Allylic Alkylation

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Regio- and Stereoselective Modification of Chiral α-Amino Ketones by Pd-Catalyzed Allylic Alkylation**

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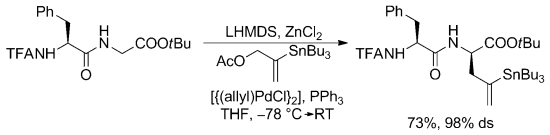
Dedicated to Professor Günter Helmchen on the occasion of his 75th birthday

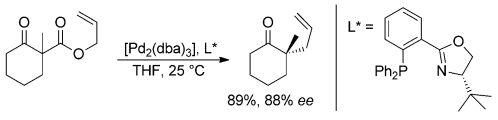
Abstract: *Chiral α-amino ketones are excellent nucleophiles for stereoselective palladium-catalyzed allylic alkylations. Both chiral as well as achiral allylic substrates can be applied, while the stereochemical outcome of the reaction is controlled by the chiral ketone enolate. The substituted amino ketones formed can be reduced stereoselectively, and up to five consecutive stereogenic centers can be obtained. This approach can be used for the synthesis of highly substituted piperidine derivatives.*

Transition-metal-catalyzed allylic alkylations have an enormous impact on modern synthetic chemistry,[1] and Pd-catalyzed processes in particular play a dominant role.[2] In the established approaches stabilized carbanions were used as preferred nucleophiles, but more recently also nonstabilized enolates, especially of esters,[3] amides,[4] and ketones have made their way into the limelight.[5] First results obtained with simple ketones such as acetophenone were reported by Trost and Keinan in 1980.[6] The ketone enolates can also be generated in situ, for example, by addition of cuprate reagents to α,β-unsaturated ketones.[7] A wide range of chiral ligands have been used to control the stereogenic center α to the carbonyl group.[8] In the last few years especially decarboxylative allylations using vinyl allyl carbonates[9] or allyl β-oxo carboxylates[10] have become very popular; this field has been influenced mainly by work in the groups of Tsuji,[11] Trost,[12] and Stoltz.[13] In most cases quaternary stereogenic centers are created (Scheme 1), especially if chiral ligands are used, probably to avoid an epimerization of the stereogenic centers under the reaction conditions used.[14]

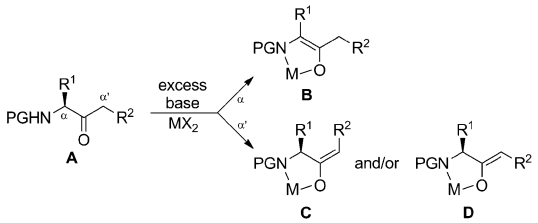
Our group has also been involved in allylic alkylation chemistry, specifically transition-metal-catalyzed allylations of chelated glycine ester enolates.[15] Besides Pd catalysts also Rh[16] and Ru[17] complexes can be applied, showing different allylation characteristics. The great advantage of this procedure is that not only amino acid esters but also deprotonated peptides can be used as nucleophiles.[18] Excellent stereoselectivities could be obtained in the presence of $ZnCl_2$ as chelating metal salt, while the stereogenic centers in the peptide chain determine the stereochemical outcome of the allylic alkylation (Scheme 2). Probably the side chains of the chiral amino acids shield one face of the glycine enolate formed. Subsequent attack of the sterically demanding π-allyl complex occurs from the opposite, sterically less shielded face. Therefore, an L-amino acid generates an adjacent D-amino acid and vice versa.



Scheme 2. Stereoselective peptide modifications by allylic alkylation. ds: diastereoselectivity.



Scheme 1. Stereoselective generation of α-quarternary ketones by means of decarboxylative allylic alkylation.



Scheme 3. Potential chelated enolates formed from N-protected α-amino ketones. PG: protecting group.

Based on these good results obtained with peptide enolates, we were interested to see whether comparable shielding effects can also be used for the stereoselective allylic alkylation of suitably protected α-amino ketones **A** (Scheme 3). These amino ketones are easily accessible from amino acids[19] and should be able to form two different chelated enolates in the presence of excess base. One equivalent of base should be required to deprotonate the

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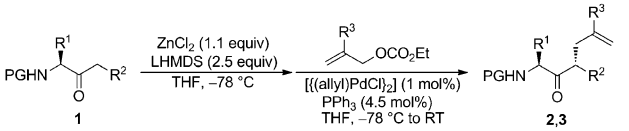
acidic amide and a second equivalent can deprotonate either the α- or the α′-position. Addition of a chelating metal salt (MX_2) should generate either an enolate **B** with an endocyclic double bond or the enolates **C** and **D** with exocyclic double bonds. Enolate **D** is expected to be favored since it has significantly lower 1,3-allyl strain.[20] While allylation of enolate **B** would generate a quaternary stereogenic center, allylation of **C** and/or **D** should result in the diastereoselective generation of a second tertiary stereogenic center. Amino ketones of type **A** are known to be rather sensitive compounds that readily epimerize.[19,21] Therefore, the α-deprotonation must be suppressed completely if the α′-allylation should be (highly) stereoselective.

In our first experiment we investigated the allylic alkylation of N-tosylated phenylalanine-derived benzyl ketone **1a** (Table 1). The N-tosyl protecting group was

Table 1: Allylic alkylations of various different protected α-amino ketones **1**.



Entry	Ketone	PG	R^1	R^2	R^3	Prod.	Yield [%][a]	d.r.[b]
1	**1a**	Tos	Bn	Ph	H	**2a**	91	95:5
2	**1b**	Tos	Me	Ph	H	**2b**	72	94:6
3	**1c**	Tos	*s*Bu	Ph	H	**2c**	87	97:3
4	**1d**	TFA	Bn	Ph	H	**2d**	68	58:42
5	**1e**	Boc	Bn	Ph	H	**2e**	93	88:12
6	**1f**	Boc	*i*Pr	Ph	H	**2f**	95	96:4
7	**1g**	Boc	*s*Bu	Ph	H	**2g**	96	97:3
8	**1e**	Boc	Bn	Ph	Me	**3e**	85	94:6
9	**1f**	Boc	*i*Pr	Ph	Me	**3f**	73	94:6
10	**1g**	Boc	*s*Bu	Ph	Me	**3g**	72	96:4
11	**1h**	Boc	*i*Pr	Me	Me	**3h**	78	94:6
12	**1i**	Boc	*s*Bu	Me	Me	**3i**	80	93:7

[a] Yield of isolated product. [b] Determined by HPLC and/or NMR analysis of the crude products.

selected to guarantee deprotonation of the rather acidic tosyl amide, and the benzyl ketone was chosen to facilitate the α′-deprotonation, generating a conjugated enolate. In addition, owiong to the sterically demanding phenyl group, *Z* enolate **D** should be significantly favored over the *E* enolate **C**. During the optimization of the reaction we varied a range of reaction parameters and the by far best results were obtained when LHMDS was used as a base and $ZnCl_2$ as the chelating metal salt. Under these conditions the desired α′-allylation product was formed exclusively in high yield and diastereoselective fashion (entry 1).

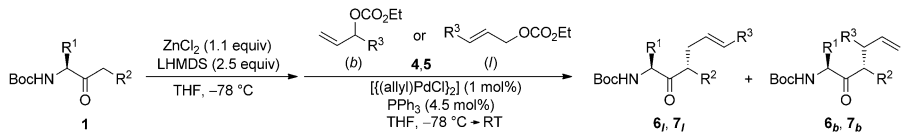
With these optimized conditions in hand, we next investigated the influence of the side chain, of the N-protecting group, and of the allylic substrate used. Even with the smallest side chain (R = Me) excellent diastereoselectivity was obtained (entry 2), which increased with the steric demand of the side chain (entry 3). Apparently the N-tosyl group is an excellent protecting group for this type of ketone allylations. On the other hand, from a synthetic point of view, this group is not very popular, since it is rather difficult to remove.[22] Therefore, we tested other, more easily removable protecting groups. In amino acid and peptide allylations the best results were obtained with the trifluoroacetyl (TFA) protecting group, whose electron-withdrawing effect is comparable to that of the tosyl group. Indeed, the reaction of the N-trifluoroacetylated ketone **1d** proceeded nicely in good yield but surprisingly without significant diastereoselectivity (entry 4). Also here only the required monoallylation product was obtained, but the stereogenic center of the amino ketone epimerized almost completely under the reaction conditions used, explaining also the low diastereoselectivities observed. Apparently, in this case the well-known lability of amino ketones could not be suppressed. Therefore, we switched to the N-Boc protecting group as a representative of the easily removable carbamate protecting groups. With this protecting group, by far the best yields could be obtained, combined with excellent diastereoselectivities, especially with the sterically demanding side chains (entries 6 and 7). Almost the same selectivities were obtained with methallyl carbonate as the allylic substrate (entries 8–10). With this allylcarbonate we also investigated the influence of the substituent on the enolate.

Up to this point, all reactions had been carried out with the phenyl-substituted enolate to favor α′-deprotonation and chelate complex **D**. Now we replaced the phenyl ring by a small methyl group to test its influence on the regio- and stereoselectivity of the allylation (entries 11 and 12). To our surprise, we observed no significant difference with regards to yield and selectivitiy.

So far, only selectivity issues in the amino ketone fragment had been addressed, since only symmetric π-allyl–Pd complexes were involved. With more complex and unsymmetrically substituted allyl complexes the situation gets more complicated since also regioisomeric products in the "allyl fragment" can be formed. To address this issue we investigated also reactions of an alkyl- and an aryl-substituted π-allyl complex. For its generation, both the corresponding branched (*b*) and linear (*l*) allyl carbonates **4** and **5** were used (Table 2). Both allylic substrates gave the linear allylation product with high preference. With the phenyl-substituted derivatives the linear product was obtained almost exclusively, independent of the ketone used. Major differences were observed in the yields and diastereoselectivities. Here, the aryl-substituted allylic systems **5** were definitely superior in both aspects. High yields and excellent selectivities were obtained, even with the ethyl ketones (**1h** and **1i**) (entries 9–11).

Finally, we also investigated allylations using chiral 1,3-disubstituted allylic substrates to access β-branched substitution products (Scheme 4). In this case a double stereodifferentiation (induced and simple diastereoselectivity) can be expected. We chose 2-(4-phenyl-3-butenyl)carbonates **8** as allylic substrates, since these substrates react with a high degree of regioretention. With chelated glycine ester enolates the reaction proceeds in a highly diastereoselective fashion with perfect retention of configuration in the allyl fragment. While the reaction with (*R*)-**8** (96% *ee*) resulted in the

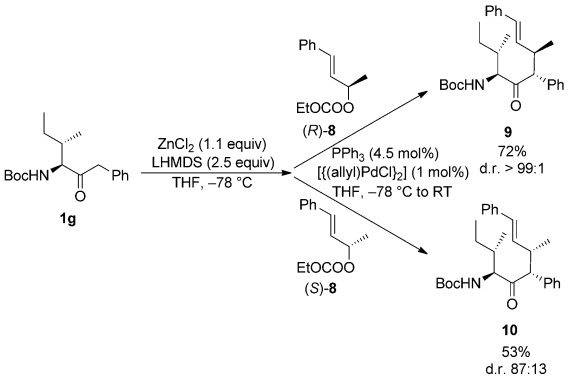
Table 2: Allylic alkylations of α-amino ketones **1** using 1- or 3-substituted allylic substrates.



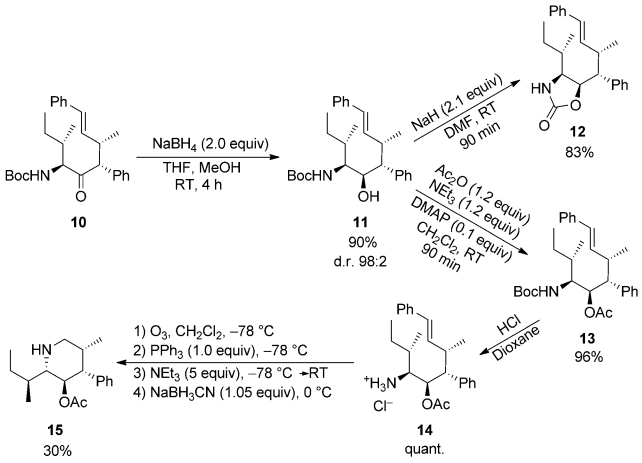
Entry	Ketone	R^1	R^2	4,5	R^3	Prod.	Yield [%][a]	l/v[b]	d.r. (l)[b]
1	**1e**	Bn	Ph	4_l	*n*Pent	**6e**	50	94:6	78:22
2	**1f**	*i*Pr	Ph	4_l	*n*Pent	**6f**	55	90:10	71:29
3	**1g**	*s*Bu	Ph	4_l	*n*Pent	**6g**	46	95:5	78:22
4	**1g**	*s*Bu	Ph	4_v	*n*Pent	**6g**	63	93:7	84:16
5	**1e**	Bn	Ph	5_l	Ph	**7e**	71	>98:2	98:2
6	**1f**	*i*Pr	Ph	5_l	Ph	**7f**	81	>99:1	99:1
7	**1g**	*s*Bu	Ph	5_l	Ph	**7g**	72	95:5	95:5
8	**1g**	*s*Bu	Ph	5_v	Ph	**7g**	86	97:3	94:6
9	**1h**	*i*Pr	Me	5_l	Ph	**7h**	82	>99:1	96:4
10	**1i**	*s*Bu	Me	5_l	Ph	**7i**	83	97:3	98:2
11	**1i**	*s*Bu	Me	5_v	Ph	**7i**	80	98:2	99:1

[a] Yield of isolated product. [b] Determined by HPLC and/or NMR analysis of the crude products.

The configuration of the stereogenic centers could clearly be assigned by ^{1}H NMR spectroscopy. Strong *trans* couplings between 2-H and 3-H ($J = 11$ Hz) as well as between 3-H and 4-H ($J = 9.8$ Hz) were observed, while a much smaller coupling ($J = 1.7$ Hz) between 4-H and 5-H is a clear indication for the *cis* orientation of the two hydrogen atoms. Significant NOEs are also observed between 2-H and 4-H and also between 3-H and the *ortho*-H of the phenyl ring (Figure 1). These results clearly indicate that the configuration at the stereogenic α′-center is almost exclusively controlled by the preferentially formed enolate **D** with an exocyclic double bond.



Scheme 4. Reactions of chiral allyl carbonates.



Scheme 5. Synthesis of piperidine **15.**

formation of a single stereoisomer (matched case), the analogous reaction with the enantiomeric (*S*)-**8** (90% *ee*) proceeded with less selectivity (mismatched case) and also in lower yield. X-ray structure analysis of **9** allowed the determination of its absolute configuration. Unfortunately, we were not able to crystallize the stereoisomeric product **10** of the mismatched reaction. In this case the interesting question arises, which chiral component has the stronger stereocontrolling effect: the ketone or the allylic substrate?

To address this issue, we converted **10** into the highly substituted piperidine derivative **15** (Scheme 5) to determine the configuration of the stereogenic centers by NMR spectroscopy. In the first step the ketone group was reduced with high stereoselectivity (**11**) and the configuration of the new formed stereogenic center could be determined after cyclization to the corresponding oxazolidinone **12**. The minor diastereomers were removed at the stage of the protected amino alcohol **11** by flash chromatography. Subsequently the OH functionality was acetylated (**13**) and the Boc protecting group was removed. Ozonolysis and successive reductive amination gave rise to **15** in good yield.

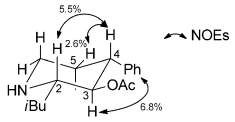


Figure 1. Determination of configuration of piperidine **15.**

In conclusion, we could show that α-amino ketones are excellent nucleophiles for palladium-catalyzed allylic alkylations. After deprotonation of the amide functionality the *Z*-enolate **D** with an exocyclic double bond is formed almost exclusively and is allylated in a highly diastereoselective fashion. Both chiral and achiral allylic substrates can be used, and the stereochemical outcome is controlled by the chiral amino ketone. The substituted amino ketones formed can be reduced stereoselectively and converted, for example, into substituted piperidines.

Keywords: allylation · asymmetric synthesis · ketones · palladium · piperidines

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