Ru(IV)-catalyzed isomerization of allylamines in water: A highly efficient procedure for the deprotection of N-allylic amines

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A general and efficient method for the deprotection of N-allylic substrates in aqueous media, using catalytic amounts of the bis(allyl)-ruthenium(IV) complexes [Ru(η^3 : η^2 : η^3-C$_{12}$H$_{18}$)Cl$_2$] (1) and [{Ru(η^3 : η^3-C$_{10}$H$_{16}$)(μ-Cl)Cl}$_2$] (2), has been developed.

Among the most important strategies in organic synthesis the search for efficient protecting groups and subsequent deprotection methodologies is a crucial issue.[1] These processes are particularly relevant in the chemistry of amines since they generally constitute unavoidable steps in a great variety of organic transformations including the synthesis of natural products and other polyfunctional complex molecules.[1] The use of allyl moieties as protecting groups in amines is becoming more and more popular since, in contrast to more classical protecting groups, they remain inert in both acidic and basic media.[1] In addition, due to the presence of an orthogonal π-bond, the final deprotection step can be easily achieved in the presence of transition metals *via* appropriate coordination.

In this regard, transition-metal catalyzed reactions are currently one of the most efficient and selective strategies for the deprotection of N-allylamines.[1,2] Nevertheless, the number of active metal catalysts is till now very scarce, showing most of them a range of limitations affecting both to the substrates as well as the reaction conditions.[1] Thus, the methodology using palladium(0) complexes, which are among the most efficient catalysts, requires the presence of stoichiometric amounts of a nucleophilic scavenger.[3] This important drawback arises from the transient formation of π-allylamine complexes which undergo the extrusion of the allyl group and elimination of the free amine *via* reaction with a nucleophile (Scheme 1; path a).[4]

Recently, it has been reported that Grubbs' carbene complexes [RuCl$_2$(=CHPh)(L)(PCy$_3$)] (L = PCy$_3$, IMes) also catalyze the allylic deprotection of a large variety of secondary and tertiary allylamines.[5] These catalysts belong to the class in which the active species are hydride complexes able to undergo isomerization of the C=C bond to give enamines (Scheme 1; path b).[6] The final N–C bond cleavage to give the deprotected amines is only achieved after acidic hydrolysis[5] or oxidation[7] of the enamines.

We have recently reported that the bis(allyl)-ruthenium(IV) complexes [Ru(η^3 : η^2 : η^3-C$_{12}$H$_{18}$)Cl$_2$] (C$_{12}$H$_8$ = dodeca-2,6,10-triene-1,12-diyl) (1) and [{Ru(η^3 : η^3-C$_{10}$H$_{16}$)(μ-Cl)Cl}$_2$] (C$_{10}$H$_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) (2) (see Fig. 1)[8] are able to promote C=C migrations in water and perform catalytic isomerizations of allylic alcohols.[9] Taking advantage of this ability, herein we report that they are also efficient catalysts for the deprotection of secondary as well as tertiary N-allylic amines in water with tolerance of common functional groups. This is the first synthetic procedure which is performed in pure aqueous media and proceeds in a one-pot manner (Scheme 1; path c). Up to now, the C=C isomerization step had only been performed in organic solvents.[5] In addition, these catalysts act selectively towards the deprotection of N,N-diallylamines in marked contrast to the Grubbs' type catalysts which lead to complex mixtures of products due probably to their competitive activity in RCM transformations.[10]
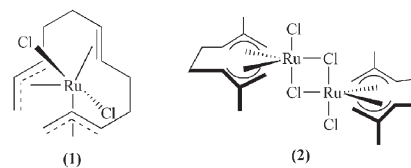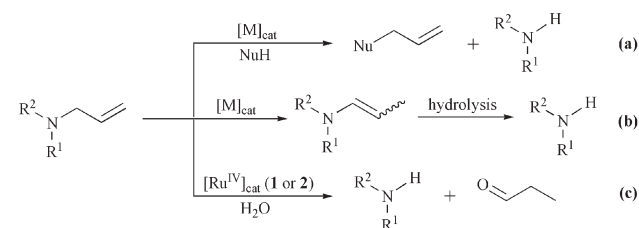

Fig. 1 Structure of the bis(allyl)-ruthenium(IV) complexes 1 and 2.

Firstly, we have checked the activity of complexes 1 and 2 in the deprotection of N-allylaniline as a model reaction. Thus, we have found that, under optimized conditions (3 mol% of Ru; 0.1 M solution of the substrate in water, 90 °C), both complexes are efficient catalysts for this transformation affording deallylated aniline in 96% yield after *ca.* 3 h (entry 1 in Table 1).† The use of lower temperatures and/or catalyst loadings slows down the reaction considerably.[11] In this reaction the allyl unit is selectively transformed into propionaldehyde (detected by GC) confirming the intermediate formation of an enamine which, due to the aqueous media, is readily hydrolyzed.

Under these optimal reaction conditions, catalysts 1 and 2 are also active in the deprotection of a large number of secondary N-allylic substrates (entries 2–13 in Table 1).[12] Thus, as observed for N-allylaniline, its *ortho*-, *meta*- and *para*-substituted derivatives undergo a fast (≤3 h) and efficient removal of the allyl unit

Scheme 1 Strategies used for the catalytic deprotection of N-allylamines.

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Table 1 Ru(IV)-catalyzed deprotection of *N*-allylamines in water[a]

$$R^2\text{-N}(R^1)\text{-allyl} \xrightarrow[\text{H}_2\text{O / 90}^\circ\text{C}]{\textbf{1 or 2} (3 \text{ mol\% of Ru})} R^2\text{-N}(R^1)\text{H} + \text{O=CH-CH}_2\text{CH}_3$$

Entry	Substrate	Catalyst	Time	Yield[b]	Entry	Substrate	Catalyst	Time	Yield[b]
1	Ph—N(H)—allyl	1	3.5 h	96%	12	Cy—N(H)—allyl	1	3 h	99%
		2	3 h	96%			2	1.5 h	99%
2	2-Cl-C6H4—N(H)—allyl	1	2 h	>99%	13	Bz—N(H)—allyl	1	6 h	95%
		2	2 h	>99%			2	7 h	97%
3	3-Cl-C6H4—N(H)—allyl	1	45 min	>99%	14	Ph—N(Ph)—allyl	1	1 h	>99%
		2	15 min	>99%			2	1 h	>99%
4	4-Cl-C6H4—N(H)—allyl	1	15 min	>99%	15	Ph—N(Et)—allyl	1	3.5 h	99%
		2	15 min	>99%			2	3.5 h	95%
5	4-Br-C6H4—N(H)—allyl	1	15 min	97%	16	Ph—N(Me)—allyl	1	1 h	97%
		2	30 min	>99%			2	1.5 h	95%
6	4-I-C6H4—N(H)—allyl	1	1.5 h	>99%	17	Cy—N(Cy)—allyl	1	1.2 h	>99%
		2	2 h	>99%			2	2 h	>99%
7	4-O2N-C6H4—N(H)—allyl	1	45 min	>99%	18	Bz—N(CHMePh)—allyl	1	22 h	81%
		2	5 min	>99%			2	8 h	98%
8	4-Me-C6H4—N(H)—allyl	1	30 min	96%	19	2-Ph-1-allyl-tetrahydroquinoline	1	1 h	>99%
		2	1.5 h	>99%			2	3 h	98%
9	4-MeO-C6H4—N(H)—allyl	1	2 h	98%	20	1-allyl-indoline	1	45 min	>99%
		2	1.5 h	97%			2	2 h	96%
10	2-(PhCO)-C6H4—N(H)—allyl	1	3 h	>99%	21	1-allyl-indole	1	7 h	90%
		2	2 h	>99%			2	7 h	>99%
11	2-(EtOCO)-C6H4—N(H)—allyl	1	20 min	>99%	22	1-allyl-imidazolidine-2-thione	1	6 h	99%
		2	20 min	>99%			2	4.5 h	99%

[a] Reactions performed under N$_2$ atmosphere at 90 °C using 1 mmol of the corresponding *N*-allylamine (0.1 M in water). [b] Yields determined by GC.

(≥96% yield) regardless of the presence of electron-withdrawing or electron-donating groups (entries 2–11). Different functionalities at the aryl ring, such as halides (entries 2–6), nitro (entry 7), alkoxy (entry 9), ketone (entry 10) and ester (entry 11), are tolerated in this transformation. Special mention deserves the ability shown by complexes **1** and **2** for the selective deprotection of halide-substituted anilines (entries 2–6) since, using the classical

Pd(0) deallylation methodology, competitive oxidative addition of the halide–C$_{aryl}$ bond to the metal could be envisaged. Secondary alkyl–allylamines (entries 12–13), as well as tertiary diaryl- (entry 14), aryl–alkyl- (entries 15–16) and dialkyl–allylamines (entries 17–18), can also be efficiently deprotected (≥95% yield within 1–8 h),[13] assessing the generality of this catalytic methodology.‡ It is interesting to note that no epimerization reaction takes place

during the deallylation of (S)-N-allyl-N-benzyl-α-methylbenzyl-amine (entry 18).[14] Thus, this method can be applied in the preparation of optically active compounds.

It is also worth noting that this deallylation procedure can be applied to substrates of synthetic interest serving as crucial intermediates for the preparation of a large variety of both natural products and pharmacologic agents. Thus, we have found that N-allyl-1,2,3,4-tetrahydroquinoline (entry 19), N-allylindoline (entry 20), N-allylindole (entry 21) and N-allylimidazolidine-2-thione (entry 22) can be easily deallylated in high yields (≥90%). Of particular significance is the chemoselectivity observed in the reaction of N-allylimidazolidine-2-thione (entry 22) containing a free NH unit and a thiocarbonyl group.

Remarkably, N,N-diallylaniline and N,N-diallyl-p-nitroaniline can also be completely deallylated to give the corresponding primary anilines in excellent yields (≥96%) after 7–9 h (see Scheme 2). No RCM products have been detected by GC-MS. As far as we know these are the first ruthenium catalysts which are able to perform chemoselectively the deprotection of N,N-diallylic amines.[10]

R = H; cat 1; >99% yield (9 h)
R = H; cat 2; 96% yield (9 h)
R = NO₂; cat 2; >99% yield (7 h)
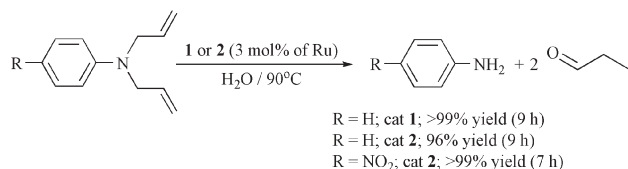
Scheme 2 Deprotection of N,N-diallylamines catalyzed by 1 and 2.

In summary, an operationally simple, inexpensive and efficient procedure for the removal of the allyl protecting group in amines has been developed. This one-pot catalytic transformation using the readily available bis(allyl)-ruthenium(IV) complexes [Ru($\eta^3 : \eta^2$: η^3-C$_{12}$H$_{18}$)Cl$_2$] (1) and [{Ru($\eta^3 : \eta^3$-C$_{10}$H$_{16}$)(μ-Cl)Cl}$_2$] (2) is based on their ability to promote C=C migrations in water, allowing the direct hydrolysis of the initially formed enamines. It represents a new chemoselective methodology which provides a competitive route for the deprotection of N-allylic amines, allowing the limitations of the other previously reported approaches to be overcome and the double deprotection of N,N-diallylamines to be performed. In addition, by the first time these transformations have been performed in water. Providing that organic reactions in water are of primary interest specially when they proceed under catalytic conditions,[15] the chemoselective deallylation methodology presented herein is of interest in organic synthesis with potential industrial applications. Further studies on the scope and limitations of this catalytic reaction, as well as detailed mechanistic investigations, are now in progress.

Notes and references

† *General procedure for the deallylation reactions:* Under a nitrogen atmosphere, the corresponding N-allylic substrate (1 mmol), the ruthenium catalyst precursor 1 or 2 (3 mol% of Ru) and water (10 mL) were introduced in a Schlenk flask and the reaction mixture stirred at 90 °C for the indicated time. The course of the reaction was monitored by regular sampling and analysis by gas chromatography. The identity of the resulting deallylated products was assessed by comparison with commercially available pure samples (Aldrich Chemical Co. or Acros Organics) and by their fragmentation in GC-MS.

‡ We note that all these reactions can be performed in a preparative scale. *Representative example*: Under a nitrogen atmosphere, N-allylcyclohexylamine (3 g, 21.5 mmol), complex 2 (0.199 g, 0.324 mmol) and water (200 mL) were introduced in a Schlenk flask and the reaction mixture stirred at 90 °C for 3 h (quantitative conversion by GC). The resulting aqueous solution was then saturated with NaCl and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over MgSO₄, concentrated and purified by column chromatography over silica gel, using diethyl ether as eluent, to give 1.96 g (19.8 mmol) of analytically pure cyclohexylamine (92% yield).

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3 See for example: F. Guibé, *Tetrahedron*, 1998, **54**, 2967 and references therein.
4 The use of nickel catalysts, which also require the presence of a nucleophilic scavenger, has been reported: T. Taniguchi and K. Ogasawara, *Tetrahedron Lett.*, 1998, **39**, 4679.
5 (a) C. Cadot, P. I. Dalko and J. Cossy, *Tetrahedron Lett.*, 2002, **43**, 1839; (b) B. Alcaide, P. Almendros and J. M. Alonso, *Chem. Eur. J.*, 2003, **9**, 5793.
6 Formation of an active hydride intermediate by decomposition of the Grubbs' carbenes has been proposed but no experimental evidence has been provided (see ref. 5b). Nevertheless, it should be noted that isomerization of N-allylic substrates to give the corresponding enamines catalyzed by Ru-hydride complexes has been extensively studied in organic media: S. Krompiec, M. Pigulla, N. Kuźnik, M. Krompiec, B. Marciniec, D. Chadyniak and J. Kasperczyk, *J. Mol. Catal. A: Chem.*, 2005, **225**, 91 and references therein.
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8 Complexes 1 and 2 are easily prepared by reacting ethanolic solutions of RuCl₃·nH₂O with butadiene and isoprene, respectively. See: (a) J. K. Nicholson and B. L. Shaw, *J. Chem. Soc. A*, 1966, 807; (b) L. Porri, M. C. Gallazzi, A. Colombo and G. Allegra, *Tetrahedron Lett.*, 1965, 4187.
9 Complexes 1 and 2 are efficient catalysts for the isomerization of allylic alcohols into carbonyl compounds in both organic and aqueous media. See: V. Cadierno, S. E. García-Garrido and J. Gimeno, *Chem. Commun.*, 2004, 232.
10 B. Alcaide, P. Almendros, J. M. Alonso and A. Luna, *Synthesis*, 2005, 668.
11 Yields up to 95% were obtained, after 26 h at 90 °C, using a catalyst loading of 2 mol% of Ru. Yields up to 81% were obtained, after 24 h at 70 °C, using a catalyst loading of 3 mol% of Ru.
12 Close examination revealed that the reaction mixtures are in most of the cases emulsions rather than homogeneous solutions.
13 The presence of a benzyl substituent seems to promote slower transformations (entries 13 and 18). A clear example of this situation is the deprotection of (S)-N-allyl-N-benzyl-α-methylbenzylamine catalyzed by complex 1 in which only 81% of conversion was attained after 22 h (entry 18). At present, no explanation for this particular behaviour can be provided.
14 Confirmed by GC, using a Supelco Beta-Dex® 120 (30 m, 250 μm) chiral column, by comparison with a commercially available pure sample of (S)-N-benzyl-α-methylbenzylamine.
15 (a) C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751 and references therein; (b) For a recent review on ruthenium-catalyzed reactions in aqueous media see: M. Wang and C. J. Li, in *Ruthenium Catalysts and Fine Chemistry*, ed. C. Bruneau and P. H. Dixneuf, Springer-Verlag, Berlin, 2004.