Hz), 126.4, 127.2, 127.8 (d, J_{P-C} = 4.5 Hz), 128.4 (d, J_{P-C} = 99.0 Hz), 128.8, 132.2 (d, J_{P-C} = 99.0 Hz), 132.87, 132.90 (d, J_{P-C} = 14.5 Hz), 133.9 (d, J_{P-C} = 9.1 Hz), 134.1 (d, J_{P-C} = 7.3 Hz), 143.8 (d, J_{P-C} = 8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 37.03. GC t_R = 29.24 min[c]; GC-MS (EI, 70 eV) *m/z* = 383 (26), 382 [M] (93), 381 (100), 354 (11), 353 (36), 299 (18), 283 (16), 253 (16), 252 (23), 173 (34), 165 (13), 141 (10), 128 (40), 127 (23), 126 (11), 79 (10), 77 (16), 53 (12). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}OP$ 383.1559, found 383.1550.

Cyclohex-1-en-1-yldi(3,5-di-*tert*-butylphenyl)phosphine oxide (7f). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.177 g, 1.10 mmol) and di(3,5-di-*tert*-butylphenyl)phosphine oxide (0.427 g, 1.00 mmol), using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.426 g (84%); R_f = 0.52 (Hexane/MTBE/*i*-PrOH 12:3:1); m.p. 150.8-152.3 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (s, 36H), 1.63-1.71 (m, 4H), 2.11-2.18 (m, 2H), 2.20-2.27 (m, 2H), 6.48 (dm, J_{P-H} = 19.9 Hz, 1H), 7.46-7.48 (m 2H), 7.49-7.51 (m, 2H), 7.54-7.57 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7, 22.3 (d, J_{P-C} = 8.2 Hz), 24.8 (d, J_{P-C} = 9.1 Hz), 26.4 (d, J_{P-C} = 14.5 Hz), 31.3, 35.0, 125.5 (d, J_{P-C} = 2.7 Hz), 126.1 (d, J_{P-C} = 10.9 Hz), 130.7 (d, J_{P-C} = 101.7 Hz), 132.2 (d, J_{P-C} = 98.1 Hz), 142.4 (d, J_{P-C} = 8.2 Hz), 150.6 (d, J_{P-C} = 11.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.74. HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{34}H_{52}OP$ 507.3750, found 507.3759.

Cyclohex-1-en-1-yldicyclohexylphosphine oxide (7g). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.089 g, 0.55 mmol) and dicyclohexylphosphine oxide (0.107 g, 0.50 mmol) using CuI (0.0095 g, 0.05 mmol), DMCyDA (24 μL, 0.15 mmol), Cs_2CO_3 (0.326 g, 1.00 mmol), NaI (0.112 g, 0.75 mmol), as a white solid, yield: 0.053 g (36%); R_f = 0.48 (Hexane/MTBE/*i*-PrOH 10:3:1); m.p. 147.7-149.5 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17-1.32 (m, 6H), 1.32-1.47 (m, 4H), 1.61-1.72 (m, 8H), 1.72-1.87 (m, 6H), 1.91-1.99 (m, 2H), 2.00-2.07 (m, 2H), 2.16-2.27 (m, 2H), 6.62 (dm, J_{P-H} = 17.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8 (d, J_{P-C} = 1.8 Hz), 22.4 (d, J_{P-C} = 7.3 Hz), 24.9 (d, J_{P-C} = 3.6 Hz), 25.7 (d, J_{P-C} = 12.7 Hz), 25.98, 25.99 (d, J_{P-C} = 8.2 Hz), 26.1 (d, J_{P-C} = 11.8 Hz), 26.4 (d, J_{P-C} = 11.8 Hz), 26.7 (d, J_{P-C} = 2.7 Hz), 34.6 (d, J_{P-C} = 66.3 Hz) 128.6 (d, J_{P-C} = 80.8 Hz), 142.6 (d, J_{P-C} = 4.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 44.53. GC t_R = 11.58 min; GC-MS (EI, 70 eV) *m/z* = 294 [M] (20), 213 (23), 212 (100), 211 (20), 170 (36), 131 (20), 130 (44), 129 (45), 111 (17), 83 (13), 81 (47), 80 (12), 79 (31), 67 (25), 55 (77), 53 (15). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{31}NaOP$ 317.2005, found 317.2001.

***Tert*-butyl(cyclohex-1-en-1-yl)phenylphosphine oxide (7h).** This compound was prepared according to the general procedure from 1-bromocyclohexene (0.177 g, 1.10 mmol) and *tert*-butyl(phenyl)phosphine oxide (0.182 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32.3 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.0 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.167 g (64%); R_f = 0.46 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 87.0-88.6 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (d, J_{P-H} = 14.5 Hz, 9H), 1.57-1.74 (m, 4H), 2.18-2.37 (m, 4H), 6.78 (dm, J_{P-H} = 18.3 Hz, 1H), 6.84-6.92 (m, 1H), 7.43-7.54 (m, 3H), 7.80-7.87 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 22.4 (d, J_{P-C} = 7.3 Hz), 25.5, 26.5 (d, J_{P-C} = 13.6 Hz), 26.6 (d, J_{P-C} = 8.2 Hz), 33.6 (d, J_{P-C} = 69.9 Hz), 128.0 (d, J_{P-C} = 10.9 Hz), 130.3 (d, J_{P-C} = 85.4 Hz), 130.4 (d, J_{P-C} = 89.0 Hz), 131.2 (d, J_{P-C} = 1.8 Hz), 132.1 (d, J_{P-C} = 8.2 Hz), 142.8 (d, J_{P-C} = 6.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 40.94. GC t_R = 9.87 min; GC-MS (EI, 70 eV) *m/z* = 207 (25), 206 [M-C_4H_9+H] (100), 205 (50), 157 (13), 125 (18), 91 (14), 81 (18), 79 (23), 77 (13), 57 (15), 53 (13), 47 (31). HRMS (ESI-TOF) *m/z* $[2M+Na]^+$ calcd for $C_{32}H_{46}NaO_2P_2$ 547.2865, found 547.2871.

Cyclohex-1-en-1-ylbis(4-fluorophenyl)phosphine oxide (7i). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.155 g, 0.96 mmol) and bis(4-fluorophenyl)phosphine oxide (0.208 g, 0.87 mmol) using CuI (0.017 g, 0.09 mmol), DMEDA (28 μL, 0.26 mmol), Cs_2CO_3 (0.571 g, 1.75 mmol), NaI (0.197 g, 1.32 mmol), as a white solid, yield: 0.182 g (65%); R_f = 0.37 (Hexane/EtOAc/MeOH 10:3:1); m.p. 88.8-90.1

^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62-1.74 (m, 4H), 2.11-2.26 (m, 4H), 6.39 (dm, $J_{P\text{-}H}$ = 20.5 Hz, 1H), 7.13-7.21 (m, 4H), 7.63-7.71 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 22.0 (d, $J_{P\text{-}C}$ = 9.1 Hz), 24.5 (d, $J_{P\text{-}C}$ = 9.1 Hz), 26.4 (d, $J_{P\text{-}C}$ = 14.5 Hz), 115.9 (dd, $J_{F\text{-}C}$ = 20.89 Hz, $J_{P\text{-}C}$ = 12.7 Hz), 127.3 (dd, $J_{P\text{-}C}$ = 104.5 Hz, $J_{F\text{-}C}$ = 2.7 Hz), 131.5 (d, $J_{P\text{-}C}$ = 100.8 Hz), 134.3 (dd, $J_{F\text{-}C}$ = 10.9 Hz, $J_{P\text{-}C}$ = 9.1 Hz) 143.8 (d, $J_{P\text{-}C}$ = 8.2 Hz), 165.0 (dd, $J_{F\text{-}C}$ = 252.5 Hz, $J_{P\text{-}C}$ = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.95. GC t_R = 11.09 min; GC-MS (EI, 70 eV) *m/z* = 319 (19), 318 [M] (100), 317 (88), 290 (14), 289 (20), 238 (16), 237 (35), 221 (13), 219 (12), 143 (22), 95 (20), 79 (23), 77 (44), 76 (11), 75 (21), 53 (17), 51 (14), 47 (13). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{18}OF_2P$ 319.1058, found 319.1051.

Cyclohex-1-enyl(methyl)phenylphosphine oxide (7j). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.177 g, 1.1 mmol) and methyl(phenyl)phosphine oxide (0.140 g, 1.0 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol) as a colourless oil darkening in air, yield: 0.053 g (24%); R_f = 0.39 (Hexane/EtOAc/MeOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59-1.69 (m, 4H), 1.77 (d, $J_{P\text{-}H}$ = 12.93 Hz, 3H), 1.93-2.15 (m, 2H), 2.16-2.25 (m, 2H), 6.63 (dm, $J_{P\text{-}H}$ = 19.86 Hz, 1H), 7.43-7.54 (m, 3H), 7.66-7.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2 (d, $J_{P\text{-}C}$ = 72.7 Hz), 21.4, 22.0 (d, $J_{P\text{-}C}$ = 9.1 Hz), 23.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 26.1 (d, $J_{P\text{-}C}$ = 13.6 Hz), 128.5 (d, $J_{P\text{-}C}$ = 11.8 Hz), 130.4 (d, $J_{P\text{-}C}$ = 10.0 Hz), 131.4 (d, $J_{P\text{-}C}$ = 1.8 Hz), 132.7 (d, $J_{P\text{-}C}$ = 97.2 Hz), 133.3 (d, $J_{P\text{-}C}$ = 99.0 Hz), 140.4 (d, $J_{P\text{-}C}$ = 7.3 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 30.74. GC t_R = 9.25 min.; GC-MS (EI, 70 eV) *m/z* = 221 (14), 220 [M] (100), 219 (85), 205 (19), 191 (14), 141 (20), 140 (39), 139 (48), 125 (41), 91 (12), 81 (13), 79 (29), 78 (10), 77 (46), 51 (11), 47 (16).

Cyclohex-1-en-1-yl(phenyl)(pyridin-2-yl)phosphine oxide (7k). This compound was formed in trace quantities in a reaction according to the general procedure from 2-bromopyridine (37 μL, 0.39 mmol) and cyclohex-1-en-1-yl(phenyl)phosphine oxide **6o** (90% purity; 0.073 g, 0.35 mmol) using CuI (6.8 mg, 0.036 mmol), DMCyDA (17 μL, 0.107 mmol), K_2CO_3 (0.097 g, 0.70 mmol). Identified by GC-MS: GC t_R = 11.23 min.; GC-MS (EI, 70 eV) *m/z* = 283 [M] (54), 282 (22), 206 (100), 203 (10), 202 (33), 186 (10), 185 (13), 159 (26), 158 (33), 131 (13), 130 (15), 126 (24), 79 (29), 78 (32), 77 (18), 53 (11), 52 (11), 51 (20), 47 (20).

Diethyl cyclohex-1-en-1-ylphosphonate (7l). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.322 g, 2.00 mmol) and diethyl phosphite

(0.139 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), as a colorless oil, yield: 0.134 g (61%); R_f = 0.20 (Hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, $J_{H\text{-}H}$ = 7.3 Hz, 6H), 1.59-1.70 (m, 4H), 2.13-2.21 (m, 4H), 4.00-4.12 (m, 4H), 6.76 (dm, $J_{P\text{-}H}$ = 22.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.3 (d, $J_{P\text{-}C}$ = 6.4 Hz), 21.3, 21.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 24.2 (d, $J_{P\text{-}C}$ = 9.1 Hz), 25.9 (d, $J_{P\text{-}C}$ = 18.2 Hz), 61.4, 127.5 (d, $J_{P\text{-}C}$ = 180.7 Hz), 143.3 (d, $J_{P\text{-}C}$ = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 20.38. GC t_R = 6.82 min; GC-MS (EI, 70 eV) *m/z* = 218 [M] (29), 190 (18), 162 (56), 161 (17), 147 (19), 145 (17), 111 (43), 109 (36), 108 (41), 93 (17), 83 (35), 82 (24), 81 (76), 80 (100), 79 (90), 78 (10), 77 (24), 67 (10), 65 (22), 53 (33), 52 (11), 51 (11). HRMS (ESI-TOF) *m/z* $[2M+Na]^+$ calcd for $C_{20}H_{38}NaO_6P_2$ 459.2036, found 459.2031. Analytical data are in accordance with the literature.[261]

Diisopropyl cyclohex-1-en-1-ylphosphonate (7m). This compound was prepared according to the general procedure from 1-bromocyclohexene (0.322 g, 2.00 mmol) and diisopropyl phosphite (0.169 g, 1.02 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), as a colorless oil, yield: 0.143 g (58%); R_f = 0.28 (Hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (dd, $J_{P\text{-}H}$ = 22.1 Hz, $J_{H\text{-}H}$ = 6.3 Hz, 12H), 1.58-1.68 (m, 4H), 2.12-2.19 (m, 4H), 4.58-4.68 (m, 2H), 6.75 (dm, $J_{P\text{-}H}$ = 22.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 22.0 (d, $J_{P\text{-}C}$ = 10.0 Hz), 23.9 (d, $J_{P\text{-}C}$ = 4.5 Hz), 24.1 (d, $J_{P\text{-}C}$ = 3.6 Hz), 24.3 (d, $J_{P\text{-}C}$ = 8.2 Hz), 25.9 (d, $J_{P\text{-}C}$ = 18.2 Hz), 69.8 (d, $J_{P\text{-}C}$ = 5.4 Hz), 128.8 (d, $J_{P\text{-}C}$ = 181.7 Hz), 142.4 (d, $J_{P\text{-}C}$ = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 18.18. GC t_R = 6.95 min; GC-MS (EI, 70 eV) *m/z* = 204 [M-C_3H_7+H] (14), 163 (52), 162 (100), 145 (24), 81 (39), 80 (57), 79 (37), 77 (11), 53 (16). HRMS (ESI-TOF) *m/z* $[2M+Na]^+$ calcd for $C_{24}H_{46}NaO_6P_2$ 515.2662, found 515.2653.

Cyclohept-1-en-1-yldiphenylphosphine oxide (8a). This compound was prepared according to the general procedure from 1-bromocycloheptene (0.199 g, 1.14 mmol) and diphenylphosphine oxide (0.209 g, 1.04 mmol) using CuI (0.020 g, 0.11 mmol), DMEDA (34 μL, 0.32 mmol), Cs_2CO_3 (0.678 g, 2.08 mmol), NaI (0.234 g, 1.56 mmol), as a colorless oil slowly solidifying to a white solid, yield: 0.284 g (92%); R_f = 0.46 (Hexane/MTBE/MeOH 6:3:1); m.p. 73.5-75.0 ^{o}C (lit. colorless oil,[258] 74-76 ^{o}C[259]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44-1.50 (m, 2H), 1.52-1.59 (m, 2H), 1.75-1.82 (m, 2H), 2.32-2.42 (m, 4H), 6.62 (dt, $J_{P\text{-}H}$ = 21.4 Hz, $J_{H\text{-}H}$ = 6.3 Hz, 1H), 7.44-7.49 (m, 4H), 7.50-7.56 (m, 2H), 7.67-7.74 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.9, 26.8 (d, $J_{P\text{-}C}$ = 5.4 Hz), 28.9 (d, $J_{P\text{-}C}$ = 11.8 Hz), 30.1 (d, $J_{P\text{-}C}$ = 18.2 Hz), 32.0, 128.3 (d, $J_{P\text{-}C}$ = 11.8 Hz), 131.5 (d, $J_{P\text{-}C}$ = 2.7 Hz), 131.8 (d, $J_{P\text{-}C}$ = 100.8

Hz), 131.9 (d, J_{P-C} = 10.0 Hz), 137.2 (d, J_{P-C} = 97.2 Hz), 148.5 (d, J_{P-C} = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 33.05. GC t_R = 12.06 min; GC-MS (EI, 70 eV) *m/z* = 297 (19), 296 [M] (100), 295 (77), 281 (15), 268 (18), 267 (24), 202 (27), 201 (37), 183 (15), 128 (11), 125 (12), 91 (11), 77 (34), 51 (21), 47 (34). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}OP$ 297.1403, found 297.1403. Analytical data are in accordance with the literature.[258,259]

Cyclohept-1-en-1-yldi(*o*-tolyl)phosphine oxide (8b). This compound was prepared according to the general procedure from 1-bromocycloheptene (0.193 g, 1.10 mmol) and di(*o*-tolyl)phosphine oxide (0.232 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 µL, 0.30 mmol), Cs_2CO_3 (0.650 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a colorless thick oil (contains traces of solvents), yield: 0.321 g (99%); R_f = 0.68 (Hexane/MTBE/*i*-PrOH 8:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40-1.48 (m, 2H), 1.54-1.62 (m, 2H), 1.76-1.84 (m, 2H), 2.34-2.43 (m, 4H), 2.57 (s, 6H), 6.67 (dt, J_{P-H} = 21.4 Hz, J_{H-H} = 6.3 Hz), 7.14-7.26 (m, 4H), 7.26-7.31 (m, 2H), 7.37-7.43 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7 (d, J_{P-C} = 3.6 Hz), 26.0, 26.6 (d, J_{P-C} = 5.5 Hz), 29.5 (d, J_{P-C} = 10.9 Hz), 30.1 (d, J_{P-C} = 18.2 Hz), 32.1, 125.1 (d, J_{P-C} = 12.7 Hz), 130.2 (d, J_{P-C} = 99.9 Hz), 131.5 (d, J_{P-C} = 1.8 Hz), 131.9 (d, J_{P-C} = 10.0 Hz), 132.5 (d, J_{P-C} = 12.7 Hz), 136.6 (d, J_{P-C} = 95.4 Hz), 143.4 (d, J_{P-C} = 7.3 Hz), 148.8 (d, J_{P-C} = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 38.87. GC t_R = 12.21 min; GC-MS (EI, 70 eV) *m/z* = 325 (15), 324 [M] (63), 323 (22), 310 (17), 309 (74), 295 (29), 282 (29), 281 (100), 269 (13), 268 (34), 267 (50), 255 (17), 254 (11), 253 (16), 215 (16), 214 (27), 213 (17), 212 (15), 196 (15), 179 (10), 178 (11), 166 (15), 165 (28), 137 (12), 128 (11), 115 (11), 109 (14), 92 (13), 91 (69), 77 (17), 67 (11), 65 (36), 55 (15), 53 (13), 47 (24). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}OP$ 325.1716, found 325.1709.

Cyclohept-1-en-1-yldi(*o*-anisyl)phosphine oxide (8d). This compound was prepared according to the general procedure from 1-bromocycloheptene (0.193 g, 1.10 mmol) and di(*o*-anisyl)phosphine oxide (0.262 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 µL, 0.3 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.306 g (86%); R_f = 0.30 (EtOAc/MTBE/MeOH 7:7:1); m.p. 126.3-127.8 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38-1.46 (m, 2H), 1.49-1.56 (m, 2H), 1.71-1.78 (m, 2H), 2.30-2.37 (m, 4H), 3.69 (s, 6H), 6.87 (dt, J_{P-H} = 21.8 Hz, J_{H-H} = 6.3 Hz, 1H), 6.88-6.92 (m, 2H), 6.97-7.03 (m, 2H), 7.44-7.49 (m, 2H), 7.55-7.61 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.0 (d, J_{P-C} = 1.8 Hz), 26.9 (d, J_{P-C} = 7.3 Hz), 29.2 (d, J_{P-C} = 12.7 Hz), 30.2 (d, J_{P-C} = 18.2 Hz), 32.3, 55.2, 110.7 (d, J_{P-C} = 6.4 Hz), 120.5 (d, J_{P-C} = 11.8 Hz), 121.0 (d, J_{P-C} = 103.5 Hz), 133.1, 134.2 (d, J_{P-C} = 8.2 Hz), 138.1 (d, J_{P-C} = 102.6 Hz), 145.8 (d, J_{P-C} = 9.1 Hz), 161.1 (d, J_{P-C} = 1.8 Hz);

^{31}P NMR (202 MHz, $CDCl_3$) δ 29.04. GC t_R = 18.44 min; GC-MS (EI, 70 eV) *m/z* = 356 [M] (13), 339 (17), 326 (26), 325 (100), 297 (27), 248 (25), 247 (12), 235 (14), 215 (220), 199 (15), 155 (11), 141 (14), 139 (12), 137 (17) 121 (49), 109 (12), 108 (16), 107 (19), 93 (12), 91 (53), 79 (13), 77 (37), 67 (11), 65 (15), 55 (13), 53 (11), 51 (11), 47 (18). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{26}O_3P$ 357.1614, found 357.1604.

Cyclohept-1-en-1-yldicyclohexylphosphine oxide (8g). This compound was prepared according to the general procedure from 1-bromocycloheptene (0.193 g, 1.10 mmol) and dicyclohexylphosphine oxide (0.214 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.164 g (53%); R_f = 0.48 (Hexane/MTBE/*i*-PrOH 10:3:1); m.p. 138.8-140.0 ^oC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16-1.45 (m, 10H), 1.48-1.58 (m, 4H), 1.62-1.73 (m, 4H), 1.75-1.88 (m, 8H), 1.90-1.99 (m, 2H), 2.19-2.27 (m, 2H), 2.30-2.37 (m, 2H), 6.80 (dt, J_{P-H} = 18.0 Hz, J_{H-H} = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.1 (d, J_{P-C} = 3.6 Hz), 25.9 (d, J_{P-C} = 1.8 Hz), 26.0, 26.1 (d, J_{P-C} = 1.8 Hz), 26.5 (d, J_{P-C} = 11.8 Hz), 26.74 (d, J_{P-C} = 12.7 Hz), 26.75 (d, J_{P-C} = 6.4 Hz), 29.0 (d, J_{P-C} = 10.9 Hz), 30.1 (d, J_{P-C} = 15.4 Hz), 32.3, 34.4 (d, J_{P-C} = 66.3 Hz), 134.1 (d, J_{P-C} = 78.1 Hz), 148.2 (d, J_{P-C} = 5.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 46.89. GC t_R = 12.09 min; GC-MS (EI, 70 eV) *m/z* = 308 [M] (22), 265 (24), 227 (14), 226 (70), 225 (14), 197 (12), 184 (20), 183 (24), 170 (28), 145 (12), 144 (27), 143 (30), 125 (13), 97 (11), 95 (27), 93 (22), 83 (15), 81 (31), 79 (21), 67 (24), 55 (100), 53 (13). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{33}NaOP$ 331.2161, found 331.2156.

Diisopropyl cyclohept-1-en-1-ylphosphonate (8m). This compound was prepared according to the general procedure from 1-bromocycloheptene (0.193 g, 1.10 mmol) and diisopropyl phosphite (0.166 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol) as a colorless oil, yield: 0.179 g (69%); R_f = 0.39 (Hexane/EtOAc 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (dd, J_{P-H} = 26.5 Hz, J_{H-H} = 6.3 Hz, 12H), 1.48-1.57 (m, 4H), 1.73-1.80 (m, 2H), 2.26-2.35 (m, 4H), 4.56-4.66 (m, 2H), 6.96 (dt, J_{P-H} = 24.0 Hz, J_{H-H} = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.0 (d, J_{P-C} = 4.5 Hz), 24.1 (d, J_{P-C} = 4.5 Hz), 25.8 (d, J_{P-C} = 2.7 Hz), 26.7 (d, J_{P-C} = 7.3 Hz), 28.4 (d, J_{P-C} = 10.0 Hz), 29.7 (d, J_{P-C} = 21.8 Hz), 32.1, 69.8 (d, J_{P-C} = 5.4 Hz), 134.3 (d, J_{P-C} = 177.1 Hz), 148.0 (d, J_{P-C} = 10.0 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 20.07. GC t_R = 7.44 min; GC-MS (EI, 70 eV) *m/z* = 218 [M-C_3H_7+H] (12), 177 (33), 176 (100), 161 (18), 159 (14), 148 (14), 95 (27), 94 (48), 93 (14), 79 (31), 67 (19), 65 (10), 55 (13), 53 (12). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{13}H_{25}NaO_3P$ 283.1434, found 283.1440.

Cyclopent-1-en-1-yldiphenylphosphine oxide (9a). This compound was prepared according to the general procedure from 1-bromocyclopentene (0.174 g, 1.18 mmol) and diphenylphosphine oxide (0.217 g, 1.07 mmol) using CuI (0.020 g, 0.11 mmol), DMEDA (35 μL, 0.32 mmol), K_2CO_3 (0.296 g, 2.14 mmol), NaI (0.240 g, 1.60 mmol), as a white solid, yield: 0.240 g (84%); R_f = 0.43 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 90.8-92.1 ^oC (lit. 93-94 ^oC[258]); ^1H NMR (500 MHz, $CDCl_3$) δ 1.99-2.07 (m, 2H), 2.50-2.62 (m, 4H), 6.35 (dm, J_{P-H} = 10.4 Hz, 1H), 7.43-7.49 (m, 4H), 7.50-7.56 (m, 2H), 7.65-7.73 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.2 (d, J_{P-C} = 9.1 Hz), 33.6 (d, J_{P-C} = 11.8 Hz), 34.5 (d, J_{P-C} = 16.4 Hz), 128.4 (d, J_{P-C} = 11.8 Hz), 131.4 (d, J_{P-C} = 10.0 Hz), 131.7 (d, J_{P-C} = 2.7 Hz), 132.1 (d, J_{P-C} = 104.5 Hz), 137.3 (d, J_{P-C} = 103.5 Hz), 148.7 (d, J_{P-C} = 11.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 24.28. GC t_R = 11.02 min; GC-MS (EI, 70 eV) *m/z* = 269 (18), 268 [M] (100), 267 (74), 240 (20), 202 (12), 201 (52), 185 (14), 183 (29), 128 (17), 115 (11), 77 (31), 65 (11), 51 (32), 47 (36). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}OP$ 269.1090, found 269.1091. Analytical data are in accordance with the literature.[258]

Cyclopent-1-en-1-yldi(*o*-anisyl)phosphine oxide (9d). This compound was prepared according to the general procedure from 1-bromocyclopentene (0.158 g, 1.07 mmol) and di(*o*-anisyl)phosphine oxide (0.256 g, 0.97 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), Cs_2CO_3 (0.636 g, 1.95 mmol), NaI (0.224 g, 1.50 mmol), as a white solid, yield: 0.286 g (87%); R_f = 0.43 (EtOAc/MTBE/MeOH 6:6:1); m.p. 148.2-150.0 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 1.98 (quint, J_{H-H} = 7.6 Hz, 2H), 2.49-2.60 (m, 4H), 3.60 (s, 6H), 6.68 (dm, J_{P-H} = 10.7 Hz, 1H), 6.85-6.90 (m, 2H), 7.00-7.06 (m, 2H), 7.43-7.49 (m, 2H), 7.64-7.70 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3 (d, J_{P-C} = 10.0 Hz), 34.3 (d, J_{P-C} = 5.5 Hz), 34.4 (d, J_{P-C} = 10.0 Hz), 55.3, 110.8 (d, J_{P-C} = 6.4 Hz), 120.6 (d, J_{P-C} = 12.7 Hz), 121.7 (d, J_{P-C} = 108.1 Hz), 133.1, 133.7 (d, J_{P-C} = 8.2 Hz), 138.1 (d, J_{P-C} = 108.1 Hz), 146.7 (d, J_{P-C} = 10.9 Hz), 160.8 (d, J_{P-C} = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 19.86. GC t_R = 17.59 min; GC-MS (EI, 70 eV) *m/z* = 328 [M] (16), 327 (14), 312 (11), 311 (48), 298 (24), 297 (100), 248 (29), 247 (11), 229 (10), 215 (32), 213 (13), 207 (32), 199 (19), 168 (11), 155 (11), 153 (10), 141 (21), 139 (14), 137 (18), 128 (12), 121 (49), 115 (17), 109 (14), 108 (19), 107 (24), 92 (11), 91 (45), 79 (11), 77 (39), 67 (13), 65 (20), 51 (16), 47 (21). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}O_3P$ 329.1301, found 329.1303.

Diisopropyl cyclopent-1-en-1-ylphosphonate (9m). This compound was prepared according to the general procedure from 1-bromocyclopentene (0.162 g, 1.10 mmol) and diisopropyl phosphite (0.167 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30

mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.5 mmol), as a colorless oil, yield: 0.092 g (40%); R_f = 0.37 (Hexane/EtOAc 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (dd, J_{P-H} = 21.4 Hz, J_{H-H} = 6.3 Hz, 12H), 1.92-2.00 (m, 2H), 2.45-2.57 (m, 4H), 4.62-4.72 (m, 2H), 6.63 (dm, J_{P-H} = 11.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.8 (d, J_{P-C} = 12.7 Hz), 23.9 (d, J_{P-C} = 5.5 Hz), 24.1 (d, J_{P-C} = 4.5 Hz), 33.3 (d, J_{P-C} = 13.6 Hz), 34.1 (d, J_{P-C} = 21.8 Hz), 70.0 (d, J_{P-C} = 5.5 Hz), 134.0 (d, J_{P-C} = 190.7 Hz), 147.0 (d, J_{P-C} = 14.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 14.92. GC t_R = 6.33 min; GC-MS (EI, 70 eV) *m/z* = 190 [M-C_3H_7+H] (19), 175 (11), 173 (13), 149 (100), 148 (84), 147 (25), 132 (14), 131 (52), 108 (14), 67 (38), 66 (35), 65 (25). HRMS (ESI-TOF) *m/z* $[2M+Na]^+$ calcd for $C_{22}H_{42}NaO_6P_2$ 487.2349, found 487.2352. This compound has been reported but no analytical data for identification has been given.[260]

(2-Methylcyclohex-1-en-1-yl)diphenylphosphine oxide (10a). This compound was prepared according to the general procedure from a 62:38 mixture of 1-bromo-2-methylcyclohex-1-ene and 1-bromo-6-methylcyclohex-1-ene (0.193 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a waxy solid (89% purity, mixed fraction with **10a'**), overall yield: 0.104 g (35%); R_f = 0.49 (Hexane/MTBE/*i*-PrOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51-1.58 (m, 2H), 1.58-1.65 (m, 2H), 1.73-1.80 (m, 2H), 1.95 (s, 3H), 2.15-2.23 (m, 2H), 7.40-7.53 (m, 6H), 7.62-7.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.0, 22.6 (d, J_{P-C} = 9.1 Hz), 23.3 (d, J_{P-C} = 9.1 Hz), 29.7 (d, J_{P-C} = 12.7 Hz), 34.1 (d, J_{P-C} = 12.7 Hz), 123.0 (d, J_{P-C} = 98.1 Hz), 128.3 (d, J_{P-C} = 11.8 Hz), 131.3 (d, J_{P-C} = 1.8 Hz), 131.5 (d, J_{P-C} = 9.1 Hz), 133.7 (d, J_{P-C} = 100.8 Hz), 153.3 (d, J_{P-C} = 5.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 30.24. GC t_R = 11.69 min; GC-MS (EI, 70 eV) *m/z* = 296 [M] (42), 295 (100), 77 (14), 47 (17). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}OP$ 297.1403, found 297.1395. This compound has been reported but no analytical data for identification has been given.[261]

(6-Methylcyclohex-1-en-1-yl)diphenylphosphine oxide (10a'). This compound was prepared according to the general procedure from a 62:38 mixture of 1-bromo-2-methylcyclohex-1-ene and 1-bromo-6-methylcyclohex-1-ene (0.193 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a waxy solid (90% purity, mixed fraction with **10a**), overall yield: 0.017 g (6%); R_f = 0.49 (Hexane/MTBE/*i*-PrOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, J_{H-H} = 7.0 Hz, 3H), 1.51-1.58 (m, 1H), 1.60-1.67 (m, 1H), 1.68-1.80 (m, 2H), 2.10-2.25 (m, 2H), 2.67-2.77 (m, 1H), 6.14 (dt, J_{P-H} = 21.1 Hz, J_{H-H} = 3.5 Hz, 1H), 7.43-7.49 (m, 4H), 7.49-7.55 (m, 2H), 7.64-

7.75 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.4, 20.9, 26.6 (d, $J_{P\text{-}C}$ = 15.4 Hz), 29.0 (d, $J_{P\text{-}C}$ = 8.2 Hz), 30.3 (d, $J_{P\text{-}C}$ = 8.2 Hz), 128.3 (d, $J_{P\text{-}C}$ = 14.5 Hz), 128.4 (d, $J_{P\text{-}C}$ = 11.8 Hz), 131.5, 131.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 137.0 (d, $J_{P\text{-}C}$ = 96.3 Hz), 143.6 (d, $J_{P\text{-}C}$ = 10.0 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.99. GC t_R = 11.57 min; GC-MS (EI, 70 eV) *m/z* = 282 (34), 281 [M-CH_3] (100), 280 (17), 279 (13), 268 (11), 241 (13), 205 (10), 203 (42), 202 (72), 201 (48), 185 (10), 95 (25), 79 (16), 67 (12), 55 (14). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}OP$ 297.1403, found 297.1395. ^{1}H NMR shifts reported for this compound differ substantially.[262]

***Trans*-1,2-bis(diphenylphosphinoyl)tetralin (11).** This compound was prepared according to the general procedure from 1-bromodialin (0.230 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol); isolated as a mixture with diphenylphosphine oxide (0.219 g, 1:1.55) after column chromatography, this was dissolved in DCM (3 mL), water (1 mL) and iodine (0.100 g, 0.40 mmol) were added and the mixture was stirred for 20 h at room temperature. The reaction was diluted with DCM to 30 mL and excess iodine was quenched with sat. aq. Na_2SO_3 solution (10 mL), the organic phase was washed with 4x10 mL sat. aq. $NaHCO_3$ solution. After drying with $MgSO_4$ and solvent evaporation the residue was recrystallized from EtOAc to give a pale yellow crystalline solid, yield: 0.121 g (45%); R_f = 0.33 (Hexane/MTBE/MeOH 6:3:1); m.p. 199.1-200.4 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71-1.82 (m, 1H), 1.84-1.98 (m, 1H), 2.30-2.40 (m, 1H), 2.71-2.81 (m, 1H), 3.90-4.01 (m, 1H), 4.24-4.35 (m, 1H), 6.25-6.30 (m, 1H), 6.75-6.81 (m, 1H), 6.88-6.94 (m, 1H), 7.01-7.07 (m, 1H), 7.09-7.16 (m, 2H), 7.21-7.27 (m, 2H), 7.33-7.60 (m, 12H), 7.72-7.79 (m, 2H), 7.95-8.02 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.3, 27.0 (d, $J_{P\text{-}C}$ = 5.5 Hz), 30.6 (d, $J_{P\text{-}C}$ = 69.0 Hz), 41.0 (d, $J_{P\text{-}C}$ = 62.7 Hz), 125.5 (d, $J_{P\text{-}C}$ = 3.6 Hz), 127.0 (d, $J_{P\text{-}C}$ = 3.6 Hz), 127.9 (d, $J_{P\text{-}C}$ = 11.8 Hz), 128.3-128.9 (m), 129.3 (d, $J_{P\text{-}C}$ = 4.5 Hz), 129.5 (d, $J_{P\text{-}C}$ = 4.5 Hz), 131.2 (d, $J_{P\text{-}C}$ = 8.2 Hz), 131.4-132.4 (m), 132.3 (d, $J_{P\text{-}C}$ = 8.2 Hz), 139.2 (d, $J_{P\text{-}C}$ = 8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 33.68 (d, $J_{P\text{-}P}$ = 39.8 Hz), 36.70 (d, $J_{P\text{-}P}$ = 42.3 Hz). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{34}H_{30}NaO_2P_2$ 555.1613, found 555.1602.

Diphenyl(prop-1-en-2-yl)phosphine oxide (12). This compound was prepared according to the general procedure from 2-bromopropene (0.133 g, 1.10 mmol) and diphenylphosphine oxide (0.203 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a colorless oil (lit. colorless oil[263], solid, m.p. 126-128 ^{o}C[264]), yield: 0.107 g (44%); R_f = 0.42 (Hexane/MTBE/*i*-PrOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (d, $J_{P\text{-}H}$ = 12.3 Hz, 3H), 5.63 (dm, $J_{P\text{-}H}$ = 19.9 Hz, 1H), 5.95

(dm, J_{P-H} = 41.3 Hz, 1H), 7.45-7.51 (m, 4H), 7.52-7.58 (m, 2H), 7.67-7.75 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.1 (d, J_{P-C} = 11.8 Hz), 128.5 (d, J_{P-C} = 12.7 Hz), 130.5 (d, J_{P-C} = 9.1 Hz), 130.8 (d, J_{P-C} = 102.6 Hz), 131.8 (d, J_{P-C} = 9.1 Hz), 132.0 (d, J_{P-C} = 2.7 Hz), 139.2 (d, J_{P-C} = 92.6 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.40. GC t_R = 9.61 min; GC-MS (EI, 70 eV) *m/z* = 242 (17), 242 [M] (100), 241 (40), 227 (25), 202 (50), 201 (83), 200 (13), 199 (68), 185 (39), 184 (11), 183 (53), 155 (29), 154 (11), 153 (11), 152 (15), 125 (19), 121 (25), 118 (11), 115 (11), 78 (24), 77 (84), 51 (80), 50 (16), 47 (85). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}OP$ 243.0933, found 243.0940. Analytical data are in accordance with the literature.[263,264]

(*E*)-Diphenyl(prop-1-en-1-yl)phosphine oxide (13). This compound was prepared according to the general procedure from *trans*-1-bromoprop-1-ene (0.133 g, 1.10 mmol) and diphenylphosphine oxide (0.203 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.165 g (68%); R_f = 0.37 (EtOAc/MeOH 30:1); m.p. 126.5-127.3 ^{o}C (lit. 128-129 ^{o}C[265]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97-2.02 (m, 3H), 6.21-6.33 (m, 1H), 6.70 (ddq, J_{P-H} = 19.2 Hz, J_{H-H} = 17.0 Hz, J_{H-H} = 6.6 Hz, 1H), 7.42-7.49 (m, 4H), 7.49-7.55 (m, 2H), 7.67-7.74 (m 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.5 (d, J_{P-C} = 18.2 Hz), 123.4 (d, J_{P-C} = 103.5 Hz), 128.5 (d, J_{P-C} = 12.7 Hz), 131.3 (d, J_{P-C} = 10.0 Hz), 131.6 (d, J_{P-C} = 2.7 Hz), 133.1 (d, J_{P-C} = 105.4 Hz), 147.9 (d, J_{P-C} = 1.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 23.35. GC t_R = 9.91 min; GC-MS (EI, 70 eV) *m/z* = 243 (13), 242 [M] (80), 241 (100), 227 (52), 202 (44), 201 (47), 199 (12), 186 (12), 185 (30), 183 (57), 165 (16), 155 (21), 152 (16), 149 (28), 147 (18), 133 (10), 125 (14), 118 (87), 117 (58), 116 (22), 115 (36), 109 (13), 108 (13), 107 (11), 91 (20), 78 (18), 77 (75), 51 (81), 50 (17), 47 (73). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{16}OP$ 243.0933, found 243.0940. Analytical data are in accordance with the literature.[265]

(2-Methylprop-1-en-1-yl)diphenylphosphine oxide (14). This compound was prepared according to the general procedure from 1-bromo-2-methylprop-1-ene (0.133 g, 1.10 mmol) and diphenylphosphine oxide (0.203 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.217 g (85%); R_f = 0.42 (EtOAc/MeOH 30:1); m.p. 148.0-148.7 ^{o}C (lit. 149-150 ^{o}C[266]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3H), 2.07 (d, J_{P-H} = 2.2 Hz, 3H), 5.89 (d, J_{P-H} = 25.5 Hz, 1H), 7.41-7.52 (m, 6H), 7.70-7.77 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.9 (d, J_{P-C} = 8.2 Hz), 28.7 (d, J_{P-C} = 17.3 Hz), 117.0 (d, J_{P-C} = 105.4 Hz), 128.5 (d, J_{P-C} = 12.7 Hz), 130.9 (d, J_{P-C} = 9.1 Hz), 131.3 (d, J_{P-C} = 2.7 Hz), 134.9 (d, J_{P-C} = 104.50 Hz), 160.5; ^{31}P NMR

(202 MHz, $CDCl_3$) δ 20.77. GC t_R = 9.97 min; GC-MS (EI, 70 eV) *m/z* = 256 [M] (53), 255 (100), 201 (18), 183 (12), 131 (13), 130 (20), 129 (19), 115 (19), 91 (16), 77 (25), 51 (25), 47 (32). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}OP$ 257.1090, found 257.1098. Analytical data are in accordance with the literature.[265,266]

(2-Methylallyl)diphenylphosphine oxide (14a). This compound was prepared according to the general procedure from 1-bromo-2-methylprop-1-ene (0.133 g, 1.10 mmol) and diphenylphosphine oxide (0.203 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.011 g (4%); R_f = 0.50 (EtOAc/MeOH 30:1); m.p. 142.1-143.2 °C (lit. 144-145 °C[266]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H), 3.13 (d, J_{P-H} = 13.9 Hz, 2H), 4.67-4.70 (m, 1H), 4.85-4.89 (m, 1H), 7.44-7.55 (m, 6H), 7.74-7.81 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.5 (d, J_{P-C} = 2.7 Hz), 39.6 (d, J_{P-C} = 67.2 Hz), 116.0 (d, J_{P-C} = 10.0 Hz), 128.5 (d, J_{P-C} = 11.8 Hz), 131.0 (d, J_{P-C} = 9.1 Hz), 131.7 (d, J_{P-C} = 2.7 Hz), 132.9 (d, J_{P-C} = 98.1 Hz), 136.2 (d, J_{P-C} = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 29.09. GC t_R = 9.85 min; GC-MS (EI, 70 eV) *m/z* = 256 [M] (22), 255 (23), 202 (13), 201 (100), 131 (17), 77 (29), 51 (24), 47 (19). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}OP$ 257.1090, found 257.1098. Analytical data are in accordance with the literature.[266]

(3-Methylbut-2-en-2-yl)diphenylphosphine oxide (15). This compound was prepared according to the general procedure from 2-bromo-3-methylbut-2-ene (0.164 g, 1.10 mmol) and diphenylphosphine oxide (0.203 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.204 g (75%); R_f = 0.54 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 69.9-71.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (d, J_{H-P} = 13.9 Hz, 3H), 1.92 (s, 3H), 2.04 (s, 3H), 7.39-7.52 (m, 6H), 7.60-7.70 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.6 (d, J_{P-C} = 14.5 Hz), 23.5 (d, J_{P-C} = 13.6 Hz), 24.5 (d, J_{P-C} = 9.1 Hz), 120.7 (d, J_{P-C} = 2.7 Hz), 128.5 (d, J_{P-C} = 2.7 Hz), 131.4 (d, J_{P-C} = 9.1 Hz), 131.5 (d, J_{P-C} = 9.1 Hz), 134.1 (d, J_{P-C} = 100.8 Hz), 152.4 (d, J_{P-C} = 7.3 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.80. GC t_R = 10.27 min; GC-MS (EI, 70 eV) *m/z* = 270 [M] (44), 269 (100), 202 (18), 201 (30), 183 (13), 155 (13), 144 (24), 129 (40), 128 (12), 125 (14), 91 (10), 78 (13), 77 (36), 51 (23), 47 (31). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{17}H_{19}NaOP$ 293.1066, found 293.1068.

Propane-1,2-diylbis(diphenylphosphine oxide) (16). This compound was prepared according to the general procedure from 2-bromopropene (0.133 g, 1.10 mmol) and

diphenylphosphine oxide (0.203 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMEDA (32 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.089 g (40%); R_f = 0.23 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 116.0–119.0 °C (lit. 128-129 °C[270]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.25 (m, 3H), 2.45-2.62 (m, 2H), 2.93-3.05 (m, 1H), 7.37-7.58 (m, 14H), 7.67-7.77 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 26.8 (dd, J_{P-C} = 69.9 Hz, J_{P-C} = 3.6 Hz), 28.7 (d, J_{P-C} = 69.0 Hz), 128.5-129.0 (m), 130.6 (d, J_{P-C} = 10.9 Hz), 130.7 (d, J_{P-C} = 10.0 Hz), 131.0 (d, J_{P-C} = 9.1 Hz), 131.7 (d, J_{P-C} = 93.6 Hz), 131.9 (d, J_{P-C} = 10.0 Hz), 133.3 (d, J_{P-C} = 93.6 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.38 (d, J_{P-P} = 49.8 Hz), 38.00 (d, J_{P-P} = 47.3 Hz). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{26}NaO_2P_2$ 467.1300, found 467.1306. Analytical data are in accordance with the literature.[270]

Diphenyl(*m*-tolyl)phosphine oxide (18). This compound was prepared according to the general procedure from 3-bromotoluene (0.188 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMCyDA (47 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.202 g (69%); R_f = 0.56 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 125.2-125.9 °C (lit. 123.7–124.2 °C[190]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.31-7.41 (m, 3H), 7.43-7.50 (m, 4H), 7.52-7.61 (m, 3H), 7.64-7.71 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 128.3 (d, J_{P-C} = 13.6 Hz), 128.4 (d, J_{P-C} = 12.7 Hz), 129.2 (d, J_{P-C} = 10.9 Hz), 131.8 (d, J_{P-C} = 2.7 Hz), 132.1 (d, J_{P-C} = 10.0 Hz), 132.2 (d, J_{P-C} = 104.5 Hz), 132.5 (d, J_{P-C} = 10.0 Hz), 132.6 (d, J_{P-C} = 104.5 Hz), 132.7 (d, J_{P-C} = 2.7 Hz), 138.4 (d, J_{P-C} = 11.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 29.29. GC t_R = 11.78 min; GC-MS (EI, 70 eV) *m/z* = 292 [M] (11), 291 (26), 282 (11), 281 (36), 209 (14), 208 (21), 207 (100), 191 (13), 135 (10), 133 (13), 96 (16), 73 (30). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}OP$ 293.1090, found 293.1090. Analytical data are in accordance with the literature.[190]

Diphenyl(4-(trifluoromethyl)phenyl)phosphine oxide (19). This compound was prepared according to the general procedure from 1-bromo-4-(trifluoromethyl)benzene (0.247 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMCyDA (47 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.250 g (72%); R_f = 0.66 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 91.9-92.6 °C (lit. 89.0-90.0 °C[217]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.53 (m, 4H), 7.55-7.61 (m, 2H), 7.63-7.70 (m, 4H), 7.70-7.76 (m, 2H), 7.79-7.86 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.5 (q, J_{F-C} = 273.4 Hz), 125.2-125.4 (m), 128.7 (d, J_{P-C} = 12.7 Hz), 131.6 (d, J_{P-C} = 105.4 Hz), 132.0 (d, J_{P-C} = 10.0 Hz), 132.3 (d, J_{P-C} = 2.7 Hz), 132.5 (d, J_{P-C} = 10.0 Hz), 133.7 (qd,

$J_{F\text{-}C}$ = 32.7 Hz, $J_{P\text{-}C}$ = 2.7 Hz), 137.1 (d, $J_{P\text{-}C}$ = 100.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.00. GC t_R = 10.80 min; GC-MS (EI, 70 eV) *m/z* = 346 [M] (41), 345 (100), 269 (11), 267 (19), 201 (24), 199 (11), 185 (12), 183 (19), 152 (11), 77 (46), 51 (36), 47 (13). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}OF_3P$ 347.0807, found 347.0799. Analytical data are in accordance with the literature.[217]

Naphthalen-1-yldiphenylphosphine oxide (20). This compound was prepared according to the general procedure from 1-bromonaphthalene (0.228 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMCyDA (47 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.111 g (34%); R_f = 0.56 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 184.0-185.8 ^oC (lit. 183.8-184.7 ^oC[268]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.34 (m, 1H), 7.36-7.41 (m, 1H), 7.42-7.53 (m, 6H), 7.53-7.59 (m, 2H), 7.66-7.73 (m, 4H), 7.88-7.92 (m, 1H), 8.00-8.05 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.1 (d, $J_{P\text{-}C}$ = 13.6 Hz), 126.9 (d, $J_{P\text{-}C}$ = 108.1 Hz), 127.6 (d, $J_{P\text{-}C}$ = 6.4 Hz), 128.6 (d, $J_{P\text{-}C}$ = 12.7 Hz), 128.7, 128.9 (d, $J_{P\text{-}C}$ = 101.7 Hz), 131.9 (d, $J_{P\text{-}C}$ = 2.7 Hz), 132.1 (d, $J_{P\text{-}C}$ = 10.0 Hz), 132.8 (d, $J_{P\text{-}C}$ = 104.5 Hz), 133.2 (d, $J_{P\text{-}C}$ = 2.7 Hz), 133.7 (d, $J_{P\text{-}C}$ = 7.3 Hz), 133.8 (d, $J_{P\text{-}C}$ = 11.8 Hz), 133.9 (d, $J_{P\text{-}C}$ = 9.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.39. GC t_R = 20.65 min; GC-MS (EI, 70 eV) *m/z* = 328 [M] (33), 327 (100), 249 (25), 202 (16), 77 (14), 51 (13). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}OP$ 329.1090, found 329.1083. Analytical data are in accordance with the literature.[268]

Diphenyl(*o*-tolyl)phosphine oxide (21). This compound was prepared according to the general procedure from 2-bromotoluene (0.188 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMCyDA (47 μL g, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.040 g (14%); R_f = 0.54 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 122.0-123.2 ^oC (lit. 121.5-122.9 ^oC[212]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.00-7.06 (m, 1H), 7.11-7.16 (m, 1H), 7.26-7.31 (m, 1H), 7.40-7.45 (m, 1H), 7.45-7.51 (m, 4H), 7.53-7.58 (m, 2H), 7.62-7.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7 (d, $J_{P\text{-}C}$ = 5.4 Hz), 125.1 (d, $J_{P\text{-}C}$ = 13.6 Hz), 128.5 (d, $J_{P\text{-}C}$ = 11.8 Hz), 130.8 (d, $J_{P\text{-}C}$ = 103.5 Hz), 131.7 (d, $J_{P\text{-}C}$ = 1.8 Hz), 131.9 (d, $J_{P\text{-}C}$ = 10.0 Hz), 132.1 (d, $J_{P\text{-}C}$ = 2.7 Hz), 132.7 (d, $J_{P\text{-}C}$ = 103.5 Hz), 133.4 (d, $J_{P\text{-}C}$ = 12.7 Hz), 143.3 (d, $J_{P\text{-}C}$ = 8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.70. GC t_R = 11.56 min; GC-MS (EI, 70 eV) *m/z* = 292 (22), 291 (52), 282 (11), 281 (36), 209 (14), 208 (21), 207 (100), 191 (12), 135 (10), 133 (12), 96 (16), 73 (29). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}OP$ 293.1090, found 293.1092. Analytical data are in accordance with the literature.[212]

***o*-Anisyldiphenylphosphine oxide (22).** This compound was prepared according to the general procedure from 2-bromoanisole (0.206 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMCyDA (47 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid (95% purity, contaminated with 5% of S.M.), yield: 0.220 g (71%); R_f = 0.41 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 160.0-161.5 ^oC (lit. 164.2-166.6 ^oC[212]); ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (s, 3H), 6.90-6.94 (m, 1H), 7.06-7.11 (m, 1H), 7.40-7.46 (m, 4H), 7.48-7.57 (m, 3H), 7.67-7.74 (m, 4H), 7.74-7.80 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.2, 111.3 (d, J_{P-C} = 6.4 Hz), 120.2 (d, J_{P-C} = 103.5 Hz), 120.9 (d, J_{P-C} = 11.8 Hz), 128.1 (d, J_{P-C} = 12.7 Hz), 131.4 (d, J_{P-C} = 2.7 Hz), 131.8 (d, J_{P-C} = 10.0 Hz), 133.2 (d, J_{P-C} = 107.2 Hz), 134.2, 134.9 (d, J_{P-C} = 7.3 Hz), 160.8 (d, J_{P-C} = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.41. GC t_R = 17.45 min; GC-MS (EI, 70 eV) *m/z* = 309 (16), 308 [M] (75), 307 (38), 291 (15), 290 (44), 289 (15), 279 (18), 277 (43), 218 (12), 217 (92), 201 (26), 200 (14), 199 (100), 183 (26), 153 (10), 152 (33), 139 (11), 91 (29), 77 (51), 51 (45), 50 (11), 47 (19). HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{17}NaO_2P$ 331.0858, found 331.0858. Analytical data are in accordance with the literature.[212]

(2-Aminophenyl)diphenylphosphine oxide (23). This compound was prepared according to the general procedure from 2-bromoaniline (0.190 g, 1.10 mmol) and diphenylphosphine oxide (0.202 g, 1.00 mmol) using CuI (0.019 g, 0.10 mmol), DMCyDA (47 μL, 0.30 mmol), K_2CO_3 (0.276 g, 2.00 mmol), NaI (0.225 g, 1.50 mmol), as a white solid, yield: 0.126 g (43%); R_f = 0.59 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 164.9-166.0 ^oC (lit. 169.5-169.8 ^oC[269]); ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (br. s, 2H), 6.57-6.63 (m, 1H), 6.66-6.71 (m, 1H), 6.74-6.81 (m, 1H), 7.24-7.29 (m, 1H), 7.44-7.51 (m, 4H), 7.53-7.59 (m, 2H), 7.62-7.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 111.9 (d, J_{P-C} = 105.4 Hz), 116.8 (d, J_{P-C} = 12.7 Hz), 117.0 (d, J_{P-C} = 8.2 Hz), 128.5 (d, J_{P-C} = 12.7 Hz), 131.9, 132.0 (d, J_{P-C} = 10.0 Hz), 132.2 (d, J_{P-C} = 104.4 Hz), 133.2 (d, J_{P-C} = 10.9 Hz), 133.3 (d, J_{P-C} = 1.8 Hz), 152.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.45. GC t_R = 17.23 min; GC-MS (EI, 70 eV) *m/z* = 294 (12), 293 [M] (66), 292 (100), 214 (22), 207 (26), 199 (11), 167 (10), 77 (11), 51 (12), 47 (15). HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{17}NOP$ 294.1042, found 294.1039. Analytical data are in accordance with the literature.[269]

Procedure for the bromine/iodine exchange of 1-bromocyclohexene. Into a flame-dried 10 mL screw-top vial filled with argon CuI (19 mg, 0.1 mmol) was flushed with dioxane (2.5 mL). Then DMEDA (32.3 μL, 0.3 mmol) was added and the mixture was stirred vigorously for 1 min. until a pale green clear solution of the catalyst was obtained. Then 1-

bromocyclohexene (161 mg, 1.0 mmol) was added (a blue precipitate formed), followed by the addition of NaI (225 mg, 1.5 mmol). The vial was placed into a heating block preheated to 110 ^{o}C and stirred for 20 h (during the reaction the solution turns yellow with grey blue precipitate). After cooling to room temperature, hexadecane (150 μL, 0.51 mmol) was added as an internal standard and the mixture was diluted with water (2 mL) and EtOAc (4 mL), and stirred vigorously for 5 min. Then 100 μL of the organic phase was taken, diluted with DCM (1 mL) and subjected to GC-MS analysis. The aqueous phase was extracted with diethyl ether (2x4 mL), the combined organic fractions were dried with $MgSO_4$, filtered and evaporated. Yield of 1-iodocyclohexene (**24**) by GC-MS: 99%, yield after work-up by ^{1}H NMR: 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63-1.74 (m, 4H), 2.07-2.13 (m, 2H), 2.48-2.53 (m, 2H), 6.33-6.36 (m, 1H). GC t_R = 3.98 min; GC-MS (EI, 70 eV) *m/z* = 208 [M] (19), 128 (19), 127 (100), 81 (91), 80 (15), 79 (70), 78 (12), 77 (39), 66 (10), 65 (13), 53 (61), 52 (25), 51 (54), 50 (35). Analytical data are in accordance with the literature.[41e]

Kinetic study for the halogen exchange/cross-coupling at 1 mmol scale. The reaction was set up in a flame-dried 10 mL Schlenk flask connected to a vacuum/inert gas manifold and fitted with a septum according to the general procedure for the cross-coupling described below using 1-bromocyclohexene (0.177 g, 1.10 mmol), diphenylphosphine oxide (0.202 g, 1.00 mmol), CuI (0.019 g, 0.10 mmol), DMEDA (320 μL, 0.30 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), and NaI (0.225 g, 1.50 mmol). A 50 μL sample was taken out through the septum using a syringe after 1, 2, 3, 4, and 5 hours, loaded onto a layer of Celite in a pasteur pipette which was washed with dichloromethane (1.5 mL) into a vial and analyzed with GC-MS and ^{31}P NMR spectroscopy. After 5 hours the septum was sealed with Parafilm and the stopcock was closed. After 24 hours NMR and GC-MS analyses were performed.

Kinetic study for the halogen exchange/cross-coupling at 0.5 mmol scale. Four reactions were set up in flame-dried 10 mL screw-top vials according to the procedure for the cross-coupling described below using 1-bromocyclohexene (0.089 g, 0.55 mmol), diphenylphosphine oxide (0.101 g, 0.50 mmol), CuI (0.095 g, 0.05 mmol), DMEDA (160 μL, 0.15 mmol), Cs_2CO_3 (0.326 g, 1.00 mmol), and NaI (0.113 g, 0.75 mmol). The reactions were stopped after 1, 2, 3, and 20 hours respectively. For each reaction a sample of around 0.7 mL was taken out and filtered through cotton to an NMR tube with a D_2O capillary tube and analyzed using ^{31}P NMR spectroscopy. For GC-MS analysis 50 μL samples were taken, diluted to 1.5 mL using dichloromethane and filtered through Celite.

6.4. Conjugate addition reactions to cycloalkenylphosphine derivatives

General procedure for the base-catalyzed conjugate addition to cycloalkenylphosphine oxides. In a flame-dried 10 mL screw-top vial filled with argon cycloalkenylphosphine oxide (0.50 mmol) and secondary phosphine oxide (0.50 mmol) were dissolved in dioxane (2.5 mL) and LiO*t*-Bu was added (0.10 mmol). The vial was placed into a heating block preheated to 110 ^{o}C and the mixture was stirred for 20 h. After cooling to room temperature water (1 mL) was added dropwise and the mixture was stirred vigorously for 1 min., then ethyl acetate (3 mL) and saturated aq. NaCl solution (3 mL) were added and the mixture was stirred vigorously for 5 min. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (4 x 3 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated on a rotary evaporator. The pure product was obtained after recrystallization of the crude product from EtOAc (2-3 mL) and a few drops of DCM via slow evaporation of the solvents at room temperature.

***Trans*-1,2-bis(diphenylphosphinoyl)cyclopentane (25).** This compound was prepared according to the general procedure from cyclopenten-1-yldiphenylphosphine oxide (0.146 g, 0.54 mmol), diphenylphosphine oxide (0.111 g, 0.54 mmol), and LiO*t*-Bu (0.009 g, 0.11 mmol) as a white solid, yield: 0.211 g (82%); R_f = 0.45 (Hexane/EtOAc/MeOH 6:3:1); m.p. 210.2-211.1 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83-2.01 (m, 4H), 2.11-2.25 (m, 2H), 3.31-3.39 (m, 2H), 7.12-7.17 (m, 4H), 7.29-7.34 (m, 2H), 7.39-7.49 (m, 10H), 7.70-7.76 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.1, 28.9, 36.4-37.3 (m), 128.4-128.7 (m), 130.5-130.9 (m), 131.2, 131.5, 131.6-133.3 (m), 132.3-132.6 (m); ^{31}P NMR (202 MHz, $CDCl_3$) δ 36.18. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{28}NaO_2P_2$ 493.1457, found 493.1466.

***Trans*-1,2-bis(diphenylphosphinoyl)cyclohexane (26).** This compound was prepared according to the general procedure from cyclohexen-1-yldiphenylphosphine oxide (0.144 g, 0.51 mmol), diphenylphosphine oxide (0.104 g, 0.51 mmol), and LiO*t*-Bu (0.008 g, 0.10 mmol) as a white solid, yield: 0.215 g (87%); R_f = 0.43 (Hexane/EtOAc/MeOH 6:3:1); m.p. 244.2-245.4 ^{o}C (lit. 242-243 ^{o}C[271]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52-1.61 (m, 2H), 1.76-1.86 (m, 2H), 1.86-2.00 (m, 2H), 2.47-2.64 (m, 2H), 2.70-2.77 (m, 2H), 7.33-7.39 (m, 4H), 7.40-7.46 (m, 8H), 7.46-7.54 (m, 4H), 7.63-7.69 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.0, 22.9, 31.0-32.3 (m), 128.5-128.8 (m), 130.8-131.0 (m), 131.4, 131.6, 131.8-132.9 (m); ^{31}P NMR (202 MHz, $CDCl_3$) δ 36.91. Enantiomers were separated by chiral HPLC (Daicel CHIRALPAK OD-H column, flow rate 1.0 mL/min, hexane/isopropanol 96:4). HRMS (ESI-

TOF) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{30}NaO_2P_2$ 507.1613, found 507.1604. Analytical data are in accordance with the literature.[271]

***Cis*-1,2-bis(diphenylphosphinoyl)cyclohexane (26a).** This compound was prepared according to the general procedure from cyclohexen-1-yldiphenylphosphine oxide (0.070 g, 0.25 mmol), diphenylphosphine oxide (0.056 g, 0.28 mmol), LiO*t*-Bu (0.004 g, 0.05 mmol), and (+)-sparteine (0.012 g, 0.05 mmol) as a white solid, yield: 0.064 g (53%); R_f = 0.19 (DCM/MeOH 30:1); m.p. 276.5-278.3 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26-1.41 (m, 2H), 1.61-1.76 (m, 2H), 1.84-1.95 (m, 2H), 2.23-2.71 (m, 2H), 3.04-3.31 (m, 2H), 7.16-7.41 (m, 12H), 7.45-7.56 (m, 4H), 7.58-7.69 (m, 4H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.35. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{30}NaO_2P_2$ 507.1613, found 507.1617.

***Trans*-1,2-bis(diphenylphosphinoyl)cycloheptane (27).** This compound was prepared according to the general procedure from cyclohepten-1-yldiphenylphosphine oxide (0.156 g, 0.53 mmol), diphenylphosphine oxide (0.108 g, 0.53 mmol), and LiO*t*-Bu (0.009 g, 0.11 mmol) as a white solid, yield: 0.152 g (58%); R_f = 0.52 (Hexane/EtOAc/MeOH 6:3:1); m.p. 200.3-202.4 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52-1.60 (m, 2H), 1.74-1.83 (m, 2H), 1.83-1.93 (m, 4H), 2.09-2.22 (m, 2H), 3.17-3.27 (m, 2H), 7.20-7.26 (m, 2H), 7.36-7.51 (m, 12H), 7.70-7.76 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.9-25.1 (m), 27.0, 29.9, 34.7-35.7 (m), 128.4-128.7 (m), 130.8-131.1 (m), 131.1, 131.4, 131.7-132.9 (m), 132.2-132.4 (m); ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.61. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{32}NaO_2P_2$ 521.1770, found 521.1781.

(*R*)-(2-Hydroxy-2-phenylethyl)diphenylphosphine-borane (L86-BH_3). In a dry Schlenk flask (50 mL) filled with argon, diphenylphosphine (0.556 g, 2.99 mmol) was dissolved in THF (12 mL). After cooling the solution to -78 ^oC, *n*-BuLi (2.4 mL, 1.26 M in hexanes, 3.02 mmol) was added and the reaction mixture was stirred for 15 min. Then (*R*)-styrene oxide (0.38 mL, 3.29 mmol) was added, the reaction was stirred at -78 ^oC for 30 min., the cooling bath was removed and stirring was continued for 1.5 h. Then the reaction mixture was cooled in an ice/water bath and BH_3·THF (4.5 mL, 1.0 M in THF, 4.50 mmol) was added. The cooling bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction was quenched at 0 ^oC with 1.0 M aqueous HCl solution (2.0 mL), diluted with EtOAc (5 mL) and distilled water (5 mL). The aqueous phase was extracted with EtOAc (3x10 mL) and the combined organic fractions were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure to give the crude mixture (m = 1.243 g).

NMR analysis revealed incomplete complexation of the formed phosphine (the ratio of the desired phosphine-borane, the corresponding free phosphine, and the phosphine oxide was 1:0.89:0.29). Thus, the mixture was dissolved in DCM (15 mL) in a dry Schlenk flask (50 mL) under argon. The solution was cooled to 0 ^{o}C and $BH_3{\cdot}SMe_2$ (1.13 mL, 2.0 M in toluene, 2.25 mmol) was added. The cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched with 1.0 M aqueous HCl solution (2.0 mL) and diluted with distilled water (5 mL). The aqueous phase was extracted with DCM (3x5 mL), the combined organic fractions were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure to give the crude phosphine-borane (m = 1.128 g). The crude compound was purified by flash chromatography using 60 g of silica gel and hexane/Et_2O as the eluent, affording the pure product as a white powder (0.686 g, 72% yield). Recrystallization from Et_2O/hexane 1:1 (6 mL) afforded 0.567 g of the crystalline compound. R_f = 0.47 (Hexane/Et_2O 1:1); m.p. 95.5-96.3 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-1.65 (m, 3H), 2.64-2.81 (m, 2H), 3.02 (d, $J_{H\text{-}H}$ = 2.8 Hz, 1H), 5.10 (tt, $J_{H\text{-}H}$ = 9.5, $J_{H\text{-}H}$ = 2.5 Hz, 1H), 7.24-7.28 (m, 1H), 7.30-7.35 (m, 4H), 7.43-7.55 (m, 6H), 7.68-7.76 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.0 (d, $J_{P\text{-}C}$ = 33.6 Hz), 69.5, 125.4, 127.8, 128.6, 128.83 (d, $J_{P\text{-}C}$ = 95.4 Hz), 128.83 (d, $J_{P\text{-}C}$ = 10.0 Hz), 129.0 (d, $J_{P\text{-}C}$ = 10.0 Hz), 129.3 (d, $J_{P\text{-}C}$ = 96.3 Hz), 131.3 (d, $J_{P\text{-}C}$ = 1.8 Hz), 131.5 (d, $J_{P\text{-}C}$ = 1.8 Hz), 131.9 (d, $J_{P\text{-}C}$ = 9.1 Hz), 132.3 (d, $J_{P\text{-}C}$ = 9.1 Hz), 143.8 (d, $J_{P\text{-}C}$ = 11.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 11.92; GC t_R = 11.52 min.; GC-MS (EI, 70 eV) *m/z* = 306 [M-BH_3] (10), 263 (15), 262 (76), 202 (14), 200 (12), 199 (68), 186 (17), 183 (22), 121 (100), 108 (26), 107 (15), 104 (27), 103 (12), 91 (12), 79 (12), 78 (20), 77 (31), 51 (15).

Deprotection of L86-BH_3. In a dry Schlenk flask (15 mL) filled with argon, **L86**-BH_3 (0.355 g, 1.11 mmol) and DABCO (0.205 g, 1.83 mmol) were dissolved in toluene (4 mL), and the mixture was stirred at 50 ^{o}C for 22 h. The solvent was then evaporated on a rotovap under argon and the crude mixture was purified by flash chromatography under argon using hexane (100%) to Et_2O (100%) as the eluent, affording pure (*R*)-(2-hydroxy-2-phenylethyl)diphenylphosphine **L86** as a colourless oil highly sensitive to oxidation (0.286 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 1H), 2.54-2.65 (m, 2H), 4.74-4.82 (m, 1H), 7.26-7.30 (m, 1H), 7.31-7.37 (m, 9H), 7.43-7.49 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.9 (d, $J_{P\text{-}C}$ = 14.5 Hz), 72.2 (d, $J_{P\text{-}C}$ = 16.4 Hz), 125.7, 127.8, 128.4, 128.52, 128.53 (d, $J_{P\text{-}C}$ = 11.8 Hz), 128.9, 132.8 (d, $J_{P\text{-}C}$ = 59.0 Hz), 132.9 (d, $J_{P\text{-}C}$ = 59.0 Hz), 138.04 (d, $J_{P\text{-}C}$ = 51.8 Hz), 138.05 (d, $J_{P\text{-}C}$ = 75.4 Hz), 144.5 (d, $J_{P\text{-}C}$ = 6.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ -23.00.

(*E*)-Hex-1-en-1-yldiphenylphosphine oxide (28). In a dry Schlenk flask (25 mL) filled with argon, $Ph_2P(O)H$ (0.902 g, 4.46 mmol) and $RhCl(PPh_3)_3$ (0.124 g, 0.13 mmol) were dissolved in toluene (10 mL). Then hex-1-yne (0.54 mL, 4.68 mmol) was added, and the flask was put into a heating block pre-heated to 40 ^oC and stirred for 44 h. The solvent was removed on a rotovap affording the crude mixture as a dark orange-red wet solid (m = 1.490 g). The crude was passed through neutral alumina (25 g) on a sintered glass funnel using 50 mL of hexane followed by 100 mL of hexane/MTBE/MeOH 6:3:1, affording a yellow-orange solid (m = 1.276 g). This was purified using flash column chromatography using neutral alumina (60 g) and hexane/MTBE/MeOH (10:4:1), yielding 1.181 g of a pale yellow solid (93% yield). Recrystallization from DCM/hexane (~1:7) by slow evaporation at room temperature afforded colourless crystals in the shape of long needles. R_f = 0.43 (Hexane/MTBE/MeOH 6:3:1); m.p. 71.0-72.0 ^oC (lit. 73.0-75.0 ^oC[239]); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (td, J = 7.3, 1.8 Hz, 3H), 1.29–1.41 (m, 2H), 1.41–1.52 (m, 2H), 2.27-2.34 (m, 2H), 6.23 (ddq, J = 24.6, 17.0, 1.6 Hz, 1H), 6.73 (dddt, J = 19.6, 17.0, 6.6, 1.3 Hz, 1H), 7.43-7.48 (m, 4H), 7.49-7.54 (m, 2H), 7.65-7.73 (m, 4H).*;* ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.2, 30.0, 34.2 (d, $J_{P\text{-}C}$ = 16.4 Hz), 121.1 (d, $J_{P\text{-}C}$ = 103.5 Hz), 128.5 (d, $J_{P\text{-}C}$ = 11.8 Hz), 131.3 (d, $J_{P\text{-}C}$ = 10.0 Hz), 131.8, 132.7 (d, $J_{P\text{-}C}$ = 104.5 Hz), 153.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 23.51; GC t_R = 10.87 min.; GC-MS (EI, 70 eV) *m/z* = 284 [M] (30), 283 (44), 255 (42), 242 (29), 241 (31), 228 (18), 227 (24), 203 (14), 202 (100), 201 (74), 186 (15), 185 (11), 183 (28), 160 (10), 155 (18), 125 (13), 117 (30), 115 (20), 108 (12), 104 (17), 91 (16), 77 (39), 51 (21), 47 (27). Analytical data are in accordance with the literature.[239]

Cyclohex-1-en-1-yldiphenylphosphine sulfide (29). Into a dry Schlenk flask (25 mL) filled with argon, cyclohex-1-en-1-yldiphenylphosphine sulfide **6a** (0.331 g, 1.17 mmol) and P_2S_5 (0.520 g, 2.34 mmol) were added followed by toluene (8 mL). The resulting mixture was stirred at 110 ^oC for 22 h. Afterwards, the reaction flask was cooled in an ice/water bath and 10 mL of saturated aqueous $KHCO_3$ solution was added. After stirring for 15 min., the mixture was poured into an Erlenmeyer flask, the reaction flask was washed with Et_2O (3x5 mL) and the washings were added to the Erlenmeyer flask. 25 mL of aqueous 1.0 M NaOH solution were added and the mixture was stirred vigorously for 2 h. Afterwards, the aqueous phase was extracted with Et_2O (3x20 mL), the combined organic fractions were dried with $MgSO_4$, and the solvents were evaporated under reduced pressure to give the crude product as a thick yellow oil solidifying overnight (m = 0.370 g). The crude product was purified using flash chromatography using silica gel (12 g) and hexane to hexane/EtOAc (1:1) as the eluent,

affording the pure product as a thick yellow oil which was solidified by precipitation from DCM/hexane (0.327 g, 94% yield). R_f = 0.53 (Hexane/EtOAc 4:1); m.p. 88.5-89.5 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62-1.77 (m, 4H) 2.19-2.30 (m, 4H), 6.32 (dm, $J_{P\text{-}H}$ = 22.7 Hz, 1H), 7.43-7.55 (m, 6H), 7.75-7.83 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 22.4 (d, $J_{P\text{-}C}$ = 8.2 Hz), 24.7 (d, $J_{P\text{-}C}$ = 10.0 Hz), 26.7 (d, $J_{P\text{-}C}$ = 14.5 Hz), 128.4 (d, $J_{P\text{-}C}$ = 11.8 Hz), 131.35 (d, $J_{P\text{-}C}$ = 2.7 Hz), 131.37 (d, $J_{P\text{-}C}$ = 83.6 Hz), 131.4 (d, $J_{P\text{-}C}$ = 79.0 Hz), 132.1 (d, $J_{P\text{-}C}$ = 10.9 Hz), 142.7 (d, $J_{P\text{-}C}$ = 8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 44.98; GC t_R = 11.83 min.; GC-MS (EI, 70 eV) *m/z* = 299 (13), 298 [M] (46), 297 (18), 267 (11), 266 (100), 265 (25), 189 (10), 186 (10), 185 (15), 183 (47), 157 (11), 129 (11), 109 (15), 108 (26), 107 (13), 91 (14), 79 (13). Only ^{1}H and ^{31}P NMR chemical shifts have been reported for this compound.[273]

(*E*)-Hex-1-en-1-yldiphenylphosphine sulfide (30). Into a dry Schlenk flask (25 mL) filled with argon, (*E*)-hex-1-en-1-yldiphenylphosphine oxide **28** (0.406 g, 1.43 mmol) and P_2S_5 (0.692 g, 3.11 mmol) were added followed by toluene (10 mL). The resulting mixture was stirred at 110 ^{o}C for 22 h. After cooling to room temperature, it was passed through a plug of silica gel (H = 2.5 cm, Ø = 4.0 cm) using DCM as the eluent, affording the product as a yellow oil (0.427 g, 99% yield). R_f = 0.69 (Hexane/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, $J_{H\text{-}H}$ = 7.3 Hz, 3H), 1.33-1.43 (m, 2H), 1.47–1.55 (m, 2H), 2.32–2.39 (m, 2H), 6.35 (ddt, $J_{H\text{-}H}$ = 24.3 Hz, $J_{H\text{-}H}$ = 16.1 Hz, $J_{H\text{-}H}$ = 1.6 Hz, 1H), 6.87 (ddt, $J_{H\text{-}H}$ = 22.7 Hz, $J_{H\text{-}H}$ = 16.1 Hz, $J_{H\text{-}H}$ = 6.6 Hz, 1H), 7.40-7.52 (m, 6H), 7.69 – 7.80 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.3, 30.1, 33.9 (d, $J_{P\text{-}C}$ = 18.2 Hz), 121.6 (d, $J_{P\text{-}C}$ = 85.4 Hz), 128.5 (d, $J_{P\text{-}C}$ = 12.7 Hz), 131.3, 131.4 (d, $J_{P\text{-}C}$ = 10.9 Hz), 133.6 (d, $J_{P\text{-}C}$ = 86.3 Hz), 153.0 (d, $J_{P\text{-}C}$ = 2.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.78; GC t_R = 11.20 min.; GC-MS (EI, 70 eV) *m/z* = 300 [M] (29), 271 (23), 258 (16), 219 (16), 218 (100), 217 (34), 186 (15), 185 (23), 183 (44), 140 (26), 139 (16), 133 (11), 115 (11), 109 (15), 108 (16), 107 (11), 91 (11), 63 (10).

Cyclohex-2-en-1-yldiphenylphosphine oxide (32). This compound was obtained from cyclohex-1-en-1-yl(diphenyl)phosphine oxide (**7a**) (0.145 g, 0.51 mmol), *o*-anisylmagnesium bromide (0.62 mL, 1.0 M in THF, 0.62 mmol), CuI (4.9 mg, 0.026 mmol), and 1,3-bis(diphenylphosphino)propane (10.8 mg, 0.026 mmol), as a mixture was the starting material, yield: 0.037 g (26%). R_f = 0.52 (Hexane/MTBE/*i*-PrOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48-1.60 (m, 1H), 1.82-1.95 (m, 3H), 2.00-2.08 (m, 2H), 3.16-3.26 (m, 1H), 7.42-7.57 (m, 6H), 7.75-7.81 (m, 2H), 7.83-7.89 (m, 2H); ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.82; GC t_R = 11.27 min.; GC-MS (EI, 70 eV) *m/z* = 282 [M] (18), 203 (32), 202 (100), 201 (65), 155 (18), 77 (22), 51 (11), 47 (13).

[1,1'-Bi(cyclohexan)]-2-ene-2,2'-diylbis(diphenylphosphine oxide) (33). This compound was obtained from cyclohex-1-en-1-yl(diphenyl)phosphine oxide **(7a)** (0.145 g, 0.51 mmol), *o*-anisylmagnesium bromide (0.62 mL, 1.0 M in THF, 0.62 mmol), CuI (4.9 mg, 0.026 mmol), and 1,3-bis(diphenylphosphino)propane (10.8 mg, 0.026 mmol), as a white solid, yield: 0.052 g (35%). R_f = 0.25 (Hexane/MTBE/*i*-PrOH 6:3:1); m.p. 222.5-224.2 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12-2.11 (m, 15H), 2.34-2.42 (m, 1H), 2.61-2.70 (m, 1H), 6.18 (dm, J_{P-H} = 20.8 Hz), 7.39-7.50 (m, 10H), 7.50-7.57 (m, 2H), 7.59-7.68 (m, 4H), 7.73-7.80 (m, 2H), 7.80-7.87 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5 (d, J_{P-C} = 8.2 Hz), 22.6, 24.4, 24.7 (d, J_{P-C} = 9.1 Hz), 25,7 (d, J_{P-C} = 10.9 Hz), 26.3, 26.9, 27.1 (d, J_{P-C} = 8.2 Hz), 37.5 (d, J_{P-C} = 69.9 Hz), 41.1, 128.3-128.7 (m), 130.6 (d, J_{P-C} = 8.2 Hz), 130.9 (d, J_{P-C} = 9.1 Hz), 131.3 (dd, J_{P-C} = 7.3, 2.7 Hz), 131.9 (d, J_{P-C} = 9.1 Hz), 131.6-131.8 (m), 132.8 (d, J_{P-C} = 94.5 Hz), 134.1 (d, J_{P-C} = 91.7 Hz), 147.5 (d, J_{P-C} = 8.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 30.36, 33.96; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{36}H_{38}O_2P_2$ 587.2239, found 587.2236.

(6-hydroxycyclohex-1-en-1-yl)diphenylphosphine oxide (34). Identified in the post-reaction mixture as a side product (Tables 15 & 16) by GC-MS and the presence of characteristic ^{1}H NMR signals: 4.51-4.56 (m, 1H, C*H*-OH), 6.17 (dm, J_{P-H} = 19.9 Hz, olefinic C*H*). ^{31}P NMR (202 MHz, $CDCl_3$) δ 34.88; GC t_R = 11.78 min.; GC-MS (EI, 70 eV) *m/z* = 297 [M-H] (11), 282 (25), 281 (54), 279 (12), 270 (27), 269 (12), 253 (15), 243 (13), 242 (70), 241 (48), 227 (27), 209 (15), 208 (23), 207 (100), 203 (12), 202 (55), 201 (31), 191 (18), 183 (19), 155 (20), 152 (11), 149 (14), 147 (14), 135 (15), 133 (22), 128 (13), 125 (17), 116 (10), 115 (20), 96 (14), 91 (12), 79 (14), 78 (24), 77 (63), 73 (44), 51 (23), 47 (30).

(*Trans*-2-allylcyclohexyl)diphenylphosphine oxide (43) and (*Cis*-2-allylcyclohexyl)-diphenylphosphine oxide (44). These compounds were obtained as a mixture (1:0.75) using cyclohex-1-en-1-yl(diphenyl)phosphine oxide **7a** (0.084 g, 0.30 mmol), allylmagnesium bromide (0.36 mL, 1.0 M in diethyl ether, 0.36 mmol), CuI (5.7 mg, 0.030 mmol), and TMEDA (10 µL, 0.067 mmol). R_f = 0.55 (Hexane/MTBE/*i*-PrOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12-1.41 (m), 1.43-1.68 (m), 1.75-2.01 (m), 2.02-2.10 (m, 1H of **43**), 2.31-2.45 (m), 2.66-2.74 (m, 1H of **44**), 4.84-4.91 (m), 4.93-4.97 (m, 1H of **43**), 5.46 (dddd, J_{H-H} = 16.9 Hz, J_{H-H} = 10.2 Hz, J_{H-H} = 8.7 Hz, J_{H-H} = 5.5 Hz, 1H of **44**), 5.58 (ddt, J_{H-H} = 17.2 Hz, J_{H-H} = 10.1 Hz, J_{H-H} = 2.0 Hz), 7.42-7.52 (m), 7.74-7.87 (m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.7, 20.3, 23.4, 24.7, 25.1 (d, J_{P-C} = 8.2 Hz), 26.5 (d, J_{P-C} = 12.7 Hz), 28.6 (d, J_{P-C} = 12.7 Hz), 30.3 (d, J_{P-C} = 7.3 Hz), 31.6, 33.3, 35.1 (d, J_{P-C} = 2.7 Hz), 38.6 (d, J_{P-C} = 69.9 Hz), 38.9 (d, J_{P-C} = 8.2 Hz), 41.1 (d, J_{P-C} = 71.8 Hz), 115.5, 116.3, 128.3-128.6 (m), 130.6 (d, J_{P-C} = 8.2 Hz),

130.7-131.0 (m), 131.1, 131.2-131.4 (m), 136.9, 137.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.11 (*trans* isomer, **43**), 33.05 (*cis* isomer **44**); GC (major) t_R = 11.74 min.; GC-MS (EI, 70 eV) *m/z* = 324 [M] (27), 284 (16), 283 (78), 242 (11), 241 (11), 229 (26), 215 (20), 203 (29), 202 (88), 201 (100), 183 (15), 155 (28), 154 (11), 125 (27), 81 (26), 79 (27), 78 (18), 77 (58), 67 (15), 53 (13), 51 (20), 47 (37); GC (minor) t_R = 11.82 min.; GC-MS (EI, 70 eV) *m/z* = 324 [M] (36), 283 (19), 242 (13), 241 (11), 229 (45), 216 (19), 215 (42), 203 (31), 202 (100), 201 (63), 183 (14), 155 (26), 151 (14), 125 (25), 104 (10), 81 (16), 79 (25), 78 (17), 77 (53), 67 (15), 53 (11), 51 (18), 47 (37); HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{25}NaOP$ 347.1535, found 347.1530.

(*Trans*-2-allylcycloheptyl)diphenylphosphine oxide (45). This compound was obtained in the reaction of cyclohept-1-en-1-yl(diphenyl)phosphine oxide (**8a**) (0.089 g, 0.30 mmol), allylmagnesium bromide (0.36 mL, 1.0 M in diethyl ether, 0.36 mmol), CuI (6.0 mg, 0.315 mmol), TMEDA (10 μL, 0.667 mmol), and LiCl (0.017 g, 0.40 mmol), as a white solid, yield: 0.049 g (48%). R_f = 0.50 (Hexane/MTBE/*i*-PrOH 8:3:1); m.p. 102.0-103.5 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25-1.85 (m, 10H), 1.90-1.98 (m, 1H), 1.98-2.07 (m, 1H), 2.23-2.36 (m, 2H), 4.73-4.79 (m, 1H), 4.84-4.88 (m, 1H), 5.30-5.40 (m, 1H), 7.43-7.53 (m, 6H), 7.80-7.87 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7, 26.6, 29.0 (d, J_{P-C} = 14.5 Hz), 29.5 (d, J_{P-C} = 6.4 Hz), 30.6, 35.1, 40.9 (d, J_{P-C} = 6.4 Hz), 42.7 (d, J_{P-C} = 68.1 Hz), 116.2, 128.4 (d, J_{P-C} = 10.9 Hz), 128.5 (d, J_{P-C} = 10.9 Hz), 131.2 (d, J_{P-C} = 8.2 Hz), 131.3 (d, J_{P-C} = 8.2 Hz), 131.3 (d, J_{P-C} = 2.7 Hz), 131.4 (d, J_{P-C} = 2.7 Hz), 132.8 (d, J_{P-C} = 92.6 Hz), 133.2 (d, J_{P-C} = 93.6 Hz), 137.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 36.99. GC t_R = 12.20 min.; GC-MS (EI, 70 eV) *m/z* = 338 [M] (24), 298 (11), 297 (54), 229 (29), 216 (11), 215 (16), 203 (25), 202 (100), 201 (71), 155 (21), 125 (18), 95 (10), 77 (24), 67 (11), 55 (11), 47 (22).

(*Cis*-2-allylcycloheptyl)diphenylphosphine oxide (46). Minor product, isolated in a mixed fraction with **45**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49-2.56 (m, 1H, P-C*H*), 2.71-2.79 (m, 1H, allylic C*H*), 5.53-5.63 (m, 1H, internal olefinic –C*H*=CH_2); ^{31}P NMR (202 MHz, $CDCl_3$) δ 36.44.

Cyclohept-2-en-1-yldiphenylphosphine sulfide (47). This compound was obtained in the reaction of cyclohept-1-en-1-yl(diphenyl)phosphine oxide (**8a**) (0.089 g, 0.30 mmol), allylmagnesium bromide (0.36 mL, 1.0 M in diethyl ether, 0.36 mmol), CuI (6.0 mg, 0.315 mmol), TMEDA (10 μL, 0.667 mmol), and LiCl (0.017 g, 0.40 mmol), as a white solid, yield: 0.021 g (20%). R_f = 0.40 (Hexane/MTBE/*i*-PrOH 8:3:1); m.p. 116.4-118.0 ^{o}C; ^{1}H NMR (500

MHz, $CDCl_3$) δ 1.41-1.51 (m, 1H), 1.57-1.76 (m, 3H), 1.98-2.12 (m, 2H), 2.13-2.22 (m, 1H), 2.25-2.35 (m, 1H), 3.26-3.36 (m, 1H), 5.70-5.78 (m, 1H), 5.94-6.01 (m, 1H), 7.45-7.56 (m, 6H), 7.76-7.85 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.2, 26.5, 28.3, 30.7 (d, $J_{P\text{-}C}$ = 13.6 Hz), 40.1 (d, $J_{P\text{-}C}$ = 71.6 Hz), 126.6, 128.5 (d, $J_{P\text{-}C}$ = 10.9 Hz), 128.6 (d, $J_{P\text{-}C}$ = 10.9 Hz), 131.2 (d, $J_{P\text{-}C}$ = 8.2 Hz), 131.4 (d, $J_{P\text{-}C}$ = 9.1 Hz), 132.0 (d, $J_{P\text{-}C}$ = 94.5 Hz), 132.4 (d, $J_{P\text{-}C}$ = 96.3 Hz), 135.7 (d, $J_{P\text{-}C}$ = 16.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.79; GC t_R = 11.64 min.; GC-MS (EI, 70 eV) *m/z* = 296 [M] (11), 203 (18), 202 (100), 201 (43), 155 (16), 77 (16), 47 (10).

Diphenyl(*trans*-2-(*p*-tolyl)cyclohexyl)phosphine oxide (48). This compound was obtained in the reaction of cyclohex-1-en-1-yl(diphenyl)phosphine oxide (**7a**) (0.059 g, 0.21 mmol), *p*-tolylmagnesium bromide (0.27 mL, 1.0 M in THF, 0.27 mmol), $NiCl_2$(dme) (4.6 mg, 0.021 mmol), and (*R*)-BINAP (14.0 mg, 0.022 mmol), as a mixture with **49** yield: 0.008 g (10%). R_f = 0.62 (Hexane/MTBE/*i*-PrOH 12:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44-1.53 (m, 2H), 1.72-1.82 (m, 2H), 1.93-2.07 (m, 3H), 2.10 (s, 3H), 2.64-2.74 (m, 1H), 2.83-2.89 (m, 1H), 3.20 (dm, $J_{P\text{-}H}$ = 24.91 Hz, 1H), 6.68 (d, $J_{P\text{-}H}$ = 7.57 Hz, 2H), 7.02 (m, 1H), 7.05 (d, $J_{P\text{-}H}$ = 7.57 Hz, 2H), 7.08-7.13 (m, 2H), 7.20-7.25 (m, 1H), 7.34-7.42 (m, 4H), 7.65-7.71 (m, 2H). ^{31}P NMR (202 MHz, $CDCl_3$) δ 32.55. GC t_R = 20.34 min.; GC-MS (EI, 70 eV) *m/z* = 374 [M] (21), 229 (12), 203 (35), 202 (100), 201 (24), 155 (16), 129 (10), 105 (26), 91 (10), 77 (16), 47 (12).

Diphenyl(*cis*-2-(*p*-tolyl)cyclohexyl)phosphine oxide (49). This compound was obtained in the reaction of cyclohex-1-en-1-yl(diphenyl)phosphine oxide (**7a**) (0.059 g, 0.21 mmol), *p*-tolylmagnesium bromide (0.27 mL, 1.0 M in THF, 0.27 mmol), $NiCl_2$(dme) (4.6 mg, 0.021 mmol), and (*R*)-BINAP (14.0 mg, 0.022 mmol), as a mixture with **49**, yield: 0.013 g (17%). R_f = 0.55 (Hexane/MTBE/*i*-PrOH 12:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30-1.54 (m, 2H), 1.56-1.67 (m, 1H), 1.68-1.75 (m, 2H), 1.75-1.94 (m, 3H), 2.05 (s, 3H), 2.55-2.65 (m, 1H), 3.12-3.21 (m, 1H), 6.60 (d, $J_{H\text{-}H}$ = 7.6 Hz), 6.93 (d, $J_{H\text{-}H}$ = 7.6 Hz), 7.02-7.09 (m, 2H), 7.16-7.22 (m, 1H), 7.32-7.38 (m, 2H), 7.38-7.47 (m, 3H), 7.72-7.78 (m, 2H). ^{31}P NMR (202 MHz, $CDCl_3$) δ 31.98. GC t_R = 20.51 min.; GC-MS (EI, 70 eV) *m/z* = 374 [M] (6), 203 (43), 202 (100), 201 (20), 155 (16), 105 (19), 77 (12), 47 (11).

Di(cyclohex-1-en-1-yl)(phenyl)phosphine oxide (51). This compound was obtained in the reaction of cyclohex-1-en-1-yllithium, generated from 1-bromocyclohexene (0.365 g, 2.26 mmol) and *t*-BuLi (2.50 mL, 1.75 M in pentane, 4.38 mmol), and ethyl phenylphosphinate (0.15 mL, 1.00 mmol) under the conditions from Table 15, Entry 3, as a yellow waxy solid,

yield: 0.114 g (40%). R_f = 0.41 (Hexane/MTBE/MeOH 6:3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.72 (m, 8H), 2.12-2.26 (m, 8H), 6.47 (dm, $J_{H\text{-}H}$= 20.2 Hz), 7.45-7.50 (m, 2H), 7.50-7.55 (m, 1H), 7.67-7.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 22.1 (d, $J_{P\text{-}C}$ = 8.2 Hz), 24.6 (d, $J_{P\text{-}C}$ = 24.6), 26.4 (d, $J_{P\text{-}C}$ = 14.5 Hz), 128.4 (d, $J_{P\text{-}C}$ = 11.8 Hz), 130.2 (d, $J_{P\text{-}C}$ = 99.0 Hz), 130.3 (d, $J_{P\text{-}C}$ = 95.4 Hz), 131.6, 131.8 (d, $J_{P\text{-}C}$ = 9.1 Hz), 142.9; ^{31}P NMR (202 MHz, $CDCl_3$) δ; GC t_R = 11.47 min.; GC-MS (EI, 70 eV) *m/z* = 287 (19), 286 [M] (100), 285 (62), 258 (33), 257 (40), 244 (14), 243 (20), 206 (17), 205 (19), 125 (17), 109 (10), 91 (13), 81 (17), 79 (32), 77 (16) 53 (17), 47 (21).

7. Abbreviations

8-HQ – 8-hydroxyquinoline

9-BBN – 9-borabicyclo[3.3.1]nonane

bpy – 2,2’-bipyridine

Cy – cyclohexyl

BDPP – 2,4-bis(diphenylphosphino)pentane

BICP – bis(diphenylphosphino)dicyclopentane

BINAP – 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

BIPHEP - (6,6′-Dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)

BIPHEMP - 2,2'-Bis(diphenylphosphino)-6,6'-dimethylbiphenyl

Boc – *tert*-butoxycarbonyl

BOX – bis(oxazoline)

BPPM – N-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]-pyrrolidine

DABCO – 1,4-diazabicyclo[2.2.2]octane

DBTA – dibenzoyltartaric acid

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE – 1,2-dichloroethane

DIPAMP - 1,2-bis[(2-methoxyphenyl)(phenyl)phosphino]ethane

PPCP – 1-diphenylphosphino-2-(diphenylphosphinomethyl)cyclopentane

DCC – *N*,*N*′-dicyclohexylcarbodiimide

DMAP – dimethylaminopyridine

DMF – *N*,*N*-dimethylformamide

DPPCB – *trans*-1,2-bis(diphenylphosphino)cyclobutane

DPPCP – *trans*-1,2-bis(diphenylphosphino)cyclopentane

DPPCY– *trans*-1,2-bis(diphenylphosphino)cyclohexane

DPPE –1,2-bis(diphenylphosphino)ethane

DPPP – 1,3-bis(diphenylphosphino)propane

DPPB – 1,4-bis(diphenylphosphino)butane

DPPBZ –1,2-bis(diphenylphosphino)benzene

DPPF - 1,1’-bis(diphenylphosphino)ferrocene

DCYPCP – *trans*-1,2-(dicyclohexylphosphino)cyclopentane

DCYPCY – *trans*-1,2-(dicyclohexylphosphino)cyclohexane

DCYPE – 1,2-bis(dicyclohexylphosphino)ethane

DMSO – dimethyl sulfoxide

DMEDA – *N*,*N'*-dimethylethylene-1,2-diamine

DMCyDA – *N*,*N'*-dimethylcyclohexane-1,2-diamine

DPhEDA – 1,2-diphenylethylenediamine

DME – 1,2-dimethoxyethane

EG – ethylene glycol

HFIP – hexafluoroisopropanol

Ment – menthyl

Ms – mesyl

MTBE – methyl *tert*-butyl ether

Nf – nonaflyl

NMP – *N*-methylpyrrolidinone

phen – phenanthroline

PHOX – phosphinooxazoline

PPAPM – pyrrolidine-2-phosphonic acid phenyl monoester

SIMes – 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene

SIPr –1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene

TA – tartaric acid

TADDOL – α,α,α',α'-tetraaryl-2,2-dialkyl-1,3-dioxolane-4,5-dimethanol

TMEDA – *N,N,N',N'*-tetramethylethylene-1,2-diamine

TMCyDA – *N,N,N',N'*-tetramethylcyclohexane-1,2-diamine

THF – tetrahydrofuran

Ts – tosyl

Tf – triflyl

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