JOC*Note*

Isomerization-Free Allylic Alkylations of Terminal π-Allyl Palladium Complexes

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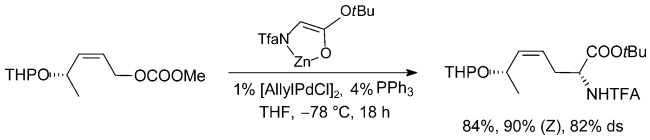
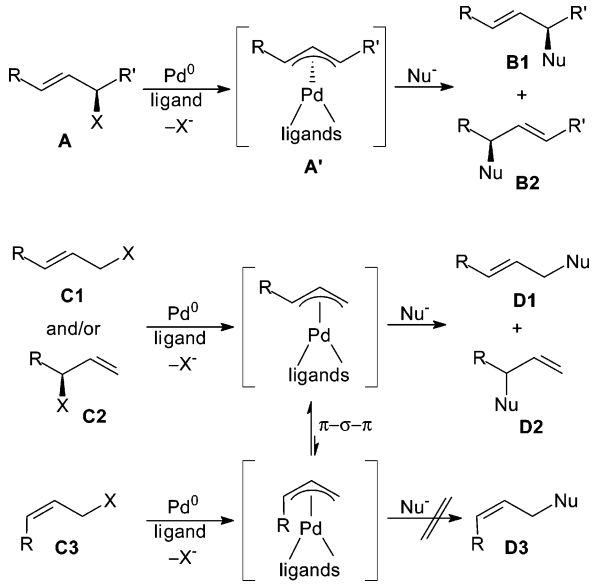


Chelated amino acid ester enolates are excellent nucleophiles for allylic alkylations. With these enolates, even terminal π-allyl palladium complexes react without significant isomerization. This allows a transfer of the *cis*-olefin geometry from the substrate into the product. Chiral substrates also show a reasonably good 1,5-induction.

π-Allylmetal complexes play an important role in modern organic syntheses.[1] Although various metals are known to form π-allyl complexes, those of palladium are especially interesting from a synthetic point of view.[1e] In the meanwhile, several asymmetric versions of allylations using these complexes have been developed. Besides heteronucleophiles, preferentially symmetrical C-nucleophiles such as malonates are used. The reason is rather simple: in this case, only one stereogenic center is formed in the allyl fragment, which can be controlled relatively easily. With asymmetric nucleophiles in general, diastereomeric mixtures are obtained, a significant limitation of this nice reaction. With respect to the allylic substrate, 1,3-disubstituted derivatives **A** (Scheme 1) are very popular. In the case of symmetric substrates (R = R′), the configuration of the newly formed stereogenic center can nicely be controlled by chiral ligands. This can be explained by a symmetrical π-allyl complex **A′**, and the attack of the nucleophile to the one or the other position is directed by the ligand. With asymmetrical substrates (R ≠ R′), the chiral information can be transferred from the substrate **A** toward the product **B** (double inversion), but in this case in general, regioisomeric products are obtained.[1e] In the case of terminal allyl complexes, as formed from substrates such as **C1**−**C3**, the regioselectivity in general is not a major problem because those complexes are preferentially attacked by the nucleophile at the sterically least-hindered position. With symmetrical nucleophiles, achiral products **D1** are obtained, even if enantiomerically pure substrates such as **C2** are used. Chiral compounds can only be obtained if the incoming nucleophile can be directed toward the sterically more hindered position.[2]

SCHEME 1. Palladium-Catalyzed Allylic Alkylations



This is possible by using suitable ligands[3] or by switching to other metals such as molybdenum,[4] rhodium,[5] iridium,[6] or tungsten.[7] Chirality can be induced to linear products **D1** by using chiral ligands and prochiral C-nucleophiles.[8] A still unsolved problem is the $\pi-\sigma-\pi$-isomerization of these terminal palladium π-allyl complexes, which is much faster compared to the 1,3-disubstituted analogues.[9] Therefore, the trans-configured substitution product **D1** is formed preferentially, independent of the substrate **C** used. Only a few examples of the transfer of the *cis*-olefin geometry from **C3** into **D3** under transition-metal-catalyzed conditions have been reported so far.[10,11]

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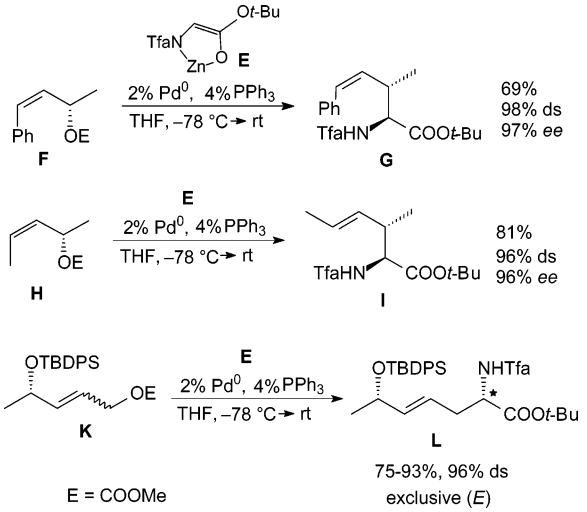
SCHEME 2. Allylic Alkylations of Chelated Enolates[a]



[a] Tfa = trifluoroacetyl.

For some time, our group has been investigating chelated amino acid ester enolates as nucleophiles **E** in palladium-catalyzed allylic alkylations (Scheme 2).[12] The great advantage of these nucleophiles is their high reactivity. Therefore, they react under much milder conditions (already at −78 °C) with π-allyl palladium complexes than the generally used nucleophiles such as malonates. As a result, these were the first C-nucleophiles showing no $\pi-\sigma-\pi$-isomerization of complexes obtained from 1,3-disubstituted substrates.[13] For example, if cis-configured carbonate **F** was reacted, the substitution product **G** was obtained with perfect conservation of the olefin geometry. With symmetrically substituted *cis*-allyl substrates of type **H**, nucleophilic attack occurs selectively at the more reactive anti position[10a,14] giving rise to **I** with excellent chirality transfer from **H** to **I**.

SCHEME 3. Allylic Alkylations of Various Substrates 1

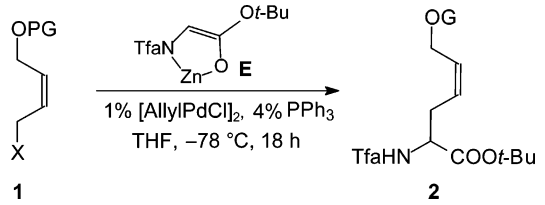


TABLE 1. Allylic Alkylations of Various Substrates 1

entry	substrate	PG	X	product	yield (%)	cis ratio (%)
1	**1a**	TBDPS	OCOOMe	**2a**	92	82
2	**1b**	TBDPS	$OPO(OEt)_2$	**2a**	86	79
3	**1c**	TBDPS	$2,4\text{-}Cl_2C_6H_3$	**2a**	84	76
4	**1d**	TBDMS	OCOOMe	**2d**	81	94
5	**1e**	THP	OCOOMe	**2e**	87	98
6	**1f**	Bn	$OPO(OEt)_2$	**2f**	99	99
7	**1g**	allyl	$OPO(OEt)_2$	**2g**	81	98
8	**1h**	Me	$OPO(OEt)_2$	**2h**	84	97
9	**1i**	Bz	$OPO(OEt)_2$	**2i**	63	94
10	**1j**	4-MeO-Bz	$OPO(OEt)_2$	**2j**	98	96

Very recently, we could also show that in reactions of chiral substrates **K** the nucleophilic attack on the terminal π-allyl intermediate could be controlled by the stereogenic center in the substrate.[15] The best results were obtained with the sterically high demanding *tert*-butyldiphenylsilyl protecting group (TBDPS). Herein, the diastereoselectivity (ds) was 96%, independent of the olefin geometry in **K**, which is a clear indication for a rather fast $\pi-\sigma-\pi$-isomerization. The opposite diastereomer could be obtained if palladium-coordinating protecting groups such as diphenylphosphinobenzoyl[16] were placed in the stereogenic center.

The sterically demanding protecting group TBDPS is required for the high selectivity, but on the other hand, it should make the nucleophilic attack at the π-allyl complex more difficult. Therefore, we were hopeful that with sterically less-hindered substrates the allylation could be carried out at a lower temperature, where the fast isomerization could be, at least in part, suppressed. Our first choice was the unsubstituted 1,4-dioxy-2-butenyl substrate **1** (Scheme 3), and we investigated the influence of the protecting group (PG) on the yield and especially the cis/trans selectivity (Table 1). To prove the influence of the protecting group and to be able to compare the results with those obtained with **K**, we started with TBDPS-protected carbonate **1a**. As a nucleophile, we used again the enolate **E**, which in general gives the best results in allylic alkylations. Although with the substituted derivative **K** the trans product **L** was formed exclusively (independent of the *E*/*Z* ratio of **K**), with **1a** the corresponding cis product was obtained preferentially (82% cis) albeit in a good yield (entry 1). Variation of the leaving group had no significant effect with respect to the selectivity (entries 2 and 3). More significant was the effect by switching to sterically less-demanding protecting groups.

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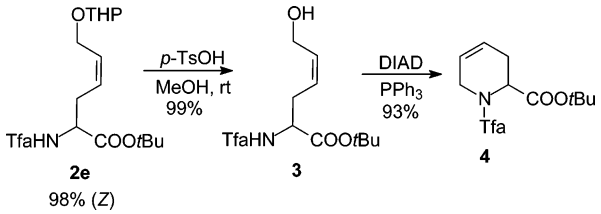
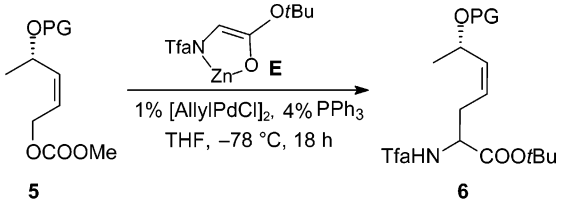
SCHEME 4. Synthesis of Unsaturated Pipecolinic Acid Derivatives



SCHEME 5. Allylic Alkylations of Chiral Substrates 5



Already with the TBDMS protecting group, a cis selectivity of >90% was obtained, and the other smaller protecting groups gave rise to only one product. This clearly illustrates that with the highly reactive glycine enolates even in the case of terminal π-allyl complexes the isomerization can be suppressed almost completely. The best results were obtained if the reactions were run constantly at −78 °C. If the reaction mixture was warmed to room temperature, the selectivities were slightly worse because isomerization becomes more competitive.

Some especially interesting substrates are the benzoyl derivatives **1i** and **1j** because in this case the protecting group is also a leaving group. However, by using the highly reactive phosphate group,[17] this leaving group can selectively be ionized. In principle, it should be possible to replace the benzoyl group by a second nucleophile. Such reactions were already accomplished with comparable C-nucleophiles, but the (*Z*)-stereochemistry of the double bond could not be retained in the allylic alkylation.[18]

Interestingly, no cyclization via the deprotonated amide was observed under the reaction conditions used. However, the corresponding pipecolinic acid derivative **4** could easily be obtained by cleavage of the O-protecting group and cyclization under Mitsunobu conditions,[19] as illustrated for the THP-protected derivative **2e** (Scheme 4).

After having the isomerization of linear, unbranched substrates under control, we switched back to the substituted optical active derivatives **5** (Scheme 5, Table 2). These are easily obtained from lactic acid, introducing the cis double bond by using the Ando version of the Horner−Wadsworth−Emmons reaction.[20]

In the reaction of TBDMS-protected substrate **5a**, we observed not only an excellent induction with respect to the newly formed stereogenic center but also a complete isomerization of the double bond, probably because of steric reasons (entry 1). The high induction obtained is in good agreement with observations made earlier.[15] On the other hand, if the silyl protecting group is replaced by a benzyl group (**5b**), the olefin geometry stays untouched, but no induction was obtained in this case. Therefore, we investigated the corresponding THP ether **5c**, which gave up to a 4:1 diastereomeric ratio in the case of the trans-configured analogue. Indeed, a very similar induction was obtained with **5c**, but in this case, also the olefin geometry could be conserved nearly completely.

TABLE 2. Allylic Alkylations of Chiral Substrates 5

entry	substrate	PG	(*Z*)-ratio (%)	product	yield (%)	(*Z*)-ratio (%)	ds
1	**5a**	TBDMS	99	**6a**	98	0	92 (*S*/*S*)
2	**5b**	Bn	88	**6b**	86	86	54 (*R*/*S*)
3	**5c**	THP	98	**6c**	84	90	82 (*R*/*S*)

In conclusion, we showed that with chelated enolates not only a high degree of chirality transfer can be obtained in allylic alkylations of terminal substrates but also the olefin geometry can be conserved under certain circumstances. The lower selectivities obtained with branched substrates probably result from a hindered π-allyl complex formation, requiring higher reaction temperatures which favor $\pi-\sigma-\pi$-isomerization. Synthetic applications of this protocol are currently under investigation.

Experimental Section

General Procedure for Allylic Alkylations of Chelated Enolates. The reaction was carried out under argon using standard Schlenk techniques. $ZnCl_2$ (76 mg, 0.55 mmol) (dried by heating in vacuo) and Tfa-Gly-O*t*Bu (114 mg, 0.50 mmol) were dissolved in dry THF (3 mL) and cooled to −78 °C. A LHMDS solution [prepared from hexamethyldisilazane (222 mg, 1.38 mmol) and *n*-BuLi (0.78 mL of a 1.6 M solution, 1.25 mmol) in THF (2 mL)] was added dropwise at this temperature, and the solution was stirred for 15 min. A solution of allyl palladium chloride dimer (1 mg, 0.0025 mmol) and PPh_3 (3 mg, 0.0113 mmol) in THF (0.5 mL) was added, and stirring was continued for 10 min. The allyl substrate (0.25 mmol) dissolved in THF (1 mL) was added dropwise, and the reaction mixture was stirred overnight at −78 °C. Then, the solution was diluted with diethyl ether before 1 M $KHSO_4$ was added. The layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica.

6-(*tert*-Butyldiphenylsilyloxy)-2-trifluoroacetylamino-4-hexenoic acid *tert*-Butyl Ester (2a). According to the general procedure for palladium-catalyzed allylation, **2a** was obtained from **1a** after purification by column chromatography (hexane/EtOAc = 9:1) as a colorless oil (123 mg, 92%) with a ratio of (*Z*)/(*E*) = 82:16. R_f (hexane/EtOAc = 9:1) = 0.30. (*Z*)-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.42 (s, 9H), 2.43 (m, 1H), 2.52 (m, 1H), 4.18 (d, J = 6.1 Hz, 2H), 4.44 (m, 1H), 5.28 (m, 1H), 5.76 (dt, J = 11.1 Hz, 6.1 Hz, 1H), 6.85 (d, J = 6.9 Hz, 1H), 7.34−7.42 (m, 6H), 7.65 (d, J = 6.7 Hz, 4H); ^{13}C NMR (125 MHz) δ 19.1, 26.8, 27.9, 29.7, 52.5, 60.1, 83.4, 115.8 (q, J = 286.5 Hz), 122.8, 127.6, 127.7, 129.6, 129.7, 133.4, 133.5, 133.8, 135.4, 135.5, 156.6 (q, J = 37.2 Hz), 169.2. (*E*)-Isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.46 (s, 9H), 2.57 (m, 1H), 2.66 (m, 1H), 4.13 (d, J = 4.1 Hz, 2H), 4.52 (m, 1H), 5.57 (m, 1H), 5.65 (dt, J = 15.2 Hz, 4.1 Hz, 1H), 6.85 (d, J = 7.0 Hz, 1H), 7.35−7.43 (m,

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6H), 7.65 (d, J = 6.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 26.7, 28.0, 34.3, 52.6, 63.7, 83.4, 115.6 (q, J = 283.3 Hz), 122.0, 127.6, 127.7, 129.6, 129.7, 133.4, 133.5, 134.5, 135.4, 135.5, 156.4 (q, J = 37.4 Hz), 169.2; HPLC (silica, hexane/EtOAc = 98:2, 2 mL/min) $t_R(Z)$ = 6.52', $t_R(E)$ = 7.13'. Anal. Calcd for $C_{28}H_{36}F_3NO_4Si$ (535.67): C, 62.78; H, 6.77; N, 2.61. Found: C, 62.50; H, 6.80; N, 2.79.

1-Trifluoroacetyl-1,2,3,6-tetrahydropyridine-2-carboxylic Acid *tert*-Butyl Ester (4). According to the procedure for Mitsunobu cyclizations,[19] PPh_3 (60 mg, 0.23 mol) and DIAD (47 mg, 0.23 mmol) were dissolved in dry THF (8 mL) and cooled to 0 °C. A solution of **3** (50 mg, 0.14 mmol) in THF (3 mL) was added dropwise, and the solution was stirred overnight. The reaction mixture was then concentrated at reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc = 9:1) on silica. Lactame **4** was obtained as a colorless oil (35 mg, 93%). R_f (hexane/EtOAc = 8:2) = 0.38. Major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.47 (m, 1H), 2.72 (dd, J = 17.3 Hz, 5.7 Hz, 1H), 4.17 (m, 2H), 5.32 (d, J = 6.6 Hz, 1H), 5.62 (m, 1H), 5.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 27.8, 42.1, 51.4, 81.6, 116.4 (q, J = 286.1 Hz), 121.9, 123.4, 157.0 (q, J = 36.2 Hz), 168.3. Minor rotamer (selected signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 (dd, J = 17.4 Hz, 6.0 Hz, 1 H, 3-H), 3.84 (d, J = 19.3 Hz, 1H), 4.33 (dd, J = 19.3 Hz, 3.2 Hz, 1H), 4.68 (d, J = 6.0 Hz, 1H,), 5.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 27.8, 42.5, 54.3, 82.9, 116.3 (q, J = 286.1 Hz), 122.2, 122.9, 168.3. Anal. Calcd for $C_{12}H_{16}F_3NO_3$ (279.26): C, 51.61; H, 5.78; N, 5.02. Found: C, 52.00; H, 5.70; N, 5.00. HRMS (CI): m/z [M + H]$^+$ calcd for $C_{12}H_{16}F_3NO_3H$, 280.1116; found, 280.1183.

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Supporting Information Available: General remarks and analytical and detailed NMR spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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