Asymmetric transfer hydrogenation of ketones using amino alcohol and monotosylated diamine derivatives of indane

Matthew J. Palmer,[a] Jennifer A. Kenny,[a] Tim Walsgrove,[b] Aparecida M. Kawamoto[a] and Martin Wills*[a]

[a] *Department of Chemistry, Warwick University, Coventry, UK CV4 7AL*
[b] *GlaxoSmithKline Pharmaceuticals, Old Powder Mills, Nr Leigh, Tonbridge, Kent, UK TN11 9AN*

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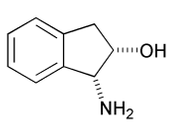
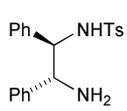
A series of 1,2-amino alcohol and 1,2-monotosylated diamine derivatives of indane have been applied as ligands in the asymmetric ruthenium(II)-catalysed transfer hydrogenation reaction of a series of ketones. Of these, the *cis*-1-aminoindan-2-ol derivative gives some of the highest asymmetric inductions reported for any amino alcohol ligand in this application.

Introduction

Asymmetric transfer hydrogenation of ketones has recently become an area of intense international research efforts.[1] This has been due to the introduction of a number of excellent ligands for use in organometallic complexes, most notably of ruthenium and rhodium. Of these, 1,2-amino alcohols[2,3] such as (1*R*,2*S*)-**1** and monotosylated 1,2-diamines[4] such as (1*R*,2*R*)-**2** have emerged as the most effective. Used in conjunction with ruthenium(II), the amino alcohol ligands have been demonstrated to generate the highest levels of rate acceleration, although their use is limited to reactions in propan-2-ol solvent. The monotosylated diamines, in contrast, are more versatile and may be employed in both propan-2-ol and formic acid–triethylamine, the two most commonly-used systems for this application. The use of both classes of ligand was first described by Noyori, who has reported extensive applications of the latter class.[4] In this paper we report the results of our studies on the applications of amino alcohol and monotosylated diamine derivatives of indane to asymmetric transfer hydrogenation reactions of ketones.[2]



(*1R,2S*)-**1**



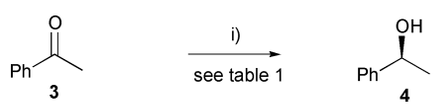
(*R,R*)-**2**

Results

At the outset of this project we were aware of the application of ephedrine derivatives to asymmetric transfer hydrogenation (reported by Noyori and co-workers)[3a] and wished to evaluate *cis*-1-aminoindan-2-ol **1** as a ligand. This compound, which has now been employed extensively in asymmetric catalysis,[5] seemed to us capable of describing a rigid and well-defined stereochemical environment around a metal to which it was chelated, an essential prerequisite for success in asymmetric catalysis.

Our initial studies involved the use of ligand (1*R*,2*S*)-**1** with various ruthenium(II) arene complexes. These were prepared according to the procedure of Bennett and Smith[6] if they were not available commercially.[7] In the case of (benzene) or (mesitylene)ruthenium(II) chloride dimer, refluxing a mixture of ruthenium(III) chloride hydrate and excess cyclohexa-1,4-diene or 1,3,5-trimethylcyclohexa-1,4-diene (prepared by the Birch reduction[8] of 1,3,5-trimethylbenzene) in ethanol overnight followed by collection of the brown solid by suction filtration afforded the ruthenium arene complexes.

The catalytic enantioselective transfer hydrogenation of acetophenone **3** was performed using similar conditions to those reported by Noyori and co-workers[3a] (Scheme 1). Thus,



3 **4**

Scheme 1 *Reagents and conditions*: i) 0.25 mol% $[Ru(cymene)Cl_2]_2$, 1 mol% **1**.

to a solution of 0.25 mol% (arene)ruthenium(II) chloride dimer and 1 mol% (1*R*,2*S*)-**1** in propan-2-ol was added a solution of acetophenone **3** (5 mmol, [**3**] = 0.1 M) in propan-2-ol, followed by 2.5 mol% KOH (0.1 M in propan-2-ol). Work up consisted of suction filtration of the reaction solution through a pad of silica gel, concentration *in vacuo* of the filtrate and flash column chromatography of the crude residue. Comparative experiments showed that, for this short series of experiments, the combination of 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$ and 1 mol% (1*R*,2*S*)-**1** provided the best conditions for the transfer hydrogenation of acetophenone; after 1.5 h at rt, (*S*)-**4** was isolated in 70% yield and 91% ee (Table 1, entry 3). Use of the other ruthenium arene complexes (at the same temperature and similar reaction times) gave products with lower enantiomeric excesses; 69 and 82% ee for the benzene- and mesitylene-substituted ruthenium complexes respectively (Table 1, entries 1 and 2). Decreasing the reaction temperature to 0 °C afforded a modest increase in enantioselectivity (93% ee) but at the cost of the reaction rate. Thus, the isolated yield of (*S*)-**4** was only 49% after 6.5 h at 0 °C (Table 1, entry 4). A further reduction in temperature to −20 °C brought no increase in enantioselectivity, but a further decrease in reaction rate; 47% isolated yield after 24 h at −20 °C (Table 1, entry 5). Allowing the reaction to proceed for 72 h at −20 °C afforded no improvement in yield but significantly eroded the enantioselectivity to 84% ee (Table 1, entry 6). Allowing the reaction to proceed for a longer time at rt also had a deleterious effect on the enantioselectivity; after 18 h with the standard ruthenium complex and ligand loadings, (*S*)-**4** was isolated in 72% yield and 83% ee

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Table 1 Asymmetric transfer hydrogenation of acetophenone catalysed by Ru(II)–(1*R*,2*S*)-**1**

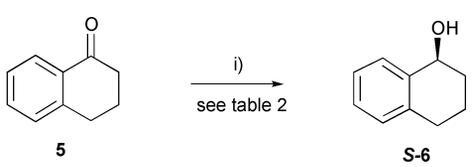
Entry	Arene	Time/h	Temp./°C	Yield/%	% Ee (*R*/*S*)
1	Benzene	1.6	rt	68	69 (*S*)
2	Mesitylene	2.0	rt	73	82 (*S*)
3	*p*-Cymene	1.5	rt	70	91 (*S*)
4	*p*-Cymene	6.5	0	49	93 (*S*)
5	*p*-Cymene	24	−20	47	90 (*S*)
6	*p*-Cymene	72	−20	47	84 (*S*)
7	*p*-Cymene	18	rt	72	83 (*S*)
8[a]	*p*-Cymene	18	rt	77	68 (*S*)

[a] 0.5 mol% $[RuCl_2(p\text{-cymene})]_2$, 1 mol% (1*R*,2*S*)-**1** used.

(Table 1, entry 7). This result was not unexpected in view of the known reversibility of transfer hydrogenations using propan-2-ol as the hydrogen source[1] and reinforced the need to avoid an unnecessarily long reaction time. The loading of ruthenium catalyst to ligand (1*R*,2*S*)-**1** was also investigated (Table 1, entry 8); the use of 0.5 mol% $[RuCl_2(p\text{-cymene})]_2$ and 1 mol% (1*R*,2*S*)-**1** (Ru : **1** mole ratio = 1 : 1) under conditions identical to those in entry 8 of Table 1 degraded the enantioselectivity from 83 to 68% ee.

The use of a 5 : 2 formic acid–triethylamine azeotropic mixture as a hydrogen source was investigated. Thus, a solution of 0.5 mol% $[RuCl_2(p\text{-cymene})]_2$ and 2 mol% (1*R*,2*S*)-**1** in propan-2-ol was heated for 30 minutes, concentrated *in vacuo* and to the residue was added neat acetophenone **2** (1.5 mmol, 2.0 M) and a 5 : 2 (molar) mixture of formic acid–triethylamine. The reaction was allowed to proceed for 60 h at rt, but TLC analysis during and after this time revealed no detectable product formation. Therefore it appears that Ru(II)–amino alcohol mediated transfer hydrogenations are not possible using this hydrogen source.

The optimum transfer hydrogenation conditions with ligand (1*R*,2*S*)-**1** were next applied to a series of ketone substrates to determine the generality of the process in terms of reactivity and enantioselectivity. The best results obtained were from the transfer hydrogenation of α-tetralone **5** (Scheme 2). Transfer



Scheme 2 *Reagents and conditions*: i) 0.25 mol% $[Ru(cymene)Cl_2]_2$, 1 mol% **1**, 2.5 mol% KOH, iPrOH.

hydrogenation of **5** at rt for 4 h using the standard catalyst–ligand loading gave an isolated 40% yield of (*S*)-α-tetralol (*S*)-**6** of 98% ee (Table 2, entry 1). Allowing the reaction to proceed for a longer time (16 h) at the same temperature achieved no increase in yield, and no erosion in ee was observed (Table 2, entry 2). However, an extended reaction time of 46 h brought a substantial decrease in enantioselectivity (Table 2, entry 3), again underlying the problem of reversibility over prolonged reaction times. The isolated yields of these transfer hydrogenations (Table 2, entries 1–3) were generally modest; however, when account is taken of the mass of recovered ketone the mass balance was generally excellent. The use of a higher reaction temperature (45 °C) for 4 h (Table 2, entry 4) gave only a slight drop in enantioselectivity (95% ee), whilst affording a more synthetically useful yield of product (63%). However, increased catalyst loading (Table 2, entry 5) at rt over 4 h gave a decrease in enantioselectivity from 98% ee (Table 2, entry 1) to 87% ee (Table 2, entry 5). Presumably, this last result can be attributed to faster reaction reversibility under the higher Ru catalyst–ligand loading.

Table 2 Asymmetric transfer hydrogenation of α-tetralone catalysed by Ru(II)–(1*R*,2*S*)-**1**

Entry	Time/h	Temp./°C	Yield (%)[a]	% Ee (*R*/*S*)
1	4	rt	40	98 (*S*)
2	16	rt	39 (85)	98 (*S*)
3	46	rt	60	67 (*S*)
4	4	45	63 (88)	95 (*S*)
5	4	rt	60 (94)	87 (*S*)

[a] Yields in parenthesis are corrected for recovered starting material.

Table 3 Asymmetric transfer hydrogenation of ketones **7** to **13** catalysed by Ru(II)–(1*R*,2*S*)-**1**

Entry	Ketone	Time/h	Temp./°C	Yield (%)[a]	% Ee (*R*/*S*)
1	**7**	1.5	rt	84	86 (*S*)
2	**7**	20	rt	70	85 (*S*)
3	**8**	1.7	rt	94	86 (*S*)
4	**8**	18	rt	89	81 (*S*)
5	**9**	1.75	rt	79	94 (*S*)
6	**10**	6	45	85	81 (*S*)
7	**11**	15	rt	52 (90)	43 (*S*)
8	**12**	1.5	rt	56	84 (*S*)
9	**13**	3	45	63	7 (*S*)

[a] Yields in parenthesis are corrected for recovered starting material.

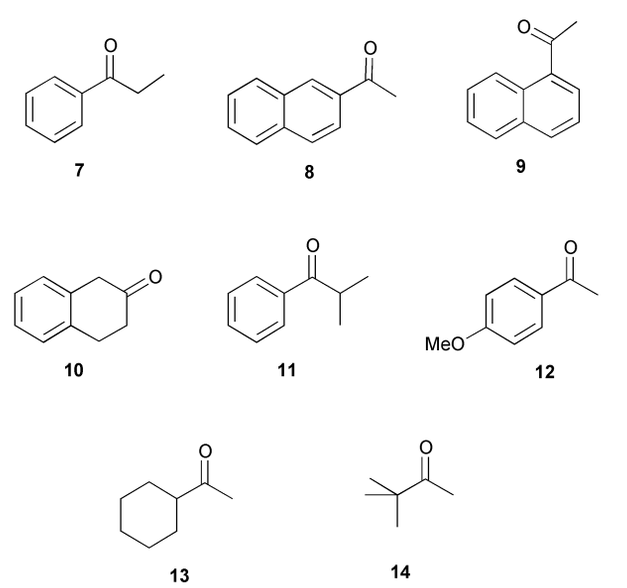
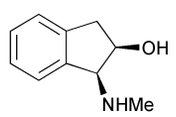


Fig. 1 Ketones used in asymmetric hydrogenation by Ru(II)–(1*R*,2*S*)-**1**.

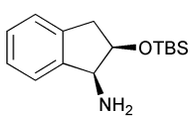
The transfer hydrogenation of various other ketones (Fig. 1, **7**–**14**) under identical Ru catalyst–ligand (1*R*,2*S*)-**1** loading was next examined (Table 3). Propiophenone **7** was reduced to (*S*)-1-phenylpropanol in 84% yield and 86% ee after 1.5 h at rt (Table 3, entry 1), whilst under similar conditions (*S*)-1-(2′-naphthyl)ethanol was obtained in 94% yield and 86% ee from 2′-acetonaphthone **8** (Table 3, entry 3). For both these ketones, allowing the transfer hydrogenation to run overnight had a detrimental effect on both yield and enantioselectivity (Table 3, entries 2 and 4). 1′-Acetonaphthone **9** underwent transfer hydrogenation at rt for 1.75 h to afford (*S*)-1-(1′-naphthyl)-ethanol in 79% yield and an excellent 94% ee (Table 3, entry 5). The transfer hydrogenation of β-tetralone **10** was achieved at elevated temperature; (*S*)-β-tetralol was obtained in 85% yield at 81% ee after 6 h at 45 °C (Table 3, entry 6). Not surprisingly, increased alkyl branching at the α position of a ketone, as in the case of isobutyrophenone **11**, produced a decrease in the enantioselectivity of reduction. Thus, after 15 h at rt, (*S*)-2-methyl-1-phenylpropanol was isolated in 52% yield and 43%

ee (Table 3, entry 7). *p*-Methoxyacetophenone **12**, a difficult substrate to reduce with satisfactory yield and enantioselectivity due to its high reduction potential,[1c,9] was reacted for 1.5 h at rt to furnish (*S*)-1-(*p*-methoxyphenyl)ethanol in 56% yield and 84% ee (Table 3, entry 8). Finally, and with the exception of β-tetralone, cyclic and acyclic aliphatic ketones do not appear to be effective substrates for transfer hydrogenation with this particular catalyst–ligand combination. Cyclohexyl methyl ketone **13** was reduced at 45 °C for 3 h to give (*S*)-1-cyclohexylethanol in 63% yield and low ee (Table 3, entry 9), whilst transfer hydrogenation of pinacolone **14** did not yield any alcohol product, even at elevated temperatures. In all cases (Table 3, entries 1–9), the sense of the transfer hydrogenation appeared to be driven by the steric difference in the groups flanking the C=O bond.

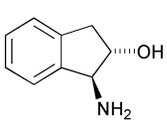
At this stage in the project, we wished to examine the effects of changes to the ligand structure. The *N*-methylated analogue (1*S*,2*R*)-**15** was obtained in four steps from (1*S*,2*R*)-**1** through *N*-Boc protection of (1*S*,2*R*)-**16**, followed by *N*-methylation and deprotection. *trans*-Aminoindanol derivative[10] (1*S*,2*S*)-**17** was prepared in three steps from indene in a process which began with low temperature Jacobsen asymmetric epoxidation[11] to give (1*R*,2*S*)-**18** in 58% yield after distillation (91% ee by ^{1}H NMR analysis using 10 mol% Eu(hfc)$_3$ chiral shift reagent).[12] Regioselective opening of (1*R*,2*S*)-**18** using sodium azide and ammonium chloride in refluxing aqueous ethanol for 2 h gave the *trans*-azido alcohol (1*S*,2*S*)-**19** in 84% yield (92% ee assayed by chiral HPLC).[13] Reduction of the azide group was achieved using excess stannous chloride[14,15] in THF–water at rt for 24 h to give *trans*-1-aminoindan-2-ol (1*S*,2*S*)-**17** in 71% yield. The *N*-Boc compound (1*S*,2*S*)-**20**, derived from (1*S*,2*S*)-**17**, was determined to be of 93% ee by HPLC analysis.



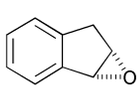
(*1S,2R*)-**15**



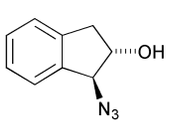
(*1S,2R*)-**16**



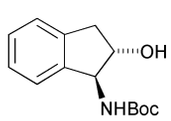
(*1S,2S*)-**17**



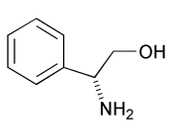
(*1R,2S*)-**18**



(*1S,2S*)-**19**



(*1S,2S*)-**20**



R-**21**

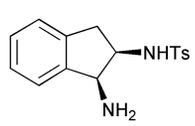
With these two ligands in hand, plus the commercially available phenylglycinol (*R*)-**21**, we were able to probe the structural elements of (1*R*,2*S*)-**1** which are important for enantioselective catalysis of transfer hydrogenation. The results from the use of 1 mol% of each ligand, in conjunction with 0.25 mol% [RuCl$_2$(*p*-cymene)]$_2$ and 2.5 mol% KOH in the transfer hydrogenation of acetophenone **3** are summarised in Table 4. Use of (*R*)-**21** gave (*S*)-**4** in 90% yield and 23% ee. This result underlined the importance of the stereochemical rigidity of (1*R*,2*S*)-**1**. The *N*-methyl derivative (1*S*,2*R*)-**15** also proved to be an inferior ligand in terms of both reaction rate and enantioselectivity; thus, after 15 h at rt, (*R*)-**4** was isolated in only 33% yield and 27% ee. It appeared that a primary amine function in the ligand was desirable for maximum selectivity. This is in contrast to the β-amino alcohol ligands reported by Noyori and co-workers,[3a] the most effective of which contain a secondary amine. *trans*-Amino alcohol (1*S*,2*S*)-**17** gave (*S*)-**4** in poor yield (20%) and 29% ee after 23 h at rt. TLC analysis of this reaction after 1.5 h, at which time (*S*)-**4** of 70% yield and 91% ee can be isolated in the transfer hydrogenation of **3** using (1*R*,2*S*)-**1** (Table 1, entry 3), revealed virtually no product formation. Therefore, perhaps not surprisingly, (1*R*,2*S*)-**1** proved to be a better ligand than **17**, presumably because the *cis* arrangement of substituents in the former permits more facile formation of a catalytic species with the ruthenium(II) arene complex.

Table 4 Asymmetric transfer hydrogenation of acetophenone catalysed by Ru(II)–ligands (1*S*,2*R*)-**15**, (1*S*,2*S*)-**17**, (*R*)-**21**

Entry	Ligand	Time/h	Temp.	Yield (%)[a]	% Ee (*R*/*S*)
1	(*R*)-**21**	2.0	rt	90	23 (*S*)
2	(1*S*,2*R*)-**15**	15	rt	33	27 (*R*)
3	(1*S*,2*S*)-**17**	23	rt	20	29 (*S*)

[a] Yields in parenthesis are corrected for recovered starting material.

In view of the excellent results achieved by Noyori, Knochel and others in the enantioselective transfer hydrogenation of ketones with monotosylated C_2-symmetric diamine ligands,[4] we felt that it would be beneficial to examine monotosylated derivatives based upon the diaminoindane structure. The main benefit expected from the use of such ligands was their compatibility with the formic acid–triethylamine reaction mixture, enabling the transfer hydrogenation to proceed under virtually irreversible conditions. In contrast to the diamine precursors to (*R*,*R*)-**2** and the related cyclohexyldiamine derivative, our proposed ligands will not possess C_2-symmetry, so that a possible total of four isomers **22**–**25** within a given enantiomeric series, may be prepared.



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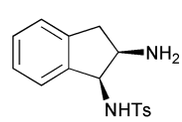

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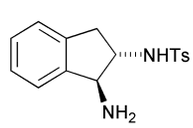

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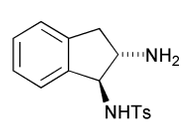

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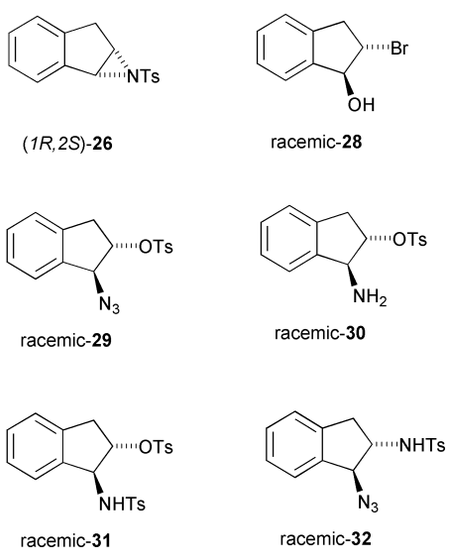
Regioselective ring-opening of enantiopure aziridine **26** with either nitrogen- or oxygen-based nucleophiles could in principle provide a direct route to the *trans* targets **24** and **25**. The most direct route to **26** would be the copper(I)-catalysed aziridination of indene by (*N*-tosylimino)phenyliodinane **27** using chiral diimine ligands developed by Jacobsen and co-workers.[16] However, the moderate yield and ee of **26** reported for this reaction, coupled with difficulties encountered in reproducibly preparing adequate quantities of **27**, forced us to consider other, albeit more circuitous, approaches. *trans*-Azido alcohol **19** was identified as being a key synthetic intermediate for the preparation of **26**. In the first instance, we required significant quantities of racemic indene oxide (±)-**18** in order to prepare (±)-**19**. Several epoxidizing reagents have been employed for the synthesis of racemic indene oxide (±)-**18**. Of these methods,

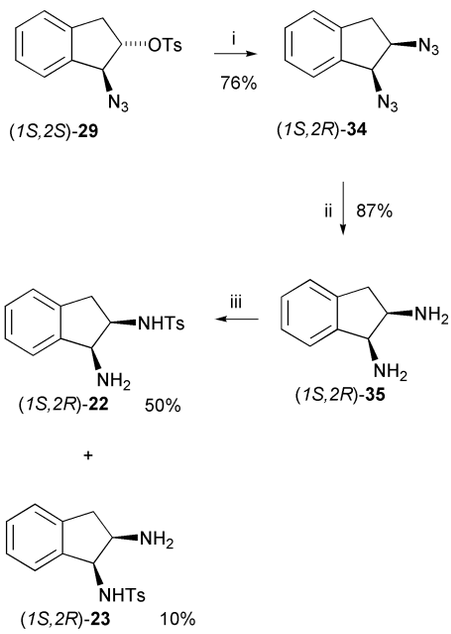
we initially chose to use either MCPBA (1.2 equiv. MCPBA, 4 equiv. $NaHCO_3$, CH_2Cl_2–H_2O (1 : 1), 0 °C⟶rt, 12 h, 58% yield)[17] or the hydrogen peroxide–acetonitrile reagent developed by Payne[18] (1.05 equiv. 30% aq H_2O_2, 1.8 equiv. MeCN, 0.2 equiv. $KHCO_3$, MeOH, 0 °C⟶rt, 19 h, 56% yield). An alternative route to (±)-**18** involved initial preparation of bromohydrin (±)-**28** (NBS, THF–water, rt, 16 h, 85% yield), followed by base-induced cyclisation to afford (±)-**18**.[13] Although employing one extra step over epoxidation, this route was more amenable to the preparation of (±)-**18** on a multigram scale. Having secured sufficient amounts of (±)-**18**, we applied a literature procedure[13] to obtain (±)-**19** in 75% yield. Tosylation of (±)-**19** proceeded well to afford *trans*-azido toluene-*p*-sulfonate (±)-**29**. Azide reduction of (±)-**29** to give the amine (±)-**30** was accomplished using stannous chloride in THF–water.[15] Although this reaction was successful, it proved to be capricious when performed on a larger scale and some problems in product isolation occurred. Hydrogenation of (±)-**29** using 10% Pd/C in ethanol at rt overnight gave only decomposition products.



Synthesis of the sulfonamido toluene-*p*-sulfonate (±)-**31** from (±)-**30** was achieved in moderate isolated yield using tosyl chloride and triethylamine. Conversion of (±)-**31** to (±)-**26** was achieved following the precedent of Craig, who has synthesized a range of homochiral 2-substituted *N*-tosylaziridines by *in situ* tosylation and immediate cyclisation of *N*-tosyl-2-amino alcohols.[19] Treatment of an ice-cold solution of (±)-**31** in THF with excess sodium hydride and stirring the mixture overnight at rt afforded aziridine (±)-**26** in 64% isolated yield.

With quantities of (±)-**26** in hand, we conducted a cursory examination of its potential as a synthetic intermediate for ligand **24**. Refluxing a mixture of (±)-**26** and sodium azide in 80% aqueous ethanol for 7 h afforded the *trans*-azido sulfonamide (±)-**32** in excellent yield. Thus it was clear that **26**, if prepared in enantiopure form, would be likely to be an excellent precursor for **24**. Interestingly, (±)-**32** was also obtained as the *unexpected* product from the reaction of (±)-**31** and sodium azide (heat in 80% aqueous ethanol for 2.5 h) in 90% yield. The reaction presumably proceeds *via in situ* formation of **26**, followed by regioselective azide attack to give **32**. The above synthesis was not pursued in enantiomerically pure form, however, because of positive results from a parallel synthetic investigation which delivered a viable alternative approach (see below).

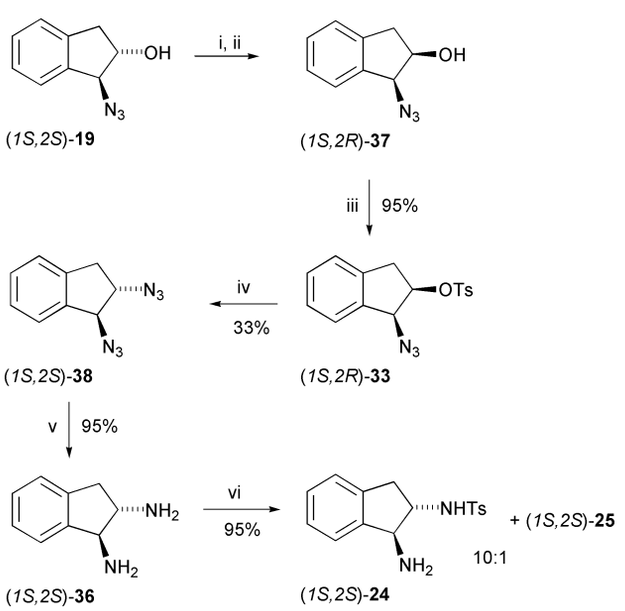
The final route to our target ligands **22**–**25**, which ultimately proved to be our preferred method, involved the use of the *trans*- and *cis*-azido toluene-*p*-sulfonates **29** and **33** respectively. Thus, heating a mixture of (±)-**29** and sodium azide in DMF at 100 °C overnight gave the racemic diazide (±)-**34** in 76% isolated yield, *via* S_N2 displacement.[20] Catalytic hydrogenation of (±)-**34** was accomplished using 10% Pd/C in ethanol at rt for 3 h to give, following concentration *in vacuo* of the reaction filtrate, *cis*-diamine (±)-**35** as a low melting brown solid in 89% yield.[21] Chiral non-racemic diamine **35** was prepared in identical fashion (Scheme 3). Tosylation of (1*S*,2*S*)-**19** (91% ee)



Scheme 3 *Reagents and conditions*: i) 1.5 equiv. NaN_3, DMF, 100 °C, 14 h; ii) H_2, 10% Pd/C, EtOH, rt, 3 h; iii) 0.95 equiv. TsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h.

afforded (1*S*,2*S*)-**29** in 80% yield, which was then heated with sodium azide in DMF for 16 h to give (1*S*,2*R*)-**34** in 76% yield. Both (1*S*,2*S*)-**29** and (1*S*,2*R*)-**34** were of 91% ee (established by chiral HPLC analysis), indicating no loss in their optical activity. Finally, hydrogenation of (1*S*,2*R*)-**34** proceeded in 87% yield to give *cis*-diamine (1*S*,2*R*)-**35**.

Although prepared initially in racemic form, enantiomerically enriched *trans*-diamine (1*S*,2*R*)-**36** was prepared as shown in Scheme 4. *cis*-Azido alcohol (1*S*,2*S*)-**19**, was first

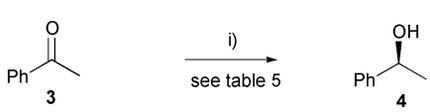


Scheme 4 *Reagents and conditions*: i) 2.0 equiv. *p*-$NO_2(C_6H_4)CO_2H$, 2.0 equiv. PPh_3, 2.0 equiv. DEAD, THF, 0 °C, 30 min, rt, 39%; ii) 3.0 equiv. NaOMe, MeOH–CH_2Cl_2, rt, 2 h, 93%; iii) 1.0 TsCl, 2.0 equiv. Et_3N, 0.1 equiv. DMAP, CH_2Cl_2, 0 °C⟶rt, 20 h; iv) 1.5 equiv., NaN_3. DMF, 100 °C, 20 h; v) H_2, 10% Pd/C, EtOH, rt, 3 h; vi) 0.95 equiv. TsCl, Et_3N, CH_2Cl_2, 0 °C, 3 h.

subjected to Mitsunobu inversion and ester hydrolysis to give (1*S*,2*R*)-**37**, tosylation to furnish *cis*-azido toluene-*p*-sulfonate (1*S*,2*R*)-**33**, which was subsequently converted to the *trans*-diazide (1*S*,2*S*)-**38**. The reason for the much lower yield (33%) for azide displacement of *cis*-(1*S*,2*S*)-**33**, as opposed to *trans*-(1*S*,2*S*)-**29**, was not immediately apparent. Both (1*S*,2*R*)-**33** and (1*S*,2*S*)-**38** were determined to be of 97% ee by chiral HPLC. Catalytic hydrogenation of (1*S*,2*S*)-**38** proceeded well to give *trans*-diamine (1*S*,2*S*)-**36** in 95% yield.

Previously reported[4] monotosylated diamine ligands had all been synthesised by monotosylation of C_2-symmetric diamine precursors. However, because **35** and **36** are not C_2-symmetric, a regioisomeric mixture of monosulfonamides could be expected from their treatment with tosyl chloride. It was this observation that had initially deterred us from preparing our ligands by this route. In the event, a solution of (1*S*,2*R*)-**35** (91% ee) in dichloromethane was treated with 0.95 equiv. of tosyl chloride at 0 °C for 3 h (Scheme 3). ^{1}H NMR analysis of the crude reaction mixture following normal aqueous work up revealed the presence of a regioisomeric mixture of monosulfonamides (1*S*,2*R*)-**22** and (1*S*,2*R*)-**23** in a ratio of approximately 5 : 1. The assignment of regiochemistry to the major and minor monosulfonamides is based upon the expectation that the non-benzylic amino group in (1*S*,2*R*)-**35** is less sterically hindered. However this is reinforced by the relative chemical shifts for the methine protons adjacent to the amine and tosylamine groups in the ^{1}H NMR spectrum. Careful flash column chromatography[22] of the crude mixture provided the pure monosulfonamides in 50 and 10% yield respectively. Repeating the monotosylation using *trans*-(1*S*,2*S*)-**36** (95% ee) for 3 h at 0 °C (Scheme 4) afforded a mixture of monosulfonamide products (1*S*,2*S*)-**24** and (1*S*,2*S*)-**25** in a ratio of *ca.* 10 : 1 (crude NMR), assigned following comparison of its ^{1}H and ^{13}C spectra with the major product from the above reaction using the *cis*-diamine. The products proved difficult to separate and, despite several attempts at flash chromatography, only the major product (1*S*,2*S*)-**24** could be isolated in impure form, containing a small amount of the regioisomer. It was decided to use this product without purification, due to the small quantity available.

In view of its close analogy with the *cis*-aminoindanol ligand, we chose to focus first on the use of (1*S*,2*R*)-**22** as ligand in the transfer hydrogenation of **3** using the formic acid–triethylamine reaction system (Scheme 5). We initially employed 0.25 mol%



Scheme 5 *Reagents and conditions*: i) 0.25 mol% $[Ru(arene)Cl_2]_2$, 0.5 mol% (1*S*,2*R*)-**22**, HCO_2H–Et_3N (5 : 2), 28 °C, [**3**] = 2 M.

$[RuCl_2(arene)]_2$ complexes and 0.5 mol% (1*S*,2*R*)-**22** in formic acid–triethylamine (5 : 2 molar ratio). Products from the reductions of a series of ketones were measured by HPLC analysis after differing reaction times (4–120 h) at various temperatures, and in the presence of a range of co-solvents (Table 5).

Of a short series of arenes in the precursor diruthenium complexes (entries 1–3), the *p*-cymene proved to be the best, giving a product of 83% ee. Conducting the reaction at slightly lower temperature (entry 4) gave no improvement to the asymmetric induction, but the reaction rate and yield were lower, whilst at 0 °C the ee increased to 90% but at the cost of a dramatic drop in rate (only 56% yield after 120 h). The effect of elevated temperature was to sharply increase the reaction rate and yield, but at the cost of ee (entries 5, 6). Use of 0.1 mol% of catalyst gave, after a long reaction time, a product of equally good ee to the 0.5 mol% reaction (entry 8), whilst the use of 2 mol% catalyst (entry 9) resulted in no improvement. A short series of investigations of the effect of co-solvents was undertaken (entries 10–12) but these resulted invariably in inferior results, in terms of both yield and ee.

We briefly examined the application of the two other new monotosylated ligands, *i.e.* (1*S*,2*R*)-**23** and (1*S*,2*S*)-**24** to the asymmetric transfer hydrogenation reaction with formic acid–triethylamine (Table 5, entries 13 and 14). The isomeric *cis*-ligand **23** performed well, but was not as effective as **22**, whilst the *trans*-ligand **24** was a very poor ligand. This may be a reflection of the more ready formation of stable five-membered ruthenium–ligand species with *cis*-ligands than with *trans*-ligands. The superior result obtained with **22** suggests that the position of the tosyl group is important, but not crucial; the *cis*-structure is much more significant to the value of the ligand.

Having achieved promising results from the acetophenone reduction with (1*S*,2*R*)-**22**, we examined the reductions of a short series of ketones, *i.e.* **5** and **7**–**12** (Table 6) in order to determine the generality of the process in terms of reactivity and enantioselectivity. Not surprisingly, both propiophenone and isobutyrophenone were reduced with significantly lower enantioselectivity than acetophenone, presumably the reflection of a stepwise reduction in the size difference between the groups flanking the ketone. *p*-Methoxyacetophenone was reduced in modest ee (60%) but good yield (75%), however the best result was achieved in the reduction of α-tetralone (92% ee and 72% yield at rt), mirroring the result obtained with the *cis*-aminoindanol **1**. β-Tetralone was reduced less effectively, giving products in 52% ee after 24 h but only 31% after 68 h. These results may well reflect reversibility in the formic-acid reaction, *i.e.* with the alcohol product competing with formic acid as the hydrogen donor. Both acetonaphthones examined gave good results (73 and 74% ee).

Conclusions

The readily available (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol ((1*R*,2*S*)-**1**) has been demonstrated to be an excellent ligand for the Ru(II)-catalysed transfer hydrogenation of various aromatic ketones with propan-2-ol. The system benefits from practical simplicity; use of relatively non-hazardous, inexpensive reagents and an easy, non-aqueous work-up, and delivers products in generally good to excellent yields and enantiomeric excesses. Reaction reversibility can be a problem, especially for certain substrates. The use of formic acid as a hydrogen source is not possible with the Ru(II) catalyst/ligand (1*R*,2*S*)-**1** system. Basic modifications to the ligand structure have revealed that a primary amine end, a *cis* relationship between amine and alcohol functions and a conformationally constrained five-membered ring are all essential elements in attaining maximum reactivity and enantioselectivity. The preparation and evaluation of a further generation of monotosylated diamine ligands, based on the diaminoindane structure, has been completed. One of these, (1*S*,2*R*)-**22**, has proved to be a promising ligand for ketone reduction and is active under formic acid/triethylamine conditions.

Experimental

General experimental details have been described in a previous article.[2h] 1,3,5-Trimethylcyclohexa-1,4-diene was prepared according to a literature procedure.[6] (*p*-Cymene)ruthenium(II) chloride dimer was purchased from Strem chemicals.

(Benzene)ruthenium(II) chloride dimer[6]

A mixture of ruthenium(III) chloride hydrate (2.00 g, 9.64 mmol) and cyclohexa-1,4-diene (10.0 mL, 11.0 equiv., 106 mmol) in ethanol (100) was refluxed for 12 h. After cooling, the brown mixture was filtered under suction and the collected brown powder was washed with methanol. The product $[RuCl_2(C_6H_6)]_2$ was isolated as a brown powder (1.96 g, 81%).

Table 5 Asymmetric transfer hydrogenation of acetophenone catalysed by Ru(II)–(1*S*,2*R*)-**22** (Scheme 5)

Entry	Ligand	Arene	Co-solvent	Time/h	Temp./°C	Yield (%)	% Ee (*R*/*S*)
1	**22**	*p*-Cymene	None	20	28	96	83 (*S*)
2	**22**	Benzene	None	20	28	94	63 (*S*)
3	**22**	Mesitylene	None	60	28	31	49 (*S*)
4	**22**	*p*-Cymene	None	40	20	77	83 (*S*)
5	**22**	*p*-Cymene	None	6.5	45	98	53 (*S*)
6	**22**	*p*-Cymene	None	4	60	>99	56 (*S*)
7	**22**	*p*-Cymene	None	120	0	56	90 (*S*)
8[a]	**22**	*p*-Cymene	None	60	28	76	82 (*S*)
9[b]	**22**	*p*-Cymene	None	20	28	87	77 (*S*)
10	**22**	*p*-Cymene	DCM	40	28	40	71 (*S*)
11	**22**	*p*-Cymene	DMF	60	28	31	64 (*S*)
12	**22**	*p*-Cymene	DMSO	60	28	14	66 (*S*)
13	**23**	*p*-Cymene	None	48	28	89	57 (*S*)
14	**24**	*p*-Cymene	None	20	28	21	1.3 (*R*)

[a] 0.05 mol% $[RuCl_2(arene)]_2$, 0.1 mol% (1*S*,2*R*)-**22** used. [b] 1 mol% $[RuCl_2(arene)]_2$, 2 mol% (1*S*,2*R*)-**22** used.

Table 6 Asymmetric transfer hydrogenation of ketones **5** and **7**–**12** with formic acid–triethylamine catalysed by Ru(II)–(1*S*,2*R*)-**22**

Entry	Ketone	Time/h	Temp./°C	Yield (%)[a]	% Ee (*R*/*S*)[b]
1	**5**	40	rt	72	92 (*S*)
2	**5**	40	28	91[c]	89 (*S*)
3	**7**	48	28	62 (90)	67 (*S*)
4	**8**	48	28	93	73 (*S*)
5	**9**	28	28	74	74 (*S*)
6	**10**	68	28	81	31 (*S*)
7	**10**	24	28	85[c]	52 (*S*)
8	**11**	60	28	21 (66)	41 (*S*)
9	**12**	120	28	75	60 (*S*)

[a] Yields in parenthesis are corrected for recovered starting material. [b] Enantiomeric excess/configuration determined by chiral HPLC. [c] NMR conversion.

(Mesitylene)ruthenium(II) chloride dimer[6]

This compound was prepared according to the procedure employed for $[RuCl_2(C_6H_6)]_2$ using 1,3,5-trimethylcyclohexa-1,4-diene (*ca.* 6.00 g, 10.0 equiv., 49.6 mmol) and ruthenium(III) chloride hydrate (1.03 g, 1.0 equiv., 4.96 mmol) in ethanol (40 mL) for 16 h at reflux. The product $[RuCl_2(C_9H_{12})]_2$ was isolated as a brown powder (910 mg, 63%).

General procedure for transfer hydrogenation of ketones using (1*R*,2*S*)-*cis*-aminoindanol

A solution of (*p*-cymene)ruthenium(II) chloride dimer (7.7 mg, 0.25 mol%, 0.0125 mmol) and (1*R*,2*S*)-(+)-*cis*-1-aminoindan-2-ol [(1*R*,2*S*)-**1**] (7.5 mg, 1 mol%, 0.05 mmol) in dry propan-2-ol (4 mL) was heated at 80 °C for 20 minutes under nitrogen. After cooling to rt, the light brown solution was transferred *via* cannula to a large sealed Schlenk flask. A solution of ketone (5 mmol) in dry degassed propan-2-ol (45 mL) was added *via* cannula, followed by KOH (1.25 mL, 2.5 mol%, 0.125 mmol, 0.1 M in propan-2-ol). The reaction was run at rt and monitored by TLC until substantially complete (typically 2 h). Work up consisted of filtering the dark brown solution through a pad of silica under vacuum (EtOAc, 2 × 50 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product which was purified by flash column chromatography.

(*S*)-(−)-1-Phenylethanol 4. Result featured in Table 1, entry 3; 91% ee (*S*) by HPLC (Chiralcel OD, ethanol–hexane = 5 : 95 (0.5 mL min^{-1}), *S* isomer 17.1 min, *R* isomer 14.8 min); $[\alpha]_D$ −48.8 (*c* 1.0, CH_2Cl_2) (lit.[23] $[\alpha]_D$ +48.6 (*c* 1.0, CH_2Cl_2), 96% ee (*R*)); δ_H (270 MHz, $CDCl_3$) 7.37–7.25 (5H, m, aryl H), 4.86 (1H, q, *J* 6.4, C*H*OH), 2.40 (1H, br s, OH), 1.48 (3H, d, *J* 6.4, CH_3).

(*S*)-(+)-1,2,3,4-Tetrahydronaphthalen-1-ol 6. Result featured in Table 2, entry 1; 98% ee (*S*) by HPLC (Chiralcel OD, propan-2-ol–hexane = 2 : 98 (0.9 mL min^{-1}), *S* isomer 17.4 min, *R* isomer 19.8 min); $[\alpha]_D$ +34.4 (*c* 1.01, $CHCl_3$) (lit.[24] $[\alpha]_D$ +25.8 (*c* 3.10, $CHCl_3$), (*S*)); δ_H (250 MHz, $CDCl_3$) 7.46–7.41 (1H, m, aryl H), 7.23–7.17 (2H, m, aryl H), 7.12–7.09 (1H, m, aryl H), 4.79 (1H, br m, C*H*OH), 2.87–2.69 (2H, m, alkyl H), 1.99–1.60 (5H, m, alkyl H and OH).

(*S*)-(−)-1-Phenylpropanol. Result featured in Table 3, entry 1; 86% ee (*S*) by HPLC (Chiralcel OD, ethanol–hexane = 5 : 95 (0.5 mL min^{-1}), *S* isomer 16.1 min, *R* isomer 14.2 min); $[\alpha]_D$ −33.0 (*c* 5.15, EtOH) (lit.[4b] $[\alpha]_D$ −34.0 (*c* 5.03, EtOH), 97% ee (*S*)); δ_H (250 MHz, $CDCl_3$) 7.36–7.23 (5H, m, aryl H), 4.60 (1H, t, *J* 6.6, C*H*OH), 1.91–1.69 (2H, m, CH_2), 1.88 (1H, br s, OH), 0.92 (3H, t, *J* 7.5, CH_3).

(*S*)-(−)-1-(2′-Naphthyl)ethanol. Result featured in Table 3, entry 3; 86% ee (*S*) by HPLC (Chiralcel OD, ethanol–hexane = 5 : 95 (0.5 mL min^{-1}), *S* isomer 26.4 min, *R* isomer 29.3 min); $[\alpha]_D$ −34.3 (*c* 1.10, EtOH) (lit.[25] $[\alpha]_D$ −41.9 (*c* 4.92, EtOH), (*S*)); δ_H (250 MHz, $CDCl_3$) 7.86–7.81 (4H, m, aryl H), 7.53–7.42 (3H, m, aryl H), 5.07 (1H, dq, *J* 6.4, 3.2, C*H*OH), 1.94 (1H, d, *J* 3.2, OH), 1.59 (3H, d, *J* 6.7, CH_3).

(*S*)-(−)-1-(1′-Naphthyl)ethanol. Result featured in Table 3, entry 5; 94% ee (*S*) by HPLC (Chiralcel OD, ethanol–hexane = 5 : 95 (0.5 mL min^{-1}), *S* isomer 24.4 min, *R* isomer 42.2 min); $[\alpha]_D$ −79.6 (*c* 1.02, Et_2O) (lit.[26] $[\alpha]_D$ +82.1 (*c* 1.0, Et_2O), 99% ee (*R*)); δ_H (250 MHz, $CDCl_3$) 8.06–8.09 (1H, m, aryl H), 7.91–7.84 (1H, m, aryl H), 7.79 (1H, d, *J* 8.1, aryl H), 7.69 (1H, d, *J* 7.3, aryl H), 7.56–7.45 (3H, m, aryl H), 5.68 (1H, q, *J* 6.4, C*H*OH), 1.91 (1H, br s, OH), 1.68 (3H, d, *J* 6.4, CH_3).

(*S*)-(−)-1,2,3,4-Tetrahydronaphthalen-2-ol. Result featured in Table 3, entry 6; 81% ee (*S*) by HPLC of (*S*)-Mosher ester (Chiralcel OD, propan-2-ol–hexane = 0.1 : 99.9 (0.9 mL min^{-1}), *S* isomer 34.4 min, *R* isomer 38.4 min); $[\alpha]_D$ −54.4 (*c* 0.70, $CHCl_3$) (lit.[27] $[\alpha]_D$ −55.4 (*c* 0.70, $CHCl_3$), 95.5% ee (*S*)); δ_H (250 MHz, $CDCl_3$) 7.15–7.07 (4H, m, aryl H), 4.16 (1H, m, C*H*OH), 3.14–2.72 (4H, m, alkyl H), 2.11–2.01 (1H, m, alkyl H), 1.90–1.75 (1H, m, alkyl H), 1.68 (1H, s, OH).

(*S*)-(−)-2-Methyl-1-phenylpropanol. Result featured in Table 2, entry 7; 43% ee (*S*) by HPLC (Chiralcel OD, propan-2-ol–hexane = 2 : 98 (0.5 mL min^{-1}), *S* isomer 25.4 min, *R* isomer 28.8 min); $[\alpha]_D$ −21.0 (*c* 1.05, Et_2O) (lit.[28] $[\alpha]_D$ +34.8 (*c* 4.90, Et_2O), 73% ee (*R*)); δ_H (250 MHz, $CDCl_3$) 7.37–7.23 (5H, m, aryl H), 4.36 (1H, d, *J* 6.7, C*H*OH), 1.96 (1H, dseptet, *J* 6.7, 6.7, C*H*$(CH_3)_2$), 1.83 (1H, br s, OH), 1.00 (3H, d, *J* 6.7, CH_3), 0.80 (3H, d, *J* 7.0, CH_3).

(*S*)-(−)-1-(*p*-Methoxyphenyl)ethanol. Result featured in Table 2, entry 8; 84% ee (*S*) by HPLC (Chiralcel OD, propan-2-ol–hexane = 10 : 90 (0.5 mL min^{-1}), *S* isomer 16.9 min, *R* isomer 15.9 min); $[a]_D$ −44.2 (*c* 1.06, $CHCl_3$) (lit.[4b] $[a]_D$ −51.9 (*c* 1.04, $CHCl_3$), 97% ee (*S*)); δ_H (250 MHz, $CDCl_3$) 7.30 (2H, d, J_{AB} 9.0, MeO(C_6H_4)CHOHMe), 6.88 (2H, d, J_{AB} 9.0, MeO-(C_6H_4)CHOHMe), 4.85 (1H, q, *J* 6.4, C*H*OH), 3.81 (3H, s, OCH_3), 1.81 (1H, br s, OH), 1.48 (3H, d, *J* 6.4, CH_3).

(*S*)-(+)-1-Cyclohexylethanol. Result featured in Table 2, entry 9; 7% ee (*S*) by HPLC of 4-nitrobenzoyl ester (Chiralcel OD, propan-2-ol–hexane = 0.1 : 99.9 (0.9 mL min^{-1}), *S* isomer 19.5 min, *R* isomer 21.4 min); $[a]_D$ +0.3 (*c* 12.3, $CHCl_3$) (lit.[29] $[a]_D$ −3.4 (*c* 1.1, $CHCl_3$), 94% ee (*R*)); δ_H (250 MHz, $CDCl_3$) 3.60–3.50 (1H, m, C*H*OH), 1.93–1.63 (5H, m, alkyl H), 1.50 (1H, br s, 1H, OH), 1.34–0.88 (6H, m, alkyl H), 1.15 (3H, d, *J* 6.1, CH_3).

(*S*)-Mosher ester of (*S*)-(−)-1,2,3,4-tetrahydronaphthalen-2-ol

To a solution of (*S*)-(−)-1,2,3,4-tetrahydronaphthalen-2-ol (8.3 mg, 0.056 mmol) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (21 mg, 1.50 equiv., 0.084 mmol) in dichloromethane (0.10 mL) at rt was added triethylamine (0.16 mL, 20.0 equiv., 1.12 mmol) and DMAP (*ca.* 1 mg). The mixture was stirred at rt for 45 minutes and then applied directly to a short silica gel column (eluting with 15% v/v ethyl acetate–petrol). The product was obtained as an oil (19 mg, 95%).

(*S*)-1-(4-Nitrobenzoyloxy)cyclohexylethanol

To a solution of (*S*)-1-cyclohexylethanol (100 mg, 0.78 mmol) in dichloromethane (3 mL) at 0 °C were added sequentially triethylamine (0.33 mL, 3.0 equiv., 2.34 mmol) and 4-nitrobenzoyl chloride (217 mg, 1.50 equiv., 1.17 mmol). The mixture was warmed to rt and stirred for 2 h. Extra reagents were then added: triethylamine (0.22 mL, 2.0 equiv., 1.56 mmol) and 4-nitrobenzoyl chloride (145 mg, 1.0 equiv., 0.78 mmol). The mixture was stirred at rt for 16 h. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (20 mL)–water (15 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were washed successively with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2.5% v/v ethyl acetate–petrol) to afford the benzoate as a yellow solid (209 mg, 97%); δ_H (250 MHz, $CDCl_3$) 8.29 (2H, d, J_{AB} 9.2, O(CO)-$C_6H_4NO_2$), 8.21 (2H, d, J_{AB} 9.2, O(CO)$C_6H_4NO_2$), 5.03 (1H, quintet, *J* 6.4, CHO), 2.33–2.22 (1H, m, alkyl H), 1.86–1.55 (6H, m, alkyl H), 1.33 (3H, d, *J* 6.4, CH_3), 1.27–1.02 (4H, m, alkyl H).

(1*S*,2*R*)-(−)-*cis*-1-(*N*-*tert*-Butoxycarbonyl)amino-2-(*tert*-butyldimethylsilyloxy)indane

To a stirred solution of (1*S*,2*R*)-*cis*-1-amino-2-(*tert*-butyldimethylsilyloxy)indane **16** (1.47 g, 5.59 mmol) in dichloromethane (10 mL) at 0 °C was added triethylamine (0.86 mL, 1.10 equiv., 6.15 mmol) and a solution of di-*tert*-butyl dicarbonate (1.22 g, 1.0 equiv., 5.59 mmol) in dichloromethane (5 mL) *via* cannula. The mixture was warmed to rt and stirred for 2 h, after which time saturated aqueous ammonium chloride solution (10 mL) was added. The separated aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (5⟶10% v/v ethyl acetate–petrol) to afford the carbamate as a low melting white solid (1.83 g, 90%); mp 37–39 °C; $[a]_D^{28}$ −22.5 (*c* 1.0, MeOH); ν_{max}(Nujol)/cm^{-1} 3450, 1718, 1495, 1254, 1170, 1118, 1090, 1071 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.35–7.15 (4H, m, aryl H), 5.17–5.07 (2H, m, C*H*OTBS and N*H*), 4.62–4.59 (1H, m, C*H*-NHBoc), 3.07 (1H, dd, *J* 16.5, 5.2, C*H*H), 2.85 (1H, dd, *J* 16.5, 1.8, CH*H*), 1.51 (10H, br s, N*H* and NH(CO)OC(CH_3)$_3$), 0.87 (9H, s, OSi(CH_3)$_2$C(CH_3)$_3$), 0.11 (3H, s, Si(CH_3)$_2$), 0.09 (3H, s, Si(CH_3)$_2$); δ_C (63 MHz, $CDCl_3$) 155.9 (C=O), 141.7 (C), 139.8 (C), 127.6, 126.7, 124.8, 124.4, 79.2 (NH(CO)O*C*(CH_3)$_3$), 73.9 (CH), 58.3 (CH), 40.4 (CH_2), 28.4 (NH(CO)OC(*C*H_3)$_3$), 25.7 (OSi(CH_3)$_2$C(*C*H_3)$_3$), 18.1 (OSi(CH_3)$_2$*C*(CH_3)$_3$), −5.0 (Si-(CH_3)$_2$); MS *m*/*z* (CI) 364 ([M + H]$^+$, 14%), 264 (69%), 250 (100%); HRMS: calc for $C_{20}H_{34}NO_3Si$: 364.2308, ([M + H]$^+$) found 364.2308.

(1*S*,2*R*)-(+)-*cis*-1-(*N*-Methyl)aminoindan-2-ol 15

To a mixture of sodium hydride (661 mg, 3.0 equiv., 16.53 mmol, 60%) in DMF (10 mL) at 0 °C was added a solution of (1*S*,2*R*)-(−)-*cis*-1-(*N*-*tert*-butoxycarbonyl)amino-2-(*tert*-butyldimethylsilyloxy)indane (2.0 g, 5.51 mmol) in DMF (10 mL) *via* cannula. After stirring the mixture for 30 minutes, methyl iodide (1.03 mL, 3.0 equiv., 16.53 mmol) was added at 0 °C. The mixture was warmed to rt and stirred for 12 h, after which time methanol (4 mL) and water (10 mL) were added. The solution was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed successively with water (60 mL) and brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was filtered through a column of silica gel (eluted with 5% v/v ethyl acetate–petrol) to afford a clear oil (1.77 g, 4.68 mmol), which was immediately dissolved in THF (15 mL)–EtOAc (5 mL). To this solution at 0 °C was added portionwise concentrated hydrochloric acid (15 mL). The mixture was warmed to rt and stirred for 2 h. The solvent was then removed *in vacuo* and the aqueous residue basified to pH 14 by the dropwise addition of 50% w/v aqueous sodium hydroxide solution at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed successively with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Amino alcohol (1*S*,2*R*)-**15** was obtained as a light beige solid (594 mg, 66% from the carbamate); mp 106–108 °C; $[a]_D^{22}$ +5.4 (*c* 1.43, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3305, 2672, 1493, 1338, 1316, 1177, 1115, 1056; δ_H (400 MHz, $CDCl_3$) 7.27–7.18 (4H, m, aryl H), 4.48 (1H, dt, *J* 5.4, 3.1, C*H*OH), 3.97 (1H, d, *J* 5.2, C*H*NCH$_3$), 3.33 (2H, br s, N*H*CH$_3$ and O*H*), 3.06 (1H, dd, *J* 16.4, 5.4, C*H*H), 2.97 (1H, dd, *J* 16.4, 3.1, CH*H*), 2.58 (3H, s, NHC*H*$_3$); δ_C (63 MHz, $CDCl_3$) 141.6 (C), 141.1 (C), 128.0, 126.6, 125.5, 123.8, 70.4 (CH), 67.3 (CH), 39.5 (CH_2), 34.8 (NCH_3); MS *m*/*z* (CI) 164 ([M + H]$^+$, 100%), 146 (10%), 104 (6%); HRMS: calc for $C_{10}H_{14}NO$: 164.1075, ([M + H]$^+$). found 164.1075.

(1*R*,2*S*)-(−)-Indene oxide 18

This compound was prepared according to a literature procedure.[11] A solution of (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)cyclohexane-1,2-diaminomanganese(III) chloride (1.54 g, 0.05 equiv., 2.42 mmol) and NMO (28.36 g, 5.0 equiv., 242.10 mmol) in dichloromethane (400 mL) was stirred at rt for 1 h. To this solution was then added indene (5.65 mL, 1.0 equiv., 48.4 mmol). The mixture was cooled to −78 °C and solid, precooled (−78 °C) MCPBA (16.71 g, 2.0 equiv., 96.84 mmol) was added in two equal portions over five minutes. The mixture was then stirred at −78 °C for 3 h before adding *via* cannula a precooled (−78 °C) solution of dimethyl sulfide (16.40 mL, 4.60 equiv., 222.7 mmol) in dichloromethane (80 mL). The solution was stirred for 10 minutes whilst slowly warming to rt and then aqueous sodium hydroxide solution (275 mL, 2.0 M) was added. The mixture was stirred for a further 15 minutes at rt after which the layers were separated. The organic layer was washed with water (300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% v/v ethyl acetate–petrol) followed by bulb-to-bulb distillation to afford (1*R*,2*S*)-

18 as a clear oil (3.72 g, 58%). The product was determined to be of 91% ee by ^{1}H NMR analysis using 10 mol% Eu(hfc)$_3$ (tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium(III) derivative); $[a]_D^{22}$ −38.4 (*c* 1.50, $CHCl_3$) (lit.[30] $[a]_D^{23}$ −40.3 (*c* 1.7, $CHCl_3$), 99% ee (1*R*,2*S*)); δ_H (250 MHz, $CDCl_3$) 7.50 (1H, d, *J* 7.0, aryl H), 7.33–7.16 (3H, m, aryl H), 4.27 (1H, d, *J* 2.9, C*H*(1)O), 4.13 (1H, t, *J* 2.9, C*H*(2)O), 3.23 (1H, d, *J* 18.0, C*H*H), 2.98 (1H, dd, *J* 18.0, 2.9, CH*H*).

(1*S*,2*S*)-(+)-*trans*-1-Azidoindan-2-ol 19[13]

A mixture of (1*R*,2*S*)-**18** (91% ee) (750 mg, 5.68 mmol), ammonium chloride (474 mg, 1.56 equiv., 8.86 mmol) and sodium azide (576 mg, 1.56 equiv., 8.86 mmol) in 80% v/v aqueous ethanol (20 mL) was refluxed for 2 h. After cooling, water (20 mL) was added to the mixture and the solution extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% v/v ethyl acetate–petrol) to afford (1*S*,2*S*)-**19** as a brown oil (831 mg, 84%). The product was determined to be of 92% ee by HPLC analysis (Chiralcel OD, propan-2-ol–hexane = 5 : 95 (0.5 mL min^{-1}), (1*S*,2*S*) isomer 25.1 min, (1*R*,2*R*) isomer 30.6 min); $[a]_D^{22}$ +71.3 (*c* 0.86, $CHCl_3$) (lit.[13] $[a]_D^{23}$ +78.3 (*c* 1.9, $CHCl_3$), 99% ee (1*S*,2*S*)); δ_H (250 MHz, $CDCl_3$) 7.39–7.23 (4H, m, aryl H), 4.70 (1H, d, *J* 4.9, CHN_3), 4.53–4.47 (1H, m, C*H*OH), 3.30 (1H, dd, *J* 15.9 and 6.7, C*H*H), 2.88 (1H, dd, *J* 15.9 and 6.1, CH*H*), 2.16 (1H, br s, OH).

(1*S*,2*S*)-(+)-*trans*-1-Aminoindan-2-ol 17[10]

To a stirred solution of tin(II) chloride dihydrate (1.35 mg, 3.0 equiv., 6.0 mmol) in THF (20 mL)–water (10 mL) at 0 °C was added a solution of (1*S*,2*S*)-**19** (92% ee) (350 mg, 1.0 equiv., 2.0 mmol) in THF (10 mL). The mixture was warmed to rt and stirred for 24 h. The solvent was then removed *in vacuo* and the residue dissolved in 10% v/v aqueous hydrochloric acid solution (15 mL). The acidic aqueous phase was then extracted with ether (3 × 20 mL). The combined ethereal extracts were discarded and the aqueous layer basified to pH 14 by the dropwise addition of 2 M aqueous sodium hydroxide solution at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford (1*S*,2*S*)-**17** as a light beige solid (212 mg, 71%). The product was determined to be 93% ee by HPLC analysis of the corresponding *N*-Boc derivative **20** (see below); $[a]_D^{22}$ +25.0 (*c* 0.14, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.34–7.17 (4H, m, aryl H), 4.20–4.08 (2H, m, 2 × CH), 3.21 (1H, dd, *J* 15.6, 6.7, C*H*H), 2.83 (1H, dd, *J* 15.6, 7.8, CHH), 2.37 (3H, br s, NH_2 and O*H* (exchangeable with D_2O)).

(±)-*trans*-1-(*N*-*tert*-Butyloxycarbonyl)aminoindan-2-ol 20

To a stirred solution of (±)-**17** (prepared from the racemic epoxide using the method described above) (135 mg, 0.91 mmol) in dichloromethane (4 mL) at 0 °C were added triethylamine (0.14 mL, 1.10 equiv., 1.0 mmol) and a solution of di-*tert*-butyl dicarbonate (198 mg, 1.0 equiv., 0.91 mmol) in dichloromethane (2 mL). The mixture was warmed to rt and stirred for 5 h. The solution was diluted with dichloromethane (15 mL) and water (10 mL). The separated aqueous layer was extracted with dichloromethane (15 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40% v/v ethyl acetate–petrol) to afford (±)-**20** as a white solid (167 mg, 74%); mp 113–114 °C; analysis ($C_{14}H_{19}NO_3$): calc. C 67.47, H 7.63, N 5.62. found C 67.49, H 7.70, N 5.45%; ν_{max}(Nujol)/cm^{-1} 3407, 3293, 2359, 1679, 1536, 1271, 1170, 1078; δ_H (250 MHz, $CDCl_3$) 7.28–7.17 (4H, m, aryl H), 5.09 (1H, br d, NH), 4.90 (1H, t, *J* 5.8, C*H*NHBoc), 4.44–4.28 (2H, m, C*H*OH and O*H*), 3.27 (1H, dd, *J* 15.9 and 7.6, C*H*H), 2.90 (1H, dd, *J* 15.9 and 7.9, CH*H*), 1.49 (9H, s, $C(CH_3)_3$); δ_C (63 MHz, $CDCl_3$) 157.3 (C=O), 140.1 (4° C), 139.3 (4° C), 128.4, 127.1, 125.1, 123.0, 81.9, 80.4, 64.0, 38.3 (CH_2), 28.3 ($C(CH_3)_3$); MS *m*/*z* (CI) 250 ([M + H]$^+$, 72%), 211 (100%), 150 (91%). HPLC data are given in the next section.

(1*S*,2*S*)-(−)-*trans*-1-(*N*-*tert*-Butyloxycarbonyl)aminoindan-2-ol 20

To a stirred solution of (1*S*,2*S*)-**17** (11 mg, 0.07 mmol) in dichloromethane (1 mL) at 0 °C was added triethylamine (0.01 mL, 1.10 equiv., 0.08 mmol) and solid di-*tert*-butyl dicarbonate (15 mg, 1.0 equiv., 0.07 mmol). The mixture was warmed to rt and stirred for 12 h. The solution was applied directly to a short silica gel column (eluting with 50% v/v ethyl acetate–petrol) to afford (1*S*,2*S*)-**20** as a white solid. The product was determined to be of 93% ee by HPLC analysis (Chiralcel OD, propan-2-ol–hexane = 2 : 98 (0.9 mL min^{-1}), (1*R*,2*R*) isomer 19.4 min, (1*S*,2*S*) isomer 23.3 min); $[a]_D^{26}$ −51.3 (*c* 0.15, $CHCl_3$).

(±)-*trans*-2-Bromoindan-1-ol 28

This compound was prepared according to a literature procedure.[13] To a stirred solution of indene (53.00 g, 456.27 mmol, 90% tech grade) in 50% v/v aqueous THF (700 mL) was added *N*-bromosuccinimide (89.33 g, 1.10 equiv., 501.90 mmol) portionwise at rt. The mixture was stirred at rt for 16 h, after which time brine (200 mL) was added. The separated aqueous layer was extracted with ethyl acetate (2 × 300 mL). The combined organic extracts were washed with 5% w/v aqueous sodium thiosulfate solution (400 mL) and brine (300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was recrystallised from ethyl acetate to afford (±)-**28** as a white solid (74.0 g, 85%); δ_H (250 MHz, $CDCl_3$) 7.46–7.12 (4H, m, aryl H), 5.29 (1H, d, *J* 5.8, C*H*OH), 4.26 (1H, obs q, *J* 5.8, C*H*Br), 3.57 (1H, dd, *J* 16.3, 7.0, C*H*H), 3.19 (1H, dd, *J* 16.3, 7.3, CH*H*), 2.73 (1H, br s, OH).

(±)-Indene oxide 18

This compound was prepared according to a literature procedure.[13] To a stirred solution of bromohydrin (±)-**28** (74.0 g, 347.0 mmol) in ether (700 mL) at rt was added powdered sodium hydroxide (34.7 g, 2.50 equiv., 868 mmol) portionwise. The suspension was stirred at rt for 12 h. To the mixture was added water (200 mL) and the separated aqueous layer extracted with ether (250 mL). The combined organic extracts were washed successively with water (250 mL) and brine (250 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2.5⟶5% v/v ethyl acetate–petrol) to afford (±)-**18** as a clear oil (35.29 g, 77%).

(±)-*trans*-1-Azidoindan-2-ol 19

This compound was prepared according to a literature procedure.[13] A mixture of (±)-**18** (500 mg, 3.79 mmol), ammonium chloride (316 mg, 1.56 equiv., 5.91 mmol) and sodium azide (384 mg, 1.56 equiv., 5.91 mmol) in 80% v/v aqueous ethanol (12 mL) was refluxed for 2 h. After cooling, water (10 mL) was added to the mixture and the solution extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% v/v ethyl acetate–petrol) to afford (±)-**19** as a brown oil (495 mg, 75%).

(±)-*trans*-1-Azido-2-(*p*-tolylsulfonyloxy)indane 29

To a stirred solution of (±)-**19** (500 mg, 2.86 mmol) in dichloromethane (10 mL) at 0 °C were added sequentially triethylamine

(0.80 mL, 2.0 equiv., 5.71 mmol), tosyl chloride (545 mg, 1.0 equiv., 2.86 mmol) and DMAP (35 mg, 0.10 equiv., 0.29 mmol). The mixture was warmed to rt and stirred for 16 h. The solution was then diluted with dichloromethane (20 mL) and washed successively with 5% v/v aqueous hydrochloric acid solution (10 mL), 5% w/v aqueous sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic extract was then dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (10% v/v ethyl acetate–petrol) to afford (±)-**29** as a white solid (691 mg, 74%); mp 71–72 °C (found C 58.15; H 4.56; N 12.85. calc for $C_{16}H_{15}N_3O_3S$ C 58.36; H 4.56; N 12.77%); ν_{max}(Nujol)/cm^{-1} 2108, 1596, 1372, 1181; δ_H (250 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.6, $SO_2(C_6H_4)CH_3$), 7.37 (2H, d, *J* 8.6, $SO_2(C_6H_4)CH_3$), 7.35–7.24 (3H, m, aryl H), 7.22–7.18 (1H, m, aryl H), 4.98–4.89 (2H, m, 2 × CH), 3.36 (1H, dd, *J* 16.8, 6.7, C*H*H), 3.05 (1H, dd, *J* 16.8, 5.5, CH*H*), 2.47 (1H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 145.2, 138.5, 136.5, 133.2, 130.0, 129.6, 127.9, 127.8, 125.1, 124.6, 85.2, 69.3, 36.9, 21.6; MS *m*/*z* (CI) 347 ([M + NH_4]$^+$, 42%), 302 (33%), 287 (73%), 155 (37%), 129 (100%), 91 (57%), 65 (17%).

(1*S*,2*S*)-(+)-*trans*-1-Azido-2-(*p*-tolylsulfonyloxy)indane 29

This compound was prepared according to the procedure employed for (±)-**29** using (1*S*,2*S*)-**19** (91% ee) (2.00 g, 11.43 mmol), tosyl chloride (2.18 g, 1.0 equiv., 11.43 mmol), triethylamine (3.20 mL, 2.0 equiv., 22.86 mmol) and DMAP (139 mg, 0.10 equiv., 1.14 mmol) in dichloromethane (15 mL) for 17 h at rt. The product was a light beige solid (1*S*,2*S*)-**29** (3.02 g, 80%) and determined to be of 91% ee by HPLC analysis (Chiralcel OD, propan-2-ol–hexane = 5 : 95 (0.5 mL min^{-1}), (1*S*,2*S*) isomer 18.8 min, (1*R*,2*R*) isomer 24.8 min); $[\alpha]_D^{28}$ +46.1 (*c* 0.80, $CHCl_3$).

(±)-*trans*-1-Amino-2-(*p*-tolylsulfonyloxy)indane 30

To a stirred solution of tin(II) chloride dihydrate (1.32 g, 3.0 equiv., 5.84 mmol) in THF (20 mL)–water (10 mL) at 0 °C was added a solution of (±)-**29** (640 mg, 1.0 equiv., 1.95 mmol) in THF (10 mL). The mixture was warmed to rt and stirred for 16 h. The solution was basified to pH 14 by the dropwise addition of 2 M aqueous sodium hydroxide solution at 0 °C. The aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (60% v/v ethyl acetate–petrol) to afford (±)-**30** as a white solid (494 mg, 84%); mp 202–204 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 3448, 1598, 1528, 1195, 1126; δ_H (250 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0, $SO_2(C_6H_4)CH_3$), 7.37 (2H, d, *J* 8.0, $SO_2(C_6H_4)CH_3$), 7.33–7.02 (4H, m, aryl H), 4.74 (1H, obs q, *J* 7.0, C*H*OTs), 4.46 (1H, d, *J* 6.4, C*H*NH_2), 3.18 (1H, dd, *J* 16.0, 7.6, C*H*H), 2.94 (1H, dd, *J* 16.0, 7.6, CH*H*), 2.33 (2H, br s, NH_2); δ_C (63 MHz, DMSO-d_6) 145.6, 139.5, 135.2, 132.6, 130.5, 130.0, 128.3, 127.8, 125.6, 125.2, 83.3, 59.2, 36.6, 20.9; MS *m*/*z* (CI) 304 ([M + H]$^+$, 2%), 244 (4%), 149 (7%), 132 (100%), 116 (2%), 108 (5%); HRMS: calc for $C_{16}H_{18}NO_3S$ 304.1007, ([M + H]$^+$) found 304.1007.

(±)-*trans*-*N*,*O*-Bis(*p*-tolylsulfonyl)-1-aminoindan-2-ol 31

To a stirred solution of (±)-**30** (300 mg, 0.99 mmol) in dichloromethane (10 mL) at 0 °C were added sequentially triethylamine (0.28 mL, 2.0 equiv., 1.98 mmol), tosyl chloride (189 mg, 1.0 equiv., 0.99 mmol) and DMAP (12 mg, 0.10 equiv., 0.01 mmol). The mixture was warmed to rt and stirred for 16 h. The solution was then diluted with dichloromethane (10 mL) and washed successively with 5% v/v aqueous hydrochloric acid solution (10 mL), 5% w/v aqueous sodium bicarbonate solution (10 mL) and brine (10 mL). The organic extract was then dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (10⟶20% v/v ethyl acetate–petrol) to afford (±)-**31** as a white solid (186 mg, 41%); mp 165–166 °C; ν_{max}(Nujol)/cm^{-1} 3242, 1596, 1359, 1149, 1091, 995; δ_H (250 MHz, $CDCl_3$) 7.78 (4H, d, *J* 8.4, aryl H), 7.39–7.12 (7H, m, aryl H), 6.99 (1H, d, *J* 7.0, aryl H), 4.92 (1H, m, C*H*OTs), 4.80 (1H, m, C*H*NTs), 4.64 (1H, d, *J* 7.0, NH), 3.22 (1H, dd, *J* 16.3, 6.6, C*H*H), 2.95 (1H, dd, *J* 16.3, 5.1, C*H*H), 2.47 (6H, s, 2 × CH_3); δ_C (63 MHz, $CDCl_3$) 145.0, 143.7, 138.4, 137.8, 137.1, 133.1, 129.9, 129.8, 129.3, 128.1, 127.8, 127.3, 125.0, 124.5, 85.4 (CH), 62.9 (CH), 36.4 (CH_2), 21.7 (CH_3), 21.6 (CH_3); MS *m*/*z* (CI) 475 ([M + NH_4]$^+$, 3%), 406 (2%), 347 (6%), 303 (10%), 286 (100%), 22 (7%). HRMS: calc for $C_{23}H_{27}N_2O_5S_2$: 475.1361, ([M + NH_4]$^+$) found 475.1361.

(±)-*trans*-1-Aminoindan-2-ol 17[10]

To a stirred solution of tin(II) chloride dihydrate (387 mg, 3.0 equiv., 1.71 mmol) in THF (5 mL)–water (3 mL) at 0 °C was added a solution of (±)-**19** (100 mg, 1.0 equiv., 0.57 mmol) in THF (3 mL). The mixture was warmed to rt and stirred for 18 h. The solvent was then removed *in vacuo* and the residue dissolved in dilute hydrochloric acid (5 mL, 2 M). The acidic aqueous phase was then extracted with ether (2 × 15 mL). The combined ethereal extracts were discarded and the aqueous layer basified to pH 14 by the dropwise addition of 2 M aqueous sodium hydroxide solution at 0 °C. The aqueous layer was extracted with ethyl acetate (5 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford (±)-**17** as a beige solid (70 mg, 82%).

(±)-*N*-Tosyl-1,1a,6,6a-tetrahydroindeno[1,2-*b*]azirene 26[16]

To a stirred solution of (±)-**31** (150 mg, 0.33 mmol) in THF (5 mL) at 0 °C was added sodium hydride (26 mg, 2.0 equiv., 0.66 mmol, 60%). The mixture was warmed to rt and stirred for 22 h. To the suspension was added water (10 mL) and the separated aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic extract was washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (15% v/v ethyl acetate–petrol) to afford (±)-**26** as a white solid (58 mg, 64%); δ_H (250 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.2, aryl H), 7.40 (1H, d, *J* 6.7, aryl H), 7.32 (2H, d, *J* 8.2, aryl H), 7.29–7.14 (3H, m, aryl H), 4.30 (1H, d, *J* 5.2, C*H(1)*NTs), 3.92–3.88 (1H, m, C*H(2)*NTs), 3.14 (2H, obs br s, CH_2), 2.44 (3H, s, CH_3).

(±)-*trans*-1-Azido-2-(*p*-tolylsulfonylamino)indane 32

A mixture of (±)-**26** (55 mg, 0.19 mmol) and sodium azide (20 mg, 1.60 equiv., 0.31 mmol) in 80% v/v aqueous ethanol (4 mL) was refluxed for 7 h. Following cooling, brine (10 mL) was added and the separated aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% v/v ethyl acetate–petrol) to afford (±)-**32** as a gummy beige solid (61 mg, 95%); mp 71–73 °C; ν_{max}(Nujol)/cm^{-1} 3259, 2097, 1322, 1161, 1087; δ_H (250 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.0, $SO_2(C_6H_4)CH_3$), 7.32 (2H, d, *J* 8.0, $SO_2(C_6H_4)CH_3$), 7.29–7.17 (3H, m, aryl H), 7.15 (1H, m, aryl H), 5.72 (1H, d, *J* 7.9), 4.66 (1H, d, *J* 6.1), 3.86 (1H, obs quintet, *J* 7.1, C*H*NHTs), 3.16 (1H, dd, *J* 16.6, 7.6, C*H*H), 2.71 (1H, dd, *J* 16.0, 7.0, CH*H*), 2.44 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 143.8 (C), 139.2 (C), 137.7 (C), 137.0 (C), 129.8, 129.2, 127.5, 127.1, 125.0, 124.4, 70.1 (CH), 60.5 (CH), 37.4 (CH_2), 21.5 (CH_3); MS *m*/*z* (CI) 346 ([M + NH_4]$^+$, 4%), 318 (4%), 301 (23%), 189 (7%), 145 (100%), 91 (10%); HRMS: calc for $C_{16}H_{20}N_5O_2S$: 346.1338, ([M + NH_4]$^+$) found 346.1338.

(±)-*cis*-1,2-Diazidoindane 34

A mixture of (±)-**29** (300 mg, 0.91 mmol) and sodium azide (89 mg, 1.50 equiv., 1.37 mmol) in DMF (3 mL) was heated at

100 °C for 14 h. Following cooling, water (5 mL) and brine (10 mL) were added and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2.5% v/v ethyl acetate–petrol) to afford (±)-**34** as a light beige oil (138 mg, 76%); ν_{max}(Nujol)/cm^{-1} 2100, 1324, 1266; δ_H (250 MHz, $CDCl_3$) 7.39–7.29 (4H, m, aryl H), 4.78 (1H, d, *J* 5.5, C*H(1)*N_3), 4.23 (1H, dt, *J* 6.4, 5.5, C*H(2)*N_3), 3.12 (2H, d, *J* 6.4, CH_2); δ_C (63 MHz, $CDCl_3$) 139.5 (C), 137.3 (C), 129.5, 127.5, 125.2, 124.7, 66.8 (CH), 63.9 (CH), 35.4 (CH_2); MS *m*/*z* (CI) 218 ([M + NH_4]$^+$, 12%), 175 (40%), 145 (96%), 130 (100%), 90 (81%), 63 (36%); HRMS: calc for $C_9H_{12}N_7$: 218.1154, ([M + NH_4]$^+$) found 218.1154.

(1*S*,2*R*)-(+)-*cis*-1,2-Diazidoindane 34

This compound was prepared according to the procedure employed for (±)-**34** using (1S,2S)-**29** (91% ee) (2.00 g, 6.08 mmol) and sodium azide (593 mg, 1.50 equiv., 9.12 mmol) in DMF (20 mL) for 16 h at 100 °C. The product (1*S*,2*R*)-**34** was a light beige oil (930 mg, 76%). The product was determined to be of 91% ee by HPLC analysis (Chiralcel OD, propan-2-ol–hexane = 5 : 95 (0.7 mL min^{-1}), (1*S*,2*R*) isomer 12.3 min, (1*R*,2*S*) isomer 21.9 min); $[\alpha]_D^{28}$ +52.4 (*c* 0.55, $CHCl_3$).

(±)-*cis*-1,2-Diaminoindane 35

A solution of (±)-**34** (150 mg, 0.75 mmol) in ethanol (4 mL) was hydrogenated on 10% Pd/C (15 mg, 10% w/w) for 3 h. After removal of the catalyst by suction filtration through Celite (filter cake washed with ethyl acetate, 10 mL), the solvent was removed *in vacuo* to afford (±)-**35** as a low melting brown solid (99 mg, 89%); ν_{max}(Nujol)/cm^{-1} 3354, 2933, 1588; δ_H (250 MHz, $CDCl_3$) 7.35–7.16 (4H, m, aryl H), 4.19 (1H, d, *J* 5.5, C*H(1)*NH_2), 3.66 (1H, dt, *J* 6.0, 4.0, C*H(2)*NH_2), 3.08 (1H, dd, *J* 15.9, 6.0, C*H*H), 2.72 (1H, dd, *J* 15.9, 4.0, CH*H*), 1.45 (4H, br s, 2 × NH_2); δ_C (63 MHz, $CDCl_3$) 144.7 (C), 140.7 (C), 127.4, 126.6, 124.9, 124.1, 58.9 (CH), 55.8 (CH), 39.0 (CH_2); MS *m*/*z* (CI) 149 ([M + H]$^+$, 50%), 132 (100%), 119 (16%), 106 (16%); HRMS: calc for $C_9H_{13}N_2$: 149.1079, ([M + H]$^+$) found 149.1079.

(1*S*,2*R*)-(−)-*cis*-1,2-Diaminoindane 35

This compound was prepared according to the procedure employed for (±)-**35** using (1*S*,2*R*)-**34** (91% ee) (870 mg, 4.35 mmol) and 10% Pd/C (87 mg, 10% w/w) in ethanol (20 mL) under hydrogen for 3 h at rt. The product was an orange glassy solid (1*S*,2*R*)-**35** (560 mg, 87%); $[\alpha]_D^{24}$ −52.5 (*c* 0.40, $CHCl_3$).

(±)-*cis*-1-Azidoindan-2-ol 37

This compound was prepared according to a literature procedure.[13] To a stirred solution of (±)-**19** (2.00 g, 11.43 mmol) and 4-nitrobenzoic acid (3.82 g, 2.0 equiv., 22.86 mmol) in THF (40 mL) at 0 °C were simultaneously added dropwise triphenylphosphine (6.00 g, 2.0 equiv., 22.86 mmol) in THF (20 mL) and DEAD (3.60 mL, 2.0 equiv., 22.86 mmol) in THF (20 mL) over 20 minutes. The mixture was stirred at 0 °C for 30 minutes and then warmed to rt and stirred for 3 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (0⟶15% v/v ethyl acetate–petrol) to afford the (±)-*cis*-benzoate as a white solid (2.07 g, 56%). A solution of sodium methoxide in methanol was prepared by the portionwise addition of sodium (437 mg, 3.0 equiv., 18.9 mmol) to methanol (40 mL) at 0 °C. To this stirred solution was added a solution of the previously prepared (±)-*cis*-benzoate (2.05 g, 6.33 mmol) in dichloromethane (30 mL) dropwise at rt. The mixture was stirred at rt for 1.5 h after which time the solvent was removed *in vacuo*. Brine (30 mL) was added to the residue, which was then extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (5⟶20% v/v ethyl acetate–petrol) to afford (±)-**37** as a clear oil (1.02 g, 92%); δ_H (250 MHz, $CDCl_3$) 7.43–7.25 (4H, m, aryl H), 4.80 (1H, d, *J* 5.5, CHN_3), 4.64–4.57 (1H, m, C*H*OH), 3.18 (1H, dd, *J* 15.9, 6.1, C*H*H), 2.88 (1H, dd, *J* 15.9, 5.8, CH*H*), 2.35 (1H, br s, OH).

(±)-*cis*-1-Azido-2-(*p*-tolylsulfonyloxy)indane 33

To a stirred solution of (±)-**37** (1.10 g, 6.29 mmol) in dichloromethane (10 mL) at 0 °C were added sequentially triethylamine (1.75 mL, 2.0 equiv., 12.57 mmol), solid tosyl chloride (1.20 g, 1.0 equiv., 6.29 mmol) and solid DMAP (77 mg, 0.10 equiv., 0.63 mmol). The mixture was warmed to rt and stirred for 15 h. The solution was then diluted with dichloromethane (20 mL) and washed successively with 5% v/v aqueous hydrochloric acid solution (10 mL), 5% w/v aqueous sodium hydrogen carbonate solution (10 mL) and brine (10 mL). The organic extract was then dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (10% v/v ethyl acetate–petrol) to afford (±)-**33** as a white solid (1.65 g, 80%); mp 71–73 °C; ν_{max}(Nujol)/cm^{-1} 2105, 1593, 1352, 1176; δ_H (250 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.5, $SO_2(C_6H_4)CH_3$), 7.40–7.22 (6H, m, aryl H), 5.22 (1H, obs q, *J* 6.0, C*H*OTs), 4.69 (1H, d, *J* 5.5, CHN_3), 3.24 (1H, dd, *J* 16.2, 6.1, C*H*H), 3.11 (1H, dd, *J* 16.2, 6.7, CH*H*), 2.47 (1H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 145.2, 138.5, 136.6, 133.3, 129.9, 129.8, 127.9, 127.8, 125.3, 124.8, 80.7, 65.3, 36.5, 21.6; MS *m*/*z* (CI) 347 ([M + NH_4]$^+$, 18%), 302 (15%), 287 (64%), 190 (5%), 146 (29%), 132 (100%), 91 (17%), 65 (6%); HRMS: calc for $C_{16}H_{19}N_4O_3S$: 347.1178, ([M + NH_4]$^+$) found 347.1178.

(±)-*trans*-1,2-Diazidoindane 38

This compound was prepared according to the procedure employed for **34** using (±)-**33** (870 mg, 2.64 mmol) and sodium azide (258 mg, 1.50 equiv., 3.97 mmol) in DMF (4 mL) for 16 h at 100 °C. The product was a yellow oil (±)-**38** (130 mg, 25%); ν_{max}(Nujol)/cm^{-1} 2106, 1476, 1256; δ_H (250 MHz, $CDCl_3$) 7.39–7.22 (4H, m, aryl H), 4.74 (1H, d, *J* 5.8, C*H(1)*N_3), 4.15 (1H, obs q, *J* 6.5, C*H(2)*N_3), 3.32 (1H, dd, *J* 15.9, 7.2, C*H*H), 2.93 (1H, dd, *J* 15.9, 6.9, CH*H*); δ_C (63 MHz, $CDCl_3$) 139.0 (C), 137.7 (C), 129.4, 127.7, 125.1, 124.5, 70.2 (CH), 67.6 (CH), 36.0 (CH_2). The compound was immediately hydrogenated (see below).

(±)-*trans*-1,2-Diaminoindane 36

This compound was prepared according to the procedure employed for **35** using (±)-**38** (130 mg, 0.65 mmol) and 10% Pd/C (13 mg, 10% w/w) in ethanol (4 mL) under hydrogen for 3 h at rt. The product (±)-**36** was a low melting brown solid (68 mg, 71%); ν_{max}(Nujol)/cm^{-1} 3342, 1593; δ_H (250 MHz, $CDCl_3$) 7.29–7.15 (4H, m, aryl H), 3.81 (1H, d, *J* 7.3, C*H(1)*NH_2), 3.22–3.08 (2H, m, C*H(2)*NH_2 and C*H*H), 2.65–2.52 (1H, m, CH*H*), 1.45 (4H, br s, 2 × NH_2); δ_C (63 MHz, $CDCl_3$) 145.3 (C), 139.8 (C), 127.2, 126.6, 124.4, 123.0, 65.1 (CH), 64.3 (CH), 39.4 (CH_2); MS *m*/*z* (CI) 149 ([M + H]$^+$, 28%), 132 (100%); HRMS: calc for $C_9H_{13}N_2$: 149.1079, ([M + H]$^+$) found 149.1079.

(±)-*cis*-1-Amino-2-(*p*-tolylsulfonylamino)indane 24 and (±)-*cis*-1-(*p*-tolylsulfonylamino)-2-aminoindane 25

To a stirred solution of (±)-**36** (200 mg, 1.35 mmol) in dichloromethane (5 mL) at 0 °C was added tosyl chloride (244 mg, 0.95 equiv., 1.28 mmol). The mixture was warmed slowly to rt and stirred for 16 h. The solution was then concentrated *in vacuo* and the residue dissolved in ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The

separated aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the regioisomers **24** and **25** as light brown solids (115 mg, **24**; 18 mg, **25**).

Compound 24. Mp 126–127 °C; ν_{max}(Nujol)/cm^{-1} 3338, 3283, 3027, 1325, 1148, 1125; δ_H (250 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0, $NSO_2(C_6H_4)CH_3$), 7.29 (2H, d, *J* 8.0, $NSO_2(C_6H_4)CH_3$), 7.20–7.08 (4H, m, aryl H), 4.08 (1H, d, *J* 6.1, C*H*NH_2), 3.87 (1H, obs q, *J* 6.7, C*H*NHTs), 2.90 (1H, dd, *J* 16.2, 7.2, C*H*H), 2.77 (1H, dd, *J* 16.2, 6.9, C*H*H), 2.42 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 143.6, 143.2, 139.6, 137.6, 129.6, 128.0, 127.0, 126.9, 124.8, 124.1, 56.8 (CH), 56.6 (CH), 36.9 (CH_2), 21.4 (CH_3); MS *m*/*z* (CI) 303 ([M + H]$^+$, 85%), 145 (100%); HRMS: calc for $C_{16}H_{19}N_2O_2S$: 303.1167, ([M + H]$^+$) found 303.1167.

Compound 25. Mp 146–148 °C; ν_{max}(Nujol)/cm^{-1} 3346, 3026, 2359, 1596, 1326, 1157, 1019; δ_H (250 MHz, $CDCl_3$) 7.84 (2H, d, *J* 8.4, $NSO_2(C_6H_4)CH_3$), 7.34 (2H, d, *J* 8.4, $NSO_2(C_6H_4)CH_3$), 7.30–7.01 (4H, m, aryl H), 4.58 (1H, d, *J* 5.5, C*H*NH_2), 3.52 (1H, dt, *J* 6.0, 3.2, C*H*NHTs), 3.05 (1H, dd, *J* 16.2, 6.0, C*H*H), 2.63 (1H, dd, *J* 16.0, 2.9, C*H*H), 2.45 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 143.5, 140.4, 140.0, 138.0, 129.8, 128.3, 127.5, 127.1, 125.2, 124.9, 60.8 (CH), 54.2 (CH), 39.8 (CH_2), 21.5 (CH_3); MS *m*/*z* (CI) 303 ([M + H]$^+$, 99%), 147 (520%), 130 (100%); HRMS: calc for $C_{16}H_{19}N_2O_2S$: 303.1167, ([M + H]$^+$) found 303.1167.

(1*S*,2*R*)-*cis*-1-Azidoindan-2-ol 37

To a stirred solution of (1*S*,2*S*)-**19** (2.00 g, 11.43 mmol) and 4-nitrobenzoic acid (3.82 g, 22.86 mmol) in THF (40 mL) at 0 °C were simultaneously added dropwise triphenylphosphine (6.00 g, 22.86 mmol) in THF (20 mL) and DEAD (3.98 mL, 22.86 mmol) in THF (20 mL) over 20 minutes. The mixture was stirred at 0 °C for 30 minutes and then warmed to rt and stirred for 3 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (0⟶15% v/v ethyl acetate–petrol) to afford the (1*S*,2*R*)-*cis*-benzoate as a white solid (1.44 g, 39%). A solution of sodium methoxide in methanol was prepared by the portionwise addition of sodium (256 mg, 11.14 mmol) to methanol (25 mL) at 0 °C. To this stirred solution was added a solution of the previously prepared (1*S*,2*R*)-*cis*-benzoate (1.20 g, 3.70 mmol) in dichloromethane (18 mL) dropwise at rt. The mixture was stirred at rt for 2 h after which time the solvent was removed *in vacuo*. Brine (30 mL) was added to the residue, which was then extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (5⟶20% v/v ethyl acetate–petrol) to afford (1*S*,2*R*)-**37** as a clear yellow oil (600 mg, 93 %); $[\alpha]_D^{24}$ +58.9 (*c* 1.0, chloroform); δ_H (250 MHz, $CDCl_3$) 2.36 (1H, d, *J* 7.9, OH), 2.94 (1H, dd, *J* 16.2, 6.1, CH*H*), 3.17 (1H, dd, *J* 15.9, 6.4, C*H*H), 4.55–4.65 (1H, m, C*H*OH), 4.79 (1H, d, *J* 5.5, C*H*N_3), 7.25–7.45 (4H, m, aryl H); 98% ee determined by HPLC analysis (Chiralcel OD, 5% propan-2-ol–hexane, 0.1% diethylamine, 0.5 mL min^{-1}), R_t 24.8 min (1*S*,2*R*) and 17.1 min (1*R*,2*S*).

(1*S*,2*R*)-*cis*-1-Azido-2-(*p*-tolylsulfonyloxy)indane 33

This compound was prepared according to the procedure employed for (1*S*,2*S*)-**29** using (1*S*,2*R*)-**37** (580 g, 3.31 mmol), triethylamine (0.92 mL, 6.62 mmol), tosyl chloride (630 g, 3.31 mmol) and DMAP (40 mg, 0.33 mmol) in dichloromethane (15 mL) for 20 h at rt. The product (1*S*,2*R*)-**33** was a light beige, viscous oil (1.03 g, 95%); $[\alpha]_D^{25}$ +30.9 (*c* 0.45, chloroform); δ_H (250 MHz, $CDCl_3$) 2.46 (3H, s, CH_3), 3.11 (1H, dd, *J* 16.3, 6.4, CH*H*), 3.23 (1H, dd, *J* 16.2, 6.1, C*H*H), 4.69 (1H, d, *J* 5.5, C*H*N_3), 5.21 (1H, dt, *J* 6.4, 5.5, C*H*OTs), 7.20–7.35 (4H, m, aryl H), 7.37 (2H, d, *J* 8.2, $SO_2(C_6H_4)CH_3$), 7.87 (2H, d, *J* 8.2, $SO_2(C_6H_4)CH_3$); 97% ee determined by chiral HPLC analysis (Chiralcel OD, 5% propan-2-ol–hexane, 0.1% diethylamine, 0.5 mL min^{-1}), R_t 31.2 min (1*S*,2*R*) and 39.2 min (1*R*,2*S*).

(1*S*,2*S*)-*trans*-1,2-Diazidoindane 38

This compound was prepared according to the procedure employed for (1*S*,2*R*)-**34** using (1*S*,2*R*)-**33** (1.00 g, 3.04 mmol) and sodium azide (300 g, 4.56 mmol) in DMF (10 mL) for 20 h at 100 °C. The product (1*S*,2*S*)-**38** was a light beige oil (200 mg, 33%); $[\alpha]_D^{24}$ +63.8 (*c* 0.26, chloroform); δ_H (250 MHz, $CDCl_3$) 2.95 (1H, dd, *J* 16.2, 6.7, CH*H*), 3.35 (1H, dd, *J* 16.2, 7.3, C*H*H), 4.17 (1H, dt, *J* 5.8, 6.7, C*H*(2)N_3), 4.77 (1H, d, *J* 5.8, C*H*(1)N_3), 7.23–7.41 (4H, m, aryl H); 97% ee determined by chiral HPLC analysis (Chiralcel OD, 5% propan-2-ol–hexane, 0.1% diethylamine, 0.7 mL min^{-1}), R_t 10.1 min (1*S*,2*S*) and 16.3 min (1*R*,2*R*).

(1*S*,2*S*)-*trans*-1,2-Diaminoindane 36

This compound was prepared according to the procedure employed for (1*S*,2*R*)-**35** using (1*S*,2*S*)-**38** (170 mg, 0.85 mmol) and 10% Pd/C (17 mg, 10% w/w) in ethanol (5 mL) under hydrogen for 3 h at rt. The product (1*S*,2*S*)-**36** was a glassy orange solid (120 mg, 95%); $[\alpha]_D^{25}$ −485.6 (*c* 0.25, chloroform); δ_H (250 MHz, $CDCl_3$) 1.62 (4H, br s, 2 × NH_2), 2.53–2.69 (1H, m, CH*H*), 3.10–3.17 (2H, m, C*H*(2)NH_2 and C*H*H), 3.84 (1H, d, *J* 7.6, C*H*(1)NH_2), 7.15–7.34 (4H, m, aryl H).

(1*S*,2*S*)-*trans*-1-Amino-2-(*p*-tolylsulfonylamino)indane 24 and (1*S*,2*S*)-*trans*-1-(*p*-tolylsulfonylamino)-2-aminoindane 25

These compounds were prepared according to the procedure employed for (1*S*,2*R*)-**22** and **23** using (1*S*,2*S*)-**36** (74 mg, 0.50 mmol) and tosyl chloride (95 mg, 0.99 equiv., 0.49 mmol) in dichloromethane (3 mL) for 3 h at 0 °C. The product was a brown solid (30 mg, 20%). ^{1}H NMR analysis of the crude product showed the presence of a regioisomeric mixture of monosulfonamides (1*S*,2*S*)-**24** and (1*S*,2*S*)-**25** in a ratio of approximately 10 : 1.

Compound (1*S*,2*S*)-24. δ_H (250 MHz, $CDCl_3$) 1.76 (3H, br s, NH and NH_2), 2.44 (3H, s, CH_3), 2.63 (1H, dd, *J* 15.4 and 9.2, CH*H*), 3.03 (1H, dd, *J* 15.4 and 7.6, C*H*H), 3.43 (1H, obs dt, *J* 7.9 and 8.9, C*H*NHTs), 4.09 (1H, d, *J* 8.6, C*H*NH_2), 7.07–7.30 (4H, m, aryl H), 7.33 (2H, d, *J* 7.9, $NSO_2(C_6H_4)CH_3$), 7.82 (2H, d, *J* 8.2, $NSO_2(C_6H_4)CH_3$); *m*/*z* (CI) 303 [M + H]$^+$.

Compound (1*S*,2*S*)-25. Not isolated in sufficient quantity for analysis.

General procedure for transfer hydrogenation of ketones using monotosylated diamine ligands

A mixture of (*p*-cymene)ruthenium(II)chloride dimer (7.7 mg, 0.0125 mmol) and (1*S*,2*R*)-*cis*-1-amino-2-(*p*-tolylsulfonylamino)indane **22** (7.6 mg, 0.025 mmol) in formic acid–triethylamine 5 : 2 azeotrope (2.5 mL) was stirred in a small flame-dried Schlenk under N_2 at 28 °C for 15 minutes. The ketone (5 mmol) was added and the orange solution stirred at the same temperature for 20 h. The reaction mixture was filtered through a pad of silica under vacuum (with ethyl acetate washings, 2 × 50 mL). The combined organic extracts were concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (ethyl acetate–petrol). The data for the reduction products have already been presented. The results of the reductions are summarised in Tables 5 and 6.

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