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A Novel Use of Grubbs' Carbene. Application to the Catalytic Deprotection of Tertiary Allylamines

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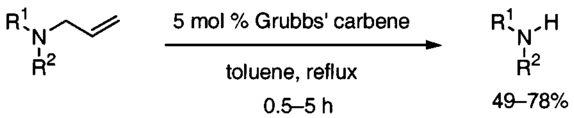
ABSTRACT

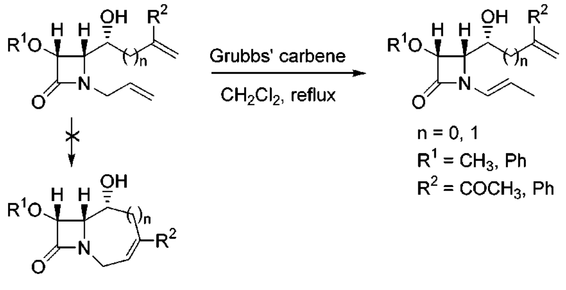


The first examples accounting for the catalytic deprotection of allylic amines by using reagents different from palladium catalysts have been achieved via Grubbs' carbene-mediated reaction. The current mechanistic hypothesis invokes a nitrogen-assisted ruthenium-catalyzed isomerization, followed by hydrolysis of the enamine intermediate. We believe that an unprecedented mode of ring opening of the ruthenacyclobutane was involved.

Neither improvements in selectivity nor the invention of new reactions have lessened the dependence of modern organic chemistry on protecting groups.[1] Allylic protecting groups and their removal through catalytic palladium π-allyl methodology have recently received growing attention,[2] 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. On the other hand, the chemistry of late transition metal carbene complexes has recently received much attention, primarily as a result of the high catalytic activity of phosphine and imidazolidine ruthenium carbene complexes in olefin metathesis.[3] The most useful Ru carbene in this series is Grubbs' catalyst, $Cl_2(Cy_3P)_2Ru{=}CHPh$, bearing a benzylidene unit.[4] Being highly active and remarkably tolerant to common functional groups, this compound found broad applications in both organic and polymer chemistry.[5] Here we present a new, synthetically simple, and general method toward N-deallylation of amines by using Grubbs' carbene. To our knowledge, there are no examples of the catalytic deprotection of allylic amines that do not use a palladium catalyst. In addition, reactions providing a straightforward rupture of C−N bonds are rare.[6]

In our ongoing project in the asymmetric synthesis of potentially bioactive products through β-lactams,[7] we found that in some cases the isomerization to the internal double bond in a *N*-allyl amide is favored versus ring-closing metathesis (Scheme 1).[8] On the basis of these results we assumed that successful catalytic C−N cleavage from an

Scheme 1



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(1) For a review, see: Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1589.

(2) For a review, see: Guibé, F. *Tetrahedron* **1998**, *54*, 2967.

(3) For some recent reviews, see: (a) Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565. (d) Fürstner, A. *Synlett* **1999**, 1523. (e) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (h) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

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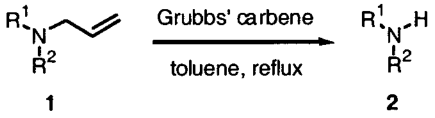
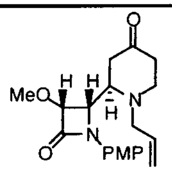
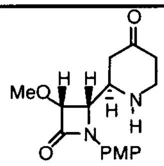
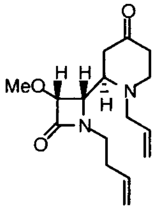
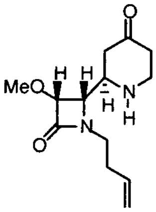
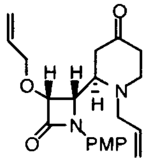
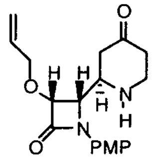
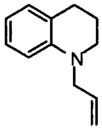
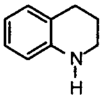
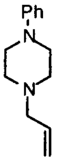
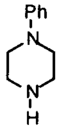
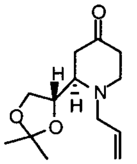
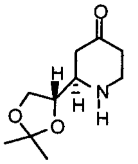
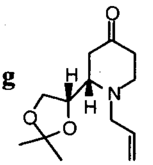
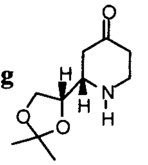
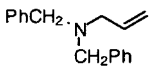
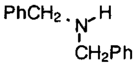
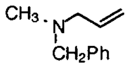
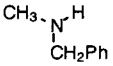
Table 1. Use of Grubbs' Carbene as Reagent for N-Deallylation[a]



entry	substrate	t (h)	product	yield (%)[b]
1	**(+)-1a** 	2	**(+)-2a** 	73
2	**(+)-1b** 	0.5	**(+)-2b** 	49[c]
3	**(+)-1c** 	0.5	**(+)-2c** 	74
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**  $PhCH_2NHCH_2Ph$	77
9	**1i** 	1.5	**2i**  CH_3NHCH_2Ph	78

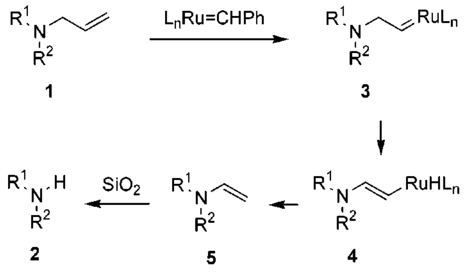
[a] All reactions were carried out on 1 mmol scale. PMP = 4-MeOC$_6$H$_4$. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] An additional 30% of RCM product was isolated as well.

enamine intermediate can be attained by using allylamines as a substrate.[9]

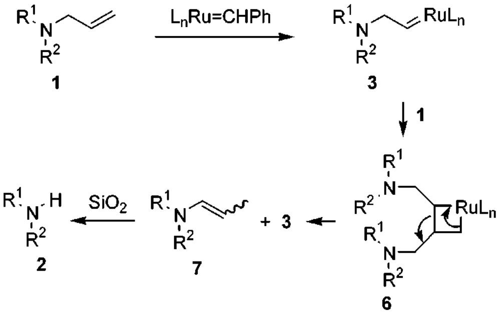
An investigation of this chemistry led to the discovery that Grubbs' ruthenium carbene is an efficient catalyst for the deprotection of allylamines. The treatment of tertiary allylamine (+)-**1a** in the presence of 5 mol % Cl$_2$(Cy$_3$P)$_2$Ru=CHPh in toluene at 110 °C for 2 h gave a deallylated product, isomerically pure secondary amine (+)-**2a**, in an isolated yield of 73% after chromatographic purification. Tertiary allylamines bearing a variety of substituents were smoothly catalytically deallylated by Grubbs' carbene to give the corresponding N-deprotected amines **2** (Table 1).[10] Aromatic as well as aliphatic amines were amenable to this novel deallylation reaction. The only exception was 1-allyl-2-phenyl indole, which gave recovered starting material together with a complex mixture of products in which the deallylated product was a minor component; this could be due to steric hindrance. Attempts to effect the reaction at temperatures lower than 50 °C (refluxing dichloromethane) notably increased the reaction time. The deallylation reactions of compounds (+)-**1b** (entry 2) and (+)-**1c** (entry 3) with the ruthenium catalyst deserve special mention, because we have previously reported the ring-closing metathesis of related β-lactam diene substrates[11] and **1a**−**b** are susceptible to both reaction pathways. Of interest is the ability of Grubbs' carbene for the selective deprotection of allylamines in the presence of allyl ethers (entry 3),[12] competing favorably with the π-allyl palladium deallylation methodology.

It may be reasonable to postulate that a nitrogen-assisted ruthenium-catalyzed isomerization to a more stable olefin took place,[13] followed by hydrolysis under chromatographic work up of the enamine intermediate to the NH-amine. From a mechanistic point of view, our results could be explained as illustrated in Scheme 2 or Scheme 3. Intermediates **3**−**7** can account for this catalytic cleavage reaction.

Scheme 2



Scheme 3



To probe the correct mechanism (Scheme 3) we must show that an allylamine does give the corresponding enamine intermediate **5** or **7** in the presence of a catalytic amount of Grubbs' carbene. This mechanistically informative result was provided by monitoring the reactions between **1d** and **1h** with $Cl_2(Cy_3P)_2Ru{=}CHPh$ by ^1H NMR spectroscopy. Indeed, we observed disappearance of the terminal vinyl group and a comparable rate of appearance of a methyl group, pointing to Scheme 3 as the correct mechanism. Intermediate metallacyclobutanes **6** evolve through a retro metathesis-like reaction involving the cleavage of bonds other than those accounting for the cycloreversion in the metathesis reaction to give enamines **7** and the metal-carbene complex **3**. Fragment **3** generated in this way could react with a new molecule of allylamine **1**, being involved again in the catalytic cycle. Not unexpectedly, enamines **7d** and **7h** were characterized by the ^1H NMR spectra of the crude reaction mixtures as a mixture of two isomers.

Grubbs' catalyst is known to be moderately termally unstable, and the thermolytic half-live of Grubbs' carbene was reported to be 8 days at 55 °C.[14] It should be mentioned that we used an experimental trick that proved to be very efficient in our previous report on RCM,[11] namely, Grubbs' carbene was added in small portions every 20 min (5 mol % is the overall amount of all the portions). In this way, the catalytic species is continuously being renewed by fresh Grubbs' carbene.

In conclusion, Grubbs' carbene efficiently catalyzes the deprotection of tertiary allylic amines. In addition to the novelty of the method, it is general, selective, and synthetically simple, offering the first ruthenium-catalyzed deallylation of allylamines. We believe that this C−N bond cleavage implicates a ruthenium-catalyzed isomerization to a more stable olefin, followed by hydrolysis of the resulting enamine. It may be involved an unprecedented mode of ring opening of the metathesis intermediate metalla-cyclobutane.

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(4) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(5) For the unexpected reactivity of Grubbs' catalyst for Kharasch addition, see: Tallarico, J. A.; Malnick, L. A.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344.

(6) For an example of a C−N bond cleavage in a Mo(IV) bispyridine complex, see: Cameron, T. M.; Abboud, K. A.; Boncella, J. M. *Chem. Commun.* **2001**, 1224

(7) (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (b) Alcaide, B.; Almendros, P. *Org. Prep. Proced. Int.* **2001**, *33*, 315.

(8) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Ranera, C. Unpublished observations.

(9) We believed that the higher stability of enamides compared with enamines favors the double bond isomerization, preventing from N-allyl cleavage.

(10) For the utility of related piperidinyl β-lactams to (+)-**2a**−**c** in the preparation of enantiopure indolizidines, see: (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F., Torres, M. R. *Synlett* **2001**, 1531. For the preparation of 4-oxopipecolic acid from related systems to (+)-**1f** and (−)-**1g**, see: (b) Badorrey, R.; Cativiela, C.; Díaz de Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1999**, *55*, 7601.

(11) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F.; Redondo, M. C. *Synlett* **2001**, 773.

(12) Conjugation of the new double bond with the lone pair of the nitrogen atom is believed to promoted the enamine intermediate formation in allylamines. This ability is excluded in allyl ethers.

(13) Unexpected ruthenium-catalyzed isomerizations to the more stable internal olefin have been recently noted. See: (a) Kinderman, S. S.; van Maarseveen, J.-H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045. (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169. (c) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (d) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (e) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635.

(14) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

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Supporting Information Available: Compound characterization data and experimental procedures for isomerically pure compounds (+)-**1c**, **1d**, (+)-**1f**, **1h**, (+)-**2c**, (+)-**2f**, **7d**, and **7h**; ^{1}H NMR spectra of crude enamines **7d** and **7h** together with allylamines **1d** and **1h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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