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Full Papers

Use of Achiral (Diphosphine)$RuCl_2$(Diamine) Precatalysts as a Practical Alternative to Sodium Borohydride for Ketone Reduction

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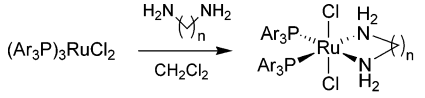
Abstract:

Stoichiometric sodium borohydride is frequently used in the chemoselective reduction of ketones to racemic secondary alcohols. Catalytic homogeneous hydrogenation using (diphosphine)$RuCl_2$(diamine) complexes provides a practical and economic alternative. A range of substrates were investigated and the optimum precatalyst identified in each case. Norcamphor was reduced with high diastereoselectivity using $(Ph_3P)_2$-$RuCl_2$(en); (*E*)-4-phenylbut-3-en-2-one was reduced with good chemoselectivity, and acetophenone was hydrogenated very efficiently using the same precatalyst. Isophorone and 3-dimethylaminopropiophenone were effectively hydrogenated using (dppf)$RuCl_2$(en).

Introduction

Reduction of ketones to secondary alcohols is an important transformation in organic synthesis, which is routinely accomplished by stoichiometric reducing agents such as sodium borohydride.[1] Whilst sodium borohydride is cheap and easy to use, the development of a homogeneous catalytic method could be advantageous, avoiding time-consuming work-up procedures and minimising waste streams. Noyori developed a system comprising tris(triphenylphosphine)-ruthenium dichloride, ethylenediamine, and potassium hydroxide in the ratio 1:1:2 that was effective for the hydrogenation of unsaturated aldehydes and ketones.[2] It was later discovered that stable $RuCl_2$(phosphine)$_2$(1,2-diamine) (**1**) or $RuCl_2$(diphosphine)(1,2-diamine) (**2**) complexes were much more efficient than the in situ catalyst.[3] Most examples of this technology focus on the use of chiral diphosphines for asymmetric hydrogenation,[4] whereas the achiral version has achieved relatively little attention to date but is potentially even wider reaching. Mechanistically it has been proposed that these reactions involve a ruthenium hydride species, and the metal does not bind directly to the substrate, which accounts for high chemoselectivity and activity of the catalyst systems.[5] Complex **1** (Ar = *p*-$CH_3C_6H_4$, $n = 2$) has been shown to be very active for hydrogenation of cyclohexanones[3] and benzophenones.[6] Here we report our results on the extension of this technology to a range of ketones important to the pharmaceutical or fragrance industries.

Scheme 1. **Preparation of $(Ar_3P)_2RuCl_2$(diamine)**



1

a Ar = Ph, n = 2, 87%

b Ar = Ph, n = 3, 55%

c Ar = 4-MeO-C_6H_4, n = 2, ~40%

d Ar = 4-MeO-C_6H_4, n = 3, ~41%

Results and Discussion

Precatalyst Synthesis. Precatalysts of the type $(Ar_3P)_2$-$RuCl_2$(diamine) (**1**) were prepared by reaction of $(Ar_3P)_3$-$RuCl_2$ with the required diamine in dichloromethane and precipitation of the product from MTBE (Scheme 1).

Compounds of the general formula, (diphosphine)$RuCl_2$-(diamine) (**2**) were prepared in an analogous way to the chiral complexes.[3] The diphosphine was reacted with dichloro-(benzene) ruthenium (II) dimer followed by treatment with the diamine (Scheme 2).

Acetophenone. To demonstrate the ease with which simple aryl ketones can be hydrogenated using this system, the reduction of acetophenone **3** with $(PPh_3)_2RuCl_2$(en) (**1a**) was carried out. Hydrogenation at 40 °C was complete in 4 h (S/C 20000), giving 1-phenylethanol **4** in 90% yield after distillation (Scheme 3).

Such simple aromatic ketones can be reduced equally efficiently to benzyl alcohols using heterogeneous catalysts such as Pd/C although the reactivity needs to be tempered

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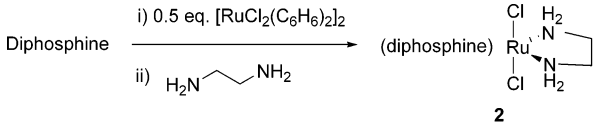
Scheme 2. **Preparation of (diphosphine)$RuCl_2$(en)**



2

Diphosphine = **a** 1,1'-bis(diphenylphosphino)ferrocene (dppf)

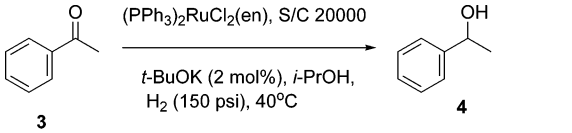
b 1,2-bis(diphenylphosphino)ethane (dppe)

c 1,4-bis(diphenylphosphino)butane (dppb)

d rac-BINAP

e 1,1'-bis(diisopropylphosphino)ferrocene (DiPFc)

Scheme 3. **Hydrogenation of acetophenone**



3 **4**

4h, 99% conversion
90% yield after distillation

Table 1. **Reduction of norcamphor**

6 **5**

entry	reagent	conditions	de (%)
1	Red-Al	THF, 0°C	80 endo
2	$NaBH_4$, NaOMe	MeOH, −20°C	88 endo
3	$NaBH_4$	*i*-PrOH, −10°C	88 endo
4	$NaBH_4$ in triglyme	MeOH, −20°C	88 endo
5	PtO_2, H_2	140 psi, MeOH, rt	86 endo 86% conv.
6	Pd/C, H_2	140 psi, MeOH, rt	0% conv.
7	Rh−(DiPFc)	100 psi, MeOH, rt	60 exo

with mild catalyst poisons such as ethylenediamine.[7] However, such systems are likely to struggle with compounds containing halides due to competing hydrodehalogenation.

Norcamphor. As part of a program to develop a practical synthesis of (*S*)-*endo*-norborneol, **(***S***)-5**, the diastereoselective reduction of norcamphor **6** was investigated. Using sodium borohydride under a variety of conditions (Table 1, entries 2−4) gave, at best, 88% de *endo*-norborneol **5**. This was not adequate for our purposes, so other reducing agents were screened, initially without much success. In fact, Rh−(DiPFc)-catalysed[8] hydrogenation even showed a preference for the *exo* isomer (Table 1, entry 7).

Encouragingly, Noyori has reported the use of the in situ system of $Cl_2Ru(PPh_3)_3$, ethylenediamine, and potassium hydroxide for the reduction of norcamphor with excellent diastereocontrol.[9] However, we preferred to use stable, isolated precatalysts, so we needed to check that this selectivity would be retained under these conditions. A screen of several achiral Noyori precatalysts (Table 2) quickly

Table 2. **Hydrogenation of norcamphor**

entry	precatalyst[a]	S/C/B	de (%)
1	(dppe)$RuCl_2$(en)	150:1:30	10 endo
2	(dppf)$RuCl_2$(en)	300:1:30	97 endo
3	$(Ph_3P)_2RuCl_2$(en)	450:1:45	98 endo
4	(DiPFc)$RuCl_2$(en)	550:1:55	20 exo
5	(rac-BINAP)$RuCl_2$-(en)	300:1:30	92 endo
6	$(Ph_3P)_2RuCl_2$(en)	2500:1:18	97 endo
7	$(Ph_3P)_2RuCl_2$(en)	10000:1:50	96 endo
8	$(PMPP)_2RuCl_2$-(en)	850:1:19	98 endo
9	(dppb)$RuCl_2$-(en)	1000:1:22	96 endo
10	$(Ph_3P)_2RuCl_2$-(diamp)	875:1:19	87 endo
11	$(PMPP)_2RuCl_2$-(diamp)	860:1:19	84 endo

[a] PMPP − tris(4-methoxyphenyl)phosphine; en − ethylenediamine; diamp − 1,3-diaminopropane.

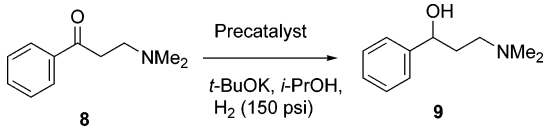
established that (dppf)$RuCl_2$(en) (**2a**) and $(Ph_3P)_2RuCl_2$(en) (**1a**) were optimal for this reaction, affording excellent reaction rates and >96% de product **5** (all reactions were carried out at room temperature and 100−140 psi hydrogen). The $(Ph_3P)_2RuCl_2$(en) system was then scaled up to 80 g input of norcamphor. Using only 50 mg of catalyst (S/C/B 10000:1:50), complete conversion was achieved in 22 h (entry 7). This level of diastereoselectivity is comparable to that obtained with Selectride reagents at low temperature.[10] The enzymatic resolution of **5** will be published at a future date.

As a result of this success, several other achiral catalysts were prepared and screened in the reduction of norcamphor, the best result coming with $(PMPP)_2RuCl_2$(en) (**1c**) (entry 8, 98% de). This is in line with the observed increase in Cram selectivity with more electron-rich triarylphosphines for the reduction of substituted cyclohexanones.[9] The catalysts **1b** and **1d** derived from 1,3-diaminopropane were found to be very reactive towards this substrate but were significantly less selective (entries 10 and 11). These preliminary results showed that the length of the alkyl tether between the two phosphine groups has a remarkable effect on the diastereoselectivity [compare entry 1, (dppe)$RuCl_2$(en), **2b** (10% endo), with entry 9, (dppb)$RuCl_2$(en) (**2c**) (96% endo)]. Thus far, we have been unable to prepare any of the other 1,*n*-bis(diphenylphosphino)alkane analogues for a more detailed examination of this effect.

Dimethylaminopropiophenone. Racemic fluoxetine is an antidepressant agent developed by Eli Lilly. Reduction of

(7) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron*, **2001**, *57*, 4817−4824.
(8) Burk, M. J.; Harper, T. G. P.; Lee, J. R.; Kalberg, C. *Tetrahedron Lett.* **1994**, *35*, 4963−4966.
(9) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872−4873.
(10) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc*. **1972**, *94*, 7159−7161.

Scheme 4. **Hydrogenation of dimethylaminopropiophenone 9**



3-dimethylaminopropiophenone, **8**, would give an intermediate suitable for fluoxetine synthesis.[11] Since the substrate, 3-dimethylaminopropiophenone, is base sensitive, it is necessary to minimise the amount of potassium *tert*-butoxide used in the reaction. For substrates of this type the (diphosphine)-$RuCl_2$(diamine) complex can be treated with potassium *tert*-butoxide prior to addition of the substrate.[12]

Using the standard **1a** catalyst, system a fast, clean reaction was observed with a S/C/B ratio of 2000:1:10. However, reducing the catalyst loading led to a rapid reduction in the rate of reaction, and the addition of more base resulted in side reactions. The best result was achieved with the (dppf)$RuCl_2$(en) catalyst, **2a**, where clean reduction was achieved at S/C 5000. The product **9** was isolated by crystallisation of its hydrochloride salt in 78% yield, thus providing a practical route to this important pharmaceutical intermediate (Scheme 4).

(*E*)-4-Phenylbut-3-en-2-one. The reduction of α,β-unsaturated ketones and aldehydes can potentially give rise to mixtures of the saturated and unsaturated alcohols, depending on the conditions used. Sodium borohydride predominantly reduces the C═O bond, but unless expensive lanthanide additives are used,[13] substantial amounts of the fully saturated alcohol are often formed. Noyori has demonstrated the chemoselective hydrogenation of unsaturated aldehydes and ketones catalysed by a $RuCl_2(PPh_3)_3$-$NH_2(CH_2)_2$-NH_2-KOH system prepared in situ.[2] We sought to extend this to the use of isolated catalysts of the type (diphosphine)-$RuCl_2$(diamine). The first test substrate was (*E*)-4-phenylbut-3-en-2-one (**10**). It has been reported that **10** can be reduced chemoselectively with sodium borohydride,[14] but even so a catalytic method may be desirable on large scale.

Reduction of **10** with **1a** proceeded smoothly at S/C/B ratio of 2000:1:10 (Table 3, entry 1). When the catalyst loading was reduced to 5000:1:8 (entry 2), initially no hydrogen uptake was observed, but upon addition of an extra 1 mol % of base, rapid reaction ensued; however, the resulting product was impure. In some instances with base-sensitive substrates, potassium carbonate[15] has been used instead of potassium *tert*-butoxide. However, we found potassium carbonate ineffective on this substrate, with very slow reaction occurring even with 5 mol % base. As was the case for the dimethylaminopropiophenone substrate, **8**, the amount of potassium *tert*-butoxide needs to be minimised to obtain pure product, and this limits the S/C ratio that can be achieved. The best small-scale result was obtained with a S/C/B ratio of 4000:1:20 at the slightly elevated temperature of 40 °C (Table 3, entry 4). The reaction was then scaled up in a 600-mL Parr hydrogenation vessel (Table 3, entries 5−9). Reaction at S/C/B 5000:1:20 only reached 97% conversion in 5.5 h (entry 5), and increased quantities of side products, the saturated ketone **12** and the saturated alcohol **13** were observed. On this scale, the best results were obtained at 20 °C, employing a S/C ratio of 2000 (entry 7). Surprisingly, attempted purification by distillation led to an increase in the level of saturated ketone **12** (entry 6). However, filtration through a pad of silica prior to distillation enabled a successful purification to be achieved (entry 7). When the reaction was carried out using (rac-BINAP)$RuCl_2$-(en) (**2d**) large quantities of the saturated alcohol **13** were observed even at 25 °C (entries 8 and 9).

Isophorone. The second example of an α,β-unsaturated ketone to be examined was isophorone **14**. The reduction of isophorone using sodium borohydride has been reported as being problematical.[14] Lithium aluminium hydride has been used successfully for this reduction,[16] but a catalytic method would avoid problems associated with quenching this highly reactive reagent and the need for an aqueous work-up.

An initial screen of several catalysts (5 mmol scale) showed that **2a** was the most active precatalyst (Table 4, entry 3). Using **1a**, the reaction could be driven to full conversion at high temperature, but at the expense of chemical purity (entry 6). When the best conditions were scaled up in a 600-mL vessel (entry 7), complete conversion was obtained in 4 h, but the product was of lower purity. To achieve both high conversion and good chemical purity at this scale, a S/C ratio of 2000 was employed at 30 °C (entry 8). This afforded isophorol **16** of 96% chemical purity.

To conclude, we have demonstrated homogeneous hydrogenation catalysed by (diphosphine)$RuCl_2$(diamine) complexes to be a viable alternative to sodium borohydride reduction for a variety of ketone substrates. In particular, norcamphor is reduced with high diastereoselectivity, and α,β-unsaturated ketones are reduced with good chemoselectivity.

Experimental Section

General Procedures. Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz (Bruker DPX 400). ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are given in Hz. IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR. Mass spectra were recorded using a Navigator LC/MS system, or a Hewlett-Packard GC/MS. Analytical thin-layer chromatography was performed on Merck silica gel precoated plates and visualised using ceric ammonium molybdate or potassium permanganate solution.

$(Ph_3P)_2RuCl_2$(en) (1a). A solution of dichlorotris(triphenylphosphine)ruthenium(II) (1.98 g, 2.06 mmol) and ethylenediamine (273 mg, 4.54 mmol) in dichloromethane

(11) Molloy, B. B.; Schmiegel, K. K. U.S. Patent 4,018,895, 1977; *Chem. Abstr.* **1997**, *87*, 134520.
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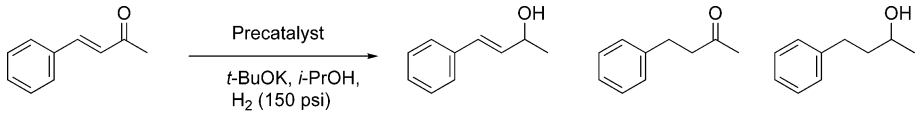
(13) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(14) Aramini, A.; Brinchi, L.; Germani, R.; Savelli, G. *Eur. J. Org. Chem.* **2000**, 1793−1797.
(15) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529−13530.
(16) Dickinson, J. M.; Murphy, J. A. *Tetrahedron* **1992**, *48*, 1317−1326.

Table 3. **Hydrogenation of (*E*)-4-phenyl-3-buten-2-one**

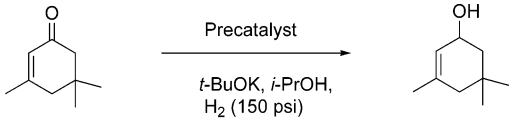


10 **11** **12** **13**

entry	precatalyst	S/C/B	conditions	conv. (%)	ratio (**10**:**11**:**12**:**13**)
1	$(Ph_3P)_2RuCl_2$(en)	2000:1:10	room temp, overnight	>98	0.6:98.4:0.7:0.1
2	$(Ph_3P)_2RuCl_2$(en)	5000:1:8	room temp, 3 h (1 mol % base added after 2 h)	>98	not measured[a]
3	$(Ph_3P)_2RuCl_2$(en)	10000:1:100	room temp, 21 h	>98	not measured[a]
4	$(Ph_3P)_2RuCl_2$(en)	4000:1:20	40 °C, 1.75 h	>98	0.6:97.9:0.4:0.5
5	$(Ph_3P)_2RuCl_2$(en)	5000:1:20	35 °C, 5.5 h	97	2.7:91.2:4.2:1.8
6	$(Ph_3P)_2RuCl_2$(en)	5000:1:20	45 °C, 7 h	97	0:91.7:2.2:6.3 (0.8:78.7:13.4:7.1)[b]
7	$(Ph_3P)_2RuCl_2$(en)	2000:1:10	20 °C, 2.5 h	>98	0.5:97.5:0.7:1.0
8	(rac-BINAP)$RuCl_2$(en)	5000:1:20	45 °C, 2 h	>98	0:78.4:2.4:20.2
9	(rac-BINAP)$RuCl_2$(en)	5000:1:20	25 °C, 21 h	97	2.4:82.0:7.0:8.8

[a] Side products observed arising from self-condensation of substrate. [b] After distillation.

Table 4. **Hydrogenation of isophorone**



14 **15**

entry	precatalyst	S/C/B	conditions	conv. (%)
1	$(Ph_3P)_2RuCl_2$(en)	2000:1:10	32 °C, 2 h	5
2	(dppf)$RuCl_2$(en)	5000:1:100	31 °C, 15 h	24
3	(dppf)$RuCl_2$(en)	3000:1:60	47 °C, 22 h	98 (GC purity 93.6%)
4	$(PMPP)_2RuCl_2$(diamp)	5000:1:50	48 °C, 16 h	29
5	$(Ph_3P)_2RuCl_2$(diamp)	3000:1:30	63 °C, 4.5 h	60
6	$(Ph_3P)_2RuCl_2$(en)	5000:1:20	55 °C, 18 h	92 (GC purity 70.7%)
7	(dppf)$RuCl_2$(en)	3000:1:60	16.5 g scale, 50 °C, 4 h	98 (71% yield after distillation, GC purity 83%)
8	(dppf)$RuCl_2$(en)	2000:1:20	16.5 g scale, 30 °C, 21 h	> 99, GC purity 96% (70% yield after distillation, GC purity 94%)

(DCM) (20 mL) was stirred overnight. The dark-brown solution was evaporated under reduced pressure. *tert*-Butyl methyl ether (MTBE) (20 mL) and DCM (10 mL) were added to produce a yellow/brown precipitate. The mixture was concentrated to approximately 10 mL and filtered. The solid was washed with MTBE (2 × 5 mL) and dried under vacuum to give a light-brown solid (1.36 g, 87%), ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.9.

The following (diarylphosphine)$RuCl_2$(diamine) complexes were prepared by the same method (the dichlorotris-[tri(*p*-anisoyl)phosphine]ruthenium(II) complex was prepared by a literature procedure):[17]

$(Ph_3P)_2RuCl_2$(1,3-diaminopropane) (**1b**) ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.0.

$[(4\text{-}MeOC_6H_4)_3P]_2RuCl_2$(en) (**1c**) ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.3.

$[(4\text{-}MeOC_6H_4)_3P]_2RuCl_2$(1,3-diaminopropane) (**1d**) ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.0.

(17) Stephenson, T. A.; Wilkinson, G. *J. Inorg. Nucl. Chem.* **1966**, *28*, 945−956.

The following bidentate complexes were prepared following a literature method.[3]

(dppf)$RuCl_2$(en) **2a** ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.6.

(dppe)$RuCl_2$(en) **2b** ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.2.

(dppb)$RuCl_2$(en) **2c** ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.5.

(rac-BINAP)$RuCl_2$(en) **2d** ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.2.

(DiPFc)$RuCl_2$(en) **2e** ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.4.

1-Phenylethanol (4). Acetophenone **3** (12.0 g, 100 mmol) and 2-propanol (100 mL) were charged to a glass-lined 600-mL Parr hydrogenation vessel. The solution was degassed by charging to 150 psi N_2, stirring, and then venting (×5). During this time the contents were heated to 40 °C. A suspension of **1a** (3.8 mg, 0.005 mmol, S/C 20000) in degassed 2-propanol (4 mL) and then potassium *tert*-butoxide (1 M in *tert*-butyl alcohol, 2.0 mL) were added. A hydrogen atmosphere was established by charging to 150 psi H_2 and venting. The vessel was charged again to 150 psi H_2, and the mixture was stirred at 40 °C for 4 h (^{1}H NMR analysis showed 99% conversion). The solution was neutralised with

2 M HCl (1 mL) and then concentrated under reduced pressure. The residue was distilled to give the *title compound* **4** as a colourless liquid (11.0 g, 90%), bp 87 °C at 22 mbar (Lit.[18] 89−90 °C at 16 mmHg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (5 H, m), 4.89 (1 H, q, *J* 7), 1.90 (1 H, br) and 1.49 (3 H, d, *J* 7); GC purity 99.1%, retention time 12.08 min (Zebron ZB5, 30 m × 0.25 mm, 60 °C for 5 min, ramp to 200 °C at 10 °C/min, hold for 5 min).

***endo*-Norborneol (5).** Norcamphor **6** (80.0 g, 726.2 mmol) and 2-propanol (400 mL) were charged to a glass-lined 2-L hydrogenation vessel. The solution was degassed by charging to 100 psi N_2, stirring, and then venting (×5). The mixture was then stirred under nitrogen pressure (100 psi) for 30 min. During this time the contents were cooled to 20 °C. The mixture was then depressurised to about 5 psi N_2 pressure, and a suspension of **1a** (50 mg, 0.07 mmol) in degassed, anhydrous 2-propanol (5 mL) was added, followed by potassium *tert*-butoxide (1 M in *tert*-butyl alcohol, 3.3 mL). A hydrogen atmosphere was established by charging to 140 psi H_2 and venting. The vessel was charged again to 140 psi H_2, and the mixture was stirred at 20 °C, maintaining the hydrogen pressure between 140 and 100 psi until hydrogen uptake ceased (922 min, ∼22h). The reaction mixture was then concentrated under reduced pressure to give the *title compound* **5** (83.2 g, >100%, 96% de) that was of sufficient purity for subsequent reactions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25−3.90 (1 H, m), 2.25 (1 H, apparent t, *J* 4), 2.16 (1 H, apparent t, *J* 4), 2.00−1.85 (2 H, m), 1.65−1.55 (1H, m), 1.40−1.25 (3H, m), 0.86 (1H, t, *J* 3.4), 0.82 (1H, t, *J* 3.4). The exo isomer is readily identified as a broad doublet at δ 3.75 (1H).

3-Dimethylamino-1-phenylpropan-1-ol hydrochloride (9 HCl salt). Dimethylaminopropiophenone (**8**) (13.23 g, 74.7 mmol) was dissolved in 2-propanol (70 mL) and charged to a glass-lined 600-mL Parr hydrogenation vessel. The solution was degassed by charging to 150 psi N_2, stirring, and then venting (×3). During this time the contents were heated to 30 °C, and the catalyst solution was prepared. **2a** (11.7 mg, 0.015 mmol, S/C 5000) was added to a 10-mL Schlenk tube. A nitrogen atmosphere was established by evacuation and refilling with nitrogen (×3). Degassed 2-propanol (3 mL) and potassium *tert*-butoxide (1 M in *tert*-butyl alcohol, 0.15 mL) were added, and the mixture was heated in an oil bath to 70 °C (external temperature) until a clear, brown solution was obtained. The pressure vessel was charged to 150 psi H_2 and vented, the catalyst solution was added, and the vessel was charged again to 150 psi H_2. The mixture was stirred rapidly for 4 h, after which ^{1}H NMR analysis showed complete conversion. The vessel was vented, and the solvent was concentrated to approximately 30 mL. The solution was cooled in an ice bath, and concentrated hydrochloric acid (6.5 mL) was added. The solution was evaporated, and acetone (20 mL) was added. The solid was filtered, washed with acetone (2 × 20 mL), and dried under vacuum to give the *title compound* (12.64 g, 78%), ^{1}H NMR (400 MHz, CD_3OD) δ 7.45−7.27 (5 H, m), 4.86 (1 H, t, *J* 6), 3.40−3.21 (2 H, m), 2.92 (6 H, s), and 2.16−2.10 (2 H, m).

(*E*)-4-Phenyl-but-3-en-2-ol (11). (*E*)-4-Phenyl-but-3-en-2-one (**10**) (14.82 g, 101.3 mmol) and 2-propanol (100 mL) were charged to a glass-lined 600-mL Parr hydrogenation vessel. The solution was degassed by charging to 150 psi N_2, stirring, and then venting (×5). Separately, a catalyst solution was prepared by dissolving **1a** (38 mg, 0.05 mmol, S/C 2000) and potassium *tert*-butoxide (1 M in *tert*-butyl alcohol, 0.5 mL) in toluene (4 mL) in a Schlenk flask under nitrogen. This solution was then added to the vessel. A hydrogen atmosphere was established by charging to 150 psi H_2 and venting. The vessel was charged again to 150 psi H_2, and the mixture was stirred at 20 °C for 2.5 h (^{1}H NMR analysis showed complete conversion). The solvent was evaporated, and the residue was filtered through a pad of silica (12 g), eluting with ethyl acetate/heptane (1:4; 200 mL). The solution was concentrated to give a brown oil which was distilled under reduced pressure to give the *title compound* **11** as a colourless liquid (12.28 g, 82%), bp 126 °C at 26 mbar (Lit.[19] 80−85 °C at 0.5 mmHg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (5 H, m), 6.57 (1 H, d, *J* 16), 6.26 (1 H, dd, *J* 16, 8), 4.49 (1 H, m), 1.62 (1 H, br s) and 1.37 (3 H, d, *J* 7); GC purity 97.5%; retention time 16.90 min (Zebron ZB5, 30 m × 0.25 mm, 60 °C for 5 min, ramp to 200 °C at 10 °C/min, hold for 5 min).

3,5,5-Trimethyl-cyclohex-2-enol (Isophorol) (15). Isophorone **14** (16.5 g, 120 mmol) and 2-propanol (120 mL) were charged to a glass-lined 600-mL Parr hydrogenation vessel. The solution was degassed by charging to 150 psi N_2, stirring, and then venting (×5). Separately, potassium *tert*-butoxide (1 M in *tert*-butyl alcohol, 1.2 mL) was added to a suspension of **2a** (47 mg, 0.06 mmol, S/C 2000) in 2-propanol (8 mL) in a Schlenk tube under nitrogen, and the mixture was stirred for 20 min. The catalyst solution was then added to the hydrogenation vessel, and a hydrogen atmosphere was established by charging to 150 psi H_2 and venting. The vessel was charged again to 150 psi H_2, the contents were heated to 30 °C, and the mixture was stirred for 21 h. ^{1}H NMR analysis showed >99% conversion. The reaction mixture was neutralised with 1 M HCl (1.2 mL) and evaporated under reduced pressure. The residue was distilled to give the *title compound* **15** as a colourless liquid (11.8 g, 70%), bp 86 °C at 28 mbar (Lit.[20] 95−100 °C at 25 mmHg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (1 H, br), 4.24 (1 H, m), 1.85 (1 H, d, *J* 16), 1.76 (1 H, dd, *J* 13, 6), 1.68 (3 H, s), 1.61 (1 H, d, *J* 16), 1.42 (1 H, br), 1.23 (1 H, dd, *J* 13, 9), 0.99 (3 H, s), and 0.88 (3 H, s); GC purity 93.8%; retention time 12.20 min (Zebron ZB5, 30 m × 0.25 mm, 60 °C for 5 min, ramp to 200 °C at 10 °C/min, hold for 5 min).

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