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Allylations of Chelated Enolates Using Dienyl Substrates

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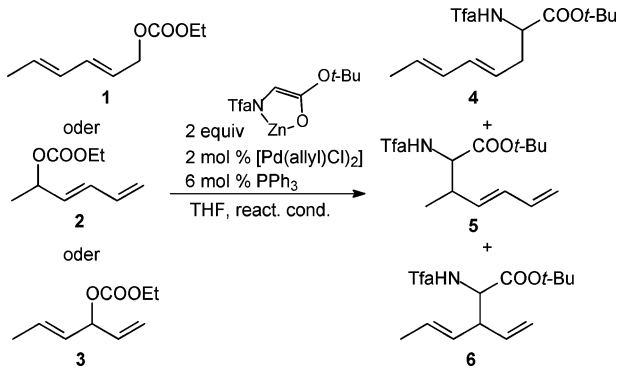
ABSTRACT



Isomerization-free reactions of dienyl carbonates (1–3) with chelated amino acid ester enolates at −78 °C provide important information concerning the mechanism of these dienylations. The formation of regioisomeric products can be explained by competing S_N2/S_N2' reactions, and the product distribution can be influenced by proper choice of the reaction conditions.

π-Allyl palladium complexes play an important role in modern organic synthesis.[1] With respect to the different synthetic applications, the allylic alkylation is probably the most popular application.[2] Herein, a π-allyl complex is attacked by a nucleophile such as an amine or a stabilized carbanion (in general malonate). Starting from the isomeric substrates **A1** and **A2** (Scheme 1) π-allyl palladium complex **B1** is formed via nucleophilic attack of Pd^0.[3] A nucleophile can react with this allyl complex at both allylic positions. In general, attack on π-allyl palladium complexes occurs at the sterically least hindered position, giving rise to linear substitution product **C1**.[2] According to this simplified model, one should expect the same product distribution, independent of the substrate (**A1** or **A2**) used, as long as the same π-allyl intermediate **B1** is formed. Interestingly, this is not always true. Quite often, a higher ratio of branched product **C2** is formed if the branched substrate **A2** is used.[4] This so-called "memory effect" was investigated carefully and probably has several origins.[5] Besides the "chloride effect",[6] the conforma-

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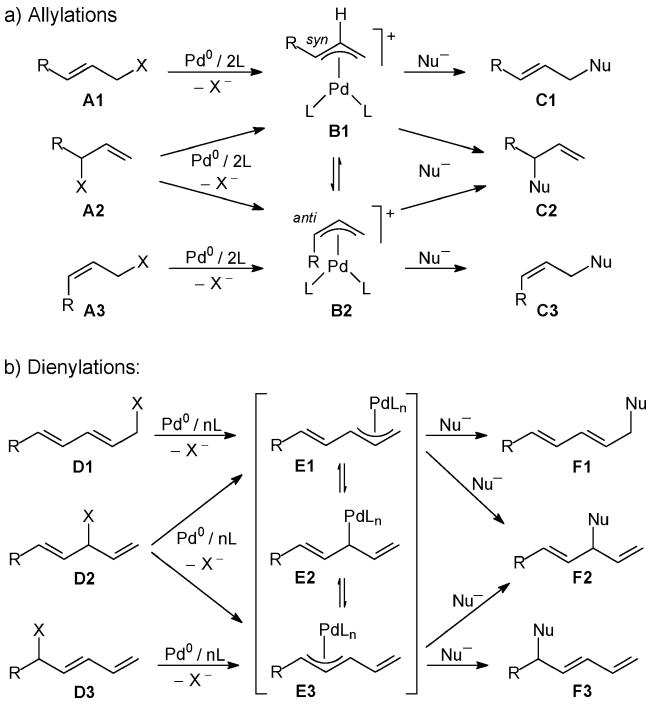
Scheme 1. Detailed Mechanism of Pd-Catalyzed Allylic Alkylation and Dienylation



tion of the allylic substrate in the ionization step also plays a crucial role because substrates of type **A2** can ionize not only to the *syn*-complex **B1** but also to the *anti*-complex **B2**, as well.[7] The higher ratio of branched product **C2** can be explained by a higher reactivity of the *anti*-position in complex **B2** compared to the *syn*-position in complex **B1**.[4b,8] This effect is relatively strong in reactions with small substituents (e.g., R = CH_3). The *anti*-complex **B2** is also formed from the (*Z*)-substrate **A3**.

A more complex situation is when the higher unsaturated compounds such as dienyl substrates **D** are reacted. In dienylations of amines and malonates with linear substrates such as **D1**, the linear product **F1** was formed preferentially in the presence of Pd catalysts,[9] while in tungsten-catalyzed reactions, the branched product **F2** was the major one.[10] The same regioselectivity can also be observed with other transition metals, such as molybdenum[11] or iridium.[12] In principle, the product formation can be explained by a π-allyl palladium intermediate **E1**, but detailed studies by Trost[13] and Bäckvall[14] indicated that the situation is much more complex.

For example, if branched substrate **D2** was reacted, the linear product **F1** was also the major one besides **F2**. This is quite surprising because **D2** can form π-allyl complexes **E1** and **E3**, as well, and therefore all three products **F1**−**F3** can be expected. In addition, **D2** should be able to form an *anti*-vinyl allyl complex,[7] analogue to **B2** (not shown here for clarity reasons), which should favor the formation of **F2**.[4b] In contrast, substrate **D3**, which should deliver **F2** and **F3** via intermediate **E3**, gave rise to a mixture of products **F1**−**F3**, while **F2** was the major one. These results can be explained by an isomerization of the π-allyl intermediates via **E2**,[13] although the different product distribution is surprising. As an alternative, the formation of **F1** from **E3** can also be explained by an allylation under S_N2' conditions. Unfortunately, under the standard reaction conditions used for malonate allylations/dienylations, no differentiation between the mechanistic pathways can be made because under these conditions isomerization is rather fast.[13] On the other hand, if it is possible to suppress these isomerizations, one should be able to obtain important information about the mechanism of these dienylations.

For several years, our group has been investigating allylic alkylations of amino acids[15] and peptides.[16] These substrates are able to form highly reactive chelated enolates which allow allylic alkylations at −78 °C. At this temperature, isomerization processes can be suppressed efficiently.[17] This is also

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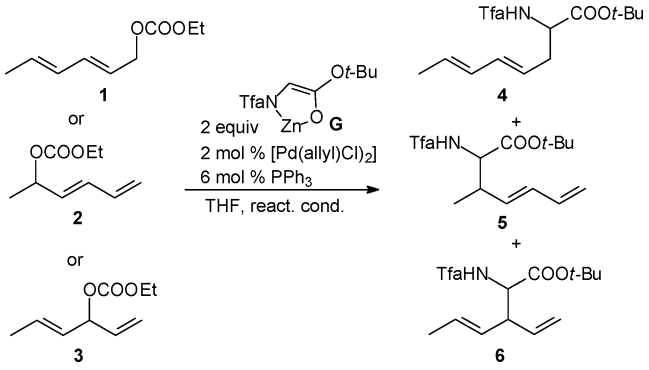
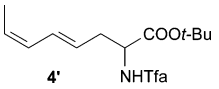
true with terminal π-allyl palladium complexes of type **B**, which provided important information concerning the already mentioned memory effect.[18] Therefore, we decided to investigate these chelated enolates also in reactions of dienyl substrates **1**−**3** (Table 1). These substrates were chosen to get results which can directly be compared to those obtained with the malonates. According to Scheme 1, substrates **1**−**3** should lead to products **4**−**6**, while the product distribution should depend on the relative ratio of the allylic complexes **E1**−**E3** (R = Me). To suppress the isomerization as much as possible, we used an excess of enolate to speed up the nucleophilic substitution. As substrates, the corresponding carbonates were used, which are more reactive than the (commonly used) acetates. The reactions were carried out at −78 °C, a temperature which allowed isomerization-free reactions with "normal" allylic substrates. In the reaction of linear substrate **1**, as expected, the linear product **4** was formed preferentially as pure (*E*/*E*)-isomer. But in contrast to the results obtained by Trost and Bäckvall,[9] the branched products **5** and **6** were obtained in a comparable amount as a 1:1 mixture (Table 1, entry 1).[19] **5** ws formed in nearly diastereomerically pure form (97% ds) while **6** was obtained as a 2:1 isomeric mixture. Especially the high ratio of **5** was surprising, because its formation can only be explained by a) a partial isomerization, or b) a significant participation of a S_N2' attack. Therefore, we next switched to substrate **2**. Under identical reaction conditions, the yield was lower, but also here the linear product was the preferred one (entry 2). Interestingly, besides **4** also the *E*/*Z*-isomer **4′** was observed in significant amount (36% of the linear product).

Table 1. Dienylation of Chelated Enolate **G**



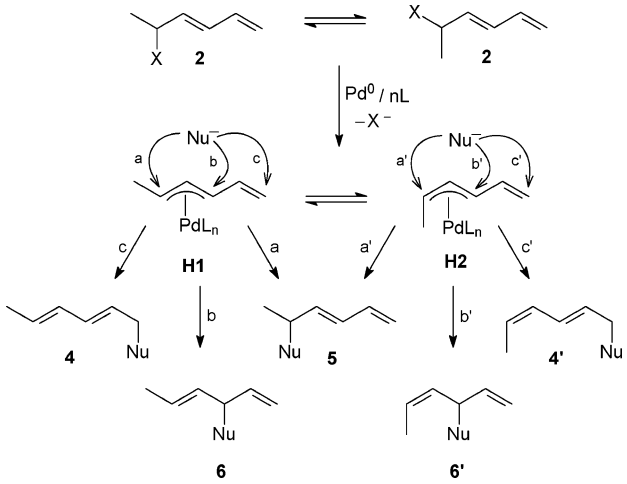
entry	substrate	reaction conditions	yield (%)	ratio **4**:**5**:**6**	dr (*anti*:*syn*) **5**	dr (*anti*:*syn*) **6**
1	**1**	−78 °C, 16 h	92	55:22:23	97:3	65:35
2	**2**	−78 °C, 16 h	64	54[a]:31:15	90:10	33:67
3	**3**	−78 °C, 16 h	87	36:13:51	95:5	50:50
4	**1**	rt	83	37:20:43	92:8	61:39
5	**2**	rt	25	35[b]:16:49	88:12	42:58
6	**3**	rt	41	31:12:57	94:6	35:65

[a] Product contains 36% (*E*/*Z*)-isomer **4′** (GC). [b] Product contains 12% isomer **4′** (GC).



The significant amount of **5** probably results from the memory effect and can be explained by the reaction mechanism (Scheme 2). Substrate **2** can undergo ionization from two different conformations,[7] which results in the formation of the two π-allyl complexes **H1** (*syn*/*syn*-complex) and **H2** (*anti*/*syn*-complex), while **H1** is the thermodynamically favored one. Therefore, at higher temperature, where both complexes are in equilibrium, this complex should be enriched. Both complexes can be attacked at both allylic positions (**a**, **b**), as well as in a S_N2' fashion (**c**). Nucleophilic attacks **a** and **a′** both provide the same product **5**, while the attacks **b**/**c** and **b′**/**c′** give rise to the isomeric products. This might be an explanation for the relatively high amount of **5** obtained. The formation of **6** is the result of attack **b** on **H1**, and the isomeric product **6′** with a (*Z*)-double bond was not observed. This is in good agreement with observations made by the Akermark group[4b] that the *anti*-position (**a′**) of *syn*/*anti*-complexes is the significantly more reactive one. In the dienyl complexes investigated here, the S_N2' attack at the terminal position (**c′**) is obviously the preferred one. This also explains the relatively high amount of (*E*/*Z*)-product **4′**.

Scheme 2. Formation of Isomeric Products **4**−**6** from Dienyl Substrate **2**



It also indicates that complexes **H1** and **H2** are formed in comparable amounts and that isomerization of the complexes under the reaction conditions used is relatively slow, at least in comparison to nucleophilic attack of the enolate. However, if the isomerization of the complexes **H1** and **H2** is very slow, one can also exclude an interconversion of the allyl complexes **E1** and **E3** (via **E2**).

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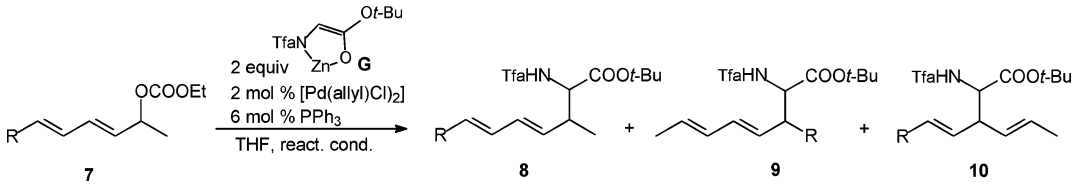
Table 2. Dienylations of Chelated Enolates **G** with Various Substrates **7**



entry	substrate	R	reaction conditions	yield (%)	ratio **8:9:10**	dr (*anti*:*syn*) **8**	**9**	**10**
1	**7a**	Me	−78 °C to rt, 16 h	89	91[a]:0:9	92:8		
2	**7b**	Et	−78 °C to rt, 16 h	85	76:15[b]:8	91:9	>97:3	50:50
3	**7b**	Et	rt	60	48:15:37	77:23	92:8	50:50
4	**7c**	Ph	−78 °C to rt, 16 h	96	78:12:10	87:13	>97:3	56:44
5	**7c**	Ph	rt	45	49:5:46	84:16	>97:3	63:37

[a] Product contains 10% (*E*/*Z*)-isomer **8a′** (GC). [b] Product contains 2% (*E*/*Z*)-isomer **9′** (GC).

Therefore, we turned our attention to the branched substrate **3** which on ionization should give rise to these two allyl complexes. In high yield, the branched product **6** was obtained preferentially. This is also quite reasonable because **6** can be formed from both allyl complexes (**E1** and **E3**). In addition, a significant memory effect might participate. Obviously, **6** is the thermodynamic product and **4** the kinetic one. This observation is in contrast to the results obtained with amines and malonates.[9,14] To prove this assumption, we carried out the reactions also at room temperature (entries 4−6), conditions where the π-allyl complexes should be more or less in an equilibrium. Indeed, under these conditions, the relative amount of **6** could be increased on cost of the linear product **4**. In these cases, the yield obtained was significantly lower, caused by a higher degree of side reactions.

To illustrate that these results can also be transferred to other dienyl systems, we investigated the reaction of several other substrates **7** (Table 2). The dimethylated compound **7a** has the big advantage that only two products (**8** = **9**) are obtained. Also, with this substrate, 10% of the (*E*/*Z*)-isomer **8′** was obtained (Table 2, entry 1). By increasing the sterical size of the substituent R, the ratio of S_N2' attack at this position decreases and, as a result of that, also the relative amount of (*E*/*Z*)-isomer. No (*E*/*Z*)-isomer at all was formed from the phenyl-substituted derivative **7c**.

If the reactions were carried out at room temperature, the yield was lower because of side reactions and also the diastereoselectivity decreased, but again, the amount of nonconjugated product **10** increased, supporting the assumption that the deconjugated product is the thermodynamic one.

In conclusion, we have shown that in dienylations of chelated enolates isomerization processes of the palladium complexes involved can be suppressed and that the formation of isomeric products is the result of competing S_N2/S_N2' reactions. By choosing proper reaction conditions (kinetic or thermodynamic control), the product ratio can be manipulated, at least in part. Further investigations, especially on the chirality transfer from optically active substrates, are currently in progress.

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Supporting Information Available: Analytical and spectroscopic data of dienylation products **4**−**6** and **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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