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The crucial role of the nitrogen substituent in the desymmetrisation of cyclic *meso*-imides using *B*-Me and *B*-OMe oxazaborolidine catalysts

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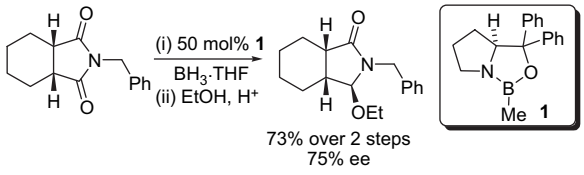
Abstract—Various cyclic *meso*-imides have been desymmetrised via enantioselective reduction using two chiral oxazaborolidine catalysts derived from (1*R*,2*S*)-*cis*-1-amino-indan-2-ol followed by the reduction of the hydroxylactam product to give the γ-lactam. The enantiomeric excesses were shown to be 27–99% by chiral HPLC and chiral GC of the γ-lactam products with the nitrogen substituent playing a pivotal role in determining yield and selectivity.

1. Introduction

Desymmetrisation of *meso*-compounds is a powerful and versatile strategy in asymmetric synthesis as the differentiation of two enantiotopic groups facilitates the formation of multiple stereocentres in a single transformation.[1] There have been several previous reports of the catalytic desymmetrisation of *meso*-imides using oxazaborolidines derived from α,α-diphenylprolinol (CBS catalyst, Scheme 1).[2]



Scheme 1. Desymmetrisation of *meso*-imides using a CBS catalyst.

Loadings of catalyst **1** of 50 mol % were required to maintain high yields and selectivities although lower loadings could be used but this was sensitive to the nature of the nitrogen substituent, *N*-phenyl substrates requiring 10 mol % catalyst to achieve an ee of 68%. The role played by the nitrogen substituent on the ee was also noted by Kang et al. who used catalytic thiazazincolidine complexes to reduce related systems.[3] In this case, *N*-aryl groups gave better selectivities than *N*-benzyl at catalyst loading of 20 mol %, with *N*-phenyl providing the better ee over the more sterically demanding *N*-2,6-dichlorophenyl (86% ee vs 50% ee).

Previous work from this group has described the use of various *B*-substituted oxazaborolidines **2** and **3** derived from (1*R*,2*S*)-*cis*-1-amino-indan-2-ol as catalysts for the asymmetric reduction of prochiral ketones (Fig. 1).[4] Following from this work, various *N*-substituted oxazaborolidines **4** (R=Me, Et and Bn) were probed as possible catalysts for the catalytic desymmetrisation of *meso*-imides. The results showed that the unsubstituted oxazaborolidine **2** proved to be the most efficient.[5]

Although *B*-OMe oxazaborolidines such as catalyst **3** have been shown to be successful in the asymmetric reduction of various prochiral ketones,[6] their use in imide reduction has not yet been explored. Herein we describe their application in the desymmetrisation of various cyclic *meso*-imides and further investigate the effect that the changing

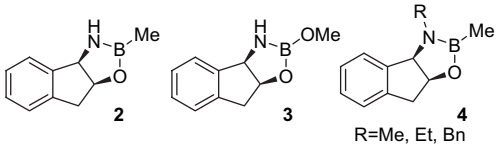


Figure 1. *cis*-1-Amino-indan-2-ol derived oxazaborolidines.

Keywords: Asymmetric reduction; Oxazaborolidine; Catalysis; Imides.
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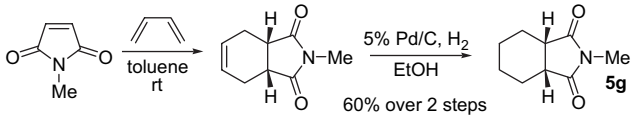
N-substituent has on the enantioselectivity of this type of asymmetric reduction.

2. Results and discussion

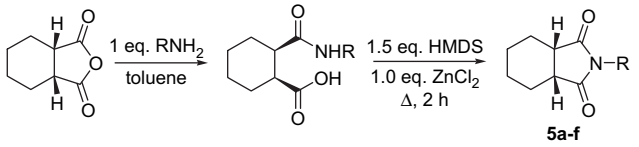
2.1. Substrate synthesis

Various *N*-substituted hexahydroisolidine-1,3-diones **5a–f** were prepared via two different methods starting from either the corresponding dicarboxylic acid or the carboxylic acid anhydride. This methodology, however, could not be applied to the *N*-methyl **5g** derivative, which was prepared from the corresponding *N*-methylmaleimide by Diels–Alder reaction with 1,3-butadiene followed by hydrogenation (Scheme 2).



Scheme 2.

The first method involved application of a previously reported procedure for the Lewis acid and hexamethyldisilazane (HMDS) promoted condensation between a primary amine and cyclohexane-1,2-dicarboxylic acid anhydride (Scheme 3, Table 1).[7] This method proved to be useful in the synthesis of all the required substrates, however, with bulky and highly electron deficient amines the yield was reduced considerably. However, this method accessed the required products in good yields.



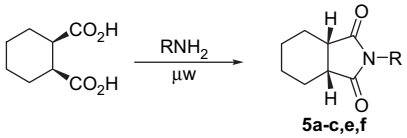
Scheme 3.

Table 1. *meso*-Imide preparation using $ZnCl_2$/HMDS promoted conditions

Entry	Amine	Product	Yield (%)
1	$BnNH_2$	**5a**	55
2	$PhNH_2$	**5b**	81
3	(*p*-OMe)$PhNH_2$	**5c**	88
4	(*p*-NO_2)$PhNH_2$[a]	**5d**	15
5	CH_2=$CHCH_2NH_2$	**5e**	69
6	*t*-$BuNH_2$	**5f**	33

[a] Reflux overnight instead of 2 h.

The second method employed for the synthesis of the *meso*-imides **5** used a microwave promoted condensation between various primary amines and *cis*-cyclohexane-1,2-dicarboxylic acid (Scheme 4).[8] For this a mixture of both the amine and dicarboxylic acid were subjected to microwave radiation in a domestic microwave oven for various periods of time (Table 2).



Scheme 4.

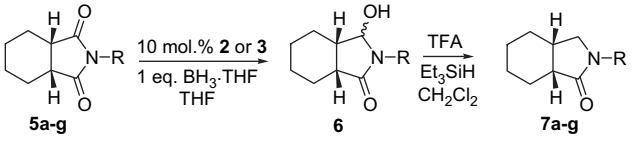
Table 2. *meso*-Imide synthesis via microwave promoted conditions

Entry	Amine	Time (min)	Product	Yield (%)
1	$BnNH_2$	15	**5a**	50
2	$PhNH_2$	25	**5b**	60
3	(*p*-OMe)$PhNH_2$	25	**5c**	33
4	CH_2=$CHCH_2NH_2$	10	**5e**	48
5	*t*-$BuNH_2$	20	**5f**	17

Imide **5d** could not be prepared in this manner, since microwave irradiation caused rapid heating and volatilisation of the aniline, presumably due to the ability of this dipolar molecule to efficiently absorb this radiation. Use of the microwave procedure enabled large amounts of the desired starting materials to be prepared quickly and efficiently in comparison to the $ZnCl_2$/HMDS promoted conditions, which took considerably longer due to prolonged purification procedures to remove impurities. However, the yield of the microwave reactions was considerably reduced, providing a trade-off between yield of product and speed of synthesis.

2.2. Desymmetrisation

Both oxazaborolidine catalysts vary in the method of preparation prior to their use in the reaction. Catalyst **2** is made separately prior to use from trimethylboroxine and *cis*-1-amino-indan-2-ol but is only stable for approximately 48 h under a nitrogen atmosphere. Conversely catalyst **3** can be made in situ from trimethyl borate and *cis*-1-amino-indan-2-ol. Hexahydroisolidinediones **5a–g** were firstly treated with 10 mol % of either catalyst **2** or **3** and 1 equiv of $BH_3\cdot THF$ at 25 °C for 18 h to yield a mixture of the optically active 5-hydroxy-2-pyrrolidinones **6** (Scheme 5). In order to simplify analysis, the crude mixture was immediately treated with TFA and Et_3SiH to give the γ-lactam **7**, which was isolated after silica gel chromatography. The enantiomeric excess was then established via either chiral HPLC or chiral GC.



Scheme 5.

Results indicated that both catalysts were as equally effective in terms of enantioselectivity of the lactam obtained (Table 3), but in all cases there was a marked difference in the yield of the reaction with the *B*-OMe catalyst **3** in comparison to the *B*-Me catalyst **2**. This is probably due to the reduced Lewis acidity of the boron centre by the additional oxygen substituent, therefore, retarding the rate of reduction. As previously observed, no background reaction was observed with $BH_3\cdot THF$, although this was not the case with $BH_3\cdot DMS$.[5]

Several important points were observed in terms of the yield of product. For alkyl substituents **5a**,**e–g** low yields were obtained for both allyl **5e** and *tert*-butyl **5f** groups, probably resulting in competitive hydroboration of the alkene for the former. In the case of the large *tert*-butyl group **5f**, poor

Table 3. Reductions of *meso*-imides **5a–g** using catalysts **2** and **3**

Entry	Imide	Catalyst **2**		Catalyst **3**	
		Yield of **7** (%)[a]	ee	Yield of **7** (%)[a]	ee
1	**5a**	57	84[b]	53	82[b]
2	**5b**	49	99[b]	23	99[b]
3	**5c**	41	99[b]	28	99[b]
4	**5d**	24	99[b]	9	99[b]
5	**5e**	24	33[c]	24	32[c]
6	**5f**	19	0[c]	21	0[c]
7	**5g**	52	75[c]	30	70[c]

[a] Refers to yield after two-step procedure.
[b] ee Determined by HPLC.
[c] ee Determined by GC.

binding to the catalyst due to the steric bulk may be responsible for the low yield, which is also reflected in the poor enantioselectivity observed for this substrate. Both benzyl **5a** and methyl **5g** gave comparable yields, which is not surprising since the benzyl group can adopt a conformation which places the phenyl group away from the catalyst, effectively mimicking a methyl group.

Those substrates with *N*-Ph and *N*-*p*-MeOPh groups gave slightly reduced yields, while *N*-*p*-NO_2Ph was very disappointing. With all of these substrates a significant amount of a doubly reduced product **8** (Fig. 2) was obtained, with more being isolated from the reaction with *N*-*p*-NO_2Ph imide **5d** (Table 4). The lower yield for all of these *N*-aryl substrates is probably a reflection of the ability of the aromatic ring to engage the lone pair of the nitrogen atom, reducing the amide character of the imide, making these more 'ketone-like' and more prone to reduction. In the case of the *p*-NO_2Ph substituent, the additional electron withdrawing group further accentuates this effect. This was confirmed from the ^{1}H NMR spectrum of the crude hydroxylactam **6d**, where approximately 10% of double reduction product was observed, demonstrating the susceptibility of this system to reduction.

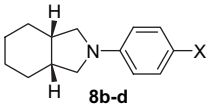


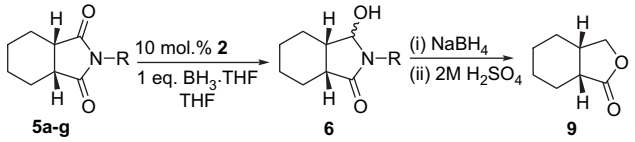
Figure 2.

Table 4. Yield of double reduction product with catalysts **2** and **3**[a]

Entry	Substrate	Product	Catalyst **2**
1	**5b**	**8b**	16
2	**5c**	**8c**	18
3	**5d**	**8d**	52

[a] Refers to yield of **8b–d** after the two-step procedure depicted in Scheme 5.

The identity of the major enantiomer formed in each case was determined by comparison of the specific rotation with those in the literature and by conversion of the intermediate hydroxylactam **6** to the lactone **9** via an established protocol (Scheme 6, Table 5). This additionally allowed the ee of the asymmetric reduction to be confirmed by a second independent method. In all these cases the major enantiomer formed was found to be the (3a*S*,7a*R*).



Scheme 6.

Table 5. Formation of lactone **9** using catalyst **2**

Entry	Imide	Yield of **9** (%)[a]	ee[b]
1	**5a**	62	88
2	**5b**	40	99
3	**5e**	25	31
4	**5f**	23	0
5	**5g**	37	75

[a] Refers to yield after two-step procedure.
[b] ee Determined by GC.

Although the enantioselectivities observed with either catalyst are nearly identical, a significant variation in ee was observed with different nitrogen substituents. In general, little variation of ee was observed with alkyl substituents **5a** and **5e**, since each of these groups appear identical when bound to the catalyst, the selectivity with the benzyl imide **5a** again resulting from this substrate adopting a conformation that locates the aromatic ring away from the catalyst.

The lower ee with the allyl group **5e** probably results from hydroboration of the alkene, which can then act as a competitive reagent and/or hydride source for reduction. Somewhat surprisingly, the more bulky *tert*-butyl group **5f** gave racemic material. As previously noted, the large steric bulk of this substrate probably inhibits tight binding to the catalyst thus resulting in a looser transition state and hence non-selective reduction. More pleasingly though, all of the *N*-phenyl substrates **5b–d** gave a single enantiomer of product irrespective of the electronic nature of the phenyl group.

The selectivities at first appear to support the previously proposed model with the prolinol derived catalyst (Fig. 3).[2] In this model, the fused ring system is considered as the small substituent (R_s) with the nitrogen moiety considered the large group (R_L). The *N*-phenyl substrates have sufficient free rotation to allow them to adopt a conformation orthogonal to the carbonyl groups similar to that proposed by Kang,[3] thus allowing optimum binding to the catalyst. It is important to note that the previously proposed model should not be blindly adopted, since making the nitrogen substituent as big as possible should result in excellent selectivity, while

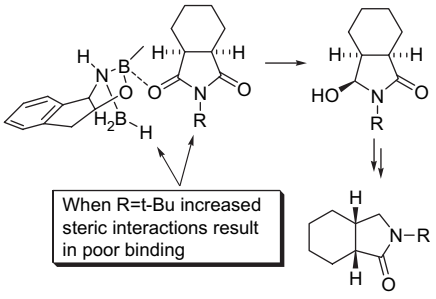


Figure 3. Model for the proposed selectivity.

in reality the *tert*-butyl substrate gives by far the worst selectivity and yield.

3. Conclusion

We have shown oxazaborolidines **2** and **3** to be effective catalysts for the enantioselective reduction of a series of *meso*-imides, with the *B*-methyl catalyst **2** providing better yields of product. More importantly we have also demonstrated that varying the nitrogen substituent on the imide greatly affects the level of enantioselectivity observed with *N*-aryl groups providing single enantiomers of product, the selectivities far exceeding those ever previously obtained with similar catalysts and conditions.

4. Experimental

4.1. General

All solvents were obtained dry from a Grubbs dry solvent system and glassware was flame dried and cooled under vacuum before use. All reactions were carried out under nitrogen. TLC was carried out using Merck aluminium TLC sheets (silica gel 60 F_{254}), visualisation of TLC plates was performed using a UV lamp or by dipping in $KMnO_4$ then exposure to heat. Flash column chromatography was carried out with Silica Gel 40–63u 60A (Fluorochem Ltd.). ^{1}H and ^{13}C NMR spectra were measured using $CDCl_3$ as a solvent unless otherwise stated, on a Bruker AC250 machine with an automated sample changer. Chemical shifts for carbon and hydrogen are given on the δ scale relative to TMS (tetramethylsilane, δ=0 ppm). Coupling constants were measured in hertz. ^{13}C NMR spectra were recorded using the JMOD method. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na D-Line) and measured at 20 °C unless otherwise stated. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR machine using 0.5 mm NaCl cells and mass spectra were recorded on a Kratos instrument. HPLC was carried out on a Gilson analytical system using a Chiralcel OD (4.8 mm×250 mm) column with 8% IPA in heptane as the solvent (unless otherwise stated). The flow rate was 1.00 cm^3 per minute and the detector was set at 254 nm. GC analysis was carried out using a Perkin–Elmer Autosystem XL gas chromatograph fitted with a Supleco fused silica capillary column (ALPHA DEX™ 120) (30 m×0.25 mm×0.25 μm film thickness) using nitrogen as the carrier gas and detection by standard FID. All chemicals were used as received without further purification except (1*R*,2*S*)-*cis*-1-amino-2-indanol, which was recrystallised from hot toluene prior to use.

4.1.1. *cis*-2-Methyl-hexahydro-isoindole-1,3-dione 5g.[9]

1,3-Butadiene was bubbled through a solution of *N*-methylmaleimide (1.38 g, 12 mmol) in toluene (30 cm^3) and the reaction stirred for 2 h. The solution was then cooled to −5 °C and the resulting white precipitate collected. This was dissolved in ethanol (5 cm^3) and 5% Pd/C was added. The suspension was left to stir for 24 h under a balloon pressure of H_2, the solution filtered through Celite and the solvent removed under vacuum to give a crude oil. Flash column chromatography eluting with 30% EtOAc/petroleum ether (40:60) gave the title compound as colourless crystals (1.2 g, 60% yield); mp 44–46 °C (lit.[9] 47–48 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.32–1.49 (4H, m, CH_2), 1.65–1.83 (4H, m, CH_2), 2.76–2.84 (2H, m, C*H*C=O), 2.91 (3H, s, CH_3); ^{13}C NMR (250 MHz; $CDCl_3$) δ_C 21.9 (*C*H$_2$), 24.0 (CH$_2$), 25.0 (CH$_3$), 40.1 (CHC=O), 180.3 (C=O). NMR data was broadly in accordance with the literature (literature multiplicities appear to have been misinterpreted).

4.2. General procedure A for the preparation of *N*-substituted *cis*-hexahydro-isoindole-1,3-diones 5a–f

A solution of cyclohexane-1,2-carboxylic acid anhydride (25 mmol) in toluene (70 cm^3) was treated with amine (25 mmol) and allowed to stir at room temperature for 1 h. Dry zinc (II) chloride (25 mmol) was added, the reaction warmed to 80 °C and hexamethyldisilazane (37 mmol) was added over a 40 min period. The reaction was heated to reflux for a further 2 h, allowed to cool to room temperature and added to 1 M HCl (30 cm^3). The product was extracted with EtOAc (3×15 cm^3) and the combined organic extracts were washed with saturated $NaHCO_3$ (3×15 cm^3), brine (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed by rotary evaporation under vacuum and the imide recrystallised from EtOAc/petroleum ether (60:80).

4.3. General procedure B for the preparation of *N*-substituted *cis*-hexahydro-isoindole-1,3-diones 5a–c, e and f

A mixture of *cis*-cyclohexane-1,2-dicarboxylic acid (25 mmol) and amine (25 mmol) were heated in a domestic microwave oven (750 W 70% of total power) until no starting materials were observed by TLC. The imide was purified via flash column chromatography eluting with 20% EtOAc/petroleum ether (40:60).

4.3.1. *cis*-2-Benzyl-hexahydro-isoindole-1,3-dione 5a.[2b]

The title compound was obtained as colourless needles either using general procedure A (55%) or B (50%); mp 58–60 °C (lit.[2b] 71–72 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.31–1.51 (4H, m), 1.60–1.91 (4H, m), 2.77–2.89 (2H, m, 2×C*H*C=O), 4.65 (2H, s, NCH_2), 7.26–7.39 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.0 (*C*H$_2$), 24.1 (*C*H$_2$), 40.2 (*C*HC=O), 42.5 (*C*H$_2$Ph), 128.2 (Ar*C*H), 129.0 (Ar*C*H), 136.5 (Ar*C*), 179.8 (*C*=O). All NMR data was in accordance with the literature.

4.3.2. *cis*-2-Phenyl-hexahydro-isoindole-1,3-dione 5b.[2b]

The title compound was obtained as white crystals either using general procedure A (81%) or B (60%); mp 134–135 °C (lit.[2b] 70.5–72.5 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.48–1.56 (4H, m), 1.82–2.02 (4H, m), 2.98–3.11 (2H, m, 2×C*H*C=O), 7.25–7.51 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.3 (*C*H$_2$), 24.4 (*C*H$_2$), 40.5 (*C*HC=O), 126.7 (Ar*C*H), 128.7 (ArC*H*), 129.5 (ArC*H*), 132.5 (Ar*C*), 179.0 (*C*=O). All NMR data was in accordance with the literature.

4.3.3. *cis*-2-(*p*-Methoxyphenyl)-hexahydro-isoindole-1,3-dione 5c.[10]

The title compound was obtained as white crystals either using general procedure A (88%) or B (33%);

mp 154–157 °C (lit.[10] 161.5–162.5 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.46–1.55 (4H, m), 1.79–2.00 (4H, m), 2.97–3.07 (2H, m, 2×C*H*C=O), 3.81 (3H, s, OCH_3), 6.96 (2H, AA′BB′, ArC*H*), 7.19 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.9 (*C*H_2), 24.0 (*C*H_2), 40.1 (*C*HC=O), 55.5 (*C*H_3), 114.6 (Ar*C*H), 124.7 (Ar*C*), 127.5 (Ar*C*H), 159.3 (Ar*C*), 178.9 (*C*=O). ^{1}H NMR data reported previously was recorded in DMSO-d_6.

4.3.4. *cis*-2-(*p*-Nitrophenyl)-hexahydro-isoindole-1,3-dione 5d. The title compound was obtained as white crystals using only general procedure A (15%); mp 186–189 °C (EtOH); (Found: C, 61.46; H, 5.05; N, 9.85. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.14; N, 10.21%); ν_{max} (KBr disc)/cm^{-1} 1781, 1610, 1494; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.51–1.54 (4H, m), 1.83–2.03 (4H, m), 3.05–3.13 (2H, m, 2×C*H*C=O), 7.61 (2H, AA′BB′, ArC*H*), 8.34 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.3 (*C*H_2), 24.4 (*C*H_2), 40.6 (*C*HC=O), 124.7 (Ar*C*H), 126.9 (Ar*C*H), 138.1 (Ar*C*), 147.1 (Ar*C*), 178.1 (*C*=O); *m*/*z* (EI) 274.0948 (100% M$^+$ $C_{14}H_{14}N_2O_4$ requires 274.0954), 109 (6, $C_7H_9O^+$), 82 (37), 67 (35), 54 (18).

4.3.5. *cis*-2-Allyl-hexahydro-isoindole-1,3-dione 5e.[11] The title compound was obtained a colourless oil either using general procedure A (69%) or B (48%); ν_{max} (film)/cm^{-1} 1785, 1703; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.33–1.51 (4H, m), 1.65–1.93 (4H, m), 2.79–2.89 (2H, m, 2×C*H*C=O), 4.05 (2H, dt, *J* 5.9, 1.4, NCH_2), 5.07–5.16 (2H, m, CH=CH_2), 5.64 (1H, ddt, *J* 17.3, 9.8 and 5.9, C*H*=CH$_2$); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.6 (*C*H_2), 23.7 (*C*H_2), 39.7 (*C*HC=O), 40.4 (N*C*H$_2$), 118.0 (CH=*C*H$_2$), 130.9 (*C*H=CH$_2$), 179.2 (*C*=O); *m*/*z* (EI) 193 (100% M$^+$), 82 (46), 67 (55), 54 (30). No NMR data were reported in the literature.

4.3.6. *cis*-2-*tert*-Butyl-hexahydro-isoindole-1,3-dione 5f.[12] The title compound was obtained as a white powder either using general procedure A (33%) or B (17%); mp 58–61 °C (lit.[12] 54–55 °C); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.41–1.86 (4H, m), 1.55 (9H, s, 3×CH_3), 1.62–1.83 (4H, m), 2.65 (2H, m, 2×C*H*C=O); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.9 (CH_2), 24.0 (CH_2), 27.4 (CH_3), 40.2 (C*H*C=O), 58.2 [N*C*(CH$_3$)$_3$], 180.7 (*C*=O). All NMR data were in accordance with the literature.

4.4. General procedure C for the reduction of imides using catalyst 3

(1*R*,2*S*)-*cis*-1-Aminoindan-2-ol (0.25 mmol) was suspended in dry toluene (2 cm^3 mmol^{-1}) and treated with trimethylboroxine (0.08 mmol). After stirring at room temperature for 30 min, toluene (5 cm^3) was added and the resulting solution was concentrated to approximately 2 cm^3 by distillation. This process was repeated twice after which the toluene was removed under reduced pressure to give the catalyst as a white solid. THF (5 cm^3) was added and the active catalyst **2** was used immediately. Thus no analytical data was obtained for this species. BH_3·THF (1 M, 2.5 mmol) was added and the solution allowed to stir at rt for 30 min. A solution of *meso*-imide **5a**–**g** (2.5 mmol) in THF (5 cm^3) was added and the solution was allowed to stir at rt for 18 h. The crude reaction mixture was extracted with CH_2Cl_2 (3×15 cm^3), the combined organic extracts were washed with 1 M HCl (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude hydroxylactam that was immediately redissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This was allowed to stir at rt for 1 h and the solution was added to an ice–water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3×15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum and purified via flash column chromatography eluting with 20% EtOAc/petroleum ether (40:60).

4.5. General procedure D for the reduction of imides using catalyst 3

A solution of (1*R*,2*S*)-*cis*-1-aminoindan-2-ol (0.25 mmol) in dry THF (20 cm^3) was treated with trimethyl borate (0.25 mmol) and the resulting solution allowed to stir at room temperature for 30 min. BH_3·THF (1 M, 2.5 mmol) was added, followed by a solution of *meso*-imides **5a**–**g** (2.5 mmol) in THF (5 cm^3) and the solution was allowed to stir at rt for 18 h. The crude reaction mixture was extracted with CH_2Cl_2 (3×15 cm^3), the combined organic extracts were washed with 1 M HCl (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude hydroxylactam that was immediately redissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This was allowed to stir at rt for 1 h and the solution was added to an ice–water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3×15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (3×15 cm^3) and dried over $MgSO_4$. The solvent was removed under vacuum and purified via flash column chromatography eluting with 20% EtOAc/petroleum ether (40:60).

4.5.1. (3a*S*,7a*R*)-2-Benzyl-octahydro-isoindol-1-one 7a.[5] The title compound was obtained as a colourless oil with imide **5a** either using general procedure C (57%, ee 84%) or D (53%, ee 82%); $[\alpha]_D$ +15.0 (*c* 1, $CHCl_3$; ee 84%), lit.[5] +19.6 (*c* 0.5, $CHCl_3$; ee 91%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 0.97–1.26 (3H, m), 1.32–1.62 (4H, m), 1.92–2.05 (1H, m), 2.15–2.27 (1H, m), 2.37–2.46 (1H, m, C*H*C=O), 2.66 (1H, dd, *J* 9.5, 2.5, 1×CH_2N), 3.16 (1H, dd, *J* 9.5, 6.0, 1×CH_2N), 4.29 (1H, d, *J* 14.5, 1×CH_2Ph), 4.45 (1H, d, *J* 14.5, 1×CH_2Ph), 7.12–7.27 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.0 (*C*H_2), 23.5 (2×*C*H_2), 27.9 (*C*H_2), 32.3 (CH), 41.9 (*C*HC=O), 46.8 (N*C*H$_2$), 50.7 (N*C*H$_2$Ph), 127.1 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 136.8 (Ar*C*), 175.9 (*C*=O); Chiral HPLC: CHIRALCEL OD, 10% *i*-PrOH in hexane, t_R 8.06 min and 10.09 min. All NMR data were in accordance with the literature.

4.5.2. (3a*S*,7a*R*)-2-Phenyl-octahydro-isoindol-1-one 7b.[10] The title compound was obtained as a white powder with imide **5b** either using general procedure C (49%, ee 99%) or D (23%, ee 99%); mp 88–90 °C (lit.[10] 87.5–89 °C); $[\alpha]_D$ +4.0 (*c* 0.5, $CHCl_3$; ee 99%), lit.[10] −4.8 (*c* 0.5, $CHCl_3$; (3a*R*,7a*S*) ee 93%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.17–1.34 (3H, m), 1.51–1.63 (3H, m), 1.69–1.77 (1H, m), 2.07–2.25 (1H, m), 2.37–2.45 (1H, m), 2.59–2.65 (1H,

m, C*H*C=O), 3.29 (1H, dd, *J* 9.4, 2.2, 1×CH_2N), 3.52 (1H, dd, *J* 9.4, 5.8, 1×CH_2N), 7.23–7.54 (5H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.1 (*C*H_2), 23.9 (*C*H_2), 24.1 (*C*H_2), 28.4 (*C*H_2), 32.3 (*C*H), 43.8 (*C*HC=O), 53.0 (*C*H_2N), 119.9 (Ar*C*H), 124.5 (Ar*C*H), 129.5 (Ar*C*H), 129.2 (Ar*C*H), 140.5 (Ar*C*), 175.5 (*C*=O); Chiral HPLC: CHIRALCEL OD, 8% *i*-PrOH in hexane, t_R 10.94 min and 12.22 min. ^{1}H NMR data were in accordance with the literature (no ^{13}C NMR data were reported).

4.5.3. (3a*S*,7a*R*)-2-(*p*-Methoxyphenyl)-octahydro-isoindol-1-one 7c.[10] The title compound was obtained as a white powder with imide **7c** either using general procedure C (41%, ee 99%) or D (28%, ee 99%); mp 76–77 °C (lit.[10] 77–78 °C); $[\alpha]_D$ +6.6 (*c* 0.6, $CHCl_3$; ee 99%), lit.[10] +4.4 (*c* 0.5, $CHCl_3$; ee 87%); ν_{max} (film)/cm^{-1} 1705, 1509; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.23–1.39 (3H, m), 1.50–1.68 (3H, m), 1.73–1.85 (1H, m), 2.09–2.23 (1H, m), 2.39–2.51 (1H, m), 2.64–2.75 (1H, m, C*H*C=O), 3.36 (1H, dd, *J* 9.4, 2.2, 1×CH_2N), 3.80–3.84 (4H, m, CH_3 and 1×CH_2N), 6.93 (2H, d, *J* 6.9, ArC*H*), 7.56 (2H, d, *J* 6.9, ArC*H*); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 23.1 (*C*H_2), 23.8 (*C*H_2), 23.9 (*C*H_2), 28.2 (*C*H_2), 32.4 (*C*H), 43.4 (*C*HC=O), 53.3 (*C*H_2N), 55.7 (O*C*H_3), 114.2 (Ar*C*H), 121.5 (Ar*C*H), 133.7 (Ar*C*), 156.5 (Ar*C*), 175.0 (*C*=O); Chiral HPLC: CHIRALCEL OD, 8% *i*-PrOH in hexane, t_R 9.81 min and 10.73 min. ^{1}H NMR data were in accordance with the literature (no ^{13}C NMR data were reported).

4.5.4. (3a*S*,7a*R*)-2-(*p*-Nitrophenyl)-octahydro-isoindol-1-one 7d. The title compound was obtained as a yellow powder with imide **7d** either using general procedure C (24%, ee 99%) or D (9%, ee 99%); mp 189–191 °C; $[\alpha]_D$ −15.0 (*c* 0.4, $CHCl_3$; ee 99%), ν_{max} (KBr disc)/cm^{-1} 2935, 1707, 1593, 1500, 1469, 1387, 1291; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.14–1.27 (3H, m), 1.45–1.64 (3H, m), 1.78–1.89 (1H, m), 2.10–2.22 (1H, m), 2.45–2.57 (1H, m), 2.69–2.80 (1H, m, C*H*C=O), 3.39 (1H, dd, *J* 9.4, 2.2, 1×CH_2N), 3.80 (1H, dd, *J* 9.4, 5.8, 1×CH_2N), 7.80 (2H, d, *J* 7.2, ArC*H*), 8.20 (2H, d, *J* 7.2, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.0 (*C*H_2), 23.7 (*C*H_2), 23.9 (*C*H_2), 28.4 (*C*H_2), 32.1 (*C*H), 44.0 (*C*HC=O), 52.9 (*C*H_2N), 118.7 (Ar*C*H), 125.1 (Ar*C*H), 143.5 (Ar*C*), 146.1 (Ar*C*), 176.4 (*C*=O); *m*/*z* (EI) 260.1150 (100%, M$^+$ $C_{14}H_{16}N_2O_3$ requires 260.1161), 217 (6), 206 (6), 151 (28), 135 (8), 120 (10), 105 (9), 95 (14), 67 (22); Chiral HPLC: CHIRALCEL OD, 8% *i*-PrOH in hexane, t_R 9.70 min and 12.40 min.

4.5.5. (3a*S*,7a*R*)-2-Allyl-octahydro-isoindol-1-one 7e. The title compound was obtained as a colourless oil with imide **7e** either using general procedure C (24%, ee 33%) or D (24%, ee 32%); $[\alpha]_D$ −0.14 (*c* 1, $CHCl_3$; ee 32%), ν_{max} (film)/cm^{-1} 2929, 2843, 1640; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.10–1.20 (3H, m), 1.38–1.68 (4H, m), 1.89–1.99 (1H, m), 2.22–2.30 (1H, m), 2.37–2.44 (1H, m, C*H*C=O), 2.81 (1H, dd, *J* 9.5, 2.1, 1×NCH_2), 3.24 (1H, dd, *J* 9.5, 5.8, 1×NCH_2), 3.76 (1H, dd, *J* 15.2, 6.1, 1×CH_2CH=CH_2), 3.88 (1H, ddt, *J* 15.2, 6.1, 1.3, 1×CH_2CH=CH_2), 5.14 (1H, dq, *J* 10.1, 1.3, 1×CH$_2$CH=CH_2), 5.17 (1H, dq, *J* 17.3, 1.3, 1×CH$_2$CH=CH_2), 5.76 (1H, ddt, *J* 17.3, 10.2, 5.8, CH$_2$C*H*=CH$_2$); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.8 (*C*H_2), 23.5 (*C*H_2), 23.6 (*C*H_2), 27.9 (*C*H_2), 32.3 (*C*H), 41.9 (*C*HC=O), 41.9 (NCH_2CH=CH$_2$), 50.8 (NCH_2CH), 117.9 (=*C*H), 132.7 (=*C*H$_2$), 175.7 (*C*=O); *m*/*z* (EI) 179.1309 (100%, M$^+$ $C_{11}H_{17}NO$ requires 179.1310), 164 (30), 152 (15), 136 (18), 124 (22), 95 (24), 70 (38), 67 (30); Chiral GC: β-DEX, 135 °C, t_R 43.52 min and 43.78 min.

4.5.6. *cis-tert*-Butyl-octahydro-isoindol-1-one 7f. The title compound was obtained as a colourless oil with imide **7f** either using general procedure C (19%, ee 0%) or D (17%, ee 0%); ν_{max} (film)/cm^{-1} 2925, 2852, 1638, 1559; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.16–1.22 (4H, m), 1.35 (9H, s, 3×CH_3), 1.48–1.53 (2H, m), 1.59–1.67 (1H, m), 1.91–1.99 (1H, m), 2.14–2.19 (1H, m, C*H*), 2.33–2.39 (1H, m, C*H*C=O), 2.96 (1H, dd, *J* 9.5, 2.1, 1×NCH_2), 3.34 (1H, dd, *J* 9.5, 5.8, 1×NCH_2); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 21.8 (*C*H_2), 23.3 (*C*H_2), 23.6 (*C*H_2), 27.6 (*C*H_3), 27.7 (*C*H_2), 31.7 (*C*H), 43.2 (*C*HC=O), 49.6 (N*C*H_2), 53.4 [N*C*$(CH_3)_3$], 175.9 (*C*=O); *m*/*z* (EI) 195.1631 (12%, M$^+$ $C_{12}H_{21}NO$ requires 195.1623), 180 (100), 178 (15), 152 (25), 140 (10), 124 (12), 95 (15); Chiral GC: α-DEX, 105 °C, t_R 67.28 min and 68.59 min.

4.5.7. (3a*S*,7a*R*)-2-Methyl-octahydro-isoindol-1-one 7g.[13] The title compound was obtained as a colourless oil with imide **7g** either using general procedure C (52%, ee 75%) or D (30%, ee 70%); $[\alpha]_D$ −17.0 (*c* 1, $CHCl_3$; ee 75%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.05–1.25 (3H, m) 1.31–1.55 (3H, m), 1.59–1.70 (1H, m), 1.86–1.99 (1H, m), 2.16–2.28 (1H, m), 2.32–2.40 (1H, m, C*H*C=O), 2.84 (3H, s, CH_3), 2.74 (1H, dd, *J* 9.4, 2.2, 1×NCH_2), 3.30 (1H, dd, *J* 9.4, 5.8, 1×NCH_2); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.1 (*C*H_2), 23.8 (*C*H_2), 23.9 (*C*H_2), 28.3 (*C*H_2), 30.2 (*C*H), 32.6 (*C*H_3), 41.9 (C*H*C=O), 54.0 (*C*H_2N), 176.2 (C=O); Chiral GC: α-DEX, 100 °C, t_R 58.85 min and 59.60 min. Only racemic material was reported in the literature. ^{1}H NMR data were in accordance with the literature (no ^{13}C NMR data were reported).

4.5.8. *cis*-2-Phenyl-octahydro-isoindole 8b.[14] The title compound was obtained as a by-product using general procedure C (30%) or D (29%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.23–1.66 (8H, m) 2.20–2.31 (2H, m), 3.09 (1H, dd, *J* 8.9, 5.2, 1×CH_2N), 3.21 (1H, dd, *J* 8.9, 6.7, 1×CH_2N), 6.43 (2H, d, *J* 7.5, ArC*H*), 6.55 (1H, t, *J* 7.5, ArC*H*), 7.10–7.18 (2H, m, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.2 (*C*H_2), 26.5 (*C*H_2), 37.4 (*C*H), 51.7 (*C*H_2), 111.1 (Ar*C*H), 114.9 (Ar*C*H), 129.1 (Ar*C*H), 148.2 (Ar*C*). No NMR data were reported in the literature.

4.5.9. *cis*-2-(4-Methoxyphenyl)-octahydro-isoindole 8c. The title compound was obtained as a by-product using general procedure C (33%) or D (33%); ν_{max} (film)/cm^{-1} 2922, 2851, 1599, 1511, 1482; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.34–1.64 (8H, m), 2.18–2.30 (2H, m), 3.06 (1H, dd, *J* 8.9, 5.2, 1×CH_2N), 3.14–3.23 (1H, m, 1×CH_2N), 3.68 (3H, s, OCH_3), 6.38 (2H, br d, *J* 8.8, ArC*H*), 6.74–6.81 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 23.2 (*C*H_2), 26.5 (*C*H_2), 37.5 (*C*H), 52.2 (*C*H_2), 56.1 (*C*H_3O), 111.6 (Ar*C*H), 115.2 (Ar*C*H), 126.2 (Ar*C*), 143.4 (Ar*C*); *m*/*z* (EI) 231.1625 (100%, M$^+$ $C_{15}H_{21}NO$ requires 231.1623), 216 (50), 149 (10), 134 (12), 121 (21).

4.5.10. *cis*-2-(4-Nitrophenyl)-octahydro-isoindole 8d. The title compound was obtained as a by-product using general procedure C (30%) or D (30%); mp 110–111 °C; ν_{max} (film)/cm^{-1} 2925, 2852, 1603, 1462; ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.33–1.68 (8H, m), 2.26–2.39 (2H, m), 3.20 (1H, dd, *J* 10.1, 5.5, 1×C*H*$_2$N), 3.34 (1H, dd, *J* 10.1, 7.0, 1×C*H*$_2$N), 6.37 (2H, AA′BB′, ArC*H*), 8.05 (2H, AA′BB′, ArC*H*); ^{13}C NMR (63 MHz; $CDCl_3$) δ_C 22.8 (*C*H$_2$), 26.0 (*C*H$_2$), 37.1 (*C*H), 52.1 (*C*H$_2$), 110.2 (Ar*C*H), 126.3 (Ar*C*H), 132.2 (Ar*C*), 152.4 (Ar*C*); *m*/*z* (EI) 246.1363 (100%, M$^+$ $C_{14}H_{18}N_2O_2$ requires 246.1368), 164 (27), 151 (5), 136 (30).

4.5.11. (3a*S*,7a*R*)-Hexahydroisobenzofuran-1-one 9.[10] A solution of hydroxylactam (1.25 mmol) in 60% ethanol (10 cm^3) was treated with sodium borohydride (2.5 mmol) and the resulting solution was stirred at 50 °C for 4 h. Once cooled EtOAc (10 cm^3) was added followed by 5% HCl (5 cm^3), upper organic layer was extracted and solvent was removed under vacuum to give crude amide. Crude product was suspended in 2 M H_2SO_4 and heated at 80 °C for 2 h. Product was extracted with CH_2Cl_2 (3×15 cm^3). Combined organic extracts were dried over $MgSO_4$. Solvent was removed under vacuum and purified via flash column chromatography eluting with 30% EtOAc/petroleum ether (40:60). Title compound was obtained as a clear oil (62%); $[\alpha]_D$ −63.0 (*c* 0.4, $CHCl_3$; ee 99%), lit.[10] −43.2 (*c* 1, $CHCl_3$; ee 89%); ^{1}H NMR (250 MHz; $CDCl_3$) δ_H 1.09–1.27 (3H, m), 1.41–1.63 (3H, m), 1.71–1.80 (1H, m), 1.98–2.10 (1H, m), 2.33–2.46 (1H, m), 2.50–2.61 (1H, m, C*H*C=O), 3.88 (1H, dd, *J* 8.9, 1.2, 1×C*H*$_2$O), 4.13 (1H, dd, *J* 8.9, 4.9, 1×C*H*$_2$O); Chiral GC: α-DEX, 100 °C, t_R 39.893 min and 40.658 min. ^{1}H NMR data were in accordance with the literature.

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