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Reactivity control in palladium-catalyzed reactions: a personal account

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Dedicated to Professor Jean-Pierre Gênet on the occasion of his 60th birthday

Abstract

Several classes of palladium-catalyzed reactions are summarized as the author's personal account. These include allylic oxidation, diastereo- and enantio-controlled allylic substitution, transmetalation of organomercurials, stereoselective rearrangements, and development of new ligands for amination of aryl halides and for asymmetric Heck addition.

Keywords: Reactivity control; Palladium-catalyzed reactions; Transition metals

1. Introduction

This is a personal, non-comprehensive account, which reflects my 20-years affair with palladium chemistry [1]. The literature coverage is limited to the papers directly relevant to our chemistry, as discussed here. The main purpose is to show the development of various ideas in the historical perspective and to illustrate the diversity of palladium chemistry, reflected in the activities of my group.

Except for an occasional use of Pd-catalyzed hydrogenation, I first encountered the 'real' palladium chemistry 20 years ago. In May 1983 I arrived in Ithaca, to join John E. McMurry at Cornell University as a postdoc. My research was to revolve around the McMurry reaction [2,3], which then had its heydays, and the application of this very efficient methodology to the synthesis of natural products, especially those with medium- and large rings (note that ring-closing metathesis was virtually non-existent at the time). John suggested to me syntheses of several medium sized-ring sesquiterpenes, by employing the low-valent titanium cyclization (as he called the reaction known to the rest of the world as McMurry coupling) of a suitable dicarbonyl precursor as the key step. Thus, for instance, a concise synthesis of helminthogermacrene (**2**), which he proposed, would require ketoaldehyde (**1**) as the substrate for the McMurry coupling (Scheme 1).

2. Palladium(II)-catalyzed allylic oxidation

For the synthesis of helmithogermacrene (**2**), we identified geranyl acetone (**3**) as a potential starting material that newly appeared in the Aldrich catalogue. Hence, the first step was to find a method that would allow a selective functionalization of the ω-position of **3** (Scheme 2)—not an easy task in the molecule with eight sp^3 carbons, of which six are allylic and the remaining two α to a carbonyl group. While selenium-type oxidation was viewed as the last resort [4], we were attracted by Trost's previous report on a stoichiometric reaction of geranyl acetone with $(CF_3CO_2)_2Pd$, followed by Bu_4NCl quench, which produced η^3-complex **4** as the result of a selective functionalization of the distal double bond [5].

The general feeling in transition metal chemistry is that what works as a stoichiometric reaction, should also work as a catalytic process. In this case, we were faced with an oxidation, so that if a catalytic cycle was

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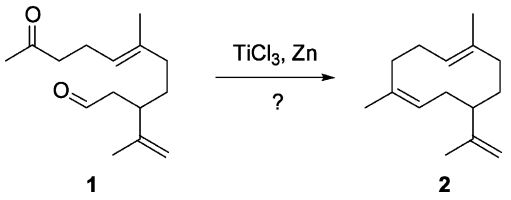
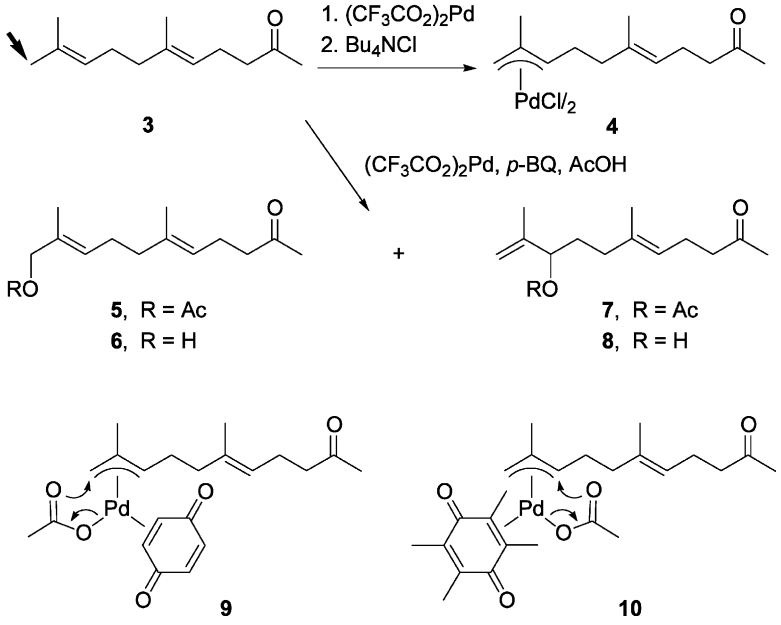


Scheme 1.

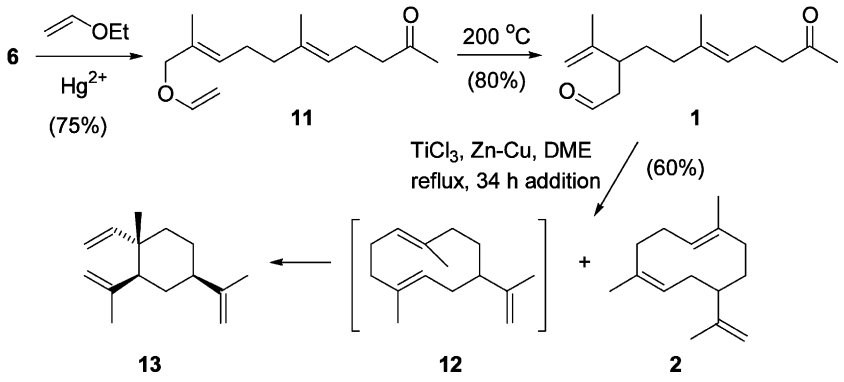
to be developed, one had to find the right oxidant that would regenerate Pd(II) in the reaction mixture and the right conditions. Being inspired by Bäckvall's work in the Pd(II)-catalyzed 1,4-functionalization of conjugated dienes [6], we focused on *p*-benzoquinone as oxidant in acetic acid [7]. Initial experiments elicited cautious optimism. At that stage, I developed an approach that would now be called 'high through-put screening', a buzz-word nonexistent in 1983: typically, six reactions were carried out in small test-tubes on one stirring hot plate, with various solvents, oxidants, palladium salts, etc.; the temperature was also varied. After some optimization, **3** was oxidized at 80 °C to afford a 2:3 mixture of two allylic isomers **5** and **7** in 56% yield. Further optimization led to the system that contained $(CF_3CO_2)_2Pd$ (5 mol%) [8], *p*-benzoquinone (2 equiv), and *o*-methoxyacetophenone as a chelating ligand, in acetic acid. The reaction was run at room temperature for 2 days to afford a 2:1 mixture of **5** and **7** in 85% yield. Hence, the original ratio that favored the branched product **7** had thus been reversed and the conditions and yield were considerably improved upon the addition of the selected chelating ligand [9]. By contrast, the more bulky duroquinone (tetramethyl-*p*-benzoquinone) exhibited opposite regioselectivity, producing **7** (up to 24:1) at 90 °C, although in only 32% yield [9].

In view of Bäckvall's more recent work, where he intercepted the η^3-Pd intermediate with *p*-benzoquinone coordinated to Pd [10], the regioselectivity of the geranylacetone oxidation can be understood as follows: In the square-planar η^3-Pd complex (**9**), the flat *p*-benzoquinone can assume the position that is *cis* toward the terpene chain, while the acetate group is transferred from Pd to the less substituted terminus of the η^3-complex, giving rise to the more substituted double bond (**5**). By contrast, the more bulky duroquinone cannot be accommodated in the same way as *p*-benzoquinone, so that it is pushed to the periphery of the molecule (**10**) and the acetate group is then transferred to the internal carbon. For further comments about the mechanism, see below.

The two isomeric acetates **5** and **7** were inseparable on a preparative scale but the corresponding alcohols **6** and **8**, obtained on methanolysis (K_2CO_3, MeOH), were readily separated by column chromatography. The rest of the synthesis proceeded uneventfully (Scheme 3): Allylic alcohol **6** was converted into vinyl ether **11**, heating of which induced Claisen rearrangement to afford keto aldehyde **1**. Optimized McMurry intramolecular coupling, under simulated high dilution (i.e., a very slow addition of the substrate to the reagent), generated helminthogermacrene **2** and its *trans*-isomer **12**, which underwent spontaneous Cope rearrangement to produce β-elemene **13**, so that a 44:55 mixture of **2** and **13** was obtained in 60%. The two isomeric trienes were readily separated by chromatography on silica gel impregnated with 2% $AgNO_3$ [11].



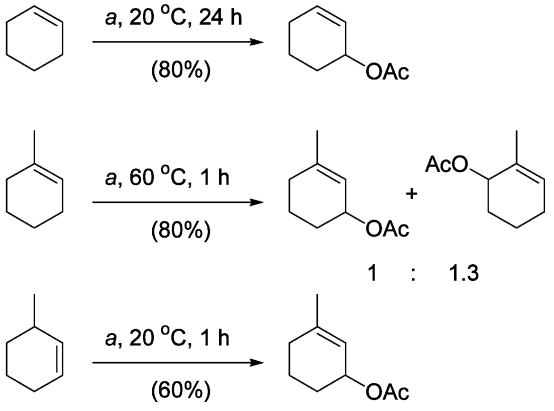
Scheme 2.



Scheme 3.

The scope of the new method of Pd-catalyzed allylic oxidation was briefly elucidated. Thus, for instance, cyclohexene and two isomeric methylcyclohexenes were efficiently oxidized using the same system and with good turnovers (Scheme 4) [9].

I left Cornell in September 1984 and went back to Prague, where I resumed my position at the Czechoslovak Academy of Sciences, and launched a couple of projects revolving around transition metal catalysis. I also continued my older work on the stereodirecting of electrophilic additions to C=C bond by neighboring groups [12]. In May 1987, I spent two weeks in Sweden as part of the exchange program between the Czechoslovak Academy of Sciences and the Swedish Royal Academy. During my visit to the Royal Institute of Technology (KTH) in Stockholm, I realized that Björn Åkermark was actually working on the same Pd-catalyzed allylic oxidation as I did at Cornell. They used the same system and obtained the same results (with the same model compounds, etc.). They actually had a paper accepted by J. Org. Chem. but, upon the appearance of our independent and practically identical paper in 1984 in Tetrahedron Lett., Björn withdrew this paper [13] and, at the time of my visit, his group were working on a substantial extension, which was very successful and published eventually in a series of papers in 1990 [14]. Here, Björn demonstrated that the allylic oxidation can occur either via the η^3-Pd complex as discussed above or via a 1,2-acetoxypalladation, depending on the actual structure of the substrate [14].

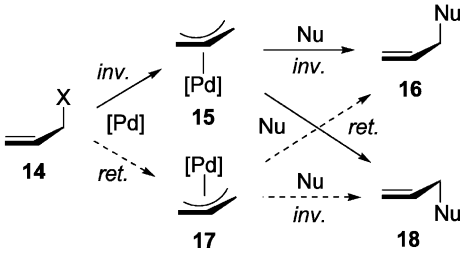


Scheme 4.

3. Stereochemistry of the Pd(0)-catalyzed allylic substitution

As a newcomer to Pd chemistry and while still at Cornell, I was intrigued by the mechanism of the Pd(0)-catalyzed allylic substitution of allylic esters (Tsuji–Trost reaction) [15]. At that time, the mechanistic knowledge was as follows: the reaction was known to proceed via η^3-complex **15** arising from an allylic ester, such as acetate **14** (X = OAc), with inversion of configuration (Scheme 5) [16]. The subsequent reaction of **15** with malonate anions and other stabilized C-nucleophiles again proceeds with inversion, giving overall retention (**16**) [16]. By contrast, organometallics and nonstabilized nucleophiles were found to react with retention in the second step (**15**→**18**) [16–18]. Hence, one could exercise control in the second step by the choice of nucleophile but not in the first, and I was going to change that.

Shortly after my return to Prague, I recruited an exceptionally able graduate student, Ivo Starý, who previously did his diploma work with me [19,20]. We focused on the lack of the stereochemical option in the first step (Scheme 5). Needless to say that, if we were capable of inverting the stereochemistry of the first step



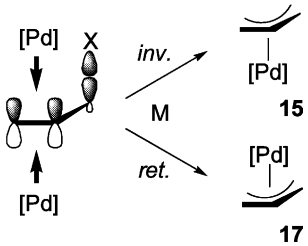
Scheme 5.

(**14**→**17**, dotted arrow), we would potentially have another two options in the second (dotted arrows to **16** and **18**), which would complete the mosaic [18].

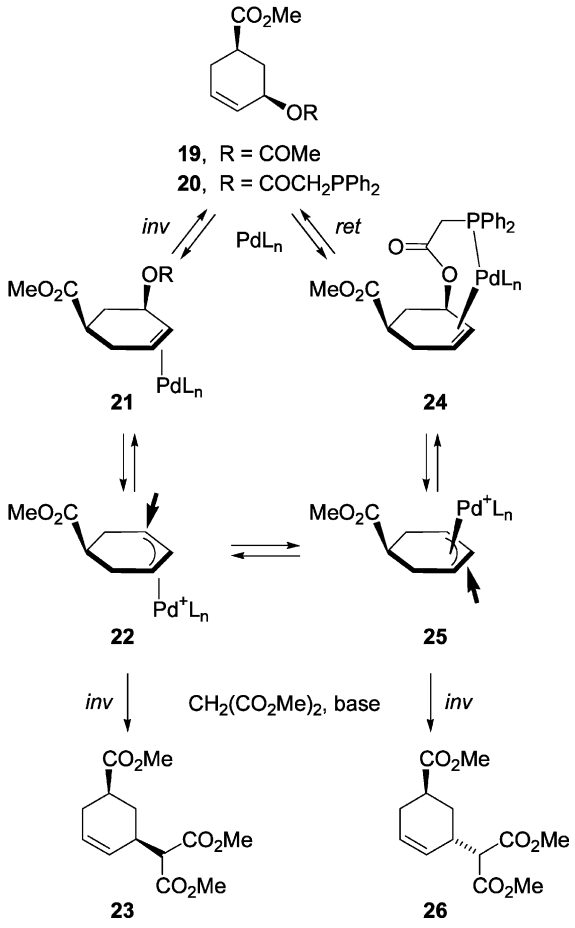
The retention mechanism should be possible, since the stereoelectronic effect, governing this reaction, dictates that the π-electrons of the C=C bond and the s-bond between the carbon and the leaving group lay in the same plane (Scheme 6). We reasoned that the retention mechanism could be enforced by coordination of the incoming Pd catalyst to the leaving group.[21]

As a suitable model compound to explore the viability of this stereochemical reversion, we chose the well known system, first employed by Trost and coworkers [16a,b] to demonstrate the classical mechanism (Scheme 7) [22,23]. Trost used acetate **19** that contained another ester group as a stereochemical marker. In the catalytic reaction, palladium(0) is coordinated from the side opposite to the leaving group (**21**), generating η^3-complex **22**, which is then attacked by malonate nucleophile, effecting the second inversion, to afford the *cis*-product **23**. We prepared the (diphenylphosphino)acetate (**20**) and hoped that pre-coordination of Pd to the leaving group (**24**) would thus inverse the stereochemistry to form the *cis*-configured η^3-complex **25**, whose reaction with malonate nucleophile would result in the formation of the *trans*-product **26**. While the reaction of acetate **19** gives the *cis*-product with a very high preference (especially when chelating diphosphines, such as dppe, are used as ligands) [24], we obtained a ~3:2 mixture of **23** and **26**, which seemed to indicate that the *ret* mechanism (**20**→**24**→**25**) was competing with the standard one [22]. However, subsequent experiments, where we varied the concentration of the catalyst and the temperature, showed that the *cis*-η^3-complex **25** was generated by isomerization of the *trans*-complex **22** (at higher temperature and higher catalyst concentration), rather than by the 'chelation' pathway via **24** [23].

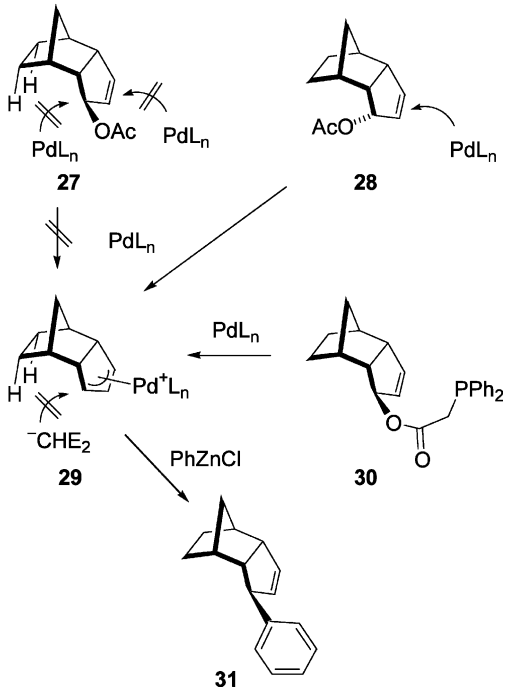
The real evidence in favor of the *ret* pathway in the first step was obtained with the tricyclic system that prevented the classical mechanism (Scheme 8) [22,23]. The *exo*-acetate **27** is inert toward Pd(0)-catalyzed allylic substitution, since the *anti* attack is precluded by steric hindrance of the *endo*-face and the *syn* attack is disfavored. By contrast, the *endo*-epimer **28** is exposed



Scheme 6.



Scheme 7.



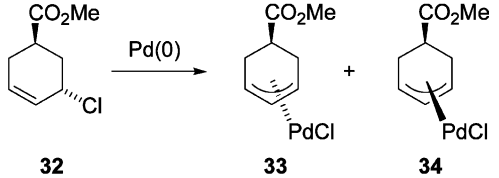
Scheme 8.

to the *exo* attack by Pd(0) and should readily form the η^3-complex **29** via the standard inversion mechanism but, since malonate nucleophiles are known to react with inversion, no reaction can be expected here, again due to the steric *endo* hindrance. On the other hand, complex **29** should react with organometallics via *ret* mechanism involving transmetalation. Indeed, Pd(0)-catalyzed reaction of *endo*-acetate **28** with PhZnCl did proceed to produce the phenyl derivative **31**, whereas *exo*-acetate **27** was inert [17g,22,23]. We have then demonstrated the *exo*-(diphenylphosphino)acetate (**30**) to work effectively, affording **31** with considerable acceleration compared to **28**, showing for the first time the *ret* mechanism in the η^3-Pd complex formation [22,23]. Another example from the terpene realm with a similar stereochemical bias lend further credence to the operation of this pathway. Indeed, precoordination of the catalyst to the leaving group was the prerequisite for the reversal but this stereochemistry was only available if the 'normal' *inv* pathway was precluded [22,23,25].

A second example of the *ret* mechanism in the η^3-complex formation was reported a year later by Hideo Kurosawa (Scheme 9), who showed that allylic chloride **32** produced the η^3-complex **33** with retention in non-coordinating or weakly-coordinating solvents, while the classical *inv* mechanism (to form **34**) prevailed in strongly coordinating solvents [26]. The occurrence of *ret* mechanism was attributed to pre-coordination of Pd to Cl as the leaving group, which is suppressed in coordinating solvents [26b,27].

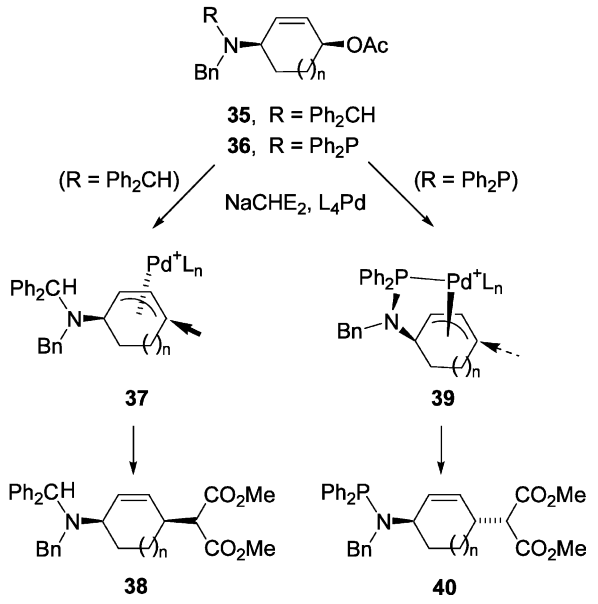
In October 1989 I went to Sweden, which I regarded as the European Mecca of palladium chemistry, and spent a fruitful sabbatical year with Jan-E. Bäckvall at the University of Uppsala. While there, I accepted an invitation by the University of Leicester, UK, joined the faculty in January 1991, and resigned my position in Prague. Naturally, all this caused some disruption, so that it took several years before we could revisit the stereochemistry of allylic substitution [28].

Since the coordination to the leaving group proved the principle but was rather limited (either to stereochemically biased substrates or to unstable allylic



C_6H_6	100	:	0
THF	95	:	5
DMF	29	:	71
DMSO	3	:	97

Scheme 9.



Scheme 10.

chlorides; Schemes 8 and 9), we intended to introduce the coordinating group elsewhere to the molecule (Scheme 10). Using Bäckvall oxidation methodology, my postdoc, Chris Farthing, synthesized new model compounds **35** and **36**, which differ by the *N*-substituent: while **36** has a potentially coordinating phosphine group attached, **35** contains a noncoordinating benzhydryl, of a comparable size to that of Ph_2P [28]. As expected, the noncoordinating benzhydryl derivative **35** afforded **38** as the product of double inversion (via **37**). The phosphino derivative **36**, however, gave the pure inversion product **40**, arising from the chelated Pd complex **39**. The direct formation of the latter complex **39** from **36**, rather than via isomerization similar to that shown in Scheme 7, was evidenced by kinetic studies; furthermore, complex **39** was intercepted by ^{31}P-NMR spectroscopy [28]. Similar steering was also observed for the Ni-catalyzed reaction of **36** with MeMgI, which gave the product of double retention, thereby completing the mosaic shown in Scheme 5 [28]. This reversal of stereochemistry is more general than that reported earlier (Schemes 8 and 9) but is confined to cyclic systems, where no rotation about the C–C bond of the allylic ester is possible [28].

The idea of coordination of the palladium in η^3-complexes has several followers, who used this trick either to control the stereochemistry of the reaction or to modify the geometry of the complex in order to control the position of the nucleophile attack [29].

4. Pd(0)-catalyzed allylic substitution using free alcohols as substrates

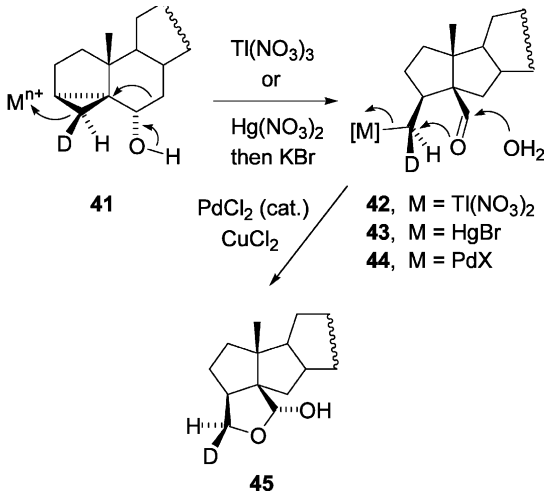
Allylic acetates and other esters and carbonates have almost invariably been used as substrates for Pd-catalyzed substitution. However, some of these esters are much less stable than the corresponding alcohols and we felt that it would be an advantage if a catalytic system were available that would allow a direct substitution with alcohols [30,31].

We have found that allylic alcohols, in form of the corresponding alkoxides, can be activated toward Pd(0)-catalyzed allylic substitution by triphenyl boron (Ph_3B). This method has the advantage that, for instance, an allylic alcoholate, generated in situ by DIBAL-H reduction or by a Grignard addition, can be directly employed in the C–C bond formation (Scheme 11) [32].

5. Catalytic transmetalation reactions

Transmetalation is a powerful methodology that combines the synthetic potential of two (or more) metals. We became interested in these reactions in connection with our studies on metal-mediated stereoselective ring-opening of cyclopropane derivatives, which originated in Prague, continued during my stay in Uppsala [12c], and came to fruition in Leicester [33], thanks to the efforts of Jiří Šrogl, an excellent graduate student from Prague (now at Emory University, Atlanta), who joined me in Leicester, two local graduate students, Jason Grech and Victoria Dunn, and a continued collaboration with Adolf Gogoll, a dedicated NMR spectrometrist in Uppsala.

Our initial studies were concerned with the stereochemistry of the cyclopropane opening with Tl(III), where we have shown, for the first time, the stereospecific 'corner' attack by isotopic labeling. Thus, the steroid derivative **41**, stereospecifically deuterated in 4β-position (Scheme 12), was opened up by $Tl(NO_3)_3$ to produce lactol **45**, whose formation is compatible with the 'corner' attack by Tl^{3+} (inversion of configuration)

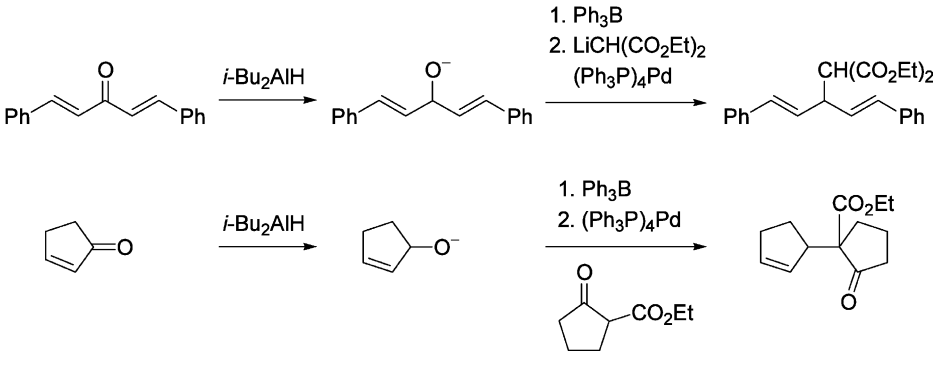


Scheme 12.

to generate the intermediate organothallium species **42**, that underwent spontaneous S_N2-type ring closure (second inversion) to produce **45** [12c,34].

With mercury(II), we could actually isolate the organomercurial **43** but were unable to determine the configuration at the C*H(D)HgBr center. In this case we sought assistance from palladium, which was known to transmetalate organomercurials with retention of configuration, and we were planning a carbonylation reaction, followed by a ring closure to obtain a rigid structure, where the NMR assignment should be easier. Rather surprisingly, however, the transient organopalladium species **44** underwent spontaneous ring closure to produce the same lactol **45** as that from the Tl(III)-mediated reaction. Since the Hg→Pd transmetalation should occur with retention, the initial and final step must proceed with inversion, showing again the stereospecific 'corner' opening of the cyclopropane ring by Hg(II) [33c,35]. The transmetalation was catalytic in Pd, provided that an excess of Cu(II) was present to reoxidize Pd and to make it available for the next catalytic cycle.

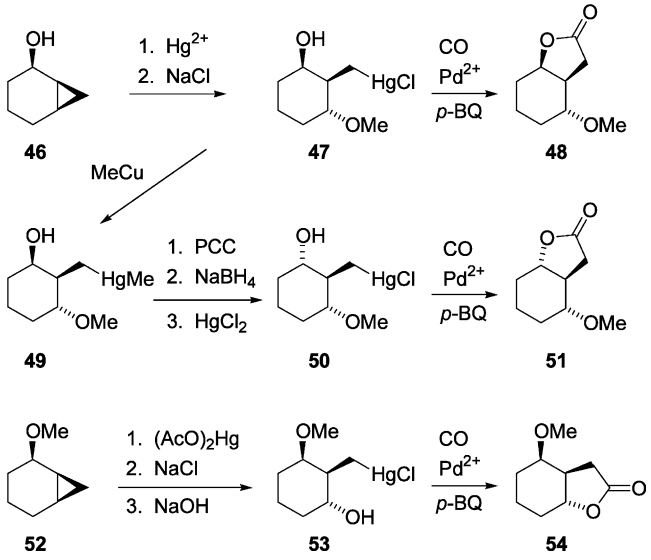
The intrinsic palladium species, generated catalytically in situ from the organomercurials, should generally



Scheme 11.

be prone to carbonylation, in spite of its absence in the previous case, where it was suppressed by a competing reaction. In order to explore this potential in connection with the organomercurials generated by the cyclopropane ring opening, we prepared various cyclopropane derivatives as starting materials with a view of opening an easy entry into a series of annulated lactones with three consecutive chiral centers (Scheme 13). Thus for instance, cyclopropyl alcohol **46**, readily obtained by the stereocontrolled Simmons–Smith cyclopropanation of cyclohexenol, was opened up by $(CF_3CO_2)Hg$ in methanol regioselectively, to produce organomercurial **47**. While attempted carbonylation in the presence of a stoichiometric amount of Pd(II) proved fruitless, giving only the product of β-elimination, a catalytic procedure turned out to be successful. The difference here was that, in the catalytic process, a reoxidant was required and we chose *p*-bezoquinone. Apparently, the coordination of *p*-benzoquinone to the intermediate organopalladium species changed its reactivity in favor of carbonylation at the expense of β-elimination [36]. Hence, the *cis*-annulated lactone **48** was prepared from the cyclopropane derivative **46** in 2 steps and the procedure was later extended to γ-lactones derived from cyclopentane and cycloheptane precursors.

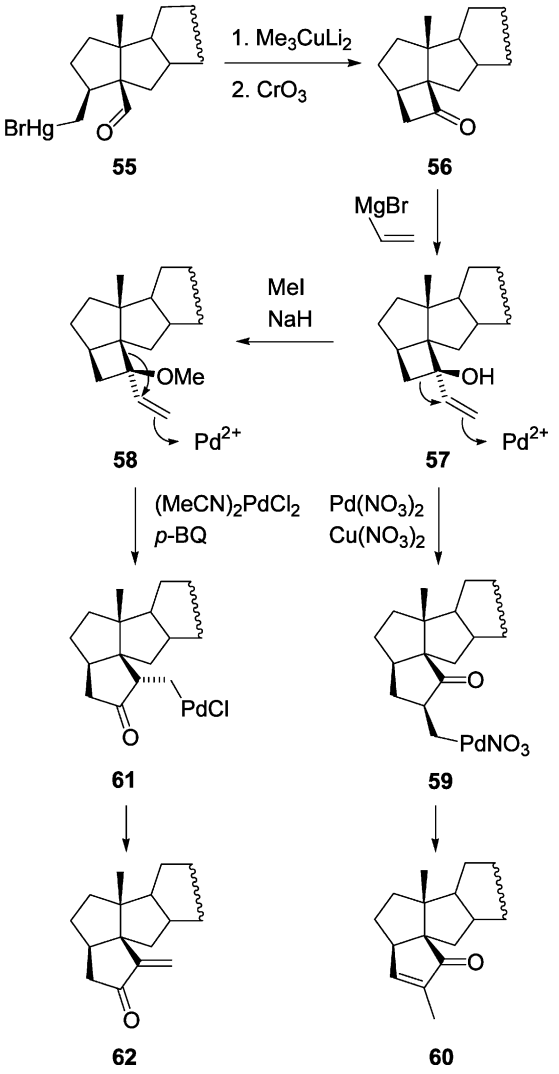
Adapting this methodology to the synthesis of *trans*-annulated γ-lactones, which are generally less readily accessible, was also explored. First, the organomercurial was protected by methylation (**47**→**49**), the configuration of the hydroxyl group was inverted by the oxidation–reduction sequence, and then mercury was deprotected by $HgCl_2$. The resulting alcohol **50** was carbonylated to afford the *trans*-annulated lactone **51**. Finally, the *trans*-configuration, generated by the ring-opening was also implemented in the manifold: the mercurio alcohol **53**, obtained by ring-opening of **52**, followed by saponification of the acetate group, underwent Pd-catalyzed carbonylation to produce *trans*-annulated γ-lactone **54** [36,37].



Scheme 13.

6. Palladium-catalyzed rearrangements

Organomercurials normally do not react with carbonyl groups, so that they can be employed as a depot of the carbon-metal bond to be activated later in the synthetic sequence. Indeed, transmetalation with Me_3CuLi_2 was developed by us as a vehicle for effecting an intramolecular addition to a neighboring aldehyde group and to an activated C=C bond of an α,β-unsaturated ketone or ester (Scheme 14) [33]. In the case of the mercurio aldehyde **55**, we were able to close up a cyclobutane ring; oxidation of the alcohol thus formed produced cyclobutanone derivative **56** [33,38]. The fused system in the latter ketone appeared to be an interesting precursor to triquinane-type isoprenoids,



Scheme 14.

provided a suitable expansion of the four-membered ring to its five-membered counterpart were developed.

Allylic alcohol **57**, obtained from ketone **56**, did rearrange in the presence of a catalytic amount of $Pd(NO_3)_2$ and $Cu(NO_3)_2$ (as reoxidant of palladium) to afford enone **60** as the major product (60%). On the other hand, the corresponding methyl ether **58** took a different course, producing mainly the isomeric enone **62** (75%) on the reaction catalyzed by $(MeCN)_2PdCl_2$ in the presence of *p*-benzoquinone as oxidant. The dramatic difference in the migration propensity was rationalized by different ways of palladium coordination to OH/OMe in the transition state [38].

7. Development of new chiral ligands for palladium-catalyzed reactions

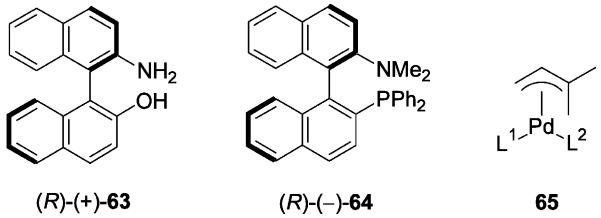
Around 1989 I started a collaboration with one of the most capable young Czech chemists, Martin Smrčina [39] of Charles University, Prague. He prepared an interesting novel heterobidentate ligand NOBIN (**63**) [40]; and others, such as MAP (**64**) [41], were in the blueprints (Scheme 15). In 1990, while I was in Sweden, I had an interesting discussion with Björn Åkermark about a series of his papers, in which he demonstrated that the chemical shifts in the NMR spectra of η^3-allylpalladium complexes **65** can be influenced by ligands L^1 and L^2 on Pd and that this ligand effect can be employed to control the regioselectivity of nucleophilic attack [42]. It occurred to me that, if a chiral, heterobidentate ligand were coordinated to palladium, an asymmetric induction could be attained through the combination of steric and electronic effects, which he accepted with cautious optimism. However, others, namely Andreas Pfaltz (Basel) [43], Günter Helmchen (Heidelberg) [44], and Jon Williams (then at Loughborough) [45] had similar ideas and independently [46] developed their now well known phosphinoxazoline ligands before we could start any activity in this field.

In 1996 Martin Smrčina resigned his academic position in Prague and accepted a much better paid industrial job with Selectide (now Aventis) in Tucson, Arizona. As a consequence, I inherited Štěpán Vyskočil, his exceptionally talented student [47]. In 1997 he synthesized MAP (**64**) [41,48], which can be regarded as the nitrogen analogue of Hayashi's MOP [49], and we set out to explore its applications in catalysis. Here, we followed two lines: (1) the original idea of using MAP as a heterobidentate chiral ligand for Pd-catalyzed allylic substitution and (2) its application in the newly emerging Hartwig–Buchwald amination of aromatic halides and related reactions [50].

In the Pd-catalyzed amination of aryl halides, Pd complex **66** with the $(t\text{-Bu})_2P$ groups was reported to be superior to the Ph_2P analogue and its efficiency was attributed to the lower stability of the chelate **66a** (Scheme 16) due to the extreme steric congestion, so that, in an equilibrium, there may exist the more reactive monocoordinated species **66b** [50]. We reasoned that a similar effect might be attained with MAP (**64**), since the bonding of Pd to the amino group (as in **67a**) should be weaker than that to the phosphorus, so that the open species **67b** could be expected to exist in the reaction mixture, mimicking the behavior of **66** by electronic effect [41a]. Apparently, the same idea occurred to Steve Buchwald, who initially synthesized the biphenyl analogue of MAP [51,52], to be followed by an impressive series of both biphenyl and binaphthyl analogues, in some of which the donation to Pd was further increased by switching from the PPh_2 group to the more donating $P(cyclohexyl)_2$ or $P(t\text{-Bu})_2$ [53].

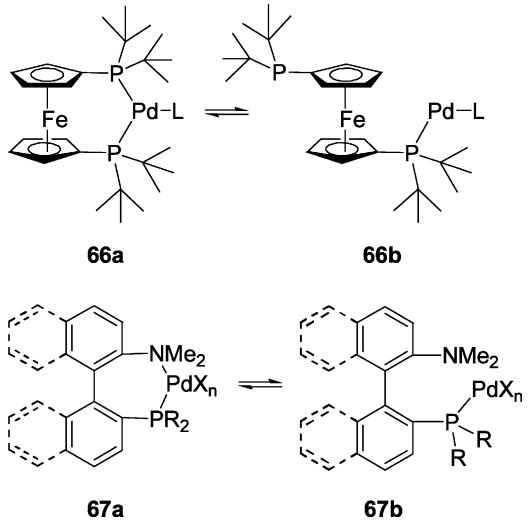
Indeed, the catalytic activity was dramatically increased in the amination, Suzuki–Miyaura coupling, and other reactions [41,51,53–55]. Since MAP (**63**) and its analogues are chiral, asymmetric reactions can be envisaged. Indeed, Buchwald has demonstrated this principle in the asymmetric Suzuki–Miyaura coupling [55].

In order to elucidate the mode of coordination of **64** to $PdCl_2$ (Scheme 17) [54,56], we teamed up with Guy Lloyd-Jones at Bristol [57]. The ^1H-, ^{13}C- and ^{31}P-NMR spectroscopy indeed confirmed the presence of the

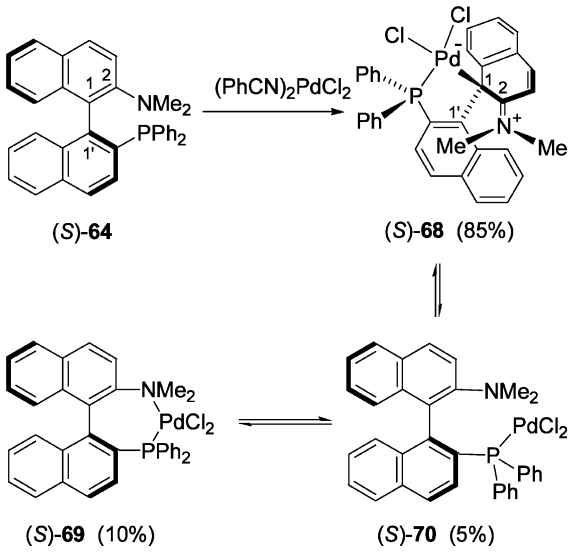


(*R*)-(+)-**63** (*R*)-(−)-**64** **65**

Scheme 15.



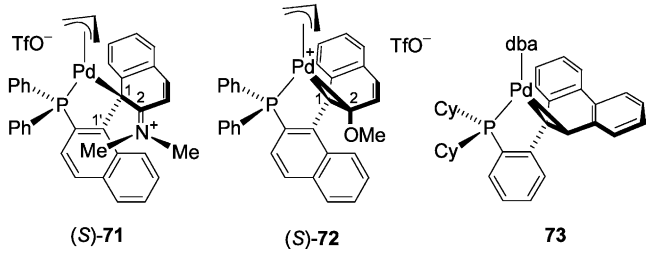
Scheme 16.



Scheme 17.

expected *P*,*N*-chelate **69** in the solution but only as a minor component (~ 10%). In this equilibrium, another minor species was identified as the *P*-monocoordinated complex **70** (~ 5%), which was still in line with the initial hypothesis. However, rather surprisingly, this mixture was dominated by **68** (~ 85%), a five-membered palladacycle with an unusual P,C_{σ}-coordination. Crystallization of the **64**/$PdCl_2$ mixture afforded **68** as a single product, whose structure was confirmed by X-ray crystallography [54]. Its formation can be understood in terms of the enamine-like behavior of the aminonaphthalene moiety in **64**, which can encourage an electrophilic attack at the *ipso*-carbon [54]; furthermore, formation of a five-membered palladacycle, as in **68**, should be thermodynamically favored over the seven-membered chelate **69**, which apparently contributes to the overall outcome.

Similar η^1-coordination pattern has been found by us in the π-allylpalladium complex of MAP (**71**), whereas the MOP complex **72** exhibited η^2-coordination to the C(1)–C(2) bond (Scheme 18) [54,56]. Recently, Buchwald has reported a crystallographic characterization of Pd(0) complex **73**, which also exhibits η^2-coordination [58]. It may be speculated that this additional donation renders the Pd very electron-rich, which may lead to the stabilization of intermediates in the catalytic cycle.



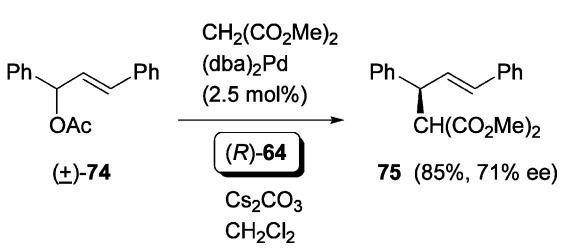
Scheme 18.

However, the actual role of this coordination in coupling reactions remains to be established [59].

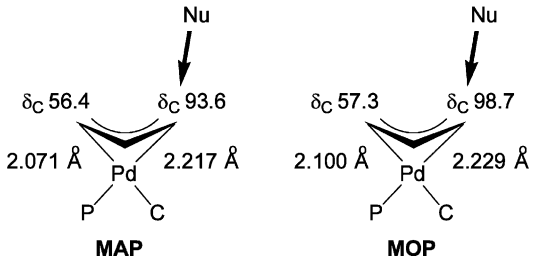
In the Pd-catalyzed allylic substitution, (*R*)-**64** exhibited modest enantioselectivity in the reaction of 1,3-diphenylprop-2-en-1-yl acetate (±)-**74** with dimethyl malonate nucleophiles (Scheme 19). The results were fairly dependent on the way of malonate activation and the solvent (from 53% ee with NaH in THF to 71% ee with Cs_2CO_3 in CH_2Cl_2) [41a].

Both NMR and crystallographic studies, carried out by Guy Lloyd-Jones in collaboration with us, for the unsubstituted allyl complexes **71** and **72**, have indicated the presence of two rotamers in ~3:2 to ~1:1 ratio, which are in an equilibrium via an η^1-allyl intermediate. Furthermore, both in the solid state and in the solution, the allyl unit is coordinated in a slightly distorted η^3-fashion so that the bond between Pd and the carbon terminus of the allyl unit *trans*-disposed to phosphorus is longer (and therefore weaker) than that of the other terminus, *trans*-related to the *ipso*-carbon (Scheme 20). Accordingly, the carbon *trans* to phosphorus has more π-character, as indicated by the respective chemical shifts in the ^{13}C-NMR spectra (Scheme 20) [56,60]. These parameters predict the preferential attack by the nucleophile at the terminus *trans* to the phosphorus [54,56,61]. Furthermore, a strong memory effect has been found to operate in the allylic substitution reactions [54,56,61].

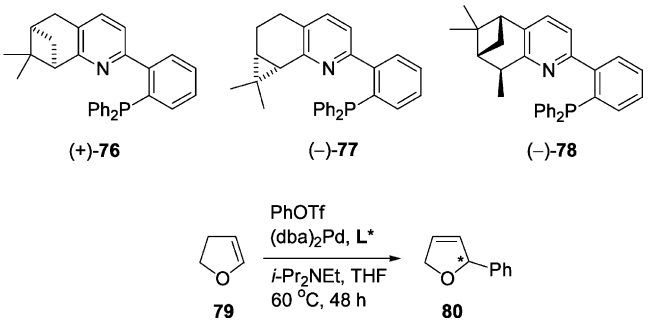
In 1999 I moved to Glasgow, where we continue the work on Pd–MAP/MOP complexes in collaboration with Guy Lloyd-Jones while several other new projects have been launched. Thus, a new class of ligands, namely phosphinopyridines **76**–**78**, based on a terpene scaffold (Scheme 21), have recently been developed by us in Glasgow as substitutes for phosphinoxazolines, where the electronics of the sp^2 nitrogen atom might potentially be tuned by substituents in the pyridine ring. Their application to asymmetric Heck addition of phenol triflate to dihydrofuran **79** gave the addition product **80** in 59, 70 and 88% ee, respectively; unlike with BINAP, no double bond isomerization of the primary product **80** has been observed in this instance [62,63]. The latter ligands are also moderately effective in asymmetric, Pd(0)-catalyzed allylic substitution in the case of allylic acetate (±)-**74** (68% ee with **76** and 71% ee with **78**) [64,65].



Scheme 19.



Scheme 20.



Scheme 21.

8. Conclusions

For 20 years (1983–2003) we have been involved in a number of areas of palladium-catalyzed chemistry, including allylic oxidation, diastereo- and enantio-control of allylic substitution, transmetalation of organomercurials, stereocontrolled rearrangements, amination of aryl halides, Suzuki–Miyaura coupling, and asymmetric Heck addition. We have developed new methods for the annulation of γ-lactones (both *cis* and *trans*) and designed new C_1-symmetrical chiral ligands for enantioselective reactions (MAP, PINPHOS, etc.). We believe that our mechanistic and structural studies have contributed to the wealth of the knowledge of the fascinating behavior of transition metals, and of Pd in particular. There are other areas, where we have been active but these are not included in this account since they do not hinge on palladium; some of the highlights are given in Refs. [1,12,66–68].

Acknowledgements

I am particularly indebted to those, who introduced me to palladium chemistry, namely Prof. John McMurry and Prof. Jan-E. Bäckvall. I would like to thank the many students, coworkers, colleagues, and external collaborators, who participated in various parts of the projects, which constitute our contribution to the palladium chemistry as highlighted in this review, and whose names appear in the reference section. In particular, I am indebted to Drs. Ivo Starý, Irena Stará, Milan Pour, Jiří Šrogl, Vratislav Langer, Vladimír Hanuš, Adolf Gogoll, Martin Smrčina, Štěpán Vyskočil, Jason Grech, Victoria Dunn, Ivana Císařová, Andrei Malkov, and Marco Bella. Particularly fruitful was the collaboration with Dr. Guy C. Lloyd-Jones and his group (Bristol). Finally, I thank NIH, NFR, ČSAV, GAČR, EPSRC, NATO, Charles University, University of Leicester, University of Glasgow, Merck Sharp & Dohme, GlaxoSmithKline, and Dr. Alfred Bader for their support at various stages of our palladium research.

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