Application of the Molybdenum-Catalysed Hydrostannation Towards a Flexible Synthesis of Substituted Unsaturated Amino Acids

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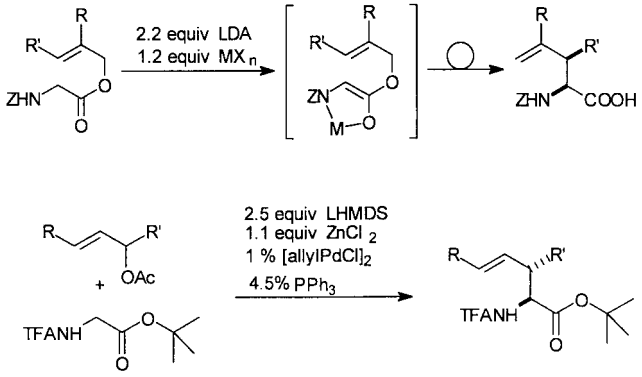
Abstract: Application of the molybdenum catalysed hydrostannation towards propargylic esters of amino acids allows for the regioselective synthesis of α-stannylated allylic esters, suitable substrates for chelate Claisen rearrangements. α-Stannylated allylic carbonates can be subjected to palladium catalysed allylic alkylations using chelated amino acid ester enolates as nucleophiles. The stannylated amino acids obtained can be further modified via cross-coupling reactions.

Key words: allylic alkylation, Claisen rearrangement, cross coupling, hydrostannation, molybdenum

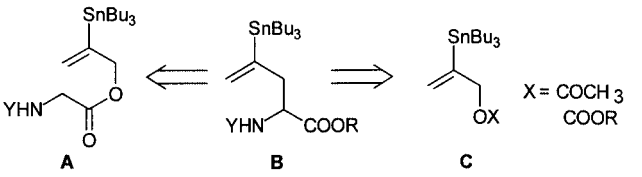
γ, δ-Unsaturated amino acids are of great interest, not only as naturally occurring non proteinogenic amino acids such as the isoleucine antagonist cyclopentenylglycine[1] and the antibiotic furanomycine,[2] but also as important intermediates for the synthesis of complex amino acids.[3] Therefore, various approaches to the synthesis of this class of amino acids have been described.[4]

Recently, we have developed a new variation of the ester enolate Claisen rearrangement, proceeding via chelated allylic ester enolates.[5] Due to the fixed enolate geometry, as a result of chelate formation, the rearrangement proceeds with a high degree of *syn*-selectivity, independent of the substitution pattern and the protecting group used.[6] The corresponding *anti*-configured products can be obtained by palladium catalysed allylic alkylations, also in a highly stereoselective fashion (Scheme 1).[7] This is especially interesting with respect to the fact that unsymmetrical nucleophiles are used,[8] and only a few applications of non stabilised ester enolates as nucleophiles in palladium catalysed allylic alkylations are described in the literature so far.[9]

The disadvantage of this protocol results from the fact that for each side chain introduced the corresponding allylic alcohol or ester has to be firstly prepared. For a more flexible approach, a modified allylic ester is desirable, giving rise to an amino acid which is suitable for further modifications. As shown by Crisp et al.,[10] the Stille coupling methodology is especially suitable for this purpose, since these reactions take place under rather mild conditions and are tolerant of a wide variety of functionalities.[11] The required amino acids with a vinylstannane sidechain **B** should be accessible from the corresponding α-stannylated ester **A** via Claisen rearrangement or from **C** via palladium catalysed allylic alkylation (Scheme 2).



Scheme 1

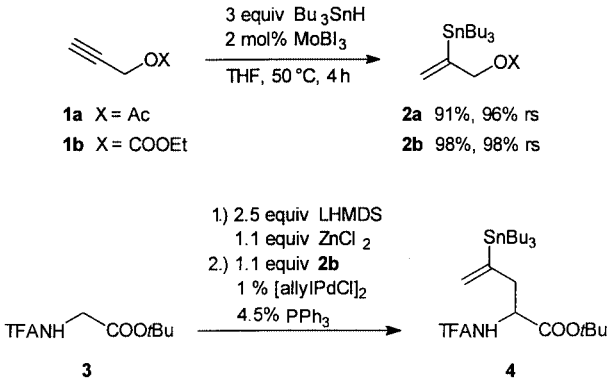


Scheme 2

Stannylated allylic alcohols can easily be obtained via hydrostannation of propargylic alcohols, although the regioselectivity of this process is a significant problem. Hydrostannation of propargylic alcohol under radical conditions preferentially results in the formation of the undesired β-substituted products as a *E/Z* isomeric mixture.[12] On the other hand, the catalytic version using Pd(0)complexes provides the α− and β−(*Z*) product as a nearly 1:1 mixture.[13] Unfortunately, the palladium catalysed reaction cannot be directly applied to propargylic esters, which decompose under these reaction conditions. For these reasons, we developed a new catalyst for regioselective hydrostannations. $Mo(CO)_3(CN^tBu)_3$ ($MoBI_3$), easily prepared by ligand exchange from $Mo(CO)_6$,[14] shows high reactivity and selectivity for various types of alkynes.[15]

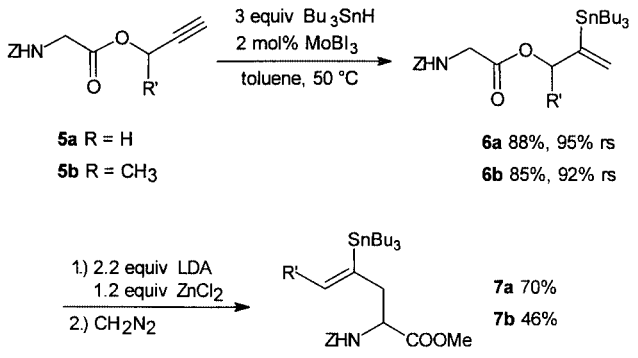
Excellent yields and α-selectivities[16] were obtained in the hydrostannation of propargylic acetate **1a** and carbonate **1b** (Scheme 3). The resulting stannylated derivatives **2** are highly interesting building blocks, bearing two reactive centers. The vinylstannane subunit should allow coupling with electrophiles under Stille conditions, and the allyl ester moiety should be suitable for Pd-catalysed allylic alkylations, allowing nucleophilic substitutions at the ter-

minal allylic position. Based on the good results obtained with chelated enolates, we investigated the palladium catalysed allylation of glycine ester **3** in the presence of zinc chloride. The reaction proceeded very cleanly, under very mild conditions, providing the desired stannylated amino acid derivative **4** as substrate for further modifications at the vinylstannane moiety.



Scheme 3

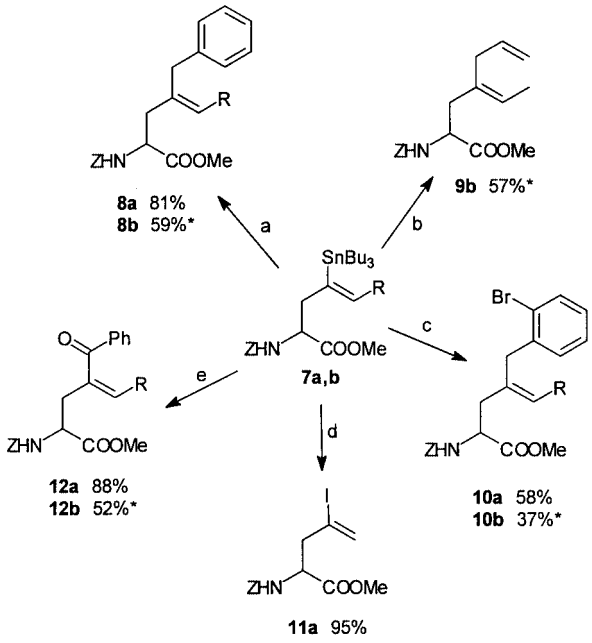
Comparable results were also obtained in the hydrostannation of glycine propargylic esters **5**, giving direct access to **6,** ideal substrates for subsequent Claisen rearrangements. These rearrangements proceeded comparable to non-stannylated allylic esters in a very clean fashion, and the amino acids obtained were directly converted into the corresponding methyl esters **7**.



Scheme 4

The moderate isolated yield obtained in the allylation reaction and the rearrangement, especially in the rearrangement of **6b,** resulted from a partially protodestannylation during workup (flash chromatography on silica). But in general, the stannylated esters obtained can be used directly without further purification for the subsequent cross coupling reactions (Scheme 5). The yields marked with an asterisk (*) were obtained by this direct conversion, and are overall yields for two steps (Claisen rearrangement and cross coupling).

Very good results were obtained in reactions using benzylbromide as an electrophile (**8a, b**),[9] especially in the presence of triphenylarsine as a ligand.[17] A comparable result was also obtained with allylbromide under the same reaction conditions (**9**). Allylic and benzylic halides are obviously more reactive in comparison to aryl halides. Therefore *o*-bromobenzylbromide reacted exclusively at the benzylic position, and no reaction at the aromatic nucleus was observed. A nearly quantitative yield was obtained in the reaction with iodine, and the vinyl iodide **11a** should be a suitable electrophile for further cross-coupling reactions. Couplings with acyl chlorides such as benzoyl chloride provided amino acids **12a, b** in a very fast reaction. These reactions can be carried out in acetone or even better in acetonitrile without additional ligands. Probably these polar solvents can coordinate to the palladium complexes formed during the reaction, keeping them in solution.[18] The amino acids obtained in these acylation reactions are interesting substrates for further modifications, e. g. via Michael additions.



a, 3 equiv benzylbromide, 2.5 mol% $[allylPdCl]_2$, 20 mol% $AsPh_3$, THF, 60 °C, 5 h; b, 3 equiv allylbromide, 2.5 mol% $[allylPdCl]_2$, 20 mol% $AsPh_3$, toluene, 50 °C, 4 h; c, 3 equiv bromobenzyl bromide, 2.5 mol% $[allylPdCl]_2$, 20 mol% $AsPh_3$, THF, 50 °C, 5 h; d, 1.2 equiv I_2, $CHCl_3$, r.t., 30 min; e, 1.05 equiv benzoyl chloride, 2.5 mol% $[allylPdCl]_2$, MeCN, 50 °C, 10 min.

Scheme 5

Molybdenum Catalysed Hydrostannations; General Procedure

The corresponding alkyne (1 mmol) was dissolved in toluene (1 mL) under Ar, before $MoBI_3$ (2 mol%) and hydroquinone (to suppress radical hydrostannations) were added, followed by Bu_3SnH (2.5 mmol). The reaction mixture was warmed to 50 °C until all alkyne was consumed (2–5 h). After cooling to r.t., the whole reaction mixture was subjected to flash chromatography on silica. Excess of tin hydride was removed using hexanes as eluent, the

stannylated products were obtained by switching to a slightly more polar solvent (hexanes/EtOAc >90:<10). It is recommended to add 1% Et_3N to the eluent to suppress protodestannylation during chromatography.

Palladium Catalysed Allylic Alkylation of Chelated Enolates; General Procedure

The protected amino acid ester (1 mmol) was dissolved in THF (4 mL). At −78 °C a freshly prepared solution of LHMDS (2.5 mmol) in THF (2 mL) was added. After 30 min at −78 °C, a solution of $ZnCl_2$ (1.1 mmol) in THF (2 mL) was added with stirring. 30 min later a solution of π-allylpalladium chloride dimer (1 mol%), PPh_3 (4.5 mol%) and the corresponding stannylated allyl ester (1.5 mmol) in THF (2 mL) was added. The solution was stirred overnight while being warmed up to r.t. Subsequently, the solution was diluted with Et_2O and hydrolysed with 1 N $KHSO_4$ solution (10 mL). The aqueous phase was extracted twice with Et_2O (15 mL each) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvent in vacuo, the crude product was purified by flash chromatography (hexanes/EtOAc). It is recommended to add 1% Et_3N to the eluent to suppress protodestannylation during chromatography.

Claisen Rearrangement of Chelated Enolates; General Procedure

A freshly prepared LDA solution (2.5 mmol) in THF (5 mL) was added to a stirred mixture of the stannylated allylic ester (1 mmol) and $ZnCl_2$ (1.1 mmol) in dry THF (5 mL) at −78 °C. The mixture was allowed to warm up to r.t. overnight. The resulting clear solution was diluted with Et_2O (20 mL) and hydrolyzed with 1 N $KHSO_4$ solution (20 mL). After separation of the aqueous layer, the crude *n*-protected amino acids were directly converted into the methyl ester by addition of a solution of diazomethane in Et_2O. After evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc/hexanes). It is recommended to add 1% Et_3N to the eluent to suppress protodestannylation during chromatography.

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