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N-Boc-α-Tosylsarcosine Ethyl Ester: An α-Amido Sulfone for the Regio- and Stereoselective Synthesis of Protected γ,δ-Unsaturated *N*-Methyl-α-Amino Acids by Palladium-catalyzed Nucleophilic Substitution

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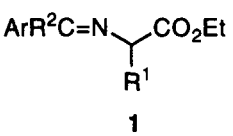
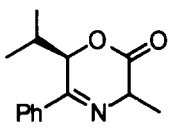
Abstract: *N*-Boc-α-tosylsarcosine ethyl ester (3) reacts under neutral conditions either with allylic carbonates or with vinyloxirane in the presence of a catalytic amount of $Pd(PPh_3)_4$ and dppe (5 mol%) to give regio- and stereoselectively the corresponding allylated products **5** and **6**, respectively. Reductive desulfonylation of these compounds with Mg-MeOH affords the corresponding protected γ,δ-unsaturated *N*-methyl-α-amino acids **7** and **8**. © 1997 Elsevier Science Ltd.

γ,δ-Unsaturated *N*-methyl-α-amino acids are important nonproteinogenic amino acids because of their biological activity[1] showing antibiotic properties and as intermediates for the synthesis of proline derivatives[2] such as bulgecinine,[3] γ- and δ-lactam constrained peptide isosteres[4] and pyrrolinone-based peptidomimetics.[5] They are generally prepared by: (a) electrophilic allylation reactions of glycine equivalents[6] and (b) Claisen rearrangement of glycine allyl esters.[7] Palladium catalyzed allylation of glycine or alanine derivatives is a good and direct method to incorporate allylic chains under neutral conditions acting allylic carbonates[8] and diene monoepoxides[9] as electrophilic reagents. This methodology requires the use of soft nucleophiles such as acyclic or cyclic imino esters **1**[8a,9] or **2**,[8b] respectively. However, in all these cases mixture of regioisomeric products are obtained with unsymmetrical substituted allylic electrophiles. We described here that the α-amido sulfone **3**[10] with sarcosine structure is a good nucleophile for the synthesis of γ,δ-unsaturated *N*-methyl-α-amino acids by means of palladium catalyzed allylation reactions[11] followed by reductive desulfonylation.



1

R^1 = H, Me
R^2 = H, Ar



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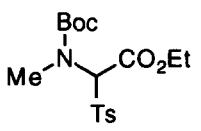
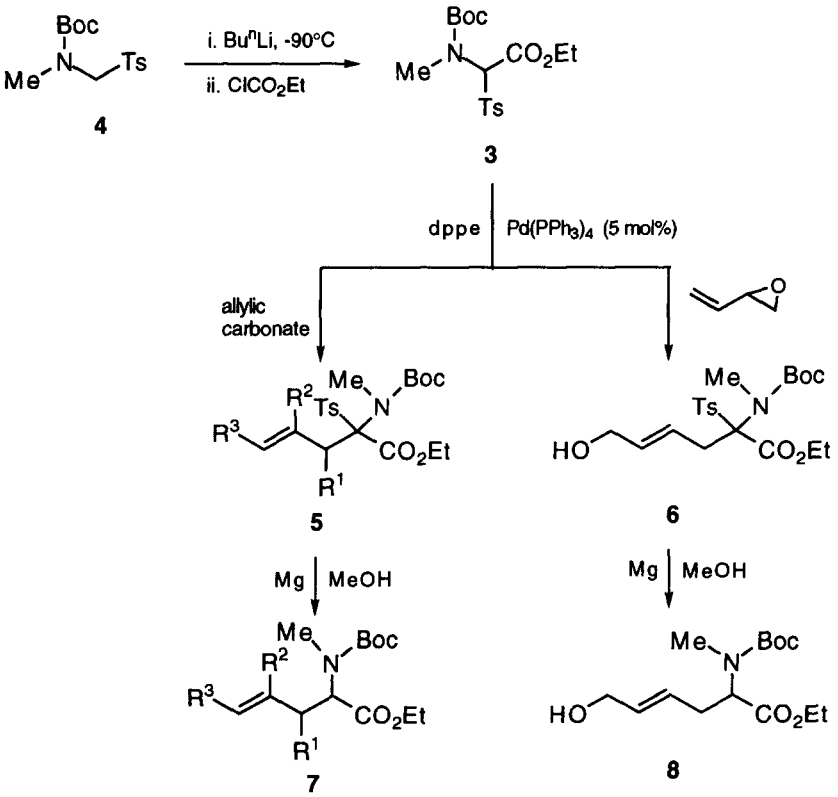


3

[Ts = *p*-$MeC_6H_4SO_2$]

When reagent **3**, prepared in 73% yield by lithiation of the amido sulfone **4** followed by reaction with ethyl chloroformate,[10] was allowed to react with different allylic carbonates in the presence of catalytic amounts of tetrakis(triphenylphoshine)palladium(0) and 1,2-bis(diphenylphosphine)ethane (dppe) (5 mol%) in THF at

room temperature for 1 d, the corresponding allylated products **5** were obtained (Scheme 1 and Table 1). The reaction was regioselective with unsymmetrical substituted carbonates affording exclusively products derived from the attack at the less substituted position of the π-allylpalladium complex, for instance in the cases of carbonates derived from crotyl, 1-methylallyl, cinnamyl and 1-vinylallyl alcohol (Table 1, entries 2, 3, 5 and 6). This high regiochemical control, not observed with imino esters **1** and **2**,[8] can be explained by the greater steric demand of this nucleophile. The process was completely steroselective giving only *E*-diastereomers **5b,d** and **e**. In the case of the reaction of compound **3** with vinyloxirane, under the same reaction conditions, the γ,δ-unsaturated 6-hydroxy substituted derivative **6** was regio and stereoselectively obtained (Scheme 1 and Table 1, entry 7).

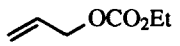
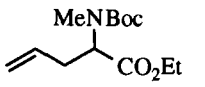
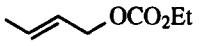
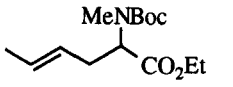
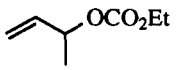
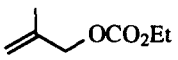
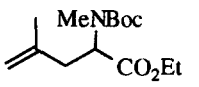
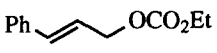
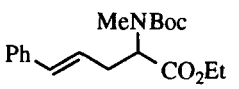
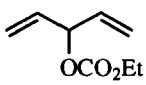
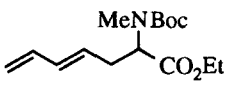
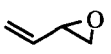


Scheme 1.

Compounds **5** and **6** were very unstable and after filtration through florisil were submitted to subsequent desulfonylation by treatment with magnesium in dry methanol at room temperature for 1 d to provide the γ,δ-unsaturated *N*-Boc-*N*-methyl-α-amino esters **7** and **8**, respectively (Scheme 1 and Table 1).

In summary, *N*-Boc-α-tosylsarcosine ethyl ester (**3**) is an appropriate reagent for the palladium catalyzed allylation reactions under neutral conditions allowing the synthesis of protected γ,δ-unsaturated *N*-methyl-α-amino acids in a regio and stereoselective manner.

Table 1. Synthesis of Protected γ,δ-Unsaturated *N*-Methyl-α-Amino Acids

		α-Amido sulfone					Protected amino acid[a]			
Entry	Electrophile	No.	R^1	R^2	R^3	Yield (%)[b,c]	No.	Structure	Yield (%)[c,d]	R_f[e]
1		**5a**	H	H	H	40	**7a**		26	0.87
2		**5b**	H	H	Me	45	**7b**		41	0.75
3		**5b**	H	H	Me	69	**7b**		69	
4		**5c**	H	Me	H	69	**7c**		42	0.83
5		**5d**	H	H	Ph	72	**7d**		52	0.86
6		**5e**	H	H	CH_2=CH	40	**7e**		41	0.80
7		**6**	-	-	-	72	**8**	-	20	0.52

[a] All products were pure (TLC, 300MHz ^{1}H NMR) and gave satisfactory spectral data (IR, ^{1}H and ^{13}C NMR, and mass spectra). [b] Isolated yield after filtration through florisil. [c] Based on compound **3**. [d] Isolated yield after flash chromatography (silica gel). [e] Hexane/EtOAc: 1/1.

Synthesis of Protected Amino Acids 7 and 8. Typical Procedure. To a solution of $(PPh_3)_4Pd$ (30 mg, 0.025 mmol) in dry THF (0.5 ml) was successively added a solution of reagent **3** (186 mg, 0.5 mmol),[10b] the corresponding electrophile (0.5 mmol) in THF (1 ml) and after 5 min stirring, dppe (10 mg, 0.025 mmol). The reaction mixture was stirred for 1 d at rt and then filtered off through a path of florisil with hexane as eluent. The solution was concentrated (15 Torr) and the residue was treated with dry MeOH (6 ml), Mg powder (50 mesh, 73 mg, 3 mmol) and a few crystals of $HgCl_2$. The resulting suspension was stirred at rt for 1 d, filtered off through celite and the filtrate was poured in H_2O-EtOAc giving after extractive work-up and purification by flash chromatography products **7** and **8**.

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