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Chelated Enolates of Amino Acid Esters—Efficient Nucleophiles in Palladium-Catalyzed Allylic Substitutions**

Uli Kazmaier* and Franz L. Zumpe

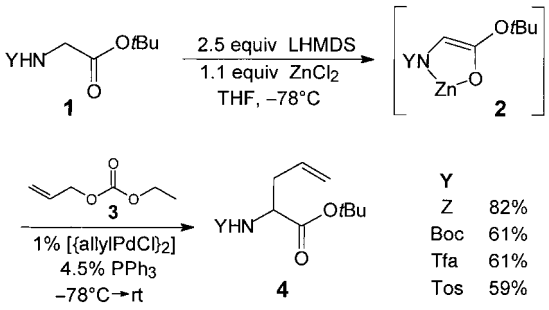
Dedicated to Professor Ulrich Schmidt on the occasion of his 75th birthday

Because of the very mild reaction conditions required, transition metal catalyzed reactions are becoming more and more popular in organic synthesis.[1] As many of these reactions tolerate a variety of functional groups, they are especially suited for the synthesis of complex molecules (natural products, etc.). Palladium, which can be used for cyclizations, cross-coupling reactions, or allylic substitutions,[2] holds a predominant position among the transition metals. Especially allylic substitutions are of particular interest, because asymmetric variations of these reactions are possible.[3] In addition to heteronucleophiles mainly symmetrical stabilized carbanions like malonates are used as C-nucleophiles. It is very advantageous that during the C–C bond forming step only one stereogenic center is generated in the allyl moiety. Thus, its configuration can be controlled quite easily.

With the use of unsymmetrical C-nucleophiles like β-keto esters[4] or imines of amino acid esters,[5] mixtures of the diastereomeres are usually obtained. This is due to the configurational lability of the allylated nucleophiles. Thus, considerably better results are obtained with alkylated derivatives.[6] Trost et al. recently reported the use of substituted azlactones as nucleophiles, giving rise to α-alkylated γ,δ-unsaturated amino acids in a highly stereoselective fashion.[7]

In contrast to the extremely 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 to only a few substrates. In the case of enolates of ketones, the best results are obtained with tin[8] and boron enolates.[9] These enolates attack the terminal positions of the allyl moiety *trans* to the palladium atom. In contrast, lithium enolates of esters preferentially attack the central position of the allyl moiety,[10] giving rise to cyclopropane derivatives.[11] The main problems with the conversion of these unstabilized enolates are probably due to coordination to the palladium atom, what might lead to inactive complexes.

This prompted us to investigate chelated enolates of amino acid esters **2** (Scheme 1) as nucleophiles in palladium-catalyzed allylic substitutions. Chelation causes a marked



Scheme 1. Synthesis of the unsaturated amino acid ester **4**. LHMDS = lithium bis(trimethylsilyl)amide, Z = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, Tfa = trifluoroacetyl, Tos = toluene-4-sulfonyl.

enhancement of thermal stability without having any negative influence on the reactivity of these enolates. Due to the fixed geometry of the enolates, their conversions often proceed with a high degree of stereoselectivity. Therefore, we are investigating conversions of these enolates providing non-natural amino acids. We are especially interested in reactions which cannot be carried out with "normal" nonchelated enolates. Thus, chelated enolates of amino acid esters undergo

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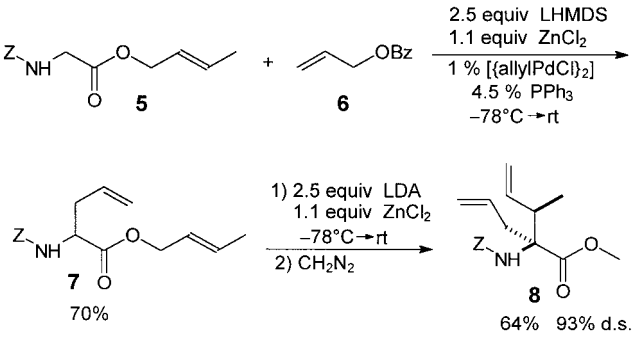
a Claisen rearrangement upon being warmed to room temperature to provide γ,δ-unsaturated amino acids.[12] With use of substituted *trans*-allyl esters the *syn*-configurated products are obtained diastereoselectively via the chairlike transition state. The *anti* products, however, cannot be obtained from the corresponding *cis*-esters as easily. Therefore, we wanted to figure out if the *anti* products might be made accessible by allylic substitutions. Bearing in mind the problems with enolates mentioned above, we found this approach to be especially interesting.

We first investigated the reactions of different N-protected glycine esters with allyl carbonate **3** (Scheme 1).[13] Deprotonation with excess LHMDS and addition of zinc chloride presumably leads to the formation of the chelated enolate **2**, which reacts with **3** in the presence of 2 mol% Pd(0) to provide the corresponding unsaturated amino acid ester **4**.[14] The best results were obtained with the Z-protected derivative. As a result of the high reactivity of the chelated enolates, the allylation already takes place under very mild conditions at $-78\,^{\circ}C$.

Consequently, this reaction can also be applied to substrates that give rise to by-products under more drastic reaction conditions. One example is crotyl ester **5** (Scheme 2). It is known that in the absence of a palladium catalyst the

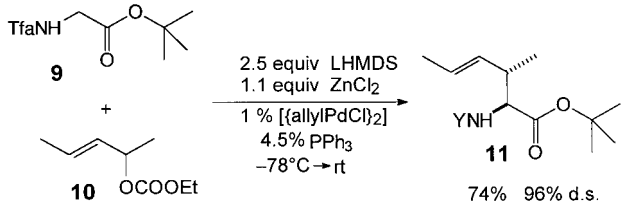


Scheme 2. Allylation of **5** and synthesis of **8**.

corresponding chelated enolate undergoes a Claisen rearrangement upon being warmed to $-20\,^{\circ}C$ to provide a γ,δ-unsaturated amino acid.[15] Like other allyl esters or allyl carbonates this crotyl ester should be able to form a π-allylpalladium complex as well. Cleavage of the ester would be the consequence.

Nevertheless, reaction of **5** with **6**[13] (after deprotonation with 2.5 equiv of LHMDS) yielded the desired allylated product **7**. No significant amounts of products resulting from cleavage or rearrangement could be detected. Even in the presence of a larger excess of LHMDS (3.5 equiv) and on warming of the reaction mixture to room temperature, Claisen rearrangement did not occur.[16] Apparently, LHMDS is not able to deprotonate the allylated product **7**. Repeated generation of a chelated complex, which would be prone to the rearrangement, did not take place. Still, deprotonation of **7** is possible when lithium diisopropylamide (LDA)[17] is applied. Thus, the allylic alkylation can be followed by a chelated enolate Claisen rearrangement resulting in the formation of the diallylated amino acid **8**. The two steregenic centers (*syn* configuration) are stereoselectively introduced by the Claisen rearrangement. By use of chiral allyl alcohols, access to optically active amino acids is possible.[18]

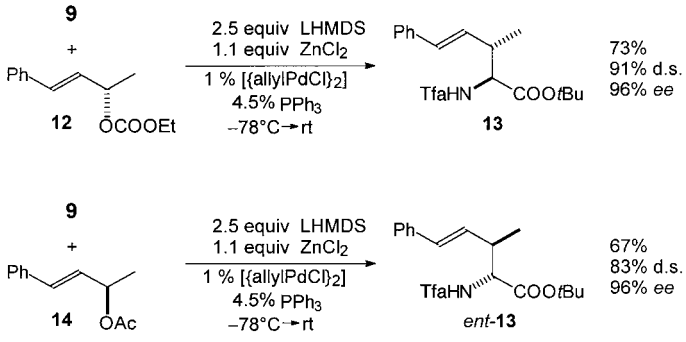
What about substituted allyl substrates? Is it possible to control the stereochemical outcome of the reactions as well? To answer this question, we investigated the reaction of 1,3-dimethylated allyl carbonate **10** with the Tfa-protected glycine ester **9** (Scheme 3). We decided to use **10**, because



Scheme 3. Diastereoselective allylation.

the intermediate π-allylpalladium complex is symmetrical. For that reason, no problem concerning regioselectivity arises in the nucleophilic attack. Ester **9** allows an easy determination of the diastereomeric ratio by gas chromatography. The desired allylated product **11** was obtained in good yield and with excellent diastereoselectivity. The diastereomerically pure product was accessible by simple recrystallization. Moreover, it was very pleasing to notice that the *anti* product was preferentially obtained from the palladium-catalyzed allylic alkylation. This allows us to synthesize both the *syn* diastereomer (by ester enolate Claisen rearrangement) and the *anti* diastereomer (by palladium-catalyzed allylic substitution). Both methods outstandingly complement one another.

Now we had to clarify if this method is also suited for the enantioselective synthesis of such unsaturated amino acids. For this purpose we used chiral allyl esters, which could easily be obtained by an enzymatic kinetic resolution of the corresponding racemic allyl alcohols.[19] The reaction of carbonate **12** with glycine ester **9** yielded the desired allylated product **13** as a single regioisomer (Scheme 4). Again, the diastereoselectivity was very high, and moreover the transfer of chirality was excellent. With the corresponding acetate **14** the enantiomeric product *ent*-**13** was obtained with a comparable *ee* value, although the diastereoselectivity was clearly lower.



Scheme 4. Enantioselective allylation.

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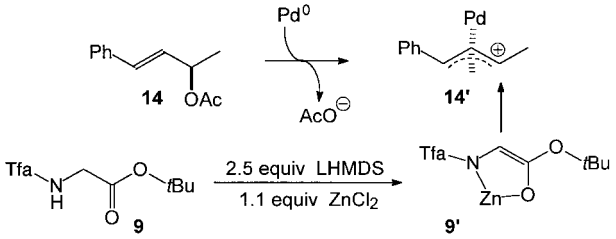
The stereochemical course of the reaction can be explained by the following model (Scheme 5): The π-allyl complex **14′** is formed by attack of palladium(0) on the allyl acetate **14** with inversion of the configuration. Subsequently **14′** reacts with



Scheme 5. Proposed mechanism.

the chelate enolate **9′** as shown. 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, so no interactions should be expected here as well. This model is in accordance with the observation that no significant diastereoselectivity can be obtained if the corresponding methyl glycinate is used. The influence of the leaving group on selecitivity as well as some applications of this reaction and the allylic substitution in the presence of chiral ligands are currently under investigation.

Experimental Section

The protected amino acid ester (1 mmol) was dissolved in THF (4 mL). At −78 °C a freshly prepared solution of LHMDS (2.5 mmol) in THF (2 mL) was added. After 30 min at −78 °C a solution of $ZnCl_2$ (1.1 mmol) in THF (5 mL) was added with stirring. After an additonal 30 min a solution of $[\{allylPdCl\}_2]$ (1 mol %), PPh_3 (4.5 mol %), and the corresponding allyl ester (1.5 mmol) in THF (3 mL) was added. The solution was stirred and warmed to room temperature overnight. Subsequently, the solution was diluted with diethyl ether and hydrolyzed with 1N $KHSO_4$ solution. The aqueous phase was extracted twice with diethyl ether, and the combined organic phases were dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude product was purified by silica gel column chromatography (eluent: hexanes/ethyl acetate).

7: M.p. 62–63 °C; ^{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 (br s, 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 $C_{13}H_{20}F_3NO_3$: C 52.88, H 6.83, N 4.74; found: C 52.85, H 6.66, N 4.71.

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