Applications of nonstabilized enolates as nucleophiles in palladium catalyzed allylic alkylations[†]

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Palladium catalyzed allylic alkylations are important reactions in organic synthesis. In general stabilized carbanions are used as soft C-nucleophiles. Nonstabilized enolates from ketones and esters often cause problems, and the developments and improvements made with these interesting nucleophiles are summarized in this review.

With respect to ketone enolates, best results are obtained with the corresponding tin derivatives, but enoxyborates also can be used. With ketone enolates α -allylated products are obtained. In the presence of suitable chiral ligands, the optically active substitution products are obtained with high stereoselectivity. In contrast, sterically hindered ester enolates do not provide allylation products, but give rise to cyclopropane derivatives, while with silylketene acetals as nucleophiles, or vinyl epoxides as allylic substrates, the α -allylated products are obtained as well. This is also true with more or less stabilized enolates derived from pyrazinones or azlactones, giving rise to α -allylated amino acid derivatives. "Normal" unsaturated amino acids can be obtained by using chelated amino acid ester enolates as nucleophiles. These enolates show a high reactivity and therefore these reactions can be carried out under very mild conditions, conditions under which the π - σ - π isomerization of the π -allyl intermediates can be suppressed. This opens up totally new synthetic possibilities. In the presence of chiral ligands optically active amino acids are obtained.

Introduction

Transition metal catalyzed reactions are becoming more and more popular in organic synthesis¹. As many of these reactions tolerate a lot of functional groups, they are especially suited for the synthesis of complex molecules. Palladium, which can be used for cyclizations, cross-coupling reactions and allylic substitutions, holds a predominant position among the transition metals². Especially the palladium-catalyzed allylic alkylation has developed into one of the standard reactions in organic synthesis, not the least because asymmetric variations of this reaction are possible³. This reaction proceeds via a π -allylpalladium intermediate, which is formed from Pd(0) and an alkene with an leaving group in the allylic position.

The stereochemical course of the Pd-catalyzed allylic substitution has been studied extensively⁴. The first step, the attack of Pd(0) on a chiral allylic substrate such as **1** occurs from "the backside" under inversion of the configuration. The nucleophilic attack of *O*-, *N*-, and soft C-nucleophiles on the π -allyl complex **A** again occurs from the *anti* face, and therefore overall retention of configuration is observed in the product **2** (Scheme 1). With unsymmetrical π -allyl-Pd complexes, attack of the nucleophile usually occurs at the less substituted position, but the

regioselectivity is strongly dependent on the structural features of the substrate and the reaction conditions². In most cases symmetrical nucleophiles such as malonates or disulfones are used to avoid a major problem of this reaction: the formation of a second stereogenic center in the "nucleophile moiety" of the product. Using unsymmetrical C-nucleophiles such as β -ketoesters⁵ or imines of amino acid esters⁶, mixtures of diastereomers are usually obtained. For example, reaction of the allylic acetate **3** with the unsymmetric nucleophile **4** gives the substitution products **5** in a 1 : 1 ratio⁷ because of the configurational lability of the allylated nucleophile (Scheme 1). Thus, considerably better results are obtained with alkylated derivatives⁸. For example, allylation of "cyclic malonate" **6** with **7** provides **8** as a single stereoisomer⁹, while the attack of a chelated enolate obtained from **9** on allylic carbonate **10** gives rise to γ,δ -unsaturated amino acid derivative **11** in a highly stereoselective fashion¹⁰.

In contrast to the well investigated reactions of stabilized 'soft' carbanions, there are only a few reports concerning unstabilized enolates, for example those of ketones or esters, although the resulting products are often more interesting. The reactions of these enolates seem to be limited with respect to the substrates used, while one has to

[†]Dedicated to Professor S. M. Mukherji.

differentiate between ketone and ester enolates. This review will describe the developments and the improvement made during the last years.

Scheme 1

Allylic alkylations of ketone enolates

In 1980 Trost and Keinan reported for the first time on allylic alkylations of enolates¹¹. Simple enolates such as that from acetophenone (**12**) reacted with allyl acetate in the presence of tetrakis(triphenylphosphine)palladium, but gave the dialkylated product **14** in 65% yield, while the desired

Scheme 2

monoallylated derivative **13** was obtained only as the side product (34%) (Scheme 2). Most attempts to improve the selectivity for monoallylation by variation of the catalyst, solvent and other reaction conditions failed. The problem arises from an equilibrium between the product and the starting enolate, which leads to loss of regioselectivity and to polyalkylation. Shortly after this first paper by Trost, Fiaud and Malleron reported on the use of sterically more demanding allylic substrates, such as cyclohexenylacetate (**15**), giving rise to the monoalkylated products **16** in acceptable yields¹². The monoallylated product was also obtained exclusively in 59% by using the less reactive silyl enol ethers of **12**, but herewith the reaction could not be extended to substituted allyl acetates.

A breakthrough brought a variation of the counterion of the enolate. Switching to tributyltin enolates such as **17** led to a remarkably rapid and clean monoalkylation with high regioselectivity (Scheme 3). Alkylation generally occurred at the sterically less hindered position of the π -allyl complex, and the *E*-configured product **19** was obtained preferentially independent of the olefin geometry of the starting allylic acetate (**18**)¹³. This can be explained by a fast π - σ - π isomerization which will be discussed in detail later on. The palladium catalyzed allylic alkylation is compatible with a wide range of functional groups such as esters, ketones (**20**), alkyl bromides and enol ether, indicating a high chemo-selectivity.

The influence of the substituent in the allylic substrate on the regioselectivity (rs) of the reaction was investigated by Shi *et al.*¹⁴. They used several fluoro- and difluorosubstituted allyl acetates (**20**) and found a preferential attack of tin enolate **17** at the terminus remote from the fluorine (**21**). The fluorinated acetates showed also a diminished reactivity in comparison to their nonfluorinated counterparts.

While the tin enolates can be generated *in situ* from the lithium enolates and tributyltin chloride, the yields in the alkylation step are not always satisfying. Better results are obtained if the tin enolates are formed from ketones and tin trifluoroacetates¹⁵. The reactivity of the tin enolates can be increased by switching from the tributyl- to the trimethyl-substituted derivatives. With these enolates acetophenone as well as several cyclic ketones can be allylated regioselectively, although the yields obtained are moderate in most cases¹⁵.

The effect of the counteranion on the outcome of the palladium catalyzed allylation was also investigated by Negishi and John in 1983¹⁶. They found, that allylation of potassium enoxyborates, obtained by reaction of ketones with either KH or KN(SiMe₃)₂, followed by treatment with

BEt_3 , proceeded well in the presence of palladium phosphine complexes (Scheme 3). Various allylic halides and acetates can be used and the regioselectivity observed with both the "kinetic" and the "thermodynamic" enolates of 2-methylcyclohexanones (**22**) is in the range of 90–95%. The allylation with trisubstituted allylic acetates such as geranyl and neryl **23** derivatives proceeds with retention of the olefin configuration (**24**). Very similar results were obtained with the corresponding zinc enolates, while a wide range of other counterions (ClMg^+ , Me_2Al^+ , $\text{Me}_3\text{Al/Li}^+$, Cp_2CITi^+ , Me_3Si^+) gave unsatisfying results or did not show any reaction at all.

Scheme 3

If optically active allylic substrates were used, the reactions proceeded with net retention. This can be explained by a double inversion, a mechanism which is typical for stabilized nucleophiles, and which is in sharp contrast to findings with aryl and vinyl metal compounds, which react under inversion (via transmetalation)¹⁷. Besides these substrate controlled allylic alkylations, asymmetric catalyzed allylations became more and more important during the last years, and therefore it is not surprising, that this elegant technique found also some application to the allylation of ketones.

In 1999 Trost and Schroeder reported on the first asymmetric allylic alkylation of tin enolates of 2-substituted cyclohexanone derivatives¹⁸. In order for chiral ligands to

effect stereochemical control in this reaction, they must influence bond making and bond breaking events occurring outside the coordination sphere of the metal. Thus, they must transmit their stereochemical information through space. Discrimination of enantiotopic faces on the nucleophile is especially difficult as the nucleophile is segregated from the chiral environment by the π -allyl moiety. For this purpose a chiral bidentate ligand **25** derived from *trans*-diaminocyclohexane was developed which gave good results with stabilized enolates and tin enolates of ketones as well¹⁹. The

Scheme 4

allylation of 2-methyltetralone (**26**) (giving **27**) with respect to the influence of the reaction parameters on the stereoselective outcome of the reaction was investigated (Scheme 4). While variations of the solvents had only moderate influence, the presence of additives and the choice of base had a significant effect. Best results are obtained by using 2 equiv. of LDA, and stannanes gave far superior results than did boranes and borates. Trimethylstannanes again proved to be the best choice. Other cyclohexanones gave comparable results.

Very recently Hou, Dai *et al.* reported on related investigations, also with **26**, with a very similar chiral ligand²⁰. They used phosphinocarboxylic acids derived from ferrocene instead of phosphinobenzoic acid and obtained similar results as reported by Trost.

Interesting investigations were carried out by Braun *et al.* not only on the enantiocontrol but also on the diastereoselective outcome of allylation reactions using 1,3-diphenyl allyl acetate (**28**) in the presence of achiral and chiral ligands²¹. Enolates of cyclohexanone (**30**) and propiophenones (such as **32**) were used as nucleophiles. First of all they investigated the influence of the base and of achiral ligands on the diastereoselectivity of the allylation. Herein best results were obtained with lithium and magnesium enolates in the presence of ferrocenyl derived ligands **29**, both with cyclic and aromatic ketones. While cyclohexanone (**30**) gave rise to the *syn*-product **31** preferentially, the *anti*-product **33** was obtained from mesitylethyl ketone **32**. Surprisingly, the enolate geometry in the latter case had no significant influence on the stereoselective outcome of the reaction. The (*E*)- as well as the corresponding (*Z*)-enolate gave the same major diastereomer, albeit the (*E*)-isomer gave the better selectivity ((*E*) : 90% ds; (*Z*) : 67% ds). It was suggested that different transition states are involved in the allylation step, a theory that has to be verified.

With the chiral ligand (*R*)-Binap **34** excellent enantio- as well as diastereoselectivities were obtained in the reaction of **30**, if the magnesium enolate was used. Unfortunately, no yields were given for the allylation step²¹.

Allylic alkylations of ester enolates

A first report on the use of ester enolates as nucleophiles in allylic alkylations was described by Hegedus *et al.* 1980²². They investigated the allylation of branched ester enolates in the presence of various ligands. The limitation of the palladium catalyzed allylic alkylation to relatively stabilized ($pK_a < \sim 17$) anions may be due to the propensity of nonstabilized carbanions to attack the metal in preference to the allyl group²³, resulting in reduction of the complex

rather than alkylation. However, addition of HMPA to this reaction completely suppresses reduction and permits the alkylation to proceed with nonstabilized carbanions as well²⁴. For example, treatment of π -allylpalladium chloride (**36**) with the enolate of methyl cyclohexanecarboxylate (**37**)

Scheme 5

(stoichiometric reaction) under standard conditions (PPh_3 , THF) led to only very low yield of the allylated product (**38**) (Scheme 5). Repeating the reaction in the presence of HMPA and triethylamine (replacing the PPh_3) gave rise not to the "expected" allylation product **38** but to the cyclopropane derivative **39** in good yield. Labelling studies indicated that the carbanion attacks the central carbon of the π -allyl complex. This is in sharp contrast to the attack of stabilized

nucleophiles and the observations made with ketone enolates. Surprisingly, cinnamyl acetate did not provide the phenyl substituted cyclopropane derivative but the linear cinnamylated product. Other substituted allylic acetates completely failed to undergo allylic alkylation. Branched ester enolates were the only carbanions studied that led to cyclopropanation. For example, anions of methyl hexanoate or acetophenone failed to give material containing an allyl fragment in any form under these reaction conditions, although the π -allylpalladium complex was consumed.

Unfortunately, attempts to trap some intermediates with carbon monoxide to obtain carbonylated products failed. Although carbon monoxide is not incorporated into the allylation product, Hoffmann *et al.* found an influence of CO on the yield of the reaction²⁵. They observed, that the combination TMEDA/CO is superior to HMPA/ NEt_3 under the same reaction conditions. Under these conditions not only sterically hindered ester enolates can be reacted with π -allylpalladium complexes such as **40**, but also deprotonated amides, lactames, ketones, sulfones as well as Evans-enolates (**41**)²⁶. Tertiary anions gave the best results.

Hoffmann *et al.* also undertook investigations concerning the mechanism of the reaction²⁷. In the reaction of a diphenylallylpalladium complex **43** with deprotonated isobutyronitrile **44** they were able to isolate the intermediate palladacyclobutane **45**, which could be characterized by X-ray structure analysis. It is very reasonable, that this palladacycle is a real intermediate in this reaction, because addition of CO resulted in a precipitation of Pd^0 and the formation of the cyclopropane derivative **46**.

Obviously, the sterically hindered nucleophile attacks directly the central carbon atom of the allyl ligand and not the palladium. The reductive elimination to the *cis*-diphenylated cyclopropane is made more difficult because of sterical hindrance between the two phenyl rings. The CO can act as a π -acid coordinating to the 16-electron metalacycle. This results in a decrease of electron density on the palladium and an easier reductive elimination giving rise to the cyclopropane derivative.

The reaction of silylketene acetals such as **47** with allylic acetates (e.g. **48**) in the presence of catalytic amounts of palladium was investigated by Santi *et al.* (Scheme 6)²⁸. They used chelating phosphine ligands and obtained mainly the α -allylated esters **49**. But attack at the central carbon atom also occurred giving rise to the corresponding cyclopropane **50**. In both cases the silyl enolate attacked the allyl group from the side opposite to Pd. The yield of the reaction was sensitive to the nature of the ligand coordinated to pal-

ladium. The 1,1'-bis(diphenylphosphino)ferrocene-(dppf)-Pd complex was the most effective catalyst.

Also α -allylated products were obtained if ester enolates were reacted with vinyloxydes (**51**) as reported by Malacria *et al.*²⁹. Sterically hindered ester enolates (**52**) were used as nucleophiles and the yields varied depending on the vinyl epoxide used. Nucleophilic attack occurred at the sterically less hindered position (**53**) and not at the allylic position close to the remaining alcohol. In general, a mixture of *E/Z*-isomers was obtained.

Scheme 6

The great importance of nonproteinogenic amino acids including α -substituted derivatives led to an investigation of modified amino acid ester enolates as nucleophiles in the palladium catalyzed allylic alkylation. Najera *et al.*³⁰ reported on the use of a chiral pyrazinone derivative (**54**), obtained from (*R*)-valine and (*S*)-alanine, as a new chiral auxiliary for the synthesis of γ,δ -unsaturated amino acids via palladium catalyzed allylation. Pyrazinone **54** underwent highly regio- and diastereoselective allylations (95–99% ds) under neutral conditions if allylic carbonates **55** are used as substrates. The alcoholate liberated is obviously basic enough to deprotonate the auxiliary, indicating that **54** forms a (partly) stabilized anion (Scheme 7). The free amino acid could be obtained under relatively drastic conditions (6 *N*

HCl, 150°), a significant limitation of this protocol, which is obviously only suitable for α -alkylated amino acids.

Trost *et al* applied α -substituted azlactones **57** as nucleophiles for the allylation in the presence of allylpalladium chloride (**36**) and chiral ligands such as **25**³¹. The requested products **59** were obtained from allylic acetate **58** in high yields and excellent stereoselectivities. Unfortunately, this protocol is also limited to α -alkylated amino acid derivatives (enolization of the azlactone) and the cleavage of the *N*-benzoyl group is not a trivial issue and might cause problems in the synthesis of amino acids with sensitive side chains. Besides allylic acetates and carbonates also *gem* diacetates **60** can be used for this purpose, as illustrated in a nice synthesis of Sphingofungin F based on this approach³².

Scheme 7

Our group is also involved in the synthesis of unnatural and nonproteinogenic amino acids since several years, while γ,δ -unsaturated amino acids play a major role. Chelated amino acid ester enolates, such as **63** were found to give especially good results in various types of standard enolate

reactions including alkylations, aldol reactions or Michael additions³³. Chelation causes a marked enhancement of thermal stability without having any negative influence on the reactivity of these enolates. Due to the fixed enolate geometry, their conversions often proceed with a high degree of stereoselectivity. We are especially interested in reactions which can not be carried out with non chelated enolates. Thus, chelated enolates of amino acid esters **63** undergo Claisen rearrangement when being warmed up to room temperature providing γ,δ -unsaturated amino acids **65** (Scheme 8)³⁴. Using substituted (*E*)-allylic esters **64** products with *syn*-configuration are obtained diastereoselectively via a chair-like transition state. The *anti*-products, however, cannot be obtained as easily from the corresponding (*Z*)-esters³⁵. For that reason, it was interesting to see if the *anti*-products might be accessible via palladium-catalyzed allylic alkylation. Stabilization of the enolate by chelation should also diminish the tendency of the enolate to coordinate to the palladium – a solution of the 'enolate problem'?

Therefore the reaction of different *N*-protected glycine esters with allyl carbonate **67** was examined. Instead of the carbonate **67**, the corresponding acetate or benzoate can be used as well, but with the more reactive carbonates the yields and selectivities are usually better. To avoid transesterifications by the liberated ethylate the *tert*-butyl esters **66** were chosen. These esters were deprotonated with excess LHMDs, and the resulting lithium enolates were transmetalated to the corresponding chelated zinc enolates by addition of zinc chloride. After a short time, a solution of the allyl carbonate **67** and the palladium source were added. In general, the best results were obtained with allylpalladium chloride **36** in the presence of triphenylphosphine. As a result of the high reactivity of the chelated enolates, the allylation already takes place under very mild conditions at -78° , giving rise to the desired monoallylated amino acid derivative **68**. Most common *N*-protecting groups can be used with comparable success, although the *Z*-derivative was superior in this special case¹⁰.

To figure out if the allylic alkylation with these nucleophiles can be carried out also diastereoselectively when substituted allyl substrates are used, the influence of the *N*-protecting group in the reaction of the 1,3-dimethylated allyl carbonate **69** was investigated. Compound **69** was chosen because this compound generates a symmetrical π -allylpalladium complex, so one can ignore regioselectivity problems. By far the best results were obtained with the trifluoroacetyl- (Tfa)-protected glycine ester **70**. The yield was very good and the diastereoselectivity excellent. The diastereomerically pure product **71** was accessible after a

single crystallization step. As determined by X-ray structure analysis, the *anti*-product was preferentially obtained from the palladium-catalyzed allylic alkylation. Thus, two different procedures for the synthesis of substituted γ,δ -unsaturated amino acids are available, which complement each another. The *syn*-diastereomers can be obtained by ester enolate Claisen rearrangement, and the *anti*-diastereomers via palladium-catalyzed allylic substitution.

To extend the potential of this approach an asymmetric version of this protocol is desirable. Depending on the allylic substrate used, two different strategies can be applied. Substrates such as **70** with two identical substituents at both allyl termini form symmetrical, achiral π -allylpalladium complexes, and therefore the stereochemical outcome of the reaction can be controlled via chiral ligands on the palladium³. This straightforward approach is very elegant, but unfortunately more or less limited to such symmetrical substrates.

In order to assess the scope of ligand directed asymmetric allylations with chelated enolates, a representative set of substrates, including a large and a small acyclic and two cyclic allylic derivatives, was investigated (Scheme 9)³⁶. As chiral ligands phosphinooxazoline **72**, which is particularly suited for acyclic substrates as well as the cymantrene derivative **73** and the phosphinomyrtanic acid **74** which are better suited for cyclic compounds, were used³⁷.

High levels of selectivity were achieved with 1,3-diphenylallyl acetate (**75**) as substrate, especially with the chiral ligands **72** a diastereoselectivity of up to 95 : 5 and

ee's up to 94% could be obtained. Recrystallization of the crude product gave diastereo- and enantiomerically pure

major isomer **76**. Allylic alkylations of cyclic substrates such as cyclohexenyl acetate (**77**) led to cyclohexenyl-glycine derivative **78**, respectively, which displays antibacterial activity and, therefore, is of particular interest³⁸. The chiral ligand **73** gave a nearly 1 : 1 diastereomeric mixture, while with **74** the *syn* product was formed preferentially. ee-Values of upto 93% could be obtained with these ligands, which is remarkable for such cyclic systems.

On the other hand, if allyl derivatives with different substituents are used, unsymmetrical π -allylpalladium complexes are formed. Attack of nucleophiles on these complexes in general provides mixtures of regioisomers, depending on the substitution pattern of the allyl moiety. Although this can be problematic, these substrates also have a big advantage : if optically active allyl substrates are used, the π -allylpalladium complexes formed are chiral, and nucleophilic attack on these complexes provides optically active substitution products.

Based on the reaction mechanism, the stereochemical control in the allyl fragment is not a problem (double inversion), in contrast to chiral centers formed in the 'nucleophile moiety'. The allylic substitutions with chiral allyl substrates (such as **79**) proceeded cleanly and with good yields (Scheme 10). The only regioisomers obtained were those with the double bond in conjugation to the phenyl ring. The diastereoselectivities of the reaction were high, depending

Scheme 10

on the substitution pattern at the allyl moiety. The methyl derivative **79** was superior to the ethyl derivative, probably because of steric reasons. It was a striking feature that the diastereoselectivities obtained with the acetates were a little worse in comparison to those obtained with the carbonates. The chirality could be transferred almost completely from the allyl derivative **79** to the product **80**.

The stereochemical course of the reaction can be explained by the following model. The π -allyl complex **79'** is formed via attack of palladium(0) on the allylic carbonate **79** with inversion of the configuration. Subsequently, this complex reacts with the chelate enolate **69'**. The attack of the nucleophile occurs in such a way, that the resulting double bond is conjugated to the aromatic π -system. Because of the staggered arrangement of the substituents, steric interactions in the transition state between the π -allyl complex and the nucleophile are minimized. The bulky *tert*-butyl group is located at the less hindered methyl-substituted side of the allyl complex. No significant interactions should be expected here as well. Obviously these interactions are stronger in the case of the corresponding ethyl substituted derivatives, resulting in lower selectivities. This model is also in accordance with the observation, that no significant diastereoselectivity can be obtained if the corresponding methyl glycinate is used.

Since the palladium-catalyzed allylic substitution with chelated ester enolates already proceeds at -78° , one might see a good chance to circumvent a nearly unsolved problem in palladium-catalyzed allylic alkylations: the π - σ - π -isomerization.

With respect to the reaction mechanism the configuration of the substitution products depends on the configuration of these π -allyl intermediates³⁹. Thus, the oxidative addition of palladium(0) to (*E*)-allyl-acetates **79** and -carbonates leads to allyl complexes with *syn/syn*-configuration (**79'**), which react with nucleophiles to provide the corresponding (*E*)-substitution products such as **80** (Scheme 10). The *syn/anti* terminology is used to describe the orien-

Scheme 11

tation of the substituents at the allyl moiety relative to the H-atom at the central carbon atom. Quite different is the situation if (*Z*)-configured substrates such as **81** are used (Scheme 11). In this case the *anti/syn*-complex **81'** is formed. Reactions of **81'** with nucleophiles would provide the (*Z*)-configured products **82** (attack a) or the (*E*)-configured product **83** (attack b)⁴⁰. But in general product **82** is not obtained. Instead, the π - σ - π -isomerization causes a fast interconversion of the π -complexes via rotation of the σ -complexes **A** and **B**, normally preferring the *syn/syn*-complex **79'**, which gives rise to (*E*)-substitution products **83** and/or **84**.

Exceptions can only be observed if steric interactions either between the substituents in the allyl substrate⁴¹ or between the allyl moiety and the ligands⁴² destabilize the *syn/syn*-complex. As a result, the *anti/syn*-complex is enriched and reactions with nucleophiles give rise to an increased amount of (*Z*)-substitution product **84**. However, selective palladium catalyzed⁴³ conversions of (*Z*)-allyl substrates with retention of the olefin geometry remain an unsolved problem. A transfer of the (*Z*)-configuration from the allyl substrate to the product would only be possible if one could run the reaction at temperatures where isomerization reactions do not yet take place. Since the palladium-

contrast, the reaction with **81** furnished a (*E/Z*)-mixture in a very low yield. The selectivities were markedly worse than those obtained with the carbonate. The major isomer (77%) was identical to the product **80** resulting from the reaction with the (*E*)-carbonate **79**, which is in good agreement with the reaction mechanism discussed.

This difference in product formation can be explained by the higher reactivity of the allyl carbonate **85**. Because this substrate already reacts at -78° , π - σ - π -isomerization obviously does not occur. In contrast, the reaction of the acetate **81** takes place at a higher temperature during the warm up. Simultaneously, the isomerization is setting in and a partial conversion of the primarily formed *anti/syn*-complex into the more stable *syn/syn*-complex can be observed. The same complex is also formed from the carbonate **79**.

If the π - σ - π -isomerization can be suppressed like in this case, further interesting questions arise : What would happen to allylic substrates with (*Z*)-configuration and the

Scheme 12

catalyzed allylic substitution with chelated ester enolates already proceeds at -78° , these nucleophiles have a good chance to fulfill these precondition.

Reactions of (*Z*)-substrates with the glycine ester **69** gave interesting results. The reaction with the (*Z*)-carbonate **85** almost exclusively yielded the desired (*Z*)-substitution product **86** (*Z/E* : > 99/1) (Scheme 12). The outstanding selectivities (98% ds, 97% ee) observed even surpassed the very good results of the reaction with the (*E*)-carbonate **79**. In

Scheme 13

same substituents at the allyl moiety (**87**)? In principle, there are two different reaction pathways, because the *anti/syn* π -allyl complex **87'** formed as an intermediate has two different allylic termini (Scheme 13). Nucleophilic attack at **a** (*anti* position) would provide a product **88** with (*E*)-configuration of the double bond, whereas the attack at **b** (*syn* position) would lead to a (*Z*)-double bond (**89**). Which position is the more reactive one, the *syn* or the *anti* position?

The clarification of this question is of major interest, because symmetrically substituted allyl derivatives are normally used in asymmetric catalyzed reactions. Irrespective of the configuration of the starting material, achiral *syn/syn* π -allylpalladium complexes are generally formed and the nucleophilic attack on complexes of this kind can be controlled, for example, by chiral ligands³. Therefore, if enantiomerically pure allyl substrates are used, the chiral information gets lost during the reaction. But if it is possible to suppress the π - σ - π -isomerization during the reaction of (*Z*)-configured substrates, and if one of the two allylic positions is pronouncedly more reactive than the other one, it should be possible to generate optically active compounds with these substrates as well.

The allylic alkylation with racemic **90** gave a very pleasing result. The only product to be isolated was the (*E*)-configured product **76** with good yield and diastereoselectivity. Keeping in mind, that the π - σ - π -isomerization does not play a significant role under these reaction conditions, one can conclude that the *anti* position is much more reactive than the *syn* position⁴⁴. For that reason, the investigation of a feasible transfer of chirality from optically active, symmetrically substituted (*Z*)-allyl substrates was obvious. The reactions with chiral allyl substrate **91** also provided the chiral (*E*)-configured substitution products **71** exclusively in a very good yields. Also in these case the selectivities, which the *anti*-products were formed with, were excellent. Moreover, the almost complete transfer of chirality shows that the reaction proceeds via the *anti/syn*-complex and not via the *syn/syn*-complex, which would inevitably lead to racemization.

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References

1. (a) J. P. Collman, L. S. Hegedus, J. R. Norton and R. G. Finke, "Principles and Applications of Organotransition Metal Chemistry", University Science Books, Mill Valley, 1987; (b) L. S. Hegedus, "Transition Metals in the Synthesis of Complex Organic Molecules", 2nd. ed., University Science Books, Herndon, 1999.
2. For a detailed survey of palladium-catalyzed reactions, see : J. C. Malleron, J. C. Fiaud and J. Y. Legros, "Handbook of Palladium-Catalyzed Organic Reactions", Academic Press, San Diego, 1997.
3. Reviews : (a) S. A. Godleski in 'Comprehensive Organic Synthesis', Vol. 4, eds. B. M. Trost, I. Fleming and M. F. Semmelhack, Pergamon, Oxford, 1991, 585; (b) T. Lübbers and P. Metz in 'Houben Weyl : Methoden Org. Chem. – Stereoselective Synthesis', eds. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart/New York, 1996, 2371; (c) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (d) J. M. J. Williams, *Synlett*, 1996, 705, and references cited therein; (e) T. J. Hayashi, *Organomet. Chem.*, 1999, **576**, 195.
4. (a) B. M. Trost and L. Weber, *J. Am. Chem. Soc.*, 1975, **97**, 1611; (b) B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton and T. J. Dietsche, *J. Am. Chem. Soc.*, 1978, **100**, 3416; (c) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435; (d) B. Akermarck, J. E. Bäckvall, A. Loewenborg and K. Zetterberg, *J. Organomet. Chem.*, 1979, **166**, C33; (e) T. Hayashi, T. Hagihara, M. Konishi and M. Kumada, *J. Am. Chem. Soc.*, 1983, **105**, 7767.
5. (a) I. Shimizu, M. Toyoda, T. Terashima, M. Oshima and H. Hasegawa, *Synlett*, 1992, 301; (b) N. Greeves and J. S. Torode, *Synthesis*, 1993, 1109; (c) T. Hayashi, A. Ohno, S. Lu, Y. Matsumoto, E. Fukuyo and K. Yanagi, *J. Am. Chem. Soc.*, 1994, **116**, 4221; (d) K. Hiroi, A. Hidaka, R. Sezaki and Y. Imamura, *Chem. Pharm. Bull.*, 1997, **45**, 769.
6. (a) D. Ferroud, J. P. Genêt and R. Kiolle, *Tetrahedron Lett.*, 1986, **27**, 23; (b) I. C. Baldwin, J. M. J. Williams and R. P. Beckett, *Tetrahedron Asym.*, 1995, **6**, 1515.
7. J. Zhu and X. Lu, *Tetrahedron Lett.*, 1987, **28**, 1897.
8. M. Sawamura, H. Nagata, H. Sakamoto and Y. Ito, *J. Am. Chem. Soc.*, 1992, **114**, 2586.
9. T. Takahashi, M. Miyazawa, H. Ueno and J. Tsuji, *Tetrahedron Lett.*, 1986, **27**, 3881.
10. U. Kazmaier and F. L. Zumpe, *Angew. Chem.*, 1999, **111**, 1572; *Angew. Chem. Int. Ed.*, 1999, **38**, 1468.
11. B. M. Trost and E. Keinan, *Tetrahedron Lett.*, 1980, **21**, 2591.
12. J. C. Fiaud and J.-L. Malleron, *J. Chem. Commun.*, 1981, 1159.
13. B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, 1976, **55**, 3215.
14. G.-Q. Shi, X.-H. Huang and F.-J. Zhang, *Tetrahedron Lett.*, 1995, **36**, 6305.
15. B. M. Trost and C. R. Self, *J. Org. Chem.*, 1984, **49**, 468.
16. E.-I. Negishi and R. A. John, *J. Org. Chem.*, 1983, **48**, 4098.

17. (a) L. V. Dunkerton and A. J. Sevino, *J. Org. Chem.*, 1982, **47**, 2812; (b) H. Matsushita and E.-I. Negishi, *J. Chem. Soc., Chem. Commun.*, 1982, 160.
18. B. M. Trost and G. M. Schroeder, *J. Am. Chem. Soc.*, 1999, **121**, 6759.
19. B. M. Trost, R. Radinov and E.-M. Grenzer, *J. Am. Chem. Soc.*, 1997, **119**, 7879.
20. S.-L. You, X.-L. Hou, L.-X. Dai and X.-Z. Zhu, *Org. Lett.*, 2001, **3**, 149.
21. M. Braun, F. Laicher and T. Meier, *Angew. Chem.*, 2000, **112**, 3637; *Angew. Chem. Int. Ed.*, 2000, **39**, 3494.
22. L.-S. Hegedus, W. H. Darlington and C. E. Russell, *J. Org. Chem.*, 1980, **45**, 593.
23. (a) S.-I. Murahashi, M. Yamamura and N. J. Mito, *Org. Chem.*, 1977, **42**, 2870; (b) S.-I. Murahashi, Y. Tamba, M. Yamamura and N. Yoshimura, *J. Org. Chem.*, 1978, **43**, 4099.
24. L. S. Hegedus, R. E. Williams, T. Hayashi and M. A. McGuire, *J. Am. Chem. Soc.*, 1980, **102**, 4973.
25. H. M. R. Hoffmann, A. R. Otte and A. Wilde, *Angew. Chem.*, 1992, **104**, 224; *Angew. Chem. Int. Ed.*, 1992, **31**, 234.
26. A. R. Otte, A. Wilde and H. M. R. Hoffmann, *Angew. Chem.*, 1994, **106**, 1352; *Angew. Chem. Int. Ed.*, 1994, **33**, 280.
27. H. M. R. Hoffmann, A. R. Otte, A. Wilde, S. Menzer and D. J. Williams, *Angew. Chem.*, 1995, **107**, 73; *Angew. Chem. Int. Ed.*, 1995, **34**, 100.
28. C. Carfagna, L. Mariani, A. Musco, G. Sallese and R. Santi, *J. Org. Chem.*, 1991, **56**, 3924.
29. (a) M. R. Elliott, A.-L. Dhimane and M. Malacria, *J. Am. Chem. Soc.*, 1997, **119**, 3427; (b) M. R. Elliott, A.-L. Dhimane and M. Malacria, *Tetrahedron Lett.*, 1998, **39**, 8849.
30. T. Abellán, C. Nájera and J. M. Sansano, *Tetrahedron Asym.*, 1998, **9**, 2211.
31. B. M. Trost and X. Ariza, *Angew. Chem.*, 1997, **109**, 2749; *Angew. Chem. Int. Ed.*, 1997, **36**, 3635.
32. B. M. Trost and C. B. Lee, *J. Am. Chem. Soc.*, 1998, **120**, 6818.
33. Reviews : (a) U. Kazmaier, *Amino Acids*, 1996, **11**, 283; (b) *Liebigs Ann./Recl.*, 1997, 285; (c) *Recent Res. Devel. in Organic Chem.*, 1998, **2**, 351.
34. U. Kazmaier, *Angew. Chem.*, 1994, **106**, 1046; *Angew. Chem. Int. Ed.*, 1994, **33**, 998.
35. (a) U. Kazmaier, *Tetrahedron*, 1994, **50**, 12895; (b) *J. Org. Chem.*, 1996, **61**, 3694.
36. T. D. Weiss, G. Helmchen and U. Kazmaier, *Chem. Commun.*, 2002, 1270.
37. Review : G. Helmchen, *J. Organomet. Chem.*, 1999, **576**, 203.
38. U. Cramer, A. G. Rehfeldt and F. Spener, *Biochemistry*, 1980, **19**, 3074.
39. G. Consiglio and R. M. Waymouth, *Chem. Rev.*, 1989, **89**, 257.
40. P. Corradini, G. Maglio, A. Musco and G. Paiaro, *J. Chem. Soc., Chem. Commun.*, 1966, 618.
41. (a) J. W. Faller, M. E. Thomsen and M. J. Mattina, *J. Am. Chem. Soc.*, 1971, **93**, 2642; (b) J. Lukas, J. E. Ramakers-Blom, T. G. Hewitt and J. J. De Boer, *J. Organomet. Chem.*, 1972, **46**, 167.
42. (a) B. Åkermark, S. Hansson and A. Vitagliano, *J. Am. Chem. Soc.*, 1990, **112**, 4587; (b) M. Sjögren, S. Hansson, P.-O. Norrby, B. Åkermark, M. E. Cucciolito and A. Vitagliano, *Organometallics*, 1992, **11**, 3954.
43. For iridium catalyzed reactions with retention of olefin geometry see : (a) R. Takeuchi and M. Kashio, *J. Am. Chem. Soc.*, 1998, **120**, 8647; (b) R. Takeuchi and N. Shiga, *Org. Lett.*, 1999, 265; (c) R. Takeuchi and K. Tanabe, *Angew. Chem.*, 2000, **112**, 2051; *Angew. Chem. Int. Ed.*, 2000, **39**, 1975.
44. B. Åkermark, S. Hansson and A. Vitagliano, *J. Am. Chem. Soc.*, 1990, **112**, 4587.