# COMMUNICATIONS

Palladium-Catalyzed Allylic Alkylations without Isomerization—Dream or Reality?[**]
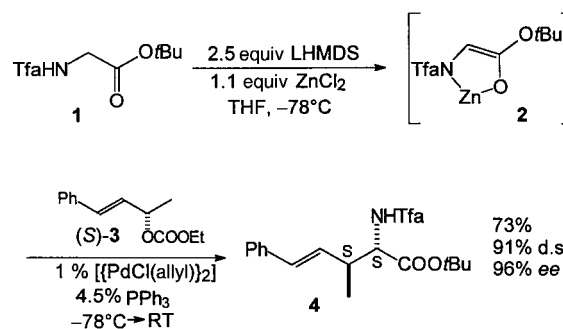
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The palladium-catalyzed allylic alkylation has developed into one of the standard reactions in organic synthesis.[1] The reaction proceeds via π-allyl–palladium complexes—the configuration of the products obtained strongly depends on the configuration of these intermediates.[2] Thus, the oxidative addition of palladium(0) to (E)-allyl acetates and carbonates leads to syn-configured allyl complexes (Scheme 1), which
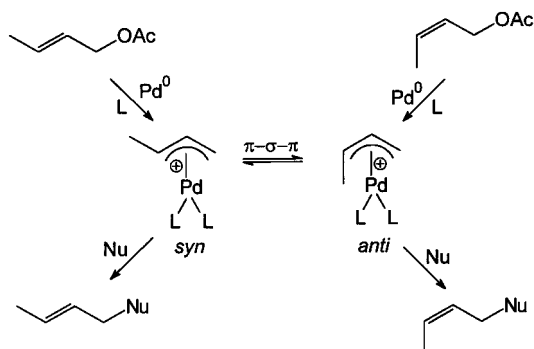
Scheme 1. Isomerization of π-allyl–palladium complexes.

react with nucleophiles (Nu) to provide the corresponding E-substitution products. The corresponding anti complexes are generated by the attack of palladium on Z substrates. Subsequent reaction with nucleophiles should result in Z-configured products, provided that no π-σ-π isomerization occurs.[3] This isomerization causes a fast interconversion of the π-allyl complexes, normally with preference for the syn complex. Exceptions can only be observed if steric interactions either between the substituents in the allylic substrate[4] or between the allyl moiety and the ligands on palladium[5] destabilize the syn complex. As a result, the anti complex is enriched, and reactions with nucleophiles give rise to an increased amount of Z-substitution product. However, selective conversion of (Z)-allyl substrates with retention of the olefin geometry still remains an unsolved problem.[6] Suppression of the π-σ-π isomerization is therefore an essential requirement for solving this problem. By using very reactive nucleophiles we were able to suppress the π-σ-π isomerization for the first time.

In the course of our investigations concerning the synthesis of unsaturated amino acids,[7] we found chelated ester enolates of amino acids (2) to be efficient nucleophiles in palladium-catalyzed allylic substitutions (Scheme 2).[8] Be-

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Scheme 2. Allylation of chelated amino acid ester enolates with (E)-allyl carbonate 3. Tfa = trifluoroacetyl; LHMDS = lithium bis(trimethylsilyl)-amide.

sides the generally used soft nucleophiles, such as malonates, only a few examples on the use of nonstabilized enolates, like those of ketones[9] or esters,[10] have been described so far. Therefore, these chelated enolates considerably enlarge the spectrum of potential nucleophiles. A further advantage is that conversions of these enolates (2) directly lead to the formation of unsaturated amino acid derivatives (4),[11] which can be further modified at the double bond in the side chain.[12] Based on the high reactivity of 2, the conversions already occur under very mild reaction conditions at −78 °C, and therefore very good selectivities are normally obtained. Thus, treatment of the amino acid ester 1 with the chiral allylic carbonate (S)-3 (97 % ee) provides the corresponding amino acid (2S,3S)-4 as a single regioisomer. The reaction proceeds in a highly diastereoselective fashion and with perfect chirality transfer. The analogous allyl acetates can be used as well, but the results obtained are in general a little worse.

Especially the very mild reaction conditions prompted us to investigate the reaction of 2 with Z-configured allylic substrates. Owing to the rather low reaction temperature, we hoped to remain under the energy barrier of the π-σ-π isomerization. The (Z)-allyl substrates 6 and 7, which are analogous to 3, were obtained from racemic propargylic alcohol 5 (Scheme 3): Compound 5 was subjected to a kinetic enzymatic resolution, which provided the (R)-acetate and the (S)-alcohol, each with high enantiomeric excess. The chiral alcohol was converted into the carbonate, and subsequent Lindlar hydrogenation of the two acetylenic derivatives provided the substrates (R)-6 and (S)-7.

Very interesting results were obtained for the reaction of these substrates with 1 (Scheme 3). The reaction with (S)-7 almost exclusively yielded the desired Z-substitution product (2S,3S)-8 (less than 1 % of the E-substitution product). The excellent selectivities (98 % d.s., 97 % ee) even surpassed the very good results obtained with (E)-carbonate 3. Also in this case, the anti-configured product was formed preferentially. In contrast, the reaction with (R)-6 furnished a E/Z mixture in very low yield. The selectivities were markedly worse than those obtained with the carbonate. The major isomer was identical to the product 4 resulting from the reaction with (S)-3.

This difference in product formation can be explained by a higher reactivity of the allylic carbonate 7. This substrate already reacts at −78 °C, and apparently at this temperature
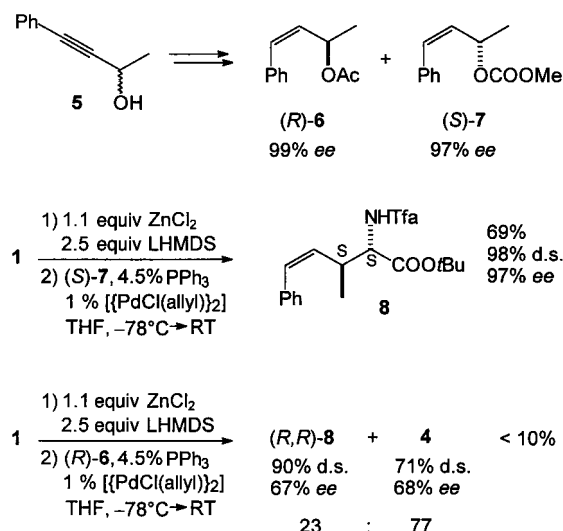
Scheme 3. Reactions of (Z)-allylic substrates (R)-**6** and (S)-**7**.

the π-σ-π isomerization does not occur. In contrast, the reaction of the acetate **6** requires a higher temperature. In this case, the reaction probably starts in the same temperature range as the isomerization, and partial conversion from the primarily formed *anti/syn* complex into the more stable *syn/syn* complex can be observed (Scheme 4). The same complex is also formed from the (S)-carbonate **3**.[13]
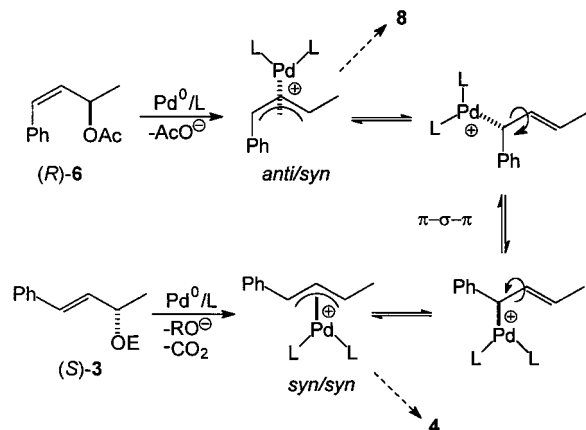
Scheme 4. Mechanism of the π-σ-π isomerization.

In the examples investigated so far, the regioselectivity of the nucleophilic attack has never been a problem, since the product with the conjugated double bond was formed exclusively. After we had succeeded in suppressing the isomerization by using allyl carbonate (S)-**7**, we turned to further interesting questions: What about (Z)-allylic carbonates with the same substituents at the allylic termini? Which position is more reactive, the "*anti*" or the "*syn*" position (Scheme 5)?
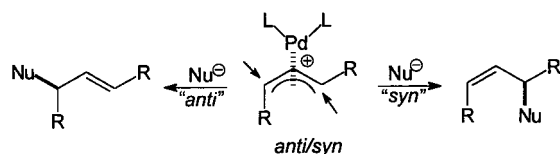
Scheme 5. Reaction pathways of *anti/syn* complexes.

The clarification of these questions is of major interest, because symmetrically substituted allyl substrates are normally used in asymmetric catalyzed reactions. From these substrates achiral π-allyl–palladium complexes are formed, independent of the configuration of the substrate, and nucleophilic attack on these complexes can be controlled, for example, by chiral ligands.[14] If enantiomerically pure allylic substrates are used, the chiral information gets lost during the reaction. However, 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 clearly more reactive, it should be possible to generate optically active compounds with these substrates as well.

We started our investigations of regioselectivity with the diphenyl derivative **9** (Scheme 6). Reaction of **9** under standard conditions surprisingly provided the E-configured *anti* product **10** exclusively in high yield. No Z isomers could
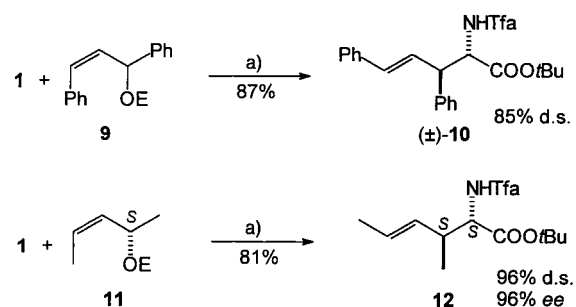
Scheme 6. Stereoselective reaction of (Z)-allyl carbonate **9**. a) See Scheme 3 and the Experimental Section for reaction conditions. E = ester group.

be detected. This indicates that the *anti* position is decisively more reactive,[5] and that attack at the *syn* position is negligible. The diastereoselectivity was significantly higher than for the reaction of the corresponding (E)-allyl carbonate (65% d.s.); the same product was formed in both cases. Clearly no appreciable π-σ-π isomerization is involved in the process. To exclude their participation completely, we investigated the reaction of the chiral carbonate (S)-**11** (99% ee), which was obtained by the method used to synthesize **6** and **7**,[15] with **1** (Scheme 6). Also in this case, the E-substituted product **12** was obtained exclusively in high yield. The diastereoselectivity was excellent, and the nearly complete transfer of chirality verifies the reaction pathway via the *anti/syn* complex and not the *syn/syn* complex, which would inevitably lead to racemization. Again, the π-σ-π isomerization could be suppressed almost completely.

Experimental Section

solvent in vacuo the crude product was purified by flash chromatography (hexanes/ethyl acetate).

8: M.p. 78–79 °C (hexanes/diethyl ether); $[\alpha]_D^{25} = +3.5$ ($c = 2.6$, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.21$ (s, 9H), 1.66 (d, $J = 4.7$ Hz, 3H), 3.59 (m, 1H), 4.74 (dd, $J = 8.6$, 8.6 Hz, 1H), 5.60–5.69 (m, 2H), 6.88 (d, $J = 8.6$ Hz, 1H), 7.19–7.34 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 17.54$, 27.36, 52.86, 56.75, 82.84, 115.52, 126.05, 127.18, 127.49, 128.20, 129.49, 138.83, 156.37, 168.80; elemental analysis calcd for C$_{18}$H$_{22}$F$_3$NO$_3$: C 60.50, H 6.20, N 3.92; found: C 60.42, H 6.44, N 3.99.

12: Colorless oil; $[\alpha]_D^{25} = +21.7$ ($c = 1.0$, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.03$ (d, $J = 6.9$ Hz, 3H), 1.45 (s, 9H), 1.65 (d, $J = 6.3$ Hz, 3H), 2.75 (m, 1H), 4.42 (dd, $J = 8.7$, 4.7 Hz, 1H), 5.24 (dd, $J = 15.3$, 7.7 Hz, 1H), 5.52 (dqd, $J = 15.3$, 6.3, 1.0 Hz, 1H), 6.65 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 16.36$, 17.63, 27.75, 39.37, 56.96, 82.83, 115.56 (q, $J = 288$ Hz), 128.03, 129.30, 156.74 (q, $J = 37.2$ Hz), 168.83; elemental analysis calcd for C$_{13}$H$_{20}$F$_3$NO$_3$: C 52.88, H 6.83, N 4.74; found: C 52.85, H 6.66, N 4.71.

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[13] The lower diastereoselectivity obtained with the acetate can also be explained by the higher reaction temperature. However, this cannot be the reason for the lower *ee* values, which probably result from enantioface exchange processes.[2]

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[15] Unfortunately the chiral diphenyl derivative **9** could not be obtained by this protocol.

A Stable, Conspicuously Active, Water-Soluble Pd Catalyst for the Alternating Copolymerization of Ethene and CO in Water**

Göran Verspui, Frank Schanssema, and Roger A. Sheldon*

Alternating copolymers of olefins and CO are relatively new, low-cost materials with interesting physical properties.[1] The discovery of active cationic palladium catalysts containing flexible *cis*-chelating diphosphanes has made the preparation of these copolymers commercially feasible.[2] Especially catalyst systems prepared in situ from a Pd precursor, a sterically demanding diphosphane such as 1,3-bis(di(2-methoxyphenyl)phosphino)propane (D-*o*-APPr), and an excess of a suitable Brønsted acid exhibit excellent catalyst performance in the ethene/CO copolymerization in organic solvents such as methanol.[3]

The current, increasing interest in sustainable technologies has intensified the research activity in organometallic catalysis in aqueous media over the past few years. Water is an environmentally friendly, economically attractive, and safe reaction medium for a variety of reactions catalyzed by homogeneous transition metal catalysts.[4]

We and others previously reported that the alternating copolymerization of ethene and CO can be performed efficiently in water by employing Pd complexes of water-soluble diphosphanes.[5] At 90 °C and 60 bar the aqueous Pd/DPPPr-S/HOTs (DPPPr-S = 1,3-C$_3$H$_6$(P(C$_6$H$_4$-*m*-SO$_3$Na)$_2$)$_2$, HOTs = *p*-toluenesulfonic acid) system exhibits catalyst ac-

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