

Chemoselective removal of allylic protecting groups using water-soluble $\text{Pd}(\text{OAc})_2/\text{TPPTS}$ catalyst

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Abstract

The removal of allylic protecting groups promoted by the catalytic system $\text{Pd}(\text{OAc})_2/\text{TPPTS}$ has been achieved on bifunctional substrates with complete chemoselectivity and high efficiency, in aqueous media. By lowering the amount of palladium catalyst, substituted allylic carboxylates remained unaffected while allylcarbamates, in the same molecule, were quantitatively removed. When using a biphasic $\text{C}_3\text{H}_7\text{CN}-\text{H}_2\text{O}$ solvent, the water-soluble catalyst could also differentiate allylcarbonates from dimethylallylcarbamates on diprotected amino alcohols. All these reactions were carried out under mild and neutral conditions which are compatible with a large range of molecules including β -lactams.

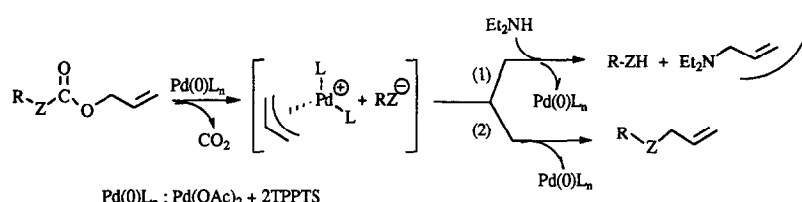
Keywords: Allylic protecting groups; Water-soluble palladium catalyst; Palladium-catalyzed deprotection; Chemoselectivity

1. Introduction

During the last twenty years, considerable advancements have been made in the field of catalysis since the development of new and efficient transition metal catalysts have become a considerable challenge for both organic chemists and industrial groups. Nevertheless, a considerable drawback of homogeneous metal catalysis lies on the separation of the reaction product from the active catalyst, which often requires costly procedures. A solution to this problem consists of anchoring the catalyst on an organic or inorganic polymer [1] insoluble in the

reaction medium. Another elegant alternative consists of using water soluble ligands which once complexed to the metal make the catalyst poorly soluble in organic media. These systems combine the advantages of homogenous and heterogeneous catalysis: easy separation of the product from the catalyst, high reactivity and high selectivity. At present, sulfonated phosphines, e.g., TPPMS (= triphenylphosphinomonosulfonate sodium salt) [2] and TPPTS (= triphenylphosphinotrissulfonate sodium salt) [3], constitute the most widely used class of water soluble ligands. They found various applications in the field of hydrogenation [4], hydroformylation [5], reduction of saturated and unsaturated

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Scheme 1.

aldehydes [6] as well as isoprenylation [7] and coupling reactions [8]¹. In our continuing interest in the area of palladium promoted reactions [10], we recently developed a water soluble catalyst prepared from Pd(OAc)_2 and the water soluble ligand TPPTS, which was proved to generate in situ a zerovalent palladium intermediate active in catalysis under aqueous conditions [11].

It was first used for various cross-coupling reactions [12]. This system also proved to be very efficient for the smooth and selective removal of allyl and allyloxycarbonyl (Alloc) groups in the presence of diethylamine as allyl scavenger, in aqueous media [13] (Scheme 1). In particular, secondary amines were deprotected without any competitive *N*-allylation reaction using biphasic conditions [13].

Moreover, as most synthetic sequences often require orthogonal systems where each protecting group can be independently removed in any order, especially in the field of carbohydrate [14], oligonucleotide [15] and peptide [16] chemistry, it was of great interest to extend our water soluble system to chemoselective depro-

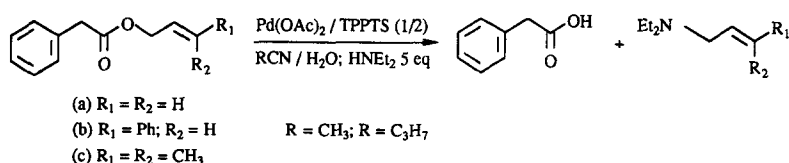
tections. We indeed developed the first efficient palladium promoted conditions for the selective removal of allylic protecting groups [17], and in this paper we wish to present our complete results in this area.

2. Results and discussion

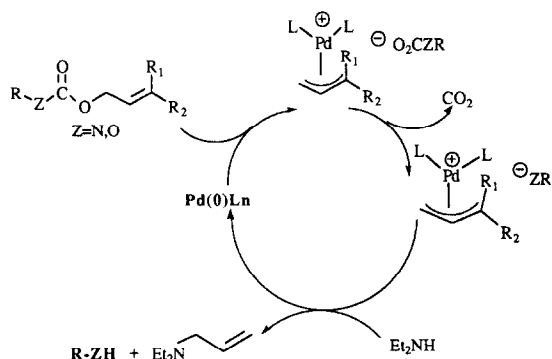
In order to determine the different factors that could allow chemoselective cleavage of allylic moiety using the water soluble Pd/TPPTS catalyst, we first compared the rate of deprotection of several phenylacetic acid allyl esters under homogeneous and biphasic conditions (Scheme 2).

In fact, the usually accepted mechanism for palladium promoted removal of allyl carbonates and carbamates involves oxidative addition of the palladium zerovalent species on the allyl group in the first step, leading to the formation of a π -allyl palladium complex which is trapped by a nucleophile to give the deprotected product and regeneration of the palladium(0) intermediate. We anticipated that substitution on the terminal position of the allyl group could disfavour the oxidative addition step by steric interactions between the substituents and the palladium (Scheme 3). We actually found that in

¹ For coupling reactions using ligandless catalytic systems see Ref. [9].



Scheme 2.

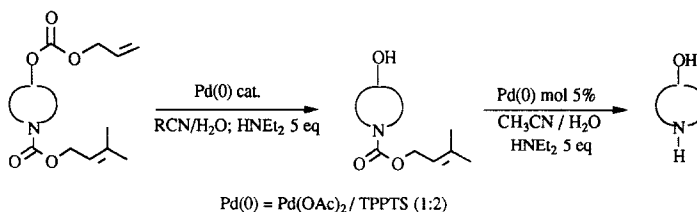


Scheme 3.

(CH₃CN/H₂O) medium the dimethylallyl group (substrate c) is cleaved within 85 min whereas removal of the cinnamyl group (substrate b) is completed within 20 min in the presence of 2 mol% of palladium(0). Under the same conditions, the allyl moiety (substrate a) is instantly removed. By comparison, in a biphasic system (C₃H₇CN/H₂O), the cinnamyl and the dimethylallyl groups remain intact in the presence of 5 mol% of Pd⁰ water soluble catalyst, even after 3 days at room temperature; whereas

Table 1

Chemoselective deprotection of diprotected amino acids in the presence of Pd(OAc)₂/TPPTS



Entry	Substrate	Product	Time (min)	Yield (%)	Product	Time (min)	Yield (%)
1 ^a							
		(65 : 35)					
2			20	100 ^b		15	100
3			20	100 ^b		15	100

the allylic ester is still cleaved to give phenylacetic acid in excellent yield.

Based on these results, we investigated the selective cleavage of an allylcarbamate in the presence of a substituted allyl carboxylate in the same molecule. The doubly protected amino acids are easily prepared in two steps. The amine is first converted to the corresponding

allyl carbamate using allyl chloroformate; then, treatment with cinnamyl bromide or 1-bromo-3-methyl but-2-ene in the presence of DBU leads to the substituted allyl carboxylate with high to quantitative yield. As shown in Table 1, the allyloxycarbamate of isonipecotic acid **1** was selectively and quantitatively cleaved under homogeneous conditions, in the presence of 1%

Table 2

Chemoselective deprotection of diprotected amino alcohols in the presence of $\text{Pd}(\text{OAc})_2/\text{TPPTS}$

$\text{Pd}(0) = \text{Pd}(\text{OAc})_2 / \text{TPPTS} (1/2)$

Entry	Substrate	Product	Time (min)	Yield ^{a)} (%)	Product	Time (min)	Yield (%)
1			20	96		10	100
2			30	100		60	100
3			30	72			
4			15	89			
5			30	100		45	100
6			30	99 ^{b)}		45	100

of Pd^0 , without affecting the dimethylallyl carboxylate (entry 1). The resulting monodeprotected product **7** was then treated with a higher amount of catalyst (5 mol%) to give the free amino acid. The same stepwise selective deprotection was achieved on a base sensitive cephalosporin **2** (entry 2); with 2.5% of water soluble catalyst the Alloc moiety was selectively removed to give the dimethylallyl carboxylate **8** within 30 min, and then the carboxylic acid was quantitatively recovered using 5% of Pd^0 .² This methodology was then applied with success to α -amino acids. Under treatment with 0.5% of $\text{Pd}(\text{OAc})_2/\text{TPPTS}$ in homogeneous medium, the *N*-allyloxycarbonyl-*O*-dimethylallyl derivatives underwent selective deprotection of the amine with high to quantitative yield (entries 3, 4 and 5). On the other hand, in the presence of a cinnamyl ester partial deprotection of the acid occurred concomitantly with cleavage of the allyl carbamate in the above conditions. It was thus necessary to perform the reaction under biphasic conditions to obtain cinnamyl proline **12** with complete selectivity (entry 6).

It is noteworthy that once the reaction is completed, simple treatment of the reaction mixture with water, followed by extraction and evaporation leads to crude products of high purity that can be engaged in further transformations without any purification, in particular in peptide coupling reactions.

In the same way, selective cleavage of allyloxycarbonates in the presence of dimethylallyl-carbamates was then performed with high efficiency (Table 2). A first attempt to selectively remove the allyloxycarbonate from (1*R*, 2*S*)-(–)-ephedrine doubly protected **13**, under homogeneous conditions, using 1% of Pd^0 , led to total deprotection of the alcohol together with

partial removal of the dimethylallyl carbamate. As the use of a biphasic medium would lower the rate of deprotection, the reaction was thus conducted in a butyronitrile-water system with 5% of Pd^0 ; under these conditions, the allyloxy-carbonyl group was smoothly removed from oxygen without affecting the dimethylallyloxy-carbonyl moiety. In a second step, the amine could be deprotected using a homogeneous medium, with acetonitrile as co-solvent, to recover the parent molecule within 15 min, with 100% yield (entry 2). Another example on 1-(2-*O*-Allyloxycarbonylethyl)-*N*-dimethylallyloxy-carbonyl piperazine **14** showed the same highly selective deprotection sequence (entry 3).

In addition, when the reaction is carried out in a biphasic system, the active catalyst can be recycled with high efficiency according to our previously reported procedure [17].

3. Conclusion

In summary, we have developed a smooth and efficient methodology for the selective cleavage of allylic protecting groups using $\text{Pd}(\text{OAc})_2/\text{TPPTS}$ catalyst in aqueous medium. On the one hand, by lowering the quantity of catalyst, dimethylallyl carboxylates remain intact while allyl carbamates are cleaved in high to quantitative yields. On the other hand, by simply replacing the homogeneous medium by a biphasic system, it is possible to discriminate allyl carbonates from dimethylallyl carbamates in the same molecule. The ease of the experimental procedure as well as the high purity of the crude deprotected substrates make this palladium promoted technology very attractive for fine synthetic applications. Moreover, the mild and neutral conditions are compatible with base sensitive molecules such as β -lactams. The assembly of peptide chains using the chemoselective deprotection of α -amino acids are currently under investigation in our laboratory.

² Test experiment: when carried out in anhydrous medium using $\text{Pd}(\text{dba})_2/\text{DPPB}$ catalyst and diethylamine as nucleophile, the reaction led to incomplete deprotection of the amine together with partial cleavage of the ester.

4. Experimental

4.1. General methods

Infrared spectra were recorded on a Perkin–Elmer 983G spectrophotometer. ^1H -NMR spectra were recorded on a Bruker AC 200 instrument at 200 MHz, in CDCl_3 as solvent; chemical shifts (δ) are reported in ppm units, by reference to Me_4Si , and coupling constants (J) are reported in Hertz and refer to apparent peak multiplicities. Abbreviations used are as follow: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ^{13}C -NMR spectra were recorded on a Bruker AC 200 instrument at 50 MHz, in CDCl_3 as solvent. Mass spectra were performed on a Hewlett–Packard Instrument. Elementary analysis were made at the Regional Service of Microanalysis (University P. et M. Curie, Paris). Thin-layer chromatography was carried out on silica gel plates (Merck F_{254}) and spots were detected by UV and Kagi-Mösher or KMnO_4 revelators. Tetrahydrofuran and diethyl ether were distilled on sodium/benzophenone. The other commercial solvents were used without any further purification.

Unless stated otherwise, all reactions were run under an atmosphere of argon. For reactions involving the $\text{Pd}(\text{OAc})_2/\text{TPPTS}$ catalytic system, solvents (acetonitrile, butyronitrile, water) and diethylamine were degased for 15 min under an argon atmosphere.

4.2. procedure for protection of the amine on amino acids and amino alcohols (A)

The substrate (10 mmol) is dissolved in acetonitrile or THF (10 ml) and the mixture is cooled at 0°C with an ice-bath. Allyl or dimethylallyl chloroformate (0.5 eq.; 5 mmol) is added dropwise on the stirred solution over 5 min. After 15 min, the reaction mixture is allowed to react at room temperature until complete consumption of the reactants. After filtration on celite and evaporation of the solvent, the resid-

ual oil is treated with water and extracted with AcOEt . The organic layer is dried over MgSO_4 and concentrated in vacuo to afford pale yellow oils that generally do not necessitate further purification.

4.3. Typical procedure for the protection of the amine on α -amino acids (B)

The α -amino acid (10 mmol) is dissolved in a vigorously stirred aqueous solution of 4 M NaOH (10 to 15 ml) and the solution is cooled at 0°C with an ice-bath. Allyl chloroformate (1.2 eq.; 12 mmol) is added dropwise over 5 min. After 15 min, the reaction mixture is allowed to react at room temperature. After completion, the mixture is acidified to pH 1 with concentrated HCl and extracted with AcOEt . The organic layer is dried over MgSO_4 and concentrated in vacuo to afford pure pale yellow oils.

4.4. Typical procedure for the protection of the carboxylic acid on N -protected amino acids (C)

The carbamate is dissolved in acetonitrile (1 mmol in 1 ml) and the solution is cooled at 0°C with an ice-bath. DBU (1.1 eq.) is introduced followed by dropwise addition of the cinnamyl bromide or 4-bromo-2-methyl but-2-ene (1 eq.). After 15 min, the reaction mixture is allowed to react at room temperature. After completion, acetonitrile is evaporated in vacuo. The residue is treated with water and extracted with AcOEt . The organic layer is dried over MgSO_4 and concentrated in vacuo to afford crude diprotected substrates that generally do not necessitate further purification.

4.5. Typical procedure for the protection of the hydroxy function on N -protected amino alcohol (D)

The carbamate is dissolved in THF or CH_2Cl_2 (1 mmol in 2 ml) and pyridine (1.5 eq.) is introduced. Allylchloroformate (1.2 eq.) is added

dropwise and the reaction mixture is stirred at room temperature. After completion, the solvent is evaporated and the residual oil is treated with water.

After extraction with AcOEt, the organic layer is washed with water and then dried over MgSO_4 and concentrated in vacuo. The crude products are purified by flash chromatography on silica gel, if necessary.

4.6. Typical procedure for selective deprotection (E)

The doubly protected substrate (1 mmol), is dissolved in butyronitrile/water or acetonitrile/water (3 ml/0.5 ml), under an argon atmosphere. Diethylamine (2.5 eq.; 2.5 mmol) is added, followed by rapid introduction of $\text{Pd}(\text{OAc})_2$ (0.5 to 1 mol%) and TPPTS (1 to 2 mol%). The reaction mixture is stirred at room temperature until complete consumption of the starting diprotected product (the reaction is monitored by TLC). After completion, the solution is concentrated in vacuo. The residue is treated with water and extracted with AcOEt. The organic layer is dried over MgSO_4 and concentrated in vacuo. The clean crude products can be directly engaged in the second deprotection step with 3 to 5% of $\text{Pd}(\text{OAc})_2$ and 6 to 10% of TPPTS. The reaction mixture is treated as described above, and the crude product is purified by flash chromatography, if necessary.

4.7. (3-methyl but-2-enyl)-4-N-allyloxycarbonyl piperidine carboxylate **1** was prepared according to procedures (A) and (C)

Pale yellow oil (68% yield).

TLC: $R_f = 0.66$ (AcOEt/cyclohexane 1/1).

IR (film, $\nu \text{ cm}^{-1}$): 3081, 2929, 2858, 1726, 1695, 1643, 1468, 1443, 1378, 1308, 1275, 1219.

$^1\text{H-NMR}$: 5.93 (1H, m, $\text{HC}=\text{C}$), 5.33 (1H, tm, $^3J = 6.1 \text{ Hz}$, $\text{HC}=\text{C}$), 5.29 (1H, dm, $^3J_{\text{trans}} = 17.3 \text{ Hz}$, $\text{H}_2\text{C}=\text{C}$), 5.20 (1H, dm, $^3J_{\text{cis}} = 10.4 \text{ Hz}$,

$\text{H}_2\text{C}=\text{C}$), 4.58 (2H, d, $^3J = 6.1 \text{ Hz}$ and 2H, d, $^3J = 5.6 \text{ Hz}$, $\text{CH}_2\text{C}=\text{C}$), 4.07 (2H, br d, $^3J = 12.5 \text{ Hz}$, CH_2), 2.91 (2H, m, CH_2), 2.47 (1H, tt, $^3J = 10.9 \text{ Hz}$ and $^3J = 4.0 \text{ Hz}$, HC cycle), 1.90 (2H, dd, $^3J = 12.5$ and 3.3 Hz , CH_2), 1.76 (3H, s, $(\text{CH}_3)_2\text{C}=\text{C}$), 1.73 (3H, s, $(\text{CH}_3)_2\text{C}=\text{C}$), 1.67 (2H, m, CH_2).

$^{13}\text{C-NMR}$: 174.28, 154.92, 139.15, 132.98, 118.32, 117.19, 65.87, 61.40, 43.09, 40.91, 27.80, 25.64, 17.92.

GC-MS (m/z): 281 (M) $^{+ \cdot}$, 240 ($M - \text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$) $^{+ \cdot}$, 212 ($M - \text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$) $^{+ \cdot}$, 172 ($M - \text{CH}_2\text{CH}=\text{CH}_2 - \text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2 + 1$) $^{+ \cdot}$, 156 ($M - \text{OCH}_2\text{CH}=\text{CH}_2 - \text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2 + 1$) $^{+ \cdot}$, 112 ($\text{C}_6\text{H}_5\text{N}(\text{Allyl}) - 1$) $^{+ \cdot}$, 69 ($\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$) $^{+ \cdot}$; 41 ($\text{CH}_2\text{CH}=\text{CH}_2$) $^{+ \cdot}$.

4.8. (3-methyl but-2-enyl)-7-N-allyloxycarbonylaminocephalosporinoate **2**

Protection of the amine was carried out in dioxane/ H_2O (1/1) in the presence of 2 eq. of NaHCO_3 and 1 eq. of allyl chloroformate. The resulting carbamate was converted to the diprotected substrate **2** according typical procedure (C).

Pale yellow solid (60% yield).

TLC: $R_f = 0.6$ (AcOEt/cyclohexane 1/1).

IR ($\nu \text{ cm}^{-1}$): 3320, 2978, 2933, 1780, 1721, 1646, 1534, 1445, 1379, 1323, 1241.

$^1\text{H-NMR}$: 5.91 (1H, m, $\text{HC}=\text{C}$), 5.64 (1H, dd, $^3J = 4.6 \text{ Hz}$ and $^3J = 8.8 \text{ Hz}$, $\text{HC}(\text{NHAllyl})$), 5.48 (1H, br d, $^3J = 8.8 \text{ Hz}$, NH), 5.38 (1H, tm, $^3J = 7.0 \text{ Hz}$, $\text{HC}=\text{C}$), 5.32 (1H, dm, $^3J_{\text{trans}} = 17.2 \text{ Hz}$, $\text{H}_2\text{C}=\text{C}$), 5.24 (1H, dm, $^3J_{\text{cis}} = 10.3 \text{ Hz}$, $\text{H}_2\text{C}=\text{C}$), 4.96 (1H, d, $^3J = 4.6 \text{ Hz}$, HC), 4.74 (2H, d, $^3J = 7.0 \text{ Hz}$, $\text{CH}_2\text{C}=\text{C}$), 4.61 (2H, d, $^3J = 5.6 \text{ Hz}$, $\text{CH}_2\text{C}=\text{C}$), 3.51 and 3.21 (2H, 2d, $^2J_{\text{gem}} = 18.3 \text{ Hz}$, CH_2), 2.17 (3H, s, CH_3), 1.77 (3H, s, $(\text{CH}_3)_2\text{C}=\text{C}$), 1.72 (3H, s, $(\text{CH}_3)_2\text{C}=\text{C}$).

$^{13}\text{C-NMR}$: 164.41, 162.11, 155.29, 139.78, 132.04, 130.86, 122.62, 118.20, 117.85, 66.38, 62.39, 60.86, 57.21, 29.97, 25.69, 19.91, 17.99.

GC-MS (m/z): 366 (M) $^{+ \cdot}$, 338 ($M -$

HC=CH₂-1) +, 325 (*M*-CH₂CH=CH₂)⁺, 298 (*M*-CH₂CH=C(CH₃)₂ + 1)⁺, 281 (*M*-CO₂CH₂CH=CH₂)⁺, 226 (*M*-CO₂CH₂CH=CH₂-CH=C(CH₃)₂)⁺, 112 (CO₂CH₂CH=C(CH₃)₂-1)⁺, 69 (CH₂CH=C(CH₃)₂)⁺, 41 (CH₂CH=CH₂)⁺.

4.9. (3-methyl but-2-enyl)-L-N-allyloxycarbonyl valinate 3 was prepared according to procedures (B) and (C)

Colourless oil (80% yield).

TLC: *R*_f = 0.81 (AcOEt/cyclohexane 1/1).

IR (film, ν cm⁻¹): 3349, 2965, 2933, 1875, 1724, 1644, 1511, 1462, 1375, 1236.

¹H-NMR: 5.90 (1H, m, HC=), 5.33 (1H, bd, *J* = 9.1 Hz, NH), 5.29 (1H, dm, ³*J*_{trans} = 16.3 Hz, H₂C=), 5.28 (1H, tm, ³*J* = 7.4 Hz, HC=), 5.20 (1H, dm, ³*J*_{cis} = 10.4 Hz); 4.61 (2H, d, ³*J* = 7.4 Hz, CH₂C=), 5.55 (2H, d, ³*J* = 5.6 Hz, CH₂C=), 4.26 (1H, dd, ³*J* = 4.6 and 9.1 Hz, HC(*i*Pr)); 2.12 (1H, m, HC(CH₃)₂), 1.74 (3H, s, (CH₃)₂C=), 1.69 (3H, s, (CH₃)₂C=), 0.94 (3H, d, ³*J* = 6.9 Hz, CH₃ (*i*Pr)); 0.87 (3H, d, ³*J* = 6.9 Hz, CH₃ (*i*Pr)).

¹³C-NMR: 171.93, 155.97, 139.68, 132.60, 117.96, 117.60, 65.65, 31.90, 58.82, 31.25, 25.58, 18.81, 17.90, 17.25.

GC-MS (*m/z*): 269 (*M*)⁺; 226 (*M*-CH(CH₃)₂)⁺; 202 (*M*-CH₂CH=C(Me)₂ + 2)⁺; 183 (*M*-OCH₂CH=C(Me)₂-1)⁺; 156 (*M*-CO₂CH₂CH=C(Me)₂)⁺; 112(CO₂CH₂CH=C(Me)₂-1)⁺; 69(CO₂CH₂CH=C(Me)₂)⁺; 41 (CH₂CH=CH₂)⁺.

Rotation: [α]_D²⁰ = -2 (*c* = 0.79, CHCl₃).

4.10. (3-methyl but-2-enyl)-L-N-allyloxy-carbonyl phenylalinate 4 was prepared according to procedures (B) and (C)

Pale yellow oil (55% yield).

TLC: *R*_f = 0.78 (AcOEt/cyclohexane 1/1).

IR (film, ν cm⁻¹): 3329, 3062, 3028, 2970, 2932, 1722, 1510, 1261.

¹H-NMR: 7.27 (3H, m, H_{arom}); 7.20 (2H, m,

H_{arom}); 5.90 (1H, m, HC=); 5.31 (1H, tm, ³*J* = 7.3 Hz, HC=); 5.29 (1H, dm, ³*J*_{trans} = 16.0 Hz, H₂C=); 5.20 (1H, dm, ³*J*_{cis} = 10.8 Hz, H₂C=), 4.66 (1H, m, HC(CH₂Ph)), 4.62 (2H, d, ³*J* = 7.3 Hz, CH₂C=), 4.57 (2H, d, ³*J* = 5.3 Hz); 3.11 (2H, 2d, ³*J* = 5.8 Hz), 1.79 (3H, s, (CH₃)₂C=), 1.71 (3H, s, (CH₃)₂C=).

¹³C-NMR: 171.35, 155.37, 139.82, 135.67, 132.55, 129.30, 128.41, 126.95, 117.88, 117.61, 65.64, 32.16, 54.63, 38.18, 25.63, 17.92.

GC-MS (*m/z*): 317 (*M*)⁺; 275 (*M*-CH₂CH=CH₂)⁺; 249 (*M*-CH₂CH=C(Me)₂ + 1)⁺; 204 (*M*-CO₂CH₂CH=C(Me)₂)⁺; 148 (CONHCH(CH₂Ph))⁺; 119 (HNCH(CH₂Ph))⁺; 69 (CH₂CH=C(Me)₂)⁺; 41 (CH₂CH=CH₂)⁺.

Rotation: [α]_D²⁰ = 13 (*c* = 1.1; CHCl₃).

Elemental analysis calcd. for C₁₈H₂₃NO₄: C, 68.14; H, 7.26; N, 4.42. Found: C, 68.09; H, 7.30; N, 4.42.

4.11. (3-methyl but-2-enyl)-L-N-allyloxy-carbonyl prolininate 5 was prepared according to procedures (B) and (C)

Pale orange oil (86% yield).

IR (film, ν cm⁻¹): 3403, 3085, 2973, 2884, 1742, 1706, 1644, 1440, 1126.

¹H-NMR: 5.85 (1H, m, HC=), 5.28 (1H, tm, ³*J* = , HC=); 5.20 (1H, dm, ³*J*_{trans} = 16.0 Hz, H₂C=), 5.11 (1H, dm, ³*J*_{cis} = 8.0 Hz, H₂C=), 4.56 (4H, m, 2CH₂C=), 4.30 (1H, td, ³*J* = 8.0 Hz and ³*J* = 4.0 Hz, HC(CO₂R)), 3.62 to 3.38 (2H, m, CH₂ cycle); 3.19 (1H, m, CH₂ cycle); 1.92 (3H, m, CH₂ cycle), 1.71 (3H, s, (CH₃)₂C=), 1.66 (3H, s, (CH₃)₂C=).

¹³C-NMR: 172.62 and 172.41, 154.51 and 154.03, 139.22 and 139.02, 132.86 and 132.66, 118.15, 117.02 and 116.70, 65.70 and 65.58, 61.73, 59.08 and 58.78, 46.71 and 46.18, 30.79 and 29.75, 25.57, 24.12 and 23.33, 17.87.

GC-MS (*m/z*): 267 (*M*)⁺; 237 (*M*-2CH₃)⁺; 183 (*M*-CO₂CH₂CH=CH₂ + 1)⁺; 154 (*M*-CO₂CH₂CH=C(Me)₂)⁺; 69 (CH₂CH=C(Me)₂)⁺; 41 (CH₂CH=CH₂)⁺.

Rotation: [α]_D²⁰ = -53 (*c* = 2.63, CH₂Cl₂).

4.12. Cinnamyl-*L*-*N*-allyloxycarbonyl proline 6 was prepared according to procedures (B) and (C)

Pale yellow oil (80% yield).

TLC: $R_f = 0.58$ (AcOEt/cyclohexane 1/1).

IR (film, ν cm⁻¹): 3079, 3055, 3024, 2978, 2951, 2878, 1742, 1701, 1643, 1595, 1490, 1444, 1405, 1191.

¹H-NMR: 7.42 to 7.27 (5H, m, H_{arom}), 6.66 (1H, d, ³*J*_{trans} = 15.9 Hz, HC=), 6.27 (1H, dt, ³*J*_{trans} = 15.9 Hz and ³*J* = 6.4 Hz, HC=), 5.86 (1H, m, HC=), 5.31 (1H, dm, ³*J*_{trans} = 17.8 Hz, H₂C=), 5.15 (1H, m, H₂C=), 4.80 (1H, d, ³*J* = 6.4 Hz, CH₂C=), 4.77 (1H, d, ³*J* = 6.4 Hz, CH₂C=), 4.62 (1H, dm, ³*J* = 5.4 Hz, CH₂C=), 4.55 (1H, m, CH₂C=), 4.40 (1H, tm, ³*J* = Hz, HC(CO₂R)), 3.65 to 3.47 (2H, m, CH₂), 2.24 (1H, m, CH₂), 2.10 to 1.88 (3H, m, CH₂).

¹³C-NMR: 172.50 and 172.32, 154.72 and 154.08, 135.97, 134.54 and 134.19, 132.87 and 132.66, 128.49, 128.06 and 127.96, 126.54, 122.77 and 122.58, 117.20 and 116.92, 65.75, 65.51, 59.16 and 58.85, 46.80 and 46.28, 30.88 and 29.84, 24.24 and 23.43.

GC-MS (*m/z*): 315 (*M*)⁺, 257 (*M* - OCH₂CH=CH₂-1)⁺, 229 (*M* - CO₂CH₂CH=CH₂-1)⁺, 198 (*M* - PhCH=CHCH₂)⁺, 182 (*M* - PhCH=CHCH₂O)⁺, 154 (*M* - PhCH=CHCH₂OCO)⁺, 70 (*M* - PhCH=CHCH₂OCO-CO₂CH₂CH=CH₂)⁺.

Rotation: $[\alpha]_D^{20} = -43$ (*c* = 0.89, CHCl₃).

4.13. (3-methyl but-2-enyl)-4-piperidine carboxylate 7 was obtained from compound 1 according to procedure (E)

Pale yellow oil (96% yield).

TLC: $R_f = 0.2$ (CH₂Cl₂/MeOH 10/1).

IR (film, ν cm⁻¹): 3350, 2829, 2855, 1723, 1637, 1445, 1377, 1172.

¹H-NMR: 5.33 (1H, tm, ³*J* = 7.2 Hz, HC=); 4.59 (2H, d, ³*J* = 7.2 Hz, CH₂C=), 3.49 (1H, br s, NH), 3.16 (2H, dt, ³*J* = 12.6 and 10.7 Hz, CH₂), 2.72 (2H, td, ³*J* = 3.8 and 4.0 Hz, CH₂),

2.47 (1H, tt, ³*J* = 10.7 and 4.0 Hz, HC), 1.96 (2H, dm, ³*J* = 10.7 Hz, CH₂), 1.77 (3H, s, (CH₃)₂C=), 1.74 (2H, m, CH₂), 1.72 (3H, s, (CH₃)₂C=).

¹³C-NMR: 174.50, 139.04, 118.39, 61.33, 45.02, 40.76, 28.17, 25.63, 17.91.

GC-MS (*m/z*): 197 (*M*)⁺, 182 (*M* - CH₃)⁺, 142 (*M* - CH=C(Me)₂)⁺, 128 (*M* - CH₂CH=C(Me)₂)⁺, 82 (*M* - CO₂CH₂CH=C(Me)₂)⁺.

4.14. (3-methyl but-2-enyl)-7-aminocephalosporinoate 8 was obtained from compound 2 according to procedure (E)

Yellow oil (100% yield).

TLC: $R_f = 0.41$ (CH₂Cl₂/MeOH 10/1).

IR (film, ν cm⁻¹): 3396, 3330, 2970, 2934, 2918, 1766, 1669, 1628, 1442, 1355, 1299.

¹H-NMR: 5.39 (1H, tm, ³*J* = 7.4 Hz, HC=), 5.43 (1H, d, ³*J* = 4.9 Hz, HC), 4.75 (2H, d, ³*J* = 7.4 Hz, CH₂C=), 4.59 (1H d, ³*J* = 4.9 Hz, HC), 3.51 (1H, d, ²*J*_{gem} = 18.2 Hz, CH₂), 3.18 (1H, d, ²*J*_{gem} = 18.2 Hz, CH₂), 2.10 (3H, s, CH₃), 1.77 (2H, br s, NH₂), 1.76 (3H, s, (CH₃)₂C=), 1.72 (3H, s, (CH₃)₂C=).

¹³C-NMR: 168.47, 162.50, 139.63, 129.52, 122.82, 117.96, 63.40, 62.35, 58.36, 29.63, 25.70, 19.94, 18.00.

Rotation: $[\alpha]_D^{20} = 157$ (*c* = 1.10, CHCl₃).

4.15. (3-methyl but-2-enyl)-*L*-valinate 9 was obtained from compound 3 according to procedure (E)

Pale yellow oil (73% yield).

TLC: $R_f = 0.42$ (AcOEt/cyclohexane 1/1).

IR (film, ν cm⁻¹): 3381, 1961, 1932, 2875, 1727, 1671, 1163.

¹H-NMR: 5.32 (1H, tm, ³*J* = 7.3 Hz, HC=), 4.58 (2H, d, ³*J* = 7.3 Hz, CH₂C=), 3.24 (1H, d, ³*J* = 5.0 Hz, HC(*i*Pr)), 1.99 (1H, m, HC(CH₃)₂), 1.73 (3H, s, CH₃)₂C=), 1.68 (3H, s, CH₃)₂C=), 1.43 (2H, br s, NH₂), 0.94 (3H, d, ³*J* = 6.9 Hz, CH₃ (*i*Pr)), 0.86 (3H, d, ³*J* = 6.9 Hz, CH₃ (*i*Pr)).

^{13}C -NMR: 174.49, 139.18, 118.32, 61.35, 59.81, 32.00, 25.57, 19.15, 17.86, 16.97.

GC-MS (m/z): 165 (M) $^{+}$; 142 (M -C(CH₃)₂) $^{+}$; 72 (M -CO₂CH₂CH=C(Me)₂) $^{+}$; 51 (CH=C(Me)₂) $^{+}$.

Rotation: $[\alpha]_{\text{D}}^{20} = 18$ ($c = 0.4$, CHCl₃)

4.16. (3-methyl but-2-enyl)-L-phenylalinate 10 was obtained from compound **4** according to procedure (E)

Yellow oil (89% yield).

TLC: $R_f = 0.16$ (AcOEt/cyclohexane 3/1).

IR (film, ν cm $^{-1}$): 3377, 3309, 3061, 3027, 2969, 2931, 2857, 1728, 1671, 1601, 1493, 1449, 1176.

^1H -NMR: 7.35 to 7.16 (5H, m, H_{arom}); 5.31 (1H, tm, $^3J = 7.3$ Hz, HC=), 4.61 (2H, d, $^3J = 7.3$ Hz, CH₂C=), 3.72 (1H, dd, $^2J = 13.4$ Hz and $^3J = 7.8$ Hz, CH₂Ph), 2.87 (1H, dd, $^2J = 13.4$ and 5.3 Hz, CH₂Ph), 1.77 (3H, s, (CH₃)₂C=), 1.69 (3H, s, (CH₃)₂C=), 1.52 (2H, br s, NH₂).

^{13}C -NMR: 174.93, 139.35, 137.16, 129.24, 128.39, 126.65, 118.23, 61.69, 55.75, 40.96, 25.65, 17.92.

GC-MS (m/z): 233 (M) $^{+}$; 202 (M -2CH₃-1) $^{+}$; 142 (M -PhCH₂) $^{+}$; 120 (H₂NCH(CH₂Ph)) $^{+}$; 69 (CH₂CH=C(Me)₂) $^{+}$; 41 (CH₂CH=CH₂) $^{+}$.

Rotation: $[\alpha]_{\text{D}}^{20} = -6$ ($c = 1.35$, CHCl₃).

4.17. (3-methyl but-2-enyl)-L-prolinate 11 was obtained from compound **5** according to procedure (E)

Yellow oil (100% yield).

TLC: $R_f = 0.23$ (AcOEt/cyclohexane 3/1).

IR (film, ν cm $^{-1}$): 3347, 2968, 2938, 2875, 1727, 1670, 1444, 1378, 1175.

^1H -NMR: 5.32 (1H, tm, $^3J = 7.0$ Hz, HC=), 4.61 (2H, d, $^3J = 7.0$ Hz, CH₂C=), 3.80 (1H, m, HC(CO₂R)), 3.49 (1H, br s, NH), 3.11 (1H, m, CH₂(NH)), 2.97 (1H, m, CH₂(NH)), 2.16 (1H, m, CH₂), 1.91 (1H, m, CH₂), 1.80 (2H, m, CH₂), 1.75 (3H, s, (CH₃)₂C=), 1.70 (3H, s, (CH₃)₂C=).

^{13}C -NMR: 174.85, 139.40, 118.14, 61.88, 59.59, 46.81, 30.07, 25.64, 25.33, 17.93.

GC-MS (m/z): 183 (M) $^{+}$; 114 (M -CH₂CH=C(Me)₂) $^{+}$; 70 (M -CO₂CH₂CH=C(Me)₂-1) $^{+}$; 41 (CH₂CH=CH₂) $^{+}$.

Rotation: $[\alpha]_{\text{D}}^{20} = -36$ ($c = 0.48$, CHCl₃).

4.18. (1R, 2S)-1-O-allyloxycarbonyl-N-(3-methyl but-2-enyl) ephedrine 13 was prepared according to the general procedures (A) and (D)

Yellow oil (50% yield).

TLC: $R_f = 0.77$ (AcOEt/cyclohexane 1/1).

^1H -NMR: 7.34 (5H, m, Harom), 5.97 (1H, m, HC=), 5.38 (1H, dm, $^3J_{\text{trans}} = 12.5$ Hz, H₂C=), 5.31 (1H, m, HC=), 5.28 (1H, dm, $^3J_{\text{cis}} = 5.7$ Hz, H₂C=), 4.89 (1H, br s, NH), 4.65 (4H, m, CH₂C=), 4.17 (1H, d, $^3J = 6.7$ Hz, HC), 4.13 (1H, m, HC), 2.74 (3H, s, CH₃), 1.78 (3H, s, (CH₃)₂C=), 1.72 (3H, s, (CH₃)₂C=), 1.25 (3H, d, $^3J = 7.1$ Hz, CH₃).

^{13}C -NMR: 141.96, 137.95, 131.43, 128.03, 127.43, 126.13, 119.31, 118.79, 76.93, 68.37, 62.25, 59.20, 25.65, 17.94.

GC-MS (m/z): 361 (M) $^{+}$; 303 (M -OCH₂CH=CH₂-1) $^{+}$; 293 (M -CH₂CH=C(Me)₂+1) $^{+}$; 259 (M -CO₂CH₂CH=CH₂-1) $^{+}$; 220 (M -(CH₃)NCO₂CH₂CH=C(Me)₂+1) $^{+}$; 170 (M -PhCHO₂CH₂CH=CH₂) $^{+}$; 58 (OCH₂CH=CH₂+1) $^{+}$.

4.19. but-2-enyl)piperazine 14 was prepared according to procedures (A) and (D)

Yellow oil (60% yield).

TLC: $R_f = 0.88$ (AcOEt/cyclohexane 1/1).

^1H -NMR: 5.90 (1H, m, HC=), 5.83 (1H, dm, $^3J_{\text{trans}} = 18.0$ Hz, H₂C=), 5.79 (1H, tm, $^3J = 7.6$ Hz, HC=), 5.74 (1H, dm, $^3J_{\text{cis}} = 8.0$ Hz), 4.62 (4H, m, CH₂C=), 4.27 (2H, t, $^3J = 5.6$ Hz, CH₂), 3.48 (4H, t, $^3J = 4.4$ Hz, CH₂), 2.66 (2H, $^3J = 5.6$ Hz, CH₂), 2.45 (4H, t, $^3J = 4.4$ Hz, CH₂), 1.75 (3H, s, (CH₃)₂C=).

^{13}C -NMR: 155.41, 154.84, 131.42, 119.28, 118.77, 68.36, 64.90, 62.21, 56.50, 52.91, 43.50, 25.64, 17.92.

GC-MS (m/z): 326 (M) $^{+}$, 269 ($M - \text{OCH}_2\text{CH}=\text{CH}_2$) $^{+}$, 257 ($M - \text{CH}_2\text{CH}=\text{C}(\text{Me})_2$) $^{+}$, 198 ($M - \text{C}_2\text{H}_4\text{OCO}_2\text{CH}_2\text{CH}=\text{CH}_2 + 1$) $^{+}$, 58 ($\text{OCH}_2\text{CH}=\text{CH}_2 + 1$) $^{+}$.

4.20. (1*R*, 2*S*)-2-*N*-(3-methyl but-2-enyl)ephedrine **15** was obtained from compound **13** according to procedure (E)

Pale yellow oil (100% yield).

TLC: R_f = 0.41 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10/1).

IR (film, ν cm^{-1}): 3417, 2957, 2929, 2880, 1722, 1669, 1446, 1273, 1151.

^1H -NMR: 7.32 (5H, m, H_{arom}), 5.43 (1H, tm, 3J = 7.8 Hz, HC=), 5.30 (1H, d, 3J = 3.6 Hz, HC(OH)), 3.39 (1H, m, HC), 2.72 (3H, s, CH_3), 1.85 (3H, s, $(\text{CH}_3)_2\text{C}=\text{}$), 1.82 (3H, s, $(\text{CH}_3)_2\text{C}=\text{}$), 1.17 (3H, d, 3J = 6.8 Hz, CH_3).

^{13}C -NMR: 141.97, 137.94, 128.36, 126.13, 119.31, 78.24, 65.73, 62.24, 53.33, 25.63, 17.93, 15.15.

4.21. 1-(2-hydroxy ethyl)-4-*N*-(3-methyl but-2-enyl)piperazine **16** was obtained from compound **14** according to procedure (E)

Pale orange oil (100% yield).

TLC: R_f = 0.37 ($\text{AcOEt}/\text{cyclohexane}$ 1/1).

^1H -NMR: 5.34 (1H, tm, 3J = 6.0 Hz, HC=), 4.12 (2H, d, 3J = 6.0 Hz), 3.64 (2H, 3J = 5.2 Hz, CH_2), 3.46 (4H, t, 3J = 5.6 Hz, CH_2), 2.54 (2H, 3J = 5.2 Hz, CH_2), 2.44 (4H, t, 3J = 5.6 Hz, CH_2), 1.74 (3H, s, $(\text{CH}_3)_2\text{C}=\text{}$), 1.69 (3H, s, $(\text{CH}_3)_2\text{C}=\text{}$).

^{13}C -NMR: 155.44, 138.12, 119.22, 62.27, 59.37, 57.66, 52.54, 43.60, 25.79, 17.91.

GC-MS (m/z): 242 (M) $^{+}$, 211 ($M - \text{CH}_2\text{OH}$) $^{+}$, 143 ($M - \text{CH}_2\text{OH} - \text{CH}_2\text{CH}=\text{C}(\text{Me})_2 + 1$) $^{+}$, 99 ($M - \text{CH}_2\text{OH} - \text{CO}_2\text{CH}_2\text{CH}=\text{C}(\text{Me})_2 + 1$) $^{+}$, 69 ($\text{CH}_2\text{CH}=\text{C}(\text{Me})_2$) $^{+}$.

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