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Organic & Biomolecular Chemistry

REVIEW

Raney cobalt – an underutilised reagent for the selective cleavage of C–X and N–O bonds

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Raney cobalt, which was first prepared in the 1930s, is known to function effectively as a catalyst for certain chemoselective reductions. However, its utility in chemical synthesis does not seem to have been fully appreciated. This first comprehensive survey of the literature on chemical transformations involving Raney cobalt attempts to redress matters by, among other things, highlighting the differences between the performance of this system and its much more well-known but usually less selective congener Raney nickel. A reliable method for preparing consistently effective Raney cobalt is presented together with a protocol that avoids the need to use it with high pressures of dihydrogen. As such, it is hoped more attention will now be accorded to the title reagent that offers considerable promise as a powerful tool for chemical synthesis, particularly in the assembly of polycyclic frameworks through tandem reductive cyclisation processes.

A. Introduction

The metal-catalysed addition of dihydrogen to both multiple and single bonds represents one of the most powerful and economically significant chemical processes known. A plethora of catalytic systems is available for this purpose and refinements of these continue to be reported in the unceasing quest to maximise chemo-, diastereo- and/or enantio-selectivity.[1,2] Given the vast body of research that has been reported in the area sometimes effective techniques can "fade from view" as the fascination with new systems and protocols captures the researcher's attention. Herein we argue this may be the case with Raney cobalt and suggest that it is a catalytic system that warrants re-examination by virtue of the capacity it offers for achieving, among other things, selective reductions within polyfunctionalised systems. Specifically, then, this review provides (to the best of our knowledge) the first substantial survey of the primary literature (including some patent filings) on Raney cobalt and its applications in chemical synthesis. The work cited herein emerged from a series of searches, conducted during 2013 and early 2014, of the chemical literature using both the SciFinder Scholar™ database and the Google Scholar™ search engine.

B. Historical development, forms of reagent, modes of preparation and sources of dihydrogen

The development of nickel-based catalysts preceded that of the cobalt-based ones.[3] In 1897 the Frenchmen P. Sabatier and J. B.

Senderens discovered that unsaturated organic compounds could be hydrogenated in the presence of finely divided nickel and nickel oxides and the process was greatly extended by the Russian chemist V. N. Ipatieff in the very early years of the 20th century. The broad utility of such methods was recognised by the award of the Nobel Prize to Sabatier (shared with V. Grignard) in 1912. Prompted by suggestions that occasionally "ultra catalysts" were encountered on using the Sabatier/Ipatieff protocols, from 1915 Murray Raney of Chattanooga, Tennessee conducted systematic studies on the performance of the nickel/nickel oxides catalyst systems in hydrogenation reactions as a function of the ratio of the metal to its oxides. While such experiments were to no avail (in terms of identifying "ultra catalysts"), his cognate studies on the industrial production of dihydrogen through the reaction of ferro-silicon with sodium hydroxide eventually led him to investigate the properties of the material derived from alkali-based digestion of finely ground nickel-aluminium alloys. In 1927 Raney was granted a patent for his discovery of the nickel-based catalyst that bears his name.[4] In 1933 another patent that "contemplates" nickel being replaced by "iron, copper, cobalt and other catalytic materials"[5] was granted. Raney's description of the "more or less spongy and porous state"[4] of the materials he produced led to the development of the trademarking of these systems as "Sponge Metals Catalysts™".[6] For similar reasons they are also sometimes referred to as "skeletal" catalysts.[7]

While Raney nickel was used from the mid-1920s for effecting the hydrogenation of vegetable oils under relatively mild conditions, it was Homer Adkins at the University of

Wisconsin who revealed, through a comprehensive series of studies started in 1930, that this catalyst had many other useful applications.[8] Adkins also made major contributions to the preparation and categorisation of the various types of Raney nickel[9] that now include W1 to W7 forms, details of which have been tabulated.[10]

Probably because of the higher cost and lower activity of Raney cobalt, there are far fewer studies on this catalyst compared with its nickel counterpart. Seemingly, most of the various procedures available for its preparation have been summarised.[11] In addition, Reeve and Eareckson have described[12] the preparation of "W7" Raney cobalt from a *ca.* 100-mesh alloy derived from 40% cobalt and 60% aluminium while Chadwell and Smith[13] report a very similar protocol and note that it is somewhat easier to prepare than Raney nickel because removal of alkali by washing can be accomplished rather quickly (a lengthy washing procedure is required for nickel).[14] A subsequent and detailed study on the preparation of Raney cobalt by Aller[15] highlighted the need to treat fine-mesh cobalt/aluminium alloy powders with alkali at 15–20 °C in order to obtain highly active forms of the catalyst. Interestingly, it was noted that the use of coarser powders tended to give massive, agglomerated catalysts that did not disperse effectively, resulting in lower activity. Aller also reported that the activity of the cobalt catalyst prepared at 100 °C, even from fine-mesh powders, is exceedingly low. In contrast, the activity of the corresponding nickel catalysts increased with increasing temperatures of preparation. The so-called Aller Raney cobalt has been described as being more active than its W7 counterpart, at least in certain contexts.[16]

While at various times Raney cobalt has been available from commercial sources, during the course of our recent studies, some of which are detailed below, we were unable to secure this catalyst by such means. Accordingly, and after considerable investigation, we have established a protocol[17] that provides material suitable for consistently achieving chemoselective reductions (at least of the types required for our purposes). A pivotal aspect to this work was the identification of a source[18] of nickel-free cobalt-aluminium alloy.[19]

The Urushibara cobalt catalysts,[1c,20] which display some reducing properties similar to Raney cobalt, are obtained by the reduction of cobalt salts (*e.g.* cobalt hexachloride) with zinc dust and leaching of the resulting precipitated and finely divided cobalt metal with aqueous sodium hydroxide, hydrochloric acid or acetic acid. Cobalt boride, which is prepared by treatment of cobalt nitrate (for example) with sodium borohydride in the presence of charcoal (as a supporting agent),[21] has proved to be an excellent reagent for the reduction of nitriles to amines while a mono-dispersed form prepared using a reversed micellar system is reported to have activity better than that of Raney cobalt in terms of its capacity to effect the hydrogenation of certain olefins.[22] However, given the scope of this review and the rather limited literature available on these (Urushibara) catalysts they will not be the subjects of any further discussion here.

The alkali leaching process associated with the preparation of Raney cobalt from the aluminium alloy normally leaves at least some dihydrogen adsorbed on its surface with the result that freshly prepared material can sometimes be used without needing to run the desired reduction process under an atmosphere of dihydrogen. Nevertheless, the norm is to run such reactions under dihydrogen, a procedure that may become essential as the catalyst "ages" through desorption of the gas. *iso*-Propanol can serve as a source of dihydrogen as demonstrated[23] by its use in the Raney cobalt-catalysed transfer hydrogenolysis of certain aromatic alcohols (see Section E for details).

C. Hydrogenolytic reactions

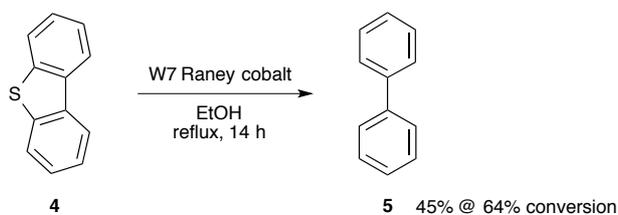### (i) Selective cleavage of carbon–halogen bonds

The capacity of the title reagent to effect the cleavage of carbon-halogen bonds, either directly or in the presence of dihydrogen, appears to have been the subject of very few studies and certainly no systematic ones. Kawashima *et al.* have reported[24] that dihydrogen in the presence of Raney cobalt is able to effect the reductive dechlorination of the ring-fused *gem*-dichlorocyclopropane **1** (Scheme 1) and does so with some levels of stereoselectivity by affording a *ca.* 2:1 mixture of the epimeric *endo*-and *exo*-forms, **2** and **3** respectively, of the corresponding mono-chloro derivative. However, Raney cobalt is not distinctive in this regard because similar outcomes are obtained by using W7 Raney nickel and Urushibara nickel B as catalysts. When PtO$_2$ is used as catalyst then a 1:1 mixture of compounds **2** and **3** was obtained.

Ratio **2**:**3** = 2:1 (yield not specified)
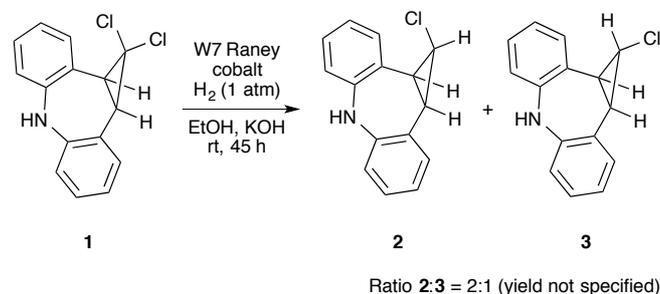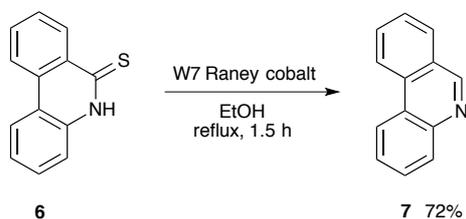
Scheme 1

(ii) Selective cleavage of carbon–sulfur bonds

While Raney nickel has been used extensively for the desulfurisation of a wide range of sulfur-containing compounds,[10] its cobalt counterpart has been less widely exploited for this purpose. A 1959 report by Badger and co-workers established[16] that the title reagent could desulfurise dibenzothiophene (**4**) [and thus providing biphenyl (**5**)] (Scheme 2) as well as a range of other compounds but in broad terms it was deemed "less effective" than Raney nickel.

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4 → **5** 45% @ 64% conversion

W7 Raney cobalt
EtOH
reflux, 14 h

Scheme 2

One instance in which Raney cobalt has proven superior involves the conversion of phenanthridinethione (**6**) into phenanthridine (**7**) (Scheme 3) which proceeds in 72% yield under the indicated conditions.[16] In contrast, when Raney nickel is used to effect the same conversion some over reduction to dihydrophenanthridine is observed and thus necessitating a subsequent dehydrogenation step. However, Raney cobalt proved less effective in terms of allowing for the clean desulfurisation of a range of other heterocyclic systems.[16]

6 → **7** 72%

W7 Raney cobalt
EtOH
reflux, 1.5 h

Scheme 3

The affinity of Raney cobalt for organosulfur compounds has been exploited in chromatographic separations. Thus, for example, the components of a 1:1 w/w mixture of isoeugenol and 2,5-dimethylthiophene could be readily separated from one another by methanol elution through a mixture of freshly prepared Raney cobalt and clean sand. The retained thiophene was then recovered by Soxhlet extraction of the adsorbent with methanol.[25]

(iii) Selective cleavage of carbon–oxygen bonds

There have been few studies on the capacity of Raney cobalt to effect C–O bond cleavage and this is almost certainly because it is not very effective for this purpose (however, see Section E). Still, the contemporary focus on the deoxygenation of biomass as a means of providing sustainable sources of fuels and other chemically valuable materials has led to extensive screening of a wide range of catalysts, including the title one, for their capacities to effect the hydrogenolysis of C–O bonds.[26,27] In one instance where Raney cobalt has been investigated for such purposes it proved to be less useful than other catalysts.[26] Nevertheless, in related studies, Raney cobalt was shown to be effective for converting glycerol (a material readily derived from biomass) into lactic acid[28] and for the isomerisation of erythritol (accessible by the yeast-mediated fermentation of sugar or sugar alcohols such as glucose and glycerol) into threitol.[29] The glycerol to lactic acid conversion is presumed to involve initial dehydrogenation of the substrate to give

glyceraldehyde, dehydration of the latter to pyruvaldehyde and hydroxide-mediated conversion of this last compound to lactate.[28]
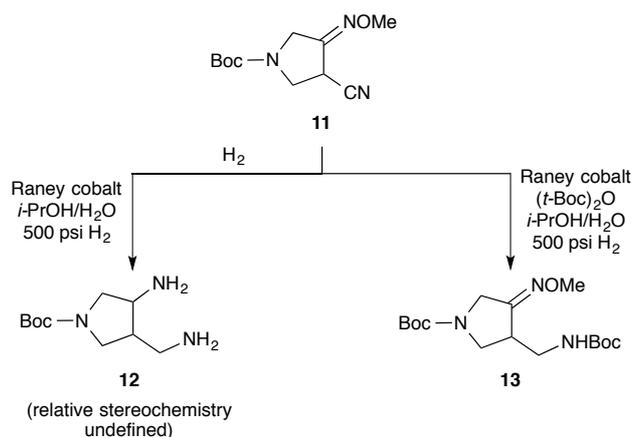
(iv) Selective cleavage of nitrogen–oxygen bonds

In 1956 Reeve and Christian demonstrated[30] that while Raney nickel effected the exhaustive addition of dihydrogen to oxime **8** (Scheme 4) and so generating amine **9** (20%) when the same substrate was hydrogenated in the presence of Raney cobalt then only C–O bond cleavage took place and so affording imine **10** (46%) as the sole reaction product. Ried and Schiller have made related observations.[31]
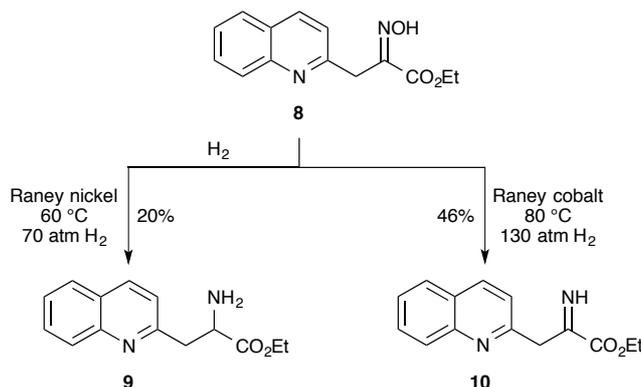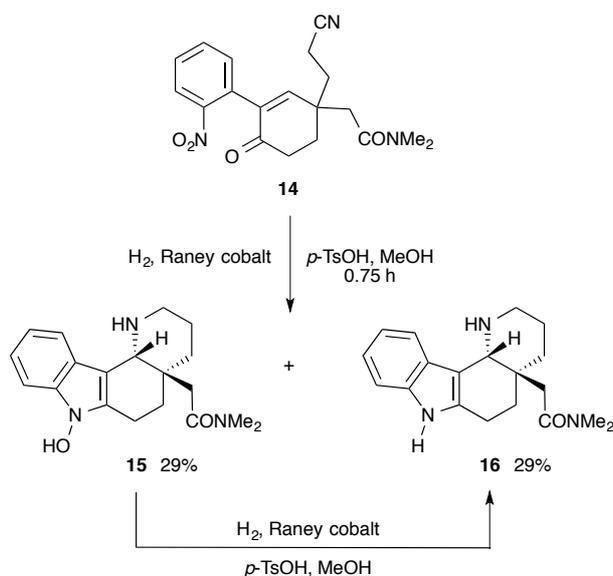

Scheme 4

During the course work directed towards the refinement of the synthesis of an intermediate associated with the manufacture of Gemifloxacin (Factive®), a novel quinolone-based antibacterial agent, Lee and co-workers established[32] that treatment of the α-cyanooxime *O*-methyl ether **11** (Scheme 5) with Raney cobalt in the presence of dihydrogen afforded the diamine **12** (unspecified yield and stereochemical outcome). This product clearly results from N–O bond cleavage as well as hydrogenation of the imine and nitrile residues (no order of events implied) within the substrate. In contrast, when the

Scheme 5

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reaction was carried out with *in situ* Boc-protection using (*t*-Boc)₂O then the 1°-amine derivative **13** was obtained with 83% selectivity over congener **12**. The selectivity for the target compound **13** rose to 91% when a nickel/chromium-doped form of the catalyst was used while the fully reduced product predominated when Raney nickel alone was employed as catalyst.

As part of a program of studies directed towards the synthesis of the alkaloid limaspermidine, we observed[33] (Scheme 6) that treatment of a methanolic solution of compound **14** with dihydrogen in the presence of Raney cobalt and *p*-toluenesulfonic acid (*p*-TsOH) for short periods of time afforded both the *N*-hydroxylated tetracyclic indole **15** (29%) and its deoxygenated counterpart **16** (29%). In contrast, sustained reaction of substrate **14** provided compound **16** (85%) exclusively as did analogous treatment of congener **15**. While a full understanding of the precise ordering of events associated with these conversions requires further investigation, it seems clear that the nitroarene residue is being converted, through N−O bond cleavage, into the corresponding *N*-hydroxyaniline and that this then engages in an intramolecular Schiff base condensation reaction. The conversion **15** → **16** clearly demonstrates that *N*-hydroxyindoles can be reduced to the equivalent indoles but whether such reductions can be extended to hydroxyamines more generally remains to be determined. Obviously the nitrile group within substrate **14** is also being reduced to the corresponding primary amine during the course of these conversions and the latter moiety then engages in an intramolecular hetero-Michael addition reaction. Related chemistry leading to the 1,5-methanoazocino[4,3-*b*]indole framework of the Uleine and *Strychnos* alkaloids has been reported.[34] Aspects of such work are presented in Section H. Further discussion of the general capacity of Raney cobalt to effect the reduction of nitriles to 1°-amines is presented in Section D(ii).

Scheme 6

It is interesting to note that when compound **14** was treated under essentially the same conditions as described above but using W7 Raney nickel in place of its cobalt counterpart then a mixture of compound **16** (48%) and the partially cyclised compound **17** (Fig. 1, 24%) was obtained.[35,36] The latter product necessarily arises from reduction of the C–C double bond of the enone moiety associated with substrate **14** at a relatively early stage in the process and thus preventing the intramolecular hetero-Michael addition reaction required for the formation of the desired compound **16**. Clearly then, Raney cobalt is a more chemoselective catalyst in this setting than is its nickel counterpart.
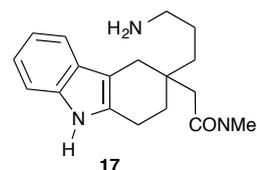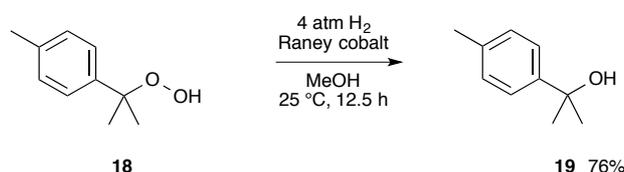

Fig. 1

(v) Selective cleavage of oxygen–oxygen bonds

A Raney cobalt-type catalyst obtained by digesting an alloy containing 42% cobalt and 58% aluminium with 20% aqueous sodium hydroxide at 50 °C has been reported[37] to facilitate the hydrogenolytic conversion of hydroperoxide **18** into the corresponding alcohol **19** in 76% yield (Scheme 7).

Scheme 7

D. Hydrogenation reactions

(i) Selective reduction of carbonyl groups

Raney cobalt can be employed for the selective reduction of the carbonyl groups within various unsaturated aldehydes and ketones. Thus, for example,[38] using a reaction temperature of 100 °C and a dihydrogen pressure of *ca*. 9 atm this catalyst has been used to effect the reduction of citral (**20**, Fig. 2) to a mixture of nerol (**21**), geraniol (**22**) and citronellol (**23**). Under such conditions a 60% conversion of the substrate was observed after 3 h and the major products of reaction were the allylic alcohols **21** and **22**. Even greater efficiencies were observed when a Urushibara-type cobalt species was used for this purpose. In contrast, when Raney nickel was used as catalyst then citronellal (**24**) was the major product of reaction.
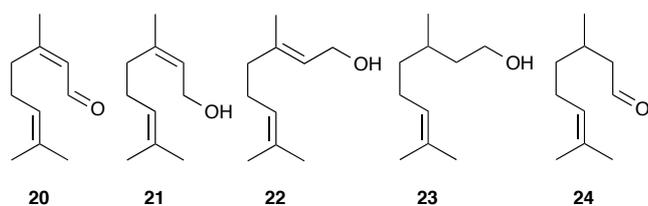
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Fig. 2

Various additives have been employed in conjunction with Raney cobalt in an effort to achieve greater selectivities in the reduction of a range of unsaturated aldehydes. In some relatively early work in this area, Hott and Kubomatsu[39] established that 2-methyl-2-pentenal was efficiently converted into the corresponding allylic alcohol (2-methyl-2-penten-1-ol) on exposure to an atmosphere of dihydrogen in the presence of a mixture of Raney cobalt and ferrous chloride at 55 °C and using *iso*-propanol as solvent. The yield of product increased with increasing amounts of ferrous chloride and the rapid appearance of the blue colour characteristic of Co(II) ions suggests that the cobalt of the catalyst was being substituted by iron. The impacts of adding $CoCl_2$, $MnCl_2$, $NiCl_2$, $PdCl_2$ acetic acid and triphenylphosphine to the reaction mixture have also been investigated.[40,41] As a result it has been concluded that both protic and Lewis acidic modifiers promote the formation of 2-methyl-2-penten-1-ol from the precursor aldehyde. Similarly, the hydrogenation of cinnamaldehyde to cinnamyl alcohol over Raney cobalt was greatly improved by modification of the catalyst with certain heteropolyacids such as $Cu_{3/2}PMo_{12}O_{40}$.[42] Similar outcomes were observed in the conversion of crotonaldehyde to crotyl alcohol.[43]

The ketonic residue within a range of non-conjugated enones is selectively reduced by dihydrogen in the presence of W4 Raney cobalt and sodium hydroxide while carbon monoxide prevents such processes.[44] The potentially enantioselective reduction of acetylacetone and ethyl acetoacetate by dihydrogen in the presence of Raney cobalt and either *S,S* or *R,R*-tartaric acid or one of eight optically active amino acids has been investigated.[45] However, only modest conversions and optical yields were observed. While such observations could be considered promising, the high yielding, enantioselective and ruthenium-based C=O reduction protocols developed by the likes of Noyori have overtaken such procedures.[46]

The reductive mono-deoxygenation of succinimide (**25**) to 2-pyrrolidone (**26**) has been effected (Scheme 8) by dihydrogen and Raney cobalt in the presence of ammonia at 240 °C and 272 atm of dihydrogen.[47]
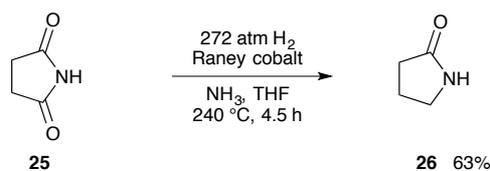
Scheme 8

(ii) Selective reduction of nitriles

Undoubtedly, the reduction of nitrile groups represents the most widely exploited application of Raney cobalt in chemical synthesis. While there are suggestions that, in certain settings at least, Raney nickel represents a superior catalyst for such purposes,[48] the literature is replete with examples indicating that Raney cobalt is highly effective. So, for instance, Reeve and Eareckson have shown[12] that the reduction of 3,4-methylenedioxyphenylacetonitrile to homopiperonylamine is best accomplished (88% yield) in the presence of W7 Raney cobalt and ammonia at 125–150 °C and using 200 atm of dihydrogen. When the same transformation is carried out using Raney nickel then the product amine is obtained in 82% yield. The reduction of *p*-cyanobenzoic acid (**27**) to the corresponding benzylamine **28** (Scheme 9) is readily effected at 25 °C using 3 atm of dihydrogen in aqueous ammonia and W6 or W7 Raney cobalt.[49] Once again, ammonia is used in the reduction to suppress the formation of 2°- and 3°-amines that would otherwise be formed through reductive alkylation processes.[50,51]
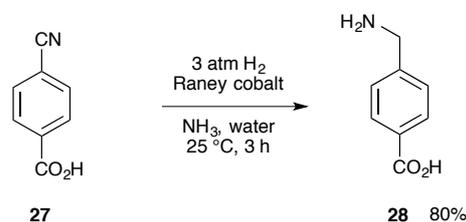
Scheme 9

As is the case in other types of reduction reactions, the use of various additives and/or refined modes of preparation of Raney cobalt have been reported to enhance the efficiencies of nitrile reduction processes.[52,53]

Nitrile reductions can be accomplished without attendant reductive dechlorination as demonstrated by the conversion of compound **29** into the corresponding 1°-amine **30** (Scheme 10), a step that has been employed in the industrial production of certain propylamine fungicides.[54]
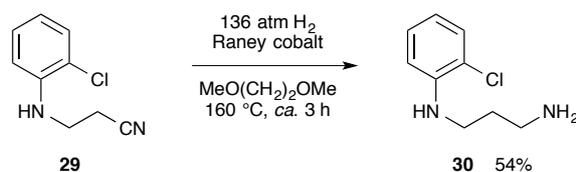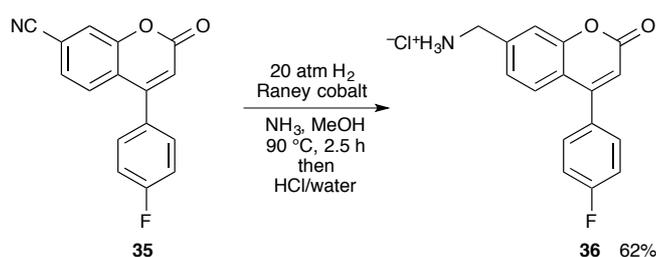

Scheme 10

As part of a study directed towards establishing a practical and scalable synthesis of the drug Eflornithine (used for the treatment of, among other things, African sleeping sickness),[55] an ethanolic solution of nitrile **31** (Scheme 11) was treated with dihydrogen in the presence of Raney cobalt and thereby producing the piperidone **32** "exclusively" and in 36% yield. In contrast, when the Schiff base, **33**, obtained by condensing substrate **31** with benzophenone, was treated under analogous

conditions and the crude reaction mixture then subjected to an aqueous work-up and treatment with HCl then compound **34** was obtained with ">99% selectivity" and in 79% yield. In neither instance was there any suggestion that competing hydrogenolysis of the C–F groups had occurred and nor was there any evidence of reduction of imine residue within compound **33**.
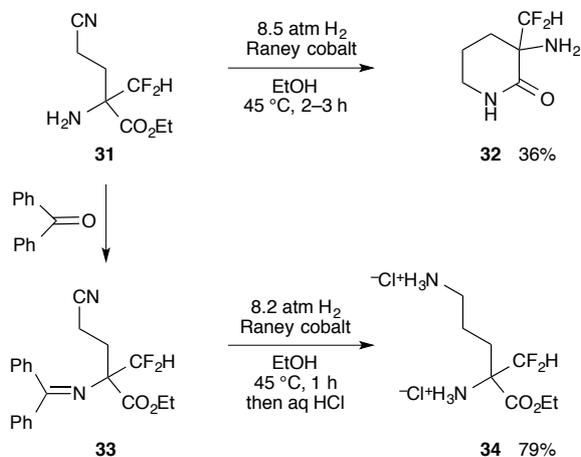
Scheme 11

During the course of the development of the synthesis of the 5-lipoxygenase inhibitor MK-0633,[56] the coumarin-based nitrile **35** (Scheme 12) was successfully reduced with Raney cobalt in the presence of methanolic ammonia to give the 7-aminomethyl-substituted congener **36** (62%). Subsequently, the reduction was carried out using aqueous acetic acid as solvent because of the instability of the product in original reaction medium. It is notable that, (i), no hydrogenolysis of the benzylic C–N bond within the product **36** was observed and (ii), no reduction of the C=C bond within the heterocyclic ring of either the substrate or the product took place. Acetal residues also survive during the course of the Raney cobalt catalysed reductions of nitriles.[57]

Scheme 12

The capacity of Raney cobalt to selectively effect the hydrogenation of unsaturated nitriles and thereby generating unsaturated 1°-amines is an important feature of this catalyst. Thus, for example, *E*-cinnamonitrile is chemoselectively reduced to 3-phenylallylamine with up to 80% selectivity and conversions of >90% when methanol in ammonia is used as the reaction medium.[58] Lower selectivities are observed with Raney nickel. When geranylnitrile (**37**, Fig. 3) was subjected to hydrogenation over Raney nickel doped with chromium then 3,7-dimethyl-6-octene-nitrile (**38**) was the favoured product of reaction while analogous treatment of the same substrate with the equivalently doped Raney cobalt catalyst gave the allylic amine **39** as the first-formed product of reaction. Sustained exposure of compound **39** to the reaction conditions led to the formation of mono-unsaturated congener **40**.[59]
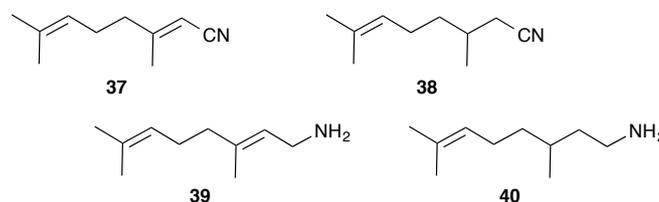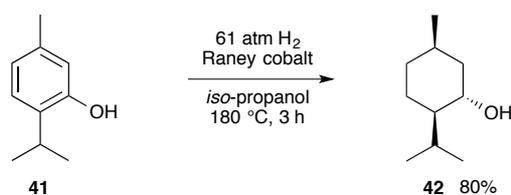

Fig. 3

More "elaborate" examples of the chemoselective reduction of nitriles embedded within polyfunctionalised substrates are presented in Section H.

Using chromium-doped Raney cobalt, polynitriles derived from the "capping", *via* hetero-Michael addition reactions, of polyols or polyamines with acrylonitrile, can be reduced to the corresponding poly 1°-amines, including ones embodied in dendritic like structures.[60–62] In those instances where exhaustive reduction of the nitrile groups cannot be accomplished using this catalyst system then a Urushibara-type reagent or dissolving metal protocol appear to be effective.[61]

(iii) Reduction of alkynes, alkenes and arenes

In many respects Raney cobalt is "prized" as a catalyst because of the capacity it offers to effect the reduction or reductive cleavage of various nitrogen- and sulfur-based functional groups in substrates also containing C–C multiple bonds. Accordingly, there is only a very modest literature dealing with the application of the title system to the reduction of alkynes, alkenes or arenes. Indeed, and perhaps a little surprisingly, we have been unable to locate a single report of the subjection of an alkyne to reaction with dihydrogen in the presence of Raney cobalt.

The exhaustive hydrogenation of the arene thymol (**41**) (Scheme 13) using Raney cobalt and dihydrogen has been reported to deliver (±)-isomenthol (**42**) in 80% yield together with minor amounts of the racemic modifications of neomenthol, neosiomenthol and menthol.[63]

Scheme 13

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Various forms of Raney cobalt generated under differing leaching conditions and/or containing additives have been studied as catalysts for the exhaustive hydrogenation of squalene (representing a model compound for the purposes of developing protocols that could eventually allow for the "upgrading" of bio-oil produced by the highly productive algae *Botryococcus braunii*).[64]

Aller[65] has investigated the effects of the promoters triethylamine and chloroplatinic acid (or combinations thereof) on the capacity of Raney cobalt to reduce a range of simple substrates containing both a carbonyl group and C=C units. When substrates such as crotonaldehyde, mesityl oxide and ethyl crotonate were involved then the C=C unit was reduced chemoselectively. Such outcomes stand in stark contrast to the those detailed at Section D(i) above and serve to emphasise the extraordinarily significant roles that additives/promoters can play in influencing the outcomes of reactions involving Raney cobalt (and, indeed, Raney metals more generally).

Interestingly, the activity of Aller's triethyamine/chloroplatinic acid-doped Raney cobalt is such that, at a temperature of 100 °C, acetophenone could be reduced to ethylbenzene, presumably *via* hydrogenolysis of the initially produced α-phenethyl alcohol.[65] In contrast, we have observed that when a methanolic solution of styrene **43** (Fig. 4) was subjected to reaction, at *ca*. 25 °C, with 1 atm of dihydrogen in the presence Raney cobalt (prepared using our protocol[17]) then the corresponding ethylbenzene **44** was produced in high yield without any accompanying hydrogenolysis of the benzyl group.[66]

Fig. 4

E. Transfer hydrogenation reactions

Raney cobalt (in this case the 2700 material obtained from W. R. Grace) has been shown[67] to catalyse the transfer of hydrogen from *iso*-propanol and by such means α-substituted aromatic alcohols containing two or more aromatic rings can be deoxygenated selectively. So, for example, each of 1,2-diphenylethanol, benzhydrol, triphenylmethanol 9-hydroxyfluorene 1-(2-fluorenyl)ethanol 1-(1-naphthyl)-ethanol and 1-(2-naphthyl)ethanol can be cleaved to give the corresponding aromatic hydrocarbon in quantitative yield. Raney nickel is less efficient in this regard but can be used to effect the hydrogenolysis of non-benzylic alcohols while its cobalt counterpart cannot. So, for example, 5-phenyl-1-pentanol is converted into pentylbenzene in 81% yield upon exposure of the former compound to Raney nickel and *iso*-propanol but no reaction is observed when Raney cobalt was employed under the same conditions.

The protocols detailed immediately above, which seem to be underutilised, avoid the need to handle gaseous dihydrogen while work up simply involves filtration and concentration of the filtrate.

F. Reactions involving (deliberate) racemisation

Raney cobalt is known to facilitate the dehydrogenation of a range of 2°-alcohols and -amines and thereby affording the corresponding ketone or imine that can themselves accept dihydrogen under appropriate conditions and so regenerating the original alcohol or amine. When optically active substrates are subjected to such conditions then the corresponding racemates are obtained. So for example,[68] when an ethereal solution of 63% ee *R*-(+)-2-amino-1-butanol (**45**, Fig. 5) was heated with Raney cobalt at 140 °C and 17 atm of dihydrogen for 6.75 h then the corresponding racemate was obtained in 96% yield. Resolution of this mixture of enantiomers through the formation and fractional recrystallisation of the derived tartrate salts then provided the essentially pure *S*-enantiomer required for the manufacture of ethambutol, a bacteriostatic antimycobacterial drug used to treat tuberculosis.
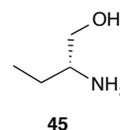
Fig. 5

R-Quinuclidin-3-ol (**46**, Fig. 6) represents a common pharmacophore associated with neuromodulators acting at cholinergic muscarinic receptors. Resolution of the corresponding racemate by various means provides the best way of generating this material and so methods for recycling the otherwise unusable *S*-enantiomer *via* its racemisation have been sought. One of the most effective methods for doing so involves treating the *S*-enantiomer with Raney cobalt in *o*-xylene under *ca*. 5 atm of dihydrogen and thereby generating the corresponding racemate in 97% yield.[69] When the same reaction was carried out in the absence of dihydrogen then the ketone was obtained.
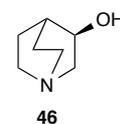
Fig. 6

A one-pot, dynamic kinetic resolution of certain 2°-amines has been reported wherein the unwanted enantiomer is racemised using Raney cobalt in the presence of dihydrogen and the desired component (enantiomer) of the resulting mixture is then acetylated enzymatically with *Candida Antarctica* lipase B.[70] Raney nickel was generally inferior in this context.

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G. Miscellaneous transformations

It has been noted[71] that Raney cobalt allows for the (sometimes high yielding) reaction of unsaturated amides with carbon monoxide to give cyclic imides. So, for example, the cyclohexenecarbonamide **47** is converted into hexahydrophthalimide (**48**) by such means (Scheme 14).
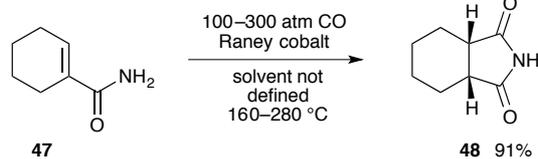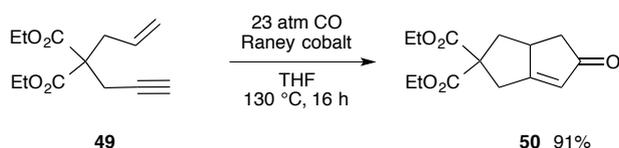

Scheme 14

In a related vein, it has recently been shown[72] that Raney cobalt serves as an effective and recyclable catalyst in the intramolecular Pauson–Khand reaction. Treatment (Scheme 15) of the enyne **49**, for example, with carbon monoxide (at pressures of *ca*. 23 atm) and Raney cobalt in THF at 130 °C for 16 h afforded the anticipated diquinane **50** in *ca*. 91% yield.
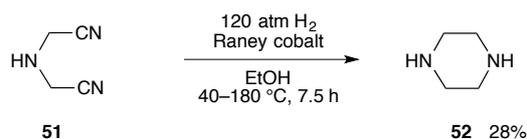

Scheme 15

Somewhat more esoteric uses of Raney cobalt include, (i), its catalysis of the Fischer–Tropsch-like reductive oligomerisation of isonitriles in the presence of dihydrogen and liquid ammonia[73] and, (ii), its conversion into dicobalt octacarbonyl under high pressures of carbon monoxide at elevated temperatures.[74]

H. Domino and related reactions

The chemoselectivities displayed in Raney cobalt catalysed reduction processes mean that these types of transformations can deliver new functionalities in the presence of others (not be affected by the reduction) and so establishing possibilities for cyclisation reactions to take place (see Scheme 6 for example). The Raney cobalt-catalysed reductive cyclisation of di(cyanomethyl)amine (**51**) to give piperazine (**52**) (Scheme 16) provided an early illustration of the possibilities in this area.[75]
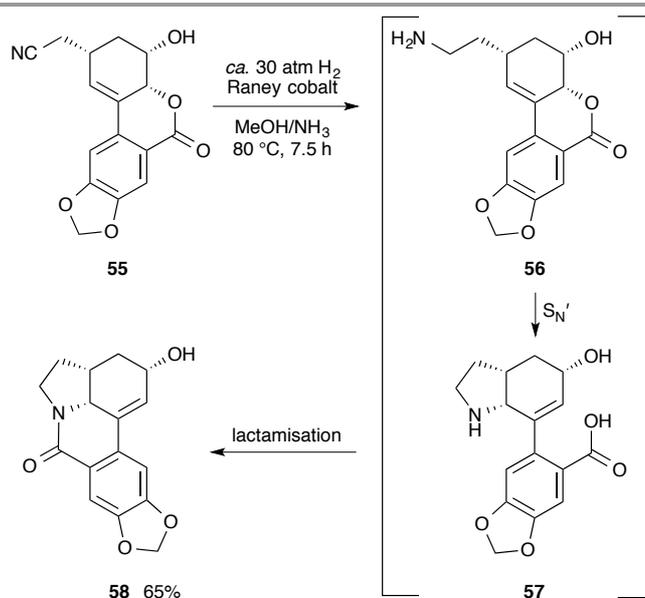

Scheme 16

The capacity of Raney cobalt to effect the reductive cyclisation of the α,β-unsaturated and enantiomerically pure nitrile **53** to the caprolactam **54** (Scheme 17) without significant racemisation or accompanying reduction of the C=C moiety has been reported by a Merck-based process research group.[76] Best results were obtained using W. R. Grace's Fe, Cr and Ni-doped Raney cobalt 2724. They noted that when Raney nickel was used for the same purpose then the C=C double bond was also reduced. With Rh and Pd-based systems only the C=C unit was removed (and so no cyclisation reaction occurred).
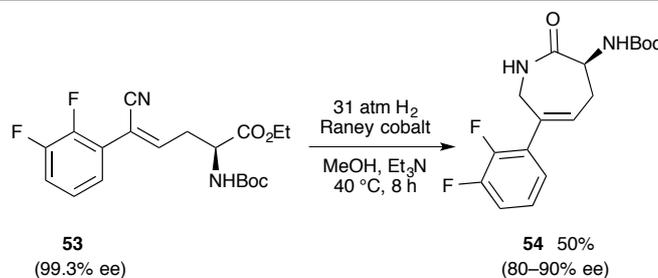
Scheme 17

In a true Domino process,[77] and as part of a synthetic program directed toward the synthesis of the *Amaryllidaceae* alkaloid lycorine, we observed[78] (Scheme 18) that when compound **55**, embodying nitrile, alkenic and allylic C–O moieties, was subjected to reaction with *ca*. 30 atm of dihydrogen in methanol/ammonia in the presence of Raney cobalt then the initially formed 1°-amine **56** (not isolated) engaged in an intramolecular S_N' reaction with the product amino-acid **57** (not isolated either) then undergoing lactamisation to give the observed product **58** (65%) that embodies the polycyclic framework of the target natural product. We have since found[79] that by using larger quantities

Scheme 18

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of Raney cobalt (normally *ca.* 200% w/w catalyst relative to substrate) then closely related nitriles can be reduced to the corresponding 1°-amine using just 1 atm of dihydrogen. Clearly, this makes for an operationally much simpler and thus far more attractive procedure. Interestingly, when compound **55** was subjected to attempted reduction using Raney nickel then only a complex mixture of products was obtained.

Upon subjecting the readily accessible and polyfunctionalised cyclohexenone **59** (Scheme 19) to a range of reductive cyclisation conditions then either partially reduced and partially cyclised, fully reduced and partially cyclised or fully reduced and completely cyclised products could be obtained.[34] Thus, treatment of the compound with dihydrogen in the presence of 10% Pd on C in methanol at 18 °C afforded indole **60** (98%) as a result of reduction of the C=C bond and reductive cyclisation of the nitro-group onto the pendant C=O (no particular order of events implied). The associated nitrile residue was clearly not affected under these conditions. On exposure to dihydrogen in the presence of Raney nickel and *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H$_2$O – this acid is added to prevent reductive alkylation reactions involving the intermediates arising from nitrile group reduction) substrate **59** engaged in the same set of reactions as encountered in the first process but, in addition, the nitrile group was also reduced to the corresponding 1°-amine (and so affording compound **61** which was obtained in 87% yield). Amine **61** was also formed (in 98% yield) when compound **60** was treated with dihydrogen in the presence of Raney nickel. Finally, and most importantly, when cyclohexenone **59** was treated with dihydrogen, Raney cobalt and *p*-TsOH•H$_2$O then two reductive cyclisation events took place, one involving an intramolecular hetero-Michael addition reaction (leading to the formation of a piperidine ring) and the other in which an intramolecular Schiff base type condensation reaction took place (leading to the formation of an indole moiety). As a result the tetracyclic compound **62** was obtained in 72% yield. The conversion **59 → 62** is of particular interest because the product embodies the 1,5-methanoazocino[4,3-*b*]indole framework associated with the Uleine and *Strychnos* alkaloids.

I. Effect of additives on the reactivity of Raney cobalt

As noted on numerous occasions in the foregoing sections, the presence of additives in Raney cobalt can have a dramatic effect on its catalytic properties.[19,39–43,64,65] The manner in which the material is prepared (particularly in terms of the initial digestion process and the subsequent washing protocols that are followed) also has an impact on activity[14] and is likely the result, in part at least, of residual aluminium-based species present at the surface of the reagent.

Beyond the effects noted above, additional studies[80] of this topic have revealed that, for example, the efficiency of reduction of various nitriles by Raney cobalt containing iron is strongly influenced by the presence of a third component selected from the group consisting of Ni, Rh, Ru, Pd, Pt Os and
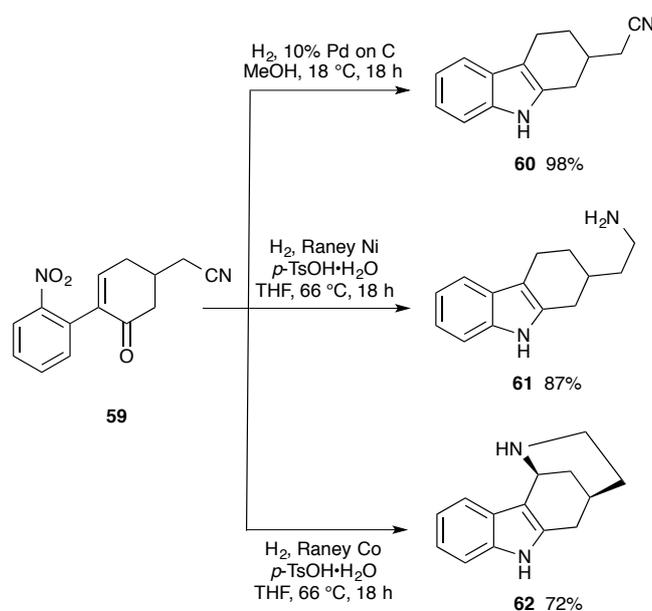
Scheme 19

Ir or mixtures thereof. Chromium species can also have significant effects[81] as can molybdenum and tungsten.[82] Similarly, when Raney cobalt is dispersed in an aliphatic 1°-, 2°- or 3°-amine, a diamine or a cyclic one[83] then alterations in reactivity are observed. The preservation of the activity of Raney cobalt (and nickel) between runs through its storage in glycols has been advocated.[84]

J. Comparisons with Raney nickel

In the foregoing sections, frequent comparisons have been made between the catalytic effects of Raney cobalt and its nickel counterpart. It is quite clear from these that the former species is the less reactive one. Indeed, the substantial change in the reactivity of Raney cobalt as a function of the presence of even small quantities (1–2%) of nickel[19] in the starting alloy stands as testimony to the significant difference in behaviours of the two systems. The consequence of this is that Raney cobalt frequently allows for more chemoselective reactions to be carried out, most particularly when the synthesis chemist is seeking to reduce nitro- and nitrile-based moieties in the presence of otherwise potentially reactive species.

K. Mechanistic studies

The literature focused on elucidating the mechanisms of reactions that employ Raney cobalt is rather sparse. Inelastic neutron scattering studies[85] of dihydrogen and butyronitrile adsorbed on various Raney cobalt catalyst systems have led to the detection of partially hydrogenated and surface-associated species including (probably) those that arise from reductive alkylation events. Intriguingly, nitrene-like intermediates appear to have been detected during the hydrogenation of CD$_3$CN on Raney cobalt.[86]

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L. Conclusions

While this survey of a rather scattered body of literature on Raney cobalt reveals that it is a reagent capable of facilitating a number of distinctly fascinating chemical transformations, most notably various chemoselective reduction reactions, it is by no means one that routinely comes to mind when synthesis chemists contemplate the vast "tool set" at their disposal. There are several factors that have contributed to this situation, the first being the seeming lack of any compilation of the suite of chemical transformations that Raney cobalt can facilitate. Hopefully this review will help redress matters in this regard. A second factor contributing to the lack of an extended "uptake" of the title reagent in chemical synthesis is the seemingly disparate array of techniques detailed in the literature for preparing Raney cobalt and its "doped"/"spiked" variants, all of which seem to display quite distinct reactivity profiles. The discontinuation of the supply of certain previously commercially available sources of Raney cobalt[87] has certainly exacerbated matters. Furthermore, the seemingly frequent need to use very high pressures of dihydrogen (and, often simultaneously, high temperatures) is also off-putting with the end result that even for all the potential chemoselectivities "on offer" the operational requirements associated with using the reagent just seem too daunting.

We believe the drawbacks mentioned above are all readily addressed by using the simple protocols defined below[17] that allow for the ready preparation of Raney cobalt possessing consistent and effective properties. Furthermore, by using larger quantities of Raney cobalt (*e.g. ca.* 200% w/w wrt substrate)[34,79b] in the reduction reactions many of these can be carried out using dihydrogen at atmospheric pressure and usually at room temperature. Our recent[88] application of such protocols to the tandem reductive cyclisation of the enone **63** (Scheme 20) to compound **64**[89] (and embodying the ABCD framework of the important alkaloid vindoline[90]) has served to reinforce our enthusiasm for Raney cobalt as a catalyst for the chemoselective reduction of polyfunctionalised substrates.
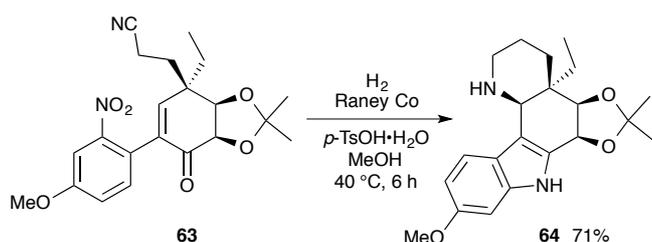
Scheme 20

We contend that Raney cobalt is an under utilised but particularly effective catalyst for the chemoselective reduction of polyfunctionalised organic substrates, notably those incorporating nitro and nitrile moieties. As such continued and systematic investigations into its catalytic properties are to be encouraged as these are very likely to reveal new and valuable patterns of reactivity.

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89 The conversion **63 → 64** was carried out as follows: A magnetically stirred solution of compound **63** (40 mg, 0.10 mmol) in methanol (10 mL) containing *p*-TsOH•H$_2$O (86 mg, 0.50 mmol) was treated with Raney cobalt (80 mg, 200% w/w) and the resulting mixture subjected to a degassing/dihydrogen flushing protocol (three times) then heated at 40 °C whilst being maintained under an atmosphere of dihydrogen (contained in a balloon) for 6 h. The cooled reaction mixture was rendered basic through the addition of ammonia-saturated methanol (*ca*. 25 mL) then filtered through Celite™. The residues thus retained were washed with additional ammonia-saturated methanol (3 × 25 mL) and these washings were also filtered through Celite™. The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane). Concentration of the relevant fractions (R_f = 0.6) then afforded compound **64** (25 mg, 71%) as a clear, colourless oil.

90 For an up-to-date point-of-entry into the literature on this important alkaloid see: L. V. White, M. G. Banwell and A. C. Willis, *Heterocycles*, 2014, DOI: 10.3987/COM-14-S(K)19.