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Review

Enantioselective palladium-catalyzed allylic substitutions with asymmetric chiral ligands☆

Günter Helmchen *

Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

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Abstract

Phosphinooxazolines are highly effective ligands in Pd catalyzed asymmetric substitutions of allylic compounds. Malonates, amines and nitronates can be employed successfully as nucleophiles. Mechanistic aspects, studied by NMR and X-ray crystal structure analyses, are presented. These studies were focused on identification of Pd-bound intermediates in order to gain a clear understanding of the enantioselective step in the catalytic cycle. Also described are reactions under catalysis with Pd complexes of a new phosphinocarboxylic acid. Applications in syntheses of physiologically active compounds are presented.

Keywords: Palladium; π-Allyl complexes; Catalysis; Asymmetric synthesis; Phosphines

1. Introduction

Soon after invention of the Wacker process (1956), which was the starting point of modern palladium chemistry [1], the first (π-allyl)Pd complex was reported (1959) by Smid and Hafner [2]. C–C bond forming substitution reactions with (π-allyl)Pd complexes were discovered in 1965 by Tsuji [3], then at Toray Industries, and were vigorously developed by Trost and co-workers since 1973 [4]. Crucial improvements in this chemistry are due to industrial chemists at Toray Industries and Union Carbide who demonstrated in 1970 that phosphines accelerate the reaction and that the precious metal can be employed in catalytic amounts [5,6] (Scheme 1).

Most allylic substitution reactions furnish a chiral product. It was logical to try to achieve enantioselectivity with the help of a chiral ligand L*. The first attempt, using a stoichiometric allylic substitution, was reported by Trost and Dietsche in 1973 [7]. Enantioselectivity achieved then was low by today's standards, and its applications in organic synthesis required the development of the catalytic reaction. For a considerable time, progress was slow because the C_2-symmetric chelate-forming diphosphines giving excellent results in hydrogenations i.e. DIOP, CHIRAPHOS, BINAP etc. gave disappointing results in allylic substitutions, particularly so with cyclic allylic substrates. Only in the early 1990s, was it demonstrated with bisoxazolines [8–10] and new types of diphosphines [11], that high enantioselectivity is possible given a proper combination of substrate and C_2-symmetric ligand. However, impressive results were earlier achieved in the second half of the 1980s [12], with asymmetric phosphinoferrocenes developed at Kyoto University. Today, Pd catalyzed asymmetric C–C and C–N bond forming substitutions at allylic compounds are being employed by many research groups (reviews: [13–16]). Here we give an

☆ Dedicated to Professor Richard F. Heck and to Professor Jiro Tsuji.

* Fax: +49-6221-544205.

E-mail address: en4@ix.urz.uni-heidelberg.de (G. Helmchen)

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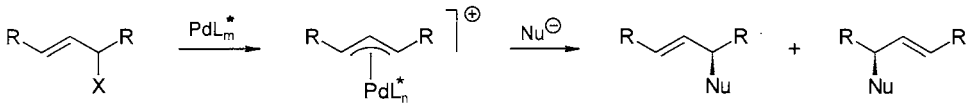
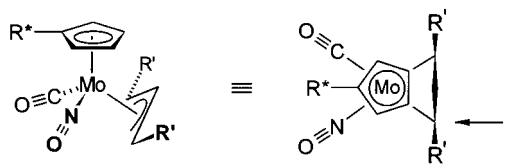


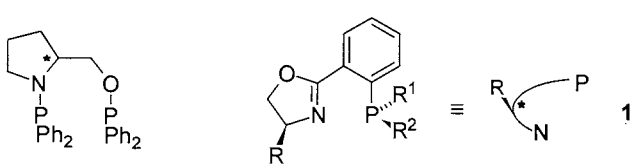
Scheme 1.

account of our work and related recent contributions of others in this area.

Our own approach was inspired by the work of Faller, who had realized remarkably high enantioselectivity in stoichiometric substitutions at (cyclopentadienyl)molybdenum complexes. Faller introduced chiral complexes containing ligands (CO, NO) with different electronic rather than steric properties [17]. The electronic ligand effect provided for highly selective attack at the allylic carbon in *cis* position to the NO ligand:



In catalysis, an equivalent approach would involve the use of a chiral chelate ligand with two electronically different donor centers. This was apparently first probed by Caesarotti with the ligand PROLOPHOS with two slightly, by bonding to O or N, differentiated P atoms [18]. A fairly low level of enantioselectivity was obtained. We felt that a more pronounced difference in electronic, as well as steric, properties was required and, therefore, chose the combination of a hard (N) and a soft (P, S or Se) donor. Realization of this proposal relied on the proven usefulness of the oxazoline moiety as demonstrated with bis- and bioxazoline ligands earlier by Pfaltz for allylic substitution reactions [19]. Aryl groups were preferred as substituents at P because triarylphosphines are normally stable to air. These considerations led to the development of phosphinooxazoline (PHOX) ligands **1** [20]. Our publication was slightly delayed in order to obtain a patent on the new ligands [21].



PROLOPHOS **PHOX**

The same concept was independently pursued since 1993/1994 by the groups of Pfaltz [22], Williams [23–25] and, with different types of P–N chelate ligands, by J.M. Brown [26] and Togni [27]. Oxazolines with an additional S or Se donor center are also readily available; however, their catalytic efficiency in allylic substitutions is lower than that of the PHOX ligands [28,43]. Likewise, applications of bisoxazolines are very limited.

2. Preparation of phosphinooxazolines

Oxazolines are available from amino alcohols which can be prepared from the chiral pool of natural amino acids (Scheme 2). There are many established routes from amino alcohols to oxazolines [29]. Usually, one step procedures are employed [30–32]. However, better yields are often achieved with a three step procedure involving formation of an *N*-acyl amino alcohol, activation of the OH group and ring closure with base [33].

Introduction of phosphorus is described in Scheme 3 [33].

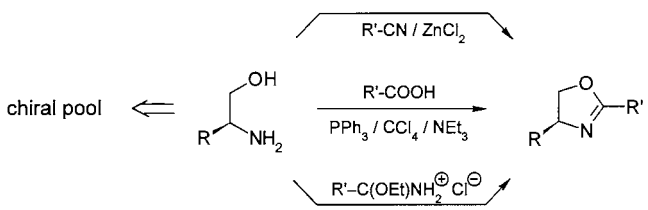
2.1. Nucleophilic substitution

Nucleophilic substitution of fluoride with a diarylphosphide proceeds reliably with 70–90% yield. In the case of stereogenic phosphorus, with, e.g. Ph and 1-naphthyl or 2-biphenylyl substituents, ca. 7:3 mixtures of diastereomers are formed which usually can be separated by flash chromatography and/or crystallization.

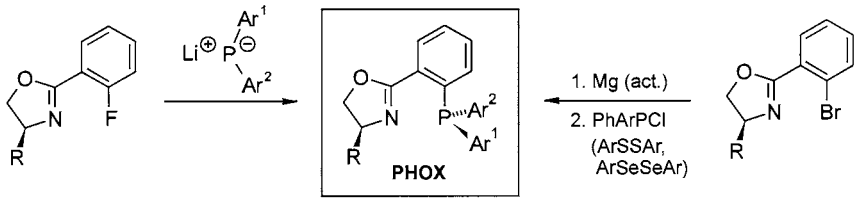
2.2. Electrophilic substitution

Electrophilic phosphorus and also sulfur and selenium compounds can react with the Grignard compound obtained from the corresponding bromo derivative and activated magnesium. Yields with halophosphines are only 30–50%, but the *P*-diastereomers are formed with fairly high selectivity of $\geq$ 85:15. Configurations at phosphorus were determined by crystal structure analysis.

Benzoic acids with halogen substituents in *ortho*-position are required for the routes described in Scheme 3. These compounds are often not commercially available. Accordingly, preparation of lithio derivatives by *ortho*-metallation of oxazolines and subsequent reaction with electrophiles is of interest (Scheme 4). This route works well with metallocenes, for example ferrocene deriva-



Scheme 2.



	R	Ar^1	Ar^2
A	*i*Pr	2-biphenylyl	phenyl
epi-A	*i*Pr	phenyl	2-biphenylyl
B	*i*Pr	2-biphenylyl	3,5-$(CF_3)_2$-C_6H_3
epi-B	*i*Pr	3,5-$(CF_3)_2$-C_6H_3	2-biphenylyl
C	phenyl	2-biphenylyl	phenyl
epi-C	phenyl	phenyl	2-biphenylyl

Scheme 3.

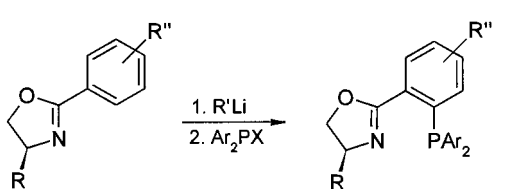
tives [34–36] (see below also). However, with normal arenes extensive variation of reaction conditions is usually required and yields are low [30] (exception [37]).

3. Acyclic substrates and mechanistic aspects

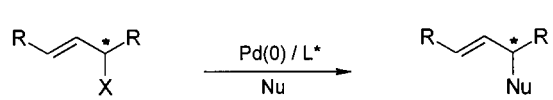
Malonates were most often used as nucleophiles in allylic substitutions [20,22,23]. In addition, a variety of other nucleophiles were investigated: glycine derivatives [38], amines [39], *N*-acylamides [39], nitro compounds [40], and sulfinates [41] (Scheme 5). As a rule, these nucleophiles are less reactive than malonates; however, enantioselectivities are very similar and the steric course is independent of the nucleophile. With acyclic substrates products with enantiomeric excess (*ee*) of 60–99% are formed, depending on the size of R. Best results are generally achieved with 1,3-diphenylallyl acetate; accordingly, this compound is most often used as a test substrate although the results with it are not informative. Critical evaluation of a new ligand should include reactions with 1,3-dimethylallyl acetate and cyclohexenyl acetate (see below).

Rationalization of the steric course of the nucleophilic substitution is difficult because there are two diastereomeric π-allyl complexes, designated *exo*- and *endo*-isomer here (**4x**, **4n** in Scheme 6). The products can be formed via four pathways and the preferred product can arise by a reaction at the allylic C *trans* to P of the *exo* or *cis* to P at the *endo* isomer. For the decision between these possibilities, a postulate of Bosnich [42] was helpful. Based on the assumption of an early transition state, this postulate states that the more abundant isomer is the more reactive one. The more abundant is generally the *exo*-isomer (see below). In conjunction with the known configuration of the products of allylic substitutions, it is deduced that the nucleophile preferentially attacks the carbon *trans* to phosphorus [43–45]. Arguments in favor of a late transition state have been presented for allylic substitutions carried out with QUINAP as the chiral ligand. Assumption of a late transition state also leads to a preference for substitution at the allylic carbon in *trans* position relative to phosphorus [26].

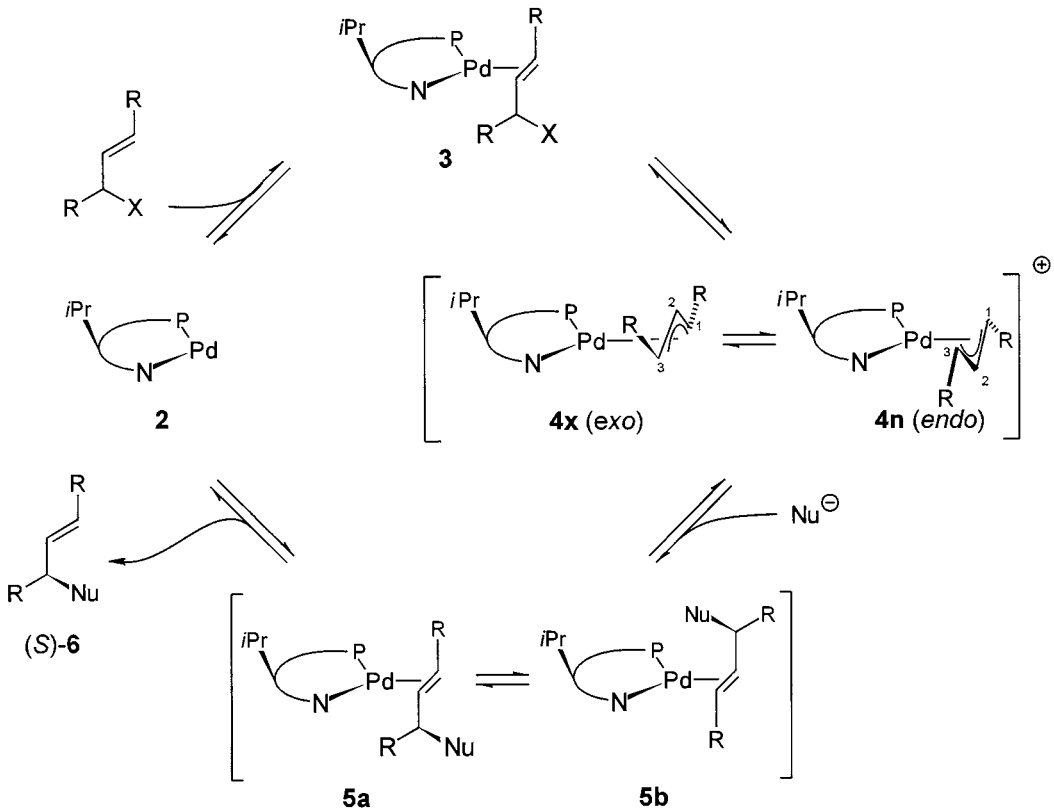
There is so far no direct proof for the mechanistic proposal described above, i.e. preferential attack at the allylic carbon *trans* to phosphorus. There is, however, support by circumstantial evidence from ^{13}C-NMR shifts, NMR studies on the interconversion of *exo* and *endo* diastereomers, X-ray crystal structures [43] and from quantum chemical calculations (DFT method) [46]. The crystal structures, for an example see Fig. 1, were particularly important because they allowed us to understand why *exo* isomers are more stable than *endo* isomers. There are several important general observations: (i) The inner chelate cycle, PdNCCCP is non-planar. (ii) A consequence of non-planarity is conformational non-equivalence of the substituents at P, one is axially, the other equatorially arranged. Aryl ring planes are nearly perpendicular to each other, with the axial group pointing its edge, and the equatorial with its face to the metal. (iii) The substituent of the oxazoline ring occupies an axial position so that only



Scheme 4.



Scheme 5. R = Me, *n*-Pr, *i*-Pr, Ph, $CH_2O\Sigma$; X = OAc, Hal, $OCOOCH_3$, $OPO(OR)_2$; Nu = $^-CH(COOR)_2$, $[Ph_2C{=}NCHCOOR]^-$, H_2NR, $^-H_2CNO_2$, ^-O_2SPh.



Scheme 6.

the equatorial H can interact with the allylic moiety. The dominating interaction is the one with the equatorial aryl group at phosphorus. Minimization of this interaction is the reason for preference of the *exo* over the *endo* diastereomer.

The analysis of X-ray structures of π-allyl complexes presented above was very helpful for an understanding of the relative stabilities of diastereomeric π-allyl complexes and the structural aspects important for selectivity. Nevertheless, it was desirable to find direct proof for the fundamental hypothesis of preferred attack of the nucleophile at the allylic carbon *trans* to phosphorus. Therefore, the reaction course was studied by modern 2 D NMR spectroscopic methods [47].

Initially the stoichiometric reaction of the π-allyl complex **4** (R = Ph; 10:1 mixture of **4x** and **4n**) with sodium dimethyl malonate was examined as follows. A solution of the complex **4** in THF-d^8, prepared at r.t., was cooled to −78°C and a precooled solution of sodium dimethyl malonate in THF-d^8 was added. Then the mixture was heated inside the NMR probehead and the progress of the reaction was monitored by ^{31}P-

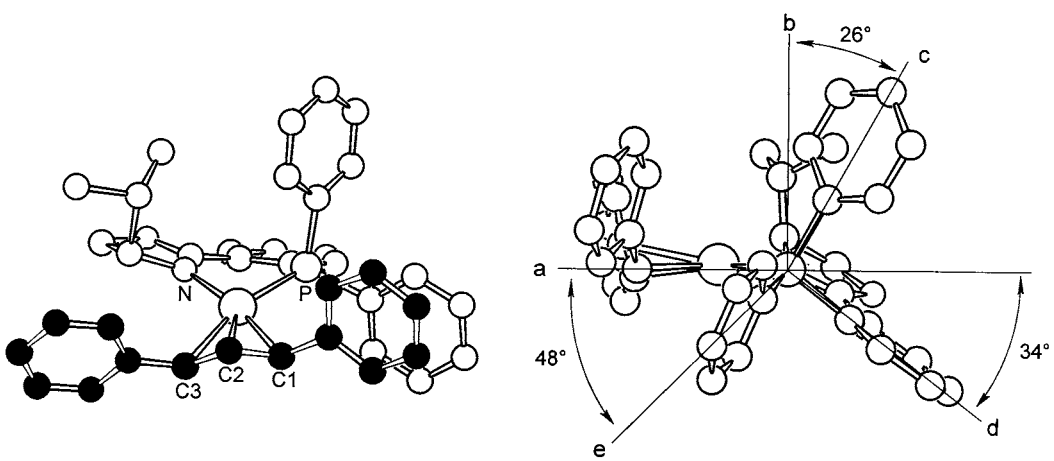
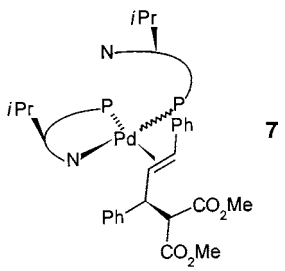


Fig. 1. Front view (left) and side view (right) of the X-ray crystal structure of complex **4x** (R = *i*-Pr, R′ = Ph).

NMR spectroscopy (Fig. 2). During the course of the reaction **4x** and **4n** are always in rapid equilibrium. As a first new species, a compound with a singlet at $\delta = 11.18$ ppm appears, whose concentration reaches a maximum already after 90 s before it is consumed within a few minutes. This compound is the Pd(0) alkene complex **5a**. Consumption of **5a** is accompanied by the appearance of a new species with a characteristic AB spin system ($\delta_A^{korr} = 9.41$, $\delta_B^{korr} = 12.91$, $^2J_{P,P} = 128$ Hz) which is the main component after a reaction time of ca. 1 h. We assign structure **7** to this long-lived intermediate. The precise geometry of this complex could not yet be determined.



7

Only traces of the metal-free product (*S*)-**6**, which is formed from **7**, were detected in the reaction mixture when the reaction was stopped at a conversion of ca. 50%. The concentration of (*S*)-**6** only increased when conversion exceeded 50%. Therefore, complex **7** is a stable by-product of the stoichiometric reaction. For the determination of the constitution of the mechanistically meaningful transient species **5a**, the reaction was carried out with ^{13}C3-labeled sodium dimethyl malonate at -20 to -30°C and stopped after 2 min by cooling to -78°C. A sample prepared in this way contained ca. 75% of the phosphorus in the form of the Pd(0) alkene complex **5a** and was stable for several weeks at -78°C in an inert atmosphere.

Assignment of the resonances of all NMR-active nuclei was possible by use of ^{13}C3-labeled malonate with a large set of 2 D NMR experiments (1H, 1H-COSY, -TOCSY, -NOESY, -ROESY, ^{13}C, 1H-HSQC, -HMBC, -HMQC-TOCSY and 31P, 1H–HMBC). By quantitative analysis of NOE- and ROE-data, information on distances of the H nuclei could be obtained, which is only in accordance with the conformer **5a** and not with **5b** (Scheme 7). For example, characteristic is the NOE between 2-H and 17-H, which is altered during the transformation of **4x** to **5a**. The value of this NOE contact in **5a** corresponds

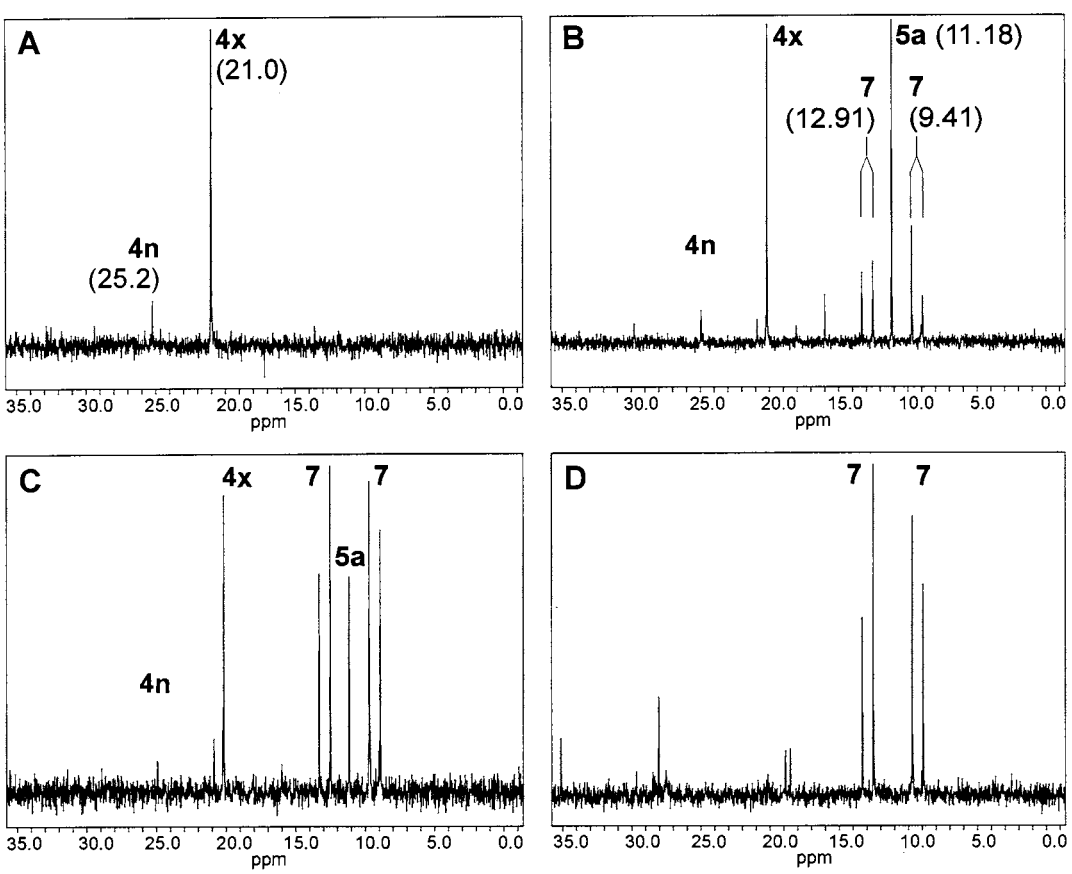
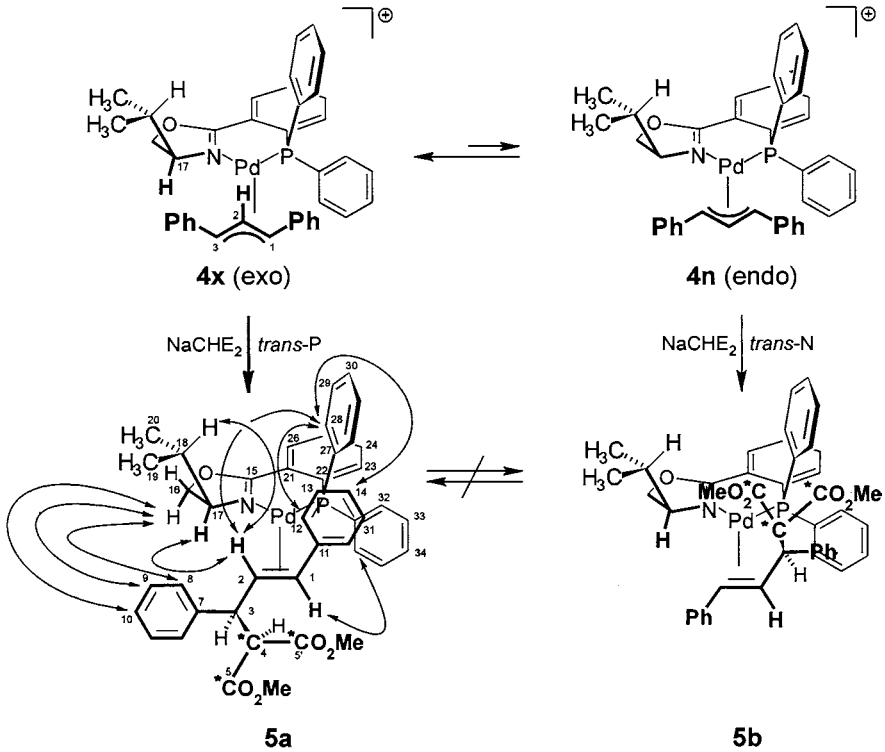


Fig. 2. ^{31}P{1H} NMR-spectra recorded at various reaction times (-60°C). (A) Equilibrating π-allyl complexes **4x** and **4n**. (B, C, D) Reaction mixtures 370, 500 s and 1 h after addition of the sodium dimethyl malonate.



Scheme 7.

to a reduction of the distance between 2-H and 17-H by 1.4 Å, as compared with the distance in **4x** determined by X-ray diffraction analysis.

Statements concerning the mechanism of the allylic substitution require the following plausible assumptions: (a) The attack of malonate at **4x** under formation of **5a** proceeds via a least motion reaction path, i.e. a rotation of 30° from **4x** to **5a** is the main process; (b) rotation of the alkene fragment relative to the N–Pd–P-plane in complex **5a** is sufficiently slow so that equilibration between **5a** and **5b** is slow compared with the rate of their formation.

Assumption (b) is supported by experiments in which the reaction was carried out in a temperature gradient (-78°C to r.t.) and monitored by ^{1}H-NMR spectroscopy. In this experiment broadening of the resonances of complex **5a**, which would be expected for a dynamic exchange process, was not found. Accepting assumption (b), the configuration of the more reactive allyl complex **4x** is conserved in the Pd(0) alkene complex **5a**. Considering the known absolute configuration of the product, an attack of the nucleophile *trans* to phosphorus at the *exo* π-allyl complex **4x** can be derived. This result is in accordance with earlier interpretations [23,43], but is here based on a precisely characterized Pd(0) alkene product complex in the Pd-complex catalyzed allylic substitution.

4. Slim substrates: problems and their solutions

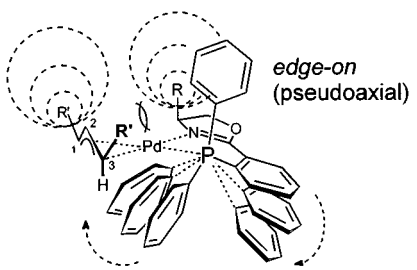
4.1. Survey

The front view in Fig. 1 shows quite clearly that the chiral phosphinooxazoline ligand mainly provides interactions at its wings. It appears likely that allylic systems with big substituents, such as phenyl, should display high *exo*:*endo* ratios and enantioselectivity, but narrow systems, with small substituents or cyclic compounds, might give low selectivity. This is what was found indeed. In Scheme 8, substrates are ordered according to their broadness and it is quite remarkable how closely the ee and er (enantiomer ratio) values parallel the steric extension (the isopropyl case is taken from [22]). The importance of this parameter is further underlined by NMR data of the corresponding π-complexes: ratios of 1.8:1, 4:1, and 9:1 for the cyclohexenyl, the 1,3-dimethyl- and the 1,3-diphenylallyl derivative ($CDCl_3$ solution), respectively. The cause of enantioselectivity, though it is a kinetic phenomenon, i.e. a function of differing reaction rates at the allylic termini in *exo* and *endo* complexes. If we generalize the assumption that only the allylic terminus *trans* to phosphorus is attacked in both *exo* and *endo* isomers, then it follows from Scheme 8 that relative rates of *endo* and *exo* isomeric (π-allyl) Pd complexes are ca. 10:1 for the 1,3-diphenylallyl complex, but ca. 1:1 for the 1,3-dimethylallyl complex. As electronic effects of the

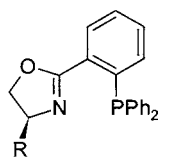
PHOX ligands on the relative rates seemed not significant, it was logical to improve selectivities by improving *exo*:*endo* ratios.

4.2. Acyclic substrates

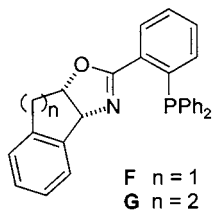
One logical approach towards improvement of the *exo*:*endo* ratios and enantioselectivities was to increase the steric bulk of the pseudoequatorial aryl substituent at phosphorus. This turned out to be rather cumbersome. A better solution was found upon inspection of crystal structures. It was observed that repulsion between substituents R or R′ and the palladium ion leads to bending of the ligand plane (N–C–C–C–P) relative to the coordination plane (P, N, C-1, C-3). Increase of bending causes the pseudoequatorial phenyl ring at P to be pushed further towards the π-allyl system; this leads to an increase in the crucial interaction between the P-phenyl group and the substituent R′ at C-3 thus destabilizing the *endo* π-allyl complex.



These observations suggested that better suited ligands might be obtained by using larger substituents at the oxazoline moiety [48–50]. Accordingly, ligands **D** and **E** with bulky substituents R were probed; ligand **E** derived from penicillamine is particularly interesting because of the possibility for further variation in the substituent at sulfur. A more successful concept involved incorporation of the substituent R into a ring in order to provide a conformational situation with maximal steric interaction between R and the palladium ion (ligands **F**, **G**). With these ligands up to 89.5% ee were achieved for the reaction of 1,3-dimethylallyl acetate with sodium dimethylmalonate. Ligand **G** stands out as it not only induces the highest selectivity, but also the fastest substitution reaction.



D R = *t*Bu
ent-**E** R = CMe_2SiBu



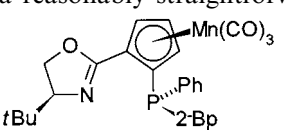
F n = 1
G n = 2

4.3. Cyclic substrates

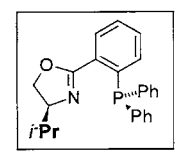
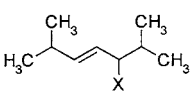
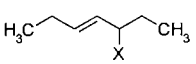
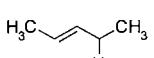
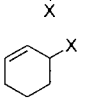
The production of racemic product from the cyclic substrate (cf. Scheme 8) was particularly unsatisfactory. As the pseudoequatorial aryl group is too far away from the area occupied by the particularly slim cycloalkenyl moieties, a ligand was required that would reach into the narrow area directly above or below the allylic sp^2 centers. As such ligands the biphenyl derivatives **A**–**C** (Scheme 3) were conceived [51]. We were able to obtain a high resolution X-ray crystal structure of the complex $[Pd(\eta^3\text{-}C_6H_9)(\mathbf{A})]SbF_6$ derived from ligand **A** (R = *i*-Pr), and indeed, in the crystal conformer α is found in which the phenyl of the 2-biphenylyl group is located directly above the allylic moiety as described in Fig. 3.

Despite the fact that conformer α is favored in the solid state, enantioselectivities resulting with the ligand **A** were not satisfactory. Distinct dependence on ring size of the substrate and, to a certain extent, on reaction conditions are apparent from the data given in Table 1. In order to enhance electronic effects, the ligand **B** with the electron withdrawing CF_3 groups was prepared. With this ligand improved enantioselectivity was obtained with methylene chloride as solvent.

Nevertheless, results were still not satisfactory. A hint towards improvement was gained by an NMR analysis of the complex $[Pd(\eta^3\text{-}C_6H_9)(\mathbf{A})]SbF_6$ which indicated the existence of several conformers in solution, including the unfavorable conformer β with the crucial phenyl group rotated away from the allylic moiety (cf. Fig. 3). In order to destabilize conformers of this type, the cymantrene-based ligand **H** was conceived and could be prepared in a reasonably straightforward way [52].



H

	ee [%]	er	exo : endo (NMR)
	98.5	99 : 1	90 : 10
	94		
	74		
	56	78 : 22	80 : 20
	0	50 : 50	64 : 36

Scheme 8.

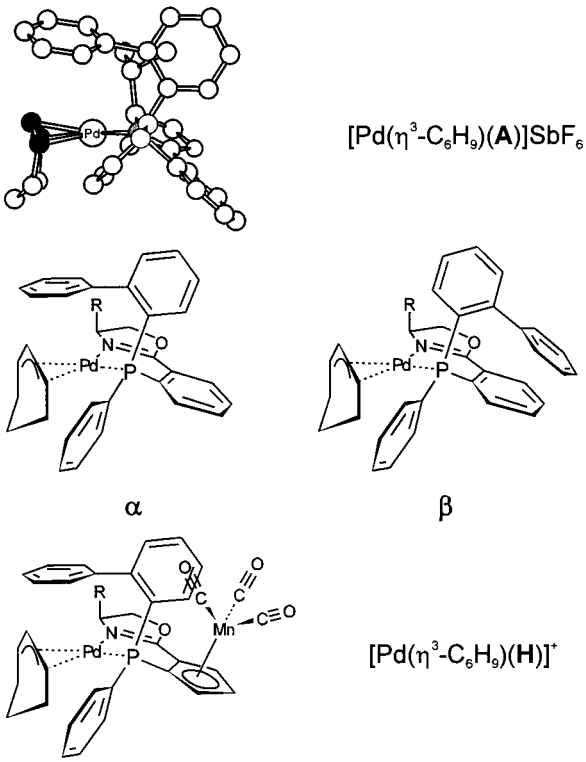


Fig. 3. Structures of (π-allyl) Pd complexes derived from cyclic substrates.

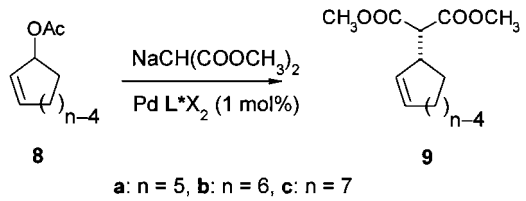
This ligand induces excellent catalytic activity and displays long shelf life. Conformers analogous to β are apparently destabilized by interaction with the manganese tricarbonyl group. High enantioselectivity with this new ligand was indeed obtained (Scheme 9 and Table 1).

In order to verify our hypothesis about the structure of the (π-allyl)Pd complexes of ligand **H** the π-allyl complex **11** was prepared as example by reaction of the known complex **10** [53] with the phosphine **H** in dichloromethane and subsequently exchanging the counter ion chloride by hexafluorophosphate (Scheme 10). The X-ray crystal structure (Fig. 4) was found to be a structure of the type described in Fig. 3. Only one species was observed by ^{31}P-NMR after dissolving the complex in THF-d_8 at −78°C. Upon warming up isomerization was not observed. Accordingly, one can conclude from the fact that substitution products **9** with (*R*)-configuration are formed that the substitution proceeds via attack at the allyl terminus *trans* to phosphorus.

Table 1
Enantiomeric excess in allylic substitutions according to Scheme 9

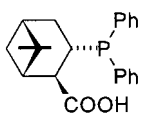
Ligand	Method[a]	% ee of		
		9a	**9b**	**9c**
A	a	56	51	83
B	a	63	53	83
B	b	64	72	85
H	c	96	94	>99

[a] Method a, 1.5 eqivalent $LiCH(COOCH_3)_2$, dioxane, r.t. Method b, 2.5 eqivalent $CH_2(COOCH_3)_2$; BSA method, methylene chloride, 0°C. Method c, 1.5 eqivalent $NaCH(COOCH_3)_2$, dimethylformamide, −50 to 0°C.



Scheme 9.

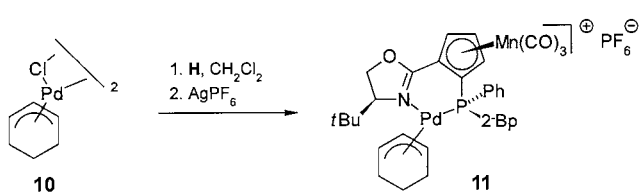
Prior to the development of the new ligand **H** high enantioselectivities with cyclic substrates were achieved with salts of the easily available β-phosphinocarboxylic acid **I** as chiral ligand [54]: enantiomeric excess of 85, 98 and >99% ee for the 5-, 6- and 7-membered ring derivatives, respectively [with $LiCH(COO\text{-}t\text{-}Bu)_2$ as nucleophile]. Products with (*S*)-configuration are formed with ligand **I**. Other phosphinocarboxylic acids had previously been used in allylic substitutions by Minami and co-workers [55,56].



I

Ligand **I** can be prepared very easily on a 100 g scale from (−)(1*S*)-α-pinene or more directly from natural (−)(1*R*)-myrtenal via *t*-butylmyrtenate in high yield using conjugate addition of $LiPPh_2$ as a key step (Scheme 11). The enantiomer *ent*-**I** is available from (+)(1*R*)-α-pinene.

Ligand **I** gave quite remarkable results for a variety of cyclic substrates (cf. Scheme 12). We had conceived the new ligand on the basis of the observation concerning the effect of the substituent of the oxazoline moiety that was discussed above (cf. Section 4.2). We felt that



Scheme 10.

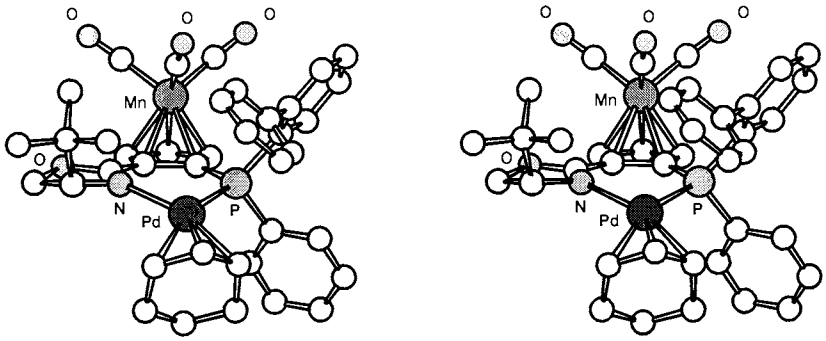
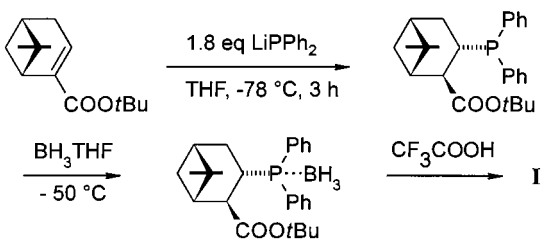


Fig. 4. Stereoview of the crystal structure of the cation of complex **11**. Hydrogen atoms are not given.



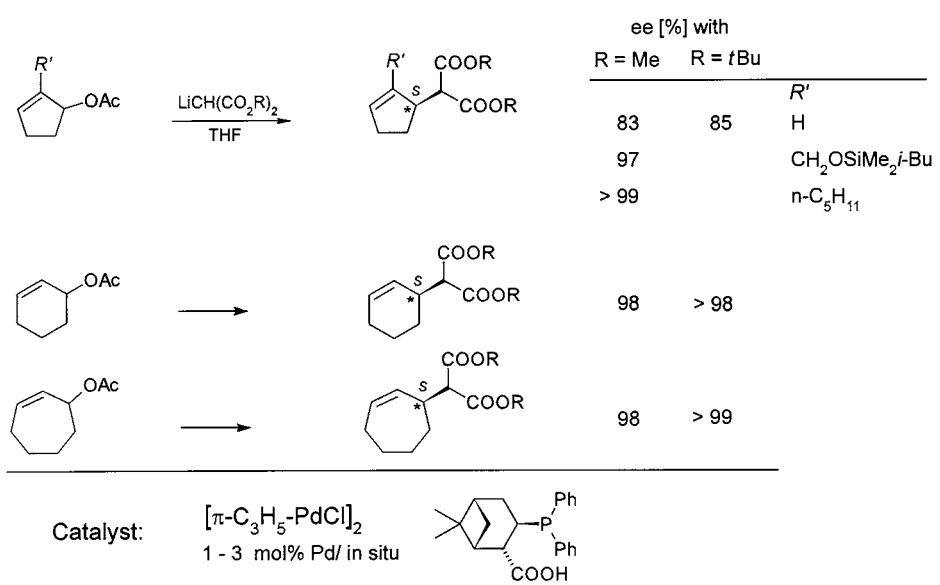
Scheme 11.

replacement of the oxazoline moiety by the small carboxylate group, likewise a hard donor compared to phosphorus, would alter the conformation of a presumed chelate complex drastically. In particular, we hoped for reversal of the bending effect described above, so that perhaps the axial aryl group, which is closer to the allyl sp^2 centers than the equatorial aryl group, might dominate the *exo*:*endo* ratio of the diastereomeric π-allyl complexes. Unfortunately, we were never able to obtain a crystalline Pd-complex despite considerable effort. However, recently we found that the dimethylamide of the carboxylic acid **I** gives similar results as ligand **I**. Mechanistic investigations indicate that this ligand acts as monodentate ligand and the catalytically active species are complexes of the type (π-allyl)L_2^*Pd. Current work is directed at determining their solution structure by NMR.

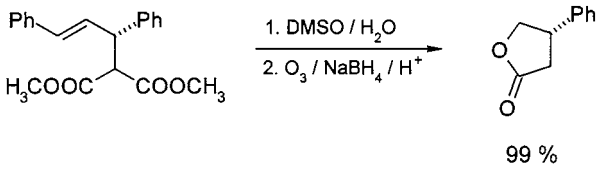
5. Applications

In 1979 this group developed a method for enantiomer resolution of chiral amines which was based on the formation of diastereomeric amides by heating a racemic amine with enantiomerically pure 3-phenylbutyrolactone [58]. At that time there was no convenient way to prepare this compound. It was gratifying that the standard example of allylic alkylation opened the straightforward access described in Scheme 13.

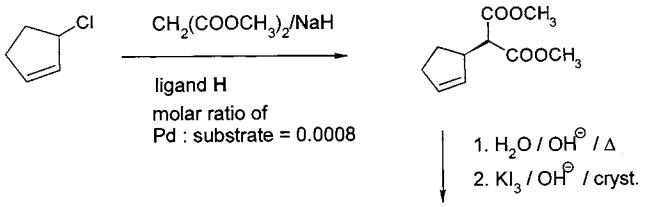
Cyclic allylic derivatives, in particular cyclopentanes as described in the previous section, are starting materi-

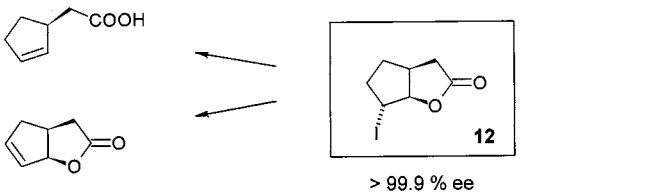


Scheme 12. Enantiomeric excess obtained for cyclic substrates with a Pd complex of ligand **I** [57].



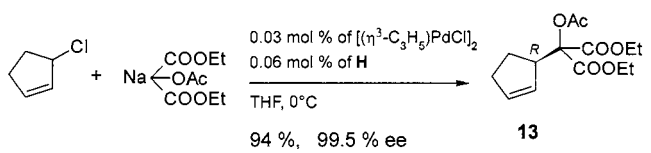
Scheme 13.



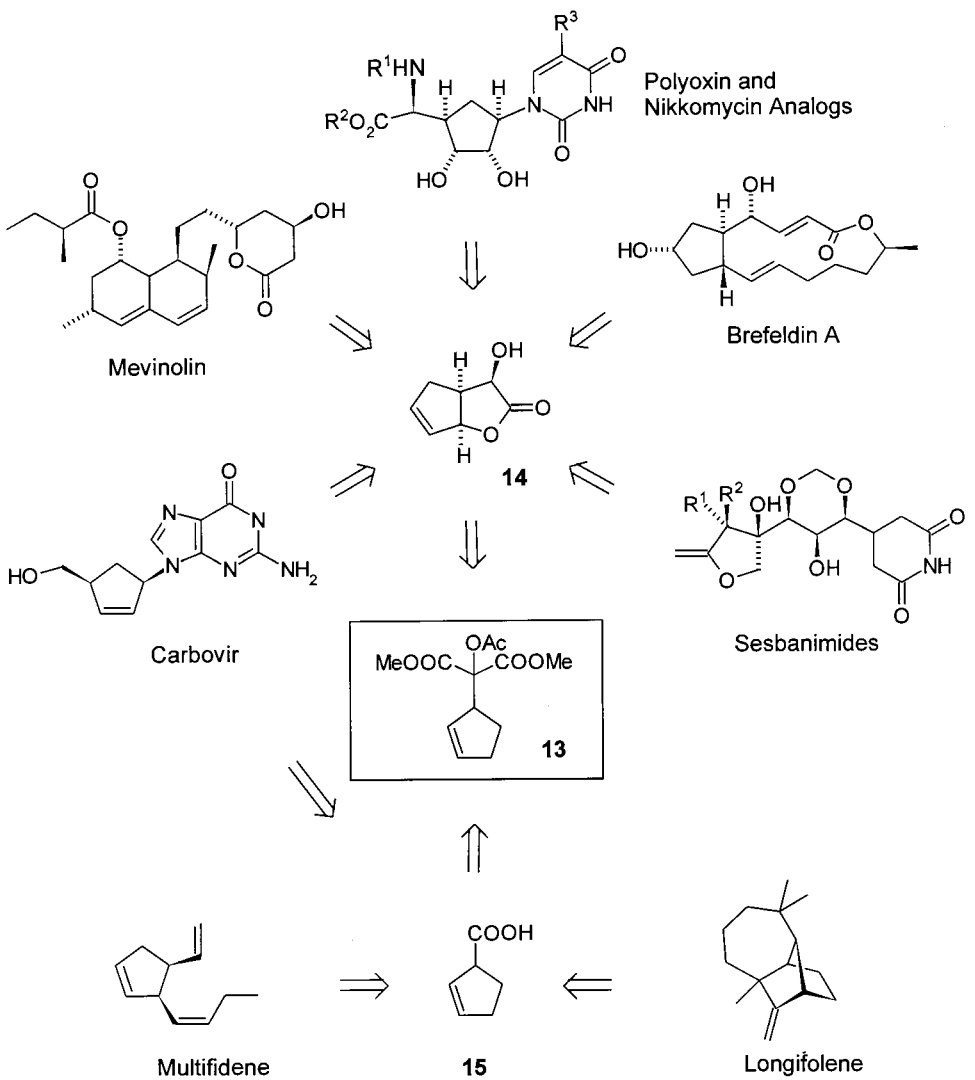


Scheme 14.

als for many applications. However, we were initially faced with two problems preventing applications: first, enantiomerically pure compounds were needed, and second, applications required a prohibitively large amount of precious material: for a 1 mol batch of ca. 150 g of product an amount of 1 mol% of catalyst means ca. 5 g of the chiral ligand. Our solution of these problems is shown in Scheme 14. The first problem could be very easily solved by using a more reactive starting material, the chloride instead of the acetate. Cyclopentenyl chloride is available by simply treating cyclopentadiene with HCl gas. High reactivity of this compound allowed the amount of catalyst to be reduced from the customary 1–3 mol% to a really satis-



Scheme 15.



Scheme 16.

factory 0.02 mol%, which corresponds to a turnover number of 5000 per ca. 3 h. Enantiomerically pure material could be obtained by saponification, decarboxylation and reaction with iodine to give the iodolactone **12**, which is obtained enantiomerically pure with remarkable ease by recrystallization.

In our report [59] on the syntheses of these synthons we had to rely on ligands **A** and **B**, which provided for cyclopentenylmalonate of typically 60% ee and gave the enantiomerically pure iodolactone **12** in ca. 30% yield. Fortunately, with the new ligand **H**, under similar conditions (0.08 mol% of catalyst), methyl cyclopentenylmalonate was formed with ee of 96% and the resultant enantiomerically pure iodolactone **12** was obtained in excellent 82% overall yield on a 100 g scale.

Iodolactone **12** can be transformed into a variety of useful compounds; for example, cyclopentenylacetic acid that has been used for a synthesis of chaulmoogric acid [60], which has been used in treatment of leprosy.

Another very useful chiral starting material is diethyl 2-acetoxy-2-(2-cyclopentenyl)-malonate (**13**) (Scheme 15) which can be prepared in very high yield almost enantiomerically pure with the help of the cymantrene based ligand **H**. Simple manipulations [61] lead to the lactone **14** (Scheme 16) which has found numerous applications in natural products synthesis. Lactone **14** was previously prepared via resolution or a chemoenzymatic route [62]. 2-Cyclopentenylcarboxylic acid (**15**) is another compound that is readily available from **13**. The inconspicuous acid **15** is a powerful building block for syntheses of carbocyclic nucleosides such as the antiviral agent carbovir [63].

Acknowledgements

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