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New ligands for asymmetric diethylzinc additions to aromatic aldehydes, demonstrating substrate-dependent nonlinear effects

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The development of several aziridine-based ligands for the asymmetric addition of diethylzinc to a selection of aromatic aldehydes is described. Positive nonlinear effects were observed, and shown to display substrate dependency.

The success of aziridines containing a β-amino alcohol moiety as effective chiral ligands for the addition of diethylzinc to aromatic aldehydes is well documented both in solution and in the solid phase.[1] There have been many reports exploring the substitution of such aziridines at all the R groups indicated in Fig. 1; Tanner, for example, has produced a range of these

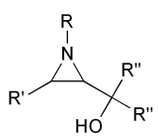


Fig. 1

aziridines.[2] We wish to report here our investigation into related ligands with substitution on the nitrogen and the oxygen atoms; other aminoalcohol ligands substituted at nitrogen and/or oxygen are also known,[3] as are related aminothiol ligands.[4]

The accepted mechanism for the reaction between diethylzinc and benzaldehyde in the presence of 1,2-aminoalcohols as ligands involves a two-zinc species in the diastereofacially selective step. One zinc atom is chelated by the aminoalcohol ligand and is also associated with the aldehyde oxygen atom; a second zinc atom, of a diethylzinc unit, is associated with both the ligand and aldehyde oxygen atoms; ethyl group transfer then takes place (Fig. 2).[5–7]

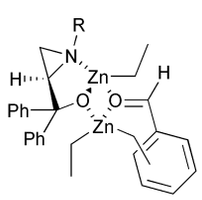


Fig. 2

This model suggests that if the ligand oxygen atom is part of a hydroxy group, then the ligand will be more successful than if it is part of an ether moiety.[3] However, we believe that an ether-containing ligand may be used if the aziridine nitrogen atom is unsubstituted, potentially resulting in reversal of the stereoselectivity of the reaction through the alternative transition state shown in Fig. 3. Indeed, reversal of the sense of induced stereochemistry upon substitution at nitrogen in the aminoalcohol ligand has previously been observed in these reactions.[7–9] It should also be noted that recent computational work has pointed to an alternative transition state assembly.[10]

The aziridine **1** was prepared from L-serine by the procedure of Zwanenburg,[11] and was de-tritylated using trifluoroacetic

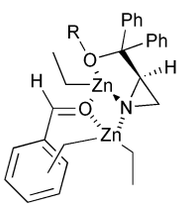
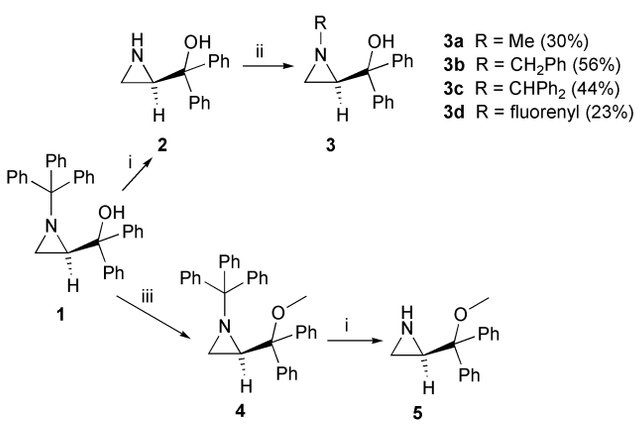


Fig. 3

acid in methanolic solution. Substitution at the nitrogen atom to give ligands **3a**–**d** was then accomplished using a range of alkyl halides with potassium carbonate as base (Scheme 1).



Scheme 1

Ligand **4** was prepared by *O*-methylation of **1** with iodomethane in the presence of sodium hydride over five days and was detritylated under the same conditions as **1**, to give ligand **5**.

The *N*-alkylation reaction used in the preparation of ligands **3** can require several days of heating under reflux in toluene solution, to produce only moderate yields. For this reason, we have developed a new synthetic route for **3c**, our most successful ligand, and this is shown in Scheme 2.

Commercial L-serine was esterified, and the nitrogen protected using benzhydryl chloride. This material was then cyclized to the aziridine using mesyl anhydride and triethylamine in the presence of catalytic DMAP. If mesyl chloride is used, as in the previous syntheses,[6] the aziridine ring suffers cleavage through nucleophilic attack by chloride to produce a chlorine-substituted secondary amine. No such ring cleavage occurs in the trityl substituted material. The methyl ester was

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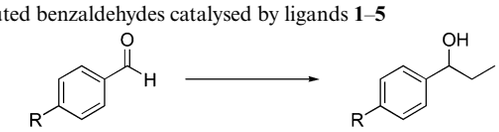
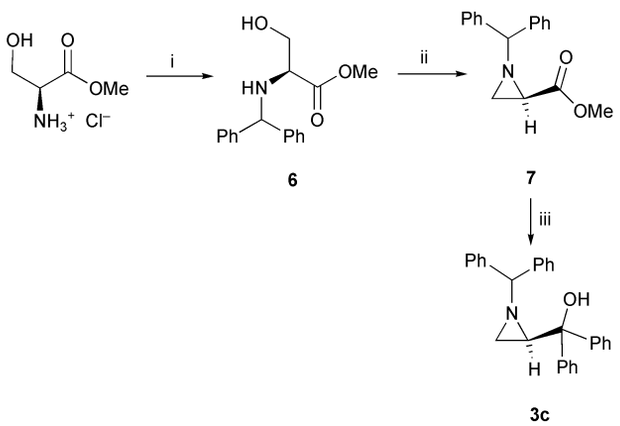
Table 1 Diethylzinc addition to substituted benzaldehydes catalysed by ligands **1**–**5**



5 mol% ligand, 2 eq. diethylzinc, toluene, rt, 24 h

Ligand	Aldehyde	Conversion [a]	ee [b]	Configuration
1 [5]	Benzaldehyde	> 99	95	*R*
2	Benzaldehyde	85	62	*R*
2	*p*-Fluorobenzaldehyde		44 [c]	*R*
2	*p*-Anisaldehyde	60	73	*R*
3a	Benzaldehyde	90	55	*R*
3b	Benzaldehyde	90	49	*R*
3c	Benzaldehyde	> 99	96	*R*
3c	*p*-Fluorobenzaldehyde	> 99	87 [c]	*R*
3c	*p*-Anisaldehyde	> 99	95	*R*
3d	Benzaldehyde	98	77	*R*
4	Benzaldehyde	24	12	*R*
5	Benzaldehyde	55	55	*S*

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC, Chiracel OD column. [c] Determined by GC, Chrompak Chirasil CB column.



i) Ph_2CHCl; Et_3N; $CHCl_3$ (49%); ii) Ms_2O, DMAP, Et_3N, $CHCl_3$ (73%); iii) PhMgBr, Et_2O (89%)

Scheme 2

then subjected to a double addition of Grignard reagent to produce the tertiary alcohol **3c**. Lacking any additional deprotection/reprotection steps, this new route is significantly more efficient than the standard method.

Ligands **1**–**5** were tested in a standard addition reaction of diethylzinc to a selection of aromatic aldehydes, carried out using 5 mol% of ligand in toluene solution at room temperature over 24 h (Table 1).[11]

For ligand **2**, where both the nitrogen and the oxygen atoms are unsubstituted, the *R* enantiomer of the alcohol is preferentially formed, fitting the expected transition state. Using ligand **4**, where both the oxygen and nitrogen atoms are substituted, the *R* enantiomer of the alcohol is again formed preferentially, but in poor ee, perhaps suggesting that neither atom is able to bind strongly to the zinc. Use of ligand **5**, which is substituted only at the oxygen atom, results in the opposite sense of enantioselectivity, inducing the *S* enantiomer of the product alcohol to be formed preferentially (coincidentally with an identical ee to the reaction using ligand **3a**), suggesting the adoption of an alternative transition state such as that shown in Fig. 3.

Ligand **3c** shows the greatest versatility of those tested, with even the electron-deficient *p*-fluorobenzaldehyde undergoing the reaction with a very high ee. Ligand **3d** was expected to give a similar result, due to the similarity in the structure; the fact that this is not the case suggests that the conformation of the molecule in the transition state must be significantly different. Single crystal X-ray analysis of these two ligands shows this to

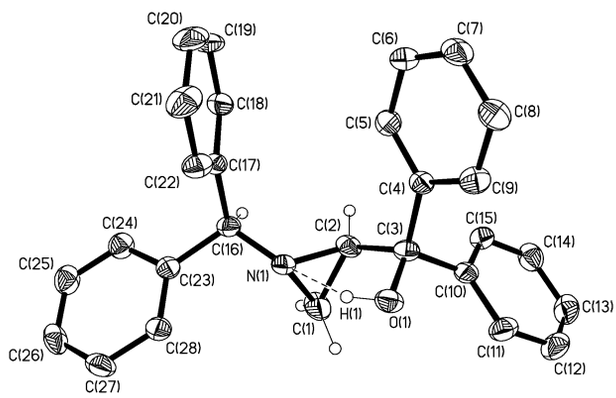


Fig. 4 Ligand **3c**.

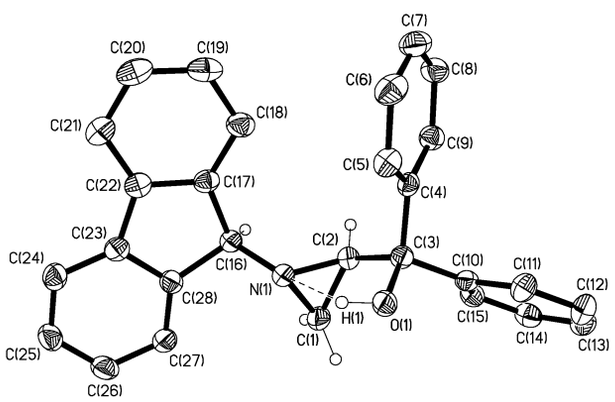


Fig. 5 Ligand **3d**.

be true in the crystalline state (Figs. 4 and 5), †although of course the conformation of the ligand–metal complexes in solution may be very different. It can clearly be seen that in structure **3c** the phenyl rings of the benzhydryl group are orthogonal. However, in **3d** the equivalent rings are co-planar. The orthogonal arrangement found in **3c** may impart a greater steric effect in the transition state, resulting in higher observed enantioselectivity in the reaction.

Single crystal X-ray analysis was also carried out on ligands **2** and **4**. Ligand **2** contains an intermolecular hydrogen bond which holds the nitrogen and oxygen atoms in close proximity,

† CCDC reference numbers 198143–198146. See http://www.rsc.org/suppdata/p1/b2/b208810j/ for crystallographic files in .cif or other electronic format.

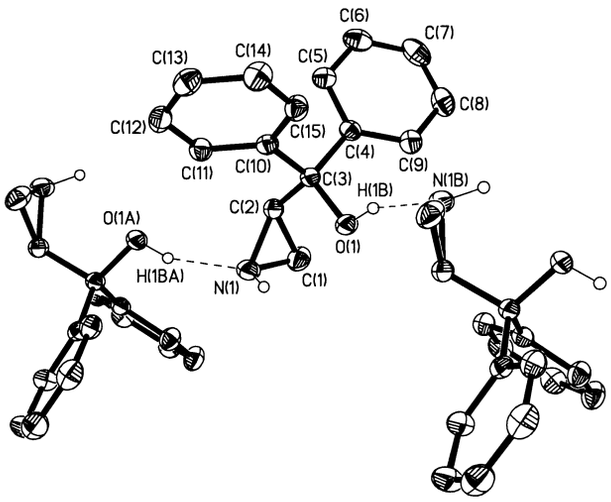


Fig. 6 Ligand **2**.

perhaps aiding transition state formation (Fig. 6). However, in ligand **4**, with both the oxygen and nitrogen atoms protected, the oxygen atom is now at the opposite side of the molecule to the nitrogen atom, so that the conformation in the crystal must be different from that in the active catalyst (Fig. 7).

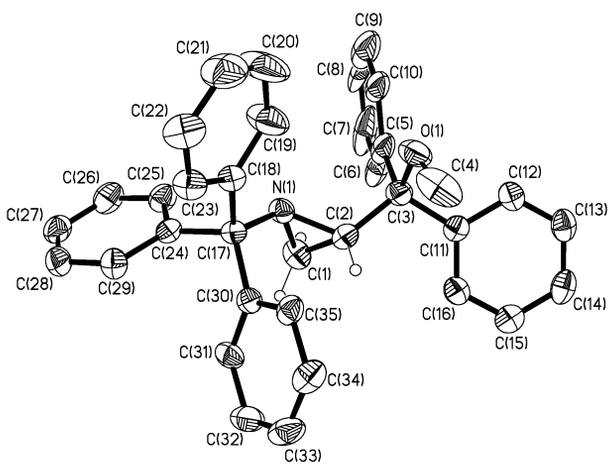


Fig. 7 Ligand **4**.

For these ligands to be useful in asymmetric catalysis, they must be effective in catalytic quantities. We have compared the catalytic activities of ligands **2** and **3c** at 5 mol% in the addition of diethylzinc to benzaldehyde with that of ligand **1**, which has previously been reported to be an effective catalyst for this reaction (Fig. 8).[12]

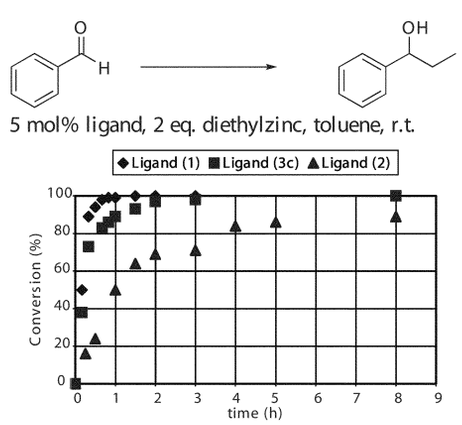


Fig. 8 Comparison of ligands **1**, **2** and **3c**.

It can be seen from Fig. 8 that ligand **1** has the greatest catalytic activity. Ligand **3c** is only a little less active. Ligand **2** provides a significantly lower rate of reaction, with the reaction not reaching completion within the 24 h test reaction time. In order to compare results from different ligands meaningfully, product ees should be measured at the same point of conversion, rather than after the same length of time. In the case of ligand **2**, the ee of the alcohol product was measured after 24 h even though the reaction had not reached completion. In order to establish whether or not the product ees vary during the reaction, we monitored the ee of the product in a reaction using ligand **2** over 50 h (Fig. 9).

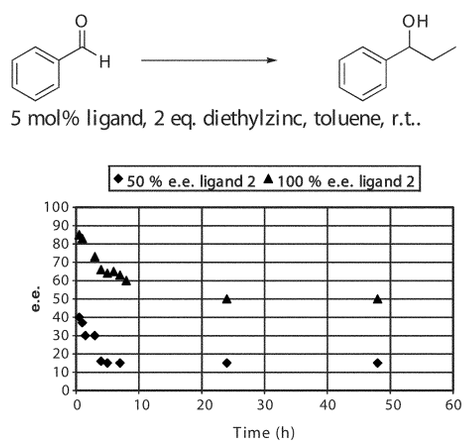


Fig. 9 Variation of ee with time, 5 mol% ligand **2**.

Fig. 9 shows the change in ee with time for the addition of diethylzinc to benzaldehyde, in the presence of 5 mol% ligand **2** of 100% ee and 50% ee. For ligand **2** of 100% ee, the ee of the alcohol product is indeed highest in the initial stages of the reaction (85% ee after 15 min). After 24 h the product ee has fallen (to 50% ee), and does not decrease further, showing that the test reaction time of 24 h is sufficient to indicate the ee of product at completion under the conditions used.

Many ligand-accelerated reactions display nonlinear effects in asymmetric catalysis.[13] For the addition of diethylzinc to aromatic aldehydes, a positive nonlinear effect is common. As highlighted by Blackmond,[5] the outcome of nonlinear effects at the end of the reaction provides information important for practical applications, although for simplicity of analysis of reaction kinetics, the initial reaction conditions are usually considered. An investigation into nonlinear effects displayed by our ligands for addition to benzaldehyde (Fig. 10) uncovered strong

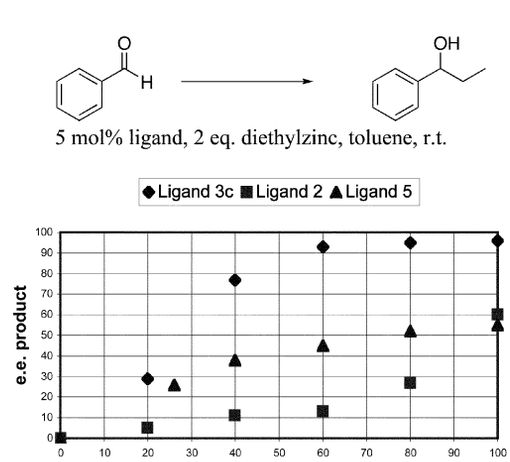


Fig. 10 Apparent non-linear effects.

Table 2 Variation of ee with reaction time

Time/h	Ligand **2** ee[a]	Ligand **3c** ee[a]
0.5	85	95
24	50	96

[a] Determined by HPLC, Chiracel OD column.

positive nonlinear effects (ligands **3c** and **5**) and in one case (ligand **2**) an unexpected apparent negative nonlinear effect. Table 2 shows that in the presence of ligand **3c** the ee is the same initially as at completion of the reaction, demonstrating a true positive nonlinear effect in this case. In the case of ligand **2** there may be no true nonlinear effect as a fall in ee of the product is observed during the reaction, presumably a result of some form of evolution of the active catalyst species. Indeed, the 0.5 h samples demonstrate a linear effect (Fig. 9).

Fig. 11 shows the remarkable variation in ee of product with reaction time during the addition of diethylzinc to benzaldehyde in the presence of stoicheiometric quantities of ligand **2**.

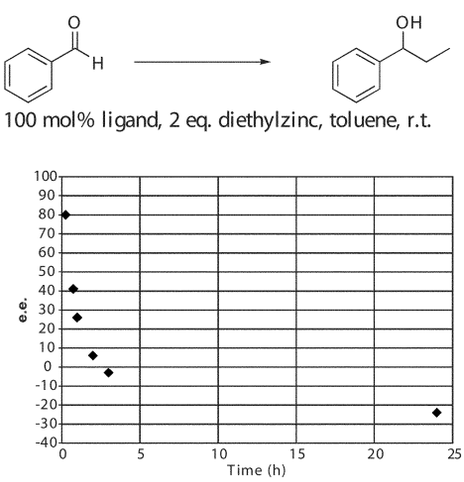


Fig. 11 Variation of ee with time, 100 mol% ligand **2**.

The 1-phenylpropanol produced after 0.25 h has an ee of 80%, but, remarkably, of the *opposite* enantiomer to that preferentially formed in the presence of 5 mol% ligand, where 85% ee is seen at the beginning of the reaction. The ee drops rapidly during the stoicheiometric reaction, the product after 24 h having an ee of 24% of the opposite enantiomer to that produced at the start of the reaction, and thus of the same enantiomer preferentially formed in the truly catalytic reaction.

Substrate dependency of nonlinear effects in the addition of diethylzinc to aldehydes has been recently reported by the Walsh group,[14] which demonstrated that adding an electron-donating substituent to the aromatic aldehyde causes an increase in the magnitude of the positive nonlinear effect. Ligand **2**, of varying ee, was tested with several different aldehyde substrates (Fig. 12). To our surprise, while the effects induced by ligand **2** in the reaction with benzaldehyde were enhanced when using *p*-fluorobenzaldehyde, this behaviour was replaced by a small positive nonlinear effect with *p*-anisaldehyde, consistent with the observations of Walsh.

The cause of the behaviour induced by ligand **2** is currently unknown, but is perhaps a result of product inhibition by newly-formed 1-phenylpropanol in the addition of diethylzinc to benzaldehyde in the presence of ligand **2**.[6] Unlike the addition to benzaldehyde, the addition of diethylzinc to *p*-anisaldehyde in the presence of ligand **2** (5 mol%) does not display any change in ee during the course of the reaction under the conditions used by us. This reaction was repeated, but with

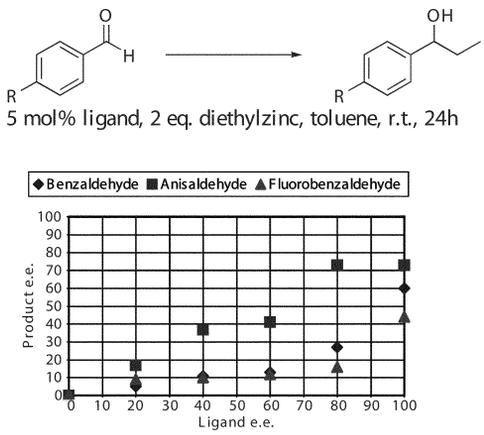


Fig. 12 Apparent non-linear effects.

the addition of racemic 1-phenylpropanol (10 mol%) to the reaction mixture prior to the addition of diethylzinc. Although the conversion of the reaction was little changed after 24 h, the change in enantioselectivity was more dramatic. In the absence of 1-phenylpropanol, the addition of diethylzinc to *p*-anisaldehyde proceeds to 60% conversion after 24 h, giving the product in 73% ee. In the presence of 1-phenylpropanol, however, after 24 h the reaction proceeds to 54% conversion, but gives product of only 32% ee. Further investigation showed that the ee varies throughout the reaction, for example being at 77% ee after 0.25 h. Product inhibition by newly-formed 1-phenylpropanol may indeed thus be a cause of the variation in product ee observed during the addition of diethylzinc to benzaldehyde in the presence of ligand **2**.

Experimental

Aziridin-2-yldiphenylmethanol 2

N-Tritylaziridin-2-yldiphenylmethanol **1** (16 g, 34 mmol) was dissolved in a mixture of dichloromethane (80 mL) and methanol (80 mL). The solution was cooled to 0 °C and TFA (60 mL) was added dropwise. The resulting mixture was concentrated, and the residue suspended in saturated aqueous sodium carbonate (100 mL). Extraction into dichloromethane (100 mL) was followed by drying over sodium sulfate. Finally the reaction mixture was evaporated to dryness to give a pale yellow solid. Trituration in diethyl ether afforded colourless crystals (6.3 g, 82%), mp 145–147 °C. $[\alpha]_D = -16.34$ (*c* 0.21, CH_2Cl_2); ν_{max}/cm^{-1}: 3288, 1671, 1187; δ_H (250 MHz, $CDCl_3$) 1.72 (d, $J = 3.7$, 1H); 1.79 (d, $J = 6.0$, 1H); 2.83–2.87 (m, 1H); 7.19–7.45 (m, 10H); *m*/*z* 225.11557 (225.11536 required), 77 (50%); 105 (100%); 183 (60%); 225 (2.5%). Anal Calcd for $C_{15}H_{15}NO$: C, 79.9, H, 6.7, N, 6.2. Found: C, 79.8, H, 6.5, N, 6.1%.

N-Methylaziridin-2-yldiphenylmethanol 3a

Aziridin-2-yldiphenylmethanol **2** (0.5 g, 2.2 mmol) and potassium carbonate (0.76 g, 5.5 mmol) were suspended in THF (20 mL). Iodomethane (2.3 mmol, 0.33 g) was added dropwise, and the mixture stirred at room temperature for 20 h. Water was introduced into the reaction, followed by extraction into dichloromethane. The solution was dried over magnesium sulfate, and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluent: 4 : 1 petroleum ether : ethyl acetate) to give colourless crystals (0.15 g, 30%), mp 88–90 °C. $[\alpha]_D = -111.84$ (*c* 0.26, CH_2Cl_2); ν_{max}/cm^{-1}: 3424, 1448, 1175; δ_H (400 MHz, $CDCl_3$) 1.30 (d, $J = 6.4$, 1H); 1.94 (d, $J = 3.6$, 1H); 2.25–2.28 (m, 1H); 2.41 (s, 3H); 7.23–7.43 (m, 10H); δ_C (100 MHz, $CDCl_3$) 31.5, 46.3, 47.3, 74.3, 126.3, 126.6, 127.0, 127.0, 128.0, 128.2, 145.0, 147.9; *m*/*z* 239.13101 (239.13101 required), 77 (70%); 105 (100%); 183 (60%); 239

(15%). Anal Calcd for $C_{16}H_{17}NO$: C, 80.3, H, 7.2, N, 5.9. Found: C, 80.1, H, 7.2, N, 5.8%.

N-Benzylaziridin-2-yldiphenylmethanol 3b

Aziridin-2-yldiphenylmethanol **2** (0.5 g, 2.2 mmol) and potassium carbonate (5.5 mmol, 0.76 g) were suspended in THF (20 mL). Benzyl bromide (2.2 mmol, 0.38 g) was added dropwise and the resulting mixture was stirred for 20 h at room temperature. Water (100 mL) was introduced, followed by extraction into dichloromethane. The mixture was then washed successively with 1 M HCl (10 mL) and water (200 mL), and dried over magnesium sulfate. Evaporation to dryness produced a colourless powder requiring no further purification (0.39 g, 56%), mp 88–92 °C. $[a]_D = -35.43$ (*c* 0.46, CH_2Cl_2); ν_{max}/cm^{-1}: 3424, 1448; δ_H (250 MHz, $CDCl_3$) 1.55 (d, *J* = 6.4, 1H); 2.05 (d, *J* = 3.4, 1H); 2.55–2.59 (m, 1H); 3.45 (d, *J* = 13.4, 1H); 3.77 (d, *J* = 13.4, 1H); 7.15–7.42 (m, 15H); δ_C (100 MHz, $CDCl_3$) 30.5, 46.3, 62.8, 74.1, 126.3, 126.3, 126.8, 127.0, 127.2, 127.3, 127.9, 127.9, 128.0, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 138.0, 122.9, 147.4; *m*/*z* 315.16231 (315.16231 required), 77 (29%); 91 (100%); 105 (49%); 183 (34%); 260 (16%).

N-Benzhydrylaziridin-2-yldiphenylmethanol 3c

Aziridin-2-yldiphenylmethanol **2** (0.5 g, 2.2 mmol) and potassium carbonate (0.59 g, 5.6 mmol) were suspended in toluene (15 mL). Benzhydryl chloride (0.68 g, 3.3 mmol) was added and the reaction heated to reflux for 9 days. The reaction was quenched with water and extracted into dichloromethane. The resulting solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. The colourless residue was recrystallized from dichloromethane–hexanes to give the product as colourless crystals (0.38 g, 44%), mp 192–194 °C. $[a]_D = -39.8$ (*c* 0.32, CH_2Cl_2); ν_{max}/cm^{-1}: 3422; δ_H (250 MHz, $CDCl_3$) 1.62 (d, *J* = 6.3, 1H); 2.16 (d, *J* = 3.7, 1H); 2.76–2.80 (m, 1H); 3.89 (s, 1H); 3.96 (s, 1H); 6.99–7.42 (m, 20H); δ_C (62.5 MHz, $CDCl_3$) 31.4, 46.9, 74.3, 77.4, 126.4, 126.6, 126.7, 127.3, 127.4, 127.7, 128.0, 128.4, 128.7, 128.8, 142.9, 143.2, 145.7, 147.2; *m*/*z* 392.20138 (392.20143 required), 136 (59%); 154 (100%); 392 (16%).

N-(9*H*-Fluoren-9-yl)aziridin-2-yldiphenylmethanol 3d

Aziridin-2-yldiphenylmethanol **2** (0.5 g, 2.2 mmol) and potassium carbonate (8.8 mmol, 1.2 g) were suspended in toluene (20 mL). 9-Bromofluorene (3.3 mmol, 0.81 g) was added and the reaction was stirred at room temperature for 2 days, then heated to reflux for a further 4 days. The reaction was quenched with water (10 mL), extracted into dichloromethane (50 mL) and dried over magnesium sulfate. The solution was evaporated to dryness and the residue purified by chromatography on silica gel (eluent 9 : 1 petroleum ether : ethyl acetate), to give the product as yellow crystals (0.2 g, 23%), mp 150–153 °C. $[a]_D = -61.78$ (*c* 0.23, CH_2Cl_2); ν_{max}/cm^{-1}: 1185, 1449, 3060, 3397; δ_H (400 MHz, $CDCl_3$) 2.14–2.17 (m, 2H); 2.95–2.99 (m, 1H); 3.89 (s, 1H); 4.15 (s, 1H); 6.42 (d, *J* = 12, 1H); 6.83–6.89 (m, 1H); 7.24–7.70 (m, 16H); δ_C (100 MHz, $CDCl_3$) 28.9, 45.0, 69.8, 75.3, 119.9, 120.3, 125.2, 125.3, 126.4, 126.9, 127.1, 127.5, 127.6, 127.7, 128.5, 128.6, 128.7, 129.1, 141.0, 141.0, 143.1, 143.8, 146.3, 148.3; *m*/*z* 389.17846 (389.17796 required), 77 (25%), 105 (50%), 165 (100%), 183 (30%), 389 (4%).

O-Methyl-*N*-tritylaziridin-2-yldiphenylmethanol 4

N-Tritylaziridin-2-yldiphenylmethanol **1** (1 g, 2.2 mmol) and sodium hydride (60% dispersion in mineral oil, 5.4 mmol, 0.13 g) were dissolved in DMF (10 mL), and stirred at room temperature for 5 min. Iodomethane (3.4 mmol, 0.46 g) was added and the reaction stirred for a further 4 days. The reaction was quenched with water (20 mL), extracted into ethyl acetate (60 mL), and washed with water (3 × 200 mL) and brine (100 mL). The solution was dried over magnesium sulfate and evaporated to dryness. The residue was purified by chromatography on silica gel (eluent 9 : 1 petroleum ether : ethyl acetate) to give the product as colourless crystals (0.90 g, 88%), mp 125–128 °C. $[a]_D = -142.19$ (*c* 0.37, CH_2Cl_2); ν_{max}/cm^{-1}: 1076, 1447, 1490, 3085, 3057; δ_H (400 MHz, $CDCl_3$) 1.20 (s, 1H); 1.44 (s, 1H); 2.12–2.13 (m, 1H); 2.99 (s, 3H); 7.15–7.50 (m, 25H); δ_C (100 MHz, $CDCl_3$) 25.2, 38.2, 52.0, 75.2, 84.2, 127.0, 127.4, 127.5, 127.5, 127.7, 127.8, 128.3, 128.5, 128.7, 128.9, 129.2, 129.7, 130.1, 130.4, 143.5, 143.7, 144.8.

O-Methylaziridin-2-yldiphenylmethanol 5

A solution of **4** (0.5 g, 1.0 mmol) in dichloromethane (5 mL) and methanol (5 mL) was cooled to 0 °C, and TFA (2 mL) was added. The reaction was allowed to reach room temperature and stirred for a further 30 min. The reaction was concentrated *in vacuo*. The residue was suspended in dichloromethane (10 mL) and poured into saturated aqueous sodium hydrogen carbonate. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was purified by chromatography on silica gel (eluent: 3 : 1 petroleum ether : ethyl acetate) to give the product as a yellow oil (0.19 g, 75%). $[a]_D = -36.8$ (*c* 0.10, CH_2Cl_2); ν_{max}/cm^{-1}: 3292, 1076; δ_H (400 MHz, $CDCl_3$) 1.47 (d, *J* = 3.6, 1H); 1.64 (d, *J* = 5.2, 1H); 2.65–2.67 (m, 1H); 3.18 (s, 3H); 7.27–7.45 (m, 10H); δ_C (100 MHz, $CDCl_3$) 22.4, 36.6, 51.5, 82.6, 127.4, 127.5, 127.6, 127.7, 127.7, 127.8, 128.0, 128.0, 128.4, 128.6, 141.5, 141.7; *m*/*z* 239.13123 (239.13101 required), 77 (55%), 105 (70%), 197 (100%), 206 (95%), 239 (> 1%).

Methyl 2-(*N*-benzhydrylamino)-3-hydroxypropanoate 6

A suspension of serine methyl ester hydrochloride (5 g, 32 mmol) in chloroform (50 mL) was cooled to 0 °C. Triethylamine (7.7 g, 77 mmol) was added, followed by benzhydryl chloride (4.4 g, 22 mmol), which was added dropwise over 10 minutes. The reaction was heated to reflux for 3 days, allowed to cool to room temperature, quenched with saturated aqueous ammonium chloride solution and extracted into dichloromethane (50 mL). The solution was dried over magnesium sulfate and evaporated to dryness. The resulting oil was purified by chromatography on silica gel (eluent 8 : 1 petroleum ether : ethyl acetate) to give the product as a yellow oil (3.08 g, 49%); $[a]_D = -31.1$ (*c* 0.28, CH_2Cl_2); ν_{max}/cm^{-1}: 3447, 1741; δ_H (400 MHz, $CDCl_3$) 3.40–3.43 (m, 1H); 3.64–3.68 (m, 2H); 3.74 (s, 3H); 4.92 (s, 1H); 7.22–7.40 (m, 10H); δ_C (100 MHz, $CDCl_3$) 52.2, 60.4, 63.1, 65.3, 127.3, 127.4, 127.6, 128.7, 128.7, 142.3, 143.5, 173.7; *m*/*z* 284.12806 (284.12865 required), 77 (50%), 105 (70%), 167 (100%), 182 (90%), 284 (< 1%).

Methyl *N*-benzhydrylaziridine-2-carboxylate 7

4-(Dimethylamino)pyridine (0.12 g, 1.1 mmol) was added to a solution of **6** (3 g, 10.5 mmol) in chloroform (200 mL). Triethylamine (2.54 g, 25.2 mmol) was added and the solution cooled to 0 °C. Methanesulfonic anhydride (2.4 g, 15 mmol) in chloroform (20 mL) was added over 30 min. The reaction was maintained at 0 °C for 1 h, then allowed to reach room temperature and heated to reflux for 24 h. The reaction was allowed to cool to room temperature, quenched with water and extracted into dichloromethane. The resulting solution was dried over magnesium sulfate and evaporated to dryness *in vacuo*. The resulting oil was purified by chromatography on silica gel (3 : 1 petroleum ether : ethyl acetate with 1% triethylamine) to give the product as pale yellow crystals (2.04 g, 73%), mp 84–87 °C; $[a]_D = -93.3$ (*c* 0.45, CH_2Cl_2); ν_{max}/cm^{-1}: 1744, 1200; δ_H (400 MHz, $CDCl_3$) 1.82 (d, *J* = 6.4, 1H); 2.25–2.27 (m, 1H); 2.30 (d, *J* = 3.2, 1H); 3.60 (s, 1H); 3.69 (s, 1H); 7.18–7.42 (m, 10H); δ_C (100 MHz, $CDCl_3$) 34.9, 38.1, 52.1, 77.9, 126.6, 127.1, 127.3,

127.4, 127.5, 127.6, 128.2, 128.4, 128.5, 128.6, 142.4, 171.0; *m*/*z* 266.11832 (266.11810 required), 77 (18%), 105 (22%), 167 (100%), 266 (12%).

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