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Ligand Development for Asymmetric Catalysis from a Historical and Didactical Perspective

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Abstract: The development of chiral ligands for enantioselective catalysis has been and still is characterized by some elements of rational design and a lot of trial-and-error experimentation.

Keywords: C_2 Symmetry · Chiral ligands · Enantioselective catalysis · Rational design

When teaching transition-metal catalysis, *e.g.* in a course on organometallic chemistry, as I did during more than two decades with a focus on enantioselective transformations, one is confronted with an ever increasing variety of chiral ligands. I always thought that it is important to convey, or at least try to convey, why a particular ligand or ligand type will lead to high selectivities in a chosen reaction while others do not. This is a complex and multifaceted question to answer. Explaining why a ligand will afford 99% *ee*, whereas another having an even only slightly modified structure will not go beyond 20% *ee* in the same reaction, is tightly related to the availability of a thorough mechanistic understanding of the reaction, including knowledge of the structure of the involved complexes. However, this knowledge may not yet be available at the time when a particular ligand is experimentally found to afford high (or low) selectivities. So the next question arises: What are the reasons and criteria for choosing a specific structure and not another? In modern terms this question addresses the issue of the *design* of ligands. Design is often explicitly and sometimes boastfully claimed in the newer literature and much less so or not at all in older pioneering works. Claiming design implies a level of rationality and planning clearly surmounting an essentially empirical approach. Furthermore, one would expect from rational design at least some degree of predictability of the outcome. But how much design is there really in this sense in ligand design?

With these questions in mind, the following considerations are intended to critically shed some light on the tortuous course of ligand development and are largely inspired by my own teaching. Thus, let us first examine the development of chiral diphosphines for the classical Rh-catalyzed hydrogenation of derivatives of dehydroamino acids, work that started in the 1960's and culminated with the first industrial application of this reaction for the synthesis of L-DOPA, introduced in 1974.[1] It all began with the obvious aim of making chiral derivatives of the Wilkinson catalyst, [RhCl(PPh$_3$)$_3$]. Pioneers of this endeavor were Knowles[2] and, independently, Kagan,[3] and then later Bosnich,[4] and the respective coworkers. Fig. 1 shows the classical ligands associated with these research groups.

What are the criteria these ligands fulfill and why have they been conceived, prepared, and used in asymmetric hydrogenation?

1) The monodentate ligand CAMP satisfies the condition of being chiral by virtue of its stereogenic and configurationally stable phosphorus atom. Ligands having a stereogenic center directly interacting with the metal center have been used also later in the history of asymmetric catalysis because they 'bring chirality as close as possible to the center of chemical action', so to speak. Alternatively, so-called 'chiral-at-metal' catalysts, *i.e.* catalysts containing a stereogenic metal center, have been inspired by an analogous reasoning.[5] Intuitively, this may sound like a sensible, even rational point. However, in view of the fact that chirality is not just the local property of a single atom but that of the molecule as a whole, this appears to be somewhat naïve, despite the success of some ligands and/or complexes of this type.

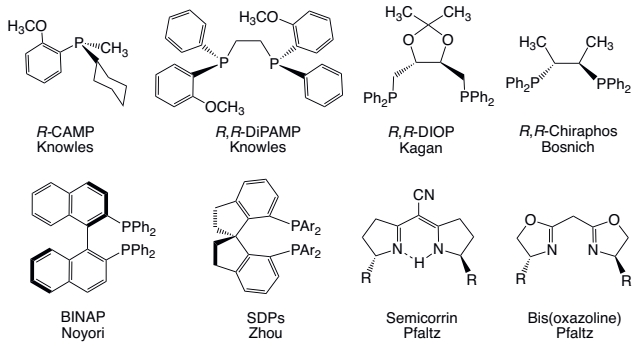

Fig. 1. The classical ligands developed for the Rh-catalyzed hydrogenation of dehydroamino acid derivatives (first row) and examples of C_2-symmetric bidentate ligands developed later (second row)

2) DIPAMP, DIOP, and Chiraphos are chelating C_2-symmetric diphosphines, conceived as such for two main reasons, these being a) the higher stability of the involved complexes (lower degree of dissociation of the chiral ligand) and b) the lower number of possible diastereomers and diastereomeric transition states involved in the catalytic cycle. In the words of Kagan, referring to DIOP:

"*A high degree of stereoselectivity in asymmetric catalysis requires catalysts which exhibit the following properties. (1) The ligand conformations must have maximum rigidity. (2) In order to avoid epimerization equilibria, ligands must stay firmly bonded to the metal. (3) Owing to their chelation power, diphosphines fulfill both these conditions. In addition, we wanted to avoid the possibility of geometric isomerism about the rhodium and thus chose a diphosphine having two equivalent phosphorus atoms. An easily accessible natural product, l(+)-tartaric acid, was chosen as the starting material.*"[6]

These arguments actually sound like sensible and realistic elements of rational design, in modern terms, and still represent some of the most sound thoughts ever expressed in this area of chemistry, despite their simplicity and their being devoid of an absolute general validity.

In fact, they persisted in this form and influenced the development of new ligands for years to come. C_2 Symmetry,

in particular, quickly mutated into a generally accepted dogma, as also previously noted by *e.g.* Feringa,[7] Noyori's BINAP,[8] Pfaltz's semicorrins and bis(oxazolines),[9] and more recently chiral ligands based on the 1,1-spirobiindane scaffold[10] are prominent examples implicitly paying heed to the dogma (see Fig.1).

The success of chelating ligands – not only bi- but also tri- and tetradentate – have only temporarily undermined the development of monodentate ligands. Whereas enantiopure P-stereogenic phosphines are often relatively difficult to prepare, phosphoramidites (see example in Fig. 2) may be accessed from chiral diols and a secondary amine in two steps from PCl_3 and are thus synthetically very versatile or modular.[7] Both the diol and the amine are often C_2-symmetric, although the resulting phosphoramidite is not because of the pyramidalization of both P and N atoms. The synthetic modularity of this type of ligand can surely be viewed as an important element of design. Correspondingly, a large number of phosphoramidites have been prepared and adapted to the needs of specific reactions. Furthermore, one important aspect of these ligands is that at least two of the substituents on the P atom need to be relatively bulky. Steric encumbrance of the substituents on the two N atoms is also a must in the case of chiral NHC ligands (NHC = N-heterocyclic carbene, see examples in Fig. 2).[11] Also in this case, chirality is usually introduced by means of the stereogenic groups on the N atoms and when these two substituents are identical, the whole ligand will be C_2-symmetric. A peculiarity of both phosphoramidites and NHC's is that they may undergo cyclometallation upon C–H activation of *e.g.* a methyl group in close proximity of the ligating atom, thus becoming bidentate. Such reactions are most likely not part of the original design but may be necessary for the functioning of the corresponding catalyst.[12]

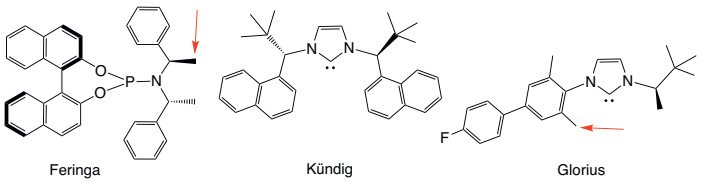

Fig. 2. Examples of phosphoramidite and carbene (NHC) monodentate ligands. The arrow indicates a position susceptible of C–H activation, leading to a bidentate situation.

Going back to phosphines, a significant deviation from the dogma of C_2-symmetry came in 1974 when Kumada, Ito and Hayashi discovered that the functionalization of Ugi's amine[13] with one or two phosphino groups led to C_1-symmetric (dissymmetric) ferrocenyl ligands, such as BPPFA[14] (see Fig. 3) that were used in a variety of reactions in the following years. A design bonus, so to speak, of BPPFA and its congeners is that the amino side chain can be modified to play an active role in catalysis by undergoing specific attractive interactions with the coordinated substrate, thus significantly contributing to enantioselectivity.[15] This is the principle of 'secondary interactions'[16] that could have possibly been exploited more (by design) also in other ligand systems.

A further extremely important advance concerning completely dissymetric bidentate ligands came in form of the combination of a phosphine with an oxazoline, thus a compound type having P and N ligating atoms[17] and also displaying a high level of synthetic modularity.[18] These ligands, originally developed by Pfaltz and Helmchen independently, have been extremely successful in Pd-catalyzed allylic substitutions and Ir-catalyzed hydrogenations

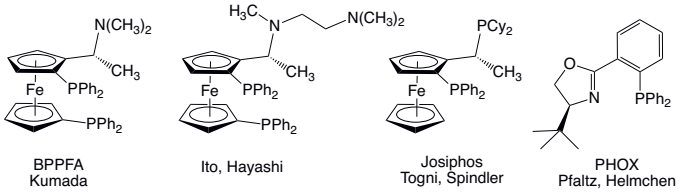

Fig. 3. Examples of C_1-symmetric (dissymetric) ligands having two constitutionally different P atoms or combining P and N donor atoms.

and have probably marked the ultimate departure from the C_2 symmetry dogma.

I have been involved with ferrocenyl ligands since 1986, in particular with the development of *Josiphos* (see Fig. 3). The original conception of this ligand was uniquely guided by the intention of making the bidentate ligand as dissymmetric as possible, by introducing two sterically and electronically different phosphino groups, in the first place *because* this was synthetically very easy to achieve – Is this 'design'? Actually, I never claimed this! The straightforward two-steps introduction of the two P ligand fragments made the system to one of the most modular.[19] *Josiphos*-type ligands turned out to afford selectivities in Rh-catalyzed hydrogenations comparable to those obtained with classical C_2-symmetric ligands. However, if we had first tried *Josiphos* in reactions affording only very low selectivities, we might have come to the conclusion that it is a 'bad' ligand and would have possibly discarded it and gone over to looking for different structures. Moreover, if we had thought purely in terms of ligand design we would have had to admit that this was highly inappropriate. This tells us that effective design must include not only potential new ligands but must take into account also the specific transition-metal used in the specific chosen reaction, including structure of substrates and reagents. I would argue that there are not many examples of developments in asymmetric catalysis that are really the result of such a comprehensive design, as opposed to have been achieved mainly starting from and following a largely empirical approach.

Design must be interpreted as the formulation of hypotheses well rooted in detailed pertinent chemical knowledge that, as already mentioned, may or may not be available to a sufficient extent in advance. So how did ligand design progress during more than fifty years since the pioneering works of Knowles and Kagan? One of the important aspects has already been mentioned: modularity. Short syntheses from readily available chiral building blocks allow for fast modifications and is suited for high-throughput screening methods for optimization. So-called Trost ligands of the type shown in Fig. 4 are highly exemplary with respect to modularity and are broadly applicable in particular in highly selective Pd-catalyzed asymmetric allylic alkylations. However, the design process, as described in detail in the original publication,[20] did not take into account the fact that such ligands are able to create different coordination environments for both a Pd(0) or a Pd(II) center, *i.e.* P,P- P,O-coordination and the formation of oligomers, as discovered later. Given that P,O-coordination leads to catalysts affording only low selectivities, it is very important to carefully control the reaction conditions under which the catalytically active species is formed. Trost's ligands have thus remained very interesting for research groups looking precisely into such coordination-chemical aspects and taking care of characterizing complexes both in solution by NMR methods and by X-ray crystallography.[21]

Additionally and more in general, knowledge of essential coordination-chemical aspects, *e.g.* geometries, coordinative unsaturation, possible isomerizations, as well as mechanistically fundamental steps of organometallic chemistry, *e.g.* σ-bond

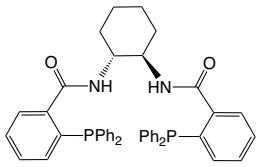

Fig. 4. One of Trost's ligands originally developed for Pd-catalyzed asymmetric allylic alkylations.

metathesis, the role of interactions between bulky aromatic groups, *i.e.* π-stacking, quantum-chemical methods for the elucidation of mechanisms, *etc.* have enormously advanced and should contribute to more reliable planning and predictions of new successful structures. Finally, it would be desirable to put the meanwhile very substantial body of experimental reaction data in asymmetric catalysis to more fruition by machine learning approaches.[22] The time appears to be ripe for this.

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[1] W. S. Knowles, *J. Chem. Educ.* **1986**, *63*, *222*, https://doi.org/10.1021/ed063p222.
[2] W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106, https://doi.org/10.1021/ar00087a006.
[3] T.-P. Dang, H. B. Kagan, *J. Chem. Soc. D* **1971**, 481, https://doi.org/10.1039/C29710000481.
[4] M. D. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **1977**, *99*, 6262, https://doi.org/10.1021/ja00461a014.
[5] L. Zjang, E. Meggers, *Chem. Soc. Rev.* **2025**, *54*, 1986, https://doi.org/10.1039/D4CS01043D.
[6] H. B. Kagan, T.-P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429, https://doi.org/10.1021/ja00773a028.
[7] J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486, https://doi.org/10.1002/anie.200904948.
[8] R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345, https://doi.org/10.1021/ar00178a005.
[9] A. Pfaltz, *Synlett* **1999** (*S1*), 835, https://doi.org/10.1055/s-1999-3122
[10] Y. Liu, W. Li, J. Zhang, *Nat. Sci. Rev.* **2017**, *4*, 326, https://doi.org/10.1093/nsr/nwx064.
[11] D. Janssen-Müller, C. Schlepphorst, F. Glorius, *Chem. Soc. Rev.* **2017**, *46*, 4845, https://doi.org/10.1039/C7CS00200A.
[12] J. H. Kim, S. Gressies, M. Boultadakis-Arapinis, C. Daniliuc, F. Glorius, *ACS Catal.* **2016**, *6*, 7652, https://doi.org/10.1021/acscatal.6b02392.
[13] D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389, https://doi.org/10.1021/ja00721a017.
[14] T. Hayashi, K. Yamamoto, M. Kumada, *Tetrahedron Lett.* **1974**, *15*, 4405, https://doi.org/10.1016/S0040-4039(01)92175-6.
[15] See e.g.: a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405, https://doi.org/10.1021/ja00280a056. See also: b) A. Togni, S. D. Pastor, *J. Org. Chem.* **1990**, *55*, 1649, https://doi.org/10.1021/jo00292a046.
[16] M. Sawamura, Y. Ito, *Chem. Rev.* **1992**, *92*, 857, https://doi.org/10.1021/cr00013a005.
[17] For a general review on chiral P,N-ligands, see: a) P. J. Guiry, C. P. Saunders, *Adv. Synth. Catal.* **2004**, *346*, 497, https://doi.org/10.1002/adsc.200303138. For a detailed analysis of steric and electronic factors governing enantioselectivity of a specific P,N-ligand, see: b) A. Togni, U. Burckhardt, V. Gramlich, P. S. Pregisin, R. Salzmann, *J. Am. Chem. Soc.* **1996**, *118*, 1031, https://doi.org/10.1021/ja953031g.
[18] G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336, https://doi.org/10.1021/ar9900865.
[19] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, , *116,* 4062, https://doi.org/10.1021/ja00088a047.
[20] B. M. Trost, D. L. van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327, https://doi.org/10.1021/ja00050a013.
[21] For selected contributions, see e.g.: a) J. Huang, T. Keenan, F. Richard, J. Lu, S. E. Jenny, A. Jean, S. Arseniyadis, D. C. Leitch, *Nat. Commun.* **2023**, *14*, 8058, https://doi.org/10.1038/s41467-023-43512-8. b) D. T. Racys, J. Eastoe, P.-O. Norrby, I. Grillo, S. E. Rogers, G. C. Lloyd-Jones, *Chem. Sci.* **2015**, *6*, 5793, https://doi.org/10.1039/C5SC01181G. c) C. Amatore, A. Jutand, L. Mensah, L. Ricard, *J. Organomet. Chem.* **2007**, *692*, 1457, https://doi.org/10.1016/j.jorganchem.2006.11.039.
[22] For examples, see: a) L. Morán-González, A. L. Burnage, A. Nova, D. Balcells, *ACS Catal.* **2025**, *15*, 9089, https://doi.org/10.1021/acscatal.5c01202 (AI approches to homogeneous catalysis). b) S. Singh, M. Pareek, A. Changotra, S. Banerjee, B. Bhaskararao, P. Balumurugan, R. B. Sunoj, *Proc. Nat. Acad. Sci. U. S. A.* **2020**, *117*, 1339, https://doi.org/10.1073/pnas.1916392117 (approach specifically concerning asymmetric hydrogenation). c) S. P. Schmid, L. Schlosser, F. Glorius, K. Jorner, *Beilstein J. Org. Chem.* **2024**, *20*, 2280, https://doi.org/10.3762/bjoc.20.196 (a review on machine learning in asymmetric organocatalysis).