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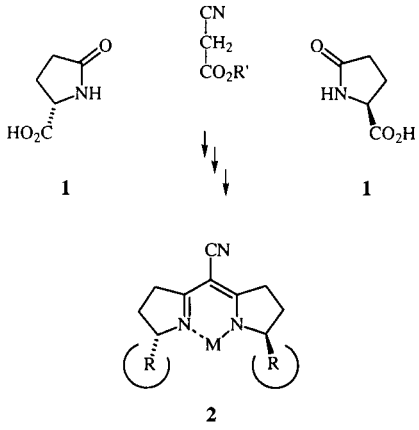
J. Heterocyclic Chem., **36**, 1437 (1999).

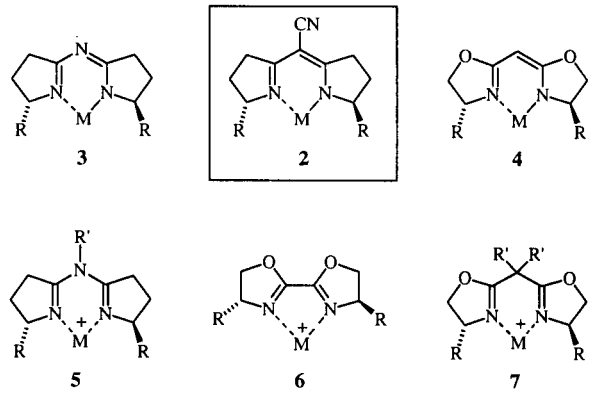
In 1986 we reported a new class of chiral ligands for asymmetric catalysis, the C_2-symmetric semicorrins **2** (Scheme 1) [1]. We assumed that these ligands, which are readily prepared from pyroglutamic acid **1**, should allow effective enantiocontrol of metal-catalyzed reactions since they possess a conformationally rigid scaffold with the two substituents at the stereogenic centers in close proximity of the coordination site. Indeed, the semicorrins were found to induce high enantioselectivities in the copper-catalyzed cyclopropanation of olefins and the cobalt-catalyzed conjugate reduction of α,β-unsaturated carboxylic esters and amides (Scheme 2) [2].

The success we had with the semicorrins prompted us and a number of other research groups to develop additional, structurally related ligands (Scheme 3) [2,3]. The aza-semicorrins in complexes **3** and **5** and the bi- and

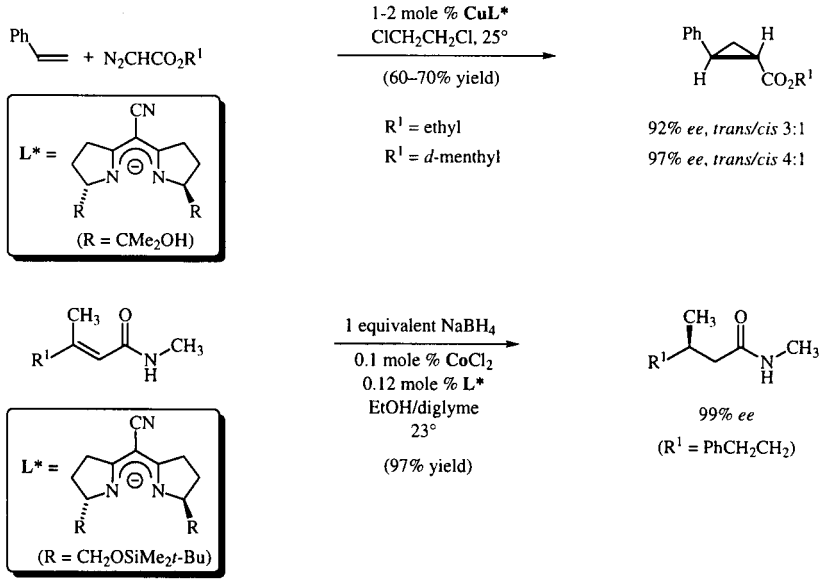
Scheme 1



Scheme 3



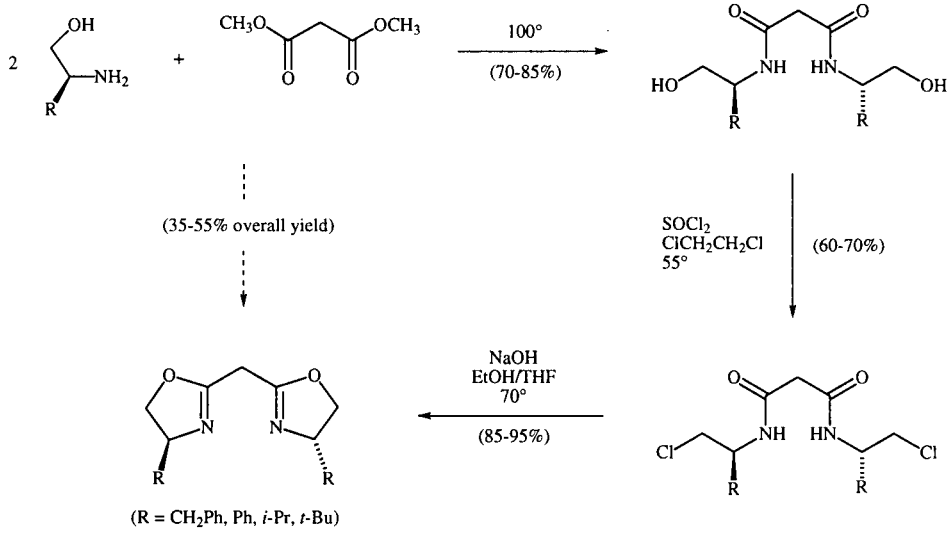
Scheme 2



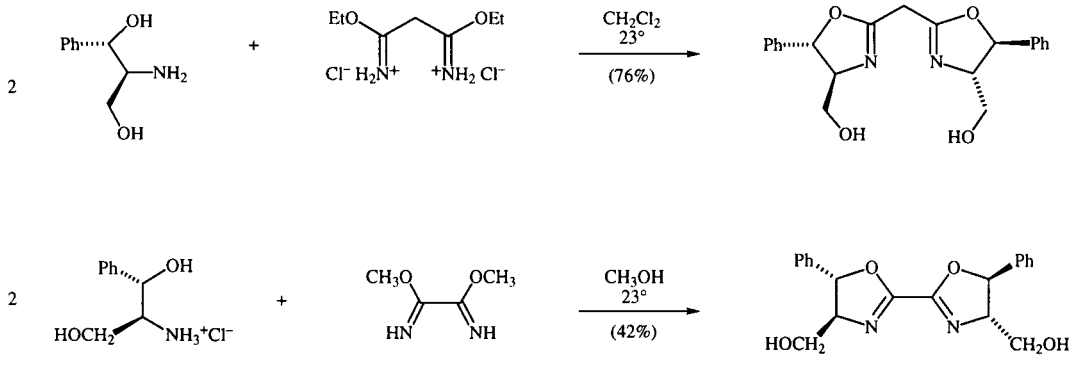
bisoxazolines in **6**, **4** and **7** all provide a steric environment around the metal center which is similar to the semicorrins. Compounds **2-4** contain anionic ligands with an electron-rich π-system, whereas compounds **5-7** incorporate neutral, less electron-donating ligands. Depending on the metal center, its oxidation state and the electronic requirements of a specific metal-catalyzed process, either anionic semicorrin type ligands or their neutral conterparts are better suited.

As illustrated in Schemes 4-7, these ligands are all readily prepared in high enantiomeric purity from inexpensive chiral precursors. Starting from different precursors, or by modification of the substituents at the stereogenic centers after building the ligand skeleton, a wide variety of different ligands can be prepared [2-4]. Since the first reports on C_2-symmetric bisoxazolines [5,6], the number of applications of bisoxazoline-metal complexes has rapidly grown and today spans an impressive range of enantioselective metal-catalyzed processes, such as cyclopropanation, aziridination, Lewis acid catalyzed cycloadditions and Mukaiyama aldol reactions, conjugate addition, allylic alkylation, as well as oxidation and reduction [2-3].

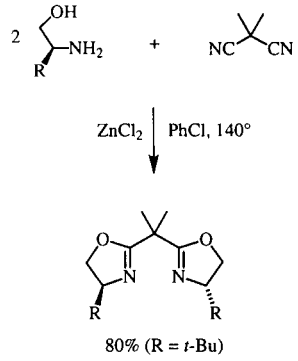
Scheme 4



Scheme 5

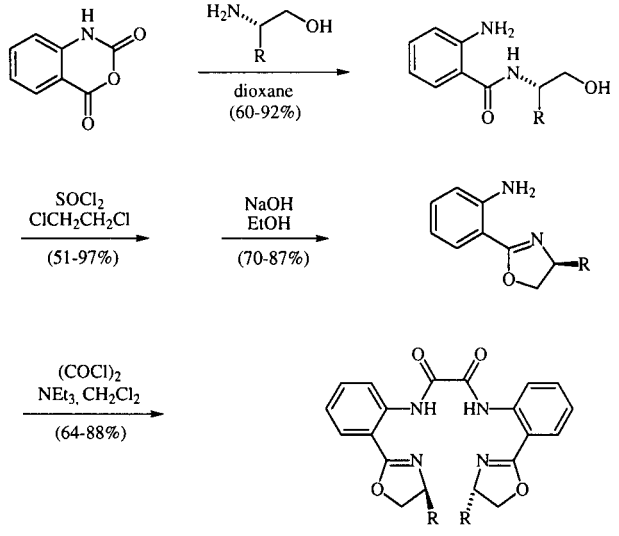


Scheme 6



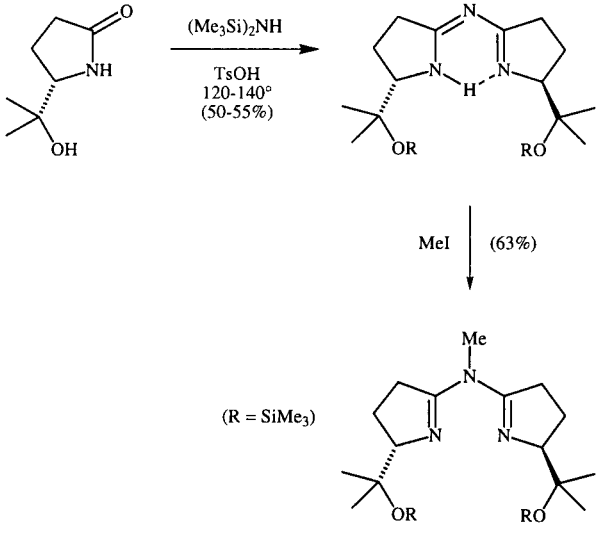
80% (R = *t*-Bu)

Scheme 8



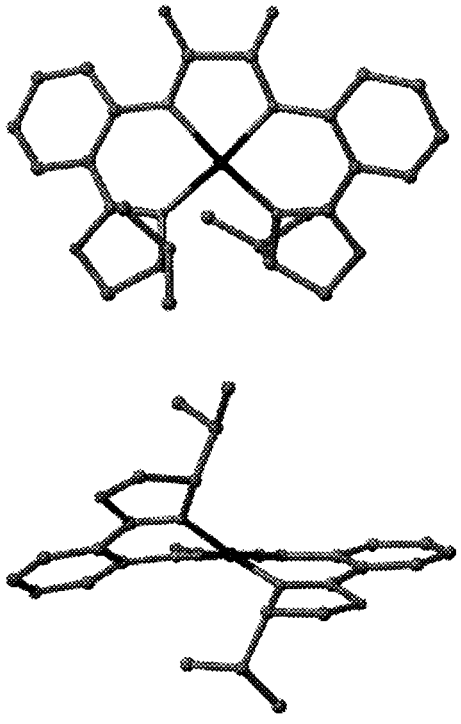
R = Me, CH_2Ph, Ph, *i*-Pr, *t*-Bu

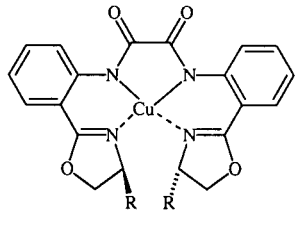
Scheme 7



(R = $SiMe_3$)

Scheme 9

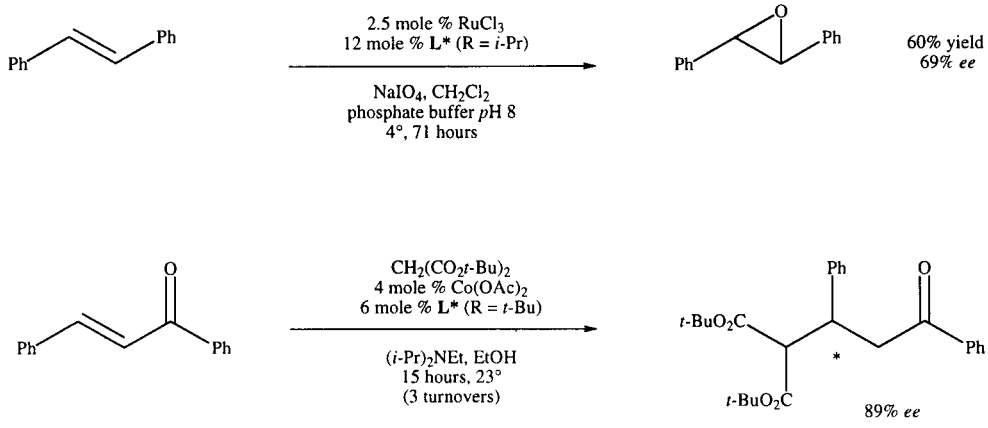


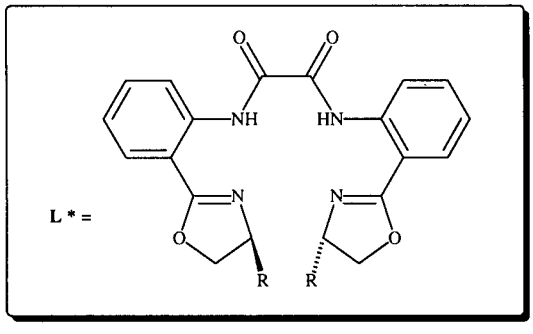


X-ray Analysis

In addition, many other bi- and tridentate bisoxazoline ligands have been developed and some of them have found interesting applications [3]. For example, Nishiyama's group has developed a versatile class of tridentate C_2-symmetric bisoxazolines derived from pyridine-2,6-bis(carboxylate) [7]. We have recently added to this list a number of tetradentate bisoxazoline ligands (Scheme 8) [8]. These ligands adopt a helical conformation when bound to metal ions such as Cu(II) or Ni(II) (Scheme 9). As shown in Scheme 10, ligands of this type can induce substantial *ee*'s in ruthenium-catalyzed epoxidation reactions and cobalt-mediated Michael additions, although the catalytic efficiencies still need to be improved.

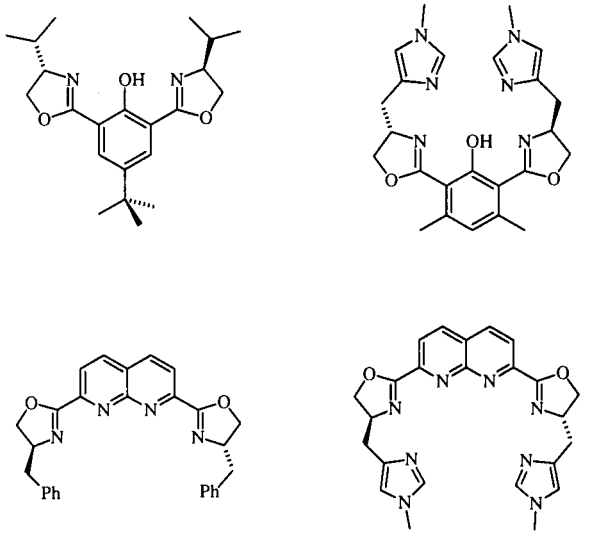
Scheme 10



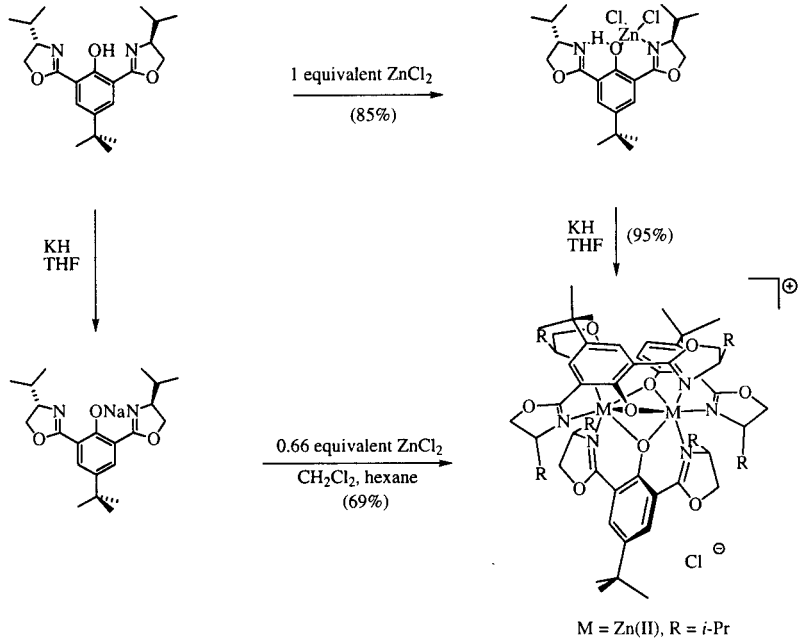


Oxazolines are also useful structural units for the construction of chiral binucleating ligands (Scheme 11) [9]. Starting from such ligands, a variety of binuclear metal complexes can be prepared (Schemes 12 and 13).

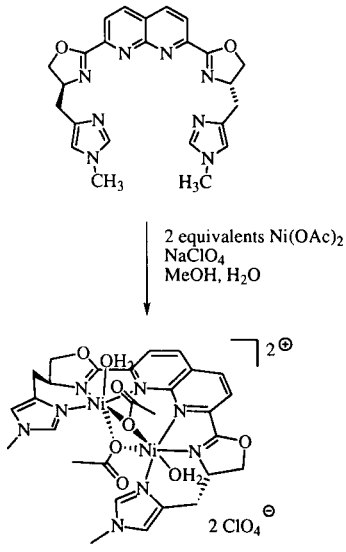
Scheme 11



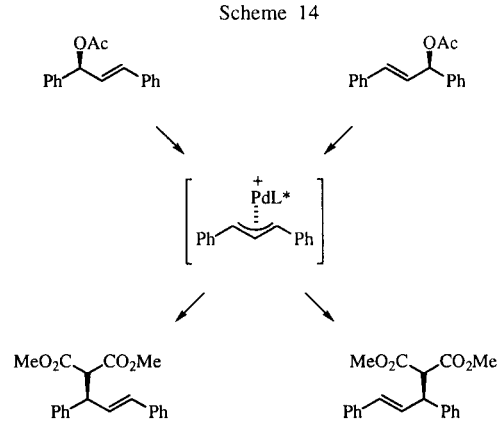
Scheme 12

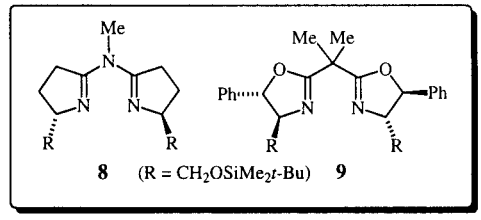


Scheme 13



Scheme 14



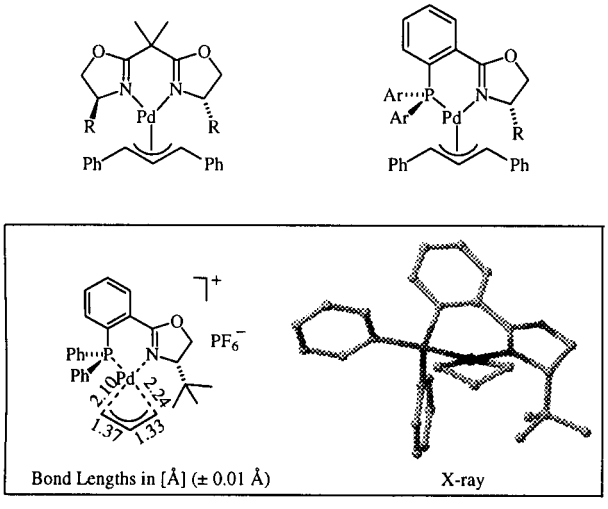


One area we became particularly interested in during the last few years is enantioselective allylic substitution. Using aza-semicorrin or bisoxazoline ligands, we obtained high enantiomeric excesses in several cases, such as the reaction of racemic 1,3-diaryl-2-propenyl acetates with dimethyl malonate (Scheme 14) [2]. In addition, structural studies led to detailed insights into the role of the chiral ligand in the enantioselection step [10,11]. However, the range of substrates and nucleophiles for these catalysts proved to be limited; with less reactive allyl derivatives, reactions were sluggish, and with nucleophiles that are good ligands for Pd(II), displacement of the chiral ligand seemed to be a problem. Therefore, we decided to search for other types of ligands which would overcome these limitations.

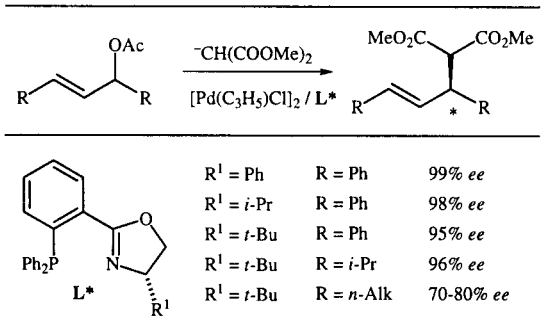
One idea was to keep one oxazoline ring as a chiral unit and replace the other by a phosphine group, which we hoped would enhance the stability as well as the reactivity

and selectivity of the catalyst (Scheme 15) [11]. Moreover, by giving up the concept of C_2-symmetry, we hoped to gain an additional means of controlling the regioselectivity of nucleophilic attack, based on electronic effects. In contrast to 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* influences of the coordinating phosphorus and nitrogen atoms (*cf.* the different Pd-C bond lengths in the crystal structure shown in Scheme 15). Two other research groups, those of Helmchen [12] and Williams [13], also reported the same ligands and their application in the allylic substitution of dimethyl malonate with racemic 1,3-diphenyl-2-propenyl acetate, independently and at the same time. We found that these ligands give very high *ee*'s not only with 1,3-diaryl-2-propenyl acetates using a range of *C*- and *N*-nucleophiles, but also with rather unreactive 1,3-dialkyl-substituted allyl derivatives such as 1,3-diisopropyl-2-propenyl acetate (Scheme 16) [14].

Scheme 15

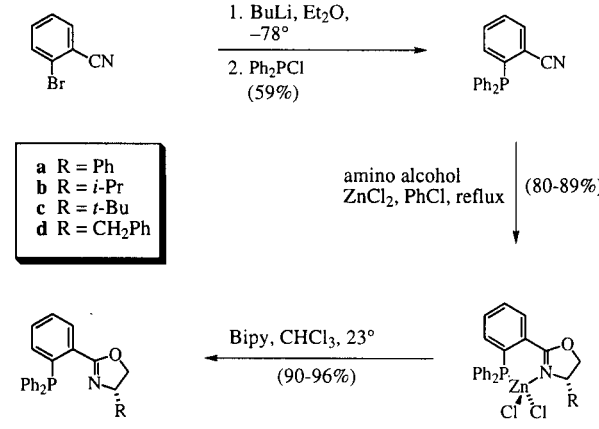


Scheme 16

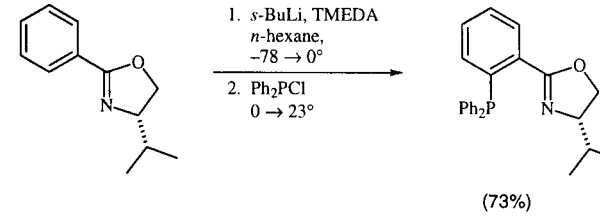


Enantiopure phosphinooxazoline ligands can be readily prepared by various efficient routes (Schemes 17 and 18) [15]. Furthermore, their modular structure allows extensive and independent variation of the backbone, the oxazoline ring, and the phosphine group. This makes it possible to optimize the steric and electronic properties of the ligand for a specific application.

Scheme 17

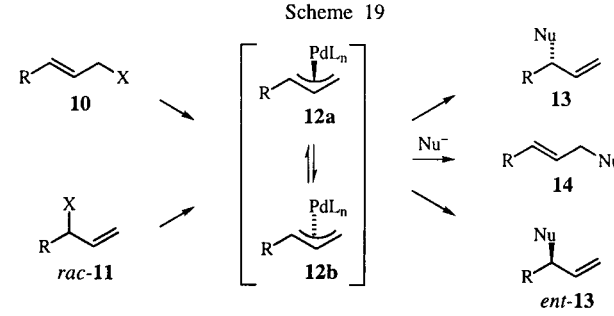


Scheme 18



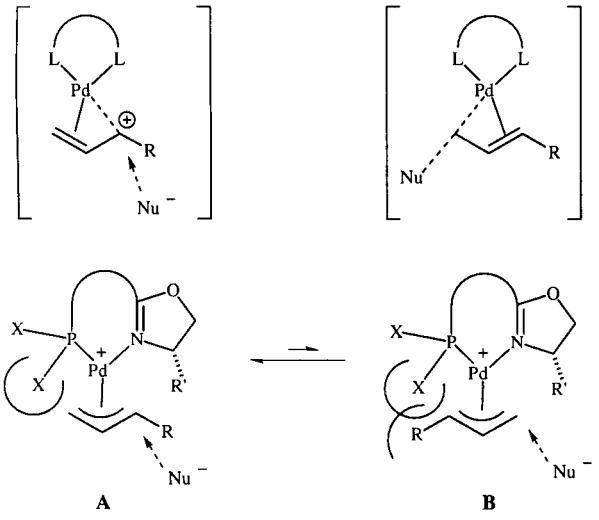
Most palladium catalysts react with monosubstituted allyl derivatives **10** or **11** predominantly at the unsubstituted terminus to give the achiral linear product **14** (Scheme 19). However, by structural variation of the ligand structure, it was possible to revert the regioselectivity in favor of the chiral branched products.

Scheme 19



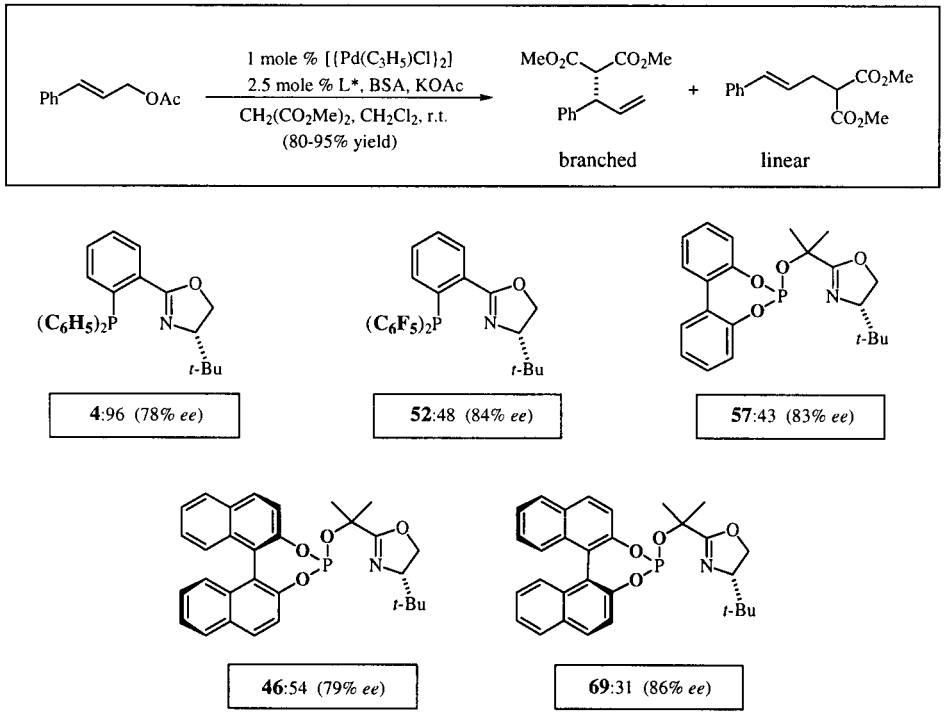
Our search for a suitable ligand was based on the following concepts (Scheme 20). An increase of the cationic character of the allyl system should facilitate nucleophilic attack at the substituted terminus. Therefore, we decided to introduce electronegative substituents at the P atom that render the Pd center more electrophilic. At the same time we wanted to increase the steric hindrance at the P atom. Bulky groups at the P atom are expected to destabilize isomer **B** as well as the transition states of the reaction pathways leading from **B** to the corresponding substitution products. Therefore, a pathway *via* **A** should be preferred and, assuming that nucleophilic attack at the allyl terminus *trans* to the Pd-P bond is electronically favored [16,17], reaction at the substituted allyl end should be facilitated.

Scheme 20

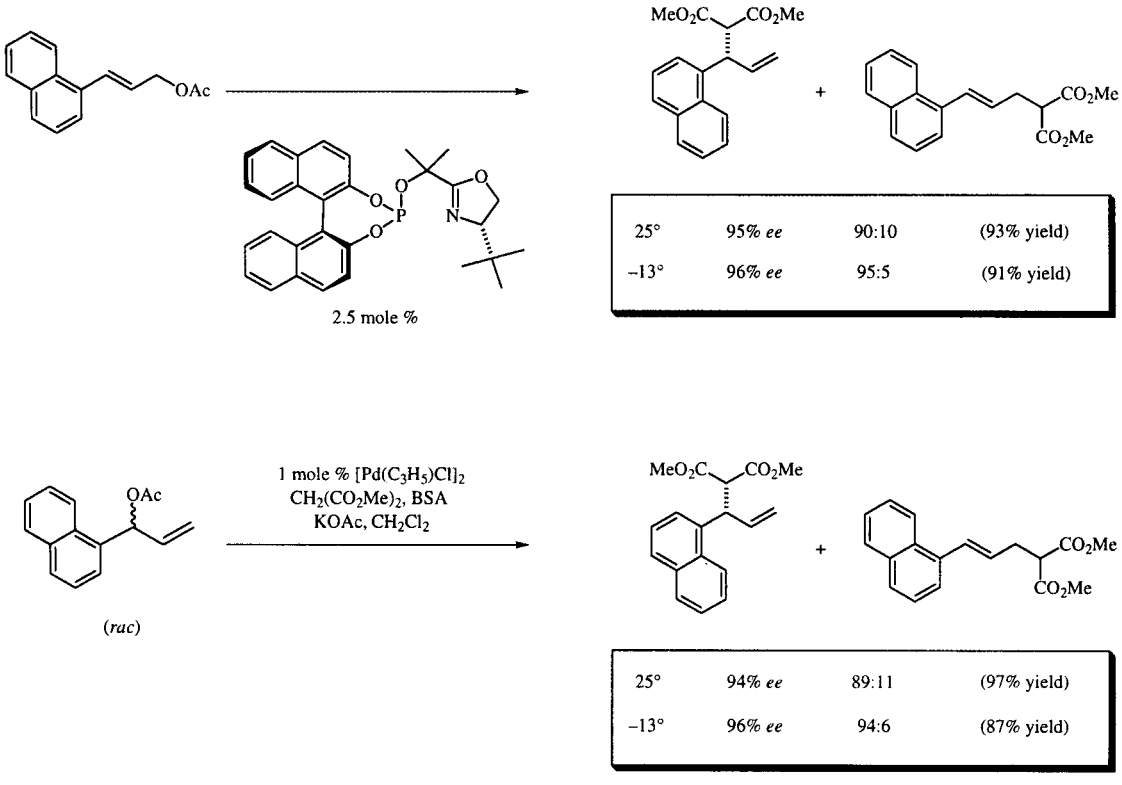


Replacement of the phenyl groups at the P atom by electron-withdrawing pentafluorophenyl groups shifted the regioselectivity in the desired direction from 4:96 to 52:48 (Scheme 21) [18]. A similar effect was observed using a ligand with a biphenyl phosphite group in place of the diphenylphosphino substituent. The regio- and enantioselectivity could be further improved by introduction of a second stereogenic unit derived from binaphthol. The best results were obtained with the (*S*,*S*)-ligand whereas the (*R*,*S*)-diastereomer gave lower regio- and enantioselectivity. Apparently, the enantioselectivity is determined largely by the chiral oxazoline ring while chiral binaphthol unit has a minor, but still significant effect. Replacement of the *tert*-butyl group at the oxazoline ring by other alkyl substituents or phenyl resulted in lower regio- or enantioselectivity. Under optimized conditions in benzene at 23°, 90% *ee* and a branched/linear ratio of 76:24 could be achieved [18-20]. Even higher regio- and enantioselectivities were obtained with the analogous naphthyl-allyl derivatives (Scheme 22).

Scheme 21

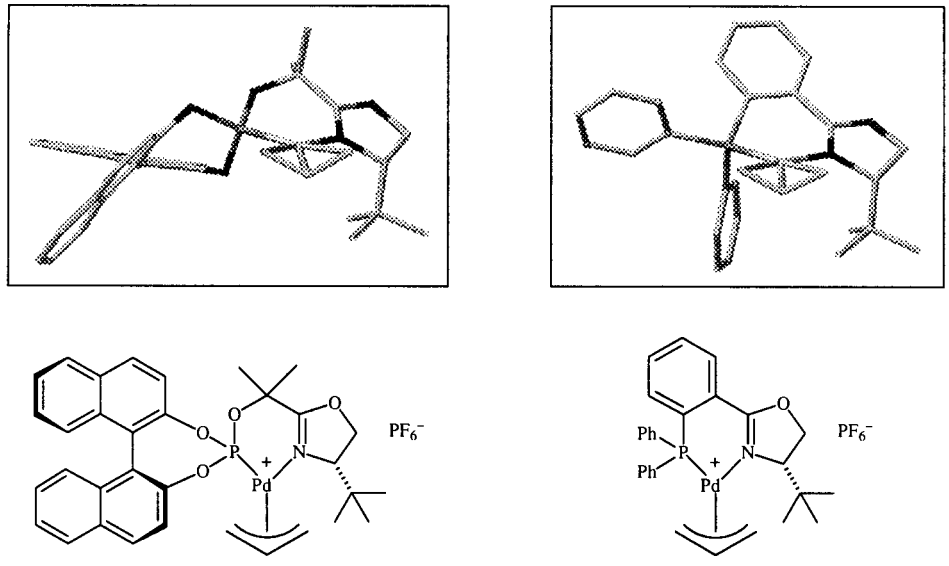


Scheme 22



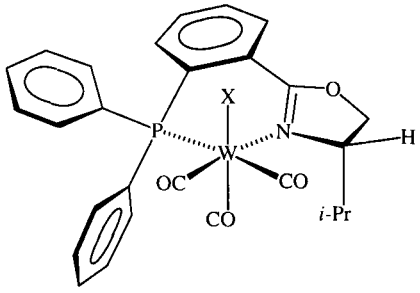
A comparison of the two crystal structures depicted in Scheme 23 shows the difference between the diphenylphosphino-oxazoline and the analogous binaphthyl phosphite ligand. The diphenylphosphine group leaves sufficient space to accomodate a substituent at the allyl terminus *cis* to the P atom, whereas the naphthyl ring system blocks this side of the allyl ligand. Therefore, a monosubstituted allyl ligand would be expected to coordinate with the substituted end located next to the oxazoline ring (see Scheme 20, complex **A**).

Scheme 23

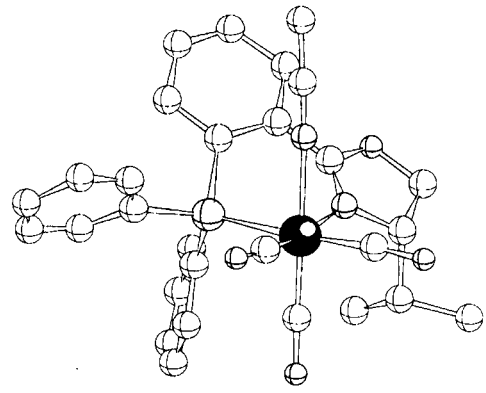


Predominant formation of the branched product with moderate to high *ee*'s is also observed with other transition metal catalysts such as tungsten (Scheme 24) [19,21] and iridium [22] phosphinooxazoline complexes. Recently, Trost and Hachiya have reported very high regio- and enantioselectivities in the reaction of 1- and 3-arylallyl carbonates using a molybdenum complex derived from the dipyridine ligand **14** (*cf.* Scheme 25)

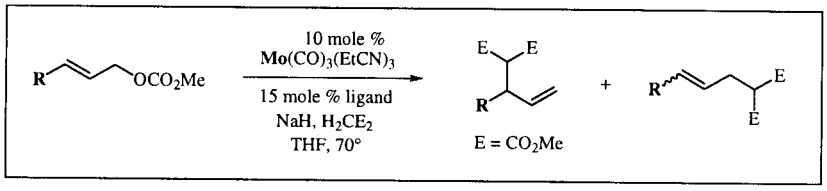
Scheme 24

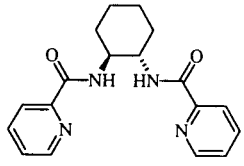


(X = CH_3CN)



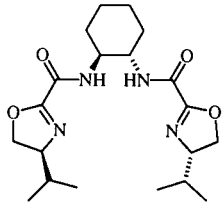
Scheme 25





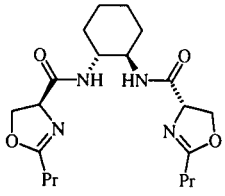
14

R = Ph	99% *ee*	49:1
R = Pr	98% *ee*	8:1
R = Me	94% *ee*	5:1



15

R = Ph	99% *ee*	14:1
R = Me	94% *ee*	3:2



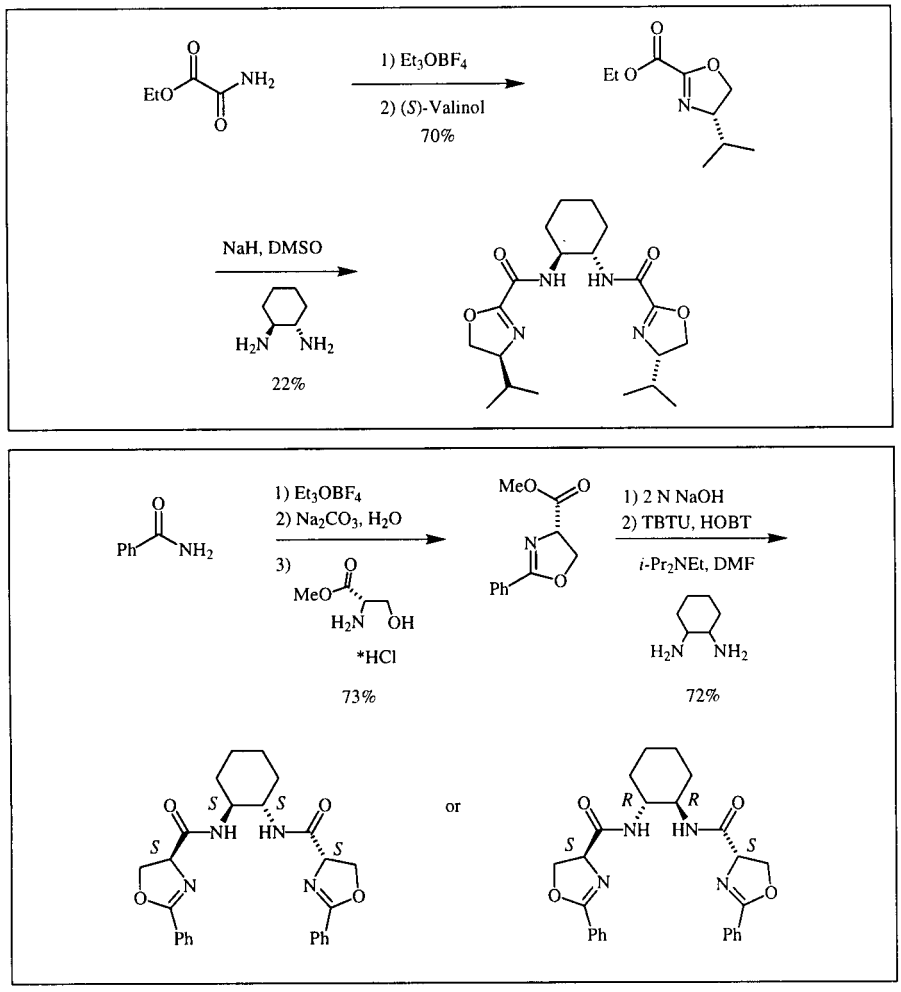
16

R = Pr	98% *ee*	8:1
R = Me	96% *ee*	11:1

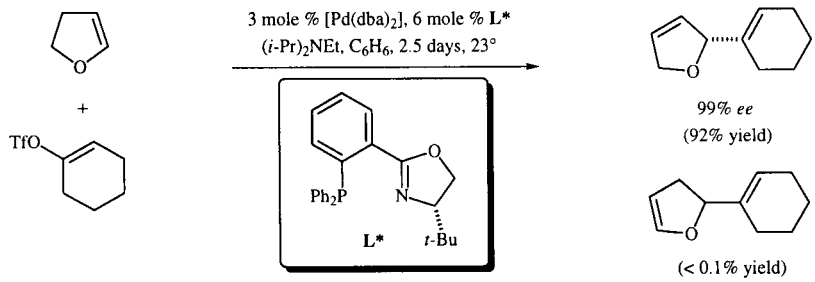
[23]. Since we had prepared related ligands of type **15** and **16** in the course of our work on bisoxazolines (*cf.* Scheme 8), we tested these ligands in molybdenum-catalyzed allylic substituions (Scheme 25) [24]. We found that the bipyridine **14** and the bisoxazolines **15** and **16** all gave excellent enantioselectivities with 1-alkylallyl carbonates. The results with ligands **14** and **16** were very similar, demonstrating that the main chiral control element is the diaminocyclohexane ring. In the case of crotyl methyl carbonate, the bisoxazoline **16** gave somewhat higher regio- and enantioselectvity. The synthesis of ligands of type **15** and **16** is shown in Scheme 26.

Although the phosphinooxazolines and related phosphite-oxazolines were originally developed for palladium-catalyzed allylic substitutions, they proved to be remarkably efficient controller ligands for other metal-catalyzed processes such as Diels-Alder reactions [25], transfer hydrogenation of ketones [26], Heck reactions (Scheme 27)

Scheme 26

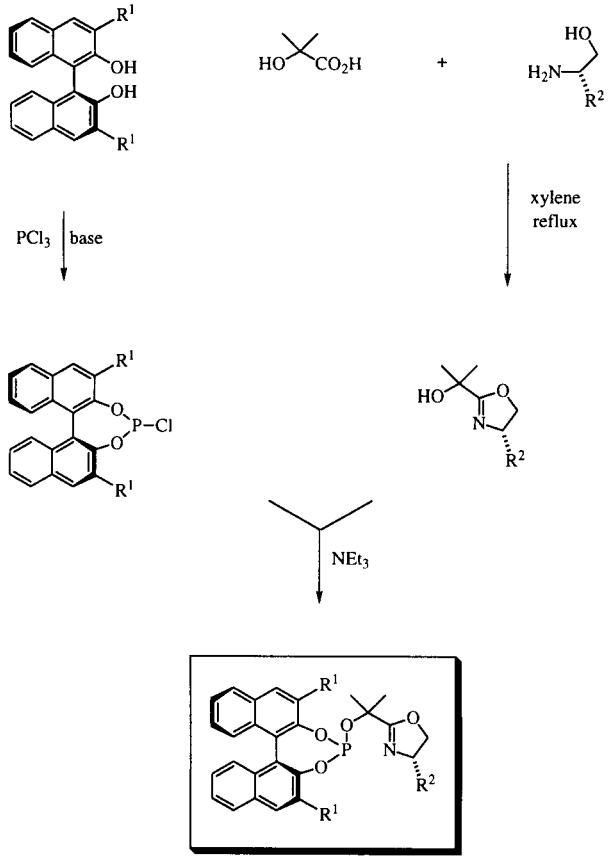


Scheme 27



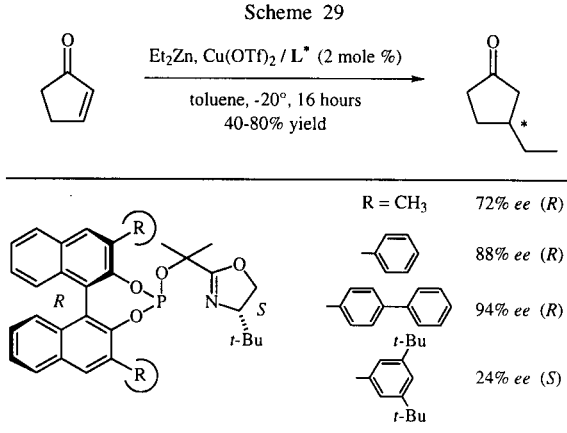
[27], conjugate addition of organozinc reagents to enones (Schemes 28 and 29) [28] and iridium-catalyzed hydrogenation of C=C and C=N double bonds [29,30].

Scheme 28

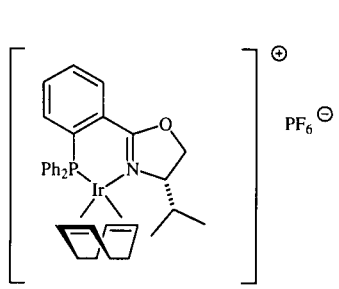


Phosphinooxazoline-iridium complexes (Scheme 30) are readily prepared and because they are air-stable, crystalline compounds, they are easy to handle. They are very

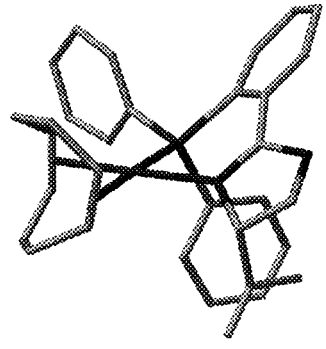
Scheme 29



Scheme 30



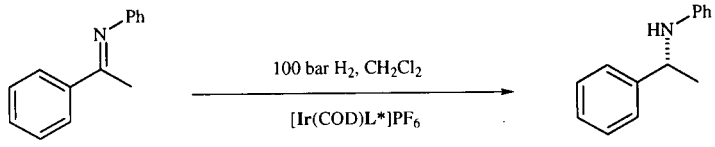
X-ray Analysis



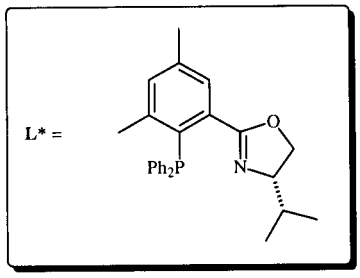
reactive catalysts for the hydrogenation of imines [29]. The best results are obatined with *N*-aryl imines derived from aryl alkyl ketones (Scheme 31). At pressures between 10-100 bar, high turnover numbers and turnover frequencies are observed, with *ee*'s in the range of 70-90%. These cationic iridium complexes are also remarkably efficient catalysts for the enantioselective hydrogenation of unfunctionalized olefins (Scheme 32) [30]. The highest enantioselectivities in the hydrogenation of trisubstituted 1,2-diarylalkenes were obtained with the bis(*o*-tolylphosphino)-(*tert*-butyloxazoline) ligand.

A difficult problem which had to be solved was catalyst deactivation during the reaction (Scheme 33). After a long and often frustrating period of extensive experimentation, the use of tetrakis[2,6-bis(trifluoromethyl)phenyl]borate (BARF) as the counter ion instead of more common non-coordinating anions, such as hexafluorophosphate or tetrafluoroborate, finally brought the solution (Scheme 34). The BARF complexes display a much longer lifetime and exhibit high catalytic activity. Full conversion and virtually identical *ee*'s can be achieved in less than 2 hours using only 0.3 mole% of catalyst. Until now, unfunction-

Scheme 31

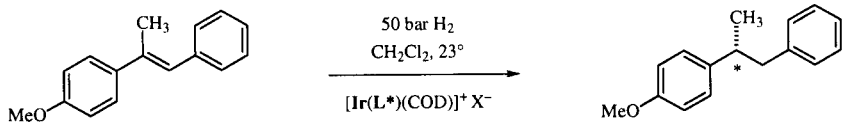


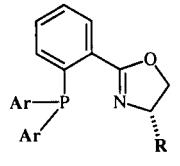
100% conversion



Temperature [°C]	Concentration of Imine [M]	Ir-Complex [mole %]	*ee* [%]
23	0.22	3.7	71
23	0.24	0.1	81
23	0.035	0.05	86
5	0.035	0.1	89

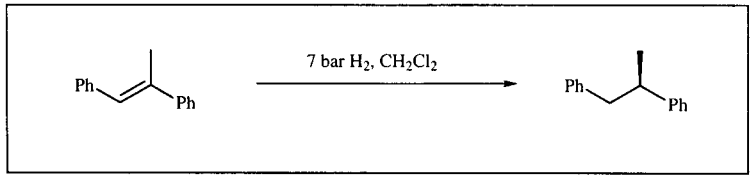
Scheme 32

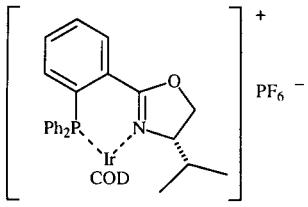




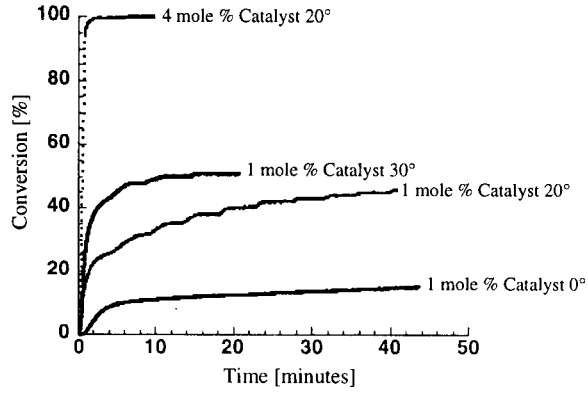
Ar	R	% *ee*
Ph	*i*-Pr	75
Ph	*t*-Bu	90
o-Tol	*i*-Pr	91
o-Tol	*t*-Bu	97

Scheme 33



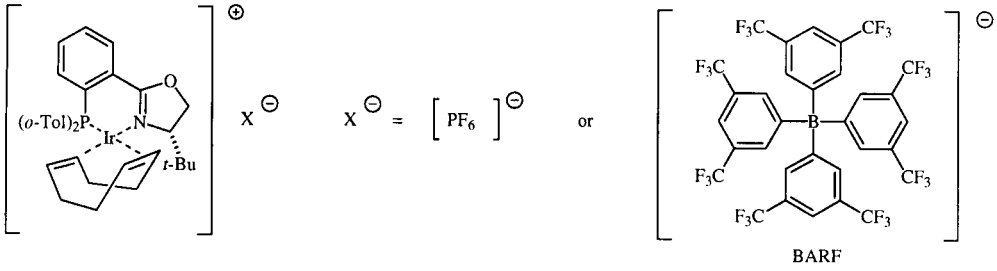


catalyst

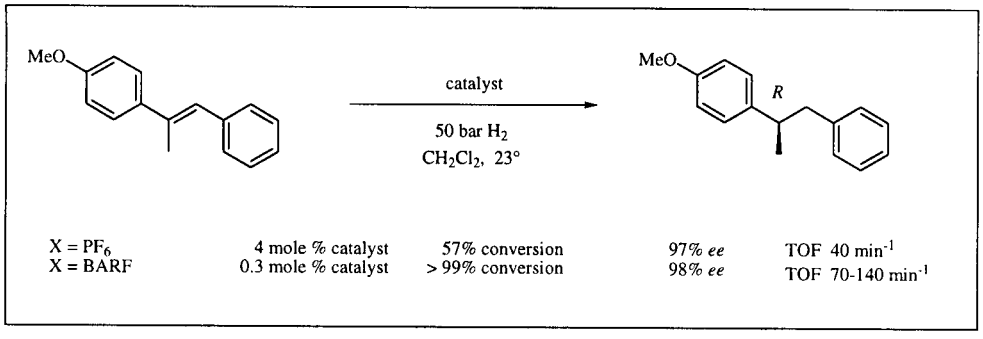


Scheme 34

Effect of the Counter Ion



BARF



alized olefins of this type could not be hydrogenated with high enantioselectivity at such low catalyst loadings (Scheme 35). Obviously, iridium complexes with chiral *P,N*-ligands are a promising new class of catalysts which enhance the scope of enantioselective hydrogenation. Interestingly, for more polar substrates such as α,β-unsat-

urated carboxylic esters or allylic alcohols, the PF_6 complexes are more efficient catalysts than the corresponding BARF complexes (Scheme 35).

The remarkable levels of selectivity achieved with phosphinooxazolines in various metal-catalyzed reactions demonstrate the considerable potential of *P,N*-ligands of this type in asymmetric catalysis. Phosphinooxazolines are very attractive ligands because they are readily synthesized in high enantiomeric purity from simple precursors. Furthermore, their modular strucure allows extensive structural variation of the backbone, the oxazoline ring and the phosphine part. In this way it should be possible to tailor the ligand structure for many other classes of metal-catalyzed reactions.

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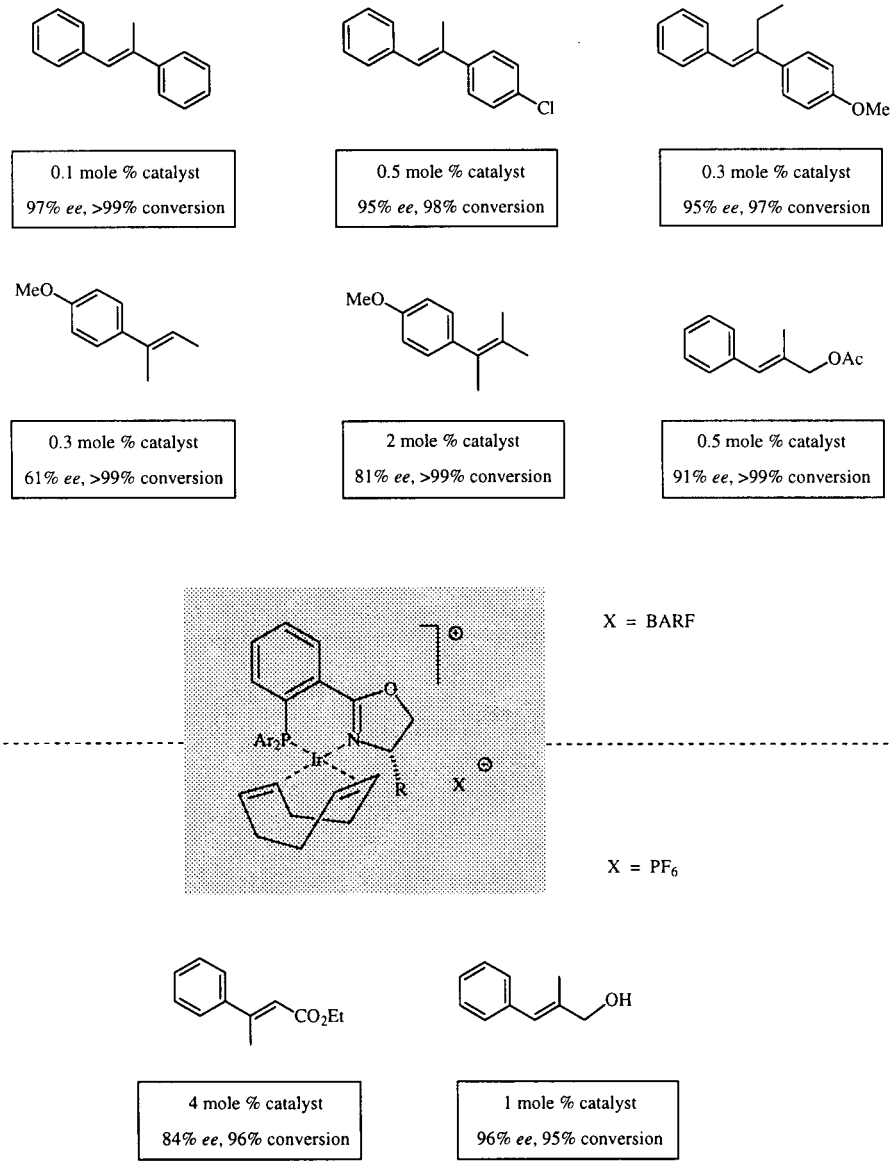
The work described herein has been carried out at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr and at University of Basel by a dedicated group of graduate students and postdocs whose names are listed in the references. I would like to thank them all for the fruitful collaboration and their enthusiasm and perserver-

Scheme 35



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