Acta Chemica Scandinavica, 1996: 50: 189–194
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Design of Chiral Ligands for Asymmetric Catalysis: from C_2-Symmetric Semicorrins and Bisoxazolines to Non-Symmetric Phosphinooxazolines†

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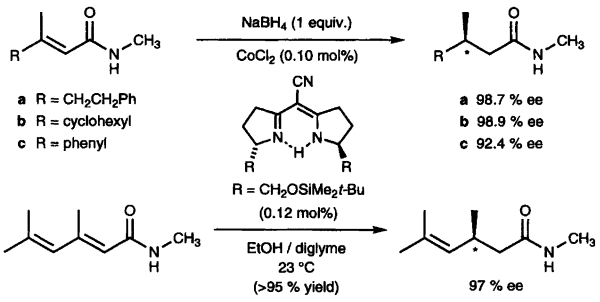
Pfaltz, A., 1996. Design of Chiral Ligands for Asymmetric Catalysis: from C_2-Symmetric Semicorrins and Bisoxazolines to Non-symmetric Phosphinooxazolines. – Acta Chem. Scand. 50: 189–194 © Acta Chemica Scandinavica 1996.

Chiral C_2-symmetric semicorrins have proved to be highly efficient ligands for Cu-catalyzed enantioselective cyclopropanation of olefins and Co-catalyzed enantioselective reduction of α,β-unsaturated carboxylic esters and amides. Based on these findings, analogous, readily accessible C_2-symmetric bisoxazolines have been developed which, in a short time, have become standard ligands in asymmetric catalysis, allowing effective enantiocontrol in a variety of metal-catalyzed reactions. More recently, our work has led us from C_2-symmetric nitrogen ligands to unsymmetric phosphinooxazolines. P,N-ligands of this type have been successfully applied in palladium- and tungsten-catalyzed allylic substitutions and in enantioselective Heck reactions of alkenyl and aryl triflates with cyclic olefins.

C_2-Symmetric semicorrins

Almost ten years ago, we introduced a new class of chiral ligands for asymmetric catalysis, the semicorrins **1**.[1–4] For a number of reasons we believed C_2-symmetric semicorrins would be useful ligands for enantiocontrol of metal-catalyzed reactions. Both enantiomers are readily prepared in optically pure form. The synthesis is flexible and allows systematic variation of the substituents at the stereogenic centers, so the ligand structure can be optimizedfor a particular application. The chiral structural units are held in close proximity to the metal by the rigid ligand scaffold, and therefore are expected to have a strong directing effect on a reaction taking place in the coordination sphere. Indeed, semicorrins were found to induce excellent enantioselectivities in copper-catalyzed cyclopropanations of olefins[1,3–5] and in cobalt-catalyzed conjugate reductions of α,β-unsaturated carboxylic esters and amides with sodium borohydride (Scheme 1).[4,6,7]



Scheme 1.

Semicorrin analogues: azasemicorrins and bisoxazolines

The exciting results obtained with semicorrins prompted us and others to develop structurally analogous ligands such as the azasemicorrins **2** and **4**[8] and the bisoxazolines **3**, **5** and **6**.[9–17] In particular the bisoxazolines **6** proved to be highly versatile, very effective ligands for many different metal-catalyzed reactions.[4] C_2-symmetric ligands of this type are very attractive because they are extremely easy to prepare from optically active amino acids or amino alcohols, and some derivatives are now commercially available. Ligands **1–6** can be divided into two complementary classes: (a) anionic ligands with an

† Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995 at Tammsvik, Bro, Sweden.

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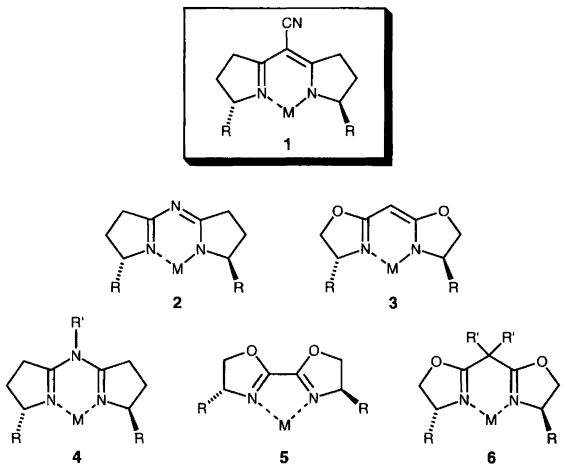
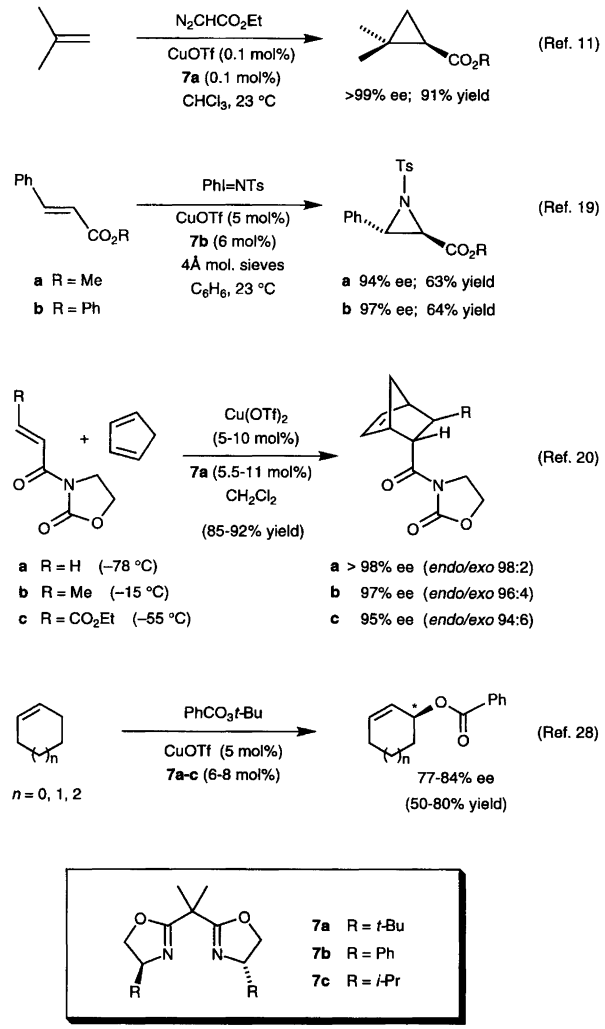


electron-rich π-system (**1–3**) and (b) neutral ligands (**4–6**), which are less strong electron donors or even π-acceptors such as **5**, and therefore should be well suited to applications requiring electrophilic cationic metal complexes. Within a short time, C_2-symmetric bisoxazolines have become standard ligands in asymmetric catalysis and the list of successful applications is steadily growing: copper-catalyzed inter- and intra-molecular cyclopropanation[4,5,9–11,18] and aziridination,[19] Diels–Alder reactions,[12,20,21] iridium-catalyzed transfer hydrogenation of ketones,[9] addition of trimethylsilyl cyanide to aldehydes,[22] inter- and intra-molecular palladium-catalyzed allylic substitution,[4,8,9,23,24] carbometalation of cyclopropenone acetals,[25] addition of organolithium reagents to imines,[26] palladium-catalyzed copolymerization of 4-*tert*-butylstyrene and carbon monoxide,[27] and allylic oxidation of olefins producing allylic esters.[28] Some representative examples, illustrating the potential of (bisoxazoline)copper catalysts, are shown in Scheme 2.



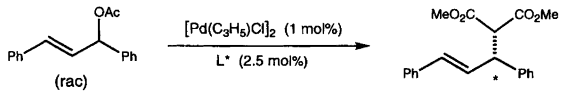
Scheme 2.

Palladium-catalyzed allylic substitution

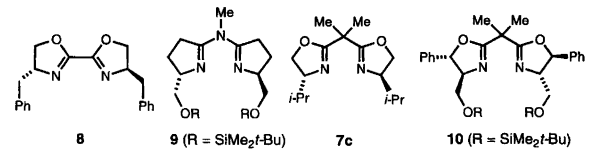
Originally, we thought that the bioxazolines **5** would be useful ligands for catalytic reactions proceeding through Pd(0) intermediates because of their potential π-acceptor properties which should stabilize low-valent oxidation states. Indeed, in the Pd-catalyzed alkylation shown in Table 1, enantioselectivities up to 77% ee could be induced with the bioxazoline derivative **8**.[9] However, screening of various semicorrins, azasemicorrins, and bisoxazolines showed that the azasemicorrin **9** and methylenebis(oxazolines) **7c** and **10** are more effective ligands. In the reaction of dimethyl malonate with racemic 1,3-diphenyl-2-propenyl acetate and related allylic acetates, these ligands afforded enantiomeric excesses of up to 97% and high yields.[4,8,23] Recently, Larock *et al.*[24] have also reported promising enantioselectivities using (bisoxazoline)Pd catalysts in annulation reactions of allenes proceeding through an enantioselective intramolecular allylic substitution as the key step.

X-Ray and NMR structural studies of Pd(allyl) complexes with bisoxazoline ligands led to important clues on the origin of enantioselection in these reactions.[23] Crystal structures of (bisoxazoline)Pd(II)(1,3-diphenylallyl) com-

Table 1. Enantioselective allylic substitution with (bisoxazoline)Pd catalysts.



Ligand	Conditions	% Yield	% ee
8	$NaCH(CO_2Me)_2$, THF, 50 °C	86	77 (*R*)
9	$CH_2(CO_2Me)_2$, BSA, KOAc, CH_2Cl_2, 23 °C	99	95 (*R*)
7c	$CH_2(CO_2Me)_2$, BSA, KOAc, CH_2Cl_2, 23 °C	95	95 (*R*)
10	$CH_2(CO_2Me)_2$, BSA, KOAc, CH_2Cl_2, 23 °C	97	97 (*S*)



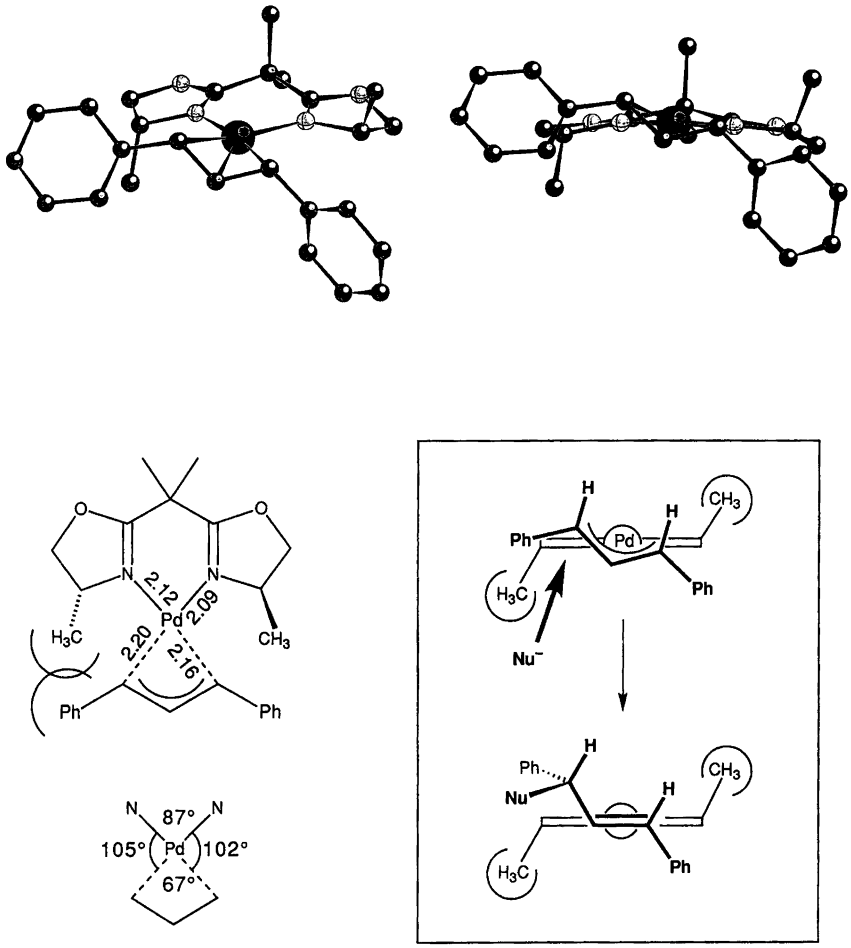


Fig. 1. Crystal structure of a [(bisoxazoline)Pd(1,3-diphenylallyl)]$^+$ PF_6^- complex (the PF_6^- ion is not shown).[29]

plexes, which are the actual intermediates in the catalytic process shown in Table 1, revealed that one of the Pd–C bonds to the allylic termini is significantly lengthened as a consequence of the repulsive interaction between the bisoxazoline ligand and one of the allylic phenyl groups (Fig. 1). From the absolute configuration of the product we know that the nucleophile preferentially attacks the longer, more strained Pd–C bond, suggesting that the release of strain associated with the cleavage of this bond may be one of the factors responsible for enantioselection (Fig. 2).

The repulsive interaction between one of the allylic phenyl groups and the adjacent substituent at the oxazoline ring can be partially relieved by deformation of the bisoxazoline ligand, as seen in a previously reported crystal structure,[23] or by rotation of the allyl system, as shown in Fig. 1.[29] In this case, the coordination geometry of the allyl ligand is in between a square-planar structure, as normally found in unstrained complexes, and the geometry of the Pd(0)-olefin complex, postulated as the primary product of the catalytic process. Rotation of the allyl ligand in the direction shown in Fig. 1 is more favorable than rotation in the opposite direction, which

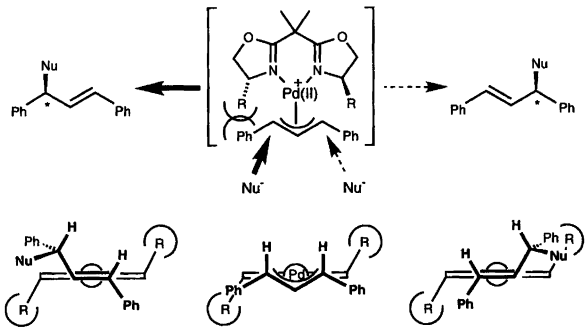


Fig. 2. Possible mechanism of enantioselection in (bisoxazoline)Pd-catalyzed allylic substitutions.

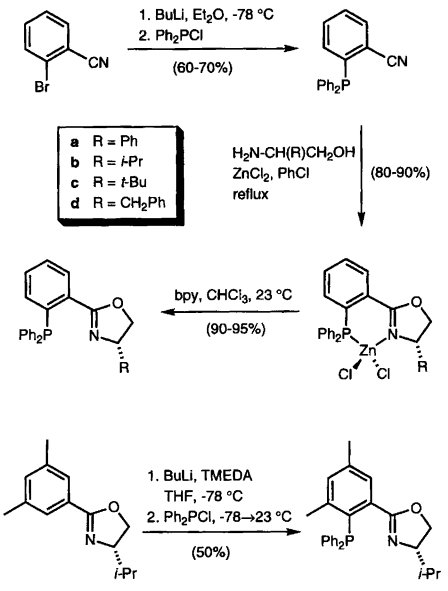
would increase the repulsive phenyl–methyl interaction and, consequently, lead to a more strained Pd(0)-olefin complex (see Fig. 2). Thus there are two likely factors contributing to the observed selectivity: (a) strain-induced selective activation of one of the allylic termini and (b) sterically controlled rotation of the allyl ligand during nucleophilic attack. The mechanistic model shown in Fig. 2 also rationalizes the results recently obtained with other types of nitrogen ligand.[30,31]

Phosphinooxazolines: a promising new class of P,N-ligands

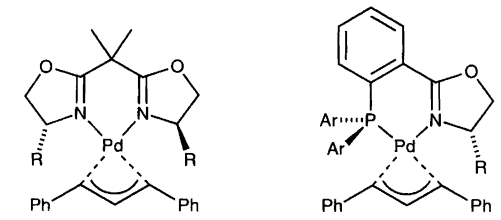
Although palladium complexes of C_2-symmetric azasemicorrins and bisoxazolines are efficient catalysts for certain allylic alkylation reactions, the range of substrates and nucleophiles that can be employed, is limited. Amines and acetylacetonate, e.g., which are good ligands for Pd(II), deactivate the catalyst. The best results are obtained with phenyl-substituted allylic acetates whereas less reactive substrates such as 1,3-dialkyl-2-propenyl acetates react sluggishly with low enantioselectivity. Our search for more reactive catalysts that overcome these limitations has led us to chiral phosphinooxazoline ligands.[32] Several short and efficient syntheses have been developed, making these ligands readily accessible from commercially available precursors (Scheme 3).[33–37] The same ligands and their application to Pd-catalyzed allylic substitution have also been reported independently by the groups of Helmchen[34] and Williams.[35]

By replacing one of the oxazoline rings with a phosphinoaryl group, we sacrifice the advantages of C_2-symmetry. On the other hand, we gain an additional means of controlling stereoselectivity based on electronic effects. In contrast with allyl complexes with C_2-symmetric ligands, complexation of the metal by P,N-ligands should result in effective electronic discrimination of the two allylic termini due to the different trans influence of phosphorus and nitrogen (Scheme 4).

Palladium complexes with phosphinooxazolines turned out to be very reactive, highly selective catalysts for the allylic substitution of 1,3-diphenyl-2-propenyl acetate with a range of *C*- and *N*-nucleophiles (Table 2).[32,34,35,38] Even the rather inert 1,3-diisopropyl-2-propenyl acetate, which reacts very sluggishly with Pd-phosphine catalysts,

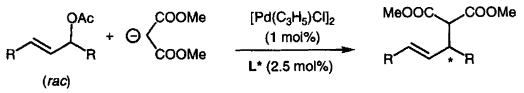


Scheme 3.

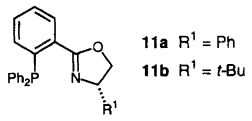


Scheme 4.

Table 2. Enantioselective allylic substitutions with (phosphinooxazoline)Pd catalysts.



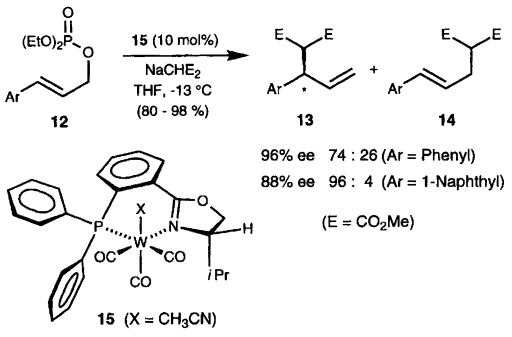
Substrate	L*	Conditions	% ee	(% yield)
R=Ph	**11a**	$CH_2(COOMe)_2$, BSA, CH_2Cl_2, 23 °C	99	(99)
R=Me	**11b**	$CH_2(COOMe)_2$, BSA, CH_2Cl_2, 23 °C	71	(96)
R=Et	**11b**	$CH_2(COOMe)_2$, BSA, CH_2Cl_2, 23 °C	79	(98)
R=Pr	**11b**	$CH_2(COOMe)_2$, BSA, CH_2Cl_2, 23 °C	69	(96)
R=*i*-Pr	**11b**	$NaCH(COOMe)_2$, DMF, 65 °C	96	(88)



11a R^1 = Ph
11b R^1 = *t*-Bu

could be converted into the desired substitution product in high yield and with excellent enantioselectivity.[32] As expected, analogous substrates with primary alkyl substituents afforded lower selectivities.

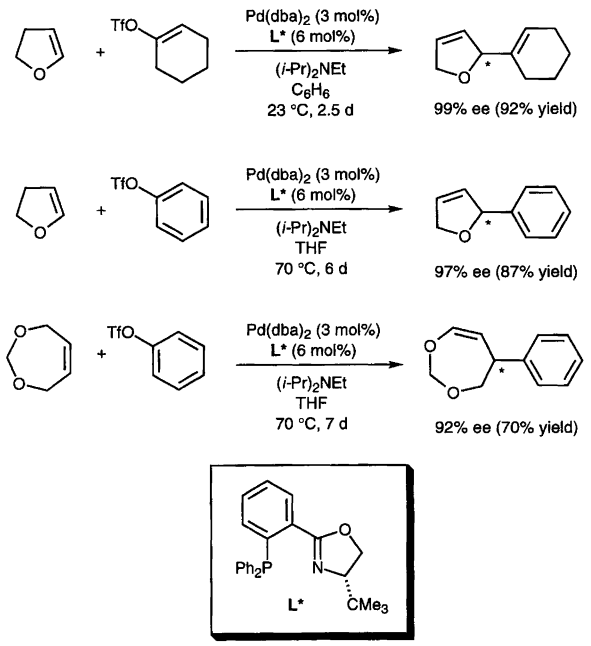
The same ligands have also been used for enantiocontrol in tungsten-catalyzed allylic alkylations (Scheme 5).[39,40] With monosubstituted allylic substrates such as **12**, Pd-catalyzed reactions with *C*-nucleophiles lead predominantly to the achiral regioisomer **14**. Although Trost and coworkers have shown several years ago that the regioselectivity can be reversed by switching from palladium to tungsten catalysts,[41] no chiral tungsten catalysts had been described when we started our work on (phosphinooxazoline)tungsten complexes. Although initial results were discouraging, eventually an efficient catalyst was found which allows the conversion of 3-aryl-2-propenyl phosphates with dimethyl sodiomalonate into the



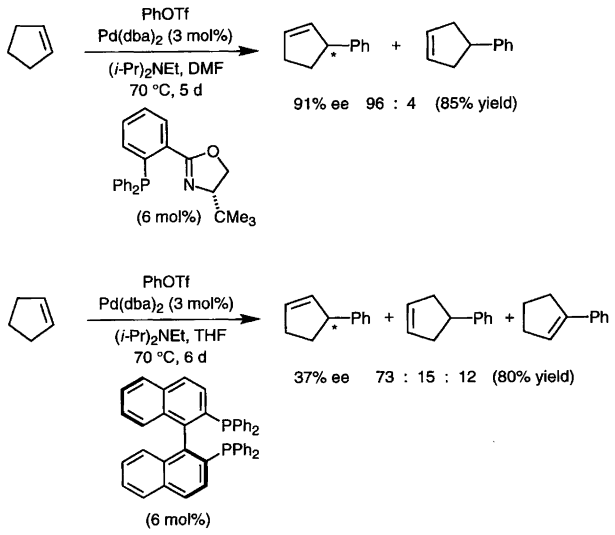
Scheme 5.

desired chiral regioisomers **13** with high enantioselectivity. The order of addition of the reactants to the precatalyst solution was found to be crucial. When complex **15** was first treated with dimethyl sodiomalonate before the allylic phosphate was added, a clean catalytic reaction was observed, whereas addition of **12** in the absence of dimethyl sodiomalonate produced a catalytically inactive tungsten(allyl) complex.

Another application of (phosphino-oxazoline)palladium complexes that we recently started to investigate is enantioselective Heck reactions[42] (Scheme 6). The pioneering work of Shibasaki, Hayashi and Overman has resulted in remarkable progress in this area over the last few years.[43–48] So far the highest enantioselectivities have been obtained with (BINAP)Pd catalysts. (Phosphino-oxazoline)Pd complexes, prepared *in situ* from $[Pd(dba)_2]$ and 1.5–2 equiv. of the corresponding P,N-ligand, were found to be highly efficient catalysts for the reaction of 2,3-dihydrofuran with 1-cyclohexenyl or phenyl triflate.[49] The corresponding 2,5-dihydrofuran derivatives were formed in high yield and with excellent enantioselectivity, in contrast with the (BINAP)Pd-catalyzed reactions,[44,45] which yield the thermodynamically more stable 2,3-dihydrofuran derivatives as the main products. With (BINAP)Pd catalysts, the best results were obtained with 1,8-bis(dimethylamino)naphthalene as base, whereas here, simpler bases such as triethylamine or ethyldiisopropylamine proved to be satisfactory. Arylation of 4,7-dihydro-1,3-dioxepine,[48] which leads to a synthetically useful intermediate, also proceeds with high enantioselectivity and satisfactory yield. The low tendency of (phosphinooxazoline)Pd catalysts to promote migration of C,C-double bonds allows the use of substrates such as cyclopentene, which with (BINAP)Pd catalysts gives



Scheme 6.



Scheme 7.

mixtures of isomers and low ee's owing to extensive double bond migration (Scheme 7).

The remarkable levels of selectivity achieved with phosphinooxazolines in allylic substitutions and Heck reactions demonstrate the considerable potential of P,N-ligands of this type in asymmetric catalysis. Phosphino-oxazolines are particularly attractive ligands because they are so easily synthesized from simple precursors. Their modular structure allows extensive structural variation of the backbone, the oxazoline ring and the phosphine part by appropriate choice of the individual precursors. In this way it should be possible to tailor the ligand structure for many other classes of metal-catalyzed reactions.

Acknowledgements. Most of the work described herein was carried out at the University of Basel by a dedicated group of graduate students and postdocs whose names are listed in the references. I would like to thank them all for the fruitful collaboration and their enthusiasm and perseverance. Financial support by the Swiss National Science Foundation and F. Hoffmann–La Roche AG, Basel, is gratefully acknowledged.

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Received August 1, 1995.