Ruthenium-Catalyzed Chemoselective N-Allyl Cleavage: Novel Grubbs Carbene Mediated Deprotection of Allylic Amines

Benito Alcaide,*[a] Pedro Almendros,*[b] and Jose M. Alonso[a]

Abstract: A novel application of the Grubbs carbene complex has been discovered. The first examples of the catalytic deprotection of allylic amines with reagents other than palladium catalysts have been achieved through Grubbs carbene mediated reaction. Significantly, the catalytic system directs the reaction toward the selective deprotection of allylic amines (secondary as well as tertiary) in the presence of allylic ethers. A variety of substrates, including enantiomerically pure multifunctional piperidines, are also usable. The new method is more convenient, chemoselective, and operationally simple than the palladium-catalyzed method. The current mechanistic hypothesis invokes a nitrogen-assisted ruthenium-catalyzed isomerization, followed by hydrolysis of the enamine intermediate. We believe that the reactive species involved in the reaction may be an Ru–H species rather than the Grubbs carbene itself. Thus, the isomerization may occur according to the hydride mechanism. The synthetic utility of this ruthenium-catalyzed allyl cleavage is illustrated by the preparation of indolizidine-type alkaloids.

Keywords: amines · carbenes · cleavage reactions · protecting groups · ruthenium

Introduction

As the coordination chemistry of ruthenium complexes has progressed, the characteristic features of ruthenium (for example, high electron transferability, low redox potentials, stability of reactive metallic species, metallacycles, and metal carbenes) have opened the way for a broad variety of catalytic transformations. These include olefin metathesis,[1] Kharasch addition reactions,[2] hydrosilylation of carbonyls,[3] and enol ester synthesis.[4] The chemistry of late-transition-metal carbene complexes has recently received much attention, primarily due to the high catalytic activity of phosphine and imidazolidine ruthenium carbene complexes in olefin metathesis. Olefin metathesis is a catalytic reaction in which alkenes are converted into new products through the rupture and reformation of C–C double bonds. Depending on the starting material (cyclic or acyclic alkenes) and the reaction parameters, ring-closing metathesis (RCM), acyclic diene metathesis (ADMET), or ring-opening metathesis polymerization (ROMP) proceed. The most useful ruthenium carbene complex in the series is the Grubbs catalyst, $[(PCy_3)_2Cl_2Ru{=}CHPh]$ (Cy = cyclohexyl), which bears a benzylidene unit.[5] Being highly active and remarkably tolerant to common functional groups, this compound has found many applications in both organic and polymer chemistry. On the other hand, neither improvements in selectivity nor the invention of new reactions have abated the dependence of modern organic chemistry on protecting groups.[6] The allyl moiety is a protecting group that permits orthogonal protection strategies with a wide range of protecting groups, a property that allows its use in multistep synthetic schemes. The removal of allylic protecting groups through catalytic π-allyl palladium methodology has recently received growing attention,[7] especially in the field of peptide chemistry. Allyl carboxylates, carbonates, carbamates, ethers, and amines have been successfully deallylated. However, this methodology requires the presence of both the palladium catalyst and a nucleophilic compound as an allyl group scavenger. In this contribution, we present full details of a novel, simple, chemoselective, and general ruthenium-catalyzed deprotection

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author and contains compound characterization data and experimental procedures for compounds **1a–k**, **2a**, **2d**, **2e**, **2g–k**, **3a–c**, **4a**, **5a–g**, (+)-**6b**, (+)-**6d**, (+)-**6f**, (−)-**6g**, (+)-**7c**, (−)-**7e**, **10d**, **10h**, and **10j**.

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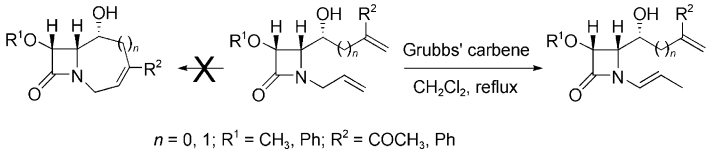
of tertiary allylic amines,[8] together with its extension to secondary allylic amines. In addition, the utility of the N-allyl cleavage is demonstrated by a process leading to indolizidines. To our knowledge, there are no other examples for the catalytic deprotection of allylic amines that do not use a palladium catalyst.[9] In addition, reactions providing a straightforward rupture of C–N bonds are rare.[10]

Results and Discussion

In our ongoing project directed toward the asymmetric synthesis of natural products and derivatives of biological interest,[11] we observed that in some cases isomerization to the internal double bond in an N-allyl β-lactam is favored over ring-closing metathesis (Scheme 1).[12] The higher stability of

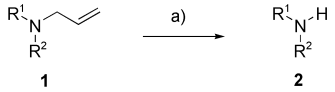


n = 0, 1; R^1 = CH_3, Ph; R^2 = $COCH_3$, Ph

Scheme 1. Grubbs catalyst promoted isomerization of N-allyl-β-lactams.

enamides in comparison with enamines favors the double-bond isomerization and thereby prevents N-allyl cleavage. On the basis of these principles, it was to be expected that successful catalytic C–N cleavage from an enamine intermediate could be attained by using allylic amines as substrates.

The highly selective properties of various transition-metal-derived reagents would seem to recommend their application to the removal of the allyl protecting group in amines, but only palladium complexes have been probed as useful catalysts.[7] However, such catalysts do not distinguish between O-allyl ethers and N-allyl amines. Therefore we were interested in the development of an alternative catalytic N-deallylation method that can smoothly provide free amines. Fortunately, an investigation of the chemistry of the Grubbs ruthenium carbene led to the discovery that it is an efficient catalyst for the deprotection of allylic amines. Among the various solvents and conditions tested, we found that toluene at reflux temperature gave the best yields of N-deprotected products. The Grubbs catalyst is known to be moderately thermally unstable,[13] with the thermolytic half-life having been reported to be eight days at 55 °C.[13a] To circumvent this problem, the Grubbs carbene was added in small portions every twenty minutes (5 mol % is the overall amount of all the portions). Thus, the catalytic species is continuously being renewed by fresh Grubbs carbene. Exposure of the tertiary allyl amines **1** to the ruthenium catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] under our standard reaction conditions (5 mol % catalyst, 0.03 M substrate, toluene, 110 °C) resulted in clean formation of the secondary amines **2** in good yields (62–81 %) after chromatographic purification (Table 1, Scheme 2). Attempts to effect the reaction at tem-



1 **2**

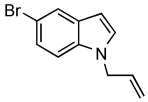
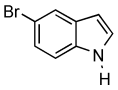
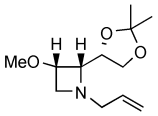
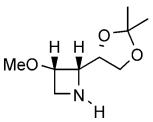
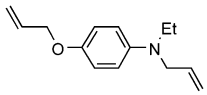
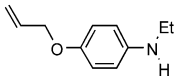
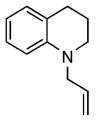
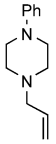
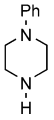
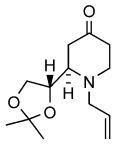
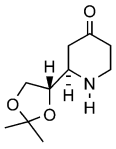
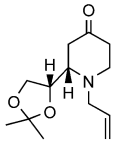
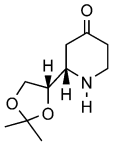
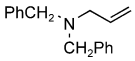
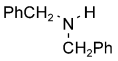
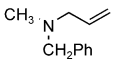
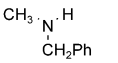
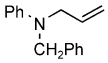
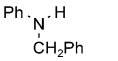
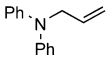
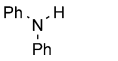
Scheme 2. Grubbs carbene catalyzed deprotection of tertiary allylic amines. a) 5 mol % [$(PCy_3)_2Cl_2Ru$=CHPh], toluene, 110 °C.

peratures lower than 50 °C slowed the reaction considerably. Incomplete conversion was observed on decreasing the amount of catalyst. On the contrary, increasing the catalyst loading from 5 to 10 mol % did increase the conversion (typically from 95 % to quantitative) but the yield of deallylated amine increased very little. Tertiary allylic amines, many of which bear pendant functionalities, were efficiently and catalytically deallylated by the Grubbs carbene. Aromatic as well as aliphatic amines were amenable to this novel deallylation reaction. As a good example, the strained four-membered cyclic amine (+)-**1b** smoothly yielded the enantiomerically pure azetidine (−)-**2b** (entry 2, Table 1). Treatment of compounds (+)-**1f** and (−)-**1g** with the Grubbs carbene forms the piperidines (+)-**2f** and (−)-**2g**, bearing two chiral centers, in 78 and 69 % yield, respectively (entries 6 and 7, Table 1). Piperidines (+)-**2f** and (−)-**2g** showed a single set of signals in their ^{1}H NMR spectra, thus proving again that this transformation proceeds without erosion of stereochemical integrity. The ability of the Grubbs carbene to selectively deprotect allylic amines in the presence of allylic ethers (entry 3, Table 1) deserves special mention, as it competes favorably with the π-allyl palladium deallylation methodology. Conjugation of the new double bond with the lone pair of the nitrogen atom is believed to promote the enamine intermediate formation in allyl amines, with this ability being minimized in allyl ethers.[14] In addition to this exquisite chemoselectivity, the extraordinary functional group tolerance of the ruthenium-based catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] coupled with its commercial availability makes it a very convenient catalyst.

As recently outlined, ligand modification in the Grubbs carbene improves its excellent application profile even further.[15] We thought that it would be of significant interest to see if the same chemistry occurs with these second-generation catalysts. Deallylation of some of the amines was effect-

Abstract in Spanish: *Se ha descubierto un método de desalilación de aminas catalizado por el carbeno de Grubbs, lo que constituye el primer ejemplo de desalilación catalítica en el que no participan complejos de paladio. El sistema catalítico lleva a cabo la desprotección selectiva de alilaminas (tanto secundarias como terciarias) en presencia de éteres alílicos. Se han utilizado una gran variedad de sustratos, como por ejemplo piperidinas enantiopuras altamente funcionalizadas. Este nuevo método es más útil y versátil que el método que utiliza paladio. Creemos que se produce una isomerización alil amina-enamina, seguida de hidrólisis. La especie catalítica activa puede ser un hidruro de rutenio derivado del carbeno de Grubbs. La utilidad sintética de esta desalilación catalítica se ha puesto de manifiesto en la preparación de indolizidinas.*

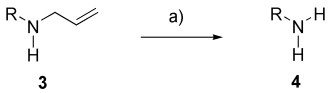
Table 1. Grubbs carbene mediated N-deallylation of tertiary allylic amines.[a]

	Substrate		t [h]	Product		Yield [%][b]
1		**1a**	5		**2a**	81
2		(+)-**1b**	1		(−)-**2b**	49
3		**1c**	1		**2c**	68
4		**1d**	5		**2d**	77
5		**1e**	4.5		**2e**	75
6		(+)-**1f**	4.5		(+)-**2f**	78
7		(−)-**1g**	2		(−)-**2g**	69
8		**1h**	3.5		**2h**	77
9		**1i**	1.5		**2i**	78
10		**1j**	3.5		**2j**	71
11		**1k**	3		**2k**	62

[a] All reactions were carried out on the 1 mmol scale. [b] Yield of pure product with correct analytical and spectral data.

ed with the more stable second-generation ruthenium-based catalyst [Cl_2(Im)(Cy_3P)Ru=CHPh] (Im = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene), which led to essentially identical results to those observed with the Grubbs carbene. As replacement of the first-generation Grubbs catalyst with its second-generation analogue neither accelerated the reaction rate nor improved the yield of N-deallylated amines **2**, we chose the less expensive first-generation Grubbs carbene for our study.

Extrapolation of the deprotection of tertiary allyl amines to secondary allyl amines is not obvious, since free bases are claimed to be ineffective for RCM mediated by the Grubbs catalyst because of poisoning of the catalyst by the amine functionality due to coordination of the amine group to the ruthenium.[16] Scheme 3 and Table 2 illustrate several examples of deprotection of nitrogen on secondary allylic amines

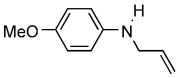
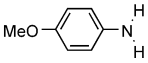
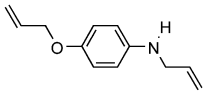
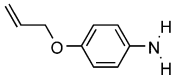
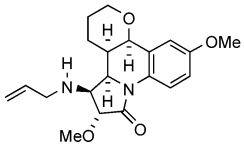
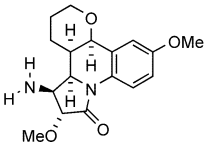


3 **4**

Scheme 3. Grubbs carbene catalyzed deprotection of secondary allylic amines. a) 5 mol% [(PCy_3)$_2$$Cl_2$Ru=CHPh], toluene, 110 °C.

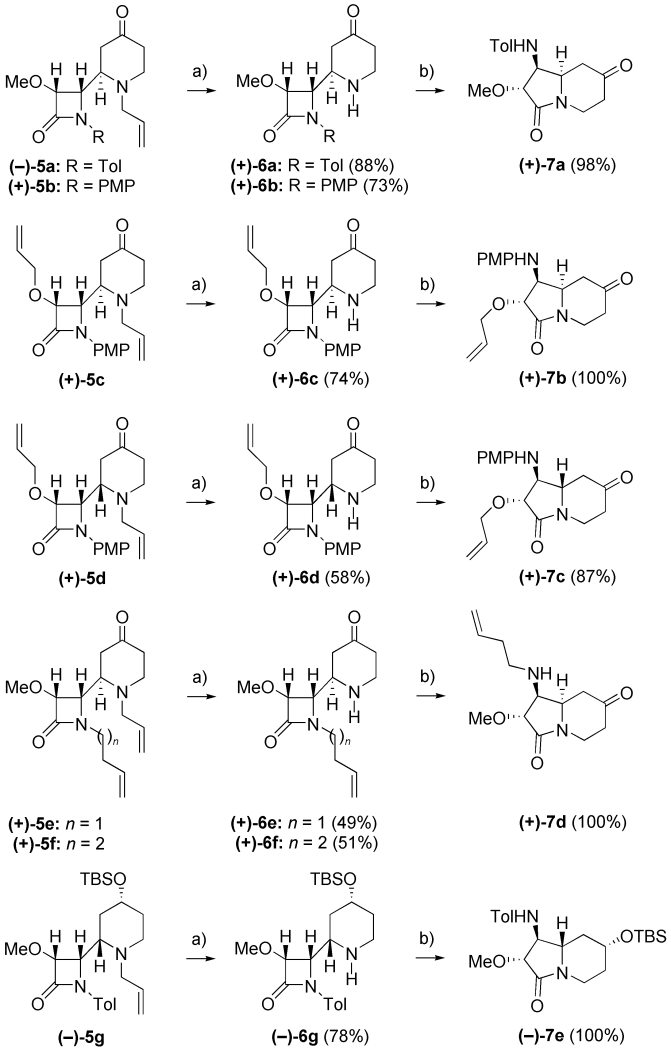
3. All substrates reacted efficiently to afford high yields of the corresponding primary amines **4**. Noteworthy cases include a chemoselective N-deallylation in presence of an O-allyl ether moiety, which remains unchanged (entry 2, Table 2), and a pyrrolidino quinoline (entry 3, Table 2), the parent system of which is of known utility in pharmacology.[17] Because of the yield of the deprotection reaction, apparently the primary and secondary amine products have no inhibiting effect.

Table 2. Grubbs carbene mediated N-deallylation of secondary allylic amines.[a]

	Substrate		*t* [h]	Product		Yield [%][b]
1		**3a**	5		**4a**	81
2		**3b**	1		**4b**	57
3		(+)-**3c**	0.5		(+)-**4c**	52

[a] All reactions were carried out on the 1 mmol scale. [b] Yield of pure product with correct analytical and spectral data.

Several of the above examples provide interesting and useful structural motifs. For example, piperidines (+)-**2f** and (−)-**2g** can be converted into derivatives of pipecolic acid, a nonproteinogenic amino acid present in several natural products, some of which are of important pharmaceutical interest.[18] A further synthetic application of the present reaction is demonstrated in the following synthesis of indolizidinones. Piperidine-β-lactams can serve in the construction of indolizidine alkaloids, natural products with diverse and potent biological activities.[19] However, we have noticed difficulties in the elimination of nitrogen protecting groups on N-protected piperidine-β-lactams. As an example, on route to indolizidine (−)-**7e**, cerium ammonium nitrate (CAN) promoted oxidative cleavage of an *N*-4-methoxyphenyl substituent provided the key intermediate piperidine-β-lactam (−)-**6g** in low yield (approximately 40%).[20] In addition, the CAN-mediated deprotection was incompatible with the ketone group. Taking into consideration all these drawbacks, we tested the Grubbs carbene catalyzed N-deallylation on the series of compounds **5**. In the event, differently functionalized deprotected piperidine-β-lactams were achieved in good yields (Scheme 4). Again, the deprotection reactions show excellent chemoselectivity. In compounds (+)-**5c** and (+)-**5d** the β,γ-unsaturated ethers remained unreacted. In addition, (+)-**5e** and (+)-**5f** show that a selective N-deallylation can be achieved in presence of γ,δ-unsaturated or δ,ε-unsaturated amines. However, it should be noted that in the Grubbs carbene promoted reaction with compounds (+)-**5e** and (+)-**5f**, in addition to the N-deallylated products (+)-**6e** and (+)-**6f**, the corresponding RCM products were isolated as minor products (approximately 30% yield). Piperidine-2-azetidinones **6** were easily converted into indolizidinones **7** in excellent yields (87–100%). Thus, the ruthenium-catalyzed synthesis of piperidines **6** gives a novel improved access to indolizidine-type alkaloids **7** (Scheme 4).

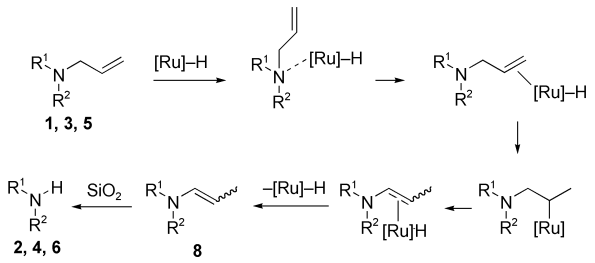


Scheme 4. Grubbs carbene catalyzed deprotection of *N*-allyl piperidines and its application to the synthesis of enantiopure indolizidines. a) 5 mol% $[(PCy_3)_2Cl_2Ru{=}CHPh]$, toluene, 110°C; b) MeONa, MeOH, room temperature. TBS = *tert*-butyldimethylsilyl, Tol = tolyl.

It may be reasonable to postulate that a nitrogen-assisted ruthenium-catalyzed isomerization to a more stable olefin took place, followed by hydrolysis under chromatographic workup of the enamine intermediate to the free amine. In order to probe this assumption we must show that an allylic amine does give the corresponding enamine intermediate **8** in the presence of a catalytic amount of the Grubbs carbene. This informative result was provided by monitoring the reactions of **1d** and **1h** with $[(PCy_3)_2Cl_2Ru{=}CHPh]$ by ^1H NMR spectroscopy. Indeed, we observed dis-

appearance of the terminal vinyl group and a comparable rate of appearance of a methyl group. Not unexpectedly, enamines **8d** and **8h** were characterized by the ^{1}H NMR spectra of the crude reaction products as a mixture of two isomers.

One piece of hypothesis that should be taken into account is that, due to the reaction conditions, it may be possible that there is not much catalyst left and the active species might well be a decomposition product derived from the Grubbs catalyst. In this case, the active catalyst is probably the corresponding hydrido derivative formed in situ under the reaction conditions rather than the Grubbs carbene. Thus, the isomerization may occur according to the hydride mechanism, by hydrometallation followed by β elimination, analogously to the double-bond migration of allyl ethers promoted by related ruthenium complexes.[21] This metal hydride mechanism for the deprotection of allylic amines is shown in Scheme 5. Precoordination of the substrate nitrogen atom directs subsequent coordination of the olefin to the metal center, with the metal-hydride addition to the



Scheme 5. Mechanistic explanation for the ruthenium-catalyzed deprotection of N-allyl amines.

olefin occurring in a Markovnikov fashion to afford a secondary metal alkyl. Subsequent β-hydride elimination gives the enamine which decomplexes and hydrolyzes to the deallylated amine. The formation of the ruthenium-hydride may arise from traces of impurities present in the commercial Grubbs carbene as well as the basic amine media under the reaction conditions.

Unfortunately, the ruthenium species derived from the Grubbs carbene and responsible for this activity is unclear, as ^{31}P and ^{1}H NMR studies are inconclusive.[14a,d] However, at the present time, we suggest that the reactive species involved in the reaction may be an Ru–H species rather than the Grubbs carbene itself. The ^{1}H NMR experiments of the reaction mixtures did not reveal whether the carbene fragment is a spectator ligand or disappears in the course of the reaction, because we were not able to observe neither a new ruthenium-hydride, nor a change in the ruthenium-alkylidene signal.

Conclusion

In conclusion, the Grubbs carbene complex efficiently catalyzes the deprotection of allylic amines. In addition to the novelty of the method (offering the first ruthenium-catalyzed deallylation of allylamines), it is general, selective, and operationally simple. The new method is more convenient than the conventional palladium-catalyzed method because Grubbs carbene is able to achieve a chemoselective deprotection of allyl amines in the presence of allyl ethers. In addition, the π-allyl palladium deallylation methodology requires the presence of both the palladium catalyst and a nucleophilic compound as an allyl group scavenger. We believe that this C–N bond cleavage involves a ruthenium-catalyzed isomerization to a more stable olefin, followed by hydrolysis of the resulting enamine. The specific ruthenium catalyst responsible for the isomerization is still in question. However, it is plausible that the reactive species involved in the reaction may be an Ru–H species rather than the Grubbs carbene itself. Taken together, these observations have the potential to significantly extend the scope of the allyl protecting group in synthesis. Application of the present efficient ruthenium catalytic cleavage to other moieties such as amides and lactams is currently underway in our group.

Experimental Section

General methods: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200 instrument. NMR spectra were recorded in $CDCl_3$ solutions unless otherwise stated. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken on a HP5989A spectrometer by using the chemical ionization mode (CI) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in deg dm^{-1} at 20 °C and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General procedure for the deallylation reaction of secondary and tertiary allylic amines: $[(PCy_3)_2Cl_2Ru{=}CHPh]$ (0.01 mmol) was added in portions to a solution of the allylic amine **1**, **3**, or **5** (0.20 mmol) in anhydrous toluene (6 mL) protected from the sunlight and under argon. The resulting mixture was heated at reflux until complete disappearance of the starting material (as monitored by thin-layer chromatography (TLC)) and was then concentrated under reduced pressure. Chromatography of the residue by eluting with hexanes/ethyl acetate mixtures gave analytically pure N-deallylated amines **2**, **4**, or **6**. Spectroscopic and analytical data for some representative pure forms of **2**, **4**, and **6** follow.[22]

Secondary amine (−)-2b: From *N*-allyl azetidine (+)-**1b** (60 mg, 0.264 mmol) and after flash chromatography by eluting with hexanes/ethyl acetate (2:1 containing 1% triethylamine), azetidine (−)-**2b** (25 mg, 49%) was obtained as a colorless oil. $[\alpha]_D = -10.3$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 4.41$ (m, 1H), 4.27 (t, $J =$ 6.2 Hz, 1H), 4.00 (m, 2H), 3.49 (m, 4H), 3.16 (s, 3H), 1.09, 1.06 (s, each 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 73.4$, 72.3, 72.0, 69.6, 68.6, 55.9, 51.0, 22.1, 22.0 ppm; MS (ES): m/z (%): 210 (11) $[M+Na]^+$, 188 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_9H_{17}NO_3$ (187.2): C 57.73, H 9.15, N 7.48; found: C 57.83, H 9.18, N 7.45.

Secondary amine 2c: From allyl (4-allyloxyphenyl)ethylamine **1c** (40 mg, 0.184 mmol) and after flash chromatography by eluting with hexanes/ethyl acetate (5:1), (4-allyloxyphenyl)ethylamine **2c** (22 mg, 68%) was obtained as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 6.74$ (m, 2H), 6.54 (m, 2H), 6.00 (m, 1H), 5.21 (m, 2H), 4.39 (m, 2H), 3.05 (q, $J = 7.0$ Hz, 2H), 1.18 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 151.6$, 143.7, 134.1, 117.5, 116.3, 114.7, 69.9, 39.9, 14.9 ppm; MS (EI): m/z (%): 178 (100) $[M]^+$; elemental analysis calcd (%) for $C_{11}H_{15}NO$ (177.2): C 74.54, H 8.53, N 7.90; found: C 74.48, H 8.50, N 7.88.

Secondary amine (+)-2f: From tertiary allylic amine (+)-**1f** (110 mg, 0.46 mmol) and after flash chromatography by eluting with ethyl acetate, piperidine (+)-**2f** (71 mg, 78%) was obtained as a colorless oil. $[\alpha]_D =$

+27.6 (c = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.93 (m, 2H), 3.68 (m, 1H), 3.36 (m, 1H), 2.85 (m, 2H), 2.38, 2.27 (m, each 2H), 2.02 (br s, 1H), 1.36, 1.29 (s, each 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 207.8, 109.4, 78.3, 66.2, 59.7, 45.2, 42.4, 26.5, 25.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3347, 1714 cm^{-1}; MS (CI): m/z (%): 200 (100) $[M+H]^+$, 199 (17) $[M]^+$; elemental analysis calcd (%) for $C_{10}H_{17}NO_3$ (199.3): C 60.28, H 8.60, N 7.03; found: C 60.36, H 8.62, N 7.01.

Primary amine 4b: From secondary allylic amine **3b** (63 mg, 0.33 mmol) and after flash chromatography by eluting with hexanes/ethyl acetate (2:1), 4-allyloxyphenylamine **4b** (28 mg, 57%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.72 (m, 2H), 6.58 (m, 2H), 5.96 (m, 1H), 5.27 (m, 2H), 4.40 (m, 2H), 3.39 (br s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 153.7, 139.8, 133.9, 117.4, 116.8, 116.1, 69.7 ppm; MS (EI): m/z (%): 150 (7) $[M+H]^+$, 149 (100) $[M]^+$; elemental analysis calcd (%) for $C_9H_{11}NO$ (189.3): C 72.46, H 7.43, N 9.39; found: C 72.57, H 7.46, N 9.43.

Primary amine (+)-4c: From secondary allylic amine (+)-**3c** (55 mg, 0.153 mmol) and after flash chromatography by eluting with ethyl acetate, the amino tetracycle (+)-**4c** (25 mg, 52%) was obtained as a colorless oil. $[\alpha]_D$ = +11.3 (c = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.95 (d, J = 8.9 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.79 (dd, J = 8.9, 2.5 Hz, 1H), 4.94 (d, J = 5.6 Hz, 1H), 3.74 and 3.71 (s, each 3H), 3.60 (m, 4H), 3.21 (d, J = 10.0 Hz, 1H), 2.36 (m, 1H), 1.41 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.8, 157.6, 129.5, 128.3, 122.6, 114.1, 112.2, 86.2, 72.6, 61.2, 59.3, 55.7, 55.6, 53.2, 32.9, 24.7, 20.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3330, 1712 cm^{-1}; MS (ES): m/z (%): 341 (11) $[M+Na]^+$, 319 (100) $[M+H]^+$, 318 (18) $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{22}N_2O_4$ (318.4): C 64.13, H 6.97, N 8.80; found: C 64.24, H 7.00, N 8.84.

Piperidine-β-lactam (+)-6a: From *N*-allyl piperidine (−)-**5a** (130 mg, 0.396 mmol) and after flash chromatography by eluting with ethyl acetate (containing 1% triethylamine), piperidine (+)-**6a** (100 mg, 88%) was obtained as a colorless oil. $[\alpha]_D$ = +116.1 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.24, 7.06 (m, each 2H), 4.60 (d, J = 5.4 Hz, 1H), 4.17 (dd, J = 5.4, 5.1 Hz, 1H), 3.62 (s, 3H), 3.32 (m, 2H), 2.72 (m, 1H), 2.34 (m, 4H), 2.24 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 207.9, 164.8, 134.5, 134.4, 129.6, 117.9, 82.8, 59.7, 57.1, 45.7, 42.9, 42.8, 20.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 1738, 1717 cm^{-1}; MS (ES): m/z (%): 289 (100) $[M+H]^+$, 288 (11) $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{20}N_2O_3$ (288.3): C 66.65, H 6.99, N 9.72; found: C 66.74, H 7.02, N 9.68.

Piperidine-β-lactam (+)-6c: From *N*-allyl piperidine (+)-**5c** (30 mg, 0.078 mmol) and after flash chromatography by eluting with ethyl acetate (containing 1% triethylamine), piperidine (+)-**6c** (20 mg, 74%) was obtained as a colorless oil. $[\alpha]_D$ = +21.4 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.28, 6.80 (m, each 2H), 5.88 (m, 1H), 5.25 (m, 2H), 4.77 (d, J = 5.4 Hz, 1H), 4.28 (m, 3H), 3.73 (s, 3H), 3.42 (m, 2H), 2.78 (m, 1H), 2.28 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 208.3, 165.1, 156.7, 133.2, 129.8, 119.2, 118.4, 114.6, 80.9, 72.5, 58.9, 57.6, 55.5, 45.9, 44.6, 43.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3350, 1740, 1715 cm^{-1}; MS (CI): m/z (%): 331 (100) $[M+H]^+$, 330 (18) $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{22}N_2O_4$ (330.4): C 65.44, H 6.71, N 8.48; found: C 65.31, H 6.69, N 8.51.

Piperidine-β-lactam (+)-6e: From *N*-allyl piperidine (+)-**5e** (65 mg, 0.223 mmol) and after flash chromatography by eluting with ethyl acetate (containing 1% triethylamine), piperidine (+)-**6e** (27 mg, 49%) was obtained as a colorless oil. $[\alpha]_D$ = +88.4 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.67 (m, 1H), 5.07 (m, 2H), 4.41 (d, J = 5.2 Hz, 1H), 3.67 (dd, J = 6.0, 5.2 Hz, 1H), 3.51 (m, 4H), 3.31 (m, 1H), 3.14 (m, 2H), 2.85 (m, 1H), 2.32 (m, 6H), 1.86 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 207.8, 167.7, 134.6, 117.2, 83.1, 59.6, 59.2, 57.5, 45.7, 45.5, 42.9, 40.6, 31.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 1739, 1714 cm^{-1}; MS (ES): m/z (%): 253 (100) $[M+H]^+$, 252 (12) $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{20}N_2O_3$ (252.3): C 61.88, H 7.99, N 11.10; found: C 61.99, H 8.02, N 11.06.

General procedure for the sodium methoxide promoted preparation of indolizidines 7: Sodium methoxide (0.6 mmol) was added in portions to a solution of the appropriate piperidine-β-lactam (0.15 mmol) in methanol (3 mL) at 0 °C. The reaction was stirred at room temperature until complete disappearance of the starting material (as monitored by TLC) and then water was added (0.5 mL). The methanol was concentrated under reduced pressure, the aqueous residue was extracted with ethyl acetate (5 × 3 mL), the organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the residue by eluting with hexanes/ethyl acetate mixtures gave analytically pure fused bicycles **7**.

Indolizidine (+)-7a: From piperidine-β-lactam (+)-**6a** (50 mg, 0.173 mmol), compound (+)-**7a** (49 mg, 98%) was obtained as an orange oil. $[\alpha]_D$ = +11.0 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.01, 6.59 (m, each 2H), 4.43 (m, 1H), 3.82 (d, J = 4.0 Hz, 1H), 3.76 (t, J = 4.0 Hz, 1H), 3.64 (s, 3H), 3.54 (m, 1H), 3.11 (m, 1H), 2.75 (dd, J = 14.3, 2.7 Hz, 1H), 2.50 (m, 3H), 2.26 (s, 3H), 1.25 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 205.1, 169.9, 143.5, 130.0, 128.4, 113.9, 83.4, 69.2, 60.5, 60.4, 47.1, 39.7, 37.9, 20.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 1725, 1715 cm^{-1}; MS (ES): m/z (%): 289 (100) $[M+H]^+$, 288 (15) $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{20}N_2O_3$ (288.3): C 66.65, H 6.99, N 9.72; found: C 66.76, H 7.02, N 9.68.

Indolizidine (+)-7b: From piperidine-β-lactam (+)-**6c** (20 mg, 0.058 mmol), compound (+)-**7b** (20 mg, 100%) was obtained as an orange oil. $[\alpha]_D$ = +83.2 (c = 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.73, 6.50 (m, each 2H), 5.87 (m, 1H), 5.24 (m, 2H), 4.47 (m, 2H), 4.26 (dd, J = 12.7, 6.1 Hz, 1H), 4.04 (m, 3H), 3.69 (s, 3H), 2.98 (m, 1H), 2.33 (m, 4H), 1.19 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 205.9, 168.2, 139.9, 137.2, 134.1, 118.5, 115.3, 114.7, 79.5, 71.4, 56.6, 55.9, 55.6, 42.3, 40.1, 38.4 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3442, 1723, 1712 cm^{-1}; MS (ES): m/z (%): 353 (9) $[M+Na]^+$, 331 (100) $[M+H]^+$, 330 (7) $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{22}N_2O_4$ (330.4): C 65.44, H 6.71, N 8.48; found: C 65.36, H 6.75, N 8.52.

Indolizidine (+)-7d: From piperidine-β-lactam (+)-**6e** (20 mg, 0.079 mmol), compound (+)-**7d** (20 mg, 100%) was obtained as an orange oil. $[\alpha]_D$ = +101.2 (c = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.69 (m, 1H), 4.99 (m, 2H), 4.39 (m, 1H), 3.80 (m, 1H), 3.76 (d, J = 7.4 Hz, 1H), 3.63 (s, 3H), 3.37 (t, J = 7.4 Hz, 1H), 2.91 (m, 1H), 2.60 (m, 2H), 2.39 (m, 6H), 1.19 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 206.5, 170.3, 135.5, 116.8, 81.9, 58.9, 58.5, 56.3, 47.2, 42.7, 40.3, 38.3, 34.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3447, 1721, 1710 cm^{-1}; MS (ES): m/z (%): 253 (100) $[M+H]^+$, 252 (9) $[M]^+$; elemental analysis calcd (%) for $C_{13}H_{20}N_2O_3$ (252.3): C 61.88, H 7.99, N 11.10; found: C 61.77, H 7.96, N 11.06.

Acknowledgments

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[1] For some reviews on olefin metathesis, see: a) R. H. Grubbs, T. M. Trnka, *Acc. Chem. Res.* **2001**, *34*, 18; b) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; c) M. R. Buchmeiser, *Chem. Rev.* **2000**, *100*, 1565; d) A. Fürstner, *Synlett* **1999**, 1523; e) D. L. Wright, *Curr. Org. Chem.* **1999**, *3*, 211; f) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; g) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371; h) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036. For recent theoretical studies of the mechanism of the ruthenium-catalyzed olefin metathesis, see: i) L. Cavallo, *J. Am. Chem. Soc.* **2002**, *124*, 8965; j) S. F. Vyboishchikov, M. Bühl, W. Thiel, *Chem. Eur. J.* **2002**, *8*, 3962; k) C. Adlhart, P. Chen, *Angew. Chem.* **2002**, *114*, 4668; *Angew. Chem. Int. Ed.* **2002**, *41*, 4484.

[2] For the unexpected reactivity of the Grubbs catalyst for Kharasch addition, see: J. A. Tallarico, L. A. Malnick, M. L. Snapper, *J. Org. Chem.* **1999**, *64*, 344.

[3] For the Grubbs carbene promoted activation of silanes in the presence of carbonyls, see: S. V. Maifeld, R. L. Miller, D. Lee, *Tetrahedron Lett.* **2002**, *43*, 6363.

[4] a) B. De Clercq, F. Verpoort, *Tetrahedron Lett.* **2001**, *42*, 8959; b) H. Doucet, B. Martín-Vaca, C. Bruneau, P. H. Dixneuf, *J. Org. Chem.* **1995**, *60*, 7247.

[5] a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100. For a review on nonmetathetic behavior patterns of the Grubbs carbene, see: b) B. Alcaide, P. Almendros, *Chem. Eur. J.* **2003**, *9*, 1258.

[6] a) T. W. Greene, G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**; b) K. Jarowicki, P. Kocienski, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2495; c) P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, **1994**; d) M. Schelhaas, H. Waldmann, *Angew. Chem.* **1996**, *108*, 2192; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2056.

[7] For a review, see: F. Guibé, *Tetrahedron* **1998**, *54*, 2967.

[8] For a preliminary communication of a part of this work, see: B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Org. Lett.* **2001**, *3*, 3781.

[9] A cleavage of allyl amines which needs 100% rhodium catalyst was reported some years ago: a) B. Moreau, S. Lavielle, A. Marquet, *Tetrahedron Lett.* **1977**, *18*, 2591. More recently, the isomerization of *N*,*N*-dimethylallyl amine to the corresponding enamine induced by $[RuClH(CO)(PPh_3)]$ has been reported: b) K. Hiraki, T. Matsunaga, *Organometallics* **1994**, *13*, 1878.

[10] For an example of C–N bond cleavage in a Mo^{IV} bispyridine complex, see: a) T. M. Cameron, K. A. Abboud, J. M. Boncella, *Chem. Commun.* **2001**, 1224. For an example of intramolecular dealkylation of diamines with Ru^{II} complexes, see: b) M. E. Morilla, G. Morfes, M. C. Nicasio, T. R. Belderrain, M. M. Díaz-Requejo, C. Graiff, A. Tiripicchio, R. Sánchez-Delgado, P. J. Pérez, *Chem. Commun.* **2002**, 1848.

[11] See, for instance: a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Eur. J.* **2002**, *8*, 1719; b) B. Alcaide, P. Almendros, C. Aragoncillo, M. C. Redondo, *Chem. Commun.* **2002**, 1472; c) B. Alcaide, P. Almendros, C. Aragoncillo. *Chem. Eur. J.* **2002**, *8*, 3646; d) B. Alcaide, P. Almendros, R. Rodríguez-Acebes, *J. Org. Chem.* **2002**, *67*, 1925; e) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, C. Pardo, E. Sáez, M. R. Torres, *J. Org. Chem.* **2002**, *67*, 7004; f) B. Alcaide, P. Almendros, J. M. Alonso, M. C. Redondo, *J. Org. Chem.* **2003**, *68*, 1426.

[12] For the ruthenium-promoted isomerization of N-allyl amides to enamides, see: a) S. Krompiec, M. Pigulla, W. Szczepankiewicz, T. Bieg, N. Kuznik, K. Leszczynska-Sejda, M. Kubicki, T. Borowiak, *Tetrahedron Lett.* **2002**, *42*, 7095; b) S. S. Kinderman, J.-H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *Org. Lett.* **2001**, *3*, 2045; c) J. K. Stille, Y. Becker, *J. Org. Chem.* **1980**, *45*, 2139.

[13] a) M. Ulman, R. H. Grubbs, *J. Org. Chem.* **1999**, *64*, 7202; b) K. Melis, T. Opstal, F. Verpoort, *Eur. J. Org. Chem.* **2002**, 3779.

[14] For several reports noting related ruthenium-catalyzed isomerizations, see ref. [5b]. Since our preliminary communication, it has been reported that the second-generation Grubbs carbene is able to mediate isomerization of allyl ethers to the corresponding vinyl ethers: a) A. E. Sutton, B. A. Seigal, D. F. Finnegan, M. L. Snapper, *J. Am. Chem. Soc.* **2002**, *124*, 13390; b) C. Cadot, P. I. Dalko, J. Cossy, *Tetrahedron Lett.* **2002**, *43*, 1839; c) B. Schmidt, *Eur. J. Org. Chem.* **2003**, 816. There has also been a report that an isomerization of a terminal olefin to the internal alkene by using the second-generation Grubbs carbene proceeds faster than RCM: d) M. Arisawa, Y. Terada, M. Nakagawa, A. Nishida, *Angew. Chem.* **2002**, *114*, 4926; *Angew. Chem. Int. Ed.* **2002**, *41*, 4732.

[15] a) T. M. Trnka, J. P. Morgan, M. S. Sanford, T. E. Wilhelm, M. Scholl, T.-L. Choi, S. Ding, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 2546; b) K. Grela, M. Kim, *Eur. J. Org. Chem.* **2003**, 963; c) B. Cetinkaya, S. Demir, I. Özdemir, L. Toupet, D. Sémeril, C. Bruneau, P. H. Dixneuf, *Chem. Eur. J.* **2003**, *9*, 2323; d) A. M. Dunne, S. Mix, S. Blechert, *Tetrahedron Lett.* **2003**, *44*, 2733; e) J. P. Morgan, C. Morrill, R. H. Grubbs, *Org. Lett.* **2002**, *4*, 67; f) H. Wakamatsu, S. Blechert, *Angew. Chem.* **2002**, *114*, 2509; *Angew. Chem. Int. Ed.* **2002**, *41*, 2403; g) A. Fürstner, O. Guth, A. Düffels, G. Seidel, M. Liebl, B. Gabor, R. Mynott, *Chem. Eur. J.* **2001**, *7*, 4811; h) A. Fürstner, L. Ackermann, B. Gabor, R. Goddard, C. W. Lehmann, R. Mynott, F. Stelzer, O. R. Thiel, *Chem. Eur. J.* **2001**, *7*, 3236; i) S. Randl, S. J. Connon, S. Blechert, *Chem. Commun.* **2001**, 1796; j) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168; k) A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz, S. Nolan, *J. Org. Chem.* **2000**, *65*, 2204.

[16] G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.

[17] The isomeric pyrrolidino[2,1-*a*]isoquinoline nucleus represents a structural fragment of the erytrinan alkaloids, which possess antidepressant, muscarinic agonist, and antileukemic properties. For a review on erythrinanes, see: a) Y. Tsuda, T. Sano in *The Alkaloids: Chemistry and Pharmacology, Vol. 48* (Ed.: G. A. Cordell), Academic Press, San Diego, **1996**, Chapter 4, pp. 249. For a selected reference, see: b) I. González-Temprano, N. Sotomayor, E. Lete, *Synlett* **2002**, 593.

[18] For selected examples, see: a) X. Ginesta, M. A. Pericás, A. Riera, *Tetrahedron Lett.* **2002**, *43*, 779; b) N. U. Sata, R. Kuwahara, Y. Murata, *Tetrahedron Lett.* **2002**, *43*, 115.

[19] Their interesting biological activities include antiviral, antitumor, and glucosidase inhibition activities. For selected reviews, see: a) J. P. Michael, *Nat. Prod. Rep.* **2001**, *18*, 520; b) A. J. Vlietinck, T. De Bruyne, S. Apers, L. A. Pieters, *Planta Med.* **1998**, *64*, 97; c) J. P. Michael, *Nat. Prod. Rep.* **1997**, *14*, 619; d) J. R. Lidell, *Nat. Prod. Rep.* **1996**, *13*, 187; e) D. J. Robin, *Nat. Prod. Rep.* **1995**, *12*, 413; f) M. Ikeda, T. Sato, H. Ishibashi, *Heterocycles* **1988**, *27*, 1465.

[20] a) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Chem. Eur. J.* **2003**, *9*, 3415-3426; b) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, M. R. Torres, *Synlett* **2001**, 1531.

[21] D. V. McGrath, R. H. Grubbs, *Organometallics* **1994**, *13*, 224.

[22] Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

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