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Recent Developments in Asymmetric Catalysis

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Abstract: Asymmetric catalysis has long been dominated by C_2-symmetric bidentate ligands. More recently, sterically and electronically unsymmetrical ligands have found increasing attention. An important family of these are the phosphinooxazoline (PHOX) ligands incorporating one P-coordinating and one N-coordinating unit. Important applications of PHOX ligands include Pd-catalyzed allylic substitution and Ir-catalyzed hydrogenation.

Keywords: Allylic substitution · Asymmetric catalysis · Chiral ligands · Enantioselective hydrogenation

In the early days of the chemical industry, asymmetric synthesis played only a minor role. However, with the trend towards more and more complex target structures, especially in medicinal chemistry (Fig. 1), efficient enantio- and diastereoselective methods for the synthesis of chiral compounds have gained increasing importance. From an industrial perspective, the most attractive way to prepare an enantipure product is asymmetric catalysis [1]. The first breakthrough in this area came with the development of chiral rhodium-phosphine catalysts for the enantioselective hydrogenation of dehydroamino acid derivatives (Scheme 1).

This work has not only led to industrially feasible hydrogenation catalysts and many efficient, widely applicable phosphine ligands, but also to important general concepts and mechanistic insights that have laid the basis for the impressive progress asymmetric catalysis has made during the last decades.

For a long time, C_2-symmetric diphosphine ligands have dominated in asymmetric catalysis. However, more recently, a number of very promising monophosphines has been found, suggesting a considerable potential for this hitherto neglected class of ligands [2].

The benefits from 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 be necessarily superior to a non-symmetric counterpart. In fact, for certain reactions (*e.g.* hydrogenation [3]) convincing arguments can be found suggesting that non-symmetrical ligands with two different coordination sites could allow more effective enantiocontrol than C_2-symmetric ligands [4]. Josiphos and related diphosphines, developed by the former Ciba-Geigy team that is now part of Solvias, are good examples [5]. The spectacular results

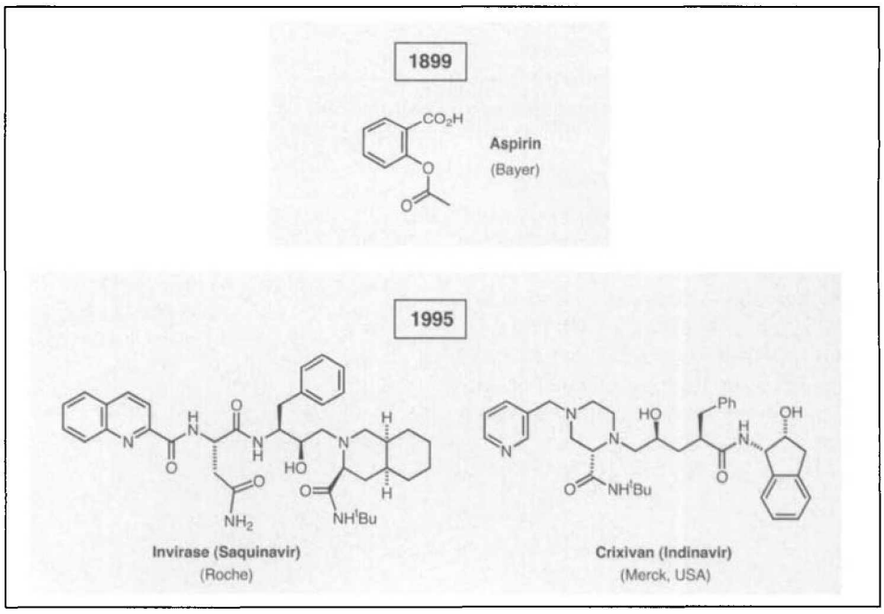

Fig. 1

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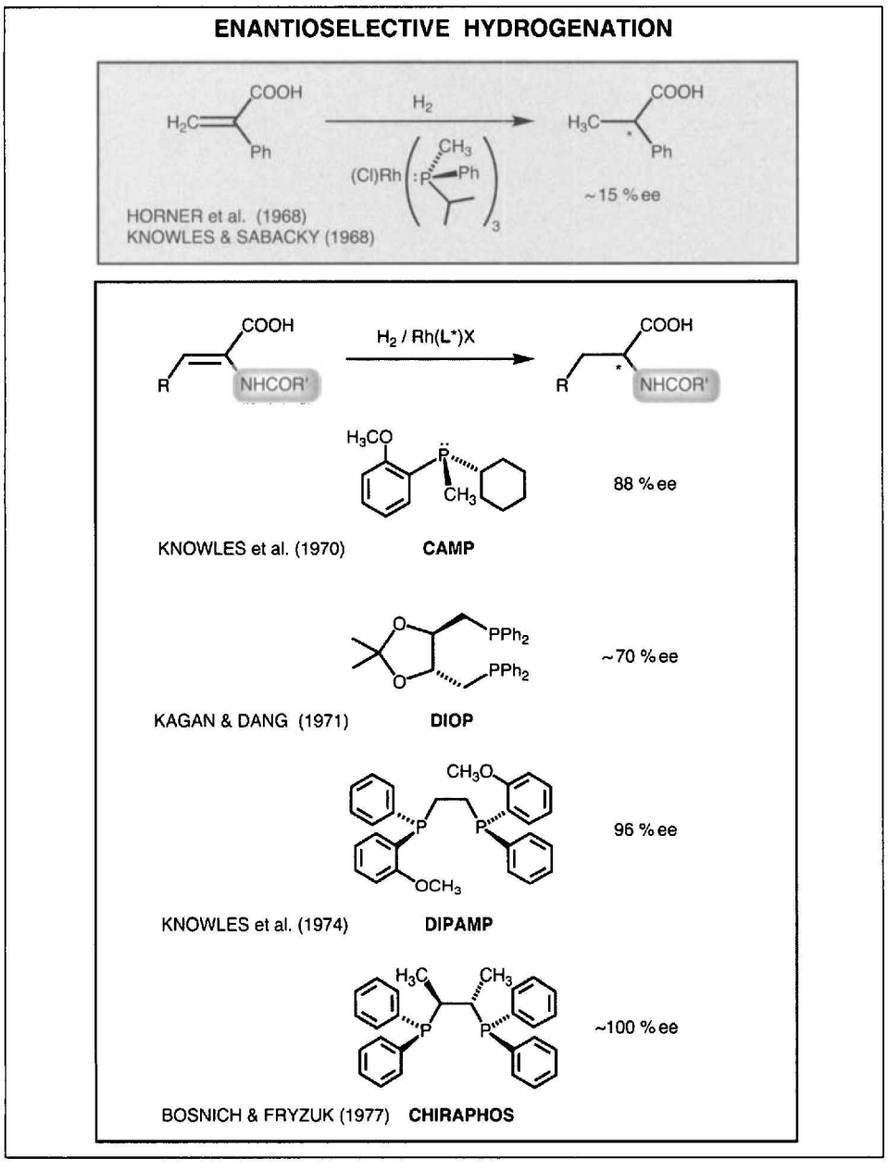
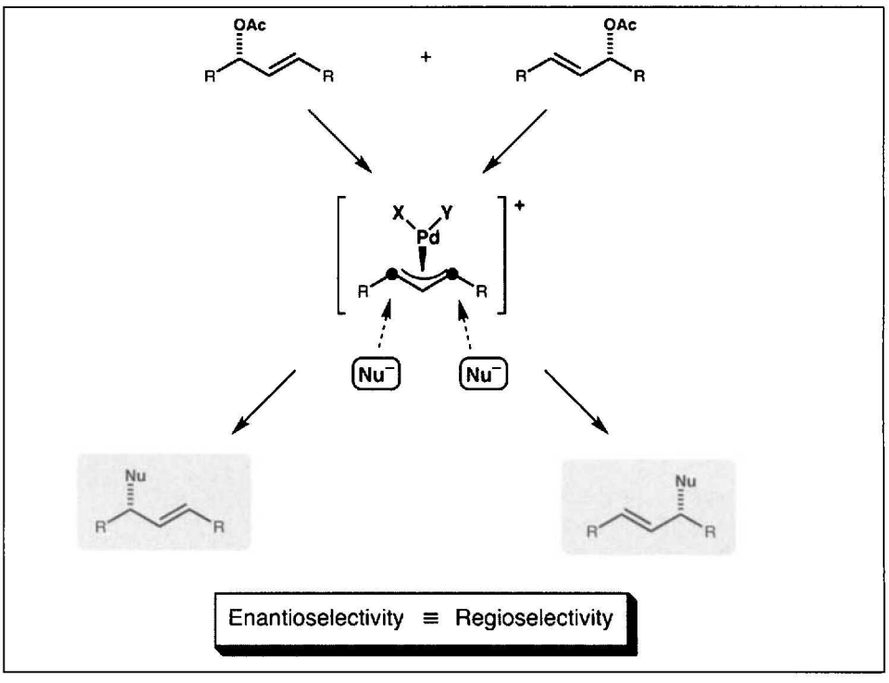
Scheme 1



achieved with these ligands (*e.g.* in the synthesis of metolachlor) are based on an individual structural optimization of the two coordinating phosphine groups.

Transition metal-catalyzed allylic substitution is another example [4][6]. In Pd-catalyzed substitutions *via* symmetric allyl complexes, the regioselectivity of nucleophilic attack determines the ratio of the two enantiomeric products (Scheme 2). If the metal center is coordinated by two electronically different groups X and Y, the two allylic termini become electronically non-equivalent and thus are expected to display different reactivity. Therefore, it can be argued that chiral ligands possessing two different coordinating atoms should allow more effective regiocontrol than C_2-sym-

Scheme 2

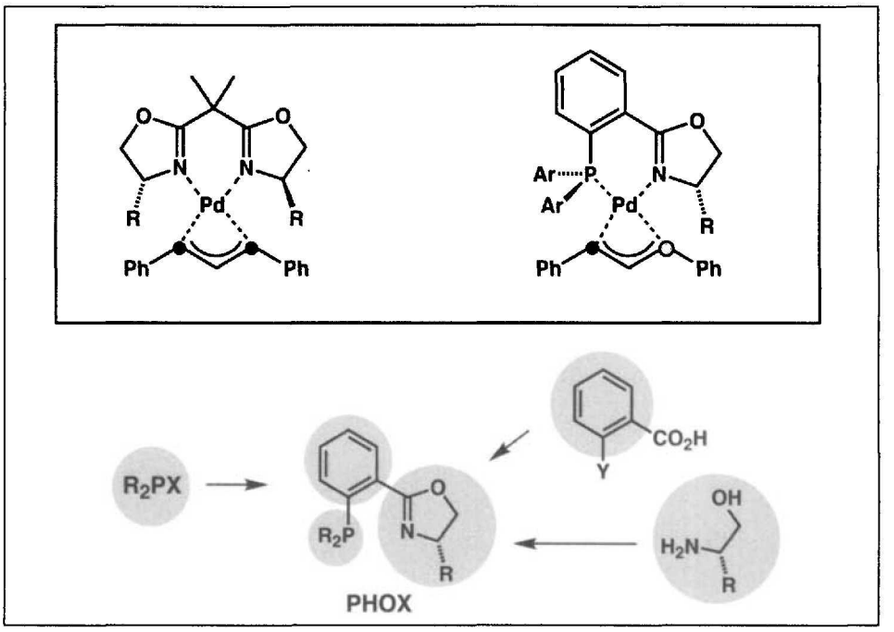


metric ligands. This led us and, independently, the groups of Helmchen and Williams to the phosphinooxazoline (PHOX) ligands (Schemes 3 and Fig. 2) [7][8]. These readily accessible, modular ligands indeed gave high enantioselectivities with symmetrically substituted allylic substrates and a range of C- and N-nucleophiles.

Chiral, enantiomerically pure palladium catalysts have also been used to control the regioselectivity of nucleophilic attack in reactions with non-racemic unsymmetrically substituted allylic acetates (Scheme 4) [9]. In contrast to reactions with achiral catalysts, where the regioselectivity is determined by the steric and electronic effects of the allylic substituents, chiral catalysts allow selective preparation of either one of the two regioisomers, depending on which enantiomer of the catalyst is employed. It is not necessary to start from an enantiomerically pure substrate, because the major and minor enantiomers are converted to different regioisomers (not to enantiomeric products), resulting in products of high ee, even if the starting material is only of moderate enantiomeric purity (Scheme 5).

So far, chiral catalysts have been used mainly to carry out enantioselective transformations of prochiral and racemic substrates, or diastereoselective reactions in which an additional stereogenic element is introduced into a chiral molecule under catalyst control (Scheme 6). As shown in Schemes 4 and 5, the specific interactions between a chiral catalyst and a chiral substrate can also be exploited for regiocontrol. The same concept has recently been used to control the regioselectivity in the nucleophilic ring opening of enantiomerically enriched epoxides [10] (for catalyst-induced regioselectivity in reactions of racemic substrates with chiral catalysts, see [11]). Moreover, a chiral catalyst can induce two completely different reactions of two enantiomeric substrates. A spectacular example is the decomposition of racemic 2-cyclohexenyl diazoacetate catalyzed by a chiral rhodium catalyst which converts one enantiomer to cyclohexenone by fragmentation while the other enantiomer undergoes intramolecular cyclopropanation [12]. Thus, a considerable potential of chiral catalysts for different types of reaction control can be envisaged, extending to areas of application beyond asymmetric catalysis.

Most palladium catalysts react with monosubstituted allyl derivatives predominantly at the unsubstituted terminus to give an achiral linear product. However, by structural variation of the ligand structure, it was possible to revert the regioselectivity in favor of the chiral branched products [13][14].



Scheme 3

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 [15]. The best results were obtained with N-arylimines derived from aryl alkyl ketones. At pressures between 10–100 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 (Scheme 7) [16].

Remarkably high enantioselectivities were obtained in the hydrogenation of trisubstituted 1,2-diarylalkenes (Scheme 8) [17]. A difficult problem, which had to be

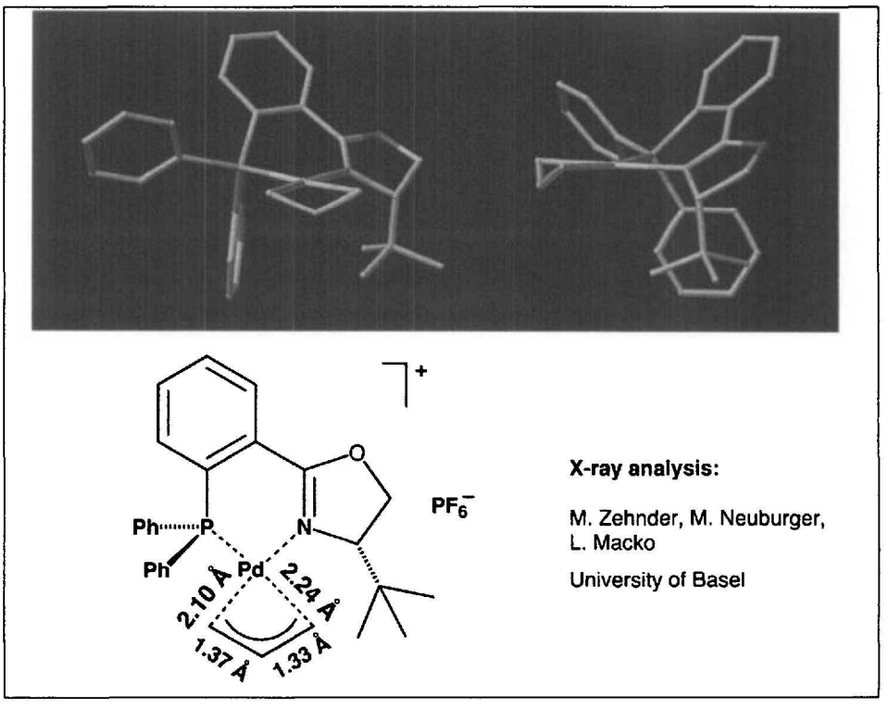
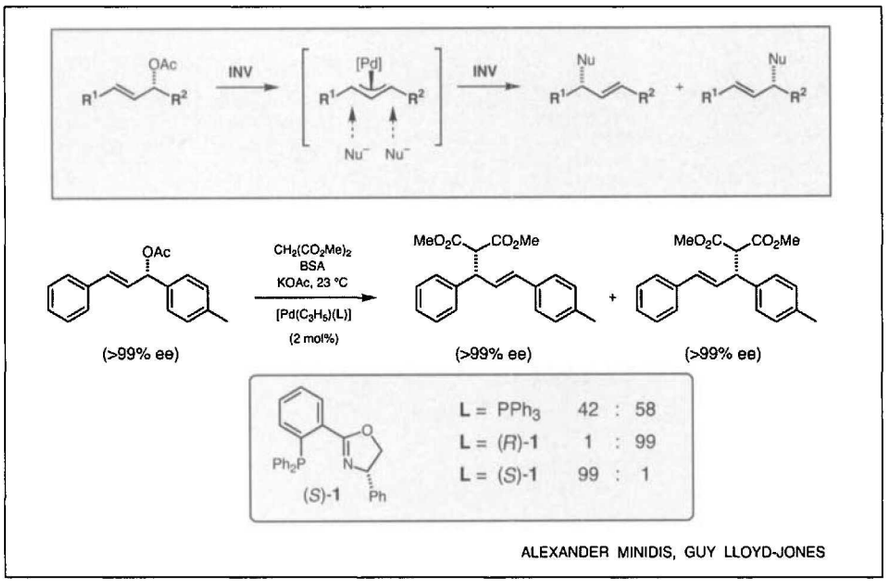
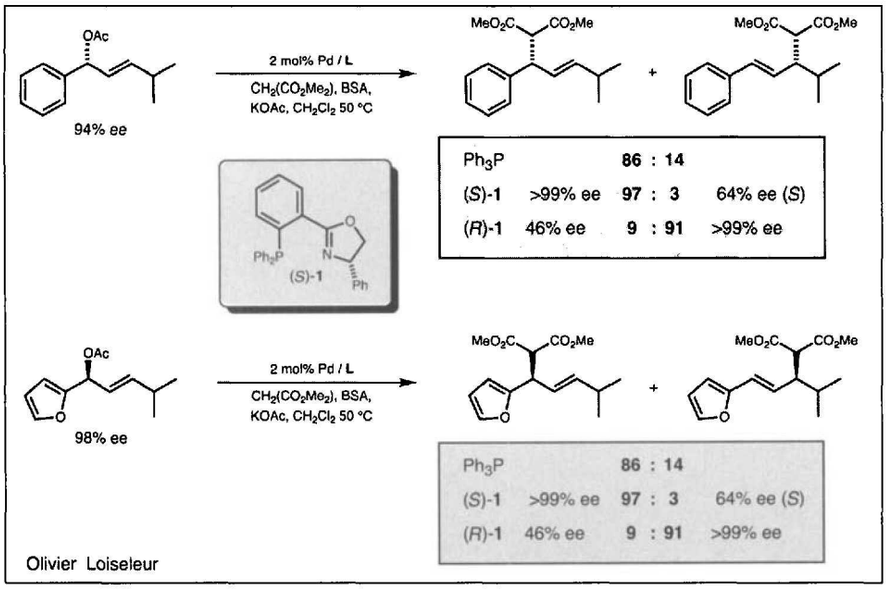


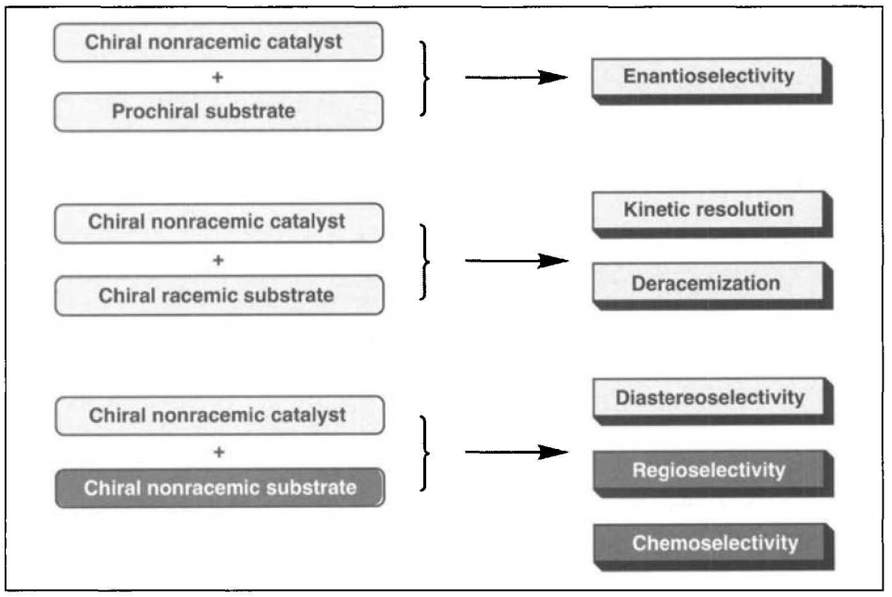
Fig. 2



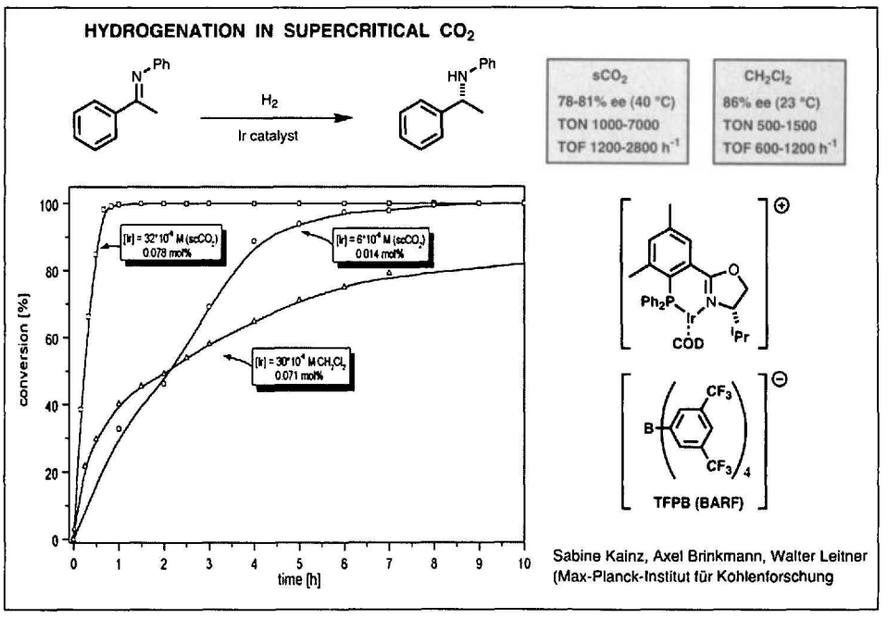
Scheme 4



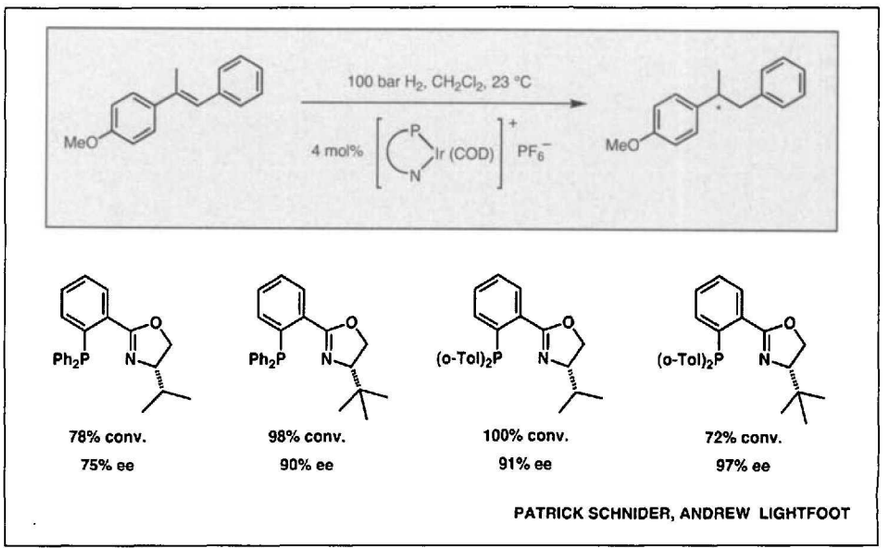
Scheme 5



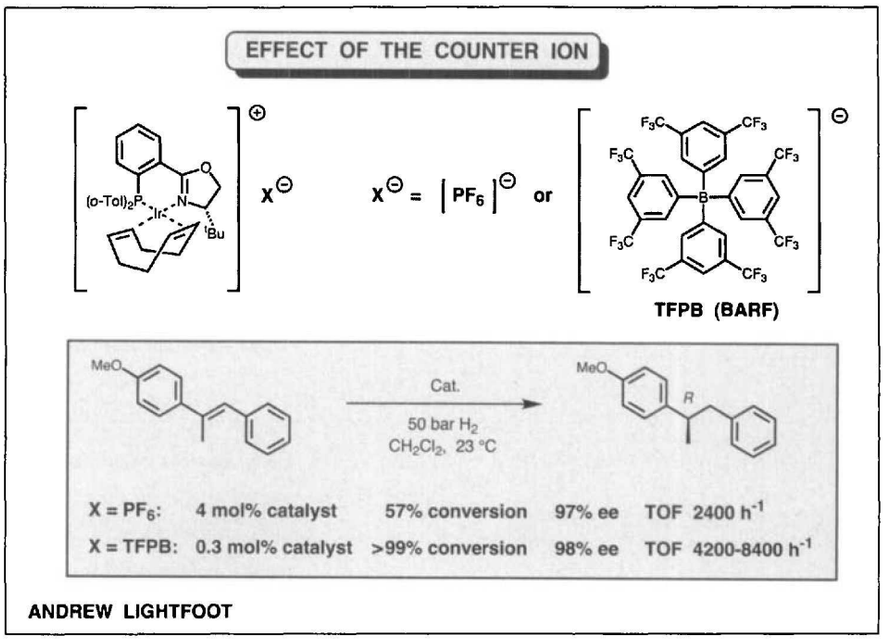
Scheme 6



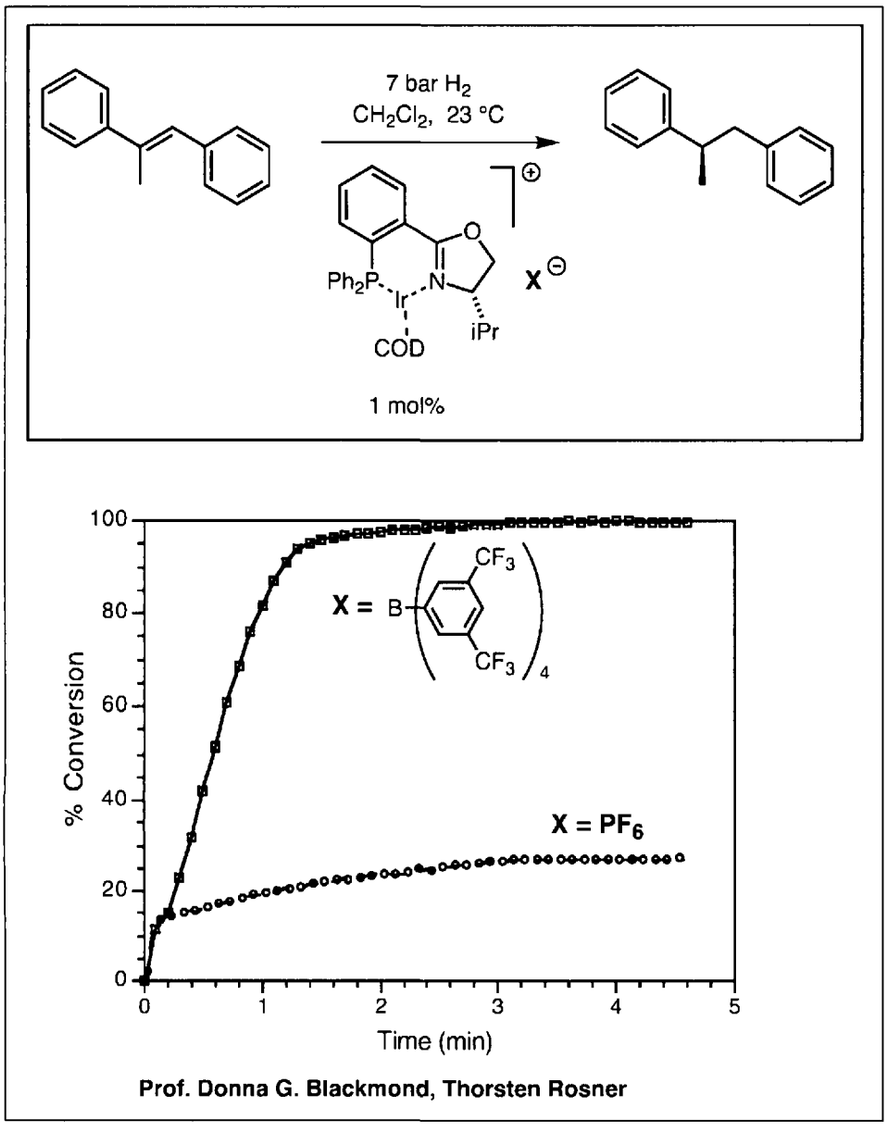
Scheme 7



Scheme 8

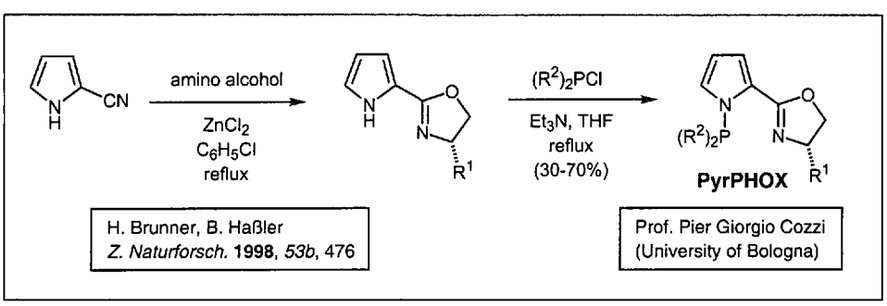


Scheme 9



Scheme 10

solved in this case, was catalyst deactivation during the reaction. After a long and often frustrating period of extensive experimentation, the use of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB or BARF) as the counter ion instead of more common non-coordinating anions, such as hexafluorophosphate or tetrafluoroborate, finally brought the solution. The TFPB salts display a much longer lifetime and exhibit high catalytic activity (Schemes 9 and 10). Full conversion and virtually identical enantioselectivities can be achieved in less than 2 h using only 0.05 mol% of catalyst. Until now, unfunctionalized olefins of this type could not be hydrogenated with high enantioselectivity at such low catalyst loadings.



Scheme 11

Motivated by these results, we set out to explore other types of P,N-ligands with the aim to expand the scope of this class of catalysts. Thus, we synthesized a series of pyridine- and quinoline-derived ligands [18], phosphite- and phosphinite-oxazolines [14] as well as the PyrPHOX ligands shown in Schemes 11 and 12 [19]. Some of these new ligands gave very encouraging results with enantioselectivities surpassing those of Ir-PHOX catalysts. The range of P,N-ligands, that we have available now, allows us to hydrogenate many different olefins with high efficiency and unprecedented enantiomeric excess (Fig. 3).

Phosphinooxazolines, originally developed for the enantiocontrol of Pd-catalyzed allylic substitution, have emerged as a highly versatile ligand class for asymmetric catalysis. The numerous successful applications of phosphinooxazolines have encouraged us and other groups to develop other P,N-ligands with N-heterocycles as coordinating groups. Considering the modular nature and the easy access to structures of this kind, P,N-ligands will undoubtedly play an important role in the future development of asymmetric catalysis.

Acknowledgements

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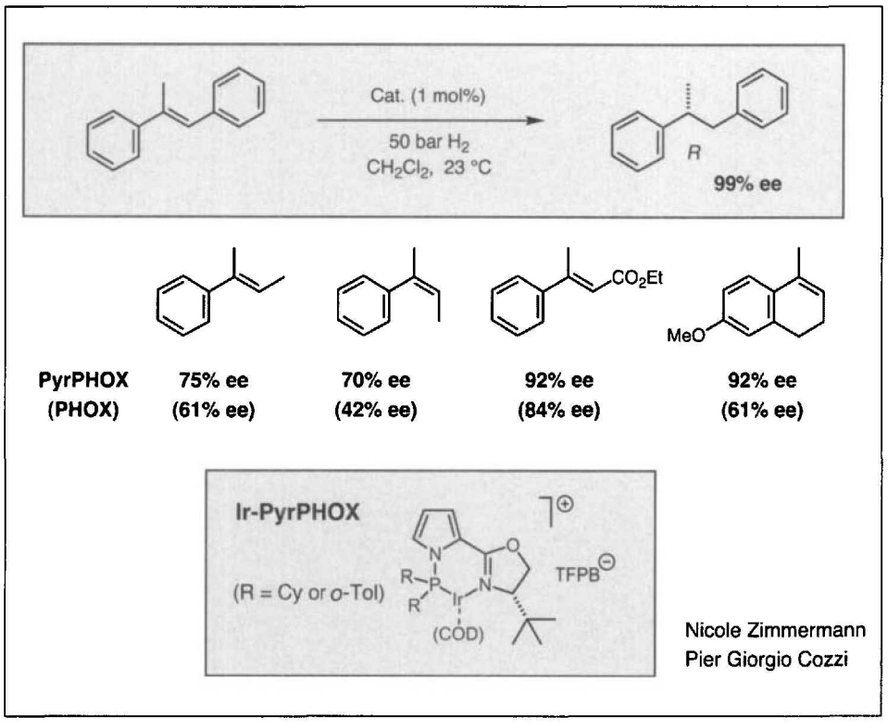

Scheme 12

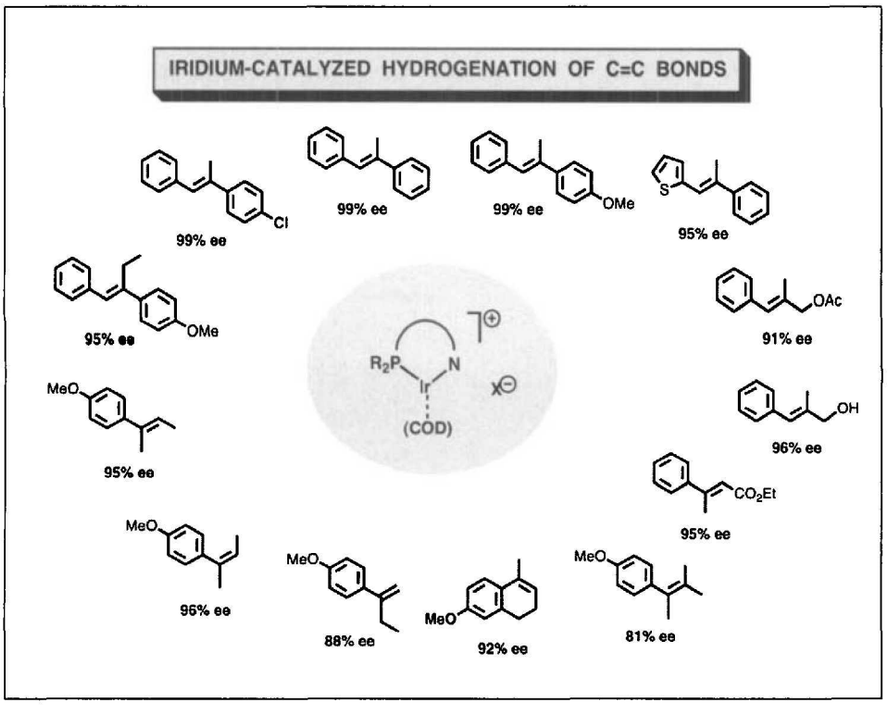

Fig. 3

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