Giambattista Consiglio (photograph by *S. Lindig*, Zurich)

Giambattista Consiglio's Passion for Homogeneous Catalysis, C–C Bond Formation, and Stereochemistry

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As we asked our mutual friend *Giambattista* (*Gianni*) *Consiglio* to define himself during a sort of scientific interview, he simply told us: '*I'm an organic chemist interested in the synthesis of small molecules*'. This may surprise more than one, considering that he has dedicated his whole scientific life to the study of transition metals, with a strong overtone on polymerization. However, the statement sounds perfectly logical if one considers that the goal of his research was the understanding of mechanistic details of stereoselective transformations of organic molecules induced by transition-metal complexes, and that a polymer is nothing else than the repetition of a small molecule. Indeed, browsing through his more than 150 publications, one central and fundamental topic emerges as *fil rouge*, that is, the control of stereochemistry in the C–C bond formation in metal-mediated reactions.

Asymmetric catalytic hydroformylation is one of *Gianni*'s pioneering contributions [1]. As he would tell you, his initial interest was very much driven by the curiosity about fundamental aspects, whereas potential application still remained in the background. The proof of concept was obtained with Rh^I complexes modified with chiral diphosphines, but the enantioselectivity with aliphatic olefins was discouragingly low [2]. Interestingly, the investigations with Co^I and Rh^I hydroformylation catalysts also revealed the first example of chain walking [3]. Finally, the breakthrough came with the development of the $[PtCl_2(P{-}P^*)]/SnCl_2$ catalyst (where P–P* is a chiral diphosphine), which converted styrene to 2-phenylpropanal (80% regioselectivity) with an enantioselectivity of up to 86% ee [4].

These studies provided intriguing insights into the mechanism of enantioface selection upon olefin coordination and into the stereochemistry of addition to the coordinated olefin. The latter is a complicated process that involves four diastereoisomeric transition states [1]. Since the early 1990s, *Gianni*'s curiosity for the stereochemical aspects of olefin coordination and insertion drew his interest to the carbon monoxide (CO)/alkene copolymerization reaction [5], which was a hot topic both in the academic world and in industry at that time because of the announcement of the commercial exploitation of polyketones. His dual interest in polymers and short-chain carbonylation products resulted later in an intense cross-fertilization that culminated, on the side of the 'small molecules', in the highly enantioselective synthesis of dimethyl phenylsuccinate and of substituted 2-oxoglutarates by double alkoxycarbonylation or by triple carbonylation of olefins [6][7], and led to important stereochemical insight [8].

Obviously, *Gianni*'s interest was drawn to the CO/alkene copolymerization by the fact that polyketones of terminal alkenes are chiral and, therefore, potentially optically active (*Fig. 1*), whereas the corresponding polyolefins are not. The development of catalytic systems to control the stereochemistry of the polymer was definitely a challenge, and comprehensive studies were started with palladium and platinum catalysts containing bidentate ligands (L–L). In an early fundamental contribution, he pointed out that N-donor ligands are required for the Pd-catalyzed copolymerization of aromatic alkenes with CO, whereas phosphine complexes give monocarbonylation only, and discussed this fact in the light of the effect of L–L on the stereochemical outcome of styrene insertion into the palladium–hydrocarbonyl bond. In fact, 1,10-phenanthroline gives branched carbonylation products from secondary insertion, whereas diphosphines favor linear products [9].

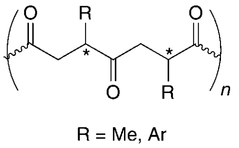


Fig. 1. *A generic polyketone chain*

To unravel the factors that determine enantioface selection during the chain growth required development of new techniques. Thus, the microtacticity of the CO/styrene polyketone was assessed by analyzing the *ipso*-C-atom region of the ^{13}C-NMR spectra [10], which showed that the Pd^{II} catalysts with C_{2v}-symmetric N–N ligands give such polyketones with a syndiotactic microstructure under chain-end control [11].

Furthermore, the use of different classes of ligands (*Fig. 2*) opened the way to the control of regio- and stereochemistry. Previously unknown polymeric materials, such as non-regioregular CO/styrene polyketones, were prepared by exploiting the tunability of hybrid P–N ligands [12][13]. The closely related N–N* ligands in *Fig. 2* led to the definition of the principle of site-selective coordination of the alkene before migratory insertion takes place [14][15]. The study of cationic Pd complexes with either *meso* or enantiomerically pure chiral bisoxazolines revealed that the counter-ion affects the configuration of the CO/styrene copolymer [16][17].

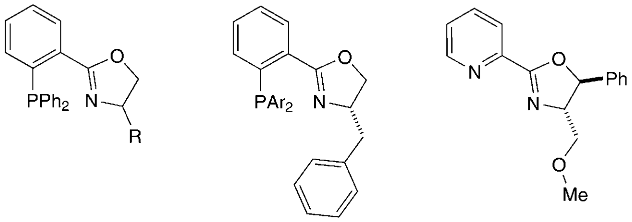


Fig. 2. *Examples of P–N* and N–N* ligands*

Besides styrene, propene was studied in the copolymerization with CO. Starting from early attempts with diphosphine-palladium complexes, which were neither regio- nor stereoregular [18], *Gianni* has developed systems based on P–P ligands (*Fig. 3*) that allowed him to prepare regioregular CO/propene polyketones with either isotactic or atactic microstructures. In particular, the Pd catalysts with the bulky, optically active P–P ligands (*Fig. 3,b*) promoted the synthesis of a regioregular, isotactic CO/propene copolymer possessing a high degree of stereoregularity (up to 96% of the *l*-diads) [19]. The electronic tuning of the 1,2-bis(diarylphosphinomethyl)benzene ligands (*Fig. 3,c*) produced a catalytic system for the isotactic CO/propene copolymer, despite the achiral nature of P–P [20].

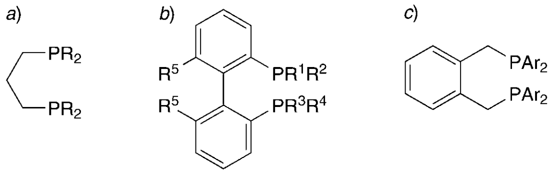


Fig. 3. *Some of the diphosphines ligands used*

On the same lines, *meso* P–P ligands (*Fig. 4,a*) turned out to perform much better than the corresponding racemic derivatives in terms of productivity, regioregularity, and stereoregularity in the CO/propene copolymerization, and give the most isotactic CO/propene ever produced [21]. Finally, the steric and electronic optimization of chiral diphosphinoferrocene ligands of the Josiphos family showed that the electronic effects of the donors boost the productivity of the Pd catalyst in the CO/propene copolymerization, with the electronic asymmetry of the P-donors and the 3,5-disubstitution of one Ar_2P group playing a pivotal role [22]. The success of such low-symmetric ligands prompted *Gianni* to tailor a new family of C_s-symmetric diphosphines based on the

1,2-bis[di(aryl)phosphinomethyl]benzene skeleton (*Fig. 4,b*) [23]. Although these ligands gave isotactic CO/propene polyketones instead of the desired syndiotactic copolymer, the results validated the principle of site-selective coordination of the alkene even in the case of propene.

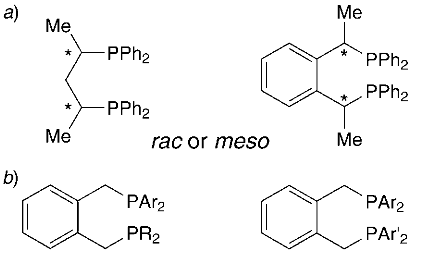


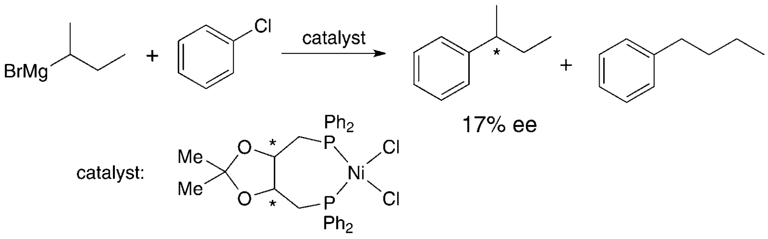
Fig. 4. *The racemic and* meso *P–P ligands investigated*

As a natural extension of the above studies, *Gianni* also studied the CO/ethylene/styrene terpolymerization [24][25]. Chiral (dihydrooxazole)(phosphino)palladium complexes with the hybrid P–N ligands of *Fig. 2* gave the optically active CO/ethene/styrene terpolymer with a very high enantioface selection, regardless of the nature of the last inserted alkene (either ethene or styrene) into the polymeric chain, as observed for the corresponding CO/styrene copolymer. Moreover, this study showed that, despite the higher reactivity of styrene with respect to ethene in the copolymerization, ethene is preferentially enchained in the terpolymer.

The above description might convey the impression that *Gianni*'s research interests have been completely absorbed by carbonylation reactions. This is not the case, though. Simultaneously to his early studies on hydroformylation, which were developed in collaboration with the late Prof. *P. Pino*, *Gianni* started independent investigations, first outcome of which was the discovery of the asymmetric cross-coupling of racemic haloalkenes. His 1973 publication on the enantioselective Ni-catalyzed coupling of secondary racemic *Grignard* reagents with PhCl or CH_2=CHCl (*Scheme 1*) [26] appeared just one year after the report of *Kumada* and co-workers [27] of the non-enantioselective version of this hitherto unknown reaction. Furthermore, he got ahead of *Kumada* himself, who published the same asymmetric Ni-catalyzed process one year later [28].

These early results triggered pioneering stereochemical investigations aimed at unveiling the mechanism of stereoselection of metal-mediated C–C bond formation, which were soon extended to related fields, in particular, to allylic alkylation. These studies produced the first well-documented example of an alkylation reaction that

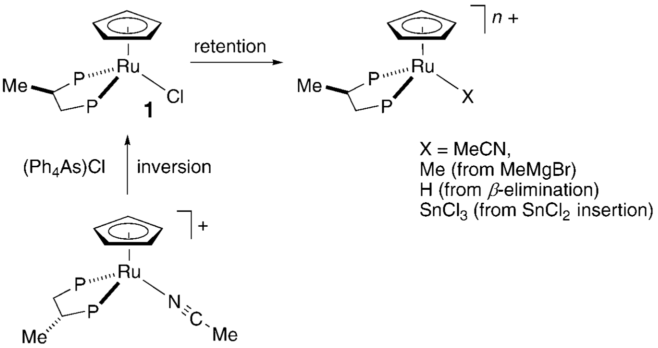
Scheme 1. *The First Asymmetric Cross-Coupling Catalytic Reaction*



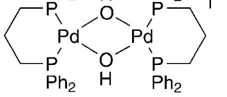
takes place at a d^8 metal center in a stereospecific way with net inversion of configuration [29]. *Gianni*'s peculiar encyclopedic knowledge of the literature enabled him to produce, together with *R. M. Waymouth*, a much-cited review article on such an enormous research field as enantioselective catalytic allylation [30].

In the quest for a deeper stereochemical understanding of olefin coordination, *Gianni* started a joint project with *Franco Morandini*, who was sort of a 'permanent visiting' fellow at the ETH Zürich at that time [31], on chiral half-sandwich complexes of type **1** (*Scheme 2*) [32]. This fruitful collaboration sparked fundamental insight into the stereochemical course of simple metallorganic reactions. Many stereospecific substitution reactions at stereogenic Ru-atom were identified. In most cases, they occur with retention of configuration, such as alkylation, β-hydride elimination, insertion of carbene and CS_2 into Ru−H, and of $SnCl_2$ into the Ru−Cl bond, and Cl displacement by MeCN [32]. Surprisingly, the substitution of MeCN by Cl, which is the reverse of the latter reaction, is a rare case of prevailing inversion of configuration (albeit with low levels of stereospecificity; *Scheme 2*) [33].

Scheme 2. *Stereochemical Course of a Selected Reaction of* **1**



Ironically, the reactions involving olefins, which had been the driving force of the project, exhibited low levels of stereocontrol. Thus, the displacement of the Cl ligand by an olefin exhibited low stereospecificity, and the enantioface selection in the diastereoisomeric equilibria of Ru half-sandwich complexes with prostereogenic olefins was low, too. Despite the fact that these studies did not produce immediate fallout in asymmetric catalysis, the last sentence of the review was prophetic in suggesting the application of chiral half-sandwich complexes as catalysts for *Lewis* acid induced reactions [32], a statement that clearly inspired further developments. On the same topic of *Lewis* acidic catalysts, a further seminal contribution from *Gianni*'s group is the bis(hydroxo) palladium(II) dimer **2** [34], which opened the way to the concept of acid/base bifunctional catalysis with late transition metals.



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As a true pioneer, *Gianni* has always coupled his curiosity for fundamental aspects of catalysis with efforts to see it applied in the industrial production of high-value chemicals. Thus, the whole copolymerization project has been developed in partnership with industry, as well as his occasional strolls into asymmetric hydrogenation [35]. In his lifelong commitment to asymmetric catalysis, *Gianni* has interacted with a large number of chemists. Therefore, we asked some of them to contribute to this special issue of *Helvetica Chimica Acta* dedicated to *Gianni* to celebrate, on the occasion of his 65th birthday on July 21, 2006, his contribution to the development of asymmetric catalysis. Knowing how much *Gianni* is appreciated in the asymmetric catalysis community, we were not surprised that so many enthusiastically supported this endeavor. We express our profound and sincere gratefulness to all of them.

As a final consideration, we note that, besides contributing to the history of asymmetric catalysis, *Gianni* kept record of the developments with a fantastic literature collection and by producing lasting review articles and accounts [1][30][32][36]. We all know that, nowadays, short-term memory is overwhelming in science and society. Thus, our students consider 'old' a reaction that has been discovered ten years ago! In our opinion, it is particularly important that the historical perspective of the development of ideas and discoveries – in science as well as in our lives and cultures – be preserved in the collective memory. For us, this is one additional reason to acknowledge the seminal contributions by a scientist who is also our friend, mentor, and example. Thank you, *Gianni*!

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