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Synthesis of Chiral Functionalised Cyclobutylpyrrolidines and Cyclobutylamino Alcohols from (–)-(*S*)-Verbenone – Applications in the Stabilisation of Ruthenium Nanocatalysts

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Stereoselective and efficient synthetic routes to pyrrolidines and amino alcohols anchored to chiral polysubstituted cyclobutane moieties have been developed from (–)-(*S*)-verbenone. These original frameworks, in particular the diamines and amino alcohols, are appropriate stabilisers of metallic nanoparticles, especially for the synthesis of ruthenium nanomaterials, which found catalytic applications in the hydrogenation of arenes and nitrobenzene derivatives to afford selectively the corresponding cyclohexane or aniline derivatives.

Introduction

Pyrrolidines are attractive targets not only for their biological and pharmacological properties and applications in medicinal chemistry[1] but also for their use in organic synthesis as organocatalysts[2] or as ligands in metal catalysis,[3] for example.

These compounds are remarkable for their wide presence in nature, their biological activities and their structural characteristics. Thus, pyrrolidines are found in a wide range of biologically active compounds. They are present in thousands of natural products including complex alkaloids, but they are also important as part of simple molecules such as the alkaloid nicotine or the amino acid proline. Owing to all these features, efforts to develop synthetic methodologies for the preparation of pyrrolidines are reasonable.

Pyrrolidines have been prepared by several different methods involving, for instance, the chlorination/cyclodehydration of amino alcohols,[4] the cyclocondensation of alkyl dihalides and primary amines in alkaline media under microwave irradiation,[5] the transformation of *N*-4-pentenyl urea into a pyrrolidine catalysed by a mixture of a gold complex and AgOTf (OTf = trifluoromethanesulfonate)[6] or the microwave-assisted intramolecular tandem cross-metathesis aza-Michael reaction.[7]

(–)-Verbenone has been used by some of us as a suitable chiral precursor to afford a variety of highly functional chiral cyclobutane derivatives such as γ-lactams,[8] amino alcohols and diamines with analgesic properties,[9] and α-,[10] β-[11] and γ-amino acids.[12] Some of these compounds have been incorporated into C_3-symmetric peptide dendrimers[13] or hybrid γ-peptides, which show properties as cell-penetrating agents,[14] as well as other peptides.[15]

The variety of functional groups present in these chiral polysubstituted cyclobutane derivatives makes them attractive stabilisers for the synthesis of metallic nanoparticles. Despite the large amount of work on organic transformations promoted by metallic nanoparticles,[16] there have been few reports of successful applications in enantioselective catalysis.[17]

In those cases, phosphorus- and nitrogen-based ligands are involved as stabilisers. One of the most relevant contributions concerns the asymmetric hydrogenation of pyruvates catalysed by Pd and Pt nanoparticles stabilised by cinchona derivatives, such as cinchonidine; the quinoline fragment presumably coordinates to the metal surface, and the chiral piperidine fragment interacts with the prochiral substrate.[17a,18] To evidence the positive π effect of the aromatic fragments with the surface, some of us have used the model bis(aryl)-based ligand, 4-(3-phenylpropyl)pyridine (**21**, see below Scheme 7), to stabilise palladium,[19] ruthenium[20] and dimetallic Pt/Ru nanoparticles.[21] Careful characterisation studies proved that the pyridine ligand **21** acts as a bidentate ligand to the metallic surface through both aromatic rings.[20a,20b]

Drawing on our expertise in both the design of chiral N-based frameworks and the stabilisation of metallic nano-

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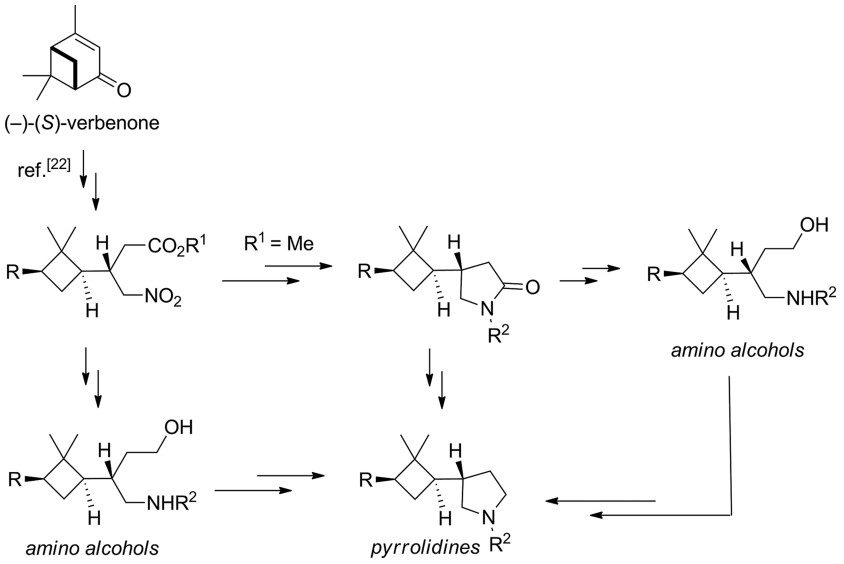


Scheme 1. General synthetic outcome.

particles, in this work, we describe synthetic routes to new δ-amino alcohols and pyrrolidines from a chiral nitro ester derivative as a common precursor, which was prepared from (–)-verbenone (Scheme 1). Alternative pathways to some of these products are presented and discussed to demonstrate the versatility and efficiency of the synthetic strategies described herein. The pyrrolidines appeared to be appropriate stabilisers of metallic nanoparticles and found applications in Ru-catalysed hydrogenation reactions.

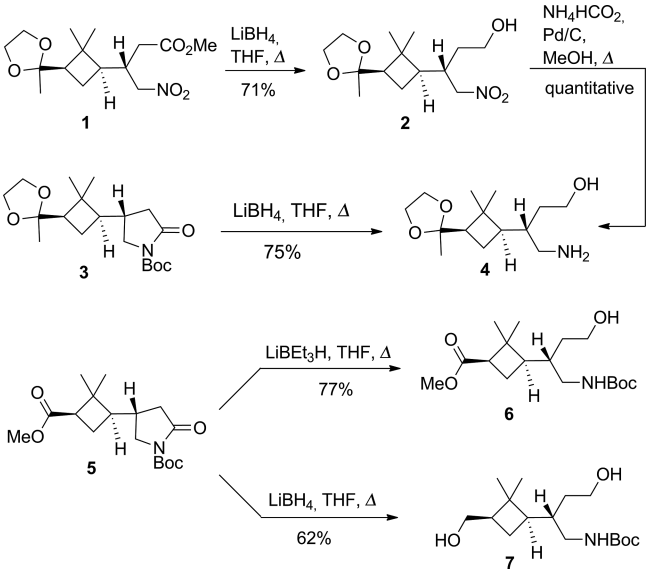
Results and Discussion

Synthesis of Amino Alcohols

Amino alcohols are interesting themselves and as intermediates in the synthesis of other products such as pyrrolidines (vide infra). They were prepared by reduction of nitro esters and lactams (Scheme 2).

The selective reduction of the methyl ester moiety in **1**, which was prepared according to a previously reported methodology,[22] with $LiBH_4$ in tetrahydrofuran (THF) under reflux for 2 h afforded the nitro alcohol **2** in 71% yield. Then, the reduction of the nitro group by the in situ generation of hydrogen from ammonium formate in the presence of Pd/C in MeOH under reflux for 1 h led to the formation of the amino alcohol **4** in quantitative yield. This two-step transformation gave better yields than that for the reduction of both functional groups in one single step with $LiBH_4$ in a mixture of THF and MeOH. However, the direct reduction of the lactam **3**[23] afforded the amino alcohol **4** in 75% yield.

The *N*-Boc-amino alcohol **6** (Boc = *tert*-butyloxycarbonyl) was prepared in 77% yield by the chemoselective reduction of the lactam **5**[8] with 2 mol of $LiBEt_3H$ (superhydride) under reflux in THF. Alternatively, when **5** reacted with 4 mol of $LiBH_4$ in THF under reflux overnight, the *N*-Boc-amino diol **7** was obtained. In no case was the reduction of the *N*-Boc carbamate group observed. In contrast, when similar conditions were applied to the lactam **3**, deprotection of the amino group occurred (Scheme 2).

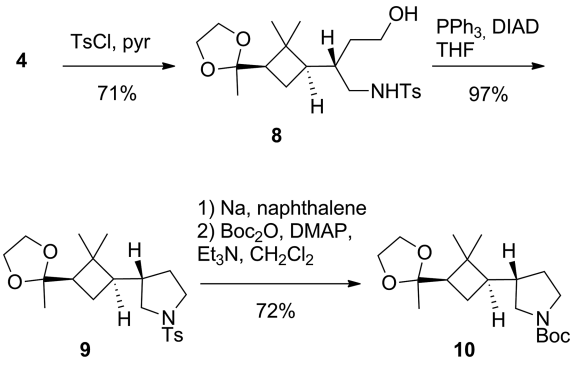


Scheme 2. Synthesis of cyclobutyl-based amino alcohols **4**, **6** and **7**.

Synthesis of Pyrrolidines

Pyrrolidines were obtained through two different synthetic routes (Schemes 3 and 4). In the first pathway (Scheme 3), the pyrrolidine ring was created from the amino alcohol **4** through a Mitsunobu-type reaction. Previously, the amino group in **4** was transformed into a sulfonamide group, because sulfonamide groups are better protecting groups in the presence of nucleophiles than carbamate groups. The chemoselective tosylation of the amine was performed with 1 equiv. of *p*-toluenesulfonyl chloride in pyridine to produce **8** in 71% yield. This compound reacted

with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in THF to trigger the cyclisation and afford the *N*-tosylated pyrrolidine **9** in 97% yield. To assess if other substitutions of the nitrogen atoms were accessible, **9** was treated with a freshly prepared solution of sodium naphthalenide followed by reaction with di(*tert*-butyl) dicarbonate in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine in CH_2Cl_2. Thus, the *N*-Boc pyrrolidine **10** was prepared in 72% yield over two steps.

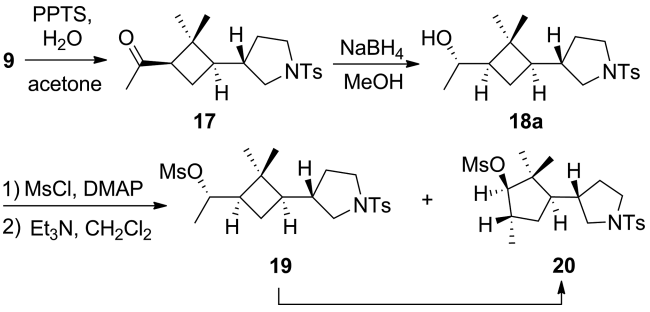


Scheme 3. Synthesis of cyclobutyl-based pyrrolidines **9** and **10** from the amino alcohol **4**.

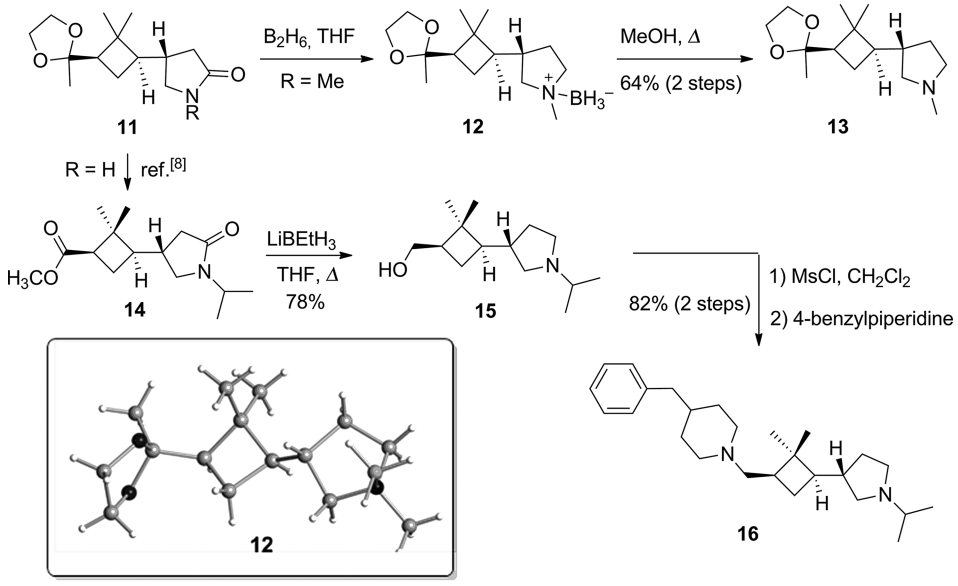
The second strategy involves a shorter synthetic route from previously synthesised lactams (Scheme 4).[8,22] Compound **11** was reacted with an excess of B_2H_6 in THF. A diastereomeric mixture of the two boron complexes **12** was obtained, and one of the two diastereomers afforded single crystals suitable for X-ray structural analysis, which proved its identity. The diastereomeric mixture **12** was heated in MeOH under reflux for 24 h, and the free pyrrolidine **13** was isolated in 64% yield for the two steps.

Alternatively, the reduction of both the lactam carbonyl group and the methyl ester moiety of **14**[8] with a large excess of $LiBEt_3H$ under reflux in THF afforded the amino alcohol **15** in 78% yield. The alcohol group in **15** was activated as a mesylate, and subsequent nucleophilic substitution with 4-benzylpiperidine gave rise to the diamine **16** in 82% yield over two steps (Scheme 4).

To synthesise secondary alcohols and some derivatives, the pyrrolidine **9** was submitted to carbonyl deprotection with pyridinium *p*-toluenesulfonate (PPTS) in wet acetone to obtain **17** in 96% yield (Scheme 5). The resulting ketone was treated with $NaBH_4$ without any chiral auxiliary to test the intrinsic stereoselectivity induced by the cyclobutylpyrrolidine. A 10:1 diastereomeric mixture of **18a** and **18b** was obtained, as determined from the corresponding ^1H NMR spectrum of the crude reaction mixture. The mixture was chromatographed to isolate the major isomer **18a** in 87% yield. The absolute stereochemistry of the newly created stereogenic centre in the major diastereomer was assigned as *S* by comparison with analogous compounds obtained by Hergueta et al.,[24] for which the stereochemistry was elucidated through NOE experiments and X-ray diffraction analyses.



Scheme 5. Synthesis of the secondary alcohol **18a** and formation of the derivative **20**.



Scheme 4. Synthesis of cyclobutyl-based pyrrolidines **13**, **15** and **16** from γ-lactams **11**, and single-crystal X-ray diffraction structure of **12**.

To prepare some derivatives, the reaction of **18a** with mesyl chloride in the presence of DMAP and triethylamine was attempted. The expected mesylate **19** was detected in the reaction mixture as the minor product along with compound **20** (Scheme 5). When this product was isolated by crystallisation (80% yield), careful analysis of the mother liquor suggested that **19** evolved to **20** with time.

The structure of **20** was determined by X-ray diffraction analysis of suitable single crystals. The product shows a ring expansion from cyclobutane to cyclopentane with concomitant migration of the mesylate group (Figure 1).

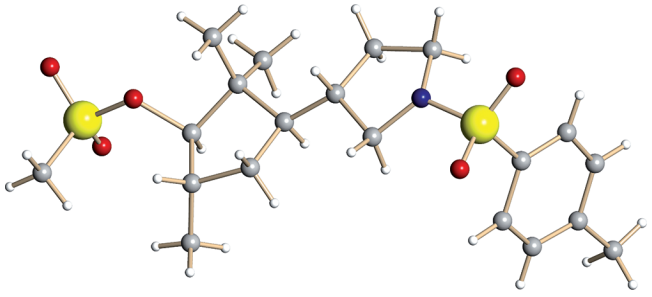
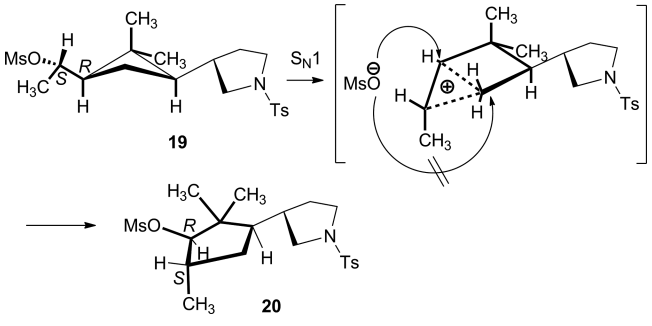


Figure 1. Single-crystal X-ray diffraction structure of **20**.

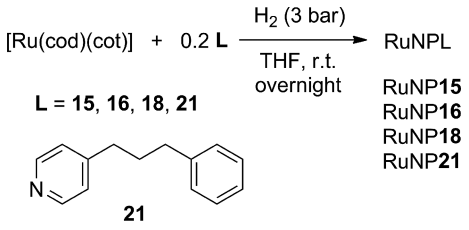
Our proposed mechanism for this transformation is based on several previously reported precedents. In work by Bentley et al., a cyclobutane ring that presented a mesylate group at the α-position of a side-chain expanded to a cyclopentane skeleton at room temperature in 24 h.[25] According to this and other previous work with norbornane derivatives,[26] we assumed that the reaction would proceed in a similar way in our case and that the stereochemistry observed in **20** would be the result of an S_N1-type process in which an ionic pair would form (Scheme 6). Assuming that the 1,2-shift would occur through the less-hindered face of the carbocation, the mesylate anion would exclusively attack the opposite side with respect to the pseudoaxial methyl group to afford the diastereomer observed by the X-ray diffraction study.



Scheme 6. Mechanism proposed for the conversion of **19** into **20**.

Synthesis of Ru Nanoparticles Stabilised by Cyclobutyl-Based Ligands – Catalytic Hydrogenation Reactions

The amino alcohols **15** and **18** and the diamine **16** were chosen as stabilisers for the synthesis of ruthenium nanoparticles (RuNPL) for application as catalytic precursors in hydrogenations. 4-(3-Phenylpropyl)pyridine (ligand **21**, Scheme 7) was also used as a reference owing to its ability to both strongly coordinate at the metallic surface and promote hydrogenation reactions.[21] RuNPL were prepared by the methodology previously described by Chaudret and coworkers.[27] The organometallic precursor [Ru(cod)(cot)] (cod = cyclooctadiene, cot = cyclooctatriene) in the presence of the appropriate ligand (**15**, **16**, **18** and **21**) was dissolved in THF, and the resulting mixture was stirred overnight under hydrogen pressure (Scheme 7).



Scheme 7. Synthesis of RuNPL stabilised by ligands **15**, **16**, **18** and **21**.

TEM analyses (Figure 2) of the as-prepared materials showed that RuNP**18** gave small, quite homogeneous [mean diameter (2.0 ± 0.6) nm] and well-dispersed nanoparticles. RuNP**16** also led to the formation of small nanoparticles that tended to self-organise. However, the synthesis of RuNP**15** resulted in inhomogeneous nanoparticles that were observed as large agglomerates. This different behaviour could be associated with the positive effect of the aromatic groups on the stabilisation and dispersion of nanoparticles for RuNP**16** and RuNP**18** (but not for RuNP**15**),

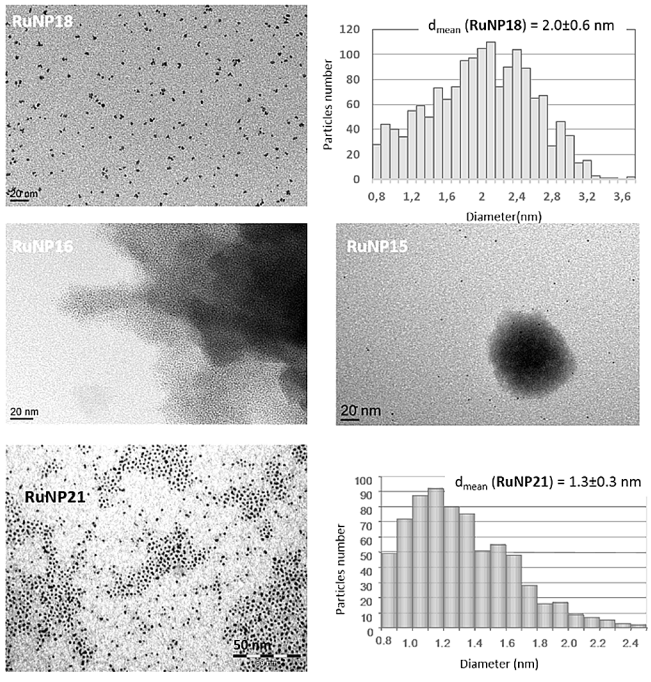
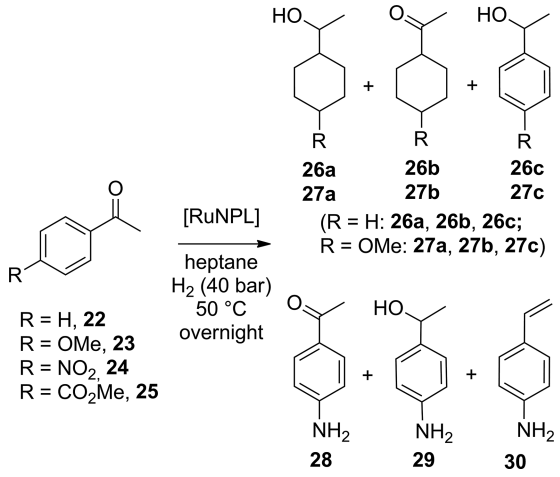


Figure 2. TEM analyses for RuNP**15**, RuNP**16**, RuNP**18** and RuNP**21**[20b] materials.

as proven for RuNP**21** with the bis(aryl)-based ligand 4-(3-phenylpropyl)pyridine.[20a,20b]

The ruthenium materials synthesised were applied in the hydrogenation of acetophenone-based substrates (Scheme 8), and the results are summarised in Table 1.



Scheme 8. Ru-catalysed hydrogenation of acetophenone-based substrates.

Table 1. Ru-catalysed hydrogenation of acetophenone-based substrates **22**–**25**.[a]

Entry	Substrate	RuNPL	Conversion [%][b]	Selectivity **a/b/c**[b]	Selectivity **28/29/30**[c]
1	**22**	RuNP**18**	100	60/40/0	–
2	**22**	RuNP**16**	42	0/100/0	–
3	**22**	RuNP**15**	100	70/30/0	–
4	**22**	RuNP**21**	82	33/62/5	–
5[d]	**22**	RuNP**21**	100	100/0/0	
6	**23**	RuNP**18**	92	79/0/21	–
7	**23**	RuNP**15**	<5	–	–
8	**23**	RuNP**21**	100	100/0/0	–
9	**24**	RuNP**18**	100	–	97/0/3
10	**24**	RuNP**15**	100	–	45/30/25
11	**24**	RuNP**21**	81	–	100/0/0
12[d]	**25**	RuNP**18**	0	–	–
13[d]	**25**	RuNP**15**	0	–	–
14[d]	**25**	RuNP**21**	0		

[a] Reaction conditions: 1 mmol of substrate in heptane (25 mL) at 50 °C, 16 h, 40 bar H_2 and the corresponding preformed nanoparticles (RuNP**15**, RuNP**16**, RuNP**18** and RuNP**21**); substrate/Ru/L = 100/1/0.2. [b] Determined by GC–MS; for **22**, the hydrogenated products correspond to **26a**, **26b** and **26c**; for **23**, the hydrogenated products correspond to **27a**, **27b** and **27c**. [c] Determined by GC–MS. [d] CH_2Cl_2 or THF used as solvent (substrate was not soluble in heptane).

For acetophenone (**22**, Table 1, Entries 1–4), the RuNPL systems were appropriate for the hydrogenation of the aromatic ring [only 5% of 1-phenylethanol **26c** was detected when RuNP**21** was used], and mixtures of 1-cyclohexylethanol (**26a**) and cyclohexylethanone (**26b**) were obtained; RuNP**18** and RuNP**15** were the most-active systems and favoured the full hydrogenation of acetophenone (Table 1, Entries 1 and 3). However, RuNP**16**, containing the diamine stabiliser, exhibited lower activity and led to the exclusive formation of **26b** (Table 1, Entry 2). The catalytic system RuNP**21** was less active and less selective than those containing the amino alcohol ligands, RuNP**18** and RuNP**15** (Table 1, Entry 4 vs. 1 and 3). However, at higher temperature (65 °C), full conversion was achieved, and the alcohol **26a** was obtained exclusively (Table 1, Entry 5). These results indicate that the reduction of the aromatic ring is faster than the carbonyl group hydrogenation, as the aromatic alcohol **26c** was practically undetected (Table 1, Entries 1–5).

With 4-methoxyacetophenone (**23**) as the substrate, RuNP**18** and RuNP**21** were more active than for the hydrogenation of **22**, owing to the electron-donating behaviour of the methoxy group,[28] and afforded more than 70% of the fully hydrogenated product **27a** (Table 1, Entries 6 and 8); in particular, RuNP**21** exclusively gave **27a** (Table 1, Entry 8). However, the RuNP**15** catalyst was inactive (Table 1, Entry 7). Unfortunately, no asymmetric induction could be observed for the chiral alcohols obtained (**26a**, **26c**, **27a**, and **27c**).

The hydrogenation of 4-nitroacetophenone (**24**) led to the formation of aniline derivatives without the reduction of the aromatic ring (Table 1, Entries 9–11). The catalytic system RuNP**18** was more selective and essentially afforded only 4-aminoacetophenone (**28**), analogously to RuNP**21** (Table 1, Entries 9 and 11, respectively). However, RuNP**15** was not chemoselective and favoured a reduction-elimination process to form 4-aminostyrene (**30**) as a byproduct (Table 1, Entry 10). These results agree with those recently reported for *N*-heterocyclic carbene stabilised (NHC-stabilised) RuNPs.[28c]

When methyl 4-acetylbenzoate (**25**) was used as the substrate, no hydrogenation products could be detected in different solvents (Table 1, Entries 12–14); this is attributed to the electron-withdrawing character of the acetyl group and is in agreement with the behaviour of 4-nitroacetophenone (Table 1, Entries 9–11).[28c]

To study the catalytic effect of the formation of the active species in the reaction medium (Table 2), the catalyst was generated in situ; the organometallic precursor [Ru(cod)(cot)], the corresponding ligand and acetophenone were

Table 2. Influence of the catalyst generation in the hydrogenation of **22**.[a]

Entry	Catalyst	Conversion [%][b]	Selectivity[b] **26a/26b/26c**
1[c]	RuNP**18**	100	58/42/0
2[d]	Ru/**18**	100	57/43/0
3[c]	RuNP**16**	42	0/100/0
4[d]	Ru/**16**	15	0/100/0
5[c]	RuNP**15**	100	70/30/0
6[d]	Ru/**15**	100	73/27/0
7[c]	RuNP**21**	82	33/62/5
8[d]	Ru/**21**	100	51/49/0

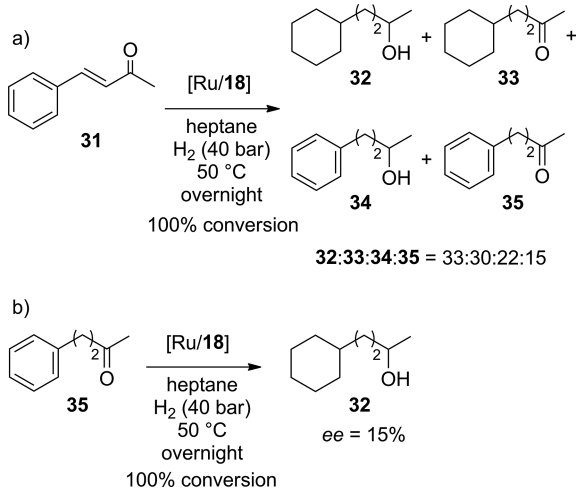
[a] Reaction conditions: 1 mmol of acetophenone (120 mg) and 0.01 mmol of Ru in heptane (25 mL) at 50 °C, 16 h, 40 bar H_2. [b] Determined by GC. [c] Results from Table 1. [d] Catalyst generated from [Ru(cod)(cot)] (0.01 mmol, 3 mg) and ligand (0.002 mmol; 0.45 mg of **15**, 0.8 mg of **16**, 0.7 mg of **18** and 0.4 mg of **21**) mixed in heptane at room temperature just before the addition of substrate and pressurisation with H_2; acetophenone/Ru/L = 100/1/0.2.

mixed in heptane at room temperature, followed by pressurisation with H_2 (40 bar) and heating at 50 °C. The results obtained with the Ru/**21** catalytic systems (Table 2, Entries 7–8) showed that the in situ methodology led to more-active catalytic species than those from preformed Ru nanoparticles and afforded an approximately equimolar mixture of **26a** and **26b** (Table 2, Entry 8). This different activity is probably because smaller nanoparticles than the preformed Ru nanoparticles form when they are generated in situ without isolation. However, for Ru systems containing ligands **18** (Table 2, Entries 1–2) and **15** (Table 2, Entries 5–6), no important differences were observed between both approaches. Independently of the method used to generate the catalyst, the Ru/**16**-based systems remained less active (Table 2, Entries 3–4); this is presumably because the tendency of these nanoparticles to auto-assemble hinders the access of the substrate to the metallic surface (see Figure 2).

To test the hydrogenation ability of these catalytic systems in the hydrogenation of more-challenging substrates, 4-methylanisole and 4-chloroanisole were investigated.[29] Disappointingly, they were not active under the same conditions described for the hydrogenation of acetophenone-based substrates (Scheme 8 and Table 1).

The reason for this behaviour could be that the disubstituted benzene substrates cannot easily approach the nanoparticles in a "flat" way because of the presence of the methyl and chloro groups, which disfavour π interactions with the metallic surface, hindered by the stabilizers.

However, the Ru/**18** catalytic system efficiently hydrogenated (*E*)-4-phenylbut-3-en-2-one (**31**), although a mixture of compounds formed as a result of the hydrogenation of the C=C and C=O bonds (Scheme 9, a), and the hydrogenation of the aromatic ring was favoured (compounds **32** and **33**). For the nonconjugated analogous substrate, 4-phenylbutan-2-one (**35**), full hydrogenation was achieved, and the saturated alcohol **32** was obtained with a low asymmetric induction (*ee* = 15%, Scheme 9, b).



Scheme 9. Hydrogenation of (a) **31** and (b) **35** catalysed by the in situ generated Ru/**18** system.

Conclusions

We have established efficient synthetic methodologies for the stereoselective preparation of chiral amino alcohols and pyrrolidines linked to a cyclobutyl framework and obtained the expected products in high yields (>60% global yield for multistep sequences). The pyrrolidines **15**, **16** and **18** were used to stabilise ruthenium nanoparticles, and the ligand **18** gave small (2.0 nm) and well-dispersed nanoparticles. These materials, together with RuNP**21** nanoparticles, were applied as catalysts in the hydrogenation of acetophenone-based substrates and showed a remarkable dependence on the electronic properties of the substrate. The most-active pyrrolidine-based system, RuNP**18**, favoured the formation of fully hydrogenated products for electron-rich substrates such as acetophenone and 4-methoxyacetophenone. However, for the substrate 4-nitroacetophenone, the corresponding aniline was exclusively obtained, and RuNP**18** was inactive for 4-acetylbenzoate. The conjugated aromatic ketone (*E*)-4-phenylbut-3-en-2-one and the corresponding nonconjugated system 4-phenylbutan-2-one were reduced to mainly give the completely hydrogenated alcohol, 4-phenylbutan-2-ol. Unfortunately, a very low enantiomeric excess was induced. These preliminary results have encouraged us to pursue the design of nitrogen-based ligands containing stereocontrolled skeletons for their applications in asymmetric catalysis.

Experimental Section

General Methods: Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents when needed. Wet acetone indicates acetone with no prior distillation. Moisture was excluded from all reactions by standard procedures under a nitrogen atmosphere. Flash column chromatography was performed with silica gel (230–400 mesh). For the synthesis of nanoparticles, all manipulations were performed by standard Schlenk techniques under an argon atmosphere. Unless stated otherwise, commercially available compounds were used without further purification. [Ru(cod)(cot)] was purchased from NanoMeps. The nanoparticles RuNP**21** were synthesised by the methodology previously reported.[20b] GC analyses were performed with an Agilent GC6890 instrument equipped with flame ionisation and mass detectors; a SGE BPX5 column composed of 5% phenylmethylsiloxane was used. Enantiomeric excesses were determined by GC with a Hewlett–Packard 5890 Series II gas chromatograph [25 m FS-cyclodex-β-I/P column: heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin/polysiloxane] with a flame ionisation detector (FID). TEM images of ruthenium nanoparticles were obtained with a JEOL JEM 1400 transmission electron microscope at 120 kV at the "Service Commun de Microscopie Electronique de l'Université Paul Sabatier, TEMSCAN". A drop of THF solution was deposited on a holey carbon-coated copper grid. The size distributions and average diameters of the nanoparticle were directly determined from TEM images by the Image-J software associated with a Microsoft Excel macro developed by Christian Pradel. ^1H and ^{13}C NMR spectra were recorded at 250 or 360 and 62.5 or 90 MHz, respectively, at the "Servei de RMN de la Universitat Autònoma de Barcelona". Melting points were determined with a hot stage. Optical rotations were measured at 22 ± 2 °C. High-resolu-

tion mass spectra were recorded with a direct inlet system (ESI). IR spectra were obtained from neat samples with an attenuated total reflectance (ATR) accessory in a Sapphire-ATR spectrophotometer.

Crystallographic Data: CCDC-969535 (for **12**) and -1022994 (for **20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(3*S*,1′*R*,3′*R*)-3-{2′,2′-Dimethyl-3′-(2′′-methyl-[1′′,3′′]dioxolan-2′′-yl)cyclobutyl}-4-nitrobutan-1-ol (2): A 2 M solution of $LiBH_4$ in THF (9.5 mL, 19 mmol) was added to a solution of **1**[22] (3.0 g, 9.5 mmol) in anhydrous THF (50 mL). The mixture was heated to reflux under a nitrogen atmosphere for 2 h. The excess hydride was eliminated by the slow addition of methanol (5 mL), and then water (30 mL) was added. The resultant solution was extracted with CH_2Cl_2 (5× 30 mL), and the combined extracts were dried with $MgSO_4$. The solvents were removed under reduced pressure, and the residue was chromatographed (CH_2Cl_2 to EtOAc) to provide **2** (1.9 g, 71% yield). Colourless oil. $[\alpha]_D^{25}$ = +8 (*c* = 1.37, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3420, 2949, 2880, 1540 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 4.39 (dd, *J* = 5.5 Hz, *J′* = 1.1 Hz, 2 H, CH_2), 3.78–4.02 (complex signal, 4 H, 2× CH_2), 3.75 (dd, *J* = 6.3 Hz, *J′* = 5.8 Hz, 2 H, CH_2), 2.35 (m, 1 H, CH), 2.10 (dd, *J* = 10.6 Hz, *J′* = 7.4 Hz, 1 H, CH), 1.43–1.79 (complex signal, 5 H, 2× CH_2 and CH), 1.23 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 109.5 (C), 77.2 (CH_2), 65.4 (CH_2), 63.6 (CH_2), 59.8 (CH_2), 48.9 (CH), 44.1 (CH), 41.4 (CH_2), 36.7 (C), 33.1 (CH), 32.0 (CH_3), 23.7 (CH_3), 23.3 (CH_3), 16.4 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{25}NNaO_5$ $[M + Na]^+$ 310.1625; found 310.1621.

(3*S*,1′*R*,3′*R*)-4-Amino-3-{2′,2′-dimethyl-3′-(2′′-methyl-[1′′,3′′]dioxolanan-2′′-yl)cyclobutyl}butan-1-ol (4): Method 1 (from nitro alcohol **2**)**:** A mixture containing nitro alcohol **2** (400 mg, 1.4 mmol), ammonium formate (682 mg, 11 mmol) and 10% Pd/C (40 mg) in anhydrous methanol (25 mL) was heated under reflux for 1 h under a nitrogen atmosphere. The reaction mixture was filtered through Celite, and the solvent was evaporated to dryness to afford **4** (360 mg, quantitative yield). Method 2 (from lactam **3**): A 1.6 M solution of $LiBH_4$ in THF (1 mL, 2 mmol) was added to a solution of lactam **3**[23] (200 mg, 0.57 mmol) in anhydrous THF (20 mL). The mixture was heated to reflux under a nitrogen atmosphere overnight. The excess hydride was eliminated by the slow addition of methanol (5 mL), and then water (20 mL) was added. The resultant solution was extracted with CH_2Cl_2 (5× 30 mL), and the combined extracts were dried with $MgSO_4$. The solvents were removed under reduced pressure, and the residue was chromatographed (EtOAc/hexane, 2:1) to provide **2** (150 mg, 75% yield). Colourless oil. $[\alpha]_D^{25}$ = +8.3 (*c* = 1.2, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3420, 2949, 2880, 1540 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 4.57 (br s, 2 H, NH_2), 3.70–4.02 (complex signal, 4 H, 2× CH_2), 3.64 (m, 1 H, CH_2), 3.44 (m, 1 H, CH_2), 2.75 (m, 1 H, CH_2), 2.35 (m, 1 H, CH_2), 1.17–2.02 (complex signal, 6 H, 2× CH and 2× CH_2), 1.16 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 109.5 (C), 65.2 (CH_2), 63.4 (CH_2), 60.0 (CH_2), 48.9 (CH), 44.5 (CH_2), 42.6 (CH_2), 41.4 (CH), 41.0 (C), 36.0 (CH), 32.1 (CH_3), 23.7 (CH_3), 23.5 (CH_2), 16.5 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{27}NNaO_3$ $[M + Na]^+$ 280.1883; found 280.1882.

Methyl (1*R*,3*R*,2′*S*)-3-[1-(*tert*-Butoxycarbonylamino)-4′-hydroxybutan-2′-yl]-2,2-dimethylcyclobutanecarboxylate (6): A 2 M solution of $LiBEt_3H$ in THF (0.77 mL, 1.54 mmol) was added to a solution of **5**[8] (250 mg, 0.77 mmol) in anhydrous THF (20 mL). The mixture was heated to reflux and stirred under a nitrogen atmosphere for 3 h. The excess hydride was eliminated by the slow addition of methanol (5 mL), and the solvents were evaporated to dryness. The residue was poured into EtOAc (20 mL), washed with $NaHCO_3$ (3× 10 mL), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane to Et_2O) to afford **6** (195 mg, 77% yield). Colourless oil. $[\alpha]_D^{25}$ = –10.6 (*c* = 1.5, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3379, 2925, 1714, 1690, 1520 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz): δ = 4.79 (br s, 1 H, NH), 3.65–3.83 (m, 2 H, CH_2), 3.70 (s, 3 H, CH_3), 3.26 (m, 1 H, CH_2), 3.01 (m, 1 H, CH_2), 2.67 (dd, *J* = 10.3 Hz, *J* = 7.8 Hz, 1 H, CH), 1.97–3.05 (complex signal, 2 H,CH_2), 1.82 (m, 1 H, CH), 1.66 (m, 1 H, CH), 1.48 (s, 9 H, 3× CH_3), 1.29 (s, 3 H, CH_3), 1.29 (m, 2 H, CH_2), 0.99 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 173.1 (C), 156.6 (C), 77.8 (C), 60.7 (CH_2), 51.2 (CH_3), 45.6 (CH), 44.7 (CH_2), 42.8 (CH), 31.2 (CH_3), 29.6 (CH_2), 28.4 (3× CH_3), 23.5 (CH_2), 17.1 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{17}H_{31}NNaO_5$ $[M + Na]^+$ 352.2094; found 352.2090.

***tert*-Butyl (2*S*,1′*R*,3′*R*)-4-Hydroxy-2-[(3′-hydroxymethyl)-2′,2′-dimethylcyclobutyl]butylcarbamate (7):** A 2 M solution of $LiBH_4$ in THF (0.8 mL, 1.6 mmol) was added to a solution of *N*-Boc-protected lactam **5**[8] (130 mg, 0.4 mmol) in anhydrous THF (20 mL). The mixture was heated to reflux under a nitrogen atmosphere overnight. The excess hydride was eliminated by the slow addition of methanol (5 mL), and the volatiles were evaporated under reduce pressure. The residue was poured into EtOAc (15 mL), washed with $NaHCO_3$ (3× 5 mL), and dried with $MgSO_4$, and the solvents were evaporated under vacuum. The crude product was purified by flash chromatography with silica gel (CH_2Cl_2) to afford **7** (73 mg, 62% yield). Colourless oil. $[\alpha]_D^{25}$ = +4 (*c* = 3.1, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3337, 2928, 1687, 1521, 1169 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz): δ = 4.82 (br s, 1 H, NH), 3.47–3.83 (complex signal, 4 H, 2× CH_2), 3.24 (m, 1 H, CH_2), 2.95 (m, 1 H, CH_2), 2.03 (complex signal, 2 H, 2× CH), 1.61–1.79 (complex signal, 4 H, CH, CH_2 and CH_2), 1.43 (s, 9 H, 3× CH_3), 1.22–1.49 (m, 1 H, CH_2), 1.19 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 156.6 (C), 79.3 (C), 63.5 (CH), 60.8 (CH_2), 44.7 (CH_2), 43.8 (CH), 39.9 (CH), 38.1 (C), 32.9 (CH_2), 31.8 (CH_3), 28.4 (3× CH_3), 25.4 (CH_2), 16.2 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{16}H_{31}NNaO_4$ $[M + Na]^+$ 324.2145; found 324.2136.

(3*S*,1′*R*,3′*R*)-4-Tosylamino-3-{2′,2′-dimethyl-3′-(2′′-methyl[1′′,3′′]-dioxolan-2′′-yl)cyclobutyl}butan-1-ol (8): A mixture containing **4** (1.48 mmol) and 4-toluenesulfonyl chloride (286 mg, 1.48 mmol) in distilled pyridine (40 mL) was stirred at room temperature under a nitrogen atmosphere for 18 h. The solvent was evaporated under vacuum. The crude product was then dissolved in EtOAc (30 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3× 15 mL) and dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was chromatographed (EtOAc/hexane 2:1) to provide tosylamide **8** (432 mg, 71% yield). Colourless oil. $[\alpha]_D^{25}$ = +8.3 (*c* = 1.2, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3489, 3280, 2949, 2880, 1540 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.71 (d, *J* = 8.1 Hz, 2 H, 2× CH), 7.27 (d, *J* = 8.1 Hz, 2 H, 2× CH), 5.93 (dd, *J* = 7.5 Hz, *J′* = 5.1 Hz, 1 H, NH), 3.78–4.02 (complex signal, 4 H, 2× CH_2), 3.60 (m, 2 H, CH_2), 2.90 (m, 1 H, CH_2), 2.59 (m, 1 H, CH_2), 2.39 (s, 3 H, CH_3), 1.95 (dd, *J* = 10.8 Hz, *J′* = 7.5 Hz, 1 H, CH), 1.74 (m, 1 H, CH), 1.2–1.62 (complex signal, 5 H, 2× CH_2 and CH), 1.17 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 143.1 (CH), 137.1 (CH), 129.6 (CH), 127.1 (CH), 109.8 (C), 65.5 (CH_2), 63.6 (CH_2), 60.7 (CH_2), 49.2 (CH), 44.5 (CH_2), 44.3 (C), 41.1 (CH), 38.3 (CH_2),

33.6 (CH), 32.1 (CH_3), 23.8 (CH_3), 23.5 (CH_2), 21.4 (CH_3), 16.7 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{33}NNaO_5S$ [M + Na]$^+$ 434.1972; found 434.1968.

(3*S*,1′*R*,3′*R*)-3-{2′,2′-Dimethyl-3′-(2′′-methyl[1′′,3′′]dioxolan-2′′-yl)cyclobutyl}-*N*-tosylpyrrolidine (9): Triphenylphosphine (144 mg, 0.55 mmol) was added to a stirred solution of **8** (150 mg, 0.36 mmol) in anhydrous THF (12 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C, and diisopropyl azodicarboxylate (0.11 mL, 0.55 mmol) was added dropwise. After the addition, the ice bath was removed, and reaction was warmed to room temperature and stirred overnight. The mixture was concentrated and poured into cold ether to precipitate most of the triphenylphosphine oxide. After filtration, the ether solution was evaporated to dryness, and the crude product was chromatographed (CH_2Cl_2) to afford **9**, which was crystallised in diethyl ether/pentane (136 mg, 97% yield). White powder, m.p. 62–64 °C (diethyl ether/pentane). $[a]_D^{25}$ = +7 (*c* = 0.92, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 2953, 2877, 1344, 1161 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.73 (d, *J* = 8.3 Hz, 2 H, 2 × CH), 7.35 (d, *J* = 8.3 Hz, 2 H, 2 × CH), 3.78–4.05 (complex signal, 4 H, 2 × CH_2), 3.18–3.39 (complex signal, 3 H, CH_2 and CH_2), 2.75 (dd, *J* = 9.7, *J*′ = 7.5 Hz, 1 H, C*H*$_2$), 2.47 (s, 3 H, CH_3), 2.1 (m, 2 H, 2 × CH), 1.82 (complex signal, 2 H, CH_2), 1.38–1.51 (complex signal, 3 H, CH_2 and CH_2), 1.22 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 143.5 (CH), 133.9 (CH), 129.7 (CH), 127.4 (CH), 109.9 (C), 65.7 (CH_2), 63.7 (CH_2), 51.7 (CH_2), 49.6 (CH_2), 47.8 (CH), 45.8 (CH), 41.1 (CH_2), 40.1 (CH), 31.9 (C), 30.5 (CH_3), 23.7 (CH_3), 23.6 (CH_2), 21.5 (CH_3), 17.1 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{31}NNaO_4S$ [M + Na]$^+$ 416.1866; found 416.1878.

***tert*-Butyl (3*S*,1′*R*,3′*R*)-3-{2′,2′-Dimethyl-3′-(2′′-methyl-[1′′,3′′]-dioxolan-2′′-yl)cyclobutyl}pyrrolidine-1-carboxylate (10):** To a solution of naphthalene (876 mg, 6.8 mmol) in anhydrous THF (20 mL) was added freshly cut sodium (154 mg, 6.8 mmol), and the resulting blue-green solution was stirred at room temperature for 2 h to give a sodium naphthalenide solution. To a solution of **9** (150 mg, 0.37 mmol) in anhydrous THF (20 mL) at –80 °C was added sodium naphthalenide solution (1.6 mL, 0.55 mmol) under a nitrogen atmosphere. The mixture was stirred for 1 h, more sodium naphthalenide solution was added (1.6 mL, 0.55 mmol) at the same temperature, and the mixture was stirred for another 1 h. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added, and the solution was warmed to room temperature and stirred for 18 h. The mixture was filtered with the aid of CH_2Cl_2 (20 mL) and concentrated under vacuum to dryness. The crude amine was dissolved in CH_2Cl_2 (15 mL) and to the resulting solution, triethylamine (0.6 mL, 0.37 mmol), Boc_2O (0.2 mL, 0.37 mmol) and DMAP (25 mg, 0.18 mmol) were added. The mixture was stirred overnight. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried with $MgSO_4$, and the solvents were evaporated to dryness. The crude residue was purified by column chromatography (EtOAc/hexane 3:1) to afford **10** (90 mg, 72% yield, two steps). Colourless oil. $[a]_D^{25}$ = +8 (*c* = 1.1, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 2954, 2973, 1693, 1402, 1167 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.86–4.16 (complex signal, 4 H, 2 × CH_2), 3.34 (m, 2 H, CH_2), 3.26 (m, 1 H, CH_2), 2.83 (m, 1 H, CH), 2.11 (m, 2 H, CH and CH_2), 1.93 (s, 3 H, CH_3), 1.87 (m, 2 H, 2 × CH_2), 1.62 (m, 2 H, CH and CH_2), 1.47 (s, 10 H, CH_2 and 3 × CH_3), 1.24 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 154.8 (C), 109.8 (C), 78.9 (C), 65.7 (CH_2), 63.7 (CH_2), 51.0 (CH), 49.6 (CH_2), 45.8 (CH_2), 41.2 (CH_2), 41.0 (CH), 31.8 (CH_3), 31.2 (C), 30.1 (CH_2), 28.6 (3 × CH_3), 23.9 (CH_3), 23.8 (CH_2), 17.1 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{19}H_{33}NNaO_4$ [M + Na]$^+$ 362.2302; found 362.2304.

(3*S*,1′*R*,3′*R*)-3-[2′,2′-Dimethyl-3′-(2′′-methyl-[1′′,3′′]-dioxolan-2′′-yl)cyclobutyl]-*N*-methylpyrrolidine (13) through Boron Complex 12: To **11**[22] (240 mg, 0.9 mmol) in anhydrous THF (15 mL) at 0 °C, 1 M B_2H_6 in THF was added dropwise (3.6 mL, 3.6 mmol), and the mixture was stirred for 18 h (from 0 °C to room temperature) under a nitrogen atmosphere. MeOH was added dropwise (5 mL) until no bubbling was observed. The intermediate boron complex **12** crystallised and was characterised. White solid, m.p. 88–89 °C (CH_2Cl_2/pentane). IR (ATR): $\tilde{\nu}$ = 2990, 2961, 2888, 2363, 2315, 1453, 1371, 1247, 1226, 1180, 1165, 1078, 1035, 947, 861 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.75–4.13 (complex signal,4 H, 2 × CH_2), 3.22–3.34 (complex signal, 2 H, CH_2), 2.70 (s, 3 H, CH_3), 2.57–2.81 (complex signal, 2 H, CH_2), 2.18–2.33 (complex signal, 2 H, CH_2), 2.10 (dd, *J* = 10.7 Hz, *J*′ = 7.5 Hz, 1 H, CH), 1.72–1.84 (m, 1 H, CH), 1.43–1.68 (complex signal, 3 H, CH and CH_2), 1.22 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 109.7 (C), 67.7 (CH_2), 65.5 (CH_2), 63.7 (CH_2), 63.0 (CH_2), 53.2 (CH_3), 49.6 (CH), 47.8 (CH), 41.2 (C), 39.1 (CH), 32.0 (CH_3), 29.2 (CH_2), 23.7 (CH_3), 23.4 (CH_2), 17.5 (CH_3) ppm. $C_{15}H_{30}NO_2B$ (267.22): calcd. C 67.42, H 11.32, N 5.24; found C 67.01, H 11.46, N 5.18.

Additional MeOH was added (50 mL), and the mixture was heated to reflux for 24 h to break the N–BH_3 bond formed during the reduction of the carbonyl group. The solvents were evaporated to dryness, and the residue was purified by flash chromatography with silica gel (EtOAc to CH_2Cl_2/MeOH 9:1) to afford the pyrrolidine **13** (145 mg, 64% yield). Colourless oil. $[a]_D^{25}$ = –10.9 (*c* = 1.4, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 2949, 2873, 2767, 1449, 1367, 1250, 1153 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 3.79–4.01 (complex signal, 4 H, 2 × CH_2), 2.44–2.66 (complex signal, 3 H, CH_2 and CH_2), 2.35 (s, 3 H, CH_3), 2.08–2.26 (complex signal, 2 H, CH and CH_2), 2.07 (dd, *J* = 11.2 Hz, *J*′ = 7.6 Hz, 1 H, CH), 1.85 (dt, *J* = 9.7, *J*′ = 7.6 Hz, 1 H, CH_2), 1.82 (m, 1 H, CH), 1.71 (dt, *J* = 10.4 Hz, *J*′ = 7.6 Hz, 1 H, CH_2), 1.48 (m, 1 H, CH_2), 1.36–1.45 (m, 1 H, CH_2), 1.23 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 110.4 (C), 65.9 (CH_2), 64.1 (CH_2), 61.2 (CH_2), 56.9 (CH_2), 49.7 (CH), 48.5 (CH), 42.8 (CH_3), 40.2 (C), 39.7 (CH), 32.5 (CH_3), 30.6 (CH_2), 24.5 (CH_2), 24.2 (CH_3), 17.9 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{15}H_{28}NO_2$ [M + H]$^+$ 254.2115; found 254.2112.

(1′*R*,3′*R*,3′′*S*)-3′-[2′,2′-Dimethyl-3′-(1′′-isopropylpyrrolidin-3′′-yl)-cyclobutyl]methanol (15): A 1 M solution of $LiBEt_3H$ in THF (10.5 mL, 10.5 mmol) was added to a solution of ester **14**[8] (380 mg, 1.42 mmol) in anhydrous THF (50 mL). The mixture was heated to reflux under a nitrogen atmosphere for 18 h. The excess hydride was eliminated by the slow addition of methanol (5 mL), and then water (30 mL) was added. The resultant solution was extracted with dichloromethane (3 × 30 mL), and the combined extracts were dried with $MgSO_4$. The solvents were removed under reduced pressure, and the residue was chromatographed (CH_2Cl_2/MeOH, 20:1) to provide alcohol **15** as a colourless oil (250 mg, 78% yield). $[a]_D$ = –9 (*c* = 3, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3377, 2968, 1461, 1366, 1011 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 0.95 (s, 3 H, CH_3), 1.06 (d, *J* = 4 Hz, 3 H, CH_3), 1.06 (d, ^3J = 4 Hz, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.27 (complex signal, 2 H, CH_2 and CH),1.71 (m, 1 H, CH_2), 1.94 (complex signal, 3 H, CH_2 and CH), 2.07 (m, 1 H, CH), 2.26 (m, 1 H, CH_2), 2.42 (complex signal, 2 H, CH_2 and CH), 2.79 (complex signal, 3 H, CH_2 and

CH_2), 3.51 (m, 2 H, CH_2) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 17.4 (CH_3), 21.6 (CH_3), 22.1 (CH_3), 22.2 (CH_3), 26.1 (CH_2), 29.9 (CH_2), 32.5 (CH), 39.7 (C), 40.2 (CH), 47.6 (CH), 50.2 (CH), 52.4 (CH), 55.4 (CH_2), 56.9 (CH_2), 69.7 (CH_2) ppm. HRMS (ESI): calcd. for $C_{14}H_{28}NO$ $[M + H]^+$ 226.2165; found 226.2168.

4-Benzyl-(1′*R*,3′*R*,3′′*S*)-1-{[3′-(1′′-isopropylpyrrolidin-3′′-yl)-2′,2′-dimethylcyclobutyl]methyl}piperidine (16): To a mixture containing alcohol **15** (150 mg, 0.66 mmol) in anhydrous CH_2Cl_2 (10 mL), triethylamine (0.12 mL, 0.86 mmol), DMAP (8 mg, 0.06 mmol) and mesyl chloride (60 μL, 0.8 mmol) were added at 0 °C. The mixture was stirred for 1 h at 0 °C. The volatiles were then evaporated under vacuum. The resulting mesylated compound was poured into anhydrous acetonitrile (10 mL), and 4-benzylpiperidine was added (1.9 mL, 6.6 mmol). The mixture was stirred overnight. The solvent was then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 to MeOH) to afford **16** as a colourless oil (210 mg, 82% over two steps). $[\alpha]_D$ = –7.3 (c = 1.3, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3406, 2941, 2658, 1454, 1243 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.92 (s, 3 H, CH_3), 1.07 (complex signal, 10 H, 3 × CH_3 and CH), 1.25 (complex signal, 4 H, 2 × CH_2), 1.30 (complex signal, 2 H, CH_2), 1.67 (complex signal, 2 H, CH and CH_2), 1.79 (complex signal, 6 H, CH_2, CH_2 and 3 × CH), 2.27 (complex signal, 4 H, 2 × CH_2), 2.53 (d, J = 6.7 Hz, 2 H, CH_2), 2.81 (m, 4 H, 2 × CH_2), 7.21 (complex signal, 5 H, CH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C): δ = 16.7 (CH_3), 21.7 and 21.8 (2 × CH_3), 29.5 (CH_2), 30.2 (2 × CH_2), 30.8 (CH), 32.2 (CH_3), 37.9 (CH_2), 39.9 (CH), 40.4 (C), 43.2 (CH_2), 48.8 (CH), 51.9 (CH), 53.7 (2 × CH_2), 54.7 (CH_2), 55.1 (CH), 56.6 (CH_2), 60.0 (CH_2), 125.6, 128.1, 129.2 and 140.7 (CH and C-Ar) ppm. HRMS (ESI): calcd. for $C_{26}H_{43}N_2$ $[M + H]^+$ 383.3421; found 383.3419.

(1′*R*,3′*R*,3′′*S*)-1-[2′,2′-Dimethyl-3′-(*N*-tosylpyrrolidin-3′′-yl)cyclobutyl]ethanone (17): A mixture of ketal **9** (360 mg, 0.92 mmol) and PPTS (115 mg, 0.92 mmol) in wet acetone (15 mL) was heated under reflux for 5 h. The reaction mixture was cooled, and the solvent was removed under reduced pressure. The residue was poured into EtOAc (30 mL), and the resultant solution was washed with saturated aqueous $NaHCO_3$ and then dried with $MgSO_4$. The solvent was evaporated under vacuum to afford a white powder, which was recrystallised from hexane to afford pure ketone **17** (310 mg, 96% yield), m.p. 87–89 °C (CH_2Cl_2). $[\alpha]_D$ = –15 (c = 5.3, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 2949, 2872, 1701, 1597, 1461, 1340, 1157 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.77 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.29 (m, 1 H, CH), 1.49–1.93 (complex signal, 5 H, CH and 2 × CH_2), 1.96 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.70 (m, 2 H, CH_2 and CH), 3.10 (m, 1 H, CH_2), 3.25 (m, 2 H, CH_2), 7.29 (d, J = 8.3 Hz, 2 H, CH), 7.64 (d, J = 8.3 Hz, 2 H, CH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.1 (CH_3), 21.3 (CH_3), 21.7 (CH_2), 30.0 (CH_2), 30.9 (2 × CH_3), 39.9 (CH), 43.2 (C), 45.1 (CH), 47.8 (CH_2), 51.6 (CH_2), 53.7 (CH), 127.6, 129.7, 133.3, 143.6 (CH and C-Ar), 207.6 (C) ppm. HRMS (ESI): calcd. for $C_{19}H_{27}NNaO_3S$ $[M + Na]^+$ 372.1604; found 372.1603.

(1*S*,1′*R*,3′*R*,3′′*S*)-1-[2′′,2′-Dimethyl-3′-(*N*-tosylpyrrolidin-3′′-yl)-cyclobutyl]ethanol (18): $NaBH_4$ (125 mg, 1.43 mmol) was added to a solution of ketone **17** (125 mg, 0.36 mmol) in anhydrous MeOH (15 mL) at 0 °C under nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 5 h. The excess hydride was eliminated by the slow addition of water (5 mL). The resultant solution was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were dried with $MgSO_4$. The solvents were removed under reduced pressure. A 10:1 mixture of diastereoisomers was obtained. The major diastereoisomer, **18**, was obtained after column chromatography (CH_2Cl_2 to EtOAc; 110 mg, 87% yield). $[\alpha]_D$ = +14 (c = 2.25, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 3529, 2956, 2871, 1339, 1158 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.97 (s, 3 H, CH_3), 1.01 (d, J = 6.2 Hz, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.37 (complex signal, 3 H, CH_2 and CH), 1.59 (m, 1 H, CH), 1.86 (complex signal, 3 H, CH_2 and CH), 2.44 (s, 3 H, CH_3), 2.68 (dd, J = 8.9 Hz, J' = 7.2 Hz, 1 H, CH_2), 3.26 (complex signal, 3 H, CH_2 and CH_2), 3.64 (m, 1 H, CH), 7.37 (d, J = 8 Hz, 2 H, CH), 7.71 (d, J = 8.3 Hz, 2 H, CH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C): δ = 16.5 (CH_3), 21.2 (CH_3), 21.5 (CH_3), 25.2 (CH_2), 30.2 (C), 31.8 (CH_3), 39.7 (CH_2), 40.1 (CH), 44.7 (CH), 47.6 (CH), 49.5 (CH_2), 51.6 (CH_2), 69.1 (CH), 127.4, 129.5, 133.9, 143.3 (CH and C-Ar) ppm. HRMS (ESI): calcd. for $C_{19}H_{29}NNaO_3S$ $[M + Na]^+$ 374.1760; found 374.1757.

(1*R*,1′*R*,5*S*,3′*S*)-2,2,5-Trimethyl-3-(1′-tosylpyrrolidin-3′-yl)cyclopentyl Methanesulfonate (20): To a mixture containing alcohol **18** (40 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (5 mL), triethylamine (30 μL, 0.14 mmol), DMAP (1.2 mg, 0.01 mmol) and mesyl chloride (1 μL, 0.13 mmol) were added at 0 °C. The mixture was stirred for 1 h at 0 °C. The volatiles were then evaporated under vacuum. The crude product contained two compounds, which evolved to the same main product. Purification by crystallisation (THF/Et_2O) afforded mesylate **20** (39 mg, 80%yield), m.p. 111–113 °C (THF/Et_2O). $[\alpha]_D$ = –53 (c = 0.3, CH_2Cl_2). IR (ATR): $\tilde{\nu}$ = 2956, 2871, 1342, 1158 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$, 25 °C): δ = 0.82 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.11 (d, J = 7.5 Hz, 3 H, CH), 1.43 (complex signal, 3 H, CH and CH_2), 1.67 (dd, J = 20.0 Hz, J' = 12.0 Hz, 1 H, CH_2), 2.03 (complex signal, 3 H, 2 × CH and CH_2), 2.47 (s, 3 H, CH_3), 2.71 (dd, J = J' = 11 Hz, 1 H, CH_2), 3.06 (s, 3 H, CH_3), 3.24 (m, 1 H, CH_2), 3.41 (complex signal, 2 H, 2 × CH_2), 4.18 (d, J = 8.5 Hz, 1 H, CH), 7.35 (d, J = 8.5 Hz, 2 H, 2 × CH), 7.72 (d, J = 8.5 Hz, 2 H, 2 × CH) ppm. ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 15.6 (CH_3), 19.1 (CH_3), 21.4 (CH_3), 26.1 (CH_3), 30.8 (CH_2), 33.8 (CH), 34.2 (CH_2), 38.8 (CH_3), 40.9 (CH), 44 (C), 47.3 (CH), 47.9 (CH_2), 52.5 (CH_2), 95.1 (CH), 127.3, 130.3, 134.2, 143.7 (CH and C-Ar) ppm. HRMS (ESI): calcd. for $C_{20}H_{32}NO_5S_2$ $[M + H]^+$ 430.1716; found 430.1713.

Synthesis of RuNP15, RuNP16 and RuNP18: [Ru(cod)(cot)] (30 mg, 0.1 mmol) and the corresponding ligand (0.02 mmol; **15**, 4 mg; **16**, 7.5 mg; **18**, 7 mg) were dissolved in THF (80 mL) and introduced to a Fischer–Porter bottle under an argon atmosphere. The system was then pressurised with 3 bar of dihydrogen and stirred at room temperature overnight. The hydrogen was then replaced by argon, and the solvent was evaporated under vacuum. The isolated particles were further washed with pentane (3 × 10 mL). The organic phases were concentrated and analysed by ^1H NMR spectroscopy, which proved the absence of ligand. The black solid was dried under reduced pressure.

General Procedure for Ru-Catalysed Hydrogenation Reactions: The substrate (1 mmol), RuNP (0.01 mmol) and neat deoxygenated heptane (25 mL) were introduced to an autoclave (Top Industrie). The system was purged under argon before pressurisation. The autoclave was pressurised at 40 bar of H_2, stirred and heated at 50 °C for 16 h. After cooling to room temperature, the autoclave was depressurised and the reaction mixture was then filtered through a Celite column, and the organic phase analysed by GC and NMR spectroscopy.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of new products, GC chromatogram for **32**.

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