Ruthenium-catalyzed selective N,N-diallylation- and N,N,O-triallylation of free amino acids[†]

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Selective N,N-diallylation and N,N,O-triallylation of free amino acids in the presence of catalytic amounts of RuCp*(MeCN)₃PF₆ is reported. The crucial influence of the solvent makes these allylation reactions selectively possible.

Amino acids belong to a very attractive and useful class of widely available natural products. They have been involved in a variety of chemical transformations, especially for the synthesis of artificial amino acids and short peptides with specific biological activities, and polypeptides in life science. In most cases, these bifunctional substrates have to be protected, either at the amino or at the carboxylic end to ensure selective transformations. Even though N-mono- and N,N-diallylated amino acids themselves have revealed photosynthesis accelerator properties and have been used as hydrogen bond surrogates for stabilization of helical conformations,¹ they have been mostly involved in chemical modifications from their ester derivatives. From N,N-diallyl- α amino esters, the most common transformation consists in the ring closing metathesis reaction, which leads to functional pyrrolines and pyrroles.² N,N-Diallyl- α -amino acid derivatives have also potential in transformations where only one N-allyl group is involved such as the Lewis acid-mediated sigmatropic migration of an allyl group to the α -carbon of amino amides,³ and the cyclization of nitrilimines into bicyclic heterocycles.⁴

The *O*-protection of the carboxylic group as an allylic ester offers an easily removable protecting group and for this reason has been used in peptide and glycopeptide syntheses.⁵

Most syntheses of *N*-allylated amino acid derivatives start from *O*-alkyl esters. They usually involve allylic bromides and take place in the presence of a base such as a carbonate,⁶ a hydroxide⁷ or a tertiary amine.⁸ The strategy based on the reaction of allylamine with bromoacetate has been exemplified in the case of glycine derivatives.⁹ Some scarce examples of the palladium-catalyzed nucleophilic substitution of allylic substrates by the amino group of amino esters have also been reported.¹⁰

For allylation of the carboxylic end, a method based on the use of allyl bromide under basic conditions has been used but it requires the prior protection of the amino group to avoid simultaneous N-allylation.¹¹ The most common procedure consists in the direct esterification in refluxing benzene under acidic conditions,

with concomitant protection of the amino group as an ammonium salt, and water removal using the Dean Stark technique.^{12,13} Recent works have revealed that Cp*Ru-containing catalyst precursors are very efficient for allylic activation and nucleophilic substitution by a variety of C, N, and O-nucleophiles.¹⁴ However, very few examples of substitution by multifunctional nucleophiles have been reported.

We report here a ruthenium-catalyzed allylic substitution reaction, which makes possible selective N,N-diallylation and N,N,Otriallylation directly from free amino acids and allyl chloride or cinnamyl chloride at room temperature without previous N- and O-protection (Scheme 1).



Scheme 1 Di- and tri-allylation of α -amino acids.

In a previous report, we highlighted the crucial role of N,O-carboxylate ligands such as quinaldic acid in the allylation of phenol with 1,3-diene dicarbonates,¹⁵ whereas RuCp*(MeCN)₃PF₆ I alone was found to be inactive with these substrates. We have also observed that in the same reaction the presence of a catalytic amount of L-alanine allowed the diastereo- and regioselective formation of the expected allylated compound suggesting that the amino acid could act as ligand (Scheme 2). Based on this result, we investigated the fate of the amino acids and their possible direct allylation.

EtO₂CO^{III}
$$\xrightarrow{PhOH, L-Alaniae (5 m0\%)}{Cat. I (5 m0\%), Cat. I (5 m0\%), PhOIII} \xrightarrow{PoPh e.e. = 20 \%}{PoPh e.e. = 20 \%}$$

Scheme 2 Influence of catalytic amount of amino acid in allylation.

From L-phenylglycine **1a** as starting material, allylation studies were attempted in the presence of allyl chloride **2a** and catalytic amounts of RuCp*(MeCN)₃PF₆,^{14c,14d,16} **I** at room temperature (Scheme 3). We found that the treatment of L-phenylglycine **1a** with two equivalents of allyl chloride **2a** in the presence of one equivalent of potassium carbonate avoiding the formation of zwitterionic ammonium-carboxylate species, led to the complete conversion within 16 hours reaction time using methanol as solvent. Filtration and acidic workup followed by ¹H-NMR analysis revealed the chemoselective formation of *N*,*N*-diallyl

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phenylglycine 3a in 75% isolated yield (Scheme 3). A blank experiment carried out in the absence of ruthenium precatalyst I led to the formation of a mixture of N-mono- and N,N-diallylated products with only 10% conversion. With I as catalyst, other polar solvents such as acetonitrile, water and acetone also led to the formation of a mixture of compounds with less than 60% conversion of the starting amino acid 1a. It is noteworthy that the use of three equivalents of allyl chloride using methanol as solvent afford exclusively N,N-diallylated compound 3a. Interestingly, during the solvent screening we observed that the use of less polar solvent such as dichloromethane or THF in the presence of potassium carbonate allowed the conversion of the starting material into the N,N,O-triallylated compound 4a in 50% yield. Further reaction optimization revealed that three equivalents of caesium carbonate were suitable for a complete conversion of 1a affording 4a in 63% yield after purification (Table 2). Chiral HPLC analysis of compounds 3a, 3b, 4a and 4b demonstrated that no racemization occurred at the stereogenic center.¹⁷



Scheme 3 Di- and tri-allylation of α -amino acids.

With these protocols in hands, the substrate scope for the chemoselective formation of N,N-diallylated 3 and triallylated compounds 4 was investigated. First the generality of the N,Ndiallylation was studied; the results are reported in Table 1.‡ Reaction of amino acids **1a-e** with 2.2 equivalents of allyl chloride 2a led to complete conversion of the amino acid and formation of the N,N-diallylated amino acids derivatives 3a-e in moderate to excellent yields (entries 1-5). Whereas, good yields were obtained with glycine 1e (entry 5), and amino acids 1a and 1b featuring an aromatic side chain (entries 1-2), lower isolated yields were obtained with amino acids 1c-d containing an aliphatic side chain suggesting that a partial solubilization in water of compounds 3c**d** occurred during the acidic workup (entries 3-5). The scope was further tested in the reaction with unsymmetrical allylic substrates. Longer reaction times were required for the transformation of the amino acids 1a, 1c and 1d and, and only the linear (E,E)-N,Ndiallylated compounds **3f-h** were obtained in high yields due to their lower solubility in the acidic water phase (entries 6-8). Under our optimized conditions for the formation of N, N, O-triallylated compound 4a, we evaluated the scope of the reaction with the amino acids 1a-i. The results are reported in Table 2.‡ Reactions were conducted at room temperature in dichloromethane in the presence of allylic substrate 2a and 3 equivalents of caesium carbonate. In all cases, triallylated amino acids products 4a-i were

	H ₂ N ^{R¹} CO ₂ H ⁺ CI 1a-e	2a-b	Ru cat. I (5 mol%) K ₂ CO ₃ (1.2 eq.) MeOH r t	$R^1 \rightarrow OH$ $R^1 \rightarrow OH$ 3a-h R^2	R ²
entry	\mathbf{R}^{1}	\mathbb{R}^2	product		yield ^e
1	Ph	Н	HO ₂ C N	3a	75%
2	Bn	Н		3b	88%
3	<i>i</i> -Pr	Н	HO ₂ C	3c	40%
4	<i>i</i> -Bu	Н	HO ₂ C	3d	60%
5	Н	Н	HO2C	3e	92%
6*	Ph	Ph	HO ₂ C N Ph	3f	81%
7 ^{<i>b</i>}	i-Pr	Ph	HO ₂ C Ph	3g	67%
8 ^b	<i>i</i> -Bu	Ph	HO ₂ C ^{Ph}	3h	79%

^{*a*} All reactions were carried out in 4 ml MeOH at rt for 16 h under an inert atmosphere with $2/1/[\text{Ru}]/\text{K}_2\text{CO}_3$ in a 2.2/1/0.05/1.2 molar ratio. ^{*b*} Reaction time 48 h. ^{*c*} Isolated yield.

obtained in moderate to good yield after purification over silica gel (entries 1-5). Under similar conditions but using four equivalents of allyl chloride **2a**, the reaction of tyrosine containing a third nucleophilic centre afforded the tetraallylated product **4h** in 66% yield (entry 7). In contrast, amino acids such as tryptophan **1g** and serine **1i** containing a less reactive third nucleophilic centre gave only triallylated compounds **4g** and **4i** in 76 and 70% yield, respectively (entries 6 and 8). We checked that when the triallylated compound **4b** was treated at room temperature in the presence of 5 mol% of catalyst **I** and 1.2 equivalent of K₂CO₃ in MeOH, the selective deprotection of the ester group took place and the acid **3b** was recovered. This is in line with previous results obtained by Kitamura *et al* concerning the deprotection of allylic carbamates into amines¹⁸ and allylic ethers into alcohols^{19a} with ruthenium catalysts.

Regarding the mechanism of the reaction, a plausible explanation for the ruthenium-catalyzed double and triple allylation of amino acid 1 is depicted in Scheme 4. It might be suggested





^{*a*} All reactions were carried out in 6 ml of DCM at rt for 16 h under an inert atmosphere with $2a/1/[Ru]/Cs_2CO_3$ in a 3.3/1/0.05/3.0 molar ratio. ^{*b*} Isolated yield



Scheme 4 Proposed active species.

that the amino acid can act as ligand in this reaction to form a ruthenium intermediate $II.^{20}$ After deprotonation, this latter may undergo oxidative addition of the allylic substrate 2 to give the *N*,*O*-aminocarboxylate η^3 -allyl ruthenium(IV) complex III as active species.¹⁹

In conclusion, we have shown that the RuCp*(CH₃CN)₃PF₆ complex **I**, is an efficient precatalyst for the selective direct synthesis of allylated amino acid derivatives *via* solvent dependent allylation reactions. The reaction is chemoselective and takes place at room temperature without racemization of the amino acid. This reactivity suggests the ability of an amino acid to coordinate to the

ruthenium centre affording (N,O)-aminocarboxylate ruthenium intermediate as active catalytic species.

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Notes and references

‡ Typical procedure for the preparation of diallylated compounds 3: Complex $RuCp*(CH_3CN)_3PF_6$ I (5.0 × 10⁻³ mmol, 5 mol%) was added to a mixture of L-amino acid 1 (0.1 mmol) in MeOH (4 mL) under inert atmosphere and the resulting solution was stirred at room temperature for two minutes. Then, potassium carbonate (0.12 mmol) and allyl chloride 2a (0.22 mmol) were successively added and the resulting mixture was stirred at room temperature for 16 hours. The crude mixture obtained after filtration and concentration in vacuo was acidified with 1 N HCl to pH 2 and then extracted with EtOAc ($5 \times 3mL$) to afford compound 3 after drying over Na₂SO₄ and evaporation. Typical procedure for the preparation of triallylated compounds 4: Complex RuCp*(CH₃CN)₃PF₆ I $(5.0 \times 10^{-3} \text{ mmol}, 5 \text{ mol}\%)$ was added to a mixture of L-amino acid 1 (0.1 mmol) in CH₂Cl₂ (6 mL) under inert atmosphere and the resulting solution was stirred at room temperature for two minutes. Then caesium carbonate (0.3 mmol) and allyl chloride 2a (0.33 mmol) were successively added and the resulting mixture was stirred at room temperature for 16 hours. The crude mixture obtained after filtration on a short pad of silica using dichloromethane as eluent and concentration in vacuo was purified by flash chromatography (silica gel) to afford 4.

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