Chemo-selective Rh-catalysed hydrogenation of azides into amines

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ABSTRACT

Rh/Al_2O_3 can be used as an effective chemo-selective reductive catalyst that combines the mild conditions of catalytic hydrogenation with high selectivity for azide moieties in the presence of other hydrogenolysis labile groups such as benzyl and benzyloxycarbonyl functionalities. The practicality of this strategy is exemplified with a range of azide-containing carbohydrate and amino acid derivatives.

1. Introduction

Amines are common functional groups present in many organic compounds. In multistep organic synthesis, reactive amine groups often require temporary protection [1]. Azides are often used to mask amines, their chemical stability and orthogonal reactivity towards other common protecting groups makes them exceedingly versatile [2]. The use of azides in carbohydrate synthesis is also very prevalent since glycosyl azides are highly useful precursors for *N*-linked glycans [3].

One of the most common ways to introduce azides in chemical synthesis consists in the displacement of halogens or other leaving groups (*e.g.* tosyl and triflyl) by NaN_3, other common protocols include acid-catalysed addition of trimethylsilyl azide, amine substitution via sulfonylazides or the use of diazonium salts among others [4,5]. Reduction of the azide moiety to an amine is also a synthetically important step, since many azides can be prepared with regio- and stereocontrol, their subsequent reduction permits controlled introduction of the amine group. To that end, the most common protocols for the reduction of azides into amines involve Pd/C or PtO_2-promoted catalytic hydrogenation [6], Staudinger reaction [7], or hydride reduction [8] (*e.g.* $LiAlH_4$, PhSeH, tris(trimethylsilyl)silane, dithiol/Et_3N), among many others [2].

Despite the numerous methods available for the reduction of the N_3 group, selectivity issues often arise due to the presence of other non-orthogonal protecting groups or labile moieties on the same molecule which can't withstand the reaction conditions. While Pd-catalysed hydrogenation is often non-selective for benzyl ethers and olefins, previous examples of selective Pd-catalysed hydrogenation of azides in presence of benzyl ethers have been reported [9]. Nonetheless, the method does not allow for selective reduction of azides in the presence

of the more labile benzyloxycarbonyl (Cbz) protecting group. On the other hand, the Staudinger reaction requires the use of water, which is often incompatible with hydrolytically labile groups; hydride-mediated reductions (e.g. $LiAlH_4$) are not selective towards N_3 groups in the presence of aldehydes or esters and in some instances the methods involve the use of toxic or/and malodourous reagents (*e.g.* selenols, thiols, tin hydrides) [2].

Rh complexes have been successfully and extensively employed in organometallic chemistry in for example metathesis reactions [10,11], hydrosilylation reactions [12], hydrogenation of olefins [13] and for reduction of nitriles to amines [14]. Rh-catalysed hydrogenation represents an alternative to the aforementioned azide reduction strategies, which has the potential to offer several advantages over more traditional methods, in terms of chemical orthogonality.

Herein we report the use of Rh as an effective and selective catalyst for the hydrogenolysis of azides. The applicability of the method is exemplified with a range of azide-containing carbohydrate and amino acid derivatives. We demonstrate that Rh/Al_2O_3 may be used as an effective reductive catalyst that combines the mild conditions used in catalytic hydrogenation with high selectivity for azide moieties in the presence of other labile groups. To the best of our knowledge there are no reported applications of the use of Rh or its complexes for the catalytic reduction of azides in biological chemistry.

2. Results and discussion

Initial studies were aimed at evaluating the effectiveness of Rh as a mild hydrogenation catalyst for the chemo-selective reduction of azides in the presence of benzyl ethers, which are typically labile under Pd-catalysed hydrogenolysis conditions [15]. To that end, glycosyl azide **1**

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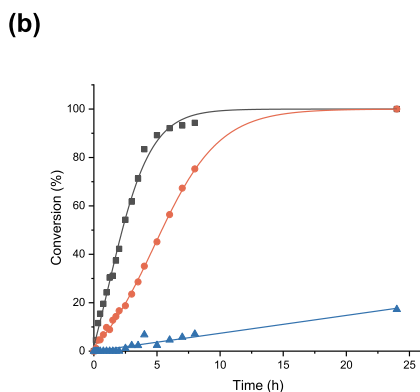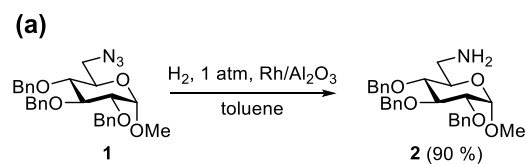 *E-mail address:* M.C.Galan@bristol.ac.uk (M.C. Galan).

(a)

1 → **2** (90 %)

(b)

(c)

Solvent	Relative conversion after 5 h
MeOH	1.00
Toluene	1.00
THF	0.95
EtOAc	0.78
CHCl₃	0.19
Toluene/EtOAc (6:1)	1.00

Scheme 1. (a) Rh-catalysed hydrogenation of **1**, reagent and conditions: H_2 1 atm, Rh/Al$_2$O$_3$ 10 mol%, AcOH, toluene 6 h, room temperature, 90%. (b) Plot of conversion of **1** into **2** at 1 mol% (blue ▲), 5 mol% (red ●) and 10 mol% (grey ■) of Rh/Al$_2$O$_3$ over time. (c) Relative conversion rates between **1** into **2** in different solvent at 5 mol% Rh/Al$_2$O$_3$, H_2 1 atm, AcOH, after 5 h.

was chosen as a model substrate (Scheme 1a) and reacted with 10 mol% commercially available Rh/Al$_2$O$_3$ in presence of an excess of acetic acid to help stabilise the resulting amine product as the acetate salt [16]. Pleasingly, the reduction of **1** to amine **2** was achieved in an excellent yield of 90% using mild conditions (H_2, 1 atm, balloon and room temperature) without affecting the surrounding benzyl groups.
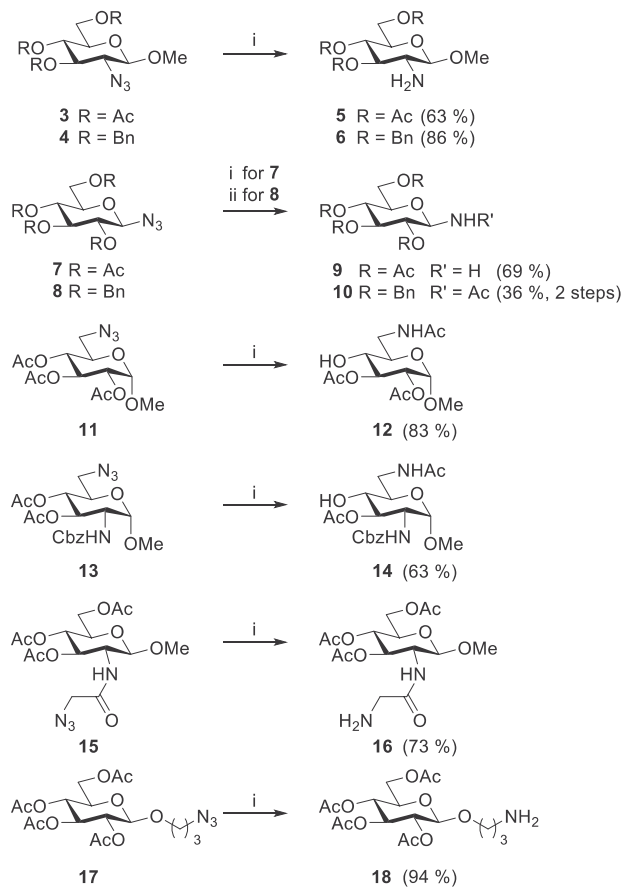
To determine the efficiency of this reduction under different catalyst loadings, a preliminary rate determination screen was performed using 10, 5 and 1 mol% of Rh/Al$_2$O$_3$ under the same reaction conditions as before. Under these conditions and for each catalyst loading, the conversion between azide **1** to amine **2** was monitored by taking aliquots of the reaction at different time intervals and analysed via NMR spectroscopy (Scheme 1b). The reduction at 10 mol% of Rh reached > 90% completion after 6 h. Similar results were achieved at 5 mol% of Rh after 13 h, while at 1 mol% load of Rh the reaction was slower and gave a 17% conversion after 24 h.

Solvent effects were then explored and the outcome of the model reaction in different solvents was monitored in order to evaluate if the nature of the solvent would influence the efficiency of the reduction. The Rh-catalysed hydrogenation of **1** into **2** was tested in toluene, EtOAc, MeOH, THF, and CHCl$_3$ under the same conditions (5 mol% catalytic load, H_2 1 atm, 5 h, room temperature). No significant difference was observed between the different solvents (Scheme 1c), except for CHCl$_3$ that gave a much lower conversion probably due to the lower solubility of H_2 in halogenated solvents [17]. Consequently, It was decided to carry out the Rh-catalysed hydrogenations in a 6:1 toluene/EtOAc mixture, providing optimal solubility conditions for both reagents and products.

Encouraged by these initial results, the scope of the Rh-catalysed azide reduction was then explored on a range of glucosides containing either primary, secondary or anomeric azides and bearing both acetyl and benzyl ether protecting groups (Scheme 2) using the optimized catalytic conditions and toluene/EtOAc (6:1) as the reaction solvent.

In most cases, the reductions proceeded smoothly in moderate to good yields at room temperature. In brief, glycosides bearing azide-groups at C2 as in **3** and **4** afforded the respective perbenzylated and peracetylated 2-aminoglycosides **5** and **6** in good yields of 63% and 86% yield, after 3 and 6 h, respectively, at room temperature. Rh-catalysed reduction of 1-azido acetyl-protected glucoside **7** resulted in the corresponding 1-amino glycoside **9** in 69% with no anomerization by-products observed. In the case of 1-azido benzyl-protected glucoside **8**, a complex mixture of amino-containing derivatives including α/β anomeric mixtures of the 1-amino derivative were obtained under this

3 R = Ac
4 R = Bn

5 R = Ac (63 %)
6 R = Bn (86 %)

i for **7**
ii for **8**

7 R = Ac
8 R = Bn

9 R = Ac R' = H (69 %)
10 R = Bn R' = Ac (36 %, 2 steps)

11 → **12** (83 %)

13 → **14** (63 %)

15 → **16** (73 %)

17 → **18** (94 %)

Scheme 2. *Reagent and conditions*: i) H_2 1 atm, Rh/Al$_2$O$_3$ 10 mol%, AcOH, toluene/EtOAc (6:1), room temperature. ii) H_2 1 atm, Rh/Al$_2$O$_3$ 10 mol%, AcOH, toluene/EtOAc (6:1), 6 h, room temperature, then Py/Ac$_2$O 1:1 16 h, room temperature.

conditions, likely due to the electron donating nature of the benzyl protecting groups which makes the resulting hemiaminal product more reactive and thus more susceptible to anomerization and/or degradation [18]. We, therefore resolved the product mixture via acetylation of the resulting reduced product using acetic acid and pyridine which lead to the isolation of the major product, β-1-N-acetyl glycoside **10** in 36%

yield after 2 steps. On the other hand, reduction of glucoside **11**, bearing a primary azide at C6, underwent reduction to the amine within 8 h with concomitant acetate migration of the acetyl group at C4 to afford acetamide derivative **12** in a 83% yield. This was confirmed by the proton shift associated for H4 (from δ 4.97 in **11** to δ 3.33 ppm for acetamide **12**) and to the presence of a cross-peak in the COSY spectrum corresponding to the broad OH signal and H4. To ascertain whether other H_2-cleavable protecting groups were amenable to the mild Rh reaction conditions, CbzN-protected glucoside **13** was also screened. Compound **13** was reduced to amide **14** in 63% yield, without loss of the carbamate protecting group. Similarly to the outcome observed for **11**, the primary amine undergoes intramolecular transacetylation affording the corresponding acetamide and leaving a free hydroxyl at position C4 of the sugar. In order to elucidate whether the transacetylation reaction occurs only for amines at position C6 of glycosides featuring OAc groups at adjacent positions (e.g. C4) of the sugar moiety or due to the general stronger nucleophilicity of primary amines over secondary or anomeric ones, the reduction of acetate containing glycosides **15** and **17**, bearing a primary azide at different positions on the sugar, were performed. Amino-derivatives **16** and **18** were obtained in good yields of 73% and 94%, respectively, without the formation of transacetylated derivatives. These results confirm that the observed acetate migration appears to be a specific feature of C6-amine containing glycosides where acetate groups are present at C4 and can undergo intramolecular rearrangement via a 6-membered transition state giving the corresponding acetamide, which is a common problem in carbohydrate chemistry [19].

To evaluate the chemical selectivity and efficiency of Rh-catalysed hydrogenation in the presence of different protecting and functional groups, orthogonally protected glycoside **19**, thioglycoside **21**, nucleosides **23** and **25** and amino acid derivatives **27** and **29** containing free amino and carboxylic acid groups, were subjected to the Rh-catalysed reduction (Scheme 3).

Reduction of **19** gave amine **20** cleanly in 74% yield without cleavage of the benzylidene acetal protecting group and without the need for anhydrous conditions. On the other hand, Rh-catalysed reduction of sulphur-bearing glycoside **21** only yielded starting material, despite of long reaction times (24 h) with a 10 mol% of Rh, likely due to catalyst poisoning by the thioether [20,21]. Our reduction conditions were then applied to azido-containing uridine derivative **23** and adenosine **25** as model pyrimidine and purine nucleoside substrates. In the case of **23**, complete reduction of the azido and double bond in the nucleobase afforded dihydrouridine amine **24** as the major product. The lack of chemo-selectivity in this instance is not completely unexpected as previous work has demonstrated the applicability of Rh in the reduction of uridine bases [22–24]. However, selective azido reduction in adenosine **27** was successful and amine **28** was obtained in 65% yield without affecting the nucleobase, in virtue of a stronger aromaticity compared to the pyrimidine model **25**. Finally, we also demonstrated that Rh-catalysed hydrogenation of azides is compatible with the presence of free acid or basic amine functions such as those found in amino acid derivatives **27** and **29,** which furnished the corresponding amines **28** and **30** in excellent yields of 92% and 86% respectively, after subjecting the parent substrates to the Rh-catalysed conditions in methanol as the solvent for solubility purposes.

3. Conclusions

In conclusion, we have demonstrated that Rh/Al_2O_3 can be used as an effective and chemo-selective catalyst for the reduction of azides in the presence of other hydrogen-labile functional groups such as O-Bn and N-Cbz protecting groups The method is mild and offers an orthogonal alternative to Pd- or Pt-catalysed hydrogenation where high specificity for the azide moiety is required. Although the presence of thiols as in thioglycosides appears to be incompatible with the protocol, in a similar way to hydrogenations carried out with Pd or Pt catalysts
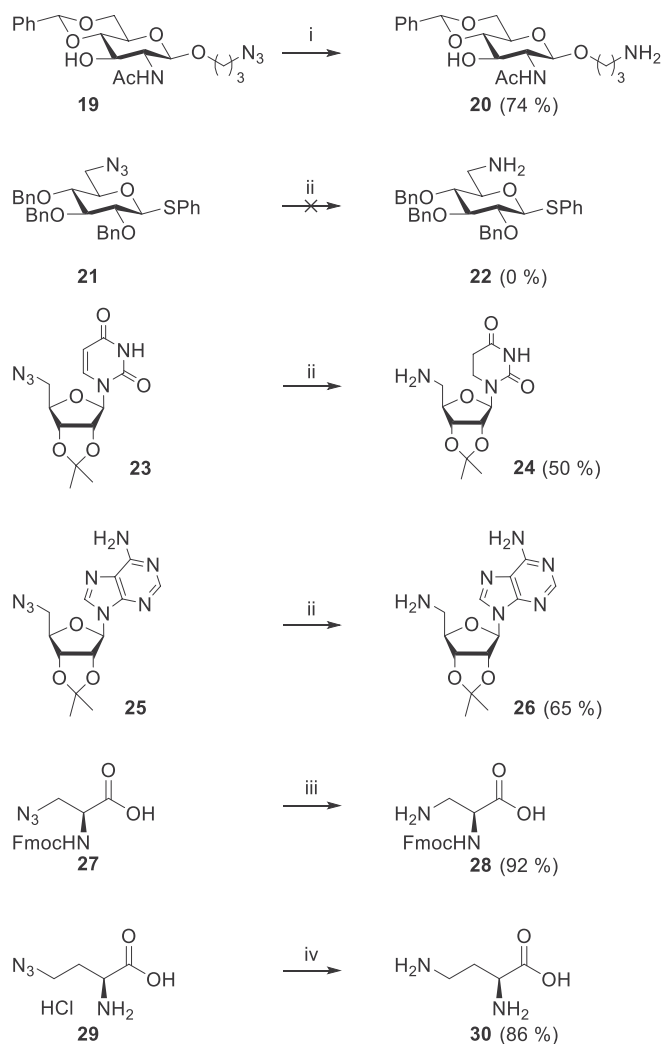
Scheme 3. *Reagent and conditions*: i) H_2 1 atm, Rh/Al_2O_3 10 mol%, AcOH, MeOH, 5 h, room temperature. ii) H_2 1 atm, Rh/Al_2O_3 10 mol%, AcOH, toluene/EtOAc (6:1), 24 h, room temperature. iii) H_2 1 atm, Rh/Al_2O_3 10 mol%, AcOH, MeOH, 5 h, room temperature. iv) H_2 1 atm, Rh/Al_2O_3 10 mol%, AcOH, MeOH, 2.5 h, room temperature.

where the catalysts are inactivated, the versatility of the protocol is exemplified in a range of glycosides and amino acid derivatives demonstrating its compatibility with other commonly used orthogonal functional groups, setting the stage for novel applications of Rh-catalysed azide reduction in organic synthesis.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2020.107948.

References

[1] P.G.M. Wuts, T.W. Greene, Protecting Groups in Organic Synthesis, fourth ed., John Wiley & Sons, Hoboken, New Jersey, 2007.

[2] E.F.V. Scriven, K. Turnbull, Azides - their preparation and synthetic uses, Chem. Rev. 88 (1988) 297–368, https://doi.org/10.1021/cr00084a001.

[3] H.S.G. Beckmann, V. Wittmann, V. Azides, S. Bräse, K. Banert (Eds.), Carbohydrate Chemistry. In Organic Azides: Syntheses and Applications, John Wiley & Sons, Ltd, Chichester, UK, 2009, pp. 469–491.

[4] Z. Györgydeák, J. Thiem, D. Horton (Ed.), Advances in Carbohydrate Chemistry and Biochemistry, vol. 60, Academic Press, 2006, pp. 103–182.

[5] E.D. Goddard-Borger, R.V. Stick, Org. Lett. 9 (2007) 3797–3800, https://doi.org/10.1021/ol701581g.

[6] J.G. de Vries (Ed.), Catalytic Reduction in Organic Synthesis 2, Georg Thieme Verlag, Stuttgart, 20182018.

[7] a) H. Staudinger, J. Meyer, Helv. Chim. Acta 2 (1919) 635–646, https://doi.org/10.1002/hlca.19190020164;
b) S. Liu, K.J. Edgar, Biomacromolecules 16 (2015) 2556–2571, https://doi.org/10.1021/acs.biomac.5b00855;
c) M. Ghirardello, I. Delso, T. Tejero, P. Merino, Asian J. Org. Chem. 5 (2016) 1525–1534, https://doi.org/10.1002/ajoc.201600497.

[8] a) R. Zhang, K.J. Edgar, Carbohydr. Polym. 122 (2015) 84–92, https://doi.org/10.1016/j.carbpol.2014.12.020;
b) H. Bayley, D.N. Standring, J.R. Knowles, Tetrahedron Lett. 19 (1978) 3633–3634, https://doi.org/10.1016/S0040-4039(01)95015-4.

[9] H. Sajiki, Tetrahedron Lett. 36 (1995) 3465–3468, https://doi.org/10.1016/0040-4039(95)00527-J.

[10] Y. Wang, Z.-X. Yu, Acc. Chem. Res. 48 (2015) 2288–2296, https://doi.org/10.1021/acs.accounts.5b00037.

[11] T. Kan, T. Asakawa, M. Inai, Heterocycles 92 (2016) 31–43, https://doi.org/10.3987/REV-15-829.

[12] A.S. Henderson, J.F. Bower, M.C. Galan, Org. Biomol. Chem. 12 (2014) 9180–9183, https://doi.org/10.1039/C4OB02056A.

[13] a) A.M. Geer, C. Tejel, J.A. López, M.A. Ciriano, Angew. Chem. Int. Ed. 53 (2014) 5614–5618, https://doi.org/10.1002/anie.201400023;
b) S. Kraft, K. Ryan, R.B. Kargbo, J. Am. Chem. Soc. 139 (2017) 11630–11641, https://doi.org/10.1021/jacs.7b07188.

[14] L. Xu, A.K. Farthing, J.F. Dropinski, P.T. Meinke, C. McCallum, E. Hickey, K. Liu, Bioorg. Med. Chem. Lett 23 (2013) 366–369, https://doi.org/10.1016/j.bmcl.2012.10.065.

[15] S. Vidal, Protecting Groups: Strategies and Applications in Carbohydrate Chemistry, Wiley-VCH, Georg Thieme Verlag, Stuttgart, 2019.

[16] The Reaction in the Absense of Acetic Acid Was Significantly Slower.

[17] E.B. Maxted, V. Stone, J. Chem. Soc. (1938) 454–455, https://doi.org/10.1039/JR9380000454.

[18] A.D. Dorsey, J.E. Barbarow, D. Trauner, Org. Lett. 5 (2003) 3237–3239, https://doi.org/10.1021/ol035111s.

[19] T.C. Baddeley, J.L. Wardell, J. Carbohydr. Chem. 28 (2009) 198–221, https://doi.org/10.1080/07328300902887672.

[20] N.S. Nasri, J.M. Jones, V.A. Dupont, A. Williams, Energy Fuels 12 (1998) 1130–1134, https://doi.org/10.1021/ef980104j.

[21] D.L. Boger, S.H. Kim, Y. Mori, J.-H. Weng, O. Rogel, S.L. Castle, J.J. McAtee, J. Am. Chem. Soc. 123 (2001) 1862–1871, https://doi.org/10.1021/ja003835i.

[22] W.E. Cohn, D.G. Doherty, G, D, J. Am. Chem. Soc. 78 (1956) 2863–2866, https://doi.org/10.1021/ja01593a063.

[23] J. Kremser, E. Strebitzer, R. Plangger, M.A. Juen, F. Nußbaumer, H. Glasner, K. Breuker, C. Kreutz, Chem. Commun. 53 (2017) 12938–12941, https://doi.org/10.1039/C7CC06747J.

[24] N.P.J. Price, M.A. Jackson, K.E. Vermillion, J.A. Blackburn, T.M. Hartman, Carbohydr. Res. 471 (2019) 43–55, https://doi.org/10.1016/j.carres.2018.10.007.