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A Practical Ruthenium-Catalyzed Cleavage of the Allyl Protecting Group in Amides, Lactams, Imides, and Congeners

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Abstract: A convenient methodology for the deprotection of *N*-allylic amide-like moieties was developed. The first examples accounting for the ruthenium-catalyzed deallylation of amides, lactams, imides, pyrazolidones, hydantoins, and oxazolidinones have been achieved by the sequential use of Grubbs carbene (isomerization step) and $RuCl_3$ (oxidation step). A variety of substrates, including enantiopure multifunctional β- and γ-lactams, can be employed.

Keywords: amides · cleavage reactions · lactams · protecting groups · ruthenium

Introduction

NH-Amides, imides, lactams, and related nitrogen-containing compounds have long attracted synthetic interest due to their relatively simple structural features and wide range of pharmacologic activity; these compounds also serve as crucial intermediates for numerous natural products. In particular, *N*-unsubstituted β-lactams are essential building blocks for the preparation of several antibiotics[1] and anticancer agents, such as paclitaxel (Taxol) and docetaxel.[2] Very often, the required free amide, imide, or lactam cannot be prepared by the established methods. However, there are relatively few methods available for the deprotection of an amide or amide-like moiety.[3] Oxidative cleavage by ceric ammonium nitrate of an activated aromatic moiety attached to the nitrogen offers the most direct synthesis of *NH*-amides, imides, or lactams.[4] However, in many cases the yields are poor as this method requires quite harsh conditions that may damage sensitive functionalities. Therefore, due to the increasing complexity of the molecules synthesized, new protecting groups with modulated reactivity and new cleavage techniques for existing protecting groups are still needed.

The allyl protecting group, which is stable under both acidic and basic conditions, permits orthogonal protection strategies with a wide range of protecting groups, allowing its use in multistep synthetic schemes. Despite the fact that allyl protecting group cleavage in ethers and amines is a well-documented methodology, especially by using palladium chemistry,[5] its extension to the deprotection of allylic imides and lactams has been scarcely documented. To the best of our knowledge, the *N*-allyl cleavage of a 4-unsubstituted-β-lactam[6] and a 2-hydroxy-γ-lactam,[7] both induced by rhodium(III) followed by $KMnO_4$ or acidic treatments, respectively, are the only available examples. In our ongoing project directed toward the asymmetric synthesis of nitrogen-containing products of biological interest,[8] we faced serious difficulties with the elimination of nitrogen protecting groups on *N*-protected lactams. For this reason, and taking into account the highly selective properties of various transition metal derived reagents that would seem to recommend their application to the removal of the allyl protecting group in amides, imides, and lactams, we were tempted to study alternative strategies for the cleavage of the N–C bond in amides and congeners. We report herein full details of a novel, mild, and efficient ruthenium-catalyzed methodology for the catalytic deprotection of *N*-allyl lactams,[9] as well as

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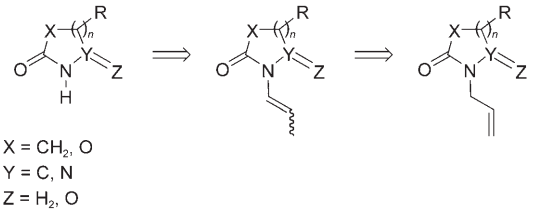
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains compound characterization data and experimental procedures for compounds **1a–d**, **2a–c**, **3a–d**, **4a–e**, **5a–c**, (+)-**6b**, (±)-**6d**, (+)-**6e**, (+)-**7**, (+)-**8**, (+)-**9**, (−)-**10**, (+)-**11**, **13a**, **13b**, **14b**, **15a**, **15b**, **16a–e**, **17a**, and **17c–e**.

its extension to the allyl cleavage of amides, imides, pyrazolidones, hydantoins, and oxazolidinones.

Results and Discussion

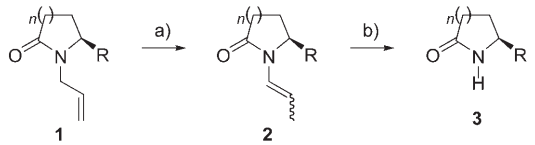
In recent years there have been several reports of nonmetathetic transformations promoted by Grubbs carbene.[10] Our exploration of this type of ruthenium-promoted reaction began after noting for the first time that allylic amines can be catalytically cleaved by using reagents other than palladium catalysts.[11] The higher stability of enamide-like moieties compared with enamines favors the double bond isomerization,[12] which prevents (CO)N-allyl cleavage. On the basis of these principles, it was to be expected that successful catalytic C–N deprotection in *N*-allyl amides, imides, lactams, and congeners would require an additional step (Scheme 1). We chose ruthenium(III) chloride, which has been probed as an excellent catalyst for the oxidative cleavage of olefins to aldehydes,[13] because it has been reported that *N*-formyl lactams smoothly loose CO under slightly basic conditions to give the corresponding NH-amides.[14]



Scheme 1. Retrosynthetic analysis for the cleavage of the allyl protecting group in lactams, imides, and analogous compounds.

First, as a model reaction we tested the deprotection of *N*-allyl γ-butyrolactam **1a**. Treatment of allylic lactam **1a** with first generation Grubbs carbene [$(PCy_3)_2Cl_2Ru$=CHPh] under optimized reaction conditions (5 mol% catalyst, 0.03 M, toluene, 110 °C) resulted in the clean formation of the corresponding enamide **2a** as an isomeric mixture (*E*/*Z* 1.2:1) in good isolated yield (90%) after chromatographic purification. Attempts to effect the reaction at lower temperatures (50 °C) slowed the reaction considerably. Incomplete conversion was observed on decreasing the amount of catalyst. The catalytic scission of the internal C=C was attained by using the system $RuCl_3$–$NaIO_4$ in 1,2-dichloroethane–H_2O (1:1), followed by an aqueous workup under slightly basic conditions (sat. aq $NaHCO_3$ containing a catalytic amount of Na_2CO_3). In this way, the *N*-unsubstituted 2-pyrrolidone **3a** was obtained in an 87% yield. Exposure of *N*-allyl L-pyroglutamic acid ethyl ester (+)-**1b**, *N*-allyl δ-valerolactam **1b**, and *N*-allyl ε-caprolactam **1c** to the above sequential catalytic conditions smoothly afforded the *NH*-lactams (+)-**3b**, **3c**, and **3d** (Table 1). Under the reaction conditions, the intermediate *N*-formyl lactams accumulate in the reaction mixture immediately after the $RuCl_3$-$NaIO_4$ system is added over the enamide, and can be isolated by using a neutral workup.

Table 1. Ruthenium-catalyzed deprotection of allylic γ-, δ-, and ε-lactams.[a]



Substrate	*n*	R	Product	*E*/*Z* ratio[b]	Yield [%][c]	Product	Yield [%][c]
1a	1	H	**2a**	55:45	90	**3a**	87
(+)-**1b**	1	COOEt	(+)-**2b**	20:80	75	(+)-**3b**	73
1c	2	H	**2c**	53:47	71	**3c**	70
1d	3	H	**2d**	0:100	72	**3d**	65

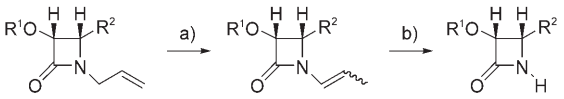
[a] Reagents and conditions: a) 5 mol% [$(PCy_3)_2Cl_2Ru$=CHPh], toluene, 110 °C; b) $RuCl_3$-$NaIO_4$, 1,2-dichloroethane-H_2O (1:1), aqueous workup (sat. aq $NaHCO_3$ + cat. Na_2CO_3). [b] The ratio was determined by the integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data.

Next, we decided to test the *N*-allyl cleavage protocol in the strained four-membered lactam series. Racemic and enantiopure allylic β-lactams **4a**–**e** were conveniently deprotected to give the corresponding *NH*-β-lactams by using both ruthenium catalysts (Table 2). This transformation tolerates different substituents on the lactam ring, such as aryl, heteroaryl, alkoxy, silyloxy, dioxolanyl, and carboxyalkyl moieties. Of special interest are the furan and electron-rich arene moieties, both of which are sensitive to oxidative deprotection conditions, as well as the acid labile silyl ether and acetonide groups. Importantly, the stereochemical integrity of the stereogenic centres on the lactam rings, when applicable, remained unaltered during the transformation of *N*-allyl compounds **4** into *NH*-products **6**.

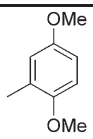
To demonstrate that the above ruthenium-catalyzed *N*-deallylation protocol can be considered in complex synthetic planning, it was successfully used for the cleavage of highly functionalized *N*-allyl bis-β- and bis-γ-lactams.[15] The precursors were obtained in an optically pure form from 4-oxoazetidine-2-carbaldehyde (+)-**7**.[16] Thus, C4,C4′-bis-β-lactam (+)-**8** was prepared by the treatment of aldehyde (+)-**7** with

Abstract in Spanish: *Se ha descubierto una metodología práctica de desprotección de N-alil amidas y compuestos relacionados tales como lactamas, imidas, pirazolidonas, hidantoínas y oxazolidinonas. Esta desprotección se lleva a cabo por tratamiento secuencial con el carbeno de Grubbs (etapa de isomerización) y $RuCl_3$ (etapa de oxidación), y constituye el primer ejemplo de desalilación catalizada por rutenio de estas funcionalidades. Las suaves condiciones de reacción permiten utilizar una gran variedad de sustratos, como por ejemplo β- y γ-lactamas polifuncionalizadas enantiopuras.*

Table 2. Ruthenium-catalyzed deprotection of allylic β-lactams[a]

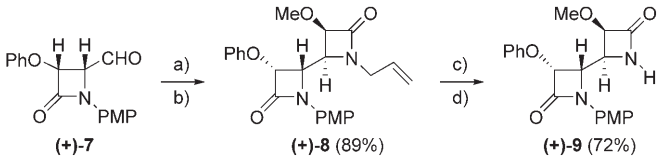


4 5 6

Substrate	R^1	R^2	Product	*E*/*Z* ratio[b]	Yield [%][c]	Product	Yield [%][c]
(±)-**4a**	Me		(±)-**5a**	76:24	62	(±)-**6a**	64
(+)-**4b**	Me		(+)-**5b**	80:20	77	(+)-**6b**	85
(+)-**4c**	TBS		(+)-**5c**	88:12	79	(+)-**6c**	95
(±)-**4d**	Ph		(±)-**5d**	95:5	72	(±)-**6d**	57
(+)-**4e**	Ph		(+)-**5e**	50:50	79	(+)-**6e**	78

[a] Reagents and conditions: a) 5 mol% [$(PCy_3)_2Cl_2Ru$=CHPh], toluene, 110°C. b) $RuCl_3$-$NaIO_4$, 1,2-dichloroethane-H_2O (1:1), aqueous workup (sat. aq $NaHCO_3$ + cat. Na_2CO_3). [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data.

allylamine, followed by ketene-imine cyclization. Bis-β-lactam (+)-**8** was conveniently deallylated by ruthenium catalysis to afford the *NH*-bis-β-lactam (+)-**9** (Scheme 2).



(+)-7 (+)-8 (89%) (+)-9 (72%)

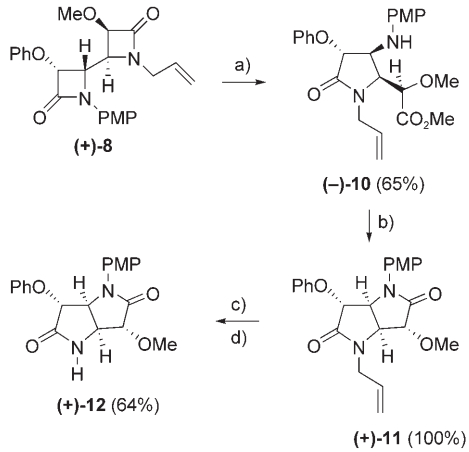
Scheme 2. Ruthenium-catalyzed deprotection of *N*-allyl bis-β-lactams. Reagents and conditions: a) Allylamine, $MgSO_4$, CH_2Cl_2, RT; b) $MeOCH_2COCl$, Et_3N, CH_2Cl_2, RT; c) 5 mol% [$(PCy_3)_2Cl_2Ru$=CHPh], toluene, 110°C; d) $RuCl_3$–$NaIO_4$, 1,2-dichloroethane–H_2O (1:1), aqueous workup (sat. aq $NaHCO_3$ + cat. Na_2CO_3). PMP = 4-$MeOC_6H_4$.

N-Allyl bis-γ-lactam (+)-**11** was obtained from compound (+)-**8** by a two-step route through sequential sodium methoxide rearrangement to give the homopyroglutamic derivative (−)-**10** followed by acid-promoted cyclization. The *NH*-bis-γ-lactam (+)-**12** was obtained in a 64% yield by using ruthenium-catalyzed allyl breakage (Scheme 3). Worthy of note are the examples in Schemes 2 and 3, which show the selective N−C bond breakage of the *N*-allyl moiety in the presence of the *N*-*p*-methoxyphenyl functionality, allowing differentiation between two chemically equivalent functional groups within the same molecule.

Next we moved to the alicyclic series, testing the *N*-allyl cleavage protocol in both aromatic and aliphatic amides **13**. As expected, the corresponding free amides **15** could be smoothly obtained via the corresponding enamides **14** through ruthenium catalysis (Scheme 4).

The extension of the above methodology to related systems bearing extra heteroatoms was studied next. Fortunately the ruthenium-catalyzed allyl cleavage worked nicely for imides, pyrazolidones, hydantoins, and oxazolidinones **16a–d** (Scheme 5). Although the 3-allyl-2-thioxo-4-thiazolidinone **16e** tolerates the isomerization reaction conditions, it was necessary to increase the catalyst loading from 5 to 15 mol%.[17] However, the 2-thioxo-4-thiazolidinone moiety was not compatible with the RuO_4 step.[18]

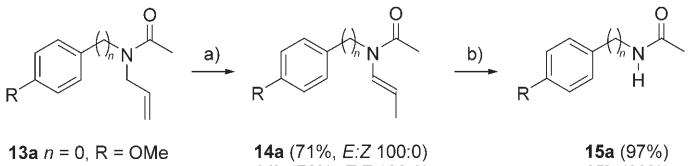
It has been reported that well-characterized ruthenium hydride species are formed by thermal decomposition of *N*-



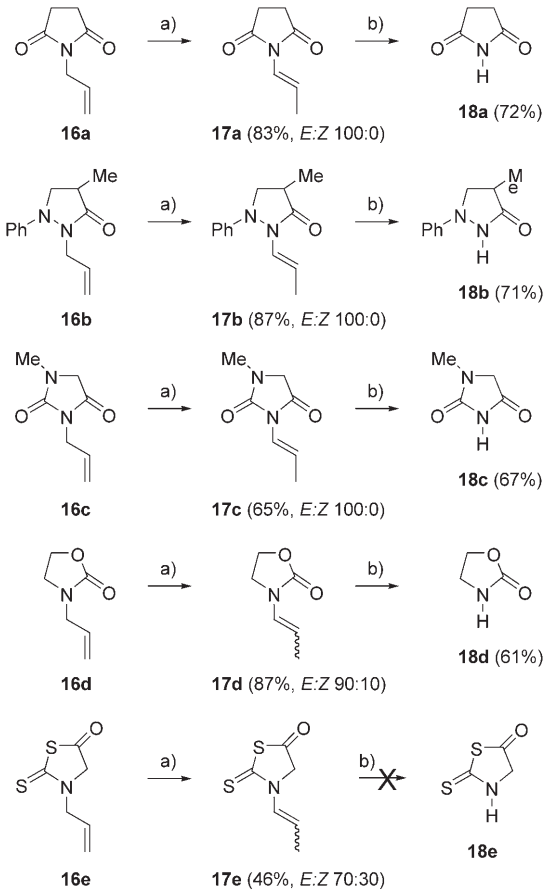
(+)-8 (−)-10 (65%) (+)-12 (64%) (+)-11 (100%)

Scheme 3. Ruthenium-catalyzed deprotection of *N*-allyl bis-γ-lactams. Reagents and conditions: a) MeONa, MeOH, RT; b) PTSA cat., Dean–Stark apparatus, toluene, reflux; c) 5 mol% [$(PCy_3)_2Cl_2Ru$=CHPh], toluene, 110°C. d) $RuCl_3$–$NaIO_4$, 1,2-dichloroethane–H_2O (1:1), aqueous workup (sat. aq $NaHCO_3$ + cat. Na_2CO_3). PMP = 4-$MeOC_6H_4$; PTSA = *p*-toluenesulfonic acid.

heterocyclic-based Grubbs carbene,[19] and it has been noted that ruthenium hydride complexes are formed as byproducts during the preparation of second-generation Grubbs catalyst.[20] In addition, a substrate-induced decomposition route involving β-hydride transfer from a ruthenacyclobutane intermediate has been investigated.[21] We believe that the isomerization process from *N*-allyl lactams, imides, and analo-

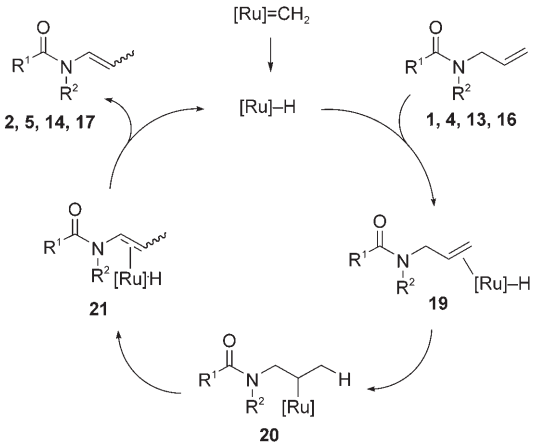


Scheme 4. Ruthenium-catalyzed deprotection of amides. Reagents and conditions: a) 5 mol% $[(PCy_3)_2Cl_2Ru{=}CHPh]$, toluene, 110 °C; b) $RuCl_3$–$NaIO_4$, 1,2-dichloroethane–H_2O (1:1), aqueous workup (sat. aq $NaHCO_3$ + cat. Na_2CO_3).



Scheme 5. Ruthenium-catalyzed deprotection of imides, pyrazolidones, hydantoins, and oxazolidinones. Reagents and conditions: a) 5 mol% $[(PCy_3)_2Cl_2Ru{=}CHPh]$, toluene, 110 °C; b) $RuCl_3$–$NaIO_4$, 1,2-dichloroethane–H_2O (1:1), aqueous workup (sat. aq $NaHCO_3$ + cat. Na_2CO_3).

gous enamide-like moieties is catalyzed by either a hydride decomposition compound or alternatively by impurities remaining from catalyst synthesis. The isomerization may occur according to the hydride mechanism, by hydrometallation followed by β-elimination, analogous to the double bond migration of allyl ethers promoted by related ruthenium complexes.[22] This metal hydride mechanism, which requires the presence of a coordinatively unsaturated ruthenium hydride species is shown in Scheme 6. Coordination of the olefin to the metal centre gives a π-allyl complex **19**, initiating the metal hydride addition to the olefin in a Markovnikov fashion to afford a σ-alkyl complex **20**. Subsequent β-hydride elimination gives the enamide π complex **21**, which decomplexes to the free enamide regenerating the catalytically active species.



Scheme 6. Mechanistic explanation for the ruthenium Grubbs' carbene-catalyzed amide-enamide isomerization.

Conclusion

In conclusion, we have presented a convenient methodology for the catalytic deprotection of *N*-allylic amide-like moieties. In addition to the novelty of the method, it is general, selective, and operationally simple, offering the first ruthenium-catalyzed deallylation of amides, lactams, imides, pyrazolidones, hydantoins, and oxazolidinones. This protocol is tolerant towards different functionalities as well as the stereocentres present in the molecule. Taking together these observations, this C–N bond cleavage has the potential to significantly extend the scope of the allyl protecting group in synthesis.

Experimental Section

General methods: Melting points were taken by using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in $CDCl_3$, except when otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). LRMS and HRMS were taken on a HP5989 A spectrometer by using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Optical rotations were measured by using a Perkin–Elmer 241 polarimeter. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 25 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na-benzophenone. Benzene, dichloromethane, and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Flash chromatography was performed by using Merck silica gel 60 (230–400 mesh).

General procedure for the isomerization reaction of *N*-allyl amides, lactams, imides, and congeners: $[Cl_2(Cy_3P)_2Ru{=}CHPh]$ (0.01 mmol) was added in portions under argon to a solution, protected from the sunlight, of the corresponding allylic compound (0.20 mmol) in anhydrous toluene (6 mL), and the mixture was heated at reflux. The reaction was monitored by TLC. After completion, the mixture was concentrated under reduced pressure, and was purified by column chromatography, eluting with EtOAc/hexanes mixtures to give analytically pure enamide-like compounds. Spectroscopic and analytical data for some representative pure forms of the above enamides follow.[23]

(*Z*)-2d: From 110 mg (0.72 mmol) of 1-allyl-azepan-2-one **1d** and after column chromatography (hexanes/EtOAc 3:1) 79 mg (72%) of compound (*Z*)-**2d** was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 6.19$ (dd, $J = 8.4$, 1.7 Hz, 1H), 5.14 (m, 1H), 3.40 (m, 2H), 2.51 (m, 2H), 1.63 (m, 6H), 1.51 ppm (dd, $J = 7.1$, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 175.6$, 133.7, 118.1, 51.0, 37.3, 29.9, 28.7, 23.3, 14.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1652\ cm^{-1}$; MS (ES): *m/z* (%): 154 (100) $[M+H]^+$, 153 (8) $[M]^+$; elemental analysis calcd (%) for $C_9H_{15}NO$ (153.2): C 70.55, H 9.87, N 9.14; found C 70.42, H 9.83, N 9.18.

(*E*)-(±)-5d: From 150 mg (0.56 mmol) of 1-allyl-β-lactam (±)-**4d** and after column chromatography (hexanes/EtOAc 5:1), 108 mg (72%) of compound (*E*)-(±)-**5d** was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.28$ (m, 1H), 7.14 (m, 2H), 6.59 (m, 3H), 6.36 (m, 1H), 6.25 (m, 1H), 6.07 (dd, $J = 9.2$, 1.7 Hz, 1H), 5.42 (d, $J = 4.6$ Hz, 1H), 5.30 (d, $J = 4.6$ Hz, 1H), 4.93 (dd, $J = 9.2$, 7.3 Hz, 1H), 1.56 ppm (dd, $J = 7.3$, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 163.3$, 157.2, 147.6, 143.3, 129.4 (2C), 122.4, 120.8, 115.7 (2C), 114.8, 110.9, 110.5, 81.6, 58.2, 15.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1751\ cm^{-1}$; MS (ES): *m/z* (%): 208 (100) $[M+H]^+$, 207 (9) $[M]^+$; elemental analysis calcd (%) for $C_{11}H_{13}NO_3$ (207.2): C 63.76, H 6.32, N 6.76; found C 63.64, H 6.29, N 6.73.

Preparation of (+)-5e: From 200 mg (0.66 mmol) of 1-allyl-β-lactam (+)-**4e** and after column chromatography (hexanes/EtOAc 2:1), 81 mg (40%) of the less polar compound (*E*)-(+)-**5e** and 79 mg (39%) of the more polar compound, its *Z* isomer were obtained.

(*E*)-(+)-5e: Colorless oil; $[\alpha]_D = +184.3$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.23$ (m, 2H), 6.99 (m, 3H), 6.36 (dd, $J = 14.3$, 1.6 Hz, 1H), 5.79 (dd, $J = 14.3$, 6.9 Hz, 1H), 5.16 (d, $J = 5.4$ Hz, 1H), 4.42 (m, 1H), 4.22 (m, 1H), 3.97 (m, 1H), 3.68 (m, 1H), 1.67 (dd, $J = 6.8$, 0.6 Hz; 3H), 1.39 (s, 3H; Me), 1.27 ppm (s, 3H; Me); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 163.0$, 157.4, 129.7 (2C), 122.8, 121.9, 115.9 (2C), 112.9, 109.9, 79.7, 76.9, 67.1, 61.9, 26.9, 26.8, 25.1, 15.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1753\ cm^{-1}$; MS (ES): *m/z* (%):304 (100) $[M+H]^+$, 303 (7) $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{21}NO_4$ (303.3): C 67.31, H 6.98, N 4.62; found C 67.43, H 6.94, N 4.59.

(*Z*)-(+)-5e: Colorless oil; $[\alpha]_D = +233.0$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.24$ (m, 2H), 6.97 (m, 3H), 5.96 (m, 1H), 5.18 (m, 2H), 4.42 (m, 1H), 4.10 (m, 2H), 3.68 (m, 1H), 1.73 (dd, $J = 7.1$, 0.6 Hz, 3H), 1.39 (s, 3H), 1.14 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 163.2$, 157.4, 129.7 (2C), 122.7, 121.9, 118.7, 115.9 (2C), 115.7, 109.9, 79.4, 66.9, 61.8, 26.8, 25.1, 14.3 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1752\ cm^{-1}$; MS (ES): *m/z* (%): 304 (100) $[M+H]^+$, 303 (10) $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{21}NO_4$ (303.3): C 67.31, H 6.98, N 4.62; found C 67.44, H 6.90, N 4.65.

Compound (*E*)-14a: From 120 mg (0.59 mmol) of 1-allyl-acetamide **13a** and after column chromatography (hexanes/EtOAc (3:1), 85 mg (71%) of compound (*E*)-**14a** was obtained as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.35$ (dd, $J = 14.3$, 1.5 Hz, 1H), 6.99 (m, 2H), 6.91 (m, 2H), 4.33 (m, 1H), 3.78 (s, 3H), 1.77 (s, 3H), 1.56 ppm (dd, $J = 6.7$, 1.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 167.5$, 159.1, 133.2, 129.9, 129.2, 115.1, 109.1, 55.5, 23.2, 15.1 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1654\ cm^{-1}$; MS (EI): *m/z* (%): 205 (100) $[M]^+$; elemental analysis calcd (%) for $C_{12}H_{15}NO_2$ (205.2): C 70.22, H 7.37, N 6.82; found C 70.10, H 7.34, N 6.78.

Compound (*E*)-17b. From 200 mg (0.926 mmol) of 2-allyl-4-methyl-1-phenyl-pyrazolidin-3-one **16b** and after column chromatography (hexanes/EtOAc 3:1), 174 mg (87%) of compound (*E*)-**17b** was obtained as a orange oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.20$ (m, 5H), 6.35 (dd, $J = 9.6$, 1.6 Hz, 1H), 4.83 (m, 1H), 3.89 (dd, $J = 11.3$, 7.6 Hz, 1H), 3.50 (t, $J = 11.3$ Hz, 1H), 2.70 (m, 1H), 1.53 (dd, $J = 4.4$, 1.6 Hz, 1H), 1.05 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 173.0$, 150.1, 129.7, 129.3, 123.6, 120.6, 118.5, 111.5, 62.9, 34.0, 13.1, 12.7 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1722\ cm^{-1}$; MS (ES): *m/z* (%): 217 (100) $[M+H]^+$, 216 (10) $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{16}N_2O$ (216.3): C 72.19, H 7.46, N 12.95; found C 72.30, H 7.50, N 13.00.

General procedure for the cleavage of enamide derivatives. Preparation of free *NH*-amides, lactams, imides, and congeners: Aqueous $RuCl_3$ (0.2 mL, 3.5 mol%) and solid $NaIO_4$ (0.4 mmol) were sequentially added to a solution of the corresponding enamide derivative (0.20 mmol) in a 1,2-dichloroethane-water mixture (2 mL, 1:1). The reaction mixture was stirred at room temperature until complete disappearance of the starting material was observed (TLC), before being quenched with aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic phase was concentrated and the resulting residue was dissolved in acetone and stirred with saturated aq $NaHCO_3$ (0.33 mL) and Na_2CO_3 (0.02 mmol). The mixture was extracted with EtOAc, washed with water, dried over $MgSO_4$, filtered, and concentrated to give pure *NH*-compounds **3**, **6**, **9**, **12**, **15**, and **18**. Spectroscopic and analytical data for some representative pure forms of the above free *NH*-compounds follow.

***NH*-β-Lactam (±)-6a**: From 87 mg (0.385 mmol) of enamide derivative (±)-**5a**, compound (±)-**6a** (58 mg, 64%) was obtained as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 6.90$ (s, 1H), 6.70 (m, 3H), 5.11 (d, $J = 4.7$ Hz, 1H), 4.65 (d, $J = 5.7$ Hz, 1H), 3.73 and 3.69 (s, each 3H), 3.16 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 168.2$, 153.6, 151.2, 125.4, 113.7, 113.4, 111.1, 86.9, 58.6, 55.8, 55.7, 53.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3408$, 1766 cm^{-1}; MS (ES): *m/z* (%): 238 (100) $[M+H]^+$, 237 (7) $[M]^+$; elemental analysis calcd (%) for $C_{12}H_{15}NO_4$ (237.3): C 60.75, H 6.37, N 5.90; found C 60.88, H 6.40, N 5.87.

***NH*-β-Lactam (+)-6c**: From 51 mg (0.15 mmol) of enamide derivative (+)-**5c**, compound (+)-**6c** (42 mg, 95%) was obtained as a colorless oil; $[\alpha]_D = +12.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 6.20$ (s, 1H), 4.70 (d, $J = 4.9$ Hz, 1H), 4.01 (m, 2H), 3.51 (m, 2H), 1.32 and 1.20 (s, each 3H), 0.77 (s, 9H), 0.09 and 0.01 ppm (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 166.2$, 107.1, 76.9, 66.5, 57.7, 26.8, 25.5, 24.9, 17.8 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3392$, 1764 cm^{-1}; MS (ES): *m/z* (%): 302 (100) $[M+H]^+$, 301 (14) $[M]^+$; elemental analysis calcd (%) for $C_{14}H_{27}NO_4Si$ (301.5): C 55.78, H 9.03, N 4.65; found C 55.80, H 8.99, N 4.62.

***NH*-Bis-γ-lactam (+)-12**: From 20 mg (0.049 mmol) of the corresponding enamide derivative, compound (+)-**12** (14 mg, 79%) was obtained as a orange oil; $[\alpha]_D = +67.1$ ($c = 0.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta = 7.21$ (m, 5H), 6.70 (m, 4H), 4.78 (d, $J = 6.7$ Hz, 1H), 4.56 (d, $J = 1.7$ Hz, 1H), 4.30 (d, $J = 5.1$ Hz, 1H), 3.64 (s, 3H), 3.62 (m, 1H), 3.49 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): $\delta = 172.2$, 171.6, 158.7, 157.5, 129.9, 129.2, 125.4, 123.1, 116.8, 115.1, 82.3, 77.6, 68.4, 60.8, 59.2, 55.9 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3390$, 1722, 1719 cm^{-1}; MS (ES): *m/z* (%): 409 (100) $[M+H]^+$, 408 (11) $[M]^+$; elemental analysis calcd (%) for $C_{20}H_{20}N_2O_5$ (368.4): C 65.21, H 5.47, N 7.60; found C 65.33, H 5.44, N 7.64.

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