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Cyclopalladated complexes in enantioselective catalysis

V V Dunina, O N Gorunova, P A Zykov, K A Kochetkov

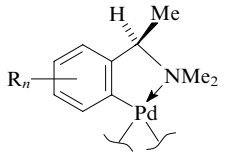
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Abstract. The results of the use of optically active palladacycles in enantioselective catalysis of [3,3]-sigmatropic rearrangements, aldol condensation, the Michael reaction and cross-coupling are analyzed. Reactions with allylic substrates or reagents and some other transformations are considered. The bibliography includes 178 references.

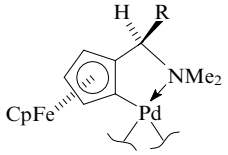
I. Introduction

The development of the chemistry of cyclopalladated complexes (CPC) has nearly a half-century history.[1] At its infancy, this field of research concerned predominantly with the development of different versions of the regioselective stoichiometric organic synthesis.[2] First optically active C*-chiral CN-palladacycles, α-arylalkylamine derivatives[3,4] (**A**) and their planar chiral aminoalkylferrocenyl analogues[5,6] (**B**) were synthesized in the 1980s and were solely used in this area for many years.



A

R_n = H, 3,4-benzo, 4,5-benzo.



B

R = H, Me; Cp = η-C_5H_5.

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Evidently, the ever-increasing interest in the extension of the structural and stereochemical diversity of this class of compounds can be considered as a progress in the chemistry of chiral CPC made in the last decades. Hundreds of optically active palladacycles, including both monocyclic CN, CS and CP complexes and their bicyclic pincer SCS, NCN and PCP analogues, were documented.

Optically active CPC have found practical use in the stoichiometric or catalytic asymmetric synthesis. For example, the separation of enantiomers of racemic phosphines, diphosphines and aminophosphines on cyclopalladated matrices[7,8] provides ligands for the asymmetric catalysis. The Diels – Alder reaction[9] and hydrophosphination[10,11] promoted by chiral CN-palladacycles serve the same purpose. The spectroscopic determination of the enantiomeric composition[12,13] and absolute configurations[14] of organic molecules with the use of optically active CN- or CP-palladacycles in the step of chiral derivatization is a simple and reliable tool for the control over every asymmetric transformation.

The direct use of chiral CPC as catalysts or their precursors (pre-catalysts) in enantioselective catalysis has been stimulated by impressive advances in the use of their achiral analogues as catalysts for cross-coupling reactions. The use of CPC instead of classical palladium coordination compounds resulted in the record efficiency of the process (TON† was up to 10^{11})[15–18] and made it possible to perform the reactions with cheaper but less reactive aryl chlorides.[19,20] The unique efficiency of this class of (pre)-catalysts is based on their very high thermal, oxidative and hydrolytic stability.

This review covers the results of research into the behaviour of chiral mono- and bicyclic CPC as catalysts for various processes published before the end of 2009. Carbene analogues of CPC and CC-type metallacyclic compounds are excluded from the consideration because they are beyond the scope of the classical definition of

† TON (turnover number) is the number of cycles a catalyst can perform before decomposition.

cyclopalladated compounds as structures containing one or several carbanionic centres stabilized by the coordination of the metal to one or more donor heteroatoms.

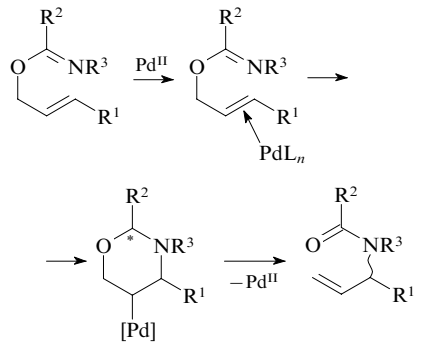
The use of palladacycles in asymmetric catalysis was mentioned in general reviews,[17,21,22] reviews dealing with particular reactions[23,24] or types of CPC;[25–27] however, no special reviews on this topic were published.

II. [3,3]-Sigmatropic rearrangements

[3,3]-Sigmatropic rearrangements are of obvious practical value in the modern fine organic synthesis,[28,29] the processes resulting in the formation of new carbon–heteroatom bonds being most useful. Since the asymmetric version of the aza-Claisen rearrangement[30] was studied in most detail, we will consider it first.

1. Aza-Claisen rearrangement

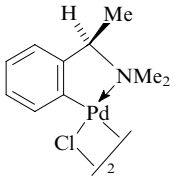
The cyclization-induced rearrangement (CIR) of prochiral allylic imidates into chiral allylamides is a route to allylamines starting from more easily available allylic alcohols. This concerted pericyclic process was discovered by Overman in 1974,[31,32] and its asymmetric version based on the catalysis of the reaction by palladium compounds has been extensively developed since 1997.[33] It was suggested that the π-coordination of the metal atom at the C=C bond of the substrate facilitates the nucleophilic attack of the imidate nitrogen atom on the alkene moiety in the step of formation of the cyclic alkylpalladium intermediate [reaction (1)].[30,34]



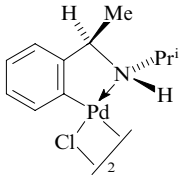
(1)

Initially, cationic coordination compounds with chiral N,N-donor ligands were used as the catalysts. These compounds have relatively low activity and produce products in moderate optical yields with an enantiomeric excess (*ee*) $<63\%$.‡ A breakthrough has been achieved only after testing of different types of neutral derivatives of CN-palladacycles as catalysts. It was shown that cationic CPC of the general formula $[(\eta^2\text{-C}\cap\text{N})\text{Pd}(\text{NCMe})_2]^+$ (C∩N is the bidentate CN ligand) are catalytically inactive,[35] whereas one of the anionic complexes $[(\eta^2\text{-C}\cap\text{N})\text{PdCl}_2]^-$ proved to be as efficient as the corresponding uncharged dinuclear complex.[36]

The possibility of the use of CN-palladacycles as catalysts for the Overman rearrangement was exemplified by the simplest representatives, such as the dinuclear μ-chloride complex containing the endocyclic C* stereocentre (compound **1a**)§ and its analogue containing the additional asymmetric nitrogen atom (**2**).[37]

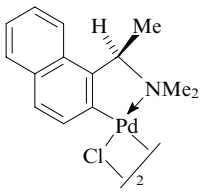


(R_C)-**1a**

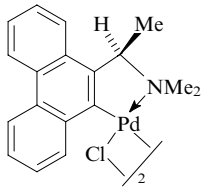


(R_C,S_N)-**2**

The reaction catalyzed by dinuclear complex **1a** (5 mol.%) affords the corresponding allylamide [see reaction (1)] in almost quantitative yield (97%) in 40 h though at elevated temperature (40 °C). However, the asymmetric induction was very low both in the case of palladacycles **1a** and **2** (0%–2% *ee*)[37] and their conformationally stabilized 1-naphthyl analogue **3** (4%–13% *ee*).[35] A certain success was achieved with the use of the derivative of tertiary 1-(phenanthryl)ethylamine (**4**), which resulted in an increase in the optical yield to 79%.[35] Apparently, the high enantioselectivity of the latter compound is determined by the steric hindrance in the immediate vicinity of the metal centre of the catalyst.



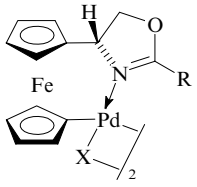
(R_C)-**3**



(R_C)-**4**

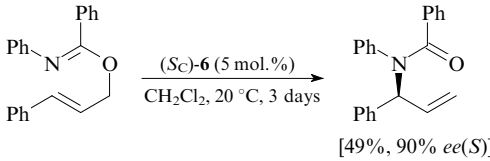
Taking into account that these experiments were carried out with dinuclear μ-Cl complexes at room temperature, the potential of α-arylalkylaminate CPC has not, apparently, been exhausted. The efficiency of these compounds can be substantially enhanced by optimizing the nature of the anion, for example, by replacing chloride with trifluoroacetate (Tfa).

The optical yield (90%) highest for C*-chiral CPC was achieved with unusual interannelated ferrocenyl complexes (S_C)-**5a**,**b** and (S_C)-**6** as catalysts resulted [reaction (2)].[38]



5a,**b**, **6**

R = Bu^t: X = OAc (**5a**), Cl (**5b**); R = Ph, X = OAc (**6**).

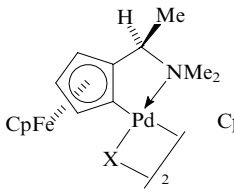


(2)

‡ Hereniafter, the optical yields of the products are given in *ee* values.

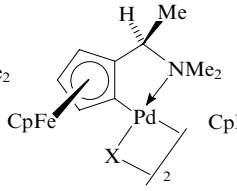
§ In the present review, the Arabic numeral in the code of the complex defines the type of the palladacycle and the Latin letters denote different forms of its existence (dinuclear and mononuclear derivatives).

The subsequent switch to of planar chiral cyclopalladated catalysts was based on the mechanistic considerations. It was suggested that the enantioselection could be implemented in the step of formation of the five-coordinate intermediate containing the η^2-bound alkene moiety. The idea of an increase in the selectivity of the process by introducing bulky substituents above and below the coordination plane of the metal in the catalyst resulted in a success. Cyclopalladated α-ferrocenylethylamines with different relations between the configurations of the chiral plane (pl) and the C* stereocentre, in particular, dinuclear complexes (S_{pl},R_C)-**7a**–**f** and (R_{pl},R_C)-**7a**,**b** with different bridging anions,[37] as well as their analogues, dinuclear complexes (R_{pl})-**8a**,**b** and (R_{pl})-**9a**,**b** containing the chiral plane as the only source of asymmetric induction, were tested as catalysts.[39]

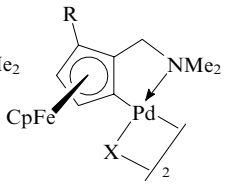


(S_{pl},R_C)-**7a**–**f**

X = Cl (**a**), OTf (**b**), OTs (**c**), BF_4 (**d**), OAc (**e**), Tfa (**f**); Ts is *p*-toluenesulfonyl (tosyl).



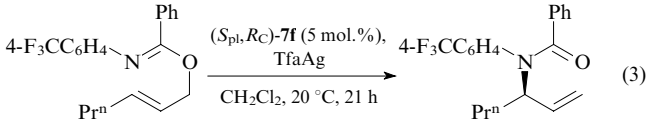
(R_{pl},R_C)-**7a**,**b**



(R_{pl})-**8a**,**b**; **9a**,**b**

X = Cl: R = Me (**8a**), $SiMe_3$ (**9a**);
X = Tfa: R = Me (**8b**), $SiMe_3$ (**9b**).

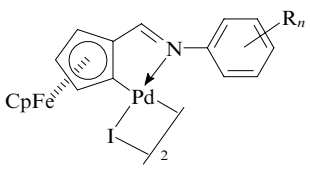
Most of these catalysts work even at room temperature, although with a different efficiency. Thus the reaction catalyzed by dinuclear complex **7f** affords allylamide in 98% yield after 21 h, whereas the reactions catalyzed by **7a** gives this compound in a yield of at most 35% even at the reaction time of 7 days. The investigation of a series of complexes (S_{pl},R_C)-**7** showed that the nature of the anions in the dinuclear complexes has a substantial effect on the enantioselectivity of reactions, which increases from 2% *ee* (**7b**) to 67% *ee* (**7a**); the yield is moderate (35%). Dinuclear trifluoroacetate complex (S_{pl},R_C)-**7f** is the catalyst of choice, because it ensures the comparable enantioselectivity (61% *ee*) and the formation of the product in an almost quantitative yield [reaction (3)].[37]



(3)

[98%, 61% *ee*(*R*)]

A similar efficiency was observed for a series of planar chiral cyclopalladated derivatives of *N*-ferrocenylmethylideneanilines (R_{pl})-**10**–**15**.[39]

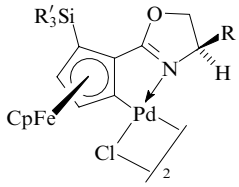


(R_{pl})-**10**–**15**

R_n = 2,4,6-Me_3 (**10**), 2,6-Pr^i_2 (**11**), H (**12**), 4-CF_3 (**13**), 4-Me (**14**), 4-OMe (**15**).

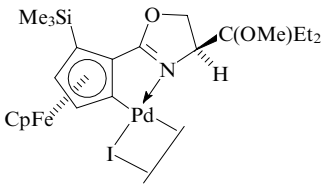
The main problem encountered when using these systems is that it is necessary to perform the dehalogenation of the starting dinuclear μ-iodide complexes (R_{pl})-**10**–**15**, which are catalytically inactive (unlike their μ-chloride analogues). To solve this problem, the dinuclear iodide complexes were transformed into acetonitrile-stabilized triflates by the *in situ* treatment with an excess of TlOTf. The reaction at room temperature with a catalyst loading of 11 mol.% affords scalemic allylamides (up to 73% *ee*) in 45%–94% yields.[39] The enantioselectivity of catalysts **10**–**15** is independent of the bulkiness of the *N*-aryl substituent in the palladacycle (45%–49% *ee*) but is strongly sensitive to the structure of the substrate. Thus the optical yields in the reactions catalyzed by complex (R_{pl})-**10** range from 43% to 73%.

The use of ferrocenyl palladacycles containing the donor 1,3-oxazoline moieties (**16**–**24**) was the next step in improving planar chiral catalysts.[34,40,41] This family of catalysts is called FOP (Ferrocenyl Oxazoline Palladacycles).

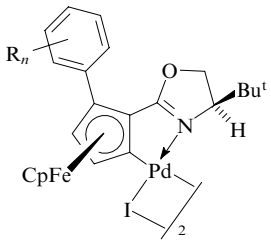


(R_{pl},S_C)-**16**, **17a**, **18**

R = Pr^i, R′ = Me (**16**);
R = Bu^t: R′ = Me (**17a**), Et (**18**).



(S_{pl},S_C)-**19a**

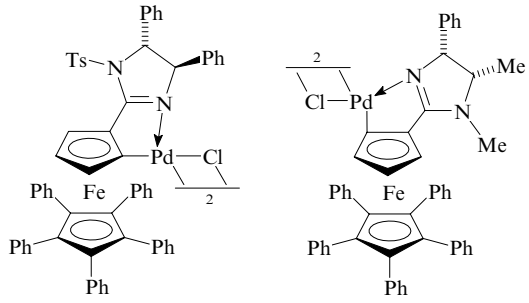


(R_{pl},S_C)-**20**–**24**

R_n = H (**20**), 2-Me (**21**), 4-SMe (**22**), 4-CF_3 (**23**), 2,6-$(OMe)_2$ (**24**).

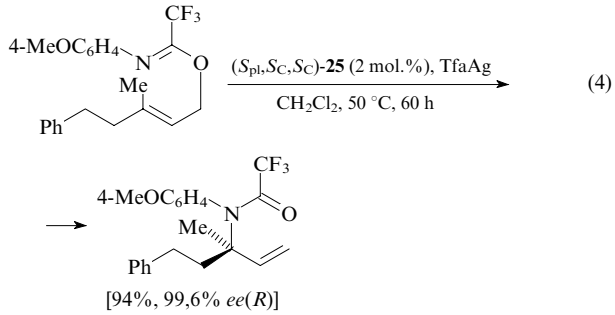
The enantioselectivity higher than 90% was achieved in the reactions with the use of complexes **16**–**19** (90%–97% *ee*),[34,41] but the catalytic activity of 3-silylated derivatives **17**–**19** was low. To obtain high yields (~90%), it is necessary to elevate the temperature to 40 °C and/or to increase the reaction time to 6 days. On the contrary, 3-arylated analogues **20**–**24** are efficient at room temperature.[40] Unfortunately, all dinuclear μ-iodide complexes require pre-activation by the dehalogenation with silver trifluoroacetate. In addition, as exemplified by complex (R_{pl},S_C)-**17a**, both the activity of the catalyst (the yields range from 11% to 96%) and the enantioselectivity of the reaction (43%–97% *ee*) are highly sensitive to the structure of the substrate.[34] It should be noted that the substituent R^1 in the allylic moiety is determined by the structure of the target allylamine and should remain intact, whereas both groups at the C=N bonds in the imidate [R^2 and R^3; see reaction (1)] only belong to the protecting function in the starting compounds, which is removed in the last step and, consequently, the modification of these groups is often an additional tool for the control of the process.

In the next step of the optimization of the structures of ferrocenyl catalysts, the steric complication of the non-metallated cyclopentadienyl ring was performed. The enantioselectivity of reaction (1) catalyzed by complexes (S_{pl},S_C,S_C)-**25**[42,43] or (R_{pl},R_C,S_C)-**26**[44] is 98% *ee* and the products are formed in high yields (94% – 96%), but these reactions generally occur at elevated temperature (40 – 50 °C).



(S_{pl},S_C,S_C)-**25** (R_{pl},R_C,S_C)-**26**

An important advantage of *N*-sulfonylated CPC (S_{pl},S_C,S_C)-**25** is that the reactions with substrates with the *E* configuration can be performed at room temperature. In addition, a substantial decrease in the catalyst loading (from 5.0 mol.% to 0.05 mol.%) is not accompanied by a decrease in its activity and the enantioselectivity of the reaction.[43] Catalyst **25** can be used to prepare allylamides containing quaternary C* stereocentres in an almost stereospecific manner (up to 99.6% *ee*) although under slight heating [reaction (4)].[42]

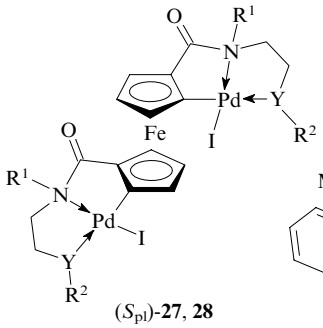


(4)

[94%, 99,6% *ee*(*R*)]

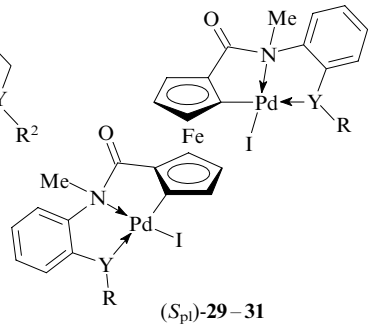
The authors suggested that the high catalytic activity of palladacycles **25** and **26** [belonging to the FIP family (Ferrocenyl Imidazoline Palladacycles)] is determined by electron-withdrawing properties of the phenyl rings enhancing the Lewis acidity of the metal centre. Apparently, the enantioselectivity of these structures is to a large extent determined by conformational restrictions imposed by the bulky Ph_5C_5 moiety. Unfortunately, both catalysts work only after pre-activation by silver salts.

The CNY-bis(palladacycles) (**27** – **31**)[45] and CN-bis(palladacycles) (**32**) containing the ferrocenyl backbone proved to be highly efficient.[46,47] The rearrangement (1) catalyzed by the trifluoroacetate analogue of complex (S_{pl})-**29** with the use of *Z*-configurated substrates affords products in high chemical and optical yields (91%, 92% *ee*) at room temperature in 0.5 h. The high efficiency of such bifunctional catalysts was attributed[45] to the simultaneous involvement of the second palladacycle in the coordination to the oxygen atom of the imidate moiety. Formally, complexes **27** – **31** belong to bicyclic CNY-type structures due to the presence of the additional donor heteroatom Y. However, since only complexes containing an alkoxy substituent proved to be highly active, these reactions are apparently also catalyzed by monocyclic CN-palladacycles.



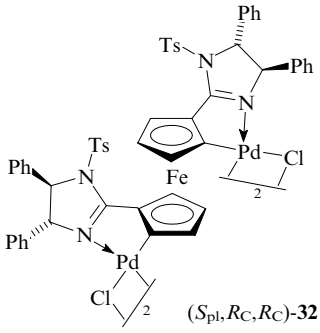
(S_{pl})-**27**, **28**

R^1 = Me, YR^2 = NMe_2 (**27**);
R^1 = $(CH_2)_2OMe$,
YR^2 = OMe (**28**).



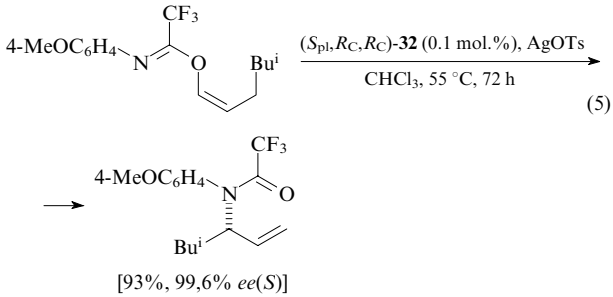
(S_{pl})-**29** – **31**

YR = SMe (**29**), OMe (**30**), OPr^i (**31**).



(S_{pl},R_C,R_C)-**32**

Excellent results have been recently obtained with the use of CN-type bis(palladacycle) (S_{pl},R_C,R_C)-**32** containing donor imidazoline groups belonging to the FBIP family [1,1′-Ferrocenyl-Bis(imidazoline) Palladacycles] as catalysts.[46,47] The activation of the staring dinuclear μ-Cl complexes with an excess of AgOTs resulted in the optical yields up to 99% at low catalyst loadings (lower than 0.5 mol.% at room temperature and even lower than 0.05 mol.% at 55 °C). This catalytic system is applicable to less reactive substrates with the *Z* configuration [reaction (5)] containing various functional groups, such as carbonyl, alkoxycarbonyl, acetal, silyl ether or protected amino groups.



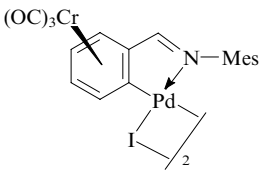
(5)

[93%, 99,6% *ee*(*S*)]

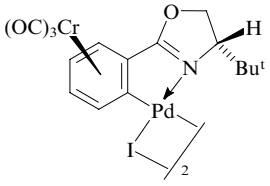
It was hypothesized[46] that the high activity of FBIP catalysts is determined by a decrease in the electron density at the metal centres as a result of the sulfonylation of the imidazoline moieties.

In spite of profound advances in the catalysis of reaction (1) by ferrocenyl CPC, their common drawback is that

they are prone to the oxidation. As a result, these complexes are often decomposed by silver(I) salts required for the dehalogenation of the pre-catalyst, which necessitates the use of toxic thallium(I) salts.[34, 39, 48] Hence, it was reasonable to study other types of planar chiral CPC. The results of experiments with chromium tricarbonyl complexes **33** and **34** were not promising. These catalysts are moderately efficient (75%, 80% *ee*) and have no prospects because of the necessity of the use of the toxic reagent (TlOTf) in the activation step.[34]

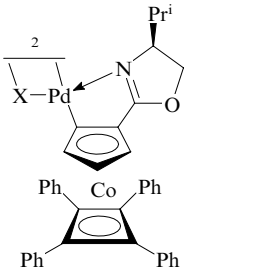


(R_{pl})-**33**



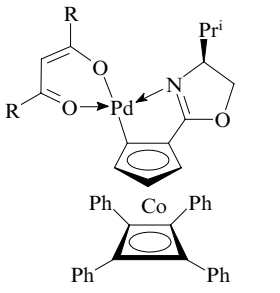
(R_{pl},S_C)-**34**

Many of the above-mentioned problems associated with the palladacycle catalysis were resolved with the use of the cobalt sandwich complexes (**35** and **36**) belonging to the COP family (Cobalt Oxazoline Palladacycles), which were synthesized for the first time by Richards.[49–52] Although one of the complexes of this type, **35d**, has been used earlier by Kang *et al.*,[53] this catalytic system was developed in detail by Overman and co-workers.[41, 50, 54–56]



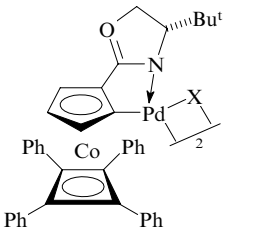
(R_{pl},S_C)-**35a–d**

X = Cl (**a**), Br (**b**), OAc (**c**), Tfa (**d**).



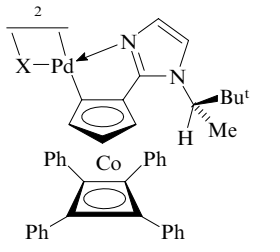
(R_{pl},S_C)-**35e**,**f**

R = Me (**e**), CF_3 (**f**).



(S_{pl},S_C)-**36a–c**

X = Tfa (**a**), Cl (**b**), OAc (**c**).



(R_{pl},S_C)-**37a–c**

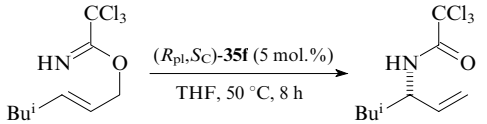
X = Cl (**a**), Tfa (**b**), OAc (**c**).

In addition to the high catalytic activity and enantioselectivity of COP-type palladacycles **35** and **36**, they have a number of considerable advantages. First, they are active directly as dinuclear μ-chloride complexes,[55, 56] whereas other types of CPC are generally inactive in this form and require the pre-dehalogenation by silver salts [34, 37, 42, 44, 47] or toxic thallium salts.[34, 39, 56] Moreover, the variation of the nature of the anions in dinuclear complexes **35** showed that both their activity (the yields of the products are 61%–72%) and enantioselectivity (93%–96% *ee*) remain virtually unchanged in the case of Cl, Br, OAc and Tfa anions; the reaction rate sharply decreases only in the reactions with the use of the dinuclear iodide complex, the optical yields remaining the same (11%, 93% *ee*).[57] Apparently, the two most popular forms of the dinuclear molecule, *viz.*, chloride (**35a**) and trifluoroacetate (**35d**), can be considered as complementary catalysts because the former provides higher optical yields in the reactions with substrates with the *E* configuration,[55, 56] whereas the latter is more favourable for *Z*-allylic amidates.[56]

A considerable advantage of this class of catalysts is their high tolerance to the structure of the substrate. Dinuclear catalysts **35a**,**d** are often almost equally efficient in the reactions with substrates having the *Z* or *E* geometry, which determines the absolute configuration of the target allylamine.[56] These catalysts can be used for the reactions with imidates containing *N*-acyl and *N*-aryl groups providing high enantioselectivity with minimal complications in the step of deprotection of allylamides. Thus the deprotection of *N*-(*p*-anisyl) trifluoroacetimidates results in 70%–80% yields,[56] whereas the removal of the benzoyl and *p*-anisyl groups generally leads to yields lower than 40%.[41] It became possible to perform the rearrangement of substrates containing various functional groups, as well as of available trichloroacetimidates, which were subjected to competitive elimination in the presence of other catalytic systems.[55] Moreover, these palladacycles are efficient in the reactions with *N*-unsubstituted trichloroacetimidates, which excludes the removal of the *N*-aryl group from the resulting amides,[56] whereas the *N*-acyl group [$Cl_3CC(O)$] in these compounds is effectively removed under various conditions.[54, 55]

Due to the high catalytic activity of oxazoline CPC **35** and **36** compared to that of their imidazole analogues **37**, the reactions with the use of these catalysts can be performed at room temperature, although they require longer time (30–60 h).[53, 56]

More success was achieved with the use of mononuclear β-diketonate derivatives **35e**,**f** instead of dinuclear μ-chloride complex **35a**. Due to their higher solubility, a wider range of various-polarity solvents can be used and the reactions can be performed in more concentrated solutions (up to 2.6 mol litre^{-1}).[54] At elevated temperature (38–50 °C), the reaction time decreases to 6–12 h (compared to 60 h for **35a**); the activity and enantioselectivity of CPC **35e**,**f** remain high at the standard catalyst loading [5 mol.%; yields of the product were 80%–99%, 91%–98% *ee*; reaction (6)] and change only slightly as the concentration of complex **35f** decreases to 1 mol.% (86%–95%, 91%–95% *ee*).



(6)

[99%, 98% *ee*(*S*)]

The drawback of these catalytic systems is that the reaction rate is substantially lower in the case of substrates with the *Z* configuration compared to the corresponding *E* isomers.

A comparison of the efficiency of dinuclear trifluoroacetate complexes (R_{pl},S_C)-**35d** and (S_{pl},S_C)-**36a** characterized by different combinations of the configurations of the C* stereocentre and the chiral plane shows that the latter

plays a decisive role. Thus the use of the catalyst (S_{pl},S_C)-**36a** leads not only to the inversion of the configuration of the reaction product but also to a decrease in the optical yield (from 81%–95% to 36%–58%) compared to the catalyst (R_{pl},S_C)-**35d** due to the mismatch contributions of two chirality inductors.[50] This effect is even more pronounced in the pair of the corresponding dinuclear μ-chloride complexes. Thus the use of complex (S_{pl},S_C)-**36b** instead of catalyst (R_{pl},S_C)-**35a** resulted in a decrease in the chemical yield from 72% to 25% and in the optical yield from 93% to 28%.[57]

The main drawback of COP-type CPC is that high catalyst loadings are required (generally 5 mol.% or 10 mol.%–11 mol.% of the dinuclear complex are used, which corresponds to 10 mol.% or 20 mol.%–22 mol.% with respect to the palladacycle).[35,39] A decrease in the concentration of catalyst **35a** to 0.25 mol.% required an increase in the temperature to 60–80 °C, but the yields of the product were at most 63%–79%, although the level of enantioselectivity was retained (89%–95% *ee*).[57] Recently, an attempt has been made to use an alternative approach to the solution of this problem by the immobilization of palladacycles on a PPh_2-containing polymer with the aim to regenerate and reuse the catalyst. The results of the first catalytic cycle were satisfactory (the yield of the product was 91%, 94% *ee*) at a concentration of the catalyst of 1.7 mol.% and at 50 °C, but the activity of the regenerated CPC in two subsequent experiments sharply decreased first to 27% and then to 17%.[57]

The practical value of a catalytic system is to a large extent determined by the availability of the catalyst. Of the above-mentioned CPC, only a few compounds are commercially available in an enantiomerically pure form (for example, both enantiomers of **1a**, **3** and **35a**,**c**); for other catalytic systems, the problem of the synthesis of optically active catalysts remains to be solved. Of the two possible approaches, the direct activation of the C–H bond by an appropriate palladium(II) compound seems to be more attractive. This method was used for the synthesis of complexes **1a**, **2**–**4**, **5a**, **6**,[35,38,58] **7**–**9**,[5,37,39] **25**, **26**,[43,44,59] **32**[46,47,60] and **35c**–**37c**[49,51,52] by the reactions of optically active ligands with $[PdCl_4]^{2-}$ or $Pd(OAc)_2$. For most of these structures, not only the activation of the C–H bond is required but also the diastereoselectivity associated with the formation of a new chiral element is of importance. Among the complexes most efficient as catalysts, only COP-type palladacycles can be synthesized as one diastereomer, whereas the diastereoselectivity¶ of the formation of their FIP- and FBIP-type analogues, though being rather high (*dr* of the product varies from 16:1 to 38:1 for complexes **25** and **26**), is complete only in the case of CPC **16** and **32** (*de* > 98%).

Most of ferrocenyl CPC, *viz*., complexes **10**–**15**,[39] **16**–**24**[34,40,41,61–63] and **27**–**31**,[45] and chromotricarbonyl compounds **33** and **34**[34,56,64] were synthesized according to an alternative procedure based on the oxidative addition of the pre-functionalized ligand to a palladium(0) compound, generally $Pd_2(dba)_3$ (dba is dibenzylideneacetone) or the transmetallation of toxic organomercury precursors followed by the separation of diastereomers.[64] These methods have the serious disadvantages compared to the above-described approach in several aspects:

1) both methods are labour-intensive and multistep; the former method often involves the double lithiation if it is necessary to protect the undesired site of metallation by the silyl group;

2) all steps are performed with the use of an optically active precursor, which leads to substantial losses of expensive chiral compounds;

3) since ligands are generally functionalized by iodination, the final CPC are formed as catalytically inactive dinuclear μ-iodide complexes, which requires the replacement of iodide by another anion.

An analysis of the results of [3,3]-sigmatropic rearrangements catalyzed by cyclopalladated complexes shows that their activity and enantioselectivity strongly depend on the structure of the substrate. The nature of the substituent R^1 in the vinyl position [see reaction (1)] is of most importance because this substituent remains intact in the final allylamine. Practically acceptable chemical and optical yields were obtained only in the reactions of substrates containing little-branched substituents (R^1 = Me, Pr^n, Bu^i, Bn, $PhCH_2CH_2$); if R^1 = Pr^i, the reaction rate is usually substantially lower. Attempts to apply this approach to substrates with R^1 = Ph or Bu^t failed even with the use of the most effective catalysts.

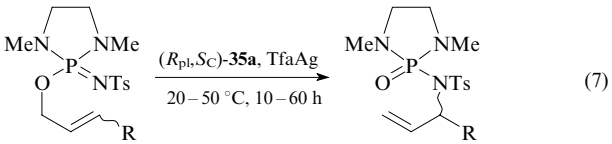
Another problem is a substantial decrease in the reaction rate in the case of substrates with the *Z* configuration compared to the corresponding *E* isomers, although the dependence of the enantioselectivity of the reaction on the geometry of the substrate is, as a rule, inverse. The removal of this undesired dependence would make it possible to synthesize both enantiomers of allylamine in the presence of catalysts with the same configuration.

Although the substituents R^2 and R^3 at the C=N bond belong only to protecting groups, which are eliminated during the transformation of amide into amine, their nature is important for two reasons: 1) their electronic and steric parameters have a substantial effect on the rate and enantioselectivity of the reaction; 2) in the design of this fragment of the substrate, the ease of the deprotection should be taken into account because it determines the final yield of the target allylamine. Unfortunately, the opposite requirements are imposed on the substituents R^2 and R^3 in the substrate in these two steps. This approach has great practical value due to the development of catalytic systems working efficiently in the reactions with *N*-unsubstituted substrates (R^3 = H), as well as with derivatives of halogenated carboxylic acids Cl_3CCO_2H and F_3CCO_2H,[30] whose amides are readily hydrolyzed.

2. Oxa- and thia-Claisen rearrangements

In recent years, asymmetric vesions of other [3,3]-sigmatropic rearrangements have attracted attention. The aza-phospha-oxa-Cope rearrangement is most closely related to the Overman rearrangement with the only difference that pentavalent phosphorus derivatives are used instead of acyl groups for the protection of the amino group.[65] The choice of these unusual protecting groups is based on the known fact that the transformation of the P^V=N bond into the P^V=O bond is thermodynamically favourable.

¶ The diastereoselectivity is expressed as the diastereomeric ratio (*dr*) or as the diastereomeric excess (*de*).



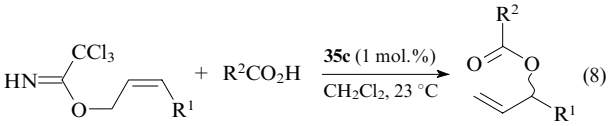
(7)

(16% – 97%, 82% – 96% *ee*)

R = Me, Et, Pr^n, CH_2OTBS (TBS is *tert*-butyldimethylsilyl).

(Allyloxy)iminodiazaphospholidines were chosen as substrates. The best results in the asymmetric version of the rearrangement of these compounds into *N*-tosylallylamines [reaction (7)] were obtained with the use of COP-type palladacycle in the form of trifluoroacetate **35d** (5 mol.%) generated *in situ* from chloride **35a** by the treatment with TfaAg. This catalytic system was studied in the reactions of alkyl-substituted substrates with unbranched groups. There is the inverse dependence of the results of the reaction on the geometry of the substrate compared to that typical of the Overman rearrangement. Thus the reaction rate for *E* substrates is substantially lower than that for their *Z* analogues, and the enantioselectivity is lower as well. For example, the chemical yields of allylamine derivatives in the reactions of the *E* and *Z* isomers (R = Et) are 43% and 97%, respectively; the optical yields are 84% and 92% for the *S* and *R* enantiomers, respectively. Unfortunately, it is difficult to evaluate the practical value of this method for the synthesis of allylamines because of the lack of data on the removal of the diazaphospholidine protecting groups.[65]

Two other versions of the [3,3]-sigmatropic rearrangement referred to as the oxa-Claisen rearrangement are suitable for the synthesis of chiral allyl carboxylates[66] or allyl ethers of phenols.[67] In these methods developed by Overman, *Z*-configured trichloroacetimidates are used as substrates, and both enantiomers of dinuclear μ-acetate complex **35c** belonging to the COP family serve as the catalyst. According to the mechanistic scheme, the former process[66] leads to the formation of a new C*—O bond after the π-coordination of palladacycle to the alkene moiety of the substrate in the step of transesterification of the starting acetimidate by an appropriate carboxylic acid.



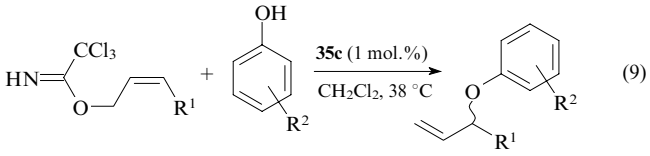
(8)

(87% – 100%, 94% – 99% *ee*)

R^1 = Pr^n, Bu^i, CH_2OH, CH_2OAc, CH_2OPMB, $(CH_2)_3OTBS$, Cy;
R^2 = Me, Pr^i, Bn, Ph, 4-$MeOC_6H_4$, 2-$O_2NC_6H_4$, 2-Naph
(PMB is *p*-methoxybenzyl, Cy is cyclohexyl, Naph is naphthyl).

The efficiency of this catalytic system is evident from the characteristics of the process presented in Scheme (8). This system can be used in reactions with a wide range of substrates; however, the presence of branched substituents (R^1 = Cy) leads to a substantial decrease in the reaction rate. The excellent characteristics are retained in a wide range of structures of carboxylic acids, which can be either aliphatic (R^2 = Me, Pr^i, Bn) or aromatic (R^2 = Ph, 2-Naph, 4-$MeOC_6H_4$, 2-$O_2NC_6H_4$). The reaction is completed in 8 – 26 h at room temperature and requires rather small amounts of catalyst **35c** (1 mol.%). The natural limitation is that only substrates with the *Z* configuration can be used. The rearrangements of these substrates into allylamines occur much more slowly compared to that of the *E* isomers, which leads to a decrease in the contribution of side reactions. The reactions catalyzed by complex (R_{pl},S_C)-**35c** afford *R* enantiomers of allyl ethers, and the problem of the preparation of both enantiomers of the final product from one and the same substrate is solved by using two enantiomeric forms of CPC **35c**.[66]

The equally high efficiency was observed in the asymmetric synthesis of 3-aryloxyalk-1-enes catalyzed by palladacycles **35c** [reaction (9)].[67]

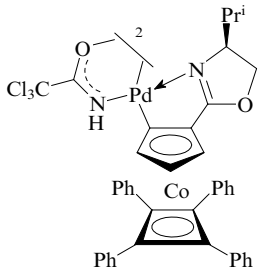


(9)

(80% – 97%, 90% – 98% *ee*)

In these reactions, the substituents in both phenols (R^2 = H, 4-Me, 4-OMe, 4-Cl, 2-Br, 2-OAc, 3-OAc, 4-OAc, 3-CHO, 2,6-F_2) and acetimidates (R^1 = Pr^n, CH_2OTBS, $CH_2OTBDPS$ (TBDPS is *tert*-butyldiphenylsilyl), CH_2CH_2Ph, CH_2CH_2OAc, CH_2CH_2OTBS) can be varied in a wide range with the retention of high chemical and optical yields. The exceptions are branched substituents at the double bond (R^1 = Cy) in acetimidates and electron-withdrawing substituents (R^2 = NO_2) in phenols.[67] In this allylation reaction of phenols, the extremely high ratio (up to 800 : 1) of branched to linear reaction products (3-aryloxyalk-1-enes and (*Z*/*E*)-1-aryloxyalk-2-enes) was obtained.[67] Among the advantages of these two versions of the asymmetric oxa-Claisen rearrangement are that both enantiomers of the catalyst are commercially available, low catalyst loadings (1 mol.%) are required and the reactions give products in high chemical (up to 100%) and optical (up to 99% *ee*) yields under mild conditions.

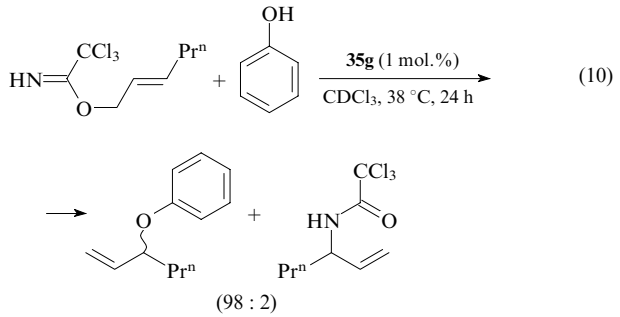
Earlier, this process has been applied only to *Z* substrates because the corresponding *E* isomers are easily rearranged into allylamines (see Section II.1). Recently, this problem has been resolved by the slight structural modification of COP catalysts.[68] The replacement of the carboxylate bridges in dinuclear complex **35c** with amidate bridges in analogue **35g** leads to a sharp decrease in the catalytic activity of the complex in the aza-Claisen rearrangement of the *E* substrates.



(R_{pl},S_C)-**35g**

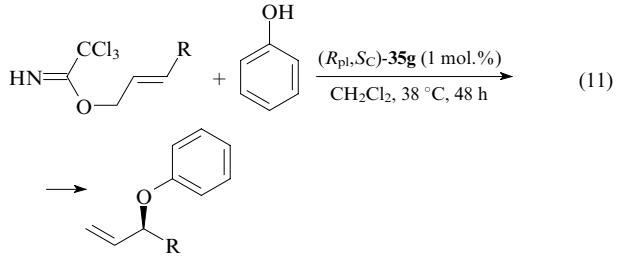
Thus the ratio of two possible products of the competitive reactions of trichloroacetimidate with phenol, *viz.*, ether and amide, is 98 : 2 in the presence of dinuclear complex **35g** as the catalyst [reaction (10)] compared to the ratios of 31 : 69 and 59 : 41 in the transformations catalyzed

by dinuclear μ-chloride and μ-acetate complexes **35a** and **35c**, respectively.



(10)

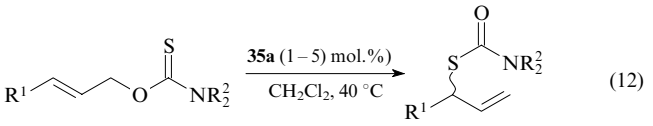
Based on these results, an excellent catalytic system was developed for the allylation of phenols with *E*-allylic trichloroacetimidates. The thorough optimization of the nature of the solvent, the reactant ratio and the catalyst loading resulted in an increase in the enantioselectivity to 98% *ee*, the products being obtained in satisfactory chemical yields [reaction (11)].[68]



(11)

R = $(CH_2)_3N(Bn)Boc$ (Boc is *tert*-butoxycarbonyl).

Overman *et al.*[69] developed also a method for the synthesis of alk-2-enethiol derivatives based on the catalytic thia-Claisen rearrangement of linear prochiral *O*-allylic thiocarbamates [reaction (12)].



(12)

(72% – 98%, 57% – 87% *ee*)

In this reaction, numerous COP-type catalysts were tested and the structure of the protecting group in the substrate was optimized. The reactions of *O*-allylic thiocarbamates (R^2 = Me, Et; or R^2_2NH is azetidine or pyrrolidine) containing unbranched substituents in the alkene moiety [R^1 = Pr^n, Bu^i, CH_2OH, CH_2CH_2Ac, CH_2OTBS, $CH_2OTBDPS$, $CH_2N(Ph)Boc$, CH_2OTIPS, where TIPS is triisopropylsilyl] catalyzed by dinuclear μ-chloride complex **35a** (1 mol.% – 5 mol.%) at high temperature afford thiocarbamates in yields up to 98% with an enantiomeric purity of up to 87%. Advantages of this method are that the reactions are highly regioselective, the starting substrates can be easily synthesized and the corresponding thiols can be prepared by the simple reduction of the resulting *S*-allylic thiocarbamates.[69]

In spite of the excellent advances in the enantioselective catalysis of the [3,3]-sigmatropic rearrangements employing palladacycles, there are still several areas to be developed. First, most of the designed systems are based on large amounts of the catalyst (up to 10 mol.% of the dinuclear complex, which corresponds to 20 mol.% of the palladacycle). For their practical application, it is desirable to decrease the catalyst loading and to use milder temperature conditions; nowadays, many of the most efficient catalysts work at 50 – 70 °C. Apparently, these problems can be solved by designing and using new, more perfect CPC.

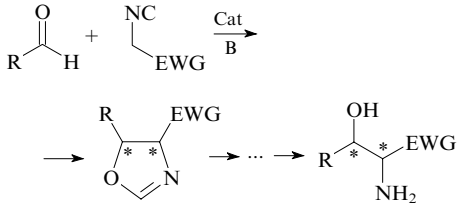
Recent detailed studies of the mechanism of the asymmetric induction by COP-type palladacycles by an example of *N*-unsubstituted trichloroacetimidates have contributed significantly to the development of this promising area of enantioselective catalysis.[36] Investigations of the kinetics and calculations of the reaction pathway by the density functional theory (DFT) method showed that the stereochemistry of the reaction is determined in the step of the formation of a new C – N bond and is controlled by the planar chirality of the catalyst.

Nowadays, the asymmetric version of the aza-Claisen rearrangement can be considered as the method of practical application. This can be exemplified by the use of allylamines or trichloroacetamides synthesized by this method for the preparation of alkaloids, antibiotics, amino sugars and non-natural α-amino acids,[28, 54] as well as of 4-vinyloxazolidinones and (*S*)-vigabatrin, which is a GABA aminotransaminase inhibitor (GABA is γ-aminobutyric acid).[55]

Recent progress in this field clearly illustrates considerable possibilities offered by palladacycles in the enantioselective catalysis of other processes.

III. Aldol condensation

The classical version of the aldol condensation involves the addition of enolates to the carbonyl group of aldehydes or ketones to form β-hydroxycarbonyl compounds. Numerous versions of asymmetric catalysis of this reaction by aldolases,[70] chiral organic compounds[71, 72] or oxophilic metal (Ti, Zr, Sc, La, Sn, Zn, Cu) complexes[70 – 72] were documented. The potential of coordination compounds of softer transition metals (Au, Ag, Rh) as catalysts for the aldol condensations is generally estimated based on the reaction of aldehydes with isocyanides containing electron-withdrawing groups (EWG) at the α-carbon atom [reaction (13)].[70, 73] This transformation affords 4,5-disubstituted 2-oxazolines as the primary products, whose hydrolysis (EWG = CO_2Alk) provides a route to β-hydroxy-α-amino acid derivatives, which are of interest not only as biologically active compounds but also as valuable building blocks for fine organic synthesis.



(13)

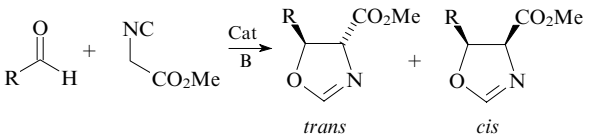
B is a base.

First versions of enantioselective catalysis of this process by transition metal coordination compounds were developed in 1986,[74] but first attempts to use optically active CPC as catalysts for these reactions were made only a decade later.[75, 76] Until recent past, the aldol condensation was catalyzed only by pincer NCN-,[78 – 84] SCS- (Ref. 85) or

PCP-type [75, 86, 87] CPC [22, 25, 27, 77] with the aim of encapsulating the metal centre into a chiral pocket. Usually, the catalyst is transformed into cationic aqua or solvated species to obtain a coordination vacancy. It was suggested [75, 80, 85] that the role of catalysts in these reactions is to activate isonitrile through its C-coordination to the metal atom thus facilitating the deprotonation of this reagent with a base. This leads to the formation of the α-cyanocarbanionic intermediate, whose chiral environment dictates the stereochemistry of its subsequent attack on aldehyde. The formation of such adducts of metallacycles with isonitriles was confirmed by spectroscopy (^{1}H NMR) of the platinum analogue of one of pincer CPC.[80]

Preliminary tests of cyclopalladated catalysts are usually performed using the model reaction of benzaldehyde with methyl isocyanoacetate [reaction (14), R = Ph]; in some cases, the structure of aldehyde [75, 78, 80, 84, 85] or isonitrile [80, 87] is then varied. As a rule, the condensation is carried out with the use of 1 mol.% of the catalyst in the presence of 10 mol.% of diisopropylethylamine (Hünig's base) as a base in dichloromethane at room temperature. Attempts to improve these standard conditions by varying the nature of the solvent (THF, toluene) [86] or the base [1,4-diazabicyclo[2.2.2]octane (DABCO), Bu^n_3N, Et_3N] [80] failed. Relatively low catalyst loadings and mild reaction conditions with the participation of CPC are indicative of their high catalytic activity.

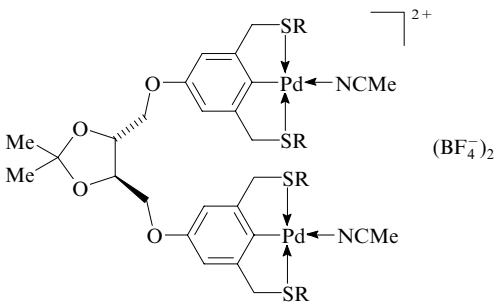
In addition to the usual problem of the enantioselectivity of the reactions, the development of a catalytic system for the aldol condensation faces also the problem of an increase in its diastereoselectivity because this process involves the formation of two C* stereocentres in oxazolines; in the general case, the latter are formed as four *trans*- and *cis*-diastereomers [see reaction (14)]. Usually, *trans* diastereomers are formed as the major products. With rare exception,[81, 84, 85] the ratio of the isomers $E:Z$ varies from 62 : 38 to 99 : 1.



(14)

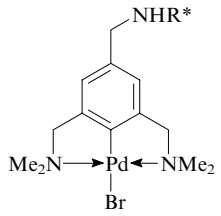
Most of NCN-type catalysts exhibit good catalytic activity (the conversion is 60% – 99%), but the diastereoselectivity of the process is, as a rule, low. The fraction of the *trans* diastereomer of oxazoline in a mixture with the *cis* isomer is in the range of 57% – 75%. The percentage of the *trans* diastereomer increases to 95% only in the reactions with aliphatic aldehydes catalyzed by SCS complexes **38** and **39**, whose selectivity is equal to that in the absence of the catalysts.

The reactions catalyzed by most of NCN and SCS complexes (**38** – **44**) afford oxazolines either as a racemate or with very low enantiomeric excess (0% – 12% *ee*). The low level of enantioselectivity (*ee* < 3%) [82, 85] is quite understandable in the case of complexes **38** – **41** whose C* stereocentres are located at the periphery of the molecule; as a result the transfer of chiral information to the reaction centre is highly unlikely.



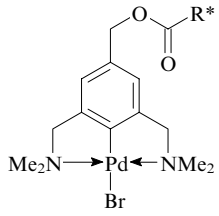
38, **39**

R = Bu^t (**38**), Ph (**39**).



40

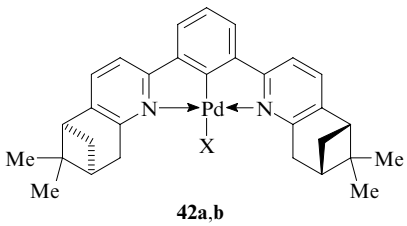
R* = (*S*)-CH(Pr^i)CO$_2$Me.



41

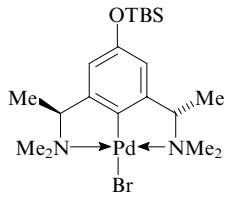
R* = (*S*)-CH(Pr^i)NHBoc.

The complete absence of the enantioselectivity in the catalysis by heptacyclic NCN complexes **42a**,**b** (0% *ee*) [79] can be attributed to both the high degree of planarity of the core of this structure and the large distance between the chiral terpene moieties and the metal centre. Additional complications can arise due to the problems associated with the formation of a coordination vacancy because the catalysis was performed with the use of derivatives containing the chloride or acetate anion strongly bound to the metal atom with the result that the reaction can occur mainly through the non-catalytic pathway.



42a,**b**

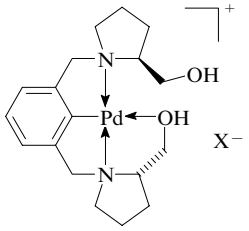
X = Cl (**a**), OAc (**b**).



43

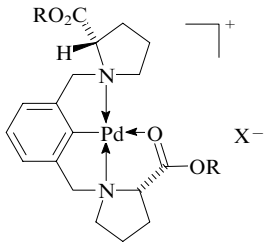
Among these inefficient catalysts, NCN complex **43** takes the first place; the standard model reaction [see reaction (14), R = Ph] in the presence of the latter complex affords oxazoline with 12% *ee*.[83] In this reaction, the catalyst was used as the cationic aqua derivative $[(N^{\frown}C^{\frown}N)Pd(OH_2)]^+$ generated *in situ* by the treatment of the starting bromide with $AgBF_4$. It could be expected that this complex would ensure the higher enantioselectivity taking into account the C_2 symmetry of the cation and the endocyclic arrangement of two C* stereocentres. The low efficiency of this catalyst can be attributed either to small steric demads of the NMe_2 groups or to dechelation of the palladacycles as a result of the replacement of the relatively hard N-donor atoms by softer C-donors of the isonitrile reagent [see reaction (14)], which is present in the reaction mixture in an excess.

A certain success was achieved with the use of NCN complexes **44**–**47** containing (*S*)-prolinate or (*S*)-prolinol moieties as the catalysts.[78,81,84] In these structures, the donor nitrogen atoms directly bound to the metal atom are asymmetric as a result of the 1,2-asymmetric induction caused by the C* stereocentres. Nevertheless, moderate optical yields of oxazoline (up to 42% for the *cis* isomer) were obtained only after the introduction of the bulky CPh_2 groups into the side chains of complexes **47**.[84] The reactions catalyzed by sterically less demanding CPC **44**–**46** give optical yields no higher than 16%.[78,81]



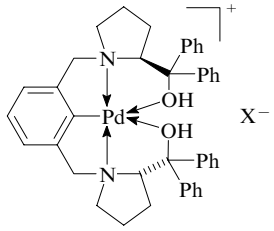
44a,**b**

X = PF_6 (**a**), BF_4 (**b**).



45a,**b**; **46a**,**b**

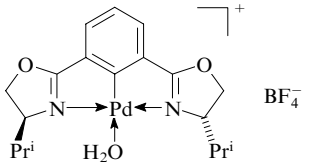
R = Me: X = PF_6 (**45a**), BF_4 (**45b**);
R = Bn: X = PF_6 (**46a**), BF_4 (**46b**).



47a,**b**

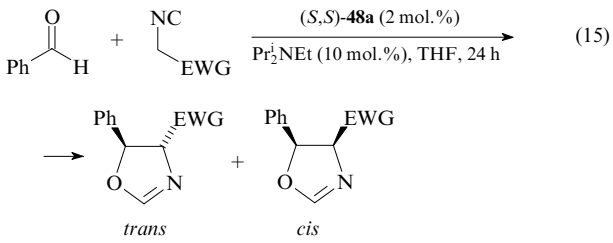
X = PF_6 (**a**), BF_4 (**b**).

An increase in the optical yield to 57% was observed in the reaction catalyzed by complex (*S*,*S*)-**48a** (X = BF_4) belonging to Phebox [phenylbis(oxazolinyl)] family of CPC.[80]



(*S*,*S*)-**48a**

This work deserves mention mainly because it showed that the enantioselectivity of the reaction can be increased by the modification of the structure of the electron-withdrawing group in the isocyanide component. A comparison of the results of the reactions with the involvement of two isocyanides shows that the replacement of the traditional methoxycarbonyl group in isocyanide by the *p*-toluenesulfonyl (tosyl) group provides not only a considerable enhancement of the enantioselectivity of the reaction (*ee* from < 3% to 57%) but also an increase in the diastereoselectivity from moderate (*trans*:*cis* = 80:20) to complete (> 99% of the *trans* diastereomer), which is particularly important in the practical aspect [reaction (15)].

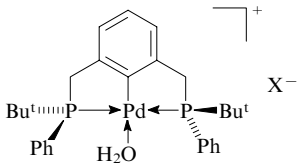


(15)

trans *cis*

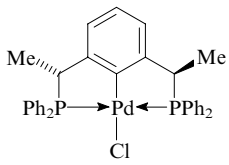
EWG = CO_2Me (23 °C): yield > 99%, 80% *trans*, *ee* < 3%;
EWG = SO_2Tol-*p* (0 °C): yield > 99%, 80% *trans*, *ee* < 57%.

Cyclopalladated PCP-type catalysts proved to be most efficient in the aldol condensation.[75,87] A series of tested pincer PCP complexes **49**–**51** is characterized by the structural and stereochemical diversity. These complexes catalysts contain phosphine (**49**, **50**) or phosphite P-donor atoms (**51**) with C* (**50**)[75] or P* stereocentres (**49**)[86] or with axial chirality elements (**51**)† (Ref. 87).

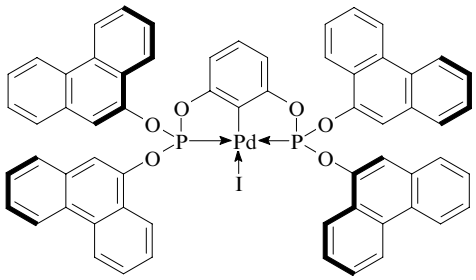


(*S*$_P$,*S*$_P$)-**49a**,**b**

X = BF_4 (**a**), OTf (**b**).



(*R*$_C$,*R*$_C$)-**50**



(*R*$_a$,*R*$_a$)-**51**

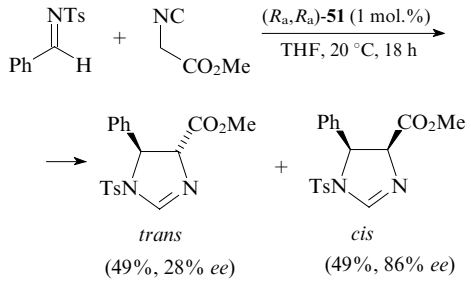
The design of P*-chiral cationic complexes **49a**,**b** was based on the idea of bringing the stereocentres in close proximity to the metal acting as the reaction centre.[86] Although the diastereoselectivity of the standard model reaction with the use of these complexes was rather high (94%–98% of the *trans* isomer), the optical yields were low (11%) in spite of attempts to optimize the reaction conditions.

Cationic derivatives of complex **50** generated *in situ* by the dehalogenation of the chloride with silver triflate were studied in most detail.[75] The standard test reaction [see reaction (14), R = Ph] affords the *cis* diastereomer of oxazoline with the 4*S*,5*S* configuration with an enantiomeric purity of 77%. The screening of a wide range of aldehydes, aromatic (including *meta*- and *para*-substituted) and heterocyclic, as well as aliphatic, revealed the high *trans*-selectivity of the reactions (67%–91% of the *trans* isomer). In all cases, the *cis* diastereomers of oxazoline are formed with a

† Hereinafter, the subscript 'a' indicates 'axial'.

higher enantiomeric purity than the corresponding *trans* isomers (the difference varies from two- to 50-fold). This is the main drawback of the catalytic system, because high optical yields can be obtained only for the minor reaction product.

The maximum enantioselectivity (86% *ee* for the *cis* isomer) was achieved in the modified version of the aldol condensation catalyzed by axially chiral complex (R_a,R_a)-**51**.[87] The condensation reactions of *N*-tosylimines instead of aldehydes with isocyanide in the absence of a base afford imidazoline derivatives [reaction (16)] in almost quantitative yield (98%), and these reaction products can be hydrolyzed to α,β-diaminocarboxylic acids.



(16)

The drawback of this catalytic system is that the diastereoselectivity of the reaction is relatively low. A comparison of the efficiency of complex (R_a,R_a)-**51** containing the bulkiest biphenanthrol moieties and its analogues synthesized from 1,1′-binaphthol or its 3,3′-bis(alkylthio) derivatives showed obvious advantages of the sterically more demanding catalyst (R_a,R_a)-**51**: the optical yields in the reactions with all other complexes were 12% – 64% for the *trans* isomer and 10% – 37% for the *cis* isomer.[87]

The solvent effects seem to be the most unusual feature in these reactions. Experiments with the catalyst (S_a,S_a)-**51** showed that the use of diglyme instead of THF leads to a substantial enhancement of the diastereoselectivity of the condensation (the *trans* : *cis* ratio increases from 1 : 1 to 4 : 1). It is more important that the enantiomeric enrichments for two diastereomers are inverted (*ee* from 18% and 72% in THF to 75% and 25% in diglyme for the *trans* and *cis* isomers, respectively). The reaction in dioxane affords both isomers in similar enantiomeric excesses (68% and 73%).[87]

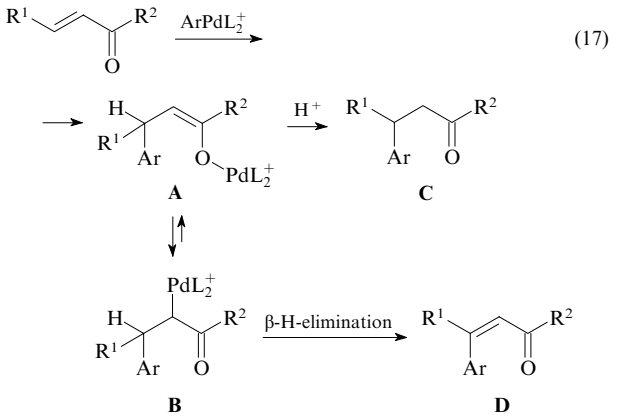
To sum up this section, it should be noted that many problems in the catalysis of the aldol condensations by cyclopalladated compounds remain to be solved. Undoubtedly, an in-depth investigation of the mechanism of these processes will be useful. A deep insight into this mechanism will assist in the development of a rational approach to the design of catalysts and the modification of the structures of substrates. It should be noted that the highest enantioselectivity of this process catalyzed by coordination compounds of gold was achieved with the use of tridentate P,P,N-donor ligands. The latter can not only be P,P-chelated to metals coordinated by isocyanide but also dictate the direction of the attack of aldehyde as a result of the interaction of the α-carbanionic moiety with the additional N-donor group located at the end of the rather long chain.[73, 74, 88] The possible contribution of secondary interactions (hydrogen bonds or π – π interactions between the aromatic rings of aldehyde and the catalyst) to the stereochemistry of the process was discussed by an example of NCN pincer CPC **47** containing additional hydroxy groups in the ligand.[84] However, the moderate enantioselectivity of the catalyst (35% – 42% *ee*) calls for the search for more efficient ways of employing secondary interactions. Perhaps, the use of monocyclic CPC containing an appropriate substituent in a sufficiently convenient position can lead to success.

The optimization of methods for the synthesis of cyclopalladated catalysts is also an important problem. Thus only a few of the above-mentioned pincer CPC (**32**,[85] **49**[86] and **50**[75]) were synthesized by the direct activation of the C – H bond of the ligand. The synthesis of these complexes is more often based on the oxidative addition of the corresponding aryl halides to palladium(0) compounds. This method was used for the synthesis of complexes **40** – **41**,[82] **43**,[83] **44**,[78] **45** – **46**,[81] **47**[84] and **49**.[86] An alternative approach involves the transmetallation of pre-mercurated[79] and pre-stannylated[80] ligands. For example, this method was used for the synthesis of catalysts **42** and **48**, respectively. An evident drawback of the latter two methods is that they are multistep because of the additional prefunctionalization of the ligand.

IV. Michael reaction

Various versions of the conjugate addition not only of carbo-[89] but also of heteronucleophiles (aza-,[90, 91] oxa-,[92] sulfa-[93] and phospha-Michael[94] reactions) to electron-withdrawing alkenes were developed. Many of these reactions were carried out in the catalyzed mode and in the asymmetric version. The most commonly used version of these transformations based on the employment of carbonucleophiles can be, by analogy, called the carbo-Michael reaction. Soft transition metals are generally used as catalysts for reactions with organometallic reagents[23, 95] or with carbanions generated *in situ* from malonates or α-cyanoacetates.[89]

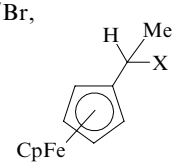
The catalysis of the conjugate addition of organometallic reagents to α,β-enones by palladium(II) compounds is not often used as a version of the Michael reaction because of a series of side reactions, resulting in a decrease in the yield of the target products. The catalytic cycle of these processes is based on the formation of the transmetallated key intermediate as an equilibrium mixture of enolate (**A**) and the major α-C-metallated species (**B**). The latter intermediate easily forms cross-coupling products (**D**) as a result of the β-hydride elimination, which competes with the main reaction giving β-arylated carbonyl compounds (**C**) from enolate **A** *via* protolysis[23] [reaction (17)].



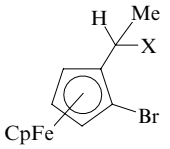
(17)

Hence, it is not surprising that only a few attempts to use CPC in the conjugate addition of organoboron reagents to α,β-unsaturated carbonyl compounds were repor-

ted.[96–98] The arylation of cyclohex-2-enone by arylboronic acids is generally used as the model reaction. The detailed investigation with the use of racemic catalysts[96,98] showed that only the introduction of 2-bromo-substituted 1-ferrocenylethylphosphine *rac*-$L^{52}Br$‡ provides the catalytic activity of $Pd(dba)_2$. It should be noted that the reaction does not proceed in the presence of 2-unsubstituted phosphine *rac*-HL^{52} and its N-donor analogues *rac*-HL^{7} and *rac*-$L^{7}Br$,



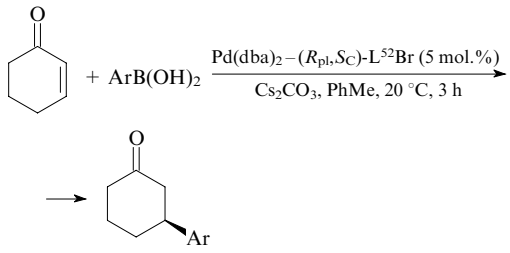
X = NMe_2: *rac*-HL^7;
X = PPh_2: *rac*-HL^{52}.



X = NMe_2: *rac*-L^7Br;
X = PPh_2: *rac*-$L^{52}Br$.

as well as of mono- (PPh_3) and diphosphines such as 1,3-bis(diphenylphosphino)propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb), 1,1′-bis(diphenylphosphino)ferrocene (dppf) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP).

The optimization of the conditions for the reaction catalyzed by the $Pd(dba)_2$–(R_{pl},S_C)-$L^{52}Br$ system resulted in high chemical and optical yields of 3-phenylcyclohexanone [92%, 76% *ee*; reaction (18) for Ar = Ph], which is quite satisfactory for the first attempt.

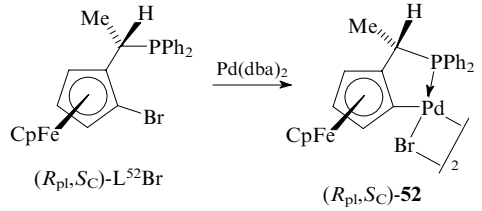


(18)

[92%, 76% *ee*(*S*)]

It was shown[96] that this catalytic system can be applied to the reactions of cyclic and acyclic α,β-enones with various arylboronic acids [Ar = 1-Naph, 4-RC_6H_4 (R = H, Me, MeO, F, Bu^t), 3-MeC_6H_4]. The enantioselectivity is in the range 42%–79% *ee*; it decreases to 25% or 4% after the introduction of the *ortho*-substituted (*o*-tolyl) or electron-withdrawing (4-$CF_3C_6H_4$) aryl group, respectively, into the reagent $ArB(OH)_2$.

Since these reactions were catalyzed only by 2-bromo-substituted phosphine (R_{pl},S_C)-$L^{52}Br$, the authors reasonably suggested that the latter undergoes oxidative addition to palladium(0) to form CP-palladacycle (R_{pl},S_C)-**52** [reaction (19)], which is the true catalyst.



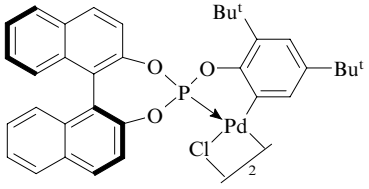
(R_{pl},S_C)-$L^{52}Br$ (R_{pl},S_C)-**52**

(19)

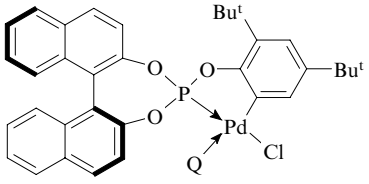
‡ Hereinafter, the superscript in the code of the ligand HL^n or L^nX corresponds to the ordinal number of the cyclopalladated complex.

This idea was at the basis of the catalytic cycle for the arylation of α,β-enones[96] involving the oxidative addition of bromide (R_{pl},S_C)-$L^{52}Br$ to palladium(0) followed by arylation of the resulting CP-palladacycle **52** with $ArB(OH)_2$ (transmetallation) and the η^2 coordination of the C=C double bond of α,β-enone to metal; in the final step, the intramolecular insertion of the alkene moiety into the Pd–C(Ar) bond occurs.

Attempts to perform the enantioselective catalysis of the same model reaction [reaction (18)] by dinuclear phosphite complex (S_a)-**53a**, its mononuclear derivative (S_a)-**53b**,**c**, as well as adducts of achiral palladacycles [(S_a)-**54** and (S_a)-**55**] with P-coordinated phosphite (S_a)-HL^{53}, failed.[97] The synthesis of dinuclear complex (S_a)-**53a** has been described earlier[99,100] and was later reproduced almost simultaneously by two research teams.[97,101] Bedford *et al.*[97] convincingly showed that the *ortho*-palladated structure of the catalyst plays a decisive role in the catalytic activity. Thus all CPC under examination provide the conversion of 84%–93% under mild conditions (at room temperature), while the conversion decreases to 14% in the case of the catalysis by the coordination complex *cis*-[$PdCl_2${(S_a)-HL^{53}}$_2$] with the same phosphite (S_a)-HL.[53] Unfortunately, the enantioselectivity was very low (4%–14% *ee*) for all catalytic systems and, consequently, it is impossible to discuss the structural factors.[97]

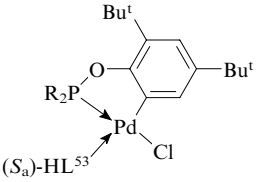


(S_a)-**53a**



(S_a)-**53b**,**c**

Q = PPh_3 (**b**), (S_a)-HL^{53} (**c**).

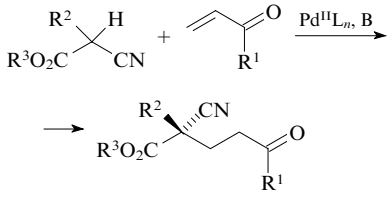


(S_a)-HL^{53}

(S_a)-**54**, **55**

R = 2,4-$Bu^t_2C_6H_3O$ (**54**), Pr^i (**55**).

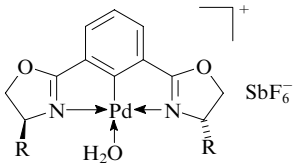
The potential of chiral CPC was evaluated in more detail in the conjugate addition reactions of pre-enolyzed α-cyanoacetates to α,β-enones. This version of the Michael reaction has certain advantages over the above-described reaction as an approach to the synthesis of functionalized structures containing the quaternary stereocentre. These compounds are valuable chiral building blocks in the fine organic synthesis [reaction (20)].



(20)

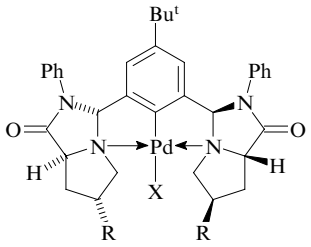
A few attempts to catalyze this process by palladacycles were documented;[76,102–105] however, the adequate analysis

of the reaction mechanism made it possible to enhance the enantioselectivity of the reaction from the initial value of 34% *ee* (Refs 76 and 105) to the practically acceptable level of 95%.[102] These reactions are generally performed with the use of 1 mol.% of the catalyst in the presence of amine Pr^i_2NEt as the base at room temperature. Initially the most popular cationic bis(oxazoline) NCN complexes (*S*,*S*)-**48** and **56**–**58** belonging to Phebox family were tested as catalysts.[76]



(*S*,*S*)-**48b**, **56**–**58**

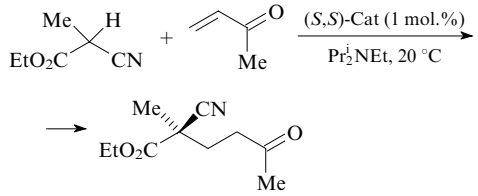
R = Pr^i (**48b**), Bu^i (**56**), Bu^t (**57a**), CH_2Cy (**58**).



(3*R*,7*aS*)-**59**–**62**

R = H: X = Cl (**59a**), OTf (**59b**); X = OTf: R = OH (**60**), OMe (**61**), OTBS (**62**).

The high catalytic activity of CPC was observed even in the first experiments with complex (*S*,*S*)-**48b**. Thus the complete conversion in the standard reaction (21) was obtained within a period shorter than 5 h, whereas the conversion in the reaction in the absence of the catalyst was only 3% after 4 h.[76] In a series of further experiments on the optimization of the catalytic system, including variations of the nature of the substituent (R = Pr^i, Bu^i, Bu^t, CH_2Cy in complexes **48** and **56**–**58**), the nature of the counterion and the solvent (dichloromethane and toluene) and the reaction time, results in an increase in the enantioselectivity from 6%–8% to 34% *ee*.[105]



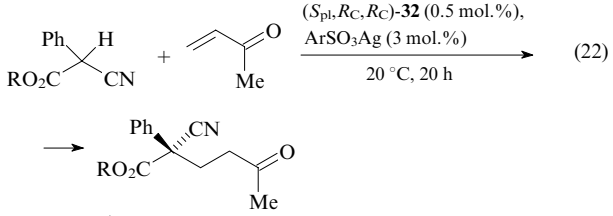
(21)

Cat.	X	Conditions	Yield (%)	*ee*(*R*) (%)
(*S*,*S*)-**48a**	BF_4	CH_2Cl_2, 3.5 h	67	8
(*S*,*S*)-**58**	SbF_6	PhMe, 120 h	86	34

Considerable progress in this field was made with the use of polycyclic pincer NCN complexes **59**–**62** containing N-donor pyrroloimidazolone moieties.[103, 104] Their catalytic activity strongly depends on the nature of the anion. Thus all complexes in the form of triflates provide high yields of the products (89%–97% after 3–4 h at 20 °C) even at low (smaller than 0.5 mol.%) catalyst loadings. By contrast, the yield of functionalized ketone in the reaction with the use of chloride derivative **59a** at twice its concentration is no higher than 2% even after 144 h as a result of coordination vacancy blocking by the chloride ion strongly bound to metal.

There is the striking difference in the enantioselectivity of four triflate derivatives **59b** and **60**–**62**. Thus only the use of complex **60** containing the hydroxy group in the pyrrole ring in the model reaction (21) resulted in optical yields of 80%–83%; the enantiomeric excess in the reactions catalyzed by its analogues **59b**, **61** and **62** is no higher than 6%–9% *ee*. This unique increase in the asymmetric induction was attributed to the fact that the hydroxy groups located near the metal centre of the catalyst fix the vinyl ketone molecule, in which the orientation of the double bond is determined by the stereochemistry of the chiral environment of the metal atom, through the OH···O=C hydrogen bond.[103] The most important result of the study under consideration is not high optical yields but the establishment of the fact that it is necessary to locate both substrates involved in the reaction on the same catalyst.

The idea of the simultaneous activation of two reagents on the same catalyst molecule was further developed in the recent study by Jautze and Peters.[102] The catalysis of the model Michael reaction by bimetallic complex (S_{pl},R_C,R_C)-**32** containing two CN-palladacycles at the ferrocene-1,1′-diyl backbone after the replacement of μ-chloride ions by arylsulfonate anions made it possible to resolve the problems typical of this transformation by the successive optimization of the structures of the reagents and the reaction conditions. The efficiency of this approach can be illustrated by the fact that the improvement of the catalytic system resulted in an increase in the optical yields from 4%–11% to 95% [reaction (22)]. The increase in the volume of the alkyl group of the CO_2R fragment in the cyanocarboxylate substrate (Me < Et < Bn < Bu^t) proved to be most efficient (the optical yields increase from 11% to 81%). A further increase in the volumes of the arylsulfonate group in the dehalogenating agent $ArSO_3Ag$ (Tol-*p* < Mes < 2,4,6-$Pr^i_3C_6H_2$), the optimization of the solvent and the discovery of the unexpected effect of acetic acid led to the record result: 95% *ee* and the quantitative yield (>99 %).



(22)

R = Me, $CHPr^i_2$.

Ar	Solvent	Yield (%)	*ee*(*R*) (%)
p-Tol	CH_2Cl_2	95	11
2,4,6-$Pr^i_3C_6H_2$	diglyme	>99	95

In addition to high enantioselectivity provided by the new catalytic system, the latter has the following advantages:

1) the restriction on the nature of the α-substituent in cyanocarboxylate is removed; all reactions were carried out with the previously forbidden α-arylated substrates, including α-Ar groups containing electron-donating and electron-withdrawing substituents in the *meta* and *para* positions;

2) the catalyst loadings are decreased to 0.1 mol.%–0.2 mol.% with almost no loss of the quality of the results;

3) the reactions do not require the presence of a base, which often causes side processes; on the contrary, the introduction of 10 mol.%–20 mol.% AcOH gives a positive effect;

4) diglyme was shown to be the solvent of choice, in which the reactions give products in quantitative yield with a high level of enantioselectivity;

5) it was found that the catalyst is not decomposed in the course of the reaction and, consequently, it can be regenerated and reused, which is cost-effective.

Only the problem of limitations on the structure of the substituent in vinyl ketones remains to be solved. Thus the rate decreases with increasing size of alkyl groups; in the reactions with aryl vinyl ketones, the enantioselectivity also decreases.

It was suggested that the success of the catalysis by bimetallic complex (S_{pl},R_C,R_C)-**32** is based on its ability to activate simultaneously both participants of the Michael reaction. The N-coordination of α-cyanocarboxylate to one palladacycle facilitates its enolization, whereas the coordination to the second palladacycle of α,β-enone through the C=C double bond leads to an increase in the electrophilicity. This gives rise to a highly organized transition state, resulting in an increase in both the catalytic activity and the degree of stereocontrol. The cooperative bimetallic mechanism of catalysis by bis(cyclopalladated) complexes was evidenced by the results obtained with the use of the monocyclic analogue (S_{pl},S_C,S_C)-**25**. The use of the latter catalyst leads to a decrease in the reaction rate by a factor of two, and the enantioselectivity not only decreases but also changes its sign.[102]

In conclusion, note that advances in the development of asymmetric versions of the Michael reaction due to the use of two-site[103] or two-centre[102] catalysis of the conjugate addition can give a powerful impetus to the further improvement of enantioselective cyclopalladated catalysts for other transformations according to the same mechanistic scheme.

V. Allylation of aldehydes and imines and allylic substitution

In this section, we consider reactions of organometallic allylic reagents at the C=O and C=N double bonds, as well as reactions of derivatives of allylic alcohols with C-nucleophiles catalyzed by chiral palladacycles.

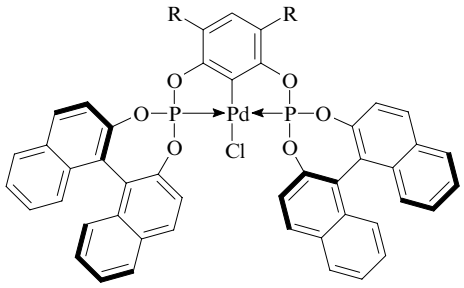
1. Allylation of aldehydes and imines

The asymmetric allylation of aldehydes and imines provides a route to chiral homoallylic alcohols and amines, respectively. Hence, these transformations are of practical importance. In these reactions catalysts generally act as Lewis acids capable of coordinating substrates through the carbonyl group thus activating it for the subsequent nucleophilic attack by allylic reagents.[106] However, the related processes with imines were assumed to occur through the transition state containing the η^1-bonded allylic group and κ^1-coordinated imine at the same metal centre.[21] The drawback of classical catalytic systems for these reactions is that they inevitably form bis(allylic) intermediates, resulting in undesirable side reactions, such as the cross-coupling of two allylic groups, as well as in the hard-to-control chemo- and regioselectivity.

In-depth studies of the catalysis of the allylation by achiral CPC[107–110] showed that these problems can be resolved by using pincer complexes. In the presence of these complexes, the reaction proceeds by another pathway, exclusively through the monoallylic intermediate because only one coordination vacancy is available in the transmetallation step due to the strong tridentate coordination of the cyclopalladated ligand.

In the initial stages of the development of these reactions, achiral phosphine[107,109,110] or phosphinite[108,111] PCP catalysts were mainly used, but the first experiments with phosphite analogues have already shown that the latter compounds have considerable advantages. Due to the high catalytic activity of the pincer complex (R_a,R_a)-**63** caused by the high π-acidity of the P-donor atoms, the reaction can be performed at 0 °C,[112] whereas the reaction catalyzed by the phosphinite analogue requires heating.[109]

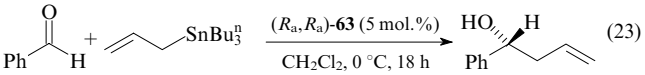
The development of asymmetric versions of the allylation of aldehydes and imines was initiated in 2006 and there are a few publications in this field. All studies were carried out with the use of pincer PCP complexes predominantly of one stereochemical type (containing phosphorus atoms in the axially chiral environment).



(R_a,R_a)-**63**, **64**

R = Bu^t (**63**), H (**64**).

The relatively successful asymmetric allylation of aldehydes was described in one brief communication,[112] where pincer complexes (R_a,R_a)-**63** and **64** were tested. After the optimization of the structure of the catalyst and the reaction conditions, homoallylic alcohol was obtained with an enantiomeric excess 62% *ee* (R_C) in 80% yield [reaction (23)].



(23)

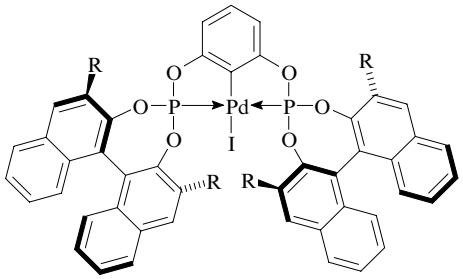
[80%, 62% *ee*(R_C)]

Catalyst (R_a,R_a)-**63** containing two bulky Bu^t substituents in the metallated aromatic ring has evident advantages over its analogue (R_a,R_a)-**64**. The latter sterically less demanding complex not only has the low catalytic activity (the conversion is 18%) but also leads to a sharp decrease in the enantioselectivity of the reaction (6% *ee*). It was suggested that the latter effect is determined by stricter control over the conformation of the 1,1′-binaphtholate moieties by the bulky substituents at positions 3 and 5 of the metallated aromatic ring. The structures containing axial chirality elements have even greater advantages compared to C*-chiral analogues. Thus pincer PCP complexes containing P-donor atoms in the dioxaphospholane moieties have a low catalytic activity (the conversion is 30%–45%), and the reactions with their use are nonenantioselective and give racemic alcohols.[112]

Attempts to use derivatives of CP-palladacycle (S_a)-**53** with similar stereochemistry for the allylation of aldehydes failed.[97] In the above-considered reaction (23), the optical

yields vary from 5% to 15%, the catalytic activity being satisfactory (the conversion is 71% – 92%, 20 °C, 24 h).

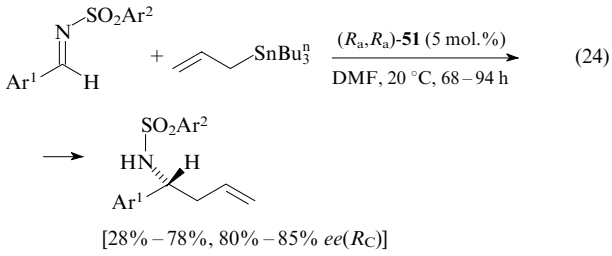
A large series of phosphite PCP complexes, including complexes with axially chiral 3,3′-disubstituted binol (**65** – **70**) or biphenanthrol (**51**) moieties, were tested in the reactions of sulfone imines with tributyl allyl stannane.[113, 114]



(R_a,R_a)-**65** – **70**

R = H (**65**), Me (**66**), Cl (**67**), SMe (**68**), SEt (**69**), SPh (**70**).

The highest enantioselectivity [85% *ee*(R_C)] was obtained with the use of the sterically most demanding catalyst (R_a,R_a)-**51** [reaction (24)] but at the expense of a decrease in the catalytic activity.[114]



(24)

[28% – 78%, 80% – 85% *ee*(R_C)]

On the way to this result, the following facts were revealed:

— even the simple replacement of the hydrogen atoms at positions 3 and 3′ of the binol moiety (compound **65**) by Cl (**67**) or Me (**66**) leads to an increase in the optical yield from 20 to 34 or 59%, respectively;[113]

— an additional increase in the enantioselectivity to 74% *ee* was observed with the use of 3,3′-bis(methylthio)-substituted catalyst **68**, but the further increase in the volume of the thioalkyl group in **69** and **70** proved to be inefficient (67% – 48% *ee*);[114]

— the reaction rate increases in the presence of electron-withdrawing groups in the substituent Ar^1 (for example, of the NO_2 group);

— since the catalyst is not decomposed in the course of the reaction,[114] it can be regenerated and reused;

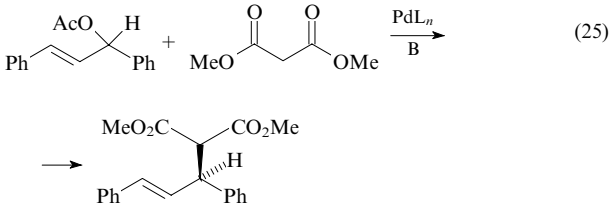
— the absolute configuration of the reaction product corresponds to that of the catalyst.

Obviously, many problems in this field remain to be solved. First, it is important to find more efficient ways of removing the sulfamide protecting group for the practical use of these catalysts, because the reduction of sulfamides by sodium in ammonia occurs without racemization [114] but gives the product in moderate yield (< 70%). Second, it is desirable to find less toxic allylating agents than stannanes used nowadays; unfortunately, the use of allylborate K[AllBF$_3$] instead of the latter agents is accompanied by a decrease in the optical yield (< 60%). Third, the range of suitable imine substrates is limited by small molecules because both the reaction rate and the enantioselectivity decrease in the presence of bulky substituents. Fourth, almost all reactions of this type are performed with high loadings of expensive optically active catalysts (5 mol.%). Fifth, the concepts of the reaction mechanism are contradictory; they assume either the activation of the allylating agent through the η^1-allylic intermediate [114] or the activation of the carbonyl compound by a pincer catalyst acting as a Lewis acid.[115] In addition, the interpretation of the ways of the enantioselection in the context of the former pathway is not convincing:[114] the formation of a new stereocentre under conditions of the attack of the terminal carbon atom of the allylic ligand η^1-bonded to palladium on the electrophilic imine carbon atom should occur at the peripheral regions of the catalyst.

It could be assumed that monocyclic CPC would be more promising catalysts for this type of reactions. These complexes can localize both participants of the reaction on one metal centre: the allylic moiety *via* transmetallation and aldehyde or imine through the coordination at the second coordination site of the C∩E palladacycle acting as a Lewis acid (*cf.* with the results of the study [116]).

2. Allylic substitution

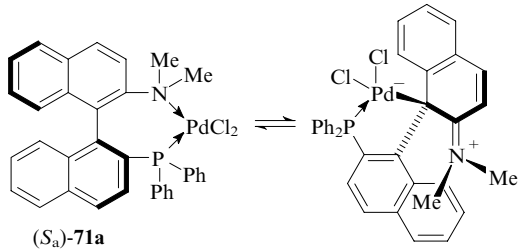
The catalysis of the reactions of allylic substrates with carbonucleophiles stabilized by electron-withdrawing substituents with the use of coordination compounds is one of the best developed areas in the palladium catalysis.[117 – 120] The main problem in the development of asymmetric versions of this reaction arises due to the fact that, in terms of the reaction mechanism, the attack of the C-nucleophile on the carbon atom of the allylic substrate η^3-bonded to the metal occurs from the side opposite to the optically active ligand, which substantially hinders the transfer of chiral information. This has stimulated the design of specific types of ligands for catalysts with additional functions capable of forming particular types of secondary interactions between the chiral ligand and the far-spaced nucleophile.[73] The standard process for testing catalysts in the allylic alkylation is based on the reaction of acylated allylic alcohol with dimethylmalonate in the presence of a base [reaction (25)].



(25)

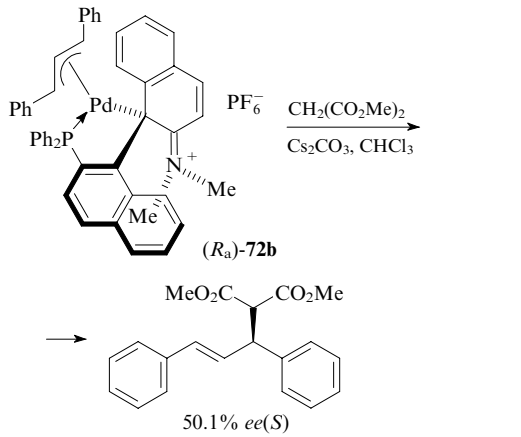
By contrast to classical catalytic systems for the asymmetric allylic alkylation studied in detail, information on the use of CPC in these reactions is scarce. The results of the use of atropisomeric aminophosphine containing the 1,1′-binaphthyl backbone, *viz.*, 2-dimethylamino-2′-diphenylphosphino-1,1′-binaphthyl (MAP), in the model reaction (25) were published in 1998.[121] After the optimization of the reaction conditions, the reaction with the use of 5 mol.% of the catalyst consisting of Pd(dba)$_2$ and (R_a)-MAP affords the allylic substitution product in an optical yield *ee*(S_C) of 71%. However, soon afterward the spectroscopic study showed [122] that the reaction performed under these conditions affords not only coordination compounds containing

P,N- (**71a**) and P-coordinated aminophosphine [$PdCl_2(\kappa^1$-MAP)] (**71b**) but also unusual phosphapalladacycle **72a** resulting from the metallation of the *ipso*-carbon atom of the 1,1′-binaphthyl backbone of aminophosphine in a ratio of 10 : 5 : 85 [reaction (26)].



(S_a)-**71a** (S_a)-**72a** (26)

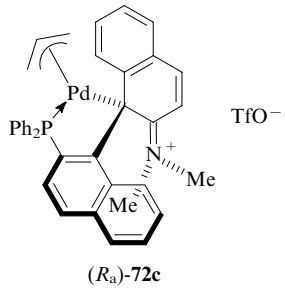
These data suggest that one of the forms of CP-palladacycle (S_a)-**72** is the true catalyst for reaction (25).[121] This suggestion can be supported by the comparable optical yields obtained in the stoichiometric reaction of CPC (R_a)-**72b** with dimethylmalonate [reaction (27)]



(R_a)-**72b** (27)

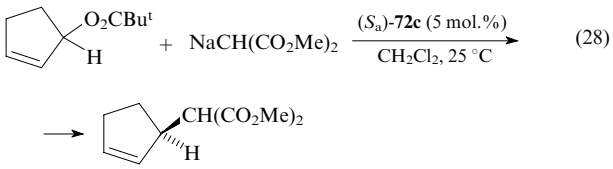
50.1% *ee*(*S*)

and in the related reaction [see reaction (25)] catalyzed by the *in situ* generated complex (R_a)-**72c** (5 mol.%); *ee* are 50.1% and 40.5%, respectively.[123]



(R_a)-**72c**

Zwitterionic dichloride complex (S_a)-**72a**[122, 124, 125] and two cationic allylic derivatives of the same CP-palladacycle, *viz*., (S_a)-**72c** and (R_a)-**72b**,[122, 123] whose structures were established by X-ray diffraction,[122–124] were tested as catalysts for the allylic substitution. The use of these CPC in the allylic substitution was only moderately successful.[125] Thus the optical yield of the *R* enantiomer in the reaction of cyclic ester with sodium dimethylmalonate catalyzed by allylic derivative (S_a)-**72c** was 51% [reaction (28)].



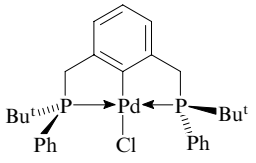
(28)

The main drawback of these catalytic systems is the pronounced stereochemical memory effect. This effect is based on the insufficiently high rate of the interconversion of two diastereomeric intermediates with the η^3-bound allylic substrate before the nucleophilic attack. As a result, each enantiomer of the racemic substrate reacts as if it remembered the starting stereochemistry.[125–127] The enantioselectivity in the allylic substitution can be achieved only under the conditions excluding this effect. For a comparison, it should be noted that the above-mentioned reaction (28) in THF affords the substitution product with a low enantiomeric enrichment [< 15% *ee*(*R*)].[125]

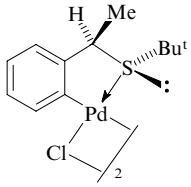
Apparently, in the present stage of the development of stereochemistry of allylic substitution reactions, cyclopalladated catalysts can hardly compete with classical coordination complexes providing high enantioselectivity.[117–120]

VI. Cross-coupling and related reactions

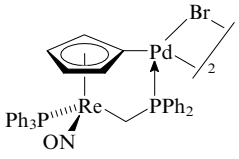
The discovery of the abnormally high catalytic activity of CPC in the C–C bond formation is the most significant event in the homogeneous metal complex catalysis of achiral transformations in the last 15 years.[15–20, 22, 128–131] The use of this class of (pre)catalysts made it possible to reduce the consumption of expensive palladium compounds by several orders of magnitude and to perform these processes with cheaper but less reactive aryl chlorides. In this context, numerous unsuccessful attempts to develop asymmetric versions of the cross-coupling catalyzed by chiral palladacycles were, at the first glance, unexpected.



(S_P,S_P)-**49c**

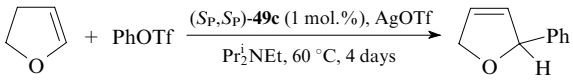


(R_C,R_S)-**73**



(S_{Re},S_{Re})-**74**

The arylation of 2,3-dihydrofuran by appropriate electrophiles is the most commonly used asymmetric version of the Heck reaction.[132, 133] This reaction catalyzed by pincer P*-chiral PCP complex (S_P,S_P)-**49c** (in the form of the *in situ* generated triflate) affords 2-phenyl-substituted 2,5-dihydrofuran in quantitative yield but as an almost racemic mixture [3% *ee*, reaction (29)].[134] In the author's opinion, the failure is due to the comparable volumes of two substituents at the P-donor atoms.

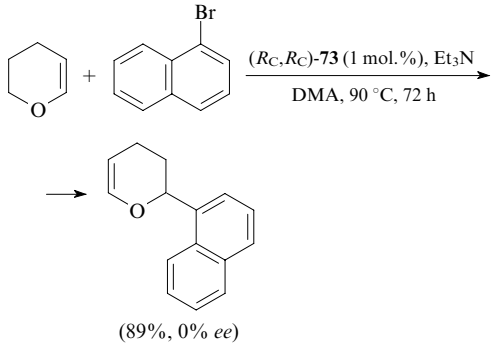


(29)

(100%, 3% *ee*)

The related reaction of 2,3-dihydrofuran with iodobenzene catalyzed by interannelated dinuclear ferrocenyl oxazoline complex (S_C)-**5b** (0.5 mol.%) can give, depending on the nature of the base, either the same product (with Ag_2O or Ag_2CO_3) or the isomeric derivative of 2,3-dihydrofuran (with the use of K_3PO_4) in moderate yields. However, both regioisomeric arylation products are formed as racemates.[135]

The same result was obtained in tests of the monocyclic CS-palladacycle containing the asymmetric sulfur donor atom. The reaction of 3,4-dihydro-2*H*-pyran with 1-bromonaphthalene catalyzed directly by dinuclear μ-chloride complex (R_C,R_S)-**73** gives the arylation product in high yield but also as a racemate [reaction (30)].[136]

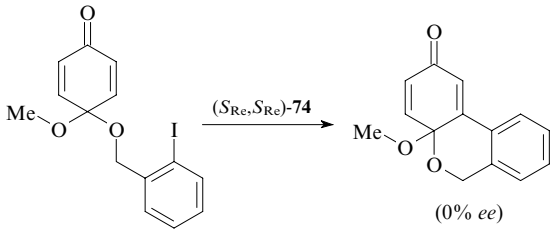


(30)

(89%, 0% *ee*)

DMA is dimethylacetamide.

Attempts to use the unusual CP-palladacycle containing the asymmetric rhenium atom in the side chain as the dinuclear μ-bromide complex (S_{Re},S_{Re})-**74** in the catalysis of the intramolecular Mizoroki–Heck reaction also failed.[137] In these experiments, the cyclization of cyclohexadienone with the iodobenzyl moiety affords a racemate [reaction (31)].[138]



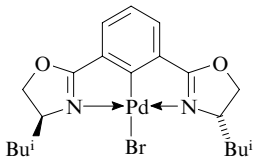
(31)

(0% *ee*)

In attempting to find the causes of the failure,[135, 136, 138] the authors concluded that the palladacycles do not function in the catalytic cycle and serve only as a reservoir supplying Pd(0) nanoparticles or their coordinated derivatives, which should be considered as the true catalysts for the reaction.

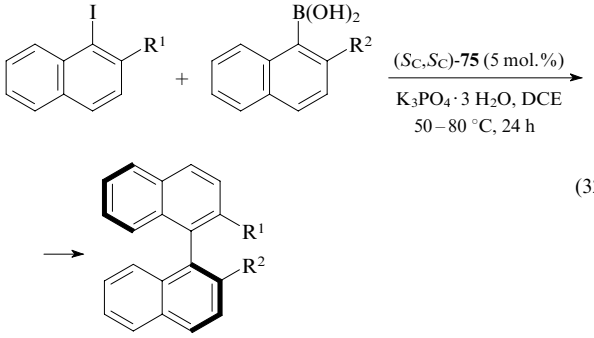
For a comparison, it should be noted that the catalysis of the intra- (Ref. 137) and intermolecular Heck cross-coupling[139, 140] by chiral palladium coordination compounds with optimized ligands results in the enantioselectivity up to 96%–99% *ee*. This classical approach has found wide use in the synthesis of complex natural molecules.[141]

From this point of view, it is surprising that the moderate enantioselectivity was observed in the Suzuki–Miyaura cross-coupling reaction catalyzed by pincer bis(isoxazoline) complex (S_C,S_C)-**75**.



(S_C,S_C)-**75**

The reactions of a series of 2-substituted iodonaphthalenes with 2-substituted 1-naphthylboronic acids afford atropisomeric 2,2′-disubstituted 1,1′-binaphthyls with 39%–49% *ee*(S_a) [reaction (32)].[142]

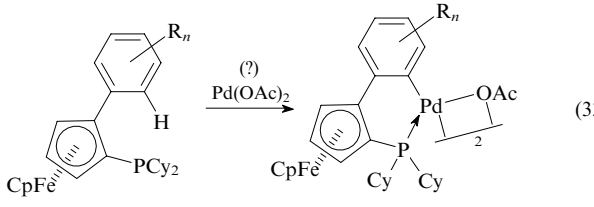


(32)

[34%–78%, 39%–49% *ee*(S_a)]

R^1 = H, Me, OMe, OPr^i, OBn; R^2 = H, Me; DCE is dichloroethane.

It should be noted that approximately the same level of enantioselectivity (43%–54% *ee*) was observed in the reaction of the 2-methyl-substituted substrate and reagent catalyzed by palladium(II) acetate in the presence of planar chiral 2-arylferrocenylphosphines (S_{pl})-HL^{76}–HL^{78} (Ref. 143). The structures of these ligands suggest that CP-palladacycles (S_{pl})-**76**–**78** can be formed under the Suzuki reaction conditions [Pd(OAc)$_2$, K$_3$PO$_4$, 60–76 °C] [reaction (33)].

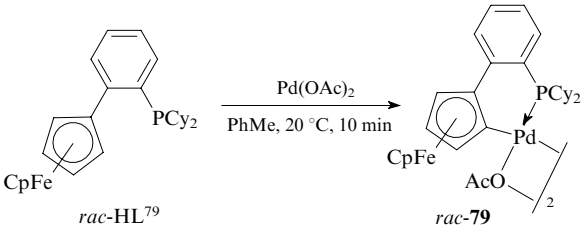


(33)

(S_{pl})-HL^{76}–HL^{78} (S_{pl},S_{pl})-**76**–**78**

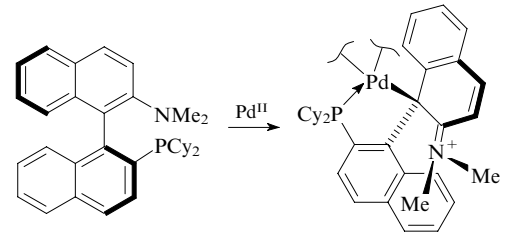
R$_n$C$_6$H$_{4-n}$ = 2-MeOC$_6$H$_4$ (**76**), 1-Naph (**77**), phenanthren-9-yl (**78**).

This hypothesis is quite reasonable taking into account that the cyclopalladation of related phosphine HL[79] proceeds under mild conditions in the absence of bases to give the product in high yield [reaction (34)], and the resulting CPC *rac*-**79** exhibits high catalytic activity in the Suzuki reaction.[144]



rac-HL[79] *rac*-**79** (34)

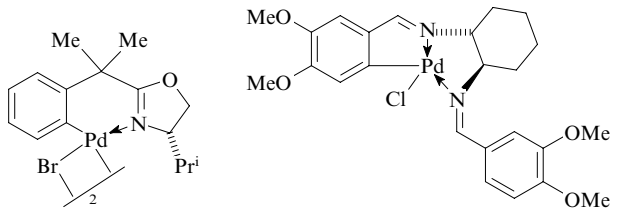
Taking into account the above-considered modest results, CPC cannot presently compete with palladium coordination compounds, which are used in the synthesis of biaryls[146–148] and in other versions of the Suzuki reaction[145] giving optical yields ranging from 85%–86%[145–147] to 92%.[148] It is noteworthy that the highest enantioselectivity (92% *ee*)[148] was obtained with aminophosphine (S_a)-MAP-PCy_2, which is the dicyclohexyl analogue of the ligand MAP. Since the latter easily forms CP-palladacycle **72** under mild conditions [see reaction (26)] *via* metallation at the *ipso*-carbon atom of the 1,1′-binaphthyl backbone,[122] the similar behaviour of the (S_a)-MAP-PCy_2 ligand cannot be ruled out. This suggests that aminophosphine (S_a)-MAP-PCy_2 can function in the catalytic cycle in the form of CP-palladacycle (S_a)-**80** at least as the pre-catalyst stabilized by the chelation [reaction (35)].



(S_a)-MAP-PCy_2 (S_a)-**80** (35)

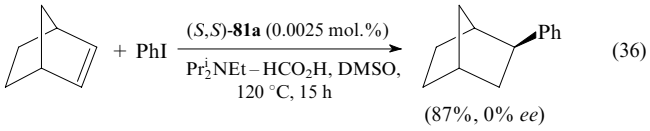
This is indirectly confirmed by the high catalytic activity of the (*S*)-MAP-PCy_2–$Pd_2(dba)_3$ system, which allows the use of lower catalyst loadings (0.2 mol.%) compared to the standard quantities (2 mol.%–4 mol.%).[148]

The hydroarylation of alkenes can be formally considered as a combination of the Heck cross-coupling and the double bond reduction. Dinuclear CN complex (*S*,*S*)-**81a**[149] and the mononuclear CNN complex (*R*,*R*)-**82**[150] were tested as catalysts for the hydoarylation of a series of norbornenes and norbornadienes.



(*S*,*S*)-**81a** (*R*,*R*)-**82**

Both catalysts have a relatively high catalytic activity due to which minimum catalyst loadings can be used. Thus the turnover numbers in the model phenylation reaction of norbornene [reaction (36)] are 10^4 at 90 °C (Ref. 150) and even 1.7×10^6 at 120 °C.[149] All reactions are characterized by the complete *exo*-diastereoselectivity but without asymmetric induction.



(87%, 0% *ee*) (36)

This area of homogeneous catalysis by palladacycles is poorly developed. In addition to the above-mentioned two studies, the use of achiral CP-palladacycles for the catalysis of this reaction was described only in one publication.[151]

Apparently, there are several factors responsible for the distressing failure in the catalysis of the cross-coupling and related reactions by palladacycles. First, most of reactions of this type occur at high temperature (90–180 °C), which is unfavourable for the enantioselection. Second, in almost none of the above-mentioned studies, the choice of a particular type of CPC as the catalyst was not based on mechanistic considerations. Finally, in none of these studies, the catalytic system was optimized, including not only the denticity of the cyclometallated ligand and the nature of donor atoms in the ligand but also the nature of the anion at the metal centre and that of the base, and the structure of the substrate or the reagent.

However, the most serious obstacle to the development of asymmetric versions of the cross-coupling based on palladacycles is that the latter can be decomposed during the functioning in the catalysis. Actually, the classical view on the catalytic cycles in the cross-coupling reactions[19,22,152] and, in particular, in the Heck[18,20,132,153,154] and Suzuki[128] reactions assumes that palladium(0)-containing species are involved in these transformations as true catalysts. According to these mechanisms, CPC serve only as pre-catalysts providing Pd^0 in a particular form to the catalytic cycle.[155] Generally, the discovery of palladium(0) nanoparticles, which were detected by transmission electron microscopy[135] or confirmed by positive mercury[135,155] or other tests based on the inhibition of the Pd^0-containing catalyst,[155] was offered as an argument in support of this conclusion. However, in terms of this interpretation of the role of palladacycles in the homogeneous catalysis of the cross-coupling, it is difficult to explain their unique efficiency.

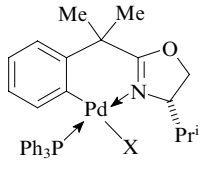
Hence it is not surprising that an alternative pathway of palladacycle-catalyzed reactions through the palladium(IV)-containing intermediate is still actively debated.[19,153,156,157] The facts that the reactions proceed without an induction period and there is no indication of the formation of palladium black, as well as the regeneration of the cyclopalladated catalyst in high yield after the completion of the reaction, are usually considered as evidence in support of the above ideas. The latter argument is not very convincing because the repeated cyclopalladation of the ligand that is released is quite possible under the conditions typical of the cross-coupling (high temperature and the presence of a base).[17,158] The use of the mercury test and the simulation of intermediates in the Heck[159] and Suzuki[160] reactions and in the coupling of alkenes with iodonium salts[161] catalyzed by pincer PCP complexes made it possible to exclude the participation of Pd^0-containing species in these processes as catalytically active forms[159,160] or suggested the formation of a pincer intermediate containing tetravalent palladium.[161] The alternative pathway of the Heck reaction based on the Pd^{II}/Pd^{IV} redox system is evidenced also by the results of quantum chemical DFT calculations of the energetics of both this system and the classical Pd^0/Pd^{II} redox system.[162]

In any case, the role of palladacycles in cross-coupling reactions remains unclear. To eliminate numerous problems, it is necessary to study the mechanism of these processes in more detail.

VII. Other transformations

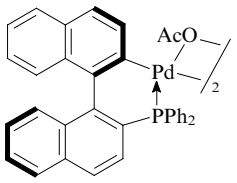
Scanty investigations of the potential of CPC as catalysts for other processes are considered in this section.

The high catalytic activity and enantioselectivity were observed in the ring opening reaction of oxabicycloalkenes as a result of their arylation catalyzed by atropisomeric phosphapalladacycle (R_a)-**83**.[163]



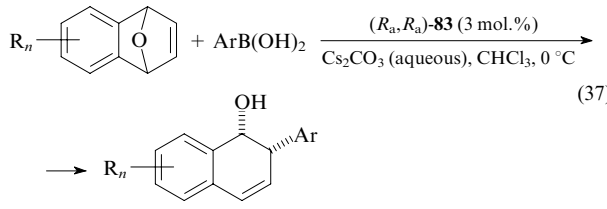
(S_C)-**81b**,**c**

X = Br (**b**), Tfa (**c**).



(R_a,R_a)-**83**

These reactions performed under mild temperature conditions with the use of moderate catalyst loadings (3 mol.%) afford (1*R*,2*S*)-1-hydroxy-2-aryl-1,2-dihydronaphthalenes in 68%–99% yields [reaction (37)]. The optical yields in the reactions of these substrates with a wide range of sterically unhindered arylating agents containing electron-donating or electron-withdrawing substituents remain high (71%–83%); however, the enantioselectivity sharply decreases (to 19%–30% *ee*) if sterically more demanding arylboronic acids (Ar is *o*-tolyl or 1-naphthyl) are used.[163]



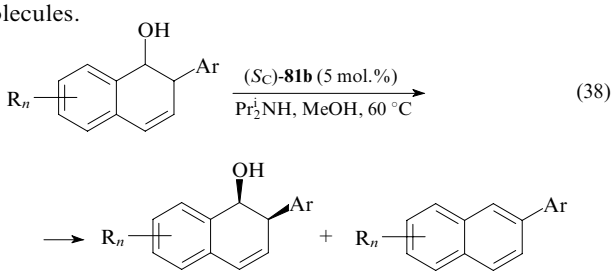
(37)

[70%–79%, 68%–83%, *ee*(1*R*,2*S*)]

R_n = H, 6,7-Me_2, 6,7-Br_2, 5,8-$(OMe)_2$; Ar = 4-XC_6H_4 (X = H, OMe, F, CF_3), 3-$MeOC_6H_4$, 3-ClC_6H_4, PhCH=CH.

This success was achieved after the thorough optimization of the structure of the cyclopalladated catalyst.[163,164] In the model reaction of the unsubstituted substrate (R_n = H) with phenylboronic acid, the following seven CN complexes of different structural types with oxazoline N-donors were tested: monocyclic and pincer, with five- or six-membered metallacycles, dinuclear μ-bromide complexes and their mononuclear phosphine derivatives. Unlike atropisomeric CP complex (R_a,R_a)-**83**, all cyclopalladated catalysts of other stereochemical types (containing C* stereocentres or the chiral plane) are characterized by the low (4% *ee*) or moderate (57% *ee*) enantioselectivity.

These authors[165] also developed an alternative approach to the synthesis of 1-hydroxy-2-aryl-1,2-dihydronaphthalenes as (1*S*,2*R*) enantiomers. This approach is based on the kinetic resolution of the corresponding racemic substrates during their dehydrogenation catalyzed by oxazoline palladacycle (S_C)-**81b** [reaction (38)]. To the best of our knowledge, this investigation is the first example of the use of chiral CPC in the kinetic resolution of organic molecules.



(38)

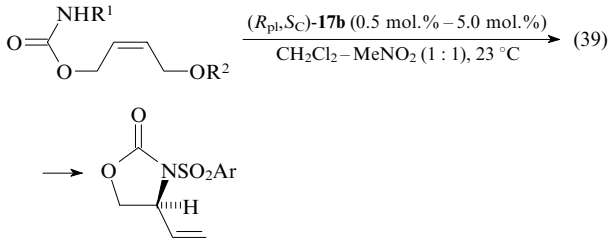
[35%–45%, 84%–99%, *ee*(1*S*,2*R*)]

R_n = H, 6,7-Me_2, 5,8-$(OMe)_2$; Ar = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 3-$MeOC_6H_4$, 3-ClC_6H_4, 2-MeC_6H_4, 1-Naph, PhCH=CH.

The high enantioselectivity of these reactions (up to 99% *ee*) compensates both the moderate yields of the target products typical of the kinetic quenching and rather large catalyst loadings (5 mol.%). A substantial advantage of the latter approach to the synthesis of arylated dihydronaphthols is the tolerance of the catalytic system to steric hindrance caused by the 2-aryl substituent. Thus the reactions of substrates containing the *o*-tolyl or 1-naphthyl substituent afford products with the highest enantioselectivity (99% *ee*). The optical yield sharply decreases (to 17%) only if the substrate contains the phenylethynyl substituent (Ar = PhC≡C).[165]

The instructive result obtained after the optimization of the catalysts for these two reactions deserves mention. The use of CP complex (R_a,R_a)-**83**, which is most efficient (up to 83% *ee*) in the arylation of oxabicyclic structures [reaction (37)], gives a very low optical yield (5%) in the kinetic resolution [reaction (38)]. On the contrary, CN complex (S_C)-**81b**, which is the bromide analogue of the trifluoroacetate catalyst (S_C)-**81c** optimal for the latter reaction, does not exhibit catalytic activity in the former process. These facts only confirm the lock-and-key principle well known for catalytic systems; the progress in the design of new catalysts depends to a large extent on the search for the complementarity either empirical or based on mechanistic considerations.

Transformations of various allylic substrates catalyzed by palladium coordination compounds occupy a prominent place among different methods for the synthesis of heterocyclic compounds.[166,167] In the recent past, a new version of the cyclization was developed based on planar chiral CN-palladacycles as catalysts.[168,169] The cyclization of (*Z*)-but-2-ene-1,4-diol derivatives in the presence of these catalytic systems provides a route to 4-vinyloxazolidin-2-ones with a high enantiomeric purity [reaction (39)].

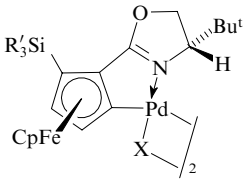


(39)

[80%–98%, 89%–93% *ee*(S_C)]

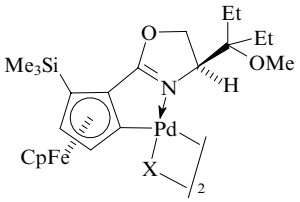
R^1 = SO_2Ar, Ts, 4-$O_2NC_6H_4$; R^2 = H, Ac, $C(O)CF_3$, C(O)NHTs; Ar = 2-MeC_6H_4, 4-XC_6H_4 (X = H, Me, Cl, F).

In mechanistic terms, the process is most closely related to the above-considered [3,3]-sigmatropic rearrangements (Section II). In both cases, the intramolecular aminopalladation of the double bond in allylic substrates is a key step of the transformation. Even in early stages of the search for the conditions of this reaction, high chemical (86% – 98%) and optical yields (89% – 99%) were obtained with FOP-type ferrocenyl CPC, *viz*., with dinuclear μ-trifluoroacetate complexes (R_{pl},S_C)-**17b** and (S_{pl},S_C)-**19b**. In these processes, the stereochemistry of the reaction product is completely determined by the configuration of the chiral plane. The reactions catalyzed by complex (R_{pl},S_C)-**17b** give (*S*)-oxazolidin-2-one derivatives, whereas the reactions with the use of its analogue (S_{pl},S_C)-**19b** afford the same heterocycles with the opposite *R* configuration.[168]



(R_{pl},S_C)-**17b**,**c**

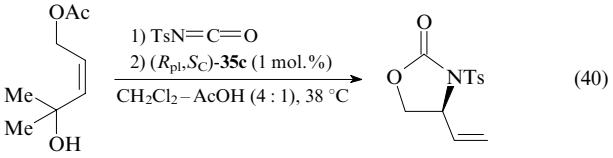
X = Tfa (**b**), I (**c**).



(S_{pl},S_C)-**19a**,**b**

X = I (**a**), Tfa (**b**).

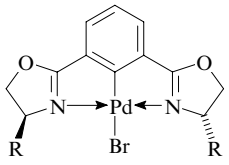
The drawback of these catalytic systems is that it is necessary to preactivate iodide precursors **17c** and **19a** of catalysts **17b** and **19b** with an excess of a silver salt (up to four equivalents). The problem was solved with the use of COP-type sandwich CN-palladacycles (R_{pl},S_C)-**35c** and (R_{pl},S_C)-**35f**, which appeared to be equally active in the form of dinuclear μ-acetate complexes or β-diketonate derivatives (the yields of the product are in the range of 87% – 99%) and also provide high enantioselectivity (87% – 98% *ee*).[169] The process was substantially improved by the *in situ* generation of intermediate carbamates from the corresponding alcohols without the isolation of these labile compounds [reaction (40)].



[96%, 91% *ee*(S_C)] (40)

The natural limitation of this method is that it can be applied to allylic substrates only with the *Z* configuration.

Copper, rhodium and ruthenium complexes play a leading role in the enantioselective catalysis of the cyclopropanation;[170,171] a few examples of the use of palladium compounds were mentioned in reviews, if at all, only in the Section 'Other catalysts'. It is commonly assumed that reactions of this type proceed through metal carbenoid intermediates. Only in the end of the 20th century, several attempts were made to use CPC as catalysts for the cyclopropanation. The reactions of ethyl diazoacetate or diazomethane with styrenes are the most widely used model versions of this process. The NCN-type pincer bis(oxazoline) complexes (**57b**, **84** and **85**)[172] and a series of benzylaminate CN-palladacycles and their derivatives were tested in these reactions.[173]

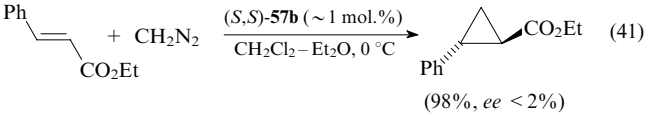


(*S*,*S*)-**57b**, **84**, **85**

R = Bu^t (**57b**), Bn (**84**), CMe_2Ph (**85**).

The choice of NCN complexes **57b**, **84** and **85** as catalysts was determined not only by their similarity to the most efficient NNN-type bis(oxazoline) or semicorrin copper catalysts for the cyclopropanation but also by the desire to achieve the strong coordination of the chiral ligand to metal, because spectroscopic studies of classical catalytic systems based on N,N-chelated bis(oxazolines) showed that these ligands can be partially dechelated.[172]

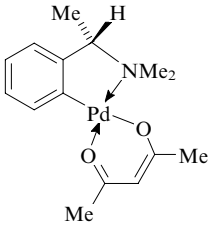
The catalytic activity of pincer complexes is very high. Thus reaction (41) of ethyl (*E*)-cinnamate with diazomethane catalyzed by these complexes affords products in almost quantitative yields (up to 98%) with complete *trans*-diastereoselectivity. However, these catalysts do not provide the enantioselectivity, and the reactions always give racemates (*ee* ⩽2%).



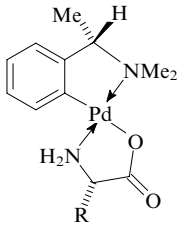
(98%, *ee* < 2%) (41)

Control experiments showed that the absence of the asymmetric induction cannot be attributed to the racemization of the initially formed scalemic derivative of cyclopropane. The replacement of bromide in catalyst **57b** by noncoordinating anions (X = TfO, PF_6, BPh_4) did not lead to the success. This modification of the catalyst did not provide enantioselection and, moreover, it led to a decrease in the catalytic activity.[172]

Unlike the detailed study,[172] the reasons for the choice of benzylaminate CN complexes (**1b** – **e**, **86a** – **c**) as catalysts for the cyclopropanation remain unclear.[173] In the latter study, β-diketonate (**1b**) and α-aminoacidate derivatives of monocyclic C*-chiral CN-palladacycle (**1c** – **e**), as well as adducts of its achiral analogue with optically active α-amino acids (**86a** – **c**), were tested.

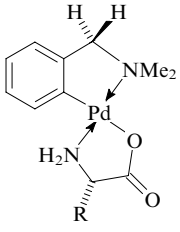


(S_C)-**1b**



(S_C,S_C)-**1c** – **e**

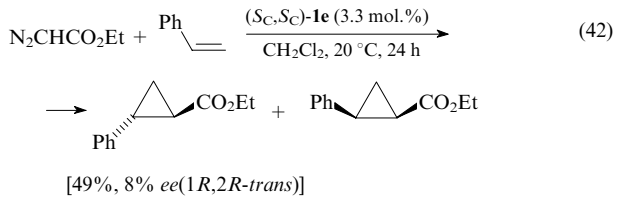
R = Me (**c**), Bn (**d**), Pr^i (**e**).



(S_C)-**86a** – **c**

R = Me (**a**), Bn (**b**), Pr^i (**c**).

This investigation did not lead to the success either. The optical yields in reaction (42) of styrene with ethyl diazoacetate range from 3% to 8%.[173]

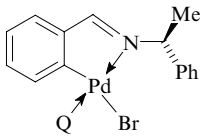


(42)

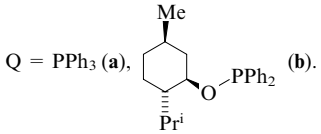
[49%, 8% *ee*(1*R*,2*R*-*trans*)]

The location of the C* stereocentre only in palladacycle (**1b**), only in the auxiliary α-aminoacidate ligand (**86**) or, alternatively, in both ligands (**1c**–**e**) has virtually no effect on the asymmetric induction. The level of enantioselectivity in the reactions in the presence of all types of catalysts remains relatively low (3%–8% *ee*). The drawbacks of these cyclopalladated benzylamines are their lower catalytic activity (yields are 32%–63%) compared to pincer complexes **57**, **84** and **85** and the low diastereoselectivity (the ratio of the *trans* to *cis* isomers of substituted cyclopropane was ~1.90).

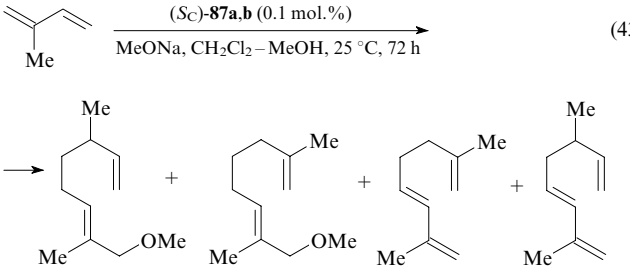
An attempt to use adducts of cyclopalladated imine with P-donor ligands [(S_C)-**87a**,**b**] as catalysts for the telomerization of isoprene in the presence of methanol [reaction (43)] also failed.[174]



(S_C)-**87a**,**b**



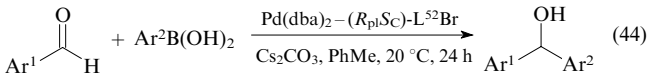
This catalytic system has a complete set of drawbacks: 1) due to the low catalytic activity, the conversion of diene was no higher than 21%; 2) due to the low chemoselectivity the target diene ether is formed in a mixture with comparable amounts of the achiral analogue and two nonfunctionalized dienes, the percentage of the major product being 51%–67%; 3) taking into account losses during the separation of the reaction products, the yield of chiral diene ether is at most ~10%; 4) the main drawback is that the target product is formed as a racemate (1%–2% *ee*).[174]



(43)

Conceivably, not only the fact that the C* stereocentres of both the CN-palladacycle and the auxiliary phosphinite ligand are distant from the metal centre of the catalyst but also their location in rotamerically labile moieties of the complexes (either in the exocyclic *N*-substituent or in the monodentate P-coordinated phosphinite Q) are the main factors responsible for the absence of the enantioselectivity.

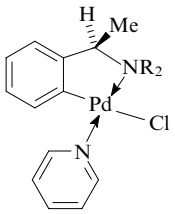
The 1,2-addition of carbonucleophiles to carbonyl compounds are usually catalyzed by rhodium(I) compounds.[175] The examination of CPC in this process was stimulated by the fact that the reaction of the substrate (4-chlorobenzaldehyde) with phenylboronic acid catalyzed by *ortho*-palladated phosphine $PhCH_2PBu^t_2$ gives substantial amounts (up to 56%) of arylation products of the formyl group of this substrate as by-products.[95] Japanese researchers[96,176] showed that the 1,2-addition of arylboronic acids to aldehydes [reaction (44)] is efficiently catalyzed by planar chiral ferrocenyl CP-palladacycles (R_{pl},S_C)-**52** generated *in situ* by the oxidative addition of bromide (R_{pl},S_C)-$L^{52}Br$ to $Pd(dba)_2$ (see Section II.3). The reactions with the use of this catalytic system afford diarylmethanols in yields from 71 to >99%, although this system is less efficient in the reactions with aliphatic and hetaryl aldehydes (19%–78%). Unfortunately, the enantioselectivity of these reactions is low (2%–11% *ee*).



(44)

Ar^1 = Ph, Ar^2 = 1-Naph [11% *ee*(*S*)]; Ar^1 = 1-Naph, Ar^2 = Ph [11% *ee*(*R*)].

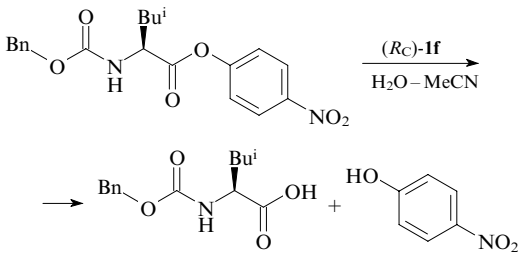
Probably, the transformations of optically active substrates, which are not associated with the formation of new stereocentres but which are selective in the presence of chiral catalysts, can be, with certain reservations, assigned to enantioselective reactions.[177,178] Thus the kinetic studies of the hydrolysis of protected optically active α-amino acid *p*-nitrophenyl esters catalyzed by pyridine adducts of (S_C) and (R_C) enantiomers of benzylaminate palladacycles (**1f**, **88**) showed that the reaction rate depends on the relation between the configurations of the C* stereocentres in the substrate and the catalyst,[131] as well as on the nature of the N-donor in CN-palladacycle containing the tertiary (**1f**) or primary (**88**) amino group.[178]



(R_C)-**1f**, **88**

R = Me (**1f**), H (**88**).

It was shown that the rate constants of the hydrolysis of enantiomers of N-protected leucine [reaction (45)] increase by a factor of 3–5 in the case of the opposite configurations of the substrate and catalyst compared to the reactions catalyzed by palladacycle having the same configuration.[177]



(45)

The drawback of this system is the competition with the main hydrolysis reaction without the involvement of CPC.

The investigation of the hydrolysis of (*S*)-*N*-Boc-methionine showed that the rate of the reaction catalyzed by primary amine derivative **88** is almost two orders of magnitude higher than that of the reaction performed in the presence of the catalyst based on cyclopalladated tertiary benzylamine **1f**; however, the enantioselectivity in these reactions is almost absent.[178]

VIII. Conclusions

An analysis of the state of the art in the enantioselective catalysis by palladacycles shows that this field was developed unevenly. The impressive progress in certain area is accompanied by distressing failure experience in other areas, which force one to think about the reasons for this contrast.

Excellent results in the asymmetric catalysis of [3,3]-sigmatropic rearrangements by palladacycles were obtained due to the following facts: 1) the structural and stereochemical diversity of palladacycles under examination is of primary importance; 2) the success in studies is essentially determined by the choice of the structure of the catalysts based on the mechanistic considerations; 3) the rational improvement of the ways of the chiral information transfer from the catalyst to the substrate makes an important contribution; 4) the thorough optimization of the reaction conditions also plays an important role.

It would be expected that impressive results will be obtained for other types of palladacycle-catalyzed transformations on the condition that the problem will be developed in depth. Essential requirements are the detailed investigation of the ways of the chiral information transfer from the catalyst to the substrate and/or reagent and the estimation of the possibility to retain the cyclic structure of the catalyst during its functioning in the catalytic cycle. It should be noted that CPC were used as catalysts for most of reactions only sporadically, the choice of the processes was not motivated, and it was not analyzed whether there is the correlation between the structure of the complex and the mechanism of transformation.

The lock-and-key principle in the catalysis retains its significance. Therefore, it would be expected that a chiral cyclopalladated catalyst can be chosen (or designed) for almost every reaction presently catalyzed by palladium coordination compounds on the condition of the clear understanding of all aspects of the problem. Hence, the synthesis of new chiral cyclopalladated compounds of different structural and stereochemical types is an important problem.

References

1. A C Cope, R W Siekman *J. Am. Chem. Soc.* **87** 3272 (1965)
2. J M Vila, M T Pereira, in *Palladacycles. Synthesis, Characterization and Applications* Ch. 5 (Eds J Dupont, M Pfeffer) (Weinheim: Wiley-VCH, 2008) p. 87
3. S Otsuka, A Nakamura, T Kano, K Tani *J. Am. Chem. Soc.* **93** 4301 (1971)
4. D G Allen, G M McLaughlin, G B Robertson, W L Steffen, G Salem, S B Wild *Inorg. Chem.* **21** 1007 (1982)
5. V I Sokolov, L L Troitskaya, O A Reutov *J. Organomet. Chem.* **133** C28 (1977)
6. V I Sokolov, L L Troitskaya *Chimia* **32** 122 (1978)
7. J-P Djukic, in *Palladacycles. Synthesis, Characterization and Applications* Ch. 7 (Eds J Dupont, M Pfeffer) (Weinheim: Wiley-VCH, 2008) p. 123
8. S B Wild *Coord. Chem. Rev.* **166** 291 (1997)
9. P-H Leung *Acc. Chem. Res.* **37** 169 (2004)
10. F L Liu, S A Pullarkat, Y Li, Sh Chen, M Yuan, Z Y Lee, P-H Leung *Organometallics* **28** 3941 (2009)
11. W-C Yeo, S-Y Tee, G-K Tan, L L Koh, P-H Leung *Inorg. Chem.* **43** 8102 (2004)
12. V V Dunina, L G Kuz'mina, M Yu Kazakova, Yu K Grishin, Yu A Veits, E I Kazakova *Tetrahedron: Asymmetry* **8** 2537 (1997)
13. V V Dunina, O N Gorunova, M V Livantsov, Yu K Grishin *Tetrahedron: Asymmetry* **11** 2907 (2000)
14. V V Dunina, L G Kuz'mina, M Yu Rubina, Yu K Grishin, Yu A Veits, E I Kazakova *Tetrahedron: Asymmetry* **10** 1483 (1999)
15. C Najera, D A Alonso, in *Palladacycles. Synthesis, Characterization and Applications* Ch. 8 (Eds J Dupont, M Pfeffer) (Weinheim: Wiley-VCH, 2008) p. 155
16. R B Bedford, in *Palladacycles. Synthesis, Characterization and Applications* Ch. 9 (Eds J Dupont, M Pfeffer) (Weinheim: Wiley-VCH, 2008) p. 209
17. J Dupont, C S Consorti, J Spencer *Chem. Rev.* **105** 2527 (2005)
18. I P Beletskaya, A V Cheprakov *Chem. Rev.* **100** 3009 (2000)
19. R B Bedford, C S J Cazin, D Holder *Coord. Chem. Rev.* **248** 2283 (2004)
20. N J Whitcombe, K K Hii, S E Gibson *Tetrahedron* **57** 7449 (2001)
21. L F Tietze, H Ila, H P Bell *Chem. Rev.* **104** 3453 (2004)
22. J Dupont, M Pfeffer, J Spencer *Eur. J. Inorg. Chem.* 1917 (2001)
23. A Gutnov *Eur. J. Org. Chem.* 4547 (2008)
24. P S Pregosin, R Salzmann *Coord. Chem. Rev.* **155** 35 (1996)
25. J T Singleton *Tetrahedron* **59** 1837 (2003)
26. M E van der Boom, D Milstein *Chem. Rev.* **103** 1759 (2003)
27. M Albrecht, G van Koten *Angew. Chem., Int. Ed.* **40** 3750 (2001)
28. L E Overman *Tetrahedron* **65** 6432 (2009)
29. E A Ilardi, C E Stivala, A Zakarian *Chem. Soc. Rev.* **38** 3133 (2009)
30. L E Overman, N E Carpenter *Org. React.* **66** 1 (2005)
31. L E Overman *J. Am. Chem. Soc.* **96** 597 (1974)
32. L E Overman *Acc. Chem. Res.* **13** 218 (1980)
33. M Calter, T K Hollis, L E Overman, J Ziller, G G Zipp *J. Org. Chem.* **62** 1449 (1997)
34. T K Hollis, L E Overman *J. Organomet. Chem.* **576** 290 (1999)
35. P-H Leung, K-H Ng, Y Li, A J P White, D J Williams *Chem. Commun.* 2435 (1999)
36. M P Watson, L E Overman, R G Bergman *J. Am. Chem. Soc.* **129** 5031 (2007)
37. T K Hollis, L E Overman *Tetrahedron Lett.* **38** 8837 (1997)
38. A Moyano, M Rosol, R M Moreno, C López, M A Maestro *Angew. Chem., Int. Ed.* **44** 1865 (2005)
39. F Cohen, L E Overman *Tetrahedron: Asymmetry* **9** 3213 (1998)
40. C E Anderson, Y Donde, C J Douglas, L E Overman *J. Org. Chem.* **70** 648 (2005)
41. Ya Donde, L E Overman *J. Am. Chem. Soc.* **121** 2933 (2000)
42. D F Fisher, Zh-q Xin, R Peters *Angew. Chem., Int. Ed.* **46** 7704 (2007)
43. M E Weiss, D F Fisher, Zh-q Xin, S Jautze, W B Schweizer, R Peters *Angew. Chem., Int. Ed.* **45** 5694 (2006)
44. R Peters, Zh-q Xin, D F Fischer, W B Schweizer *Organometallics* **25** 2917 (2006)

45. J Kang, Y K Han, T H Kim, D H Choi *Tetrahedron Lett*. **43** 9509 (2002)
46. S Jautze, P Seiler, R Peters *Chem. – Eur. J*. **14** 1430 (2008)
47. S Jautze, P Seiler, R Peters *Angew. Chem., Int. Ed*. **46** 1260 (2007)
48. D F Fischer, A Barakat, Zh-q Xin, M E Weiss, R Peters *Chem. – Eur. J*. **15** 8722 (2009)
49. M R Yeamine, C J Richards *Tetrahedron: Asymmetry* **18** 2613 (2007)
50. R S Prasad, C E Anderson, C J Richards, L E Overman *Organometallics* **24** 77 (2005)
51. G Jones, Ch J Richards *Organometallics* **20** 1251 (2001)
52. A M Stevens, Ch J Richards *Organometallics* **18** 1346 (1999)
53. J Kang, T H Kim, K H Yew, W K Lee *Tetrahedron: Asymmetry* **14** 415 (2003)
54. S F Kirsch, L E Overman, M P Watson *J. Org. Chem*. **69** 8101 (2004)
55. C E Anderson, L E Overman *J. Am. Chem. Soc*. **125** 12412 (2003)
56. L E Overman, C E Owen, M M Pavan *Org. Lett*. **5** 1809 (2003)
57. H Nomura, Ch J Richards *Chem. – Eur. J*. **13** 10216 (2007)
58. O A Zalevskaya, V V Dunina, V M Potapov, L G Kuz'mina, Yu T Struchkov *Zh. Obshch. Khim*. **55** 1332 (1985) [a]
59. J S Fossey, C J Richards *Tetrahedron Lett*. **44** 8773 (2003)
60. S Jautze, S Diethelm, W Frey, R Peters *Organometallics* **28** 2001 (2009)
61. J-B Xia, Sh-L You *Organometallics* **26** 4869 (2007)
62. Ch J Richards, A W Mulvaney *Tetrahedron: Asymmetry* **7** 1419 (1996)
63. T Sammakia, H A Latham, D R Schaad *J. Org. Chem*. **60** 10 (1995)
64. A Berger, J-P Djukic, M Pfeffer, A de Cian, N Kyritsakas-Gruber, J Lacour, L Vial *Chem. Commun*. 658 (2003)
65. E E Lee, R A Batey *J. Am. Chem. Soc*. **127** 14887 (2005)
66. S F Kirsch, L E Overman *J. Am. Chem. Soc*. **127** 2866 (2005)
67. S F Kirsch, L E Overman, N S White *Org. Lett*. **9** 911 (2007)
68. A C Olson, L E Overman, H F Sneddon, J W Zillera *Adv. Synth. Catal*. **351** 3186 (2009)
69. L E Overman, S W Roberts, H F Sneddon *Org. Lett*. **10** 1485 (2008)
70. T D Machajewski, Ch-H Wong *Angew. Chem., Int. Ed*. **39** 1352 (2000)
71. L M Geary, Ph G Hultin *Tetrahedron: Asymmetry* **20** 131 (2009)
72. B Alcaide, P Almendros *Eur. J. Org. Chem*. 1595 (2002)
73. M Sawamura, Y Ito *Chem. Rev*. **92** 857 (1992)
74. Y Ito, M Sawamura, T Hayashi *J. Am. Chem. Soc*. **108** 6405 (1986)
75. J M Longmire, X Zhang *Organometallics* **17** 4374 (1998)
76. M A Stark, Ch J Richards *Tetrahedron Lett*. **38** 5881 (1997)
77. M Q Slagt, D A P van Zwieten, A J C M Moerkerk, R J M Klein Gebbink, G van Koten *Coord. Chem. Rev*. **248** 2275 (2004)
78. S Gosiewska, S H Martinez, M Lutz, A L Spek, G van Koten, R J M Klein Gebbink *Eur. J. Inorg. Chem*. 4600 (2006)
79. B Soro, S Stoccoro, G Minghetti, A Zucca, M A Cinellu, M Manassero, S Gladiali *Inorg. Chim. Acta* **359** 1879 (2006)
80. Y Motoyama, H Kawakami, K Shimozono, K Aoki, H Nishiyama *Organometallics* **21** 3408 (2002)
81. S Gosiewska, M Huis'int Veld, J J M de Pater, P C A Bruijnincx, M Lutz, A L Spek, G van Koten, R J M Klain Gebbink *Tetrahedron: Asymmetry* **17** 674 (2006)
82. G Guillena, G Rodríguez, G van Koten *Tetrahedron Lett*. **43** 3895 (2002)
83. M Albrecht, B M Kocks, A L Spek, G van Koten *J. Organomet. Chem*. **624** 271 (2001)
84. S Gosiewska, S M Herreras, M Lutz, A L Spek, R W A Havenith, G P M van Klink, G van Koten, R J M Klein Gebbink *Organometallics* **27** 2549 (2008)
85. R Giménez, T M Swager *J. Mol. Catal. A* **166** 265 (2001)
86. B S Williams, P Dani, M Lutz, A L Spek, G van Koten *Helv. Chim. Acta* **84** 3519 (2001)
87. J Aydin, A Rydén, K J Szabó *Tetrahedron: Asymmetry* **19** 1867 (2008)
88. A Togni, S D Pastor *J. Org. Chem*. **55** 1649 (1990)
89. N Krause, A Hoffmann-Röder *Synthesis* 171 (2001)
90. P R Krishna, A Sreeshailam, R Srinivas *Tetrahedron* **65** 9657 (2009)
91. L-W Xu, C-G Xia *Eur. J. Org. Chem*. 633 (2005)
92. C F Nising, S Braese *Chem. Soc. Rev*. **37** 1218 (2008)
93. D Enders, K Luettgen, A A Narine *Synthesis* 959 (2007)
94. D Enders, A Saint-Dizier, M-I Lannou, A Lenzen *Eur. J. Org. Chem*. 29 (2006)
95. S Gibson, D F Foster, G R Eastham, R P Tooze, D J Cole-Hamilton *Chem. Commun*. 779 (2001)
96. Y Suzuma, S Hayashi, T Yamamoto, Y Oe, T Ohta, Y Ito *Tetrahedron: Asymmetry* **20** 2751 (2009)
97. R B Bedford, H Dumycz, M F Haddow, L T Pilarski, A G Orpen, P G Pringle, R L Wingad *Dalton Trans*. 7796 (2009)
98. Y Suzuma, T O Yamamoto, Y Ito *Chem. Lett*. **36** 470 (2007)
99. V V Dunina, P A Zykov, M V Livantsov, I V Glukhov, K A Kochetkov, I P Gloriozov, Yu K Grishin *Organometallics* **28** 425 (2009)
100. P A Zykov, V V Dunina, M V Livantsov, I V Glukhov, K A Kochetkov, I P Gloriozov, Yu K Grishin *Izv. Akad. Nauk, Ser. Khim*. 2247 (2009) [b]
101. J Li, M A Siegler, M Lutz, A L Spek, R J M Klain Gebbink, G van Koten *Organometallics* **28** 5323 (2009)
102. S Jautze, R Peters *Angew. Chem., Int. Ed*. **47** 9284 (2008)
103. K Takenaka, M Minakawa, Y Uozumi *J. Am. Chem. Soc*. **127** 12273 (2005)
104. K Takenaka, Y Uozumi *Org. Lett*. **6** 1833 (2004)
105. M A Stark, G Jones, C J Richards *Organometallics* **19** 1282 (2000)
106. S E Denmark, J Fu *Chem. Rev*. **103** 2763 (2003)
107. O A Wallner, K J Szabó *Chem. – Eur. J*. **12** 6976 (2006)
108. K J Szabó *Synlett* 811 (2006)
109. N Solin, J Kjellgren, K J Szabó *J. Am. Chem. Soc*. **126** 7026 (2004)
110. N Solin, J Kjellgren, K J Szabó *Angew. Chem., Int. Ed*. **42** 3656 (2003)
111. J Li, A J Minnaard, R J M Klein Gebbink, G van Koten *Tetrahedron Lett*. **50** 2232 (2009)
112. R A Baber, R B Bedford, M Betham, M E Blake, S J Coles, M F Haddow, M B Hursthouse, A G Orpen, L T Pilarski, P G Pringle, R L Wingada *Chem. Commun*. 3880 (2006)
113. O A Wallner, V J Olsson, L Eriksson, K J Szabó *Inorg. Chim. Acta* **359** 1767 (2006)
114. J Aydin, K S Kumar, M J Sayah, O A Wallner, K J Szabó *J. Org. Chem*. **72** 4689 (2007)
115. O Piechaczyk, T Cantat, N Mezailles, P L Floch *J. Org. Chem*. **72** 4228 (2007)
116. P He, Y Lu, C-G Dong, Q-S Hu *Org. Lett*. **9** 343 (2007)
117. B M Trost, M R Machacek, A Aponick *Acc. Chem. Res*. **39** 747 (2006)
118. B M Trost *J. Org. Chem*. **69** 5813 (2004)
119. B M Trost, M L Crawley *Chem. Rev*. **103** 2921 (2003)
120. B M Trost, D L Van Vranken *Chem. Rev*. **96** 395 (1996)
121. Š Vyskočil, M Smrčina, V Hanuš, M Polášek, P Kočovský *J. Org. Chem*. **63** 7738 (1998)
122. P Kočovský, Š Vyskočil, I Císařová, J Sejbal, I Tišlerová, M Smrčina, G C Lloyd-Jones, S C Stephen, C P Butts, M Murray, V Langer *J. Am. Chem. Soc*. **121** 7714 (1999)
123. Y Wang, J Li, K Ding *Organometallics* **22** 1856 (2003)

124. P Kočovský *J. Organomet. Chem.* **687** 256 (2003)
125. G C Lloyd-Jones, S C Stephen, M Murray, C P Butts, Š Vyskočil, P Kočovský *Chem. – Eur. J.* **6** 4348 (2000)
126. I J S Fairlamb, G C Lloyd-Jones, Š Vyskočil, Š Vyskočil *Chem. – Eur. J.* **8** 4443 (2002)
127. G C Lloyd-Jones, S C Stephen *Chem. – Eur. J.* **4** 2539 (1998)
128. F Bellina, A Carpita, R Rossi *Synthesis* 2419 (2004)
129. W A Herrmann, K Öfele, V van Preysing, S K Schneider *J. Organomet. Chem.* **687** 229 (2003)
130. R B Bedford *Chem. Commun.* 1787 (2003)
131. W A Herrmann, V P W Böhm, C-P Reisinger *J. Organomet. Chem.* **576** 23 (1999)
132. K K Hii, T D W Claridge, J M Brown, A Smith, R J Deeth *Helv. Chim. Acta* **84** 3043 (2001)
133. M Shibasaki, C D J Boden, A Kojima *Tetrahedron* **53** 7371 (1997)
134. D Morales-Morales, R E Cramer, C M Jensen *J. Organomet. Chem.* **654** 44 (2002)
135. M Rosol, A Moyano *J. Organomet. Chem.* **690** 2291 (2005)
136. J Dupont, A S Gruber, G S Fonsec, A L Monteiro, G Ebeling *Organometallics* **20** 171 (2001)
137. R Imbos, A J Minnaard, B L Feringa *J. Am. Chem. Soc.* **124** 184 (2002)
138. F K Friedlein, K Kromm, F Hampel, J A Gladysz *Chem. – Eur. J.* **12** 5267 (2006)
139. M Rubina, W M Sherrill, M Rubin *Organometallics* **27** 6393 (2008)
140. Y Hashimoto, Y Horie, M Hayashi, K Saigo *Tetrahedron: Asymmetry* **11** 2205 (2000)
141. A B Dounay, L E Overman *Chem. Rev.* **103** 2945 (2003)
142. T Takemoto, S Iwasa, H Hamada, K Shibatomi, M Kameyama, Y Motoyamac, H Nishiyama *Tetrahedron Lett.* **48** 3397 (2007)
143. J F Jensen, M Johannsen *Org. Lett.* **5** 3025 (2003)
144. F X Roca, Ch J Richards *Chem. Commun.* 3002 (2003)
145. M C Willis, L H W Powell, C K Claverie, S J Watson *Angew. Chem., Int. Ed.* **43** 1249 (2004)
146. A N Cammidge, K V L Crépy *Tetrahedron* **60** 4377 (2004)
147. A N Cammidge, K V L Crépy *Chem. Commun.* 1723 (2000)
148. J Yin, S L Buchwald *J. Am. Chem. Soc.* **122** 12051 (2000)
149. K Yuan, T K Zhang, X L Hou *J. Org. Chem.* **70** 6085 (2005)
150. J Bravo, C Cativiela, R Navarro, E P Urriolabeitia *J. Organomet. Chem.* **650** 157 (2002)
151. J M Brunel, A Heumann, G Buono *Angew. Chem., Int. Ed.* **39** 1946 (2000)
152. G P McGlacken, I J S Fairlamb *Eur. J. Org. Chem.* 4011 (2009)
153. V Polshettiwar, Á Molnár *Tetrahedron* **63** 6949 (2007)
154. A F Schmidt, A Al Halaiqa, V V Smirnov *Synlett* 2861 (2006)
155. C S Consorti, F R Flores, J Dupont *J. Am. Chem. Soc.* **127** 12054 (2005)
156. B L Shaw, S D Perera, E A Staley *Chem. Commun.* 1361 (1998)
157. B L Shaw *New J. Chem.* **22** 77 (1998)
158. V V Dunina, O N Gorunova *Usp. Khim.* **73** 339 (2004) [*Russ. Chem. Rev.* **73** 309 (2004)]
159. J L Boliger, O Blacque, C M Frech *Chem. – Eur. J.* **14** 7969 (2008)
160. D Olsson, O F Wendt *J. Organomet. Chem.* **694** 3112 (2009)
161. J Aydin, J M Larsson, N Selander, K J Szabó *Org. Lett.* **11** 2852 (2009)
162. A Sundermann, O Uzan, J M L Martin *Chem. – Eur. J.* **7** 1703 (2001)
163. T-K Zhang, D-L Mo, L-X Dai, X-L Hou *Org. Lett.* **10** 3689 (2008)
164. T-K Zhang, K Yuan, X-L Hou *J. Organomet. Chem.* **692** 1912 (2007)
165. T-K Zhang, D-L Mo, L-X Dai, X-L Hou *Org. Lett.* **10** 5337 (2008)
166. C Hyland *Tetrahedron* **61** 3457 (2005)
167. J Muzart *Tetrahedron* **61** 4179 (2005)
168. L E Overman, T P Remarchuk *J. Am. Chem. Soc.* **124** 12 (2002)
169. S F Kirsch, L E Overman *J. Org. Chem.* **70** 2859 (2005)
170. M P Doyle, D C Forbes *Chem. Rev.* **98** 911 (1998)
171. H Pellissier *Tetrahedron* **64** 7041 (2008)
172. S E Denmark, R A Stavenger, A-M Faucher, J P Edwards *J. Org. Chem.* **62** 3375 (1997)
173. R Navarro, E P Urriolabeitia, C Cativiela, M D Diaz-de-Villegas, M P Ldpez, E Alonso *J. Mol. Catal. A* **105** 111 (1996)
174. P Dani, J Dupont, A L Monteiro *J. Braz. Chem. Soc.* **7** 15 (1996)
175. K Fagnou, M Lautens *Chem. Rev.* **103** 169 (2003)
176. T Yamamoto, T Ohta, Y Ito *Org. Lett.* **7** 4153 (2005)
177. A D Ryabov, G M Kazankov, S A Kurzeev, P V Samuleev, V A Polyakov *Inorg. Chim. Acta* **280** 57 (1998)
178. S A Kurzeev, G M Kazankov, A D Ryabov *Inorg. Chim. Acta* **305** 1 (2000)

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[b] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*