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Phosphinooxazolines—A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis

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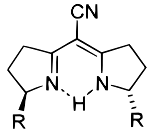
ABSTRACT
Chiral phosphinooxazolines (PHOX ligands), which coordinate to a metal center with a N- and a P-atom, allow effective enantiocontrol in a variety of metal-catalyzed reactions. They are readily synthesized, and because of their modular structure, the steric and electronic properties can be tailored for a specific application by variation of the oxazoline ring, the backbone, and the phosphine moiety.

I. Introduction

With the famous DIOP ligand, Kagan introduced the important concept of C_2-symmetry in ligand design.[1] As a consequence, C_2-symmetric ligands were to dominate in asymmetric catalysis for a long time. We were also attracted by the obvious advantages and aesthetics of C_2-symmetry, when we and a number of other groups developed chiral bisoxazoline ligands such as **2** and **3** which were patterned after the semicorrins **1**. Since then, bisoxazolines of this type have been successfully used in an impressive range of different metal-catalyzed processes and have established themselves among the most versatile ligands in asymmetric catalysis.[2]



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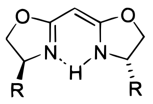

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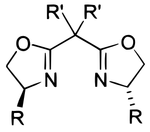

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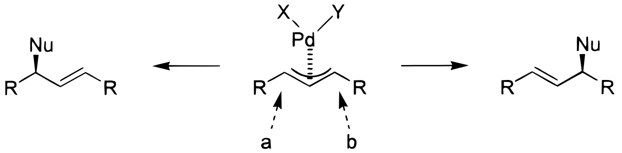
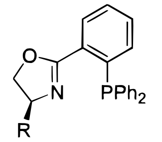
The benefits of C_2-symmetry are related to the fact that it reduces the number of possible catalyst−substrate arrangements and, consequently, the number of reaction pathways and transition states. This is of particular advantage in mechanistic and structural studies and facilitates an analysis of the ligand−substrate interactions that may be responsible for enantioselection. However, there is no fundamental reason why a C_2-symmetric ligand should necessarily be superior to a nonsymmetric counterpart. In fact, for certain reactions, good arguments can be found which suggest that nonsymmetrical ligands with two different coordinating heteroatoms could allow more effective enantiocontrol than C_2-symmetric ligands. Transition metal-catalyzed allylic alkylation via symmetric allyl complexes is a good example (Scheme 1).

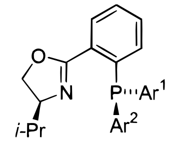
Scheme 1



In such reactions, the regioselectivity of nucleophilic attack determines the ratio of the two enantiomeric products. If the metal center is coordinated by two electronically different groups X and Y, the two allylic termini become electronically nonequivalent and thus are expected to display different reactivity. Electronic differentiation of this type has been convincingly demonstrated by Faller[3] in stoichiometric nucleophilic additions to allylmolybdenum complexes. Consequently, it can be argued that chiral ligands possessing two different coordinating atoms should allow more effective regiocontrol than C_2-symmetric ligands. Because of the high enantioselectivities induced by C_2-symmetric bisoxazolines **3** in Pd-catalyzed allylic alkylations,[2] we were intrigued by the idea that replacement of one of the oxazoline rings by a phosphino group might lead to even more efficient ligands. Coincidentally, we independently synthesized a number of phosphinooxazolines such as **L1**−**L6** in our laboratories at the Universities of Heidelberg[4] and Basel,[5] while in the U.K. a third group led by J. M. J. Williams[6] followed the same line of thought. As hoped, our new



L1 R = *i*-Pr
L2 R = *t*-Bu
L3 R = Ph
L4 R = CH_2Ph
L5 R = Me



Ar^1 = phenyl,
Ar^2 = 1-naphthyl

L6

Günter Helmchen received his undergraduate education at the TH Hannover and a Ph.D. from the ETH Zürich in 1971 (V. Prelog). He then began a “Habilitation” at the University of Stuttgart and was appointed “Privatdozent” in 1980. In 1981 he joined the faculty of the University of Würzburg as an associate professor, and in 1985 he became a full professor at the University of Heidelberg. His current research interests include asymmetric synthesis of natural products and asymmetric catalysis.

Andreas Pfaltz was born in Basel in 1948. He received a diploma in natural sciences and a Ph.D. from the ETH Zürich. After completing his thesis under the direction of Albert Eschenmoser in 1978, he joined the research group of Gilbert Stork at Columbia University. In 1980 he returned to the ETH where he was appointed “Privatdozent” in 1987. From 1990 to 1995 he was Professor of Organic Chemistry at the University of Basel. After four years as a director at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, he returned to the University of Basel in 1999. His main interests are in the areas of homogeneous and heterogeneous catalysis, with special emphasis on asymmetric catalysis.

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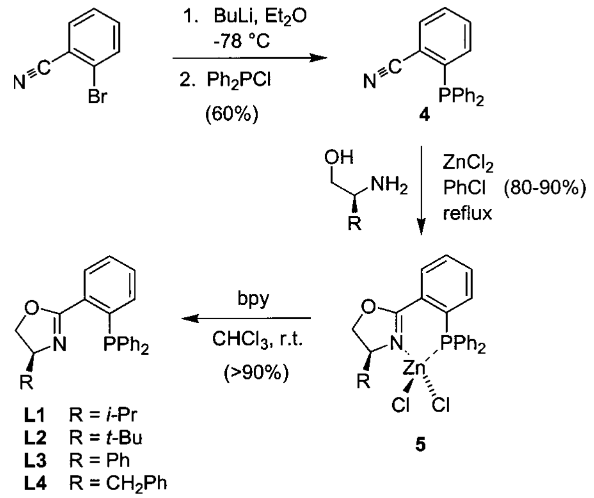
ligands were found to induce excellent enantioselectivities in Pd-catalyzed allylic alkylations with 1,3-diphenylallyl acetate and other symmetrically substituted allyl substrates. Further evaluation of these readily accessible ligands led to several other useful applications in asymmetric catalysis. In this Account, we discuss the unique properties and various applications of this new and versatile class of chiral P,N-ligands.[7]

II. Synthesis of Phosphinooxazoline (PHOX) Ligands

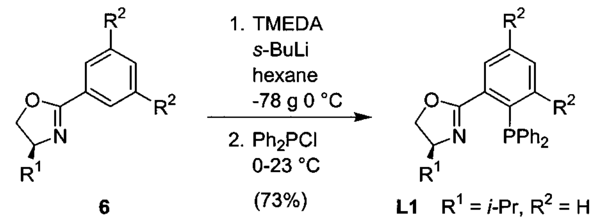
There are many convenient methods for preparing enantiopure oxazolines with a stereogenic center next to the nitrogen atom.[8] The standard precursors, an amino alcohol and a carboxylic acid derivative, can be selected from a wide variety of readily available compounds. As illustrated by the syntheses in Schemes 2–4, the phosphine moiety may be introduced either before or after oxazoline ring formation. The former option is preferred if a series of ligands with different substituents in the oxazoline part is prepared, the latter if different P-substituents are introduced. The first synthesis (Scheme 2),[9] which commences from 2-bromobenzonitrile, can be conveniently carried out on a multigram scale since the intermediates **4** and **5** are crystalline compounds which, in general, can be purified by recrystallization without prior chromatography. From the air-stable Zn complexes **5**, the corresponding ligands **L1**–**L4** are readily obtained by treatment with bipyridine and removal of the resulting insoluble Zn(bpy)$_2$Cl$_2$ complex by filtration.

Scheme 2



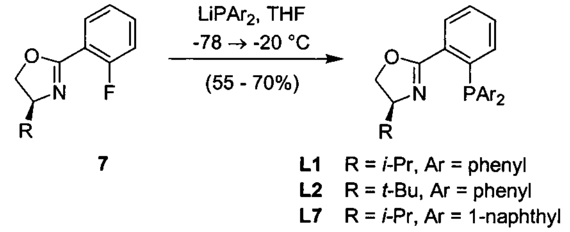
Orthometalation of 2-aryloxazolines with *sec*-butyllithium/TMEDA in hexane provides a short and convenient route to phosphinoaryl-oxazolines on a laboratory scale (Scheme 3)[9,10] A nonaqueous workup proved to be crucial in this case; reproducible yields could only be obtained when the reaction was quenched by addition of dry silica gel under argon. By this route, additional substituents in the aryl backbone (e.g., R^2 = Me)[9] can be introduced.

Scheme 3



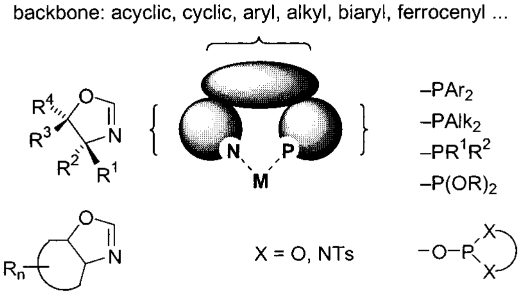
Another efficient route uses (2-fluorophenyl)oxazolines **7** as intermediates (Scheme 4).[11] In this case, the phosphino group is introduced by nucleophilic aromatic substitution, and many different ligands have been prepared by this method.

Scheme 4



Considering the easy access to these ligands and the almost unlimited selection of suitable, readily available precursors, it is not surprising that, after the first studies on phosphinooxazolines had appeared, an impressive variety of representatives were continuously added to this class of ligands (Scheme 5). Derivatives with chiral backbones derived from ferrocene,[12] CpMn(CO)$_3$,[13] or binaphthol[14] have been reported, many different substituents, some of them containing additional heteroatoms or an additional ring, have been attached to the oxazoline ring, and a variety of aryl, alkyl, alkoxy, and tosylamino groups has been linked to the phosphorus atom (for examples, see the next sections). Recently, oxazine analogues have also been reported[15] as another variation on the theme.

Scheme 5

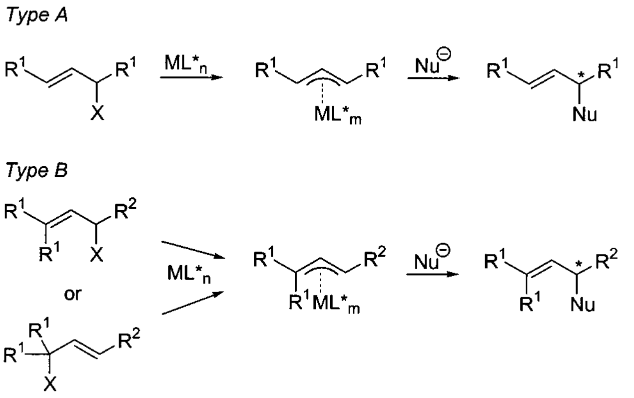


At present, the simple phosphinoaryl-oxazolines such as **L1** and **L2** are still the most versatile ligands. However, as shown in the next sections, for certain applications which gave unsatisfactory results with the standard ligands, it has been possible to greatly improve the performance of the catalyst by specific optimization of the ligand structure. Hence, it is quite certain that this family of P,N-ligands will continue to grow over the next few years.

III. Asymmetric Catalysis with PHOX Complexes

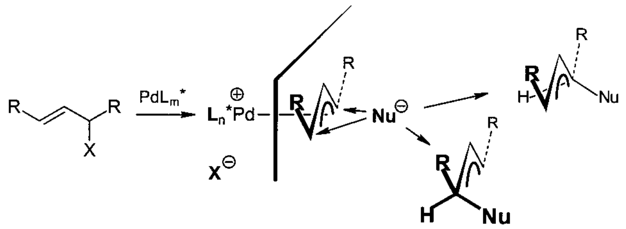
A. Allylic Substitution. Pd-catalyzed enantioselective C−C and C−N bond-forming substitutions at allylic positions are an important area of current research.[16] Scheme 6 shows two important classes of allylic substitutions that can be carried out enantioselectively with chiral catalysts (for additional classes, see ref 16). Reactions of class A start from racemic substrates and proceed via symmetrical allyl systems. In this case, the enantioselectivity is determined by the regioselectivity of nucleophilic attack. In class B, racemic or prochiral substrates possessing two identical geminal substituents R^1 at one of the allylic termini react via π-allyl intermediates which can isomerize by the well-established $\pi-\sigma-\pi$ mechanism. In this case enantioselection can occur in the ionization step, leading to the allyl intermediate, or in the nucleophilic addition step. Phosphinooxazoline complexes of Pd, W, Ir, and Pt have been successfully used as catalysts in both classes of reactions.

Scheme 6



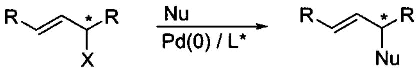
Reactions via Symmetrically Substituted Allyl Systems (Type A). In these reactions, the enantioselectivity depends on the ability of the chiral ligand to differentiate between the two allylic termini (Scheme 7). Traditional C_2-symmetric chelate diphosphines developed for hydrogenations, such as CHIRAPHOS and BINAP, were not well suited for this purpose. However, it was demonstrated by one of us with C_2-symmetric bisoxazolines[2,5] and by Trost,[16] using a new class of C_2-symmetric diphosphines which induce a wide bite angle, that very high enantioselectivity is possible with a proper substrate−ligand combination. As pointed out above, application of phosphinooxazolines as ligands relies on the concept of *electronic differentiation*.

Scheme 7



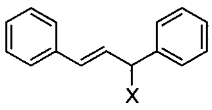
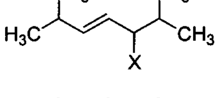
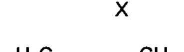
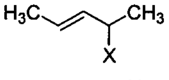
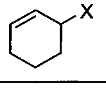
Typical results obtained with dimethyl sodiomalonate as nucleophile are given in Scheme 8. Sodio- and lithiomalonates are the nucleophiles most commonly used in conjunction with allylic acetates or carbonates as substrates. A variety of other nucleophiles was also investigated (Scheme 8): amines and *N*-acylamides,[17] nitro compounds, and sulfinates.[19] These nucleophiles are less reactive than malonates and require a carbonate or phosphate as the leaving group; however, enantioselectivities are very similar, and the steric course is independent of the nucleophile. The standard solvent used for these reactions is THF, although occasionally DMF has been employed. In less coordinating solvents, such as CH_2Cl_2, metallomalonates are insoluble. This problem can be circumvented by reacting the protonated, neutral nucleophile with carbonates or acetates in combination with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of sodium acetate (BSA method[16]). Recently, the reaction of 1,3-diphenylallyl acetate with malonate was also carried out with Pt complexes of a PHOX ligand as catalysts (up to 90% ee).[18]

Scheme 8. Enantiomeric Excess (ee) and Enantiomer Ratios (er) for Products of Allylic Substitutions—Comparison with Isomer Ratios ($CDCl_3$) of Corresponding (π-Allyl)Pd Complexes



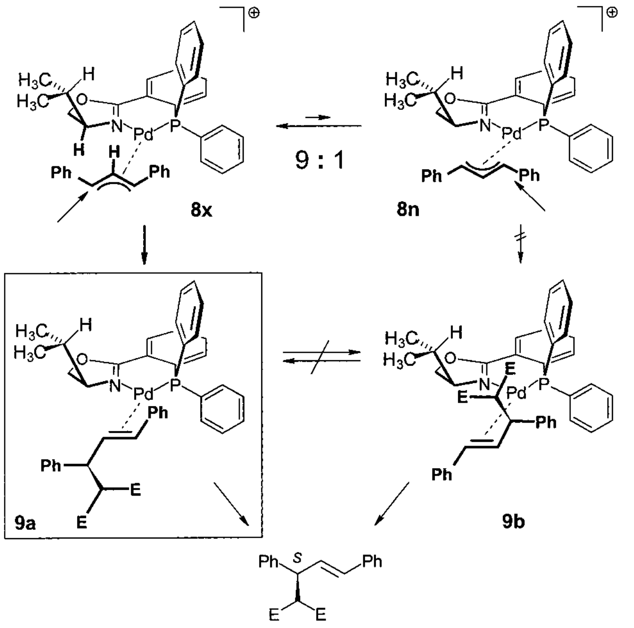
R	Me, *n*-Pr, *i*-Pr, Ph, $CH_2O\Sigma$
X	OAc, Hal, OCOOMe, $OPO(OR)_2$
Nu	$^-CH(COOR)_2$, H_2NR, $^-CH_2NO_2$, ^-O_2SPh

Examples:

$Nu = {}^-CH(COOMe)_2$ $L^* = $ **L1**	ee (%)	er	*exo-endo* ratio (NMR)
	98.5	99 : 1	90 : 10
	94		
	74		
	56	78 : 22	80 : 20
	0	50 : 50	64 : 36

One characteristic is the very high enantioselectivity for “broad” substrates and the very low degree of enantioselection for “slim” substrates. However, improvement has been possible based on mechanistic studies. The kinetic scheme in this case is very complex because the two diastereomeric π-allyl intermediates **8x** (*exo*) and **8n** (*endo*) are rapidly equilibrating (Scheme 9). Each of the two enantiomeric products can be formed via either **8x** or **8n.** The preferred product can arise by reaction at the allylic C *trans* to P of the *exo* isomer or *cis* to P of the *endo* isomer. A number of arguments[19] based on NMR studies[20] and structural data suggested that the nucleophile preferentially attacks the carbon *trans* to P of the *exo* isomer. More direct corroboration for this hypothesis was obtained by studying the reaction course by modern 2D NMR spectroscopic methods.[21] The reaction of dimethyl sodiomalonate with complexes **8** is slower than the *exo*–*endo* isomerization process, and, therefore, the reaction of the intermediates **8x** and **8n** could not be directly observed by NMR spectroscopy. However, it was possible to identify the labile olefin complex **9a** generated by the substitution reaction (Scheme 9). This complex must be formed by attack of the malonate ion at the allylic terminal C *trans* to P of the *exo* isomer via a least motion process involving a rotation of the allylic moiety by 30°. X-ray crystal structures (Figure 1) have been important because they have provided clues to why the *exo* isomers are more stable than the *endo* isomers.[20a,22] It appears that the dominant interaction between ligand and allylic moiety originates from the equatorial P-aryl group (black in Figure 1) which repels the substituent at C1 of the allyl group. This repulsive interaction is smaller for the *exo* than the *endo* diastereomer.

Scheme 9



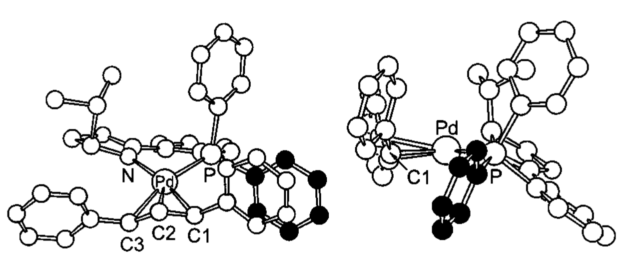
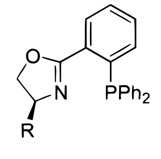


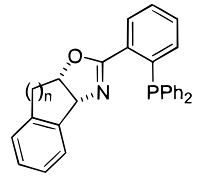
FIGURE 1. Front view (left) and side view (right) of the X-ray crystal structure of the *exo*-allyl complex **8x**.

The front view in Figure 1 shows that the chiral phosphinooxazoline ligand interacts with the substrate mainly at its wings. As a consequence, allylic systems with big substituents display high *exo*–*endo* ratios and enantioselectivity, whereas narrow systems give low selectivity, as illustrated by Scheme 8. If we generalize the finding that only the allylic terminus *trans* to phosphorus is attacked in both *exo* and *endo* isomers, then it follows from the *exo*–*endo* ratios given in Scheme 8 that relative rates of the *exo* and *endo* isomers are ca. 10:1 for the 1,3-diphenylallyl complex, but ca. 1:1 for the 1,3-dimethylallyl complex.

It was surmised that increasing the size of the substituent of the oxazoline moiety leads to an enhanced bending of the chelate ring with the consequence that the crucial equatorial P-phenyl group is pushed nearer to the allyl group, leading to destabilization of the *endo* isomer. Accordingly, larger substituents in the oxazoline moiety should give rise to higher enantioselectivity.[23] Indeed, the corresponding ligands **L2**, **L8**–**L10** furnished up to 89.5% ee for the reaction of 1,3-dimethylallyl acetate with sodium dimethylmalonate. Ligand **L10** stands out as it induces not only the highest selectivity but also the highest reaction rate.



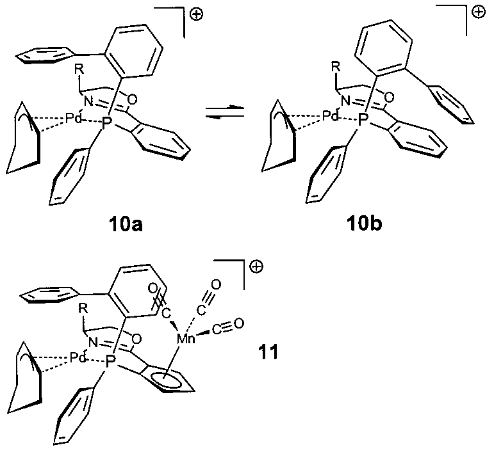
L2 R = *t*-Bu
ent-**L8** R = $CMe_2S(i\text{-}Bu)$



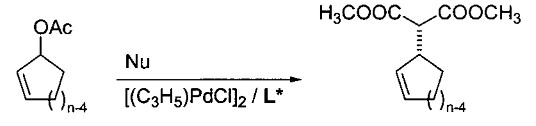
L9 n = 1
L10 n = 2

Initial results with cyclic substrates were unsatisfactory due to the unfavorable *exo*–*endo* ratio (cf. Scheme 8). Improvement of the *exo*–*endo* ratio would require a ligand that would reach into the narrow area directly above or below the allylic sp^2 centers (C1–C3 in Figure 1). As such, the biphenylyl derivatives **L11**–**L13** (Scheme 11) were conceived as ligands.[4] X-ray crystal structures of the complexes $[Pd(\eta^3\text{-}C_6H_9)(\mathbf{L11})]SbF_6$ (R = *i*-Pr) and $[Pd(\eta^3\text{-}C_6H_9)(ent\text{-}\mathbf{13})]SbF_6$ displayed conformer **10a** (Scheme 10) in which the phenyl of the 2-biphenylyl group is located directly above the allyl moiety. However, despite the favorable conformation in the solid state, enantioselectivities induced by ligand **L11** were not satisfactory. A dependence on the ring size of the substrate and the reaction conditions is apparent from the data given in Scheme 11. The ligand **L12** with electron-withdrawing CF_3 groups furnished improved enantioselectivity with methylene chloride as solvent (BSA method).

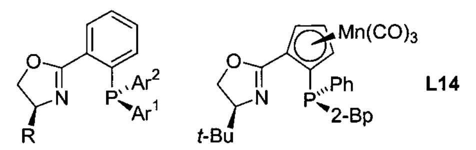
Scheme 10



Scheme 11



ligand	conditions	ee (%)		
		n = 5	n = 6	n = 7
L11	1.5 eq $LiCH(COOMe)_2$ dioxane, rt	56	51	83
L12	1.5 eq $LiCH(COOMe)_2$ dioxane, rt	63	53	83
L12	2.5 eq $CH_2(COOMe)_2$, BSA method, CH_2Cl_2, 0°C	64	72	85
L14	1.5 eq $NaCH(COOMe)_2$ DMF, −50°C to 0°C	95	93	>99

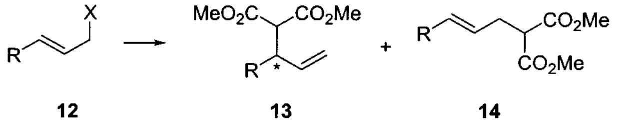


	R	Ar^1	Ar^2
L11	*i*-Pr	2-biphenylyl	phenyl
epi-L11	*i*-Pr	phenyl	2-biphenylyl
L12	*i*-Pr	2-biphenylyl	3,5-$(CF_3)_2$-C_6H_3
epi-L12	*i*-Pr	3,5-$(CF_3)_2$-C_6H_3	2-biphenylyl
L13	phenyl	2-biphenylyl	phenyl
epi-L13	phenyl	phenyl	2-biphenylyl

It was speculated that solutions of complexes **L11** contain several conformers, including the unfavorable conformer **10b** in which the crucial phenyl group is rotated away from the allylic moiety (Scheme 10). To destabilize conformers of this type, the cymantrene-based ligand **L14** was conceived.[13] This ligand induces excellent catalytic activity and displays excellent stability and long shelf life. Conformers analogous to **10b** are impossible because of interaction with the manganese tricarbonyl group. High enantioselectivity with this new ligand was indeed obtained, and the crystal structure of the corresponding (cyclohexenyl)Pd complex **11** (Scheme 10) displayed the expected conformer.[13] High enantioselectivities with cyclic substrates have also been achieved with salts of 3-diphenylphosphinomyrtanic acid as chiral ligand[4] and the diphosphines developed by Trost.[16]

Inter- and Intramolecular Allylic Substitutions of Type B. Allylic substitutions with monosubstituted allylic compounds **12** (Scheme 12) are of interest because the substrates are readily accessible and the branched products **13** can be transformed into useful chiral intermediates. The regioselectivity of these reactions is a function of the metal. Mo, W, Fe, Rh, and Ir complexes are biased in favor of the branched, Pd complexes in favor of the linear products. PHOX ligands have been probed with W, Mo, Pd, and Ir complexes.

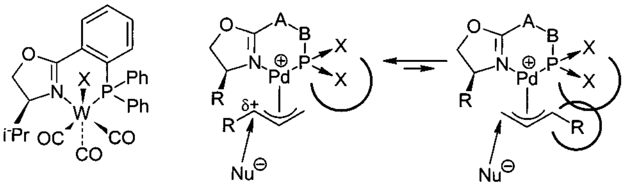
Scheme 12. Allylic Alkylations at Monosubstituted Allylic Derivatives with Tungsten, Palladium, and Iridium Catalysts



R	X	temp. (°C)	regiosel. **13** : **14**	yield (%)	ee (%)
$NaCH(CO_2Me)_2$, 10 mol% $W(CO)_3(MeCN)_3$ / **L1**, THF					
C_6H_5	$OPO(OEt)_2$	-10	75 : 25	95	96 (*R*)
1-naphthyl	$OPO(OEt)_2$	24	96 : 4	95	88 (*R*)
$CH_2(COOMe)_2$ / BSA, 1 mol% $[(C_3H_5)PdCl]_2$, 2.4 mol% **L***, KOAc (cat.), CH_2Cl_2					
L* = **L15**:					
C_6H_5	OAc	50	69 : 31	84	86 (*S*)
4-$(H_3CO)C_6H_4$	OAc	50	76 : 24	-	-
4-$(NC)C_6H_4$	OAc	50	13 : 87	-	-
1-naphthyl	OAc	25	90 : 10	93	95 (*S*)
CH_3	OAc	50	30 : 70	75	41
L* = **L16**:					
C_6H_5	OAc	rt	84 : 16	90	94 (*S*)
1-naphthyl	OAc	rt	98 : 2	90	98 (*S*)
$NaCH(CO_2Me)_2$, 4 mol% Ir(COD)Cl/**L17**, THF					
C_6H_5	OAc	65	95 : 5	99	91 (*R*)
4-$(H_3CO)C_6H_4$	OAc	65	99 : 1	98	95 (*R*)
$CH_2CH_2C_6H_5$	OAc	65	62 : 38	93	78 (*R*)

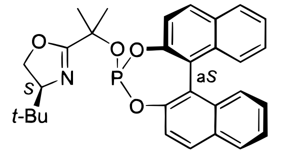
Tungsten complexes[24] are less reactive than Pd catalysts. Accordingly, the more reactive diethyl phosphates had to be used as substrates rather than acetates or carbonates (Scheme 12). Careful exclusion of oxygen and the order of addition of the reactants were found to be crucial. Thus, the precatalyst was reacted first with the chiral ligand at 60 °C, and then dimethyl sodiomalonate and finally the allylic phosphate were added. The isolated complex **15** (Scheme 13) afforded an equally selective but more reactive catalyst than a complex generated in situ. High enantiomeric excesses and good regioselectivities could be achieved with a range of arylallyl derivatives, while substrates with aliphatic substituents gave unsatisfactory results.

Scheme 13

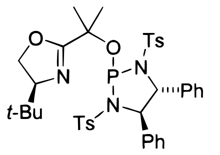


15 (X = CH_3CN) **16a** **16b**

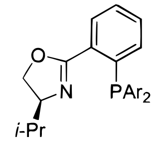
Pd complexes with allylic substituents larger than methyl normally favor the linear addition product because the reaction has S_N2 character and is orbital controlled. Nevertheless, reversal of the preferred mode of substitution was attempted by inducing charge control, i.e., S_N1-type characteristics.[24a] This idea was realized for reactions proceeding via transition states **16a** and **16b** (Scheme 13) by introducing bulky, electronegative substituents at phosphorus in order to render the Pd center more electrophilic and to destabilize the transition state and the corresponding allyl complex **16b** by steric effects. Given the *trans* influence of the phosphorus center, it was hoped that a reaction pathway via **16a** would be preferred. Of the variety of corresponding ligands studied, the phosphite **L15** and the bis(tosylamino)phosphine **L16** furnished the best results.



L15



L16



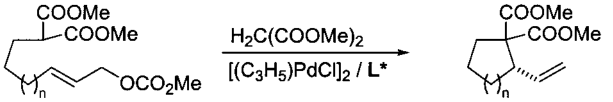
L1 Ar = Ph
L17 Ar = 4-$CF_3C_6H_4$

Iridium PHOX complexes provided another solution to the regioselectivity problem. Using a modification of Takeuchi's procedure, developed for achiral Ir catalysts,[25] the catalyst Ir(COD)Cl/**L17** furnished branched products **13** (R = aryl) in good yields with >90% ee (Scheme 12).[26a] With ligand **L1** the reaction was relatively slow and nonselective. However, electron-withdrawing substituents, as in **L17**, are beneficial, as reported for the achiral catalysts. As with Pd and W catalysts, substrates with a nonaromatic substituent gave unsatisfactory regio- and enantioselectivities.

In addition to PHOX ligands, Ir phosphoramidite,[26] Pd monophosphine,[24c] and Mo complexes of C_2-symmetric N,N-ligands[27] were successfully used for this class of substrates. In contrast to the other catalysts, the Ir phosphoramidite complexes and, particularly, the Mo catalysts give high regio- and enantioselectivities with both aryl- and *n*-alkylallyl derivatives.

Intramolecular reactions leading to cyclopentane[28a] and cyclohexane[28b] derivatives were examined (Scheme 14). It was found that ligand, leaving group, solvent, and concentration all play a role in the regio- and ambidoselectivity (C- vs O-alkylation) of the cyclization. The configuration of the alkene does not affect the selectivity, supporting the notion that $\pi-\sigma-\pi$ rearrangement of the intermediary complexes is faster than alkylation.

Scheme 14

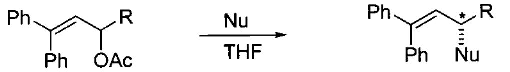


	conditions:	
n = 1	BSA(TF), KOAc, **L3** benzene, 5 °C	87 % ee (60 %)
n = 2	$LiCH(COOMe)_2$, **L2** THF, rt	49 % ee (54 %)

Reactions of geminally disubstituted substrates (Scheme 15) are of interest as both electronic and steric effects guarantee a high degree of regioselectivity in favor of the chiral product. With remarkable indifference to the properties of the substituent at the chirality center, phosphinooxazolines induced >95% ee and excellent chemical yields.[6] For the amination of **17** with benzylamine, the very bulky ligand **L18** was successfully employed.[29] An interesting application of the alkylation with malonate is the synthesis of lactone **19**, a precursor of the therapeutically useful muscle relaxant baclofen. In a similar fashion, the bis(trimethylsilyl) derivative **20** can be alkylated with a high degree of regioselectivity.

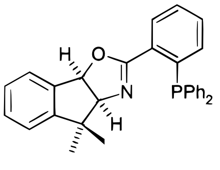
Scheme 15

17

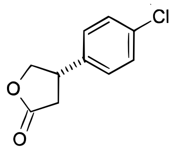


18

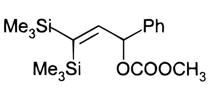
R	Nu / conditions	yield (%)	ee (%)
Me	$NaCH(COOMe)_2$ 2.5 mol% $[Pd(C_3H_5)Cl]_2$ 10 mol% **L1**	95	95
Ph		88	99
p-ClC_6H_4		91	>95
Me	$BnNH_2$ (10 eq) 5 mol% $[Pd(C_3H_5)Cl]_2$ 12 mol% **L18** 10 eq AcOH, reflux	82	98
n-Bu		30	94



L18



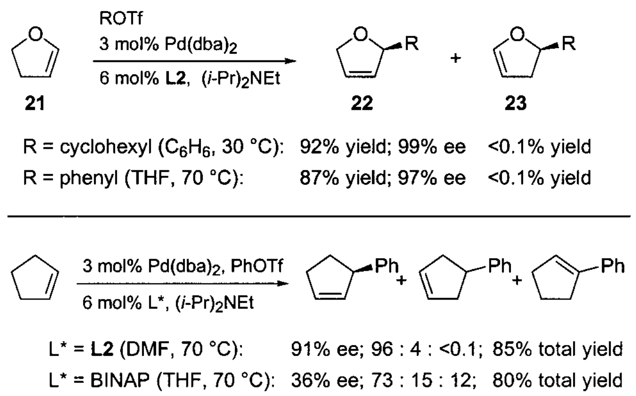
19



20

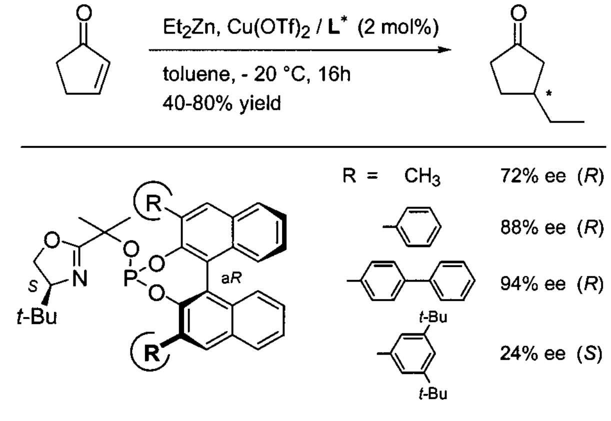
B. Heck Reactions. Phosphinooxazolines are highly effective ligands for the enantiocontrol of Heck reactions (Scheme 16).[30] The reaction of 2,3-dihydrofuran with cyclohexenyl or aryl triflates leads exclusively to the corresponding 2,5-dihydrofuran derivatives **22** with excellent enantioselectivities and high yields. Interestingly, analogous reactions with Pd–BINAP catalysts produce a mixture of the 2,5- and the 2,3-dihydro isomers **22** and **23** with the more stable **23** as the main product.[31] In contrast to Pd catalysts derived from BINAP, which was previously clearly the best ligand for enantioselective Heck reactions, virtually no C—C double bond migration is observed with Pd—PHOX catalysts. Hence, particularly in cases where double bond migration leads to undesired products or mixtures of isomers, phosphinooxazolines are the ligands of choice (cf. the reaction with cyclopentene in Scheme 16). Because the catalysts are deactivated by traces of halides, alkenyl and aryl bromides or iodides give unsatisfactory results. The best selectivities and yields have been obtained in intermolecular reactions of aryl and alkenyl triflates with substrates containing a C—C double bond embedded in a five-membered ring. Ripa and Hallberg have also reported an example of an intramolecular Heck reaction where the PHOX ligand **L2** (cf. Scheme 2) gave much higher enantioselectivities and yields than BINAP.[32]

Scheme 16



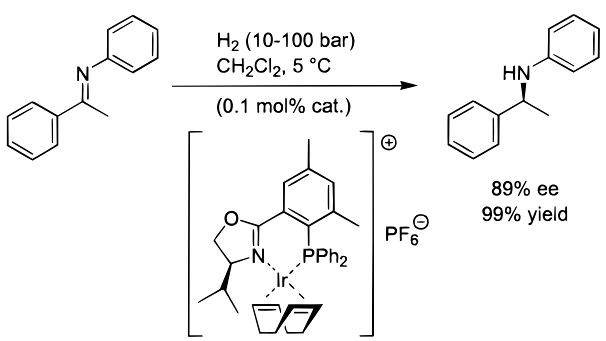
C. Conjugate Additions to Enones. Not only have oxazoline-phosphites allowed effective regio- and enantiocontrol in allylic alkylations with 1- and 3-arylallyl acetates (Scheme 12), they have also given promising results in the Cu-catalyzed conjugate addition of organozinc reagents to enones (Scheme 17).[33] Again, the option to modify the ligand structure was crucial. By proper adjustment of the *ortho* substituents R, up to 94% ee could be achieved in the reaction with cyclopentenone, which exceeds the enantioselectivities of other catalysts for this notoriously difficult substrate.[34] High enantioselectivities could also be obtained for cyclohexenone (up to 96% ee) and (*E*)-1-phenylbut-1-en-3-one (87% ee).

Scheme 17



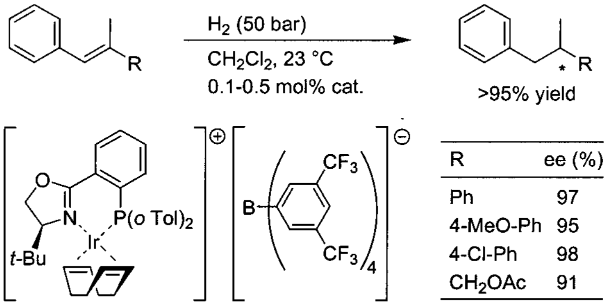
D. Enantioselective Hydrogenation. Iridium phosphinooxazoline complexes have emerged as a promising new class of catalysts for the enantioselective hydrogenation of imines and olefins. The COD complexes, which serve as precatalysts, are readily prepared and easy to handle as they are air-stable crystalline compounds. They are very active catalysts for the hydrogenation of imines; the best results being obtained with *N*-arylimines derived from aryl alkyl ketones (Scheme 18). At pressures between 10 and 100 bar, turnover numbers of >1000 and up to 89% ee could be achieved. Even higher catalyst activities were observed in supercritical CO_2, a solvent which allowed easy recovery and recycling of the catalyst.[35a]

Scheme 18



Remarkably high enantioselectivities were obtained in the hydrogenation of trisubstituted 1,2-diarylalkenes[35b] (Scheme 19). A difficult problem, which needed to be solved in this case, was catalyst deactivation during the reaction. After a long and often frustrating period of extensive experimentation, the use of tetrakis[2,6-bis(trifluoromethyl)phenyl]borate (TFPB) as the counterion instead of more common noncoordinating anions, such as hexafluorophosphate or tetrafluoroborate, finally brought the solution. The TFPB salts display a much longer lifetime and exhibit high catalytic activity. Full conversion and virtually identical enantioselectivities can be achieved in less than 2 h using only 0.1 mol % of catalyst. Until now, unfunctionalized olefins of this type could not be hydrogenated with high enantioselectivity at such low catalyst loadings.[36] Interestingly, the TFPB salts gave unsatisfactory results in the hydrogenation of polar substrates such as allylic alcohols. In this case, the corresponding PF_6 salts proved to be more efficient catalysts.

Scheme 19



R	ee (%)
Ph	97
4-MeO-Ph	95
4-Cl-Ph	98
CH2OAc	91

E. Transfer Hydrogenation of Ketones and Imines. Transfer hydrogenation of ketones using 2-propanol or

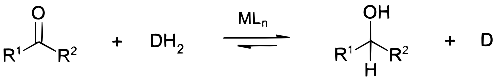
Table 1. Transfer Hydrogenation of Various Ketones (cf. Scheme 20) with Ru Complexes of Phosphinooxazolines

entry	*c* (M)	substrate R^1	 R^2	catalyst	*t* (h)	conv (%)	ee (%) (config)
1	1[a]	Ph	CH_3	**24** + **L7**	0.5	77	94 (*R*)
2	1[a]	Ph	CH_3	**24** + **L7**	1	81	91 (*R*)
3	1[a]	Ph	CH_2CH_3	**24** + **L7**	1	78	97 (*R*)
4	1[a]	Ph	$CH(CH_3)_2$	$RuCl_2(PPh_3)$**L19**	0.16	74	93 (*R*)
5	1[a]	cyclohexyl	CH_3	**24** + **L7**	0.5	59	63 (*S*)
6	0.073[b]	Ph	CH_2CH_3	**24** + **L21**	1	85	96 (*R*)
7	0.02[c]	Ph	CH_3	$RuCl_2(PPh_3)_2$**L20**	2	94	>99.6 (*R*)
8	0.02[c]	2-F−C_6H_4	CH_3	$RuCl_2(PPh_3)_2$**L20**	2	92	96.6 (*R*)
9	0.02[c]	$C(CH_3)_3$	CH_3	$RuCl_2(PPh_3)_2$**L20**	16[d]	81	>99 (*S*)
10	0.02[c]	cyclohexyl	CH_3	$RuCl_2(PPh_3)_2$**L20**	24	68	52 (*S*)

[a] Conditions: 0.1 mol % catalyst, 2.5 mol % NaOH, 82 °C (ref 40). [b] Conditions: 0.2 mol % catalyst, 2.5 mol % KO-*i*-Pr, 50 °C (ref 41b). [c] Conditions: 0.5 mol % catalyst, 2.5 mol % NaO-*i*-Pr, room temperature (ref 41c). [d] At 50 °C.

formates as hydrogen source is an attractive alternative to catalytic reduction with molecular hydrogen (Scheme 20).[37] In 1991, Bäckvall[39] reported that the complex $RuCl_2(PPh_3)_3$ (0.1%) in conjunction with NaOH (2%) is an active catalyst with 2-propanol as hydrogen donor. It was soon demonstrated that Ru complexes derived from a broad variety of chiral ligands can be employed in reductions of alkyl aryl ketones. Work carried out by the Noyori group with Ru complexes of *N*-tosyldiamine ligands was particularly successful.[37]

Scheme 20



In earlier work, we had probed bioxazoline complexes of Ir and Rh in transfer reductions[5] and hydrosilylations,[38] respectively. The use of PHOX ligands for transfer hydrogenations began in 1996 with a study of the reduction of acetophenone with a catalyst prepared in situ by simply mixing the ligand with $RuCl_2(PPh_3)_3$ and otherwise employing Bäckvall's conditions.[39] This catalyst induced high enantioselectivity and reactivity (Table 1, entries 1−5). Even higher activity could be obtained with complexes $RuCl_2(PPh_3)L^*$ prepared by ligand exchange at room temperature. Complexes obtained from **L7** and **L19** were characterized by X-ray crystal structure analysis. Chelate complexes are much more active than the parent complex **24** (cf. Figure 2A). An important aspect of the reaction at substrate concentrations >0.1 M is its reversibility, which can lead to low enantioselection due to racemization of the product, as demonstrated in Figure 2. Nevertheless, the very high but preparatively realistic concentration of 1 M was used. Racemization is negligible if conversion is monitored carefully and ligands with bulky substituents at phosphorus, i.e., **L7**, are employed (Figure 2B).[40]

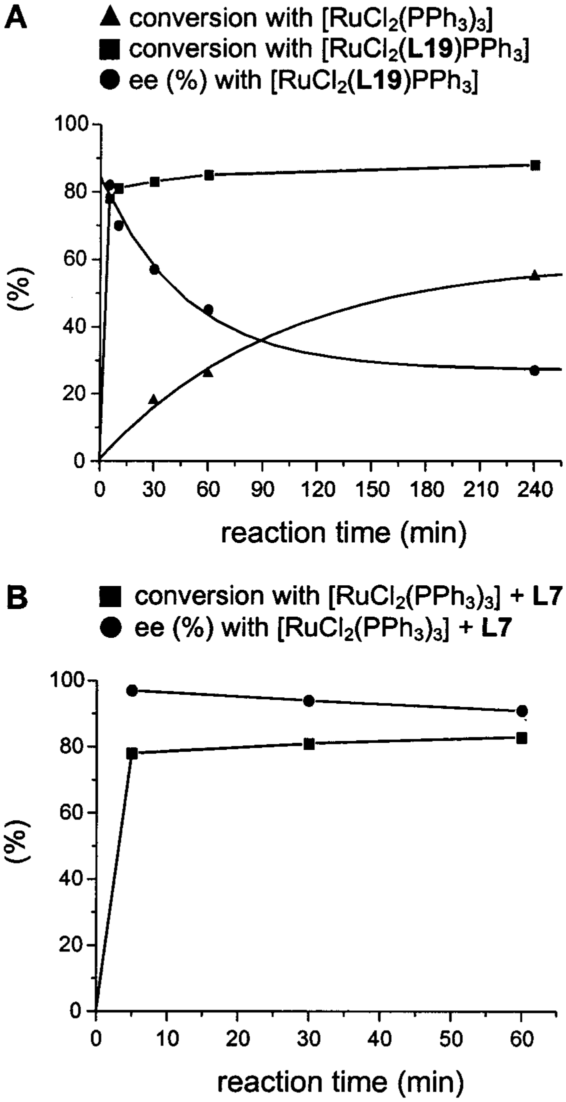
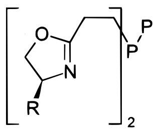


FIGURE 2. Dependence of conversion and enantioselectivity upon reaction time in the catalytic transfer hydrogenation of acetophenone with various catalysts (for conditions, see Table 1).

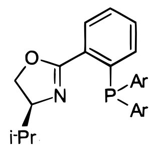
Excellent results were also obtained by Sammakia[41a] using (phosphinoferrocenyl)oxazolines such as **L21** as ligands (Table 1, entry 6). The catalyst $RuCl_2(PPh_3)$**L20** gave up to 96% ee in reductions of alkyl aryl ketones, using a 0.073 M 2-propanol solution. This work was extended by Uemura et al., who found relatively low activity and enantioselectivity under the standard conditions (1 M solution)[41b] but extremely high degrees of enantioselection when a very low concentration was employed (0.02 M solution)[41c] (entries 7−10). The Uemura group also investigated kinetic resolution in the oxidation of racemic *sec*-alcohols with acetone.[41c]

RuCl$_2$(PPh$_3$)$_3$

24

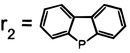


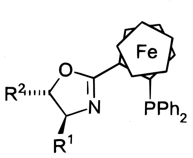
L23



L7 Ar = 1-Naphthyl

L19 PAr$_2$ =





L20 R^1 = *i*-Pr, R^2 = H

L21 R^1 = Ph, R^2 = H

L22 R^1 = R^2 = Ph

The ligands **L23** and **L20** gave excellent results, up to 99% ee, with *tert*-butyl methyl ketone[42] and 2,2-dimethylcyclohexanone.[41c] With *sec*-alkyl methyl ketones the best result was 66% ee.

IV. Conclusion

The phosphinooxazolines, although originally designed for Pd-catalyzed allylic substitution, have emerged as remarkably versatile ligands for enantiocontrol in a variety of metal-catalyzed processes. In addition to the applications discussed in this Account, PHOX ligands have also been used in hydrosilylations of ketones,[43] alkene/CO-copolymerizations,[44] aza-Claisen rearrangements,[45] and Diels–Alder[46] reactions. The modular structure of PHOX ligands allows extensive variation of the oxazoline ring, the backbone, and the phosphine moiety. Thus, it should be possible to tailor the ligand structure for many other classes of metal-catalyzed reactions.

We thank our collaborators, whose names appear in the references, for their many experimental and intellectual contributions, as well as their enthusiasm and perseverance. Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Max-Planck-Institut für Kohlenforschung, the Swiss National Science Foundation, and F. Hoffmann-La Roche AG, Basel, is gratefully acknowledged.

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