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Substrate-Controlled Palladium-Catalyzed Allylic Alkylations of Chelated Enolates – Scope and Limitations

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Dedicated to Prof. Helmchen on the occasion of his 65th birthday.

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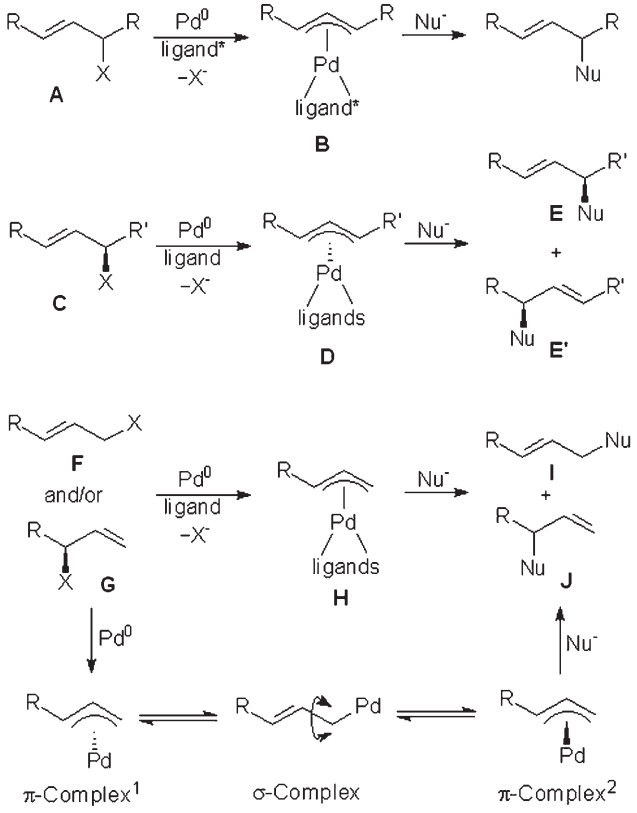
Abstract: Chelated enolates of amino acid derivatives were found to be excellent nucleophiles for stereoselective palladium-catalyzed allylic alkylations *via* terminal π-allyl complexes. Neither the olefin geometry (linear substrates) nor the configuration of secondary allylic substrates has an influence on the newly formed stereogenic centre of the amino acid. This is exclusively controlled by the protecting group on the chiral centre. Therefore, depending on the protecting group used, both diastereomeric amino acids can be obtained in a highly stereoselective fashion (up to 96% ds for 1,5 induction) from one allylic alcohol.

Keywords: allylic alkylation; amino acids; chelates; enolates; palladium; stereoselective synthesis

Introduction

π-Allyl metal complexes play an important role in modern organic synthesis. Among the different metals used, palladium plays a dominant role, but other metals, especially later transition metals enlarge the synthetic potential of these important intermediates.[1] Their most popular applications are palladium-catalyzed allylic alkylations, not least because of the different possibilities to control the stereochemical outcome of the reaction.[2] In general, heteronucleophiles as well as symmetrical stabilized carbanions such as malonates are used as *C*-nucleophiles. The advantage of the symmetrical *C*-nucleophiles results from the fact that in their reactions only one stereogenic centre is created in the allyl fragment. In contrast, the use of unsymmetrical nucleophiles (Nu) such as β-keto esters[3] or imines of amino acid esters[4] in general results in the formation of diastereomeric mixtures. This can be explained by the configurational lability of the allylated nucleophiles. Thus, considerably better results are obtained with alkylated derivatives.[5]

So far, most examples in the literature dealing with the stereochemical outcome of the allylic alkylation focus on 1,3-disubstituted allylic systems (Scheme 1). In applications of substrates of type **A**, which form a symmetrical π-allyl-palladium complex **B**, the stereochemical outcome of the reactions can be controlled by chiral li-



Scheme 1. Asymmetric palladium-catalyzed allylic alkylations.

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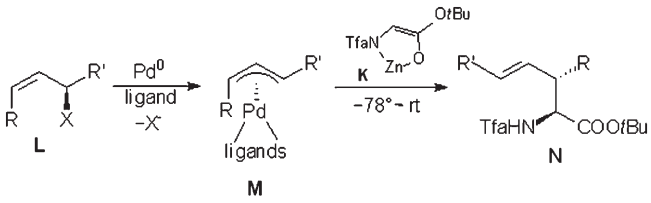
gands (ligand*). In contrast, unsymmetrical substrates **C** under inversion give rise to a chiral allyl complex **D**, allowing an overall chirality transfer from the starting material **C** towards the product **E**.[2] The only snag is the problem of regioselectivity. Especially, the reaction of substrates bearing very similar substituents R and R′ results in the formation of product mixtures (**E** and **E**′).[6] This problem is less significant with substrates **F** and **G**, forming terminal π-allyl-palladium complexes **H**, which in general are attacked at the sterically least hindered position (**I**). But with respect to stereoselective synthesis, these substrates are relatively uninteresting, because in reactions of symmetrical nucleophiles only achiral products are obtained, while the application of unsymmetrical nucleophiles gives rise to racemic mixtures. To the best of our knowledge up to date there is no suitable protocol to transfer the chiral information from the allyl substrate to the stereogenic centre in the attacking nucleophile.

Even the use of enantiomerically pure substrates **G** is not a solution to this problem, because the chiral information is lost nearly immediately *via* π–σ–π-isomerization.[7] The π–σ–π isomerization is an important mechanistic feature in the π-allyl-palladium chemistry and results in a fast interconversion of π-allyl complexes into σ-complexes and reverse. At the stage of the σ-allyl complex rotations around σ-bonds are possible and therefore either the thermodynamically most stable complexes are formed, or like in this case the π-complexes undergo epimerization.

In principle, because this isomerization is fast, the application of chiral ligands can provide optically active products **J**, if the nucleophilic attack can be directed towards the sterically more hindered position. This goal can be reached, for example, if the allylic alkylation is performed not in an inter- but in an intramolecular fashion. In this case, the formation of the "preferred ring size" can direct the nucleophilic attack to the sterically more hindered position.[8] Pfaltz et al. observed the same tendency in intermolecular reactions by switching the reaction mechanism from an S_N2-type more towards an S_N1-type mechanism.[9] If the nucleophile attacks in an S_N2-type fashion, attack should occur at the sterically least hindered position, while if the reaction proceeds *via* an S_N1-type mechanism, with a cationic transition state, the opposite regioselectivity can be expected. And indeed, with phosphite ligands[10] instead of phosphanes, the branched products **J** are formed preferentially. These can be obtained in an enantiomerically enriched form if chiral phosphite oxazolines[9] or sterically demanding monophosphanes are used.[11] Other metals such as molybdenum,[12] tungsten[13] or iridium[14] also have a higher tendency for the formation of branched product **J**. It is also known that rhodium complexes in general do not undergo π–σ–π-isomerization, and therefore they allow a chirality transfer from an optically active substrate into product **J**.[15]

Results and Discussion

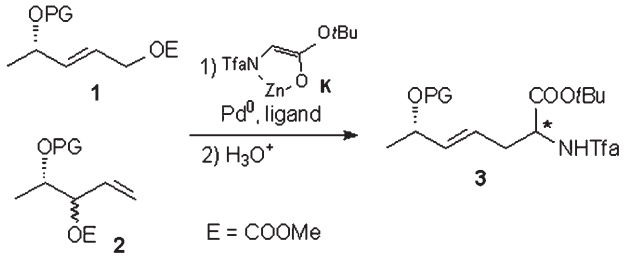
Our group is investigating reactions of chelated amino acid ester enolates (**K**), which were found to be excellent nucleophiles in a wide range of reactions,[16] including palladium-catalyzed allylic alkylations.[17] These nucleophiles react under much milder conditions in comparison to malonates or the other "standard nucleophiles". In addition, they also allow the generation of a second stereogenic centre at the α-position of the amino acid, and this generally in a highly stereoselective fashion. Because these chelated enolates react at temperatures as low as −78 °C, in their reaction the π–σ–π-isomerization can be suppressed nearly completely.[18] Therefore, for example, (*Z*)-configured allyl substrates **L** can be converted into the corresponding *syn*/*anti*-allyl complex **M** (without isomerization), which then is attacked by **K** regioselectively at the "*anti*-position" (Scheme 2). This



Scheme 2. Regioselective allylic alkylations.

allows a chirality transfer from **L** to **N**, and also regioselective reactions of allyl substrates bearing similar substituents R and R′.[19] Under "standard conditions" such substrates are critical, normally giving mixtures of regioisomers. The diastereoselectivity with which the allylation product **N** is formed depends on the substituent R, and increases with decreasing steric size of R.

Therefore, one might expect the best selectivity for R = H, and we focused our attention on reactions of substrates such as **1** and **2** (Scheme 3), which should provide



Scheme 3. Allylic alkylations using substrates **1** and **2**.

the same diastereomeric π-allyl-palladium complexes which can interconvert *via* a very rapid π–σ–π-isomerization. In this case, attack of the nucleophile on the terminal position of the π-allyl complex generates only one

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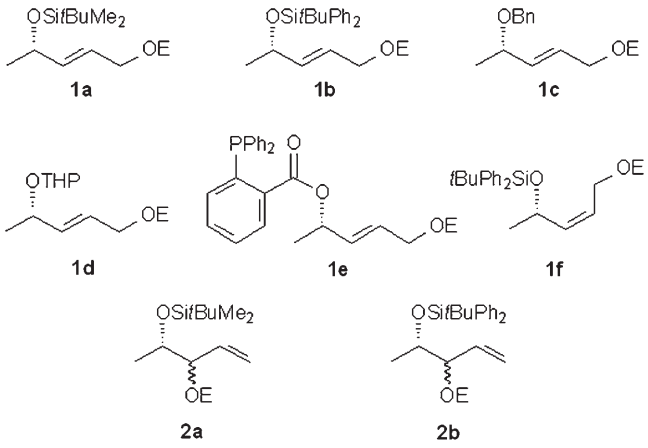


Figure 1. Allylic substrates obtained from lactic acid.

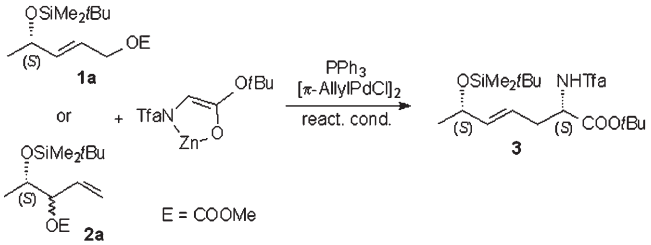
stereogenic centre, and we hoped that the high selectivity of the nucleophilic attack could be used for chirality transfer from the *O*-functionality directly to the α-position of the amino acid formed.[20]

Both substrate types could easily be obtained from lactic acid using standard operations, and we synthesized several protected derivatives to investigate the influence of the *O*-protecting group (PG) on the stereochemical outcome of the reaction (Figure 1). We decided to use the carbonate leaving group (E = COOMe), because in previous investigations this group proved superior to the acetate group, and with diacylated substrates such as **1e** selective reactions should be possible. The diphenylphosphinobenzoyl group (dppb) (**1e**) was chosen to prove the option to direct the palladium *via* precoordination.[21]

We began our investigations with the TBDMS-protected derivative **1a**, using allylpalladium chloride dimer as catalyst in the presence of PPh_3. In substrates of type **1** the leaving group is located on a primary, achiral position and the coordination of the palladium, resulting in the π-allyl complex formation, should be directed by the *O*-protecting group. Based on our experience that allylic alkylations of chelated enolates in general proceed in the same temperature range as the π–σ–π-isomerization, we first investigated the influence of the reaction temperature in reactions of substrate **1a** (Table 1). Warming up the reaction mixture from −90 °C to room temperature overnight (entry 1) provided substitution product **3a** in excellent yield and high diastereoselectivity.

The selectivity could slightly be increased by keeping the temperature lower (entries 2 to 4), although this effect was not dramatic. Quenching the reaction mixture at −68 °C after 1.5 h gave 87% ds, but the reaction was incomplete and 52% of starting material **1a** was recovered. Prolonging the reaction time solved this problem without significant influence on the selectivity (entry 5). Nearly independent of the reaction conditions, the yields and selectivities obtained were both reproducible in the range of 85%. In contrast to reactions of 1,3-disubstituted allylic substrates, the temperature obviously has no significant influence on the stereochemical outcome of the reaction. This might be an indication that for terminal π-allyl-palladium complexes π–σ–π-isomerization takes place, even at these very low temperatures. But it was not obvious if the selectivity results

Table 1. Influence of the temperature on the diastereoselectivity.



Entry	Substrate	Reaction Conditions[a]	Yield of **3a** [%]	ds[b] [%]
1	**1a**	−90 °C to rt, 12 h	88	84
2	**1a**	−78 °C to −68 °C, 1.5 h	32	87
3	**1a**	−78 °C to −60 °C, 3 h	93	86
4	**1a**	−78 °C to −42 °C, 4 h	84	88
5	**1a**	−70 °C, 24 h	85	82
6	**2a**	−90 °C to rt, 12 h	94	81
7	**2a**	−78 °C to rt, 12 h	66	83
8	**2a**	−40 °C, 12 h	48	88
9	**2a***[c]	−90 °C to rt, 12 h	61	82

[a] 1) 0.05 M enolate solution in THF, 5 mol % $[allylPdCl]_2$, 20 mol % PPh_3, temperature program, 2) 1 M $KHSO_4$.
[b] Selectivity determined by HPLC.
[c] The corresponding acetate was used.

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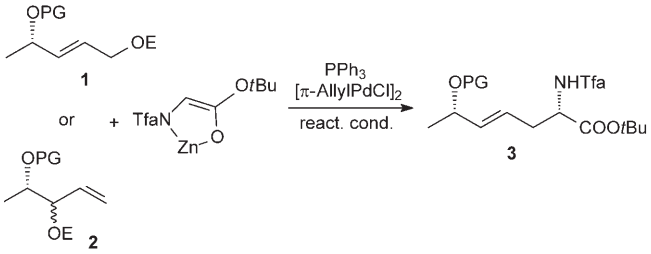
Table 2. Allylic alkylations using different substrates **1** and **2**.[a]



Entry	Substrate	PG	Product	Yield [%]	ds [%]
1	**1a**	Si*t*BuMe$_2$	**3a**	99	84[b]
2	**1b**	Si*t*BuPh$_2$	**3b**	93	96[b]
3	**1c**	Bn	**3c**	99	87[c]
4	**1d**	THP	**3d**	96	80[c]
5	**1e**	dppb	**3e**[d]	43	91[b]
6	**1f** (*Z*-**1b**)	Si*t*BuPh$_2$	**3b**	75	96[b]
7	**2a**	Si*t*BuMe$_2$	**3a**	66	83[b]
8	**2b**	Si*t*BuPh$_2$	**3b**	98	95[b]
9	**2b***[e]	Si*t*BuPh$_2$	**3b**	99	91[b]

[a] E = COOMe.
[b] Determined by HPLC.
[c] Determined by ^{13}C NMR.
[d] The product with the opposite configuration at C-2 (2*R*) was obtained (see Scheme 5).
[e] The corresponding acetate was used.

from a diastereotopic differentiation in the π-allyl complex formation and/or equilibration of the π-allyl complexes. To get further insight into the mechanism we subjected also substrate **2a** as a diastereomeric mixture to the same reaction conditions. Interestingly, the selectivities observed were nearly the same as obtained with **1a**, and the yields dropped if the reactions were run at higher temperature, while the selectivity increased. The best selectivity (88% ds) was obtained by running the reaction at −40 °C overnight. To prove the influence of the chelating metal we carried out this reaction without $ZnCl_2$, but no reaction was observed under these conditions, and only starting material was recovered. We also replaced the carbonate leaving group by an acetate (**2a***, entry 9), but the selectivities were comparable, although the yield was lower. Increasing the amount of base used had also no influence on the yield or the selectivity.

If the stereochemical outcome of the reaction is solely controlled by the steric demand of the O-protecting group, one might expect a more or less direct correlation of these parameters. And indeed, increasing the "bulkiness" by using the sterically more demanding TBDPS protecting group (Table 2, entry 1) resulted in the best selectivities obtained so far, while with the "smaller" benzyl- (entry 3) and THP protecting groups (entry 4) the diastereoselectivity was comparable to the TBDMS derivative. Under standard conditions the reaction mixtures were allowed to warm up from −78 °C to room temperature overnight. Again, the selectivities obtained with the diastereomeric mixture of **2b** (entry 8) were identical to those obtained with the linear substrate **1b**. Replacing the carbonate leaving group by acetate (entry 9) gave a lower selectivity (as observed previously) albeit in nearly quantitative yield.

The diastereomeric ratio for the silylated derivative **3b** could be determined by HPLC using the chiral column Daicel OD-H, while for the less selectively formed derivatives **3c**/**d** the second set of signals in the ^{13}C NMR spectra could be utilized. Based on the specification of the chiral column, the HPLC analysis could also be used to determine the absolute configuration of the amino acids obtained. With the column used, α-(*R*)-amino acids are eluted prior to α-(*S*)-amino acids. To make sure that all stereoisomers can be separated and to figure out which major isomer is formed, we also synthesized *rac*-**1b** and subjected it to our allylation conditions. The HPLC chromatogram of *rac*-**3b** is shown in Figure 2a, while Figure 2b corresponds to **3b** obtained from

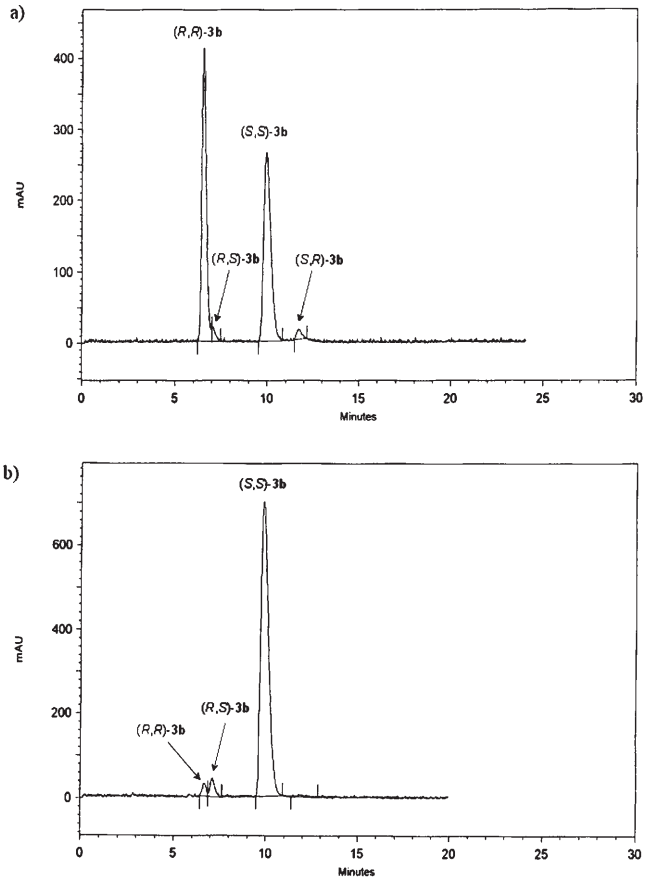


Figure 2. Determination of stereoselectivity *via* HPLC (column: Daiced OD-H). **a**) *rac*-**3b**; **b**) **3b** obtained from **1b**/**2b**.

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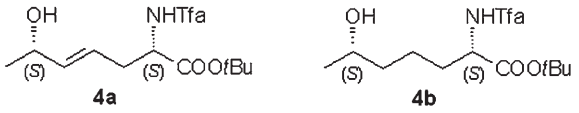
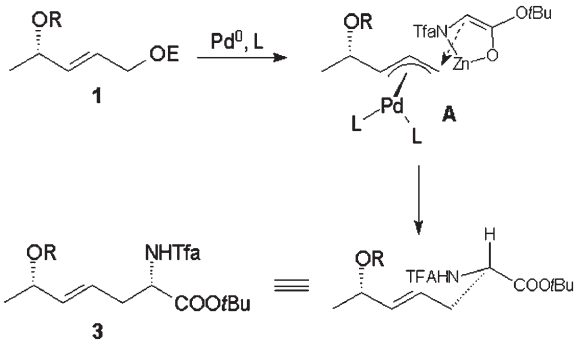


Figure 3. Common cleavage products.

1b. The small peak designated as (*R*,*R*)-**3b** results from a partial epimerization during the synthesis of the starting materials.

This clearly indicates that the (2*S*,6*S*)-isomer is the major product which was formed in all reactions investigated. From all products **3** obtained, cleavage of the protecting groups provided the same ε-hydroxyamino acid derivatives **4a** and **4b** (Figure 3), respectively.

The formation of the (*S*,*S*)-product can be explained by the following rationale (Scheme 4). Obviously the

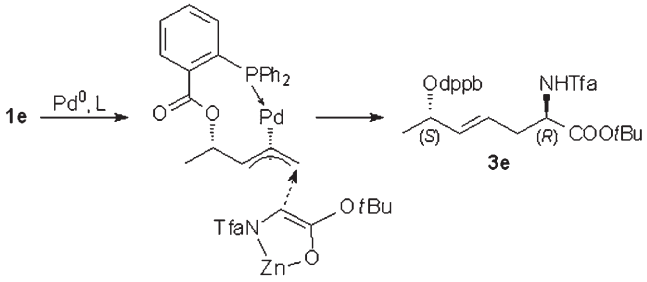


Scheme 4. Substrate directed allylic alkylation.

O-functionality directs the attacking palladium to the opposite face of the double bond, giving rise to complex **A**, with the Pd in front of the allyl fragment. Nucleophilic attack occurs from the back face in such a way that steric interactions are minimized.[17a] This is in good agreement with calculations carried out by Szabó et al.[22] These indicate that electron-withdrawing substituents adjacent to the π-allyl-palladium complex are oriented more or less antiperiplanar to the palladium, and that the nucleophilic attack occurs at the allylic position away from the heteroatom.

In this situation for us it was interesting to see if the (2*R*)-stereoisomer can also be obtained by directing the palladium to the opposite face, e.g., by using a coordinating protecting group such as the diphenylphosphinobenzoyl (dppb) group (Scheme 5). This directing group was introduced by Breit et al. preferentially for rhodium-catalyzed hydroformylations.[21] And indeed, subjecting allylic substrate **1e** to our reaction conditions provided (2*R*,6*S*)-**3e** with high selectivity but moderate yield.

Therefore, from one chiral allylic alcohol both stereoisomeric amino acid derivatives can be obtained, depending on the O-protecting group used. The comparatively



Scheme 5. Allylic alkylation *via* precoordination.

moderate yield obtained with **1e** might be caused by the fact that the Pd-directing group is also an allylic leaving group and probably **3a** undergoes a second ionization. The Pd complex formed then can react with other nucleophiles in solution. Unfortunately, we were not able to get a significant amount of a definite side product.

So far, only substrates with an (*E*)-olefin geometry were used. Our investigations with 1,3-disubstituted allyl complexes clearly indicated that (*Z*)-allylic substrates are more reactive and selective in comparison to the corresponding (*E*)-analogues. With (*Z*)-substrates a *syn*/*anti*-π-allyl complex is formed in first instance which is attacked preferentially at the *anti* position, as far as π–σ–π-isomerization can be suppressed. With the substrates investigated herein, the isomerization seems to be much faster than nucleophilic attack of the enolate. Therefore **1f** should give more or less the same result as **1b**. Compound **1f** was obtained from TBDPS-protected lactic aldehyde by the Ando version[23] of the Horner–Emmons reaction and subsequent Dibal reduction/esterification. And indeed, **3b** was formed exclusively [no (*Z*)-double bond of other regioisomers was detected] with the same selectivity as obtained from **1b**, albeit the yield was lower (Table 2, entry 6). This clearly indicates that also the olefin geometry has no influence on the selectivity.

To prove the generality of this approach we also investigated the influence of the substitution pattern on the outcome of the reaction. The substrates used are shown in Table 3. The phenyl derivative **5a** was obtained from methyl mandelate, **5b** from valine[24] *via* standard protocols. The polyoxygenated derivatives **5c** and **5d** were synthesized starting from mannitol, **5e** from tartaric acid.[25] All substrates gave the expected amino acids **6** in high to nearly quantitative yields. With the isopropyl derivative **5b** the selectivity was the same as observed with **1b**, interestingly the phenyl derivative **5a** reacted less selectively. The ketal-protected derivatives **5c** to **5e** gave selectivities in the same range and comparable to the benzyl- and THP-protected substrates **1c** and **1d**. The high yields obtained clearly indicate that this protocol can be used for the introduction of highly functionalized side chains.

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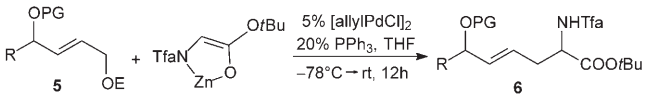
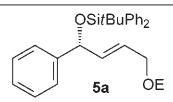
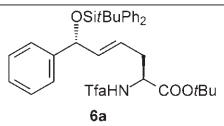
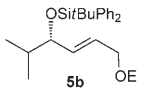
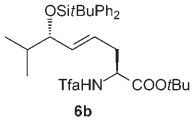
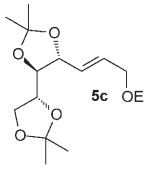
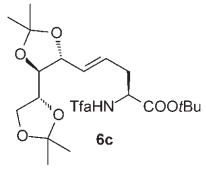
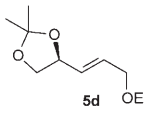
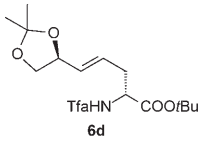
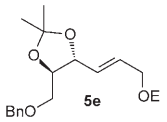
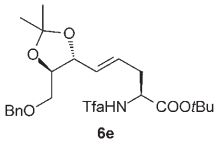
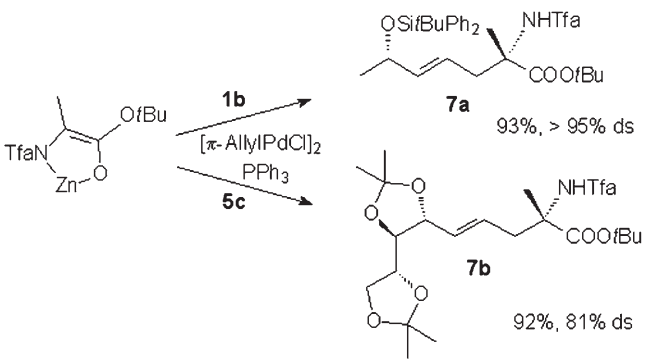
Table 3. Allylic alkylations using substrates **5**.[a]



Entry	Substrate	Product	Yield [%]	ds [%]
1			97	85
2			95	86
3			95	81
4			77	81
5			99	88

[a] E = COOMe.

Last but not least we also varied the nucleophile. From a pharmaceutical point of view, α-methylated amino acids are especially interesting, because their incorporation into potential drug candidates increases their stability versus proteolytic cleavage. Therefore, we also investigated the allylic alkylation of TFA-protected *tert*-butyl alaninate with two different substrates (Scheme 6). While LHMDS is suitable for the generation of the chelated glycine enolate, this base is not strong enough to deprotonate the corresponding alanine derivative. But with LDA deprotonation was not a problem. Both substrates investigated gave nearly the same results as obtained with the glycine enolates, and the yields were still very high.



Scheme 6. Synthesis of α-alkylated amino acids.

Conclusion

In conclusion, we have shown that chelated enolates are good nucleophiles for stereoselective allylations of not only 1,3-disubstituted but also terminal allylic substrates. The position and configuration of the leaving group as well as the olefin geometry have no influence on the stereochemical outcome of the reaction. This is exclusively controlled by the O-protecting group used. Further investigations are in progress.

Experimental Section

General Remarks

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from $LiAlH_4$ and stored over molecular sieves. The products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of EtOAc and hexanes were generally used as eluents. TLC: commercially precoated Polygram® SIL-G/UV 254 plates (Machery-Nagel). Visualization was accomplished with UV light and $KMnO_4$ solution. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR: Bruker DRX-500 spectrometer. Selected signals for the minor diastereomers were extracted from the spectra of the diastereomeric mixture. Enantiomeric and diastereomeric excesses were determined either by GC and/or by HPLC and NMR. For GC analyses a Varian 3400 and a Varian CP-3380 gaschromatograph with a Chira-Si-*L*-Val and a permethyl-β-cyclodextrin capillary column (Chrompack) was used, in combination with the software Star GC Workstation Ver. 5.3 (Varian). For HPLC analyses a Shimazu SPD-M10AT VP Liquid Chromatograph was used with an LC-10AT VP diode array detector, in combination with the Shimazu software Class-VP and a chiral Daicel "Chiralcel OD-H" column. Optical rotations were measured on a Perkin-Elmer polarimeter PE 241. High resolution mass spectra were recorded on a Joel JMS-700 (FAB) and a Finnigan MAT 90 (CI) mass spectrometer. Elemental analyses were carried out at the Department of Chemistry, University of Saarbrücken.

General Procedure A for the Preparation of Allyl Carbonates 1 and 5

A solution of the corresponding allylic alcohol (10 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. Pyridine (25 mmol) and DMAP (2 mmol) were added, followed by methyl chloroformate (20 mmol). The mixture was allowed to warm to room

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temperature overnight, before it was hydrolyzed with 1N $KHSO_4$. The hydrolysis of the ketal substrates **5c** to **5e** was performed using saturated NH_4Cl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and after filtration evaporated under vacuum. The crude product was purified by flash chromatography or by distillation.

***(4S)*-tert-*Butyldimethylsilyloxy-2-pentenyl Methyl Carbonate* (1a):** According to the general procedure A, **1a** was obtained from (4*S*)-*tert*-butyldimethylsilyloxy-2-penten-1-ol[26] (0.87 g, 4.02 mmol) after flash chromatography (hexanes/EtOAc 9:1) as a pale yellow liquid; yield: 1.08 g (3.94 mmol, 98%); $[\alpha]_D^{20}$: +4.8° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.02, 0.03 (2 s, 6H, 8-H), 0.87 (s, 9H, 7-H), 1.18 (d, $J_{5,4}$ = 6.6 Hz, 3H, 5-H), 3.76 (s, 3H, 10-H), 4.30 (m, 1H, 4-H), 4.59 (d, $J_{1,2}$ = 6.0 Hz, 2H, 1-H), 5.70 (ddt, $J_{2,3}$ = 15.5 Hz, $J_{2,1}$ = 6.0 Hz, $J_{2,4}$ = 1.3 Hz, 1H, 2-H), 5.79 (dd, $J_{3,2}$ = 15.5 Hz, $J_{3,4}$ = 4.7 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −4.8, −4.7 (2q, C-8), 18.2 (s, C-6), 24.1 (q, C-5), 25.8 (3q, C-7), 54.7 (q, C-10), 67.9 (t, C-1), 68.2 (d, C-4), 121.5 (d, C-2), 140.1 (d, C-3), 155.6 (s, C-9); HRMS (ESI): calcd. for $C_{13}H_{26}O_4SiNa$ $[M+Na]^+$: 297.1498; found: 297.1483; $C_{13}H_{26}O_4Si$ (274.44): calcd. C 56.90, H 9.55; found: C 56.77, H 9.92.

General Procedure B for the Preparation of Allyl Carbonates 2

A solution of vinylmagnesium bromide (1 M, 5.5 mL, 5.5 mmol) was added dropwise under Ar to a solution of the *O*-silylated lactic aldehyde (5 mmol) in THF (10 mL) at 0 °C. After complete addition the cooling bath was removed, the reaction mixture was warmed to room temperature, and the reaction was monitored by TLC. After complete consumption of the aldehyde the mixture was again cooled to 0 °C before methyl chloroformate (12.5 mmol) was added. After warming up to room temperature overnight, work-up was carried out according to general procedure A.

***(2S,3R/S)*-2-tert-*Butyldimethylsilyloxy-4-penten-3-yl Methyl Carbonate* (2a):** According to general procedure B **2a** was obtained from TBDMS-protected (*S*)-methyl lactate in 3 steps as a diastereomeric mixture (*syn*/*anti* = 12:88); yield: 3.49 g (15.0 mmol, 68%). *anti*-**2a:** ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.03 (s, 6H, 8-H), 0.86 (s, 9H, 7-H), 1.10 (d, $J_{5,4}$ = 6.2 Hz, 3H, 5-H), 3.75 (s, 3H, 10-H), 3.94 (dq, $J_{4,5}$ = 6.2, $J_{4,3}$ = 4.0 Hz, 1H, 4-H), 4.87 (dd, $J_{3,2}$ = 7.1, $J_{3,4}$ = 4.0 Hz, 1H, 3-H), 5.17 (d, $J_{1trans,2}$ = 10.2 Hz, 1H, 1-H), 5.27 (d, $J_{1cis,2}$ = 17.0 Hz, 1H, 1-H), 5.85 (ddd, $J_{2,1cis}$ = 17.0 Hz, $J_{2,1trans}$ = 10.2 Hz, $J_{2,3}$ = 7.1 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −4.9, −4.7 (2q, C-8), 18.0 (s, C-6), 19.5 (q, C-5), 25.7 (3q, C-7), 54.6 (q, C-10), 69.4 (d, C-4), 82.8 (d, C-3), 119.3 (t, C-1), 132.6 (d, C-2), 155.3 (s, C-9); *syn*-**2a** (selected signals): ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.05 (s, 6H, 8-H), 3.86 (m, 1H, 4-H), 4.94 (dd, $J_{3,2}$ = $J_{3,4}$ = 6.6 Hz, 1H, 3-H), 5.79 (ddd, $J_{2,1cis}$ = 17.2, $J_{2,1trans}$ = 10.6, $J_{2,3}$ = 6.6 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −5.0 (2q, C-8), 19.2 (q, C-5), 25.7 (3q, C-7), 54.6 (q, C-10), 69.1 (d, C-4), 82.3 (d, C-3), 118.7 (t, C-1), 155.2 (s, C-9); GC (Chirasil-Val, 140 °C, isothermic): $t_{R(2S,3R)}$ = 36.85 min, $t_{R(2S,3S)}$ = 37.43 min; HPLC (OD-H, Hex/*i*-PrOH = 99.75:0.25, flow: 1.0 mL/min): $t_{R(2S,3S)}$ = 4.13 min, $t_{R(2S,3R)}$ = 4.31 min; HR-MS (EI): calcd. for $C_{13}H_{25}O_4Si$ $[M+H]^+$: 273.1509; found: 273.1522.

General Procedure C for Palladium-Catalyzed Allylic Alkylations

In a Schlenk flask hexamethyldisilazane (226 mg, 1.40 mmol) or diisopropylamine (142 mg, 1.40 mmol) was dissolved in THF (1.5 mL) under argon. After cooling the solution to −78 °C *n*-BuLi (1.6 M, 0.80 mL, 1.25 mmol) was added slowly. After stirring for 20 min at this temperature the cooling bath was removed and stirring was continued for further 15 min. In a second Schlenk flask *tert*-butyl *N*-trifluoroacetylglycinate (114 mg, 0.50 mmol) or *tert*-butyl *N*-trifluoroacetylalaninate (121 mg, 0.50 mmol) was dissolved in THF (3 ml). The solution was cooled to −78 °C, before the freshly prepared LHMDS solution was added. After 15 min a solution of dried $ZnCl_2$ (75 mg, 0.55 mmol) in THF (0.5 mL) was added and stirring was continued for 30 min.

A solution was prepared from allylpalladium chloride dimer (10 mg, 0.025 mmol) and PPh_3 (30 mg, 0.113 mmol) in THF (5 mL). After stirring for 15 min at room temperature, this solution was added to the chelated enolate at −78 °C. At the same temperature the allyl substrate (0.3 mmol) was added in THF (0.5 mL) before the mixture was allowed to warm to room temperature overnight. The solution was diluted with ether before 1 M $KHSO_4$ was added (NH_4Cl for ketal-protected substrates). After separation of the layers, the aqueous layer was extracted three times with ether and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography.

tert-*Butyl (2S,6S)-2-Trifluoroacetylamino-6*-tert-*butyldimethylsilyloxy-4-heptenoate* (3a): According to general procedure C **3a** was obtained from (*S*)-**1a** (87 mg, 0.317 mmol) – and for analytical purposes from *rac*-**1a** – as a colorless oil; yield: 135 mg (0.317 mmol, 99%); ds = 84%. The reactions with the secondary allylic carbonate **2a** were performed under the conditions described in Table 1. $[\alpha]_D^{20}$: +31.8° (*c* 1.2, $CHCl_3$, 84% ds).

(2*S*,6*S*)-3a: ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.01, 0.02 (2 s, 6H, 10-H), 0.86 (s, 9H, 9-H), 1.15 (d, $J_{7,6}$ = 6.3 Hz, 3H, 7-H), 1.47 (s, 9H, 12-H), 2.53 (m, 1H, 3-H^a), 2.64 (m, 1H, 3-H^b), 4.24 (m, 1H, 6-H), 4.48 (m, 1H, 2-H), 5.39 (dt, $J_{4,5}$ = 15.1, $J_{4,3a}$ = $J_{4,3b}$ = 6.9, $J_{4,6}$ = 1.3 Hz, 1H, 4-H), 5.57 (dd, $J_{5,4}$ = 15.1, $J_{5,6}$ = 4.7 Hz, 1H, 5-H), 6.82 (d, $J_{NH,2}$ = 6.6 Hz, 1H, N<u>H</u>); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −5.0, −4.8 (2q, C-10), 18.2 (s, C-8), 24.3 (q, C-7), 25.8 (3q, C-9), 28.0 (3q, C-12), 34.0 (t, C-3), 52.6 (d, C-2), 68.3 (d, C-6), 83.4 (s, C-11), 115.7 (q, $J_{14,F}$ = 287.9 Hz, C-14), 120.2 (t, C-4), 140.6 (d, C-5), 156.4 (q, $J_{13,F}$ = 37.4 Hz, C-13), 169.3 (s, C-1).

(2*R*,6*S*)-3a (selected signals): ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −4.9 (2q, C-10), 18.2 (s, C-8), 24.4 (q, C-7), 28.0 (3q, C-12), 34.2 (t, C-3), 52.6 (d, C-2), 68.5 (d, C-6), 83.4 (s, C-11), 120.4 (t, C-4), 169.2 (s, C-1); GC (Chirasil-Val, 140 °C, isothermic): $t_{R(2R,6S)}$ = 52.43 min, $t_{R(2S,6S)}$ = 53.83 min; HPLC (OD-H, Hex/*i*-PrOH = 99.85:0.15, flow: 1.1 mL/min): $t_{R(2R,6R)}$ = 5.73 min, $t_{R(2R,6S)}$ = 7.65 min, $t_{R(2S,6S)}$ = 8.52 min, $t_{R(2S,6R)}$ = 10.40 min; HR-MS (CI): calcd. for $C_{19}H_{34}F_3NO_4Si$ $[M]^+$: 425.2209; found: 425.2204; $C_{19}H_{34}F_3NO_4Si$ (425.56): calcd. C 53.63, H 8.05, N 3.29; found C 53.65, H 8.29, N 3.23.

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tert-*Butyl (2S,6S)-2-Trifluoroacetylamino-6-*tert-*butyldiphenylsilyloxy-4-heptenoate* (3b): According to general procedure C **3b** was obtained from (*S*)-**1b** (120 mg, 0.301 mmol) – and for analytical purposes from *rac*-**1a** – as a colorless oil; yield: 153 mg (0.279 mmol, 93%); ds = 96%; $[\alpha]_D^{20}$: +15.2° (*c* 1.1, $CHCl_3$, 96% ds, 96% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (s, 9H, 9-H), 1.06 (d, $J_{7,6}$ = 6.3 Hz, 3H, 7-H), 1.44 (s, 9H, 15-H), 2.47 (m, 1H, 3-H^a), 2.57 (m, 1H, 3-H^b), 4.25 (m, 1H, 6-H), 4.46 (m, 1H, 2-H), 5.30 (dt, $J_{4,5}$ = 15.1, $J_{4,3}$ = 7.8 Hz, 1H, 4-H), 5.56 (dd, $J_{5,4}$ = 15.1, $J_{5,6}$ = 5.1 Hz, 1H, 5-H), 6.78 (d, $J_{NH,2}$ = 6.9 Hz, 1H, NH), 7.33–7.40 (m, 6H, 12-H/13-H), 7.60, 7.65 (4d, $J_{11,12}$ = 6.9 Hz, 4H, 11-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 19.2 (s, C-8), 24.1 (q, C-7), 26.9 (3q, C-9), 28.0 (3q, C-15), 34.0 (t, C-3), 52.5 (d, C-2), 69.3 (d, C-6), 83.3 (s, C-14), 115.6 (q, $J_{17,F}$ = 287.9 Hz, C-17), 120.6 (d, C-4), 127.47, 127.48 (4d, C-12), 129.58, 129.59 (2d, C-13), 134.0, 134.4 (2 s, C-10), 135.82, 135.84 (4d, C-11), 140.2 (d, C-5), 156.4 (q, $J_{16,F}$ = 37.4 Hz, C-16), 169.20 (s, C-1); HPLC (OD-H, Hex/*i*-PrOH = 99.75:0.25, flow: 1.0 mL/min): $t_{R(2R,6R)}$ = 6.58 min, $t_{R(2R,6S)}$ = 7.12 min, $t_{R(2S,6S)}$ = 10.03 min, $t_{R(2S,6R)}$ = 12.01 min; HR-MS (CI): calcd. for $C_{29}H_{38}F_3NO_4Si$ $[M]^+$: 549.2522; found: 549.2517; $C_{29}H_{38}F_3NO_4Si$ (549.71): calcd. C 63.36, H 6.97, N 2.55; found C 63.09, H 7.04, N 2.70

tert-*Butyl (2S,6S)-2-Trifluoroacetylamino-6-hydroxy-4-heptenoate* (4a): The deprotected alcohol **4a** was obtained under standard cleaving conditions of the protecting groups used. In the case of the TBDMS derivative **3a** it was directly obtained after the acidic work-up and storage of the crude product at room temperature for 24 h; $[\alpha]_D^{20}$: +52.9° (*c* 1.0, $CHCl_3$, 84% ds).

(2*S*,6*S*)-**4a:** ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (d, $J_{7,6}$ = 6.6 Hz, 3H, 7-H), 1.47 (s, 9H, 9-H), 1.65 (bs, 1H, OH), 2.48 (ddd, $J_{3a,3b}$ = 13.6, $J_{3a,4}$ = 7.3, $J_{3a,2}$ = 6.3 Hz, 1H, 3-H^a), 2.66 (ddd, $J_{3b,3a}$ = 13.6, $J_{3b,4}$ = 7.3, $J_{3b,2}$ = 6.3 Hz, 1H, 3-H^b), 4.25 (m, 1H, 6-H), 4.51 (m, 1H, 2-H), 5.48 (dt, $J_{4,5}$ = 15.5, $J_{4,3}$ = 7.3 Hz, 1H, 4-H), 5.62 (dd, $J_{5,4}$ = 15.5, $J_{5,6}$ = 6.0 Hz, 1H, 5-H), 6.91 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.2 (q, C-7), 28.0 (3q, C-9), 34.5 (t, C-3), 52.6 (d, C-2), 68.1 (d, C-6), 83.6 (s, C-8), 115.6 (q, $J_{11,F}$ = 287.9 Hz, C-11), 122.4 (d, C-4), 139.7 (d, C-5), 156.5 (q, $J_{10,F}$ = 37.4 Hz, C-10), 169.2 (s, C-1).

(2*R*,6*S*)-**4a** (selected signals): ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.3 (q, C-7), 34.6 (t, C-3), 68.2 (d, C-6), 83.6 (s, C-8), 122.4 (d, C-4), 139.7 (d, C-5); HPLC (OD-H, Hex/*i*-PrOH = 99.75:0.25, flow: 1.0 mL/min): $t_{R(2R,6S)}$ = 17.15 min, $t_{R(2S,6S)}$ = 20.73 min; HRMS (CI): calcd. for $C_{13}H_{20}F_3NO_4$ $[M]^+$: 311.1344; found: 311.1336.

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