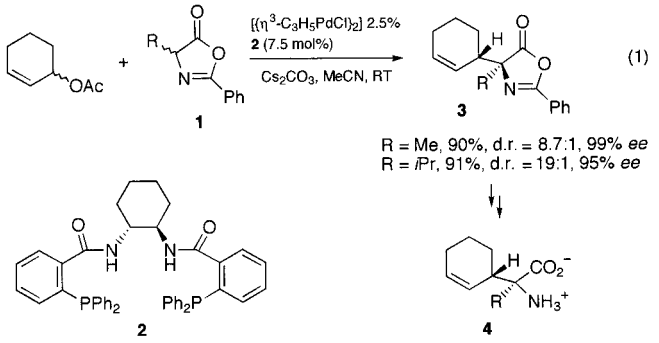
Palladium-Catalyzed Enantioselective Organic Transformations

Alphonse Tenaglia and Andreas Heumann*

The remarkable development of the palladium-catalyzed allylation has been characterized as a metamorphosis from the cinderella to a princess of catalysis.[1] Once this point was reached the flow of excellent new ligands has never stopped, and the powerful and efficient systems that are now available for the allylic alkylation may easily run into the first hundred.[2] This spectacular progress and the level of comprehension[3] has somewhat overshadowed the developement of other highly enantioselective palladium-catalyzed organic reactions, though the useful Heck reaction has emerged more or less rapidly as an immense tool in the stereocontrolled construction of organic molecules.[4] It is the purpose of this article to discuss these other promising reactions.

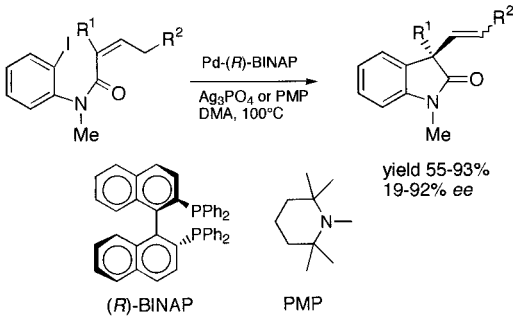
No account on enantioselective palladium chemistry may ignore a recent contribution by B. M. Trost et al. that promises a breakthrough in the control of chiral reactions.[5] A new method for the synthesis of α-alkylated amino acids, an important family of compounds, is based on the "chiral pocket" concept[6] with diphosphane **2**. The nucleophile fits in the chiral space created from **2** and an η^3-allyl palladium complex, and the control of two newly formed chiral centers is highly efficient, even at the one quite remote from the chiral ligand. Thus, for the first time asymmetric alkylation of the readily available azlactones **1** with 3-acetoxycyclohexene can be achieved with high diastereoselectivity and enantioselectivity (d.r. > 19:1, 95% *ee*). Hydrolysis of the products **3** provide the amino acids **4** [Eq. (1)].



(1)

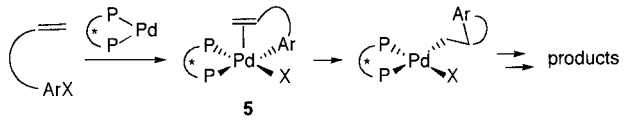
In addition, the same reaction with acyclic geminal dicarboxylates allows differentiation between enantiotopic leaving groups, and the reaction with the enantiotopic faces of the azlactone enolate was used as a key step in the synthesis of sphingosin analogues such as sphingofusin F.[7]

The asymmetric Heck reaction[8] was first investigated independently in the laboratories of Shibasaki[9] and Overman by means of the intramolecular cyclization of (*Z*)-alkenyl and aryl iodides or triflates by using mainly (*R*)-2,2′bis(diphenylphosphanyl)-1,1′-binaphthyl ((*R*)-BINAP).[10] Selectivities were rapidly raised to fairly good up to very good [Eq. (2)].



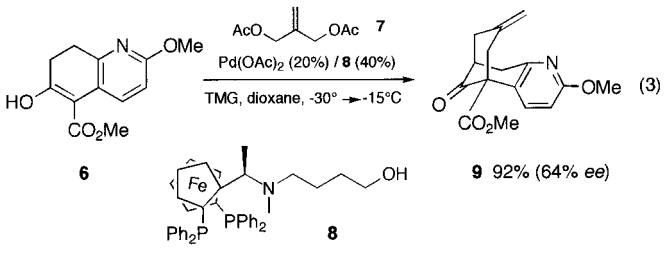
(2)

Recent studies by Overman et al.[4, 11] focussed on the mechanism of the reaction. The dramatic enhancement of enantioselectivity observed (from 43 to 95% *ee*) with chiral diphosphane ligands in the intramolecular cycloarylation is in agreement with a mechanism in which no phosphane dissociation is involved in the elementary steps (oxidative addition, double-bond insertion with formation of a chiral quarternary carbon atom, and finally β-elimination). In addition, the increased enantioselectivity that results from further addition of halide (in the form of quaternary ammonium salts) is in favor of the formation of a neutral pentacoordinate palladium intermediate **5** (with iodide or triflate coordinated to the palladium center; Scheme 1).



Scheme 1.

Cycloaddition reactions through palladium-catalyzed allylic substitution are usually much less enantioselective than reactions with simple allylic systems.[12] For example, the asymmetric bicycloannulation of a β-ketoester **6** with 2-methylene-1,3-propanediol diacetate **7** and chiral ferrocenylphosphane ligands such as **8** provides a bicyclo[3.3.1]nonane derivative **9** in *only* 64% *ee* [Eq. (3); TMG = 1,1,3,3-tetrame-



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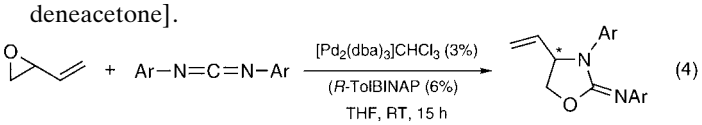
[*] Dr. A. Heumann, Dr. A. Tenaglia
Université d'Aix-Marseille
Faculté de St-Jérôme
ENSSPICAM, UMR-CNRS 6516
F 13397 Marseille Cedex 20 (France)
Fax: (+33) 491288278
E-mail: heumann@spi-chim.u-3mrs.fr

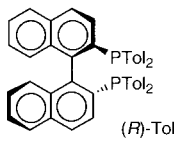
  1433-7851/99/3815-2180 $ 17.50+.50/0

thylguanidine-thiogalactoside].[13] However, this compound is a key intermediate to (−)-huperzine, a potent reversible acetylcholinesterase inhibitor and therefore a promising agent for the treatment of Alzheimer's disease. These more-complex allylic substitutions will certainly attract interest in the future.

Reasonable chiral inductions have been recorded by Hayashi et al. in the [3+2] cycloaddition of alkenes substituted with electron withdrawing groups and 2-phenylsulfonylmethyl-3-ethoxycarbonyloxyprop-1-ene in the presence of chiral ferrocenyldiphosphane ligands.[14] Disubstituted methylene cyclopentanes with 73% *ee* are thus available. The first example of an asymmetric 1,3-dipolar cycloaddition involving cationic (*S*)-BINAP-Pd^{II} complexes, a nitrone, and alkenes substituted with *N*-carbonyl-1,3-oxazolidin-2-one to fully substituted isoxazolines proceeds both in high yields and high enantioselectivity ($\leq$91% *ee*).[15] More recently, the insertion of carbodiimides **11** into the 2-vinyloxiranes **10** was investigated by Alper et al.[16] using (*S*)- or (*R*)-2,2′bis(ditolylphosphanyl)-1,1′-binaphthyl ((*S*)- and (*R*)-TolBINAP, respectively) and Pd^0 to synthesize 4-vinyl-1,3-oxazolidin-2-imines **12** with high yields and 94% *ee* [Eq. (4); dba = dibenzylideneacetone].

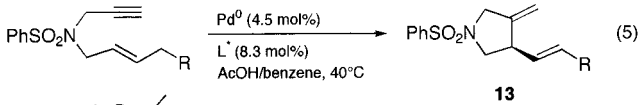


10 **11** Ar = *p*-ClC_6H_4 **12** 95% (94% *ee*)

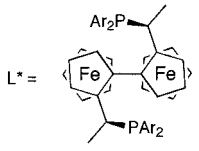


(*R*)-TolBINAP

Enyne cycloisomerization was developed by B. M. Trost et al.[17] as a powerful tool for synthesizing cyclic and polycyclic compounds. The early contributions with chiral carboxylic acids (Mosher's acid, α-methoxy-α-trifluoromethylphenyl acetic acid, MTPA) gave fairly low induction,[18] which could be improved by the use of amide–diphospane ligands.[19] More efficient ligands such as *trans*-coordinating (*S*,*S*)-(*R*,*R*)-TRAP-bisferrocenyldiphosphanes lead to five-membered heterocyclic rings **13** with the highest induction [95% *ee*; Eq. (5)].[20] The phosphane ligands reduce the reaction rate, but increase the selectivity; *trans* coordination is essential since *cis*-coordinating chiral diphosphanes reduce the induction level to about 15% *ee*.

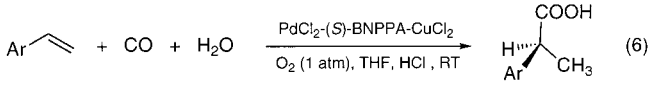


13
R = $SiMe_3$ 95% *ee*

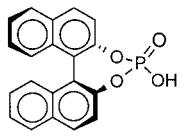


(*R*,*R*)-TRAP-bisferrocenyldiphosphane

Carbonylation with palladium catalysts is one of the most fundamental and long known reactions[21] and enantioselective transformations are of general interest. Thus, the hydrocarboxylation of styrene derivatives with the palladium–copper chloride catalyst system represents one of the most industrially attractive syntheses of α-aryl propionic acids **14** (for example, the antiflammatory drugs iboprufene and naproxene) [Eq. (6)].[22] This approach combines mild conditions and high yields with very high enantiomeric purity. The most efficient ligand is the atropisomeric 1,1′-binaphthyl-2,2′-diylhydrogen phosphate (BNPPA)[23] whose enantiomers are both commercially available.

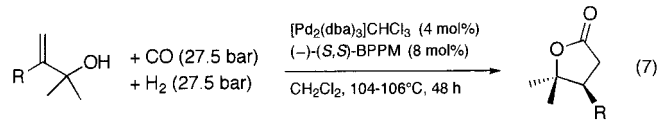


14
89%, 83-91% *ee*

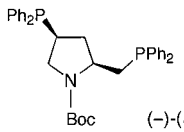


(*S*)-BNPPA

Similarly, cyclocarbonylation of unsaturated alcohols leads, under oxidative conditions, to synthetically useful γ-butyrolactones with inductions reaching 61% *ee*. Efficient ligands are poly-L-leucines.[24] In a more recent contribution, phosphane ligands such as (−)-(2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphospanyl-2-diphenylphosphanylmethylpyrrolidine ((−)-(*S*,*S*)-BPPM) with $[Pd_2(dba)_3]CHCl_3$[25] are shown to create quarternary centers with modest enantioselectivities for aliphatic allylic alcohols **15** (R = alkyl, 25–43% *ee*) [Eq. (7); Boc = *tert*-butoxycarbonyl]. Nevertheless, chiral efficiency becomes much more interesting when aromatic substituents are present, and may increase up to 84% *ee* (**15**, R = aryl).



15 R = alkyl, aryl
64-84%, 25-84% *ee*



(−)-(*S*,*S*)-BPPM

Optically active polyketones **16** are available through co-oligomerization of propene and CO. The chiral, completely stereoregular alternating copolymer forms as a spiroketal structure in the presence of BINAP ligands such as (*R*)-Cy_2BIPHEMP [see Eq. (8) for its structure] and palladium(II).[26, 27] Takaya et al.[28] showed more recently that copolymerization proceeds with very high enantioselectivity (relative to the C_2 symmetry of BINAP) even with unsymmetrical phosphane–phosphite BINAPHOS ligands such as (*R*,*S*)-BINAPHOS [see Eq. (8) for its structure; catalyst: L-[Pd(Me)(MeCN)BAr_4)].[29] The same kind of catalyst, now with bisoxazoline as a chiral ligand, was used for the styrene/CO copolymerization.[30]

In the field of chiral cross-coupling reactions axially chiral biaryls **18** are available from the selective substitution of one of the two enantiotopic biaryl triflate groups in **17** (Tf = tri-

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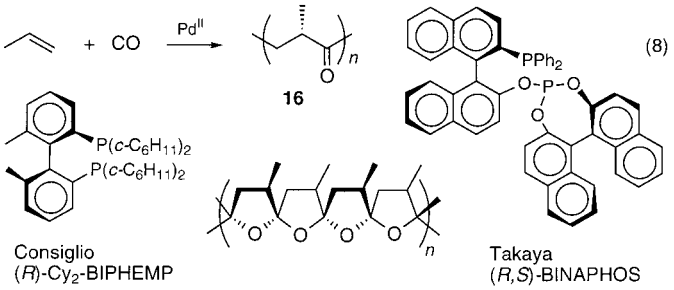
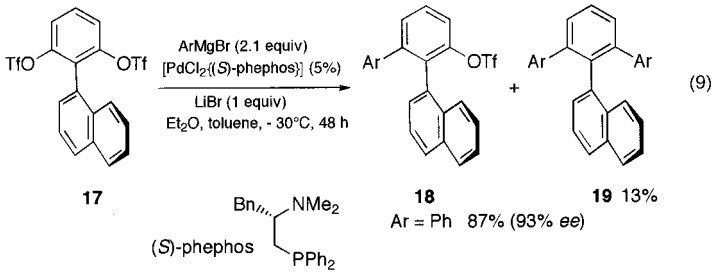
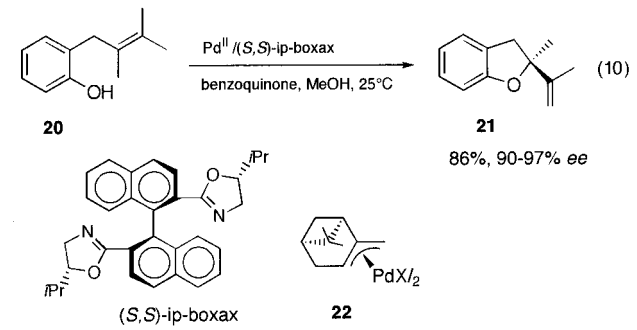


fluoromethanesulfonyl) catalyzed by the chiral P,N-bidentate ligand (*S*)-phephos coordinated to palladium dichloride [Eq. (9)].[31] The enantiomeric purity of the chiral product has been found to be dependant on the yield of a diarylation product **19**, that is, the enantiomeric purity of the optically

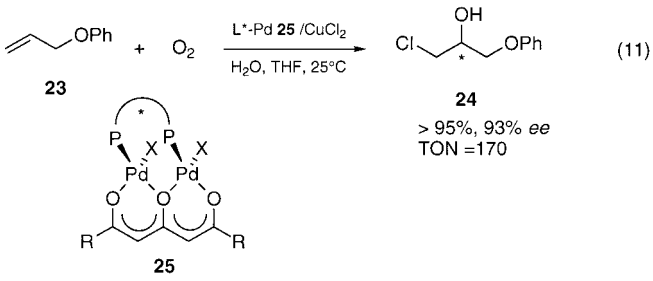


active product increases as the amount of diphenylation increases, and a kinetic resolution is demonstrated for the second cross-coupling reaction (**19**), which leads to an enhancement of the enantiopurity. Further transition metal catalyzed cross-couplings involving the remaining triflate group with lithium diphenylphosphides allow access to new chiral phosphane ligands.

Quite a few methods are still available for the enantioselective formation of C–O, or more generally for C–heteroatom bonds. Intramolecular hydroxypalladation reactions lead to oxygen-containing heterocycles.[32] The π–allyl palladium complex **22**, derived from β-pinene, catalyzes the cyclization of alkenylphenols with moderate enantiomeric excess.[33] This problem was not a result of the chemical system, simply that the high-induction ligand had to be found. Hayashi et al. combined binaphthol and oxazoline chemistry in the ip–boxax ligand.[34] With these new catalysts the alkenylphenols such as **20** could be cyclized in very good yields and extremely high ($\leq$97%) enantiomeric excess [Eq. (10)].



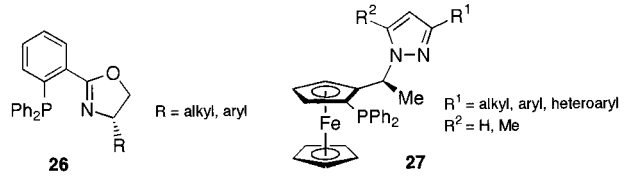
The cyclization of alkenylphenols can be considered as a Wacker-type reaction. For a long time nobody believed in enantioselective Wacker reactions, however conditions that led to chlorohydrins now proved successfull. The application of high chloride concentrations, originally established by Stangl and Jira in 1970,[35] had already shed some light onto the stereochemistry and the mechanism of the oxidation of ethylene.[36] These reaction conditions now formed the basis for Henry et al.[37] to successfully realize an asymmetric chlorohydrin synthesis. The authors had observed that when adding pyridine to the $PdCl_2-CuCl_2$ Wacker oxidation system Cl^- concentrations as low as 0.2 M catalyzed chlorohydrine formation efficiently [Eq. (11)].[38]



Unfortunately experiments with chiral amines gave only low chiral inductions. Palladium phosphane complexes are usually insoluble in the Wacker reaction medium. This problem was solved with sulfonated BINAP ligands and more importantly by a new homo-bimetallic approach with bridging diphosphanes (complex **25**). This type of coordination is possible when the cationic palladium center is bound to the dianion of 1,3,5-pentanetriones. Inductions with sulphonated chiral phosphanes are moderate to good (46–76% *ee*) with turnovers of 60–72 cycles. With the bimetallic system both values become excellent (up to 93% *ee* and turnovers up to 200). The latter catalysts are most promising since, in addition to the *ee* and turnover numbers, high regioselectivities emerge with allylic-substituted terminal alkenes **23**.

Allylic amination is rapidly developing as an interesting way to form C–N bonds catalytically and, consequently, to give access to chiral amines. In this context P,N-chelating compounds have proven to be excellent chiral ligands. Optically active phosphanooxazolines, for example, **26** developed in the laboratories of Pfaltz and Helmchen,[39] allow the enantioselective allylic amination of the corresponding acetates (or carbonates) with benzylamine, $(Boc)_2NH$, and sodium salts of *p*-toluenesulfonamides with *ee* values up to 97%. Togni's bidentate ferrocenyl phosphane pyrazole P,N-ligands **27** are also extremely useful for these transformations.[40]

General reactions to form chiral alkenes or polyenes such as the enantioselective hydride trapping of allylic systems are



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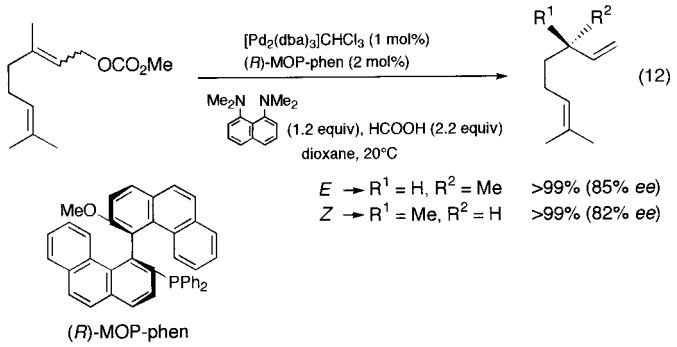
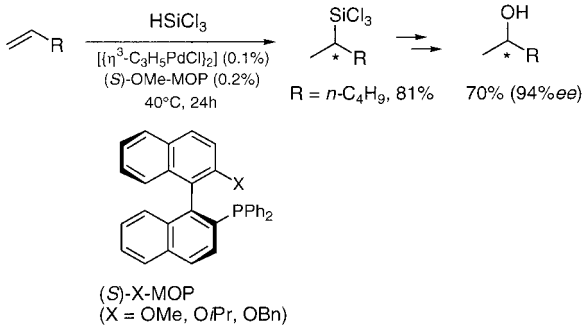
rare. The reduction of allylic carbonates with formic acid and tertiary amines with Pd–monophosphane (Pd–MOP) complexes is a stereospecific process to afford chiral α-substituted alkenes [Eq. (12)].[41]



The combination of hydrosilylation and oxidation of olefins is a powerful synthetic method for forming secondary alcohols. The first successfull palladium-catalyzed conversion of terminal alkenes into optically active alcohols ($\leq$94% *ee*) was reported by Hayashi et al. in 1991.[42] Alkyl trichlorosilanes are obtained by using a new chiral monophosphane ligand, and their oxidation by Tamao's procedure (Scheme 2)



Scheme 2.

to secondary alcohols is stereospecific (with retention of configuration). Other substrates such as cyclic alkenes,[43] styrene derivatives,[44] or cyclic dienes[45] were also transformed successfully with this reaction.

When analyzing the different reagents that exert the (generally high) enantiocontrol in these palladium-catalyzed transformations it appears that the binaphthyl chiral backbone occupies a particularly dominant position, though other systems, such as ferrocenyl or bisoxazoline structures, are becoming more topical. Another trend concerning the coordinating heteroatom is also visible and goes from uniform ligands, such as phosphanes or amines, to the combination of two (or potentially more) different heteroatoms with different coordination properties in the same molecule. Thus, the mixing of the different topological and electronical properties established in the actual efficient ligands (the binaphthyl–oxazoline Ip–boxax, for example) seems extremely promising for future developments.

German version: *Angew. Chem.* **1999**, *111*, 2316 – 2320

Keywords: C–C coupling · cyclizations · Heck reactions · Wacker oxidations

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Deposition of Data from X-Ray Structure Analyses

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