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)$_3$PF$_6$ is reported. The crucial influence of the solvent makes these allylation reactions selectively possible.

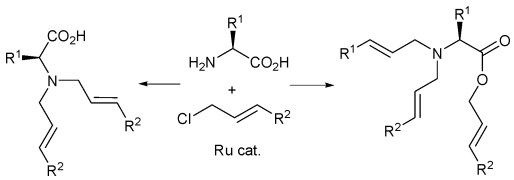
Amino acids belong to a very attractive and useful class of widely available natural products. They have been involved in a variety of chemical transformations, especially for the synthesis of artificial amino acids and short peptides with specific biological activities, and polypeptides in life science. 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 hydroxide[7] 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]

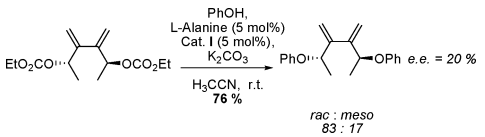
For allylation of the carboxylic end, a method based on the use of allyl bromide under basic conditions has been used but it requires the prior protection of the amino group to avoid simultaneous *N*-allylation.[11] The most common procedure consists in the direct esterification in refluxing benzene 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*,*O*-triallylation 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)$_3$PF$_6$ **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.



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)$_3$PF$_6$,[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 ^{1}H-NMR analysis revealed the chemoselective formation of *N*,*N*-diallyl

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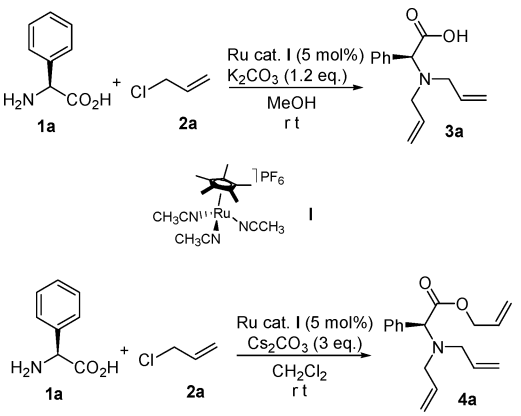
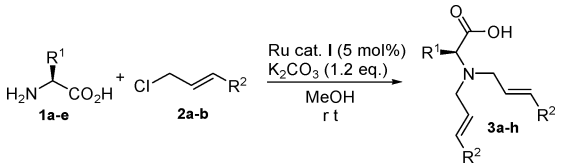
phenylglycine **3a** in 75% isolated yield (Scheme 3). A blank experiment carried out in the absence of ruthenium precatalyst **I** led to the formation of a mixture of *N*-mono- and *N*,*N*-diallylated products with only 10% conversion. With **I** as catalyst, other polar solvents such as acetonitrile, 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*,*N*-diallylation 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*,*N*-diallylated 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

Table 1 *N*,*N*-Diallylation of α-amino acids **1**[a]



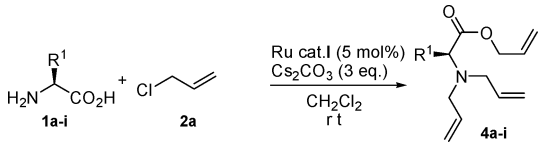
entry	R^1	R^2	product		yield[c]
1	Ph	H		**3a**	75%
2	Bn	H		**3b**	88%
3	*i*-Pr	H		**3c**	40%
4	*i*-Bu	H		**3d**	60%
5	H	H		**3e**	92%
6[b]	Ph	Ph		**3f**	81%
7[b]	i-Pr	Ph		**3g**	67%
8[b]	*i*-Bu	Ph		**3h**	79%

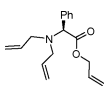
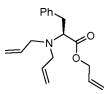
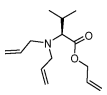
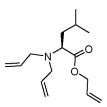
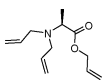
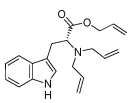
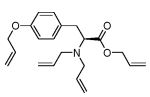
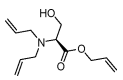
[a] All reactions were carried out in 4 ml MeOH at rt for 16 h under an inert atmosphere with **2**/**1**/[Ru]/K_2CO_3 in a 2.2/1/0.05/1.2 molar ratio. [b] Reaction time 48 h. [c] Isolated yield.

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 K_2CO_3 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 amines[18] and allylic ethers into alcohols[19a] with ruthenium catalysts.

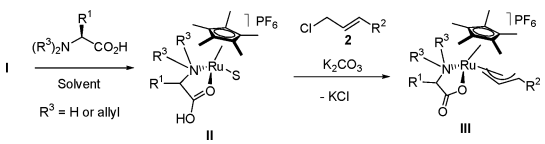
Regarding the mechanism of the reaction, a plausible explanation for the ruthenium-catalyzed double and triple allylation of amino acid **1** is depicted in Scheme 4. It might be suggested

Table 2 *N*,*N*,*O*-Triallylation of α-amino acids **1** with allyl chloride **2a**[a]



entry	R^1	product		yield[b]
1	Ph		**4a**	63%
2	Bn		**4b**	78%
3	*i*-Pr		**4c**	64%
4	*i*-Bu		**4d**	77%
5	Me		**4f**	58%
6	C_9H_8N		**4g**	76%
7	*p*-CH_2PhOH		**4h**	66%
8	CH_2OH		**4i**	70%

[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*$(CH_3CN)_3PF_6$ 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 × 3mL) to afford compound **3** after drying over Na_2SO_4 and evaporation. **Typical procedure for the preparation of triallylated compounds 4**: 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 CH_2Cl_2 (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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