Chemoselective Deprotection of Allylic Amines Catalyzed by Grubbs' Carbene

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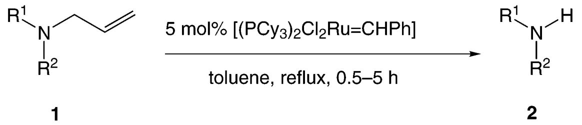
Abstract: A commercially available ruthenium complex (first generation Grubbs' carbene) was used for the catalytic deprotection of allylic amines (secondary as well as tertiary), by using for the first time reagents different from palladium catalysts. Interestingly, the catalytic system directs the reaction toward the selective deprotection of allylamines in the presence of allylic ethers.

Key words: amines, carbenes, catalytic cleavage, protecting groups, ruthenium



Scheme 1

Protecting groups often play a crucial role in many complex synthetic strategies.[1] Therefore, proper selection and cleavage of efficient protecting groups is invariably a prerequisite in such processes especially in the synthesis of natural products and polyfunctional molecules. The protection of amino groups as appropriate amine derivatives and their subsequent cleavage constitute a useful chemical transformation in organic synthesis. The allyl group is attractive due to the presence of an orthogonal π-bond, which should help in its facile cleavage in the presence of transition metal complexes.[2] However, only few examples are known dealing with the cleavage of the carbon–nitrogen bond in allyl amines through catalytic palladium π-allyl methodology.[3] A drawback of this methodology is the requirement of the presence of both the palladium catalyst and a nucleophilic compound as an allyl group scavenger.

On the other hand, the general use of ruthenium olefin metathesis catalysts has resulted in the discovery of non-metathetic reactions, expanding the synthetic utility of these complexes beyond olefin metathesis.[4] The most useful ruthenium carbene in these series is Grubbs' catalyst, $[(PCy_3)_2Cl_2Ru{=}CHPh]$, bearing a benzylidene unit.[5] Being highly active and remarkably tolerant to common functional groups, this compound found broad applications in both organic and polymer chemistry.

We have recently observed in the Grubbs' carbene promoted reaction of some *N*-allyl β-lactam-tethered alkenes, that in some cases the isomerization to the internal double bond in a *N*-allyl β-lactam is favored versus ring closing metathesis.[6] On the basis of this discovery, we have developed a ruthenium-catalyzed chemoselective *N*-allyl cleavage of amines (Scheme 1). Some results of this novel and practical methodology by using Grubbs' carbene are presented herein.

Among the various solvents and conditions tested, it was found that toluene at reflux temperature gave the best yields of *N*-deprotected products. Under optimized conditions: 5 mol% catalyst, 0.03 M substrate, toluene, reflux; secondary as well as tertiary *N*-allyl amines were efficiently deprotected (Table 1). Attempts to effect the reaction at lower temperatures slowed down the reaction considerably.

Importantly, the reaction is amenable to gram-scale syntheses. This transformation tolerates different substituents and functionalities at the amino compound, such as aryl (product **2c**), heteroaryl (product **2a**), alkoxy (product **2f**), silyloxy (product **2h**), dioxolanyl (product **2b**), bromo (product **2a**), ketone (product **2d**), and lactam (products **2f**–**h**) moieties. Besides, the catalyst tolerates a free NH group (products **2k**–**m**), as well as a free OH group (products **2i** and **2j**) at the starting substrate. The stereochemical integrity of the stereogenic centres at the amine substituents, when applicable, remained unaltered. Special mention deserves the ability of Grubbs' carbene for the selective deprotection of allylic amines in the presence of allyl ethers (products **2c**, **2g**, and **2k**), competing favorably with the π-allyl palladium deallylation methodology.

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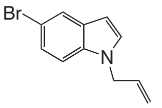
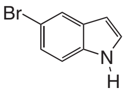
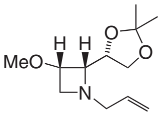
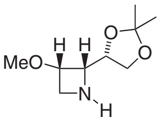
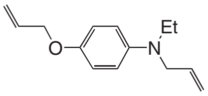
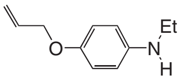
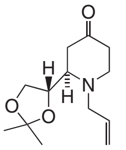
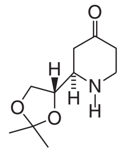
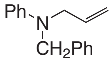
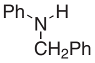
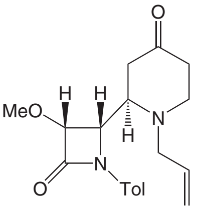
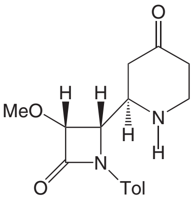
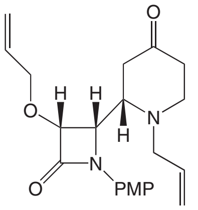
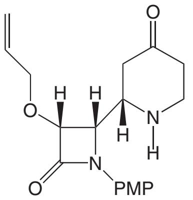
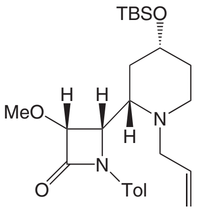
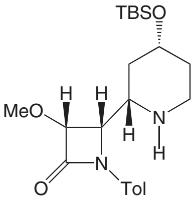
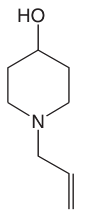
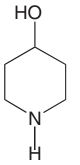
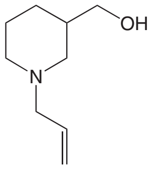
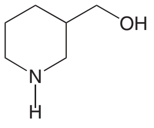
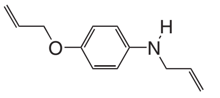
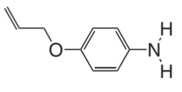
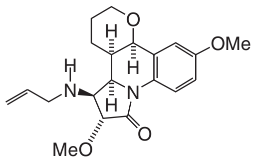
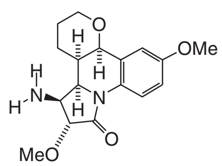
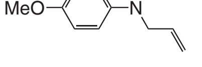
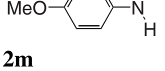
Table 1 *N*-Deallylation of Allylic Amines Mediated by Grubbs' Carbene[a]

Substrate	Product	Time (h)	Yield (%)[b]
 **1a**	 **2a**	5	81
 **1b**	 **2b**	1	49
 **1c**	 **2c**	1	68
 **1d**	 **2d**	4.5	78
 **1e**	 **2e**	3.5	71
 **1f**	 **2f**	3	88
 **1g**	 **2g**	3	58
 **1h**	 **2h**	3.5	78
 **1i**	 **2i**	4	52
 **1j**	 **2j**	4	50
 **1k**	 **2k**	1	57
 **1l**	 **2l**	0.5	52
 **1m**	 **2m**	5	81

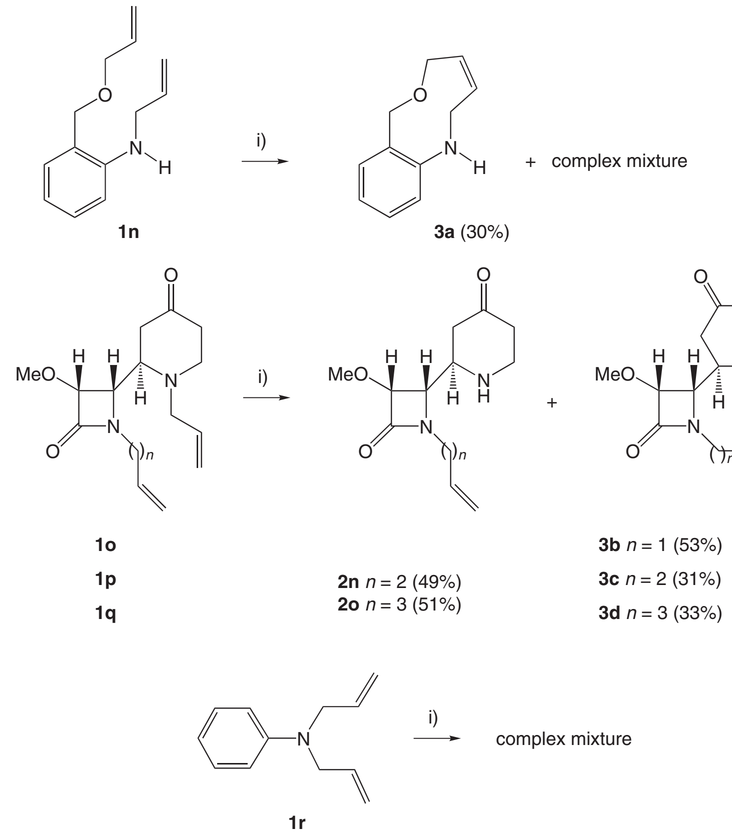
[a] PMP = 4-MeOC$_6$H$_4$.

[b] Yield of pure, isolated product with correct analytical and spectral data.

The limitations of the method arise from the fact that, in most cases the *N*-deallylation reaction is not compatible with the presence in the starting substrate of an extra alkene moiety capable of giving a stable ring through ring closing metathesis (Scheme 2). For substrates **1n** and **1o** the ring closing metathesis products **3a** and **3b** were obtained as the main products, whereas for dienes **1p** and **1q** together with the major *N*-deallylation products **2n** and **2o**, the presence of ring closing metathesis products **3c** and **3d** was observed. The treatment of the *N,N*-diallyl amine **1r** under our standard deallylation conditions afforded a complex mixture of unidentified products.

We hope that the basic research work presented herein will be of interest to synthetic chemists, and that its use will be applied to the chemical and pharmaceutical industry in the near future.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, a Varian VRX-300S or a Bruker AC-200 spectrometer. NMR spectra were measured in CDCl$_3$ solutions unless stated otherwise.



Scheme 2

Chemical shifts are given in ppm relative to TMS (^1H, 0.00 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Mass spectra were taken on a HP5989A spectrometer using the chemical ionization modes (CI) unless otherwise stated. All commercially available compounds were used without further purification.

Deallylation Reaction of Allylic Amines 1; General Procedure

To a solution of the corresponding allylic amine **1** (0.396 mmol) in anhyd toluene (12 mL) in the dark (flask was covered with aluminum foil), was added in portions $[(PCy_3)_2Cl_2Ru=CHPh]$ (0.02 mmol) under argon. The resulting mixture was refluxed until complete disappearance of the starting material by TLC (see Table 1), and was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes–EtOAc mixtures gave analytically pure *N*-deallylated amines **2** (Table 1).

Amine 2b

Colorless oil; $[\alpha]_D^{20}$ –10.3 (c = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3320 cm^{-1}.

^1H NMR: δ = 4.41 (m, 1 H), 4.27 (t, J = 6.2 Hz, 1 H), 4.00 (m, 2 H), 3.49 (m, 4 H), 3.16 (s, 3 H), 1.09 and 1.06 (s, each 3 H).

^{13}C NMR: δ = 73.4, 72.3, 72.0, 69.6, 68.6, 55.9, 51.0, 22.1, 22.0.

MS (CI): m/z (%) = 210 (M^+ + 23, 11), 188 (M^+ + 1, 100).

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.83; H, 9.18; N, 7.45.

Amine 2d

Colorless oil; $[\alpha]_D^{20}$ +27.6 (c = 0.7, $CHCl_3$).

IR ($CHCl_3$): 3347, 1714 cm^{-1}.

^1H NMR: δ = 3.93 (m, 2 H), 3.68 (m, 1 H), 3.36 (m, 1 H), 2.85 (m, 2 H), 2.38 and 2.27 (m, each 2 H), 2.02 (br s, 1 H), 1.36 and 1.29 (s, each 3 H).

^{13}C NMR: δ = 207.8, 109.4, 78.3, 66.2, 59.7, 45.2, 42.4, 26.5, 25.1.

MS (CI): m/z (%) = 200 (M^+ + 1, 100), 199 (M^+, 17).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.36; H, 8.62; N, 7.01.

Amine 2f

Colorless oil; $[\alpha]_D^{20}$ +116.1 (c = 0.5, $CHCl_3$).

IR ($CHCl_3$): 3352, 1738, 1717 cm^{-1}.

^1H NMR: δ = 7.24 and 7.06 (m, each 2 H), 4.60 (d, J = 5.4 Hz, 1 H), 4.17 (dd, J = 5.4, 5.1 Hz, 1 H), 3.62 (s, 3 H), 3.32 (m, 2 H), 2.72 (m, 1 H), 2.34 (m, 4 H), 2.24 (s, 3 H).

^{13}C NMR: 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.

MS (CI): m/z (%) = 289 (M^++1, 100), 288 (M^+, 11).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.74; H, 7.02; N, 9.68.

Amine 2g

Colorless oil; $[\alpha]_D^{20}$ +47.0 (c = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3344, 1742, 1718 cm^{-1}.

^1H NMR: δ = 2.30 (m, 4 H), 2.74 (m, 1 H), 3.37 (m, 2 H), 3.72 (s, 3 H), 4.16 (m, 2 H), 4.41 (dd, 1 H, J = 12.8, 5.4 Hz), 4.77 (d, 1 H, J = 5.4 Hz), 5.24 (m, 2 H), 5.90 (m, 1 H), 6.79 and 7.32 (m, each 2 H).

^{13}C NMR: δ = 207.8, 164.6, 156.7, 133.1, 130.2, 119.6, 118.2, 114.2, 80.7, 72.3, 60.1, 57.2, 55.4, 45.7, 45.6, 42.9.

MS (CI): m/z (%) = 331 (M^+ + 1, 100), 330 (M^+, 7).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.55; H, 6.68; N, 8.44.

Amine 2h
Colorless oil; $[\alpha]_D^{20}$ –32.5 (c = 0.6, $CHCl_3$).

^{1}H NMR: δ = 0.00 (s, 6 H), 0.79 (s, 9 H), 1.27 (m, 2 H), 1.80 (m, 2 H), 2.29 (s, 3 H), 2.55 (td, 1 H, J = 12.4, 2.2 Hz), 3.16 (m, 2 H), 3.56 (m, 1 H), 3.65 (s, 3 H), 4.16 (dd, 1 H, J = 5.9, 5.4 Hz), 4.60 (d, 1 H, J = 5.4 Hz), 6.99 (s, 1 H), 7.10 (m, 2 H), 7.31 (m, 2 H).

^{13}C NMR: δ = 165.2, 134.6, 134.3, 129.4, 118.4, 82.7, 69.7, 60.5, 59.3, 55.5, 44.5, 39.7, 36.1, 25.6, 20.7, 17.9.

MS (CI): m/z (%) = 405 (M$^+$ + 1, 100), 404 (M$^+$, 17).

Anal. Calcd for $C_{22}H_{36}N_2O_3Si$: C, 65.30; H, 8.97; N, 6.92. Found: C, 65.42; H, 9.00; N, 6.89.

Amine 2l
Colorless oil; $[\alpha]_D^{20}$ +11.3 (c = 0.8, $CHCl_3$).

IR ($CHCl_3$): 3330, 1712 cm^{-1}.

^{1}H NMR: δ = 7.95 (d, J = 8.9 Hz, 1 H), 7.03 (d, J = 2.5 Hz, 1 H), 6.79 (dd, J = 8.9, 2.5 Hz, 1 H), 4.94 (d, J = 5.6 Hz, 1 H), 3.74 and 3.71 (s, each 3 H), 3.60 (m, 4 H), 3.21 (d, J = 10.0 Hz, 1 H), 2.36 (m, 1 H), 1.41 (m, 4 H).

^{13}C NMR: 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.

MS (CI): m/z (%) = 341 (M$^+$ + 23, 11), 319 (M$^+$ + 1, 100), 318 (M$^+$, 18).

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.24; H, 7.00; N, 8.84.

Amine 2n
Colorless oil; $[\alpha]_D^{20}$ +88.4 (c = 0.5, $CHCl_3$).

IR ($CHCl_3$): 3352, 1739, 1714 cm^{-1}.

^{1}H NMR: δ = 5.67 (m, 1 H), 5.07 (m, 2 H), 4.41 (d, J = 5.2 Hz, 1 H), 3.67 (dd, J = 6.0, 5.2 Hz, 1 H), 3.51 (m, 4 H), 3.31 (m, 1 H), 3.14 (m, 2 H), 2.85 (m, 1 H), 2.32 (m, 6 H), 1.86 (br s, 1 H).

^{13}C NMR: 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.

MS (ES): m/z (%) = 253 (M$^+$ + 1, 100), 252 (M$^+$, 12).

Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.99; H, 8.02; N, 11.06.

Amine 2o
Colorless oil; $[\alpha]_D^{20}$ +107.5 (c = 0.6, $CHCl_3$).

IR ($CHCl_3$): 3348, 1741, 1711 cm^{-1}.

^{1}H NMR: δ = 1.64 (m, 2 H), 2.01 (m, 2 H), 2.33 (m, 4 H), 2.86 (m, 1 H), 3.03 (m, 2 H), 3.39 (m, 2 H), 3.53 (s, 3 H), 3.67 (dd, 1 H, J = 5.2, 4.8 Hz), 4.43 (d, 1 H, J = 4.8 Hz), 4.96 (m, 2 H), 5.74 (m, 1 H).

^{13}C NMR: δ = 207.6, 167.6, 137.1, 115.6, 83.3, 59.5, 59.4, 59.3, 57.5, 45.7, 42.9, 41.1, 31.0, 26.7.

MS (ES): m/z (%) = 267 (M$^+$ + 1, 100), 266 (M$^+$, 6).

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.23; H, 8.30; N, 10.48.

Bicycle 3a
Colorless oil.

IR ($CHCl_3$): 3352 cm^{-1}.

^{1}H NMR: δ = 4.12 (s, 4 H), 4.72 (s, 2 H), 5.85 (s, 2 H), 6.89 (m, 2 H), 7.17 (m, 2 H).

^{13}C NMR: δ = 148.0, 130.2, 128.8, 126.4, 121.5, 118.5, 65.1, 58.5, 58.4.

MS (CI): m/z (%) = 176 (M$^+$ + 1, 100), 175 (M$^+$, 9).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.52; H, 7.43; N, 7.94.

Tricycle 3b
Pale brown oil; $[\alpha]_D^{20}$ +96.7 (c = 0.3, $CHCl_3$).

IR ($CHCl_3$): 1744, 1716 cm^{-1}.

^{1}H NMR: δ = 1.55 (dd, 1 H, J = 14.6, 10.2 Hz), 1.70 (m, 2 H), 2.10 and 2.30 (m, each 2 H), 2.71 (m, 3 H), 3.02 (s, 3 H), 3.23 (dd, 1 H, J = 14.2, 6.8 Hz), 3.57 (d, 1 H, J = 4.4 Hz), 3.69 (dd, 1 H, J = 14.2, 6.4 Hz), 5.01 (m, 2 H).

^{13}C NMR: δ = 207.7, 166.4, 132.2, 123.8, 82.0, 61.1, 59.8, 58.9, 53.5, 51.3, 40.6, 39.7, 36.6.

MS (CI): m/z (%) = 251 (M$^+$ + 1, 100), 250 (M$^+$, 9).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.31; H, 7.24; N, 11.21.

Tricycle 3c
Colorless oil; $[\alpha]_D^{20}$ +119.4 (c = 0.5, $CHCl_3$).

IR ($CHCl_3$): 1744, 1715 cm^{-1}.

^{1}H NMR: δ = 2.05 (m, 1 H), 2.21 (dd, 1 H, J = 15.6, 4.8 Hz), 2.41 (m, 2 H), 2.73 (dd, 1 H, J = 15.6, 6.4 Hz), 2.99 (m, 7 H), 3.51 (dd, 1 H, J = 10.5, 4.9 Hz), 3.55 (s, 3 H), 3.79 (ddd, 1 H, J = 13.5, 11.6, 5.4 Hz), 4.27 (d, 1 H, J = 4.9 Hz), 5.56 (m, 2 H).

^{13}C NMR: δ = 210.1, 169.6, 132.3, 127.8, 82.7, 65.2, 59.2, 56.9, 53.2, 48.3, 39.2, 39.1.

MS (CI): m/z (%) = 265 (M$^+$ + 1, 100), 264 (M$^+$, 11).

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.69; H, 7.62; N, 10.62.

Tricycle 3d
Colorless oil; $[\alpha]_D^{20}$ +191.0 (c = 0.2, $CHCl_3$).

IR ($CHCl_3$): 1740, 1712 cm^{-1}.

^{1}H NMR: δ = 2.26 (m, 8 H), 3.05 (m, 4 H), 3.34 (m, 1 H), 3.48 (s, 3 H), 3.49 (m, 3 H), 4.35 (d, 1 H, J = 5.0 Hz), 5.61 and 5.79 (m, each 1 H).

^{13}C NMR: δ = 211.0, 170.8, 137.1, 128.8, 83.2, 77.0, 62.9, 59.6, 59.2, 47.3, 41.3, 37.9, 30.1, 28.1, 25.7.

MS (CI): m/z (%) = 279 (M$^+$ + 1, 100), 278 (M$^+$, 10).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.80; H, 7.98; N, 10.04.

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