A convenient methodology for the chemoselective reduction of a wide variety of functionalized alkenes

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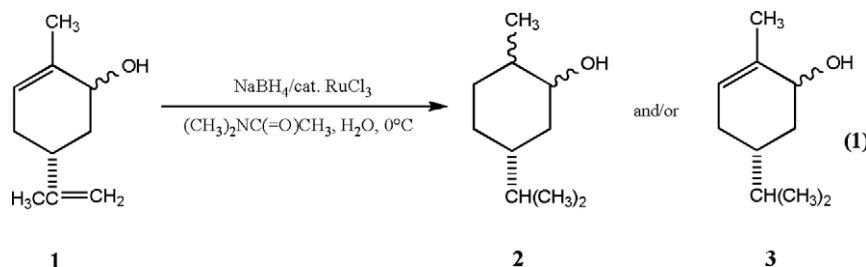
An efficient method to effect chemoselective reduction of alkenes (including trisubstituted olefins) possessing various sensitive and/or reducible groups such as acetals, allylic alcohols, benzyl ethers, epoxides, esters, halides, nitriles, and sulfones is reported. The reduction is facile at 0 °C in aqueous *N,N*-dimethyl-acetamide containing sodium borohydride in the presence of 15 mol % ruthenium(III) chloride. Regioselective reduction of dienes is also feasible if the double bonds are sufficiently different in their structural environment.

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It has been nearly 50 years since Brown and Brown reported[1] that certain platinum metal salts catalyzed the hydrolysis of sodium borohydride, thereby generating hydrogen for in situ reduction of carbon–carbon double bonds. In the decades that ensued, the combination of sodium borohydride with cobalt(II), nickel(II), copper(II), and rhodium(III) halides was employed to reduce other functional groups (e.g., nitriles and amides) which are inert to sodium borohydride alone.[2] This type of transformation continues to be of interest as evidenced by a recent communication[3] that reported the selective hydrogenation of mono- and disubstituted olefins by use of sodium borohydride in aqueous tetrahydrofuran (THF) in combination with a catalytic amount of ruthenium(III) chloride hydrate.

As part of an on-going research project we required an efficient method for the regioselective hydrogenation of (−)-carveol (**1**) to obtain allylic alcohol **3**.

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α-pinene, 1-methylcyclohexene, and cholesterol) were inert to such conditions.

Unexpectedly, we found that Sharma's methodology[3] when applied to (−)-carveol (**1**) led to a rather slow reduction; and a significant amount of hydrogenation of the trisubstituted olefin occurred once the isopropenyl moiety had been reduced by 50%. In an effort to minimize over-reduction by altering the solvent mixture, we discovered unexpected behavior[4] of the reductant in aqueous *N,N*-dimethylacetamide (DMA). The present Letter presents the results of this investigation of NaBH$_4$/cat. RuCl$_3$ in aqueous DMA for the reduction of functionalized alkenes.

Previous studies of the transition metal-catalyzed (CoCl$_2$[5] and RuCl$_3$[3]) hydrolysis of NaBH$_4$ in aqueous THF have shown such a procedure to be ineffective in the hydrogenation of trisubstituted olefins. In sharp contrast, we have found that NaBH$_4$/cat. RuCl$_3$ in aqueous DMA is considerably more robust, being capable of

The method of Sharma et al.[3] utilizing NaBH$_4$/cat. RuCl$_3$ in aqueous THF seemed to be an attractive choice for effecting the desired transformation (**1**→**3**) since trisubstituted olefins (e.g.,

reducing a variety of trisubstituted olefins (entries 1, 3, 7, 8, 10, 13, and 14 in Table 1). Despite the more reactive nature of this mixture, its use in small-scale hydrogenations is easier to control than in the related methods since the evolution of hydrogen is rather slow and pressure equipment is not required. An additional feature (in contrast with the use of NaBH$_4$/RuCl$_3$ in aqueous THF,[3] which

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Table 1
Ru+3-catalyzed reduction of functionalized alkenes using $NaBH_4$ in aqueous DMA[a]
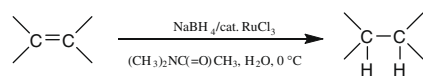
Method	$RuCl_3 \cdot xH_2O$ (mmol)	$NaBH_4$ (mmol)	Solvent
A	0.034	0.24	0.75 mL of 2:1 (v/v) DMA:H_2O
B	0.034	0.24	1.00 mL of 3:1 (v/v) DMA:H_2O
C	0.019	0.106	0.60 mL of 5:1 (v/v) DMA:H_2O
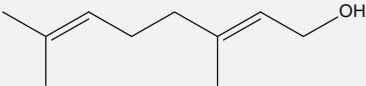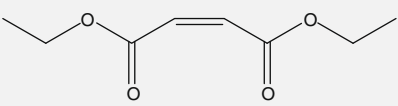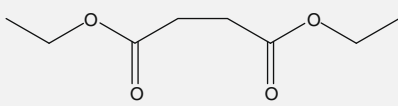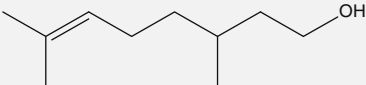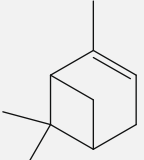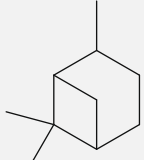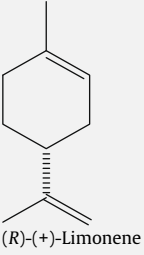
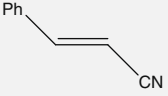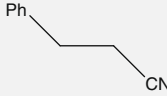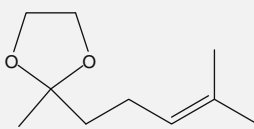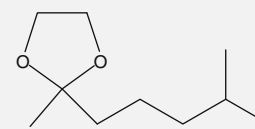| Entry	Substrate[b]	Method	Product(s)[c]	Recovery [product(s) + unreacted substrate] (%)	Isolated yield of reduction product(s) (%)
1	(−)-Carveol[d] (**1**)	A	9:1 Mixture of **2**[d]: **3**[d]	85	85
2	(−)-Carveol[d] (**1**)	C	**3**[d,e]	86	47
3	Geraniol	A	3,7-Dimethyloctan-1-ol[f]	83	83
4	Diethyl maleate	A	Diethyl succinate	71	71
5	1,2-Epoxy-9-decene	B	1,2-Epoxydecane[g]	79	79
6	1-Nonen-4-ol	A	Nonan-4-ol	83	82
7	Citronellol	A	3,7-Dimethyloctan-1-ol	92	79
8	α-Pinene	B	cis-Pinane	50[h]	13
9	10-Bromodec-1-ene	B	1-Bromodecane	65[h]	65
10	(R)-(+)-Limonene	B	1:1 Mixture of 1-isopropyl-4-methylcyclohexane[d] and 4-isopropyl-1-methylcyclohexene	65[h]	62
11	Cinnamonitrile	A	3-Phenylpropanenitrile	75	15
12	Ethyl cinnamate [ethyl 3-phenyl-(2E)-propenoate]	A	Ethyl 3-phenylpropanoate	77	58

Table 1 (*continued*)

Entry	Substrate[b]	Method	Product(s)[c]	Recovery [product(s) + unreacted substrate] (%)	Isolated yield of reduction product(s) (%)
13	6-Methyl-5-hepten-2-one	A	6:1 Mixture of 6-methylheptan-2-ol and 6-methyl-5-hepten-2-ol	75	75
14	2-Methyl-2-(4-methylpent-3-enyl)-1,3-dioxolane[i]	A	2-Methyl-2-(4-methylpentyl)-1,3-dioxolane[i]	68[j]	34

[a] All reactions were conducted by addition of NaBH$_4$ to an aqueous DMA solution of substrate (0.18–0.20 mmol) and ruthenium(III) chloride hydrate at 0 °C and by stirring the mixture at 0 °C for 60 min. An extended reaction time did not result in an increase in the isolated yield of the reduction product for entries 8, 11, and 14—an indication that the catalyst had been deactivated during the course of the reaction. See Ref. 6 for the general procedure (Method A).

[b] All substrates, except entry 14, are commercially available from Sigma–Aldrich (Milwaukee, WI, USA).

[c] Structural assignments and product ratios were based on analysis of ^{1}H NMR spectral data (300 MHz) and on comparison with that exhibited by authentic samples of these known products and substrates. See Ref. 7 for most of these spectra.

[d] Mixture of stereoisomers.

[e] Contaminated with a trace amount (<2%) of **2**.

[f] >97% reduction of both double bonds.

[g] No cleavage of the epoxide was detected.

[h] The losses upon isolation are due to the volatility of the substrate/product.

[i] For a previous synthesis of this compound, see Ref. 8.

[j] No cleavage of the acetal was detected.

required 2 M equiv of NaBH$_4$ for each double bond) is a more efficient use of hydride (e.g., entry 3 in Table 1).

In regard to the regioselective hydrogenation of (−)-carveol (**1**→**3**), enhanced selectivity for reduction of the disubstituted double bond was observed (Table 1, entry 2) by the use of less reductant and, more importantly, by decreasing the water content of the mixture. No effort was made to optimize the conditions for monohydrogenation of sterically differentiated dienes such as (−)-carveol (**1**) since we were able to effect that transformation (**1**→**3**) by use of molar excesses of both cobalt(II) chloride and NaBH$_4$ in ethanol,[9] using a method reported by Chung.[10] Instead, our efforts focused on the chemoselective reduction of the carbon–carbon double bond in various alkenes possessing sensitive and/or reducible functional groups. In addition to the substrates listed in Table 1, benzyl ether and phenyl propyl sulfone were inert to NaBH$_4$/cat. RuCl$_3$ in aqueous DMA (Method A); and o-nitrotoluene was moderately stable[11] using the conditions of Method C.

In conclusion, a robust (yet experimentally convenient) process has been developed for small-scale hydrogenation of alkenes (including trisubstituted olefins) that avoids the use of a hydrogen cylinder and pressure equipment. It uses the readily available sodium borohydride as the reducing agent in the presence of a catalytic amount of a halide salt of ruthenium, which is neither poisonous nor explosive.[3] Despite the robust nature of the process, various sensitive and/or reducible functionalities are inert to the reaction conditions, making this process an attractive method for chemoselective reduction of carbon–carbon double bonds.

References and notes

1. (a) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 1495; (b) Brown, C. A.; Brown, H. C. *J. Org. Chem.* **1966**, *31*, 3989–3995.

2. Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801–6802. and references cited therein.

3. Sharma, P. K.; Kumar, S.; Kumar, P.; Nielsen, P. *Tetrahedron Lett.* **2007**, *48*, 8704–8708. and references cited therein.

4. Consistent with the observations of Sharma et al.,[3] the addition of NaBH$_4$ to a dark-colored solution of RuCl$_3$ and alkene substrate in aqueous THF at 0 °C resulted in a rapid evolution of H$_2$, precipitation of a flocculent black powder after several minutes, and loss of color in the liquid phase. In sharp contrast, a similar reaction in aqueous DMA at 0 °C resulted in the slow 'controlled release' of H$_2$ and the appearance of a long-lasting (>20 min) dark-blue/green color in the liquid phase.

5. Satyanarayana, N.; Periasamy, M. *Tetrahedron Lett.* **1984**, *25*, 2501–2504.

6. *General procedure for alkene reduction (Method A):* To a 15-mL 1-neck reaction flask fitted with a glass stopper [*Note:* A larger-scale reaction may require the use of a pressure vessel and/or addition of NaBH$_4$ in small portions.] were added a small spin bar, 0.18–0.20 mmol of substrate, 0.50 mL of DMA (HPLC-grade), 0.25 mL of H$_2$O, and 7.0 mg (0.034 mmol) of ruthenium(III) chloride hydrate (Sigma–Aldrich Catalog No. 206229). After cooling the latter mixture to 0 °C (external ice-H$_2$O bath), 9.0 mg (0.24 mmol) of NaBH$_4$ powder was added in one portion; and the mixture was subsequently stirred at 0 °C for 60 min. The product was isolated by dilution of the reaction mixture with 10 mL of 4:1 (v/v) pentane/dichloromethane; and solid material was removed by filtration through a small pad of Hyflo Super-Cel® filtering aid. Removal of DMA was accomplished by washing the organic filtrate with 15% (w/v) aqueous NaCl (4 × 10 mL portions). The organic layer was subsequently dried over anhydrous MgSO$_4$, filtered, and the volatile organic solvents were removed by evaporation at reduced pressure.

7. The proton NMR spectral data of nearly all substrates and products are freely accessible via the Spectral Data Base System (SDBS) maintained by the Japanese National Institute of Advanced Industrial Science and Technology at: http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng.

8. Mousseron-Canet, M.; Mousseron, M.; Levallois, C. *Bull. Soc. Chim. Fr.* **1963**, 376–378.

9. Treatment of 38 mg (0.25 mmol) of (−)-carveol with 102 mg (0.43 mmol) of cobalt(II) chloride hexahydrate and 39 mg (1.03 mmol) of NaBH$_4$ in 1.00 mL of ethanol at 20 °C for 14 h afforded 31 mg (82% yield) of a 7:1 mixture of allylic alcohol **3**: unreacted carveol, with only a trace (<2%) of over-reduction.

10. Chung, S.-K. *J. Org. Chem.* **1979**, *44*, 1014–1016.

11. The isolated product was a 7:1 mixture of o-nitrotoluene/o-toluidine.