Organic & Biomolecular Chemistry

PAPER

Synthesis and evaluation of *atropos* dihydro-5*H*-dibenzazepinium halide PTCs derived from α-methylbenzylamine†‡

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A short synthetic route to diastereoisomeric *atropos* dihydro-5*H*-dibenz[*c,e*]azepinium salts *via* reaction of a single enantiomer of (*R*)-α-methylbenzylamine with a racemic *atropos* biphenol derivative is described. Compounds prepared *via* this approach are used to provide strong evidence that structurally related *tropos* dihydro-5*H*-dibenz[*c,e*]azepinium salts preferentially react *via* a single conformation in PTC reactions involving glycine imine enolates.

Introduction

Asymmetric phase transfer catalysis (PTC) has proved to be an extremely powerful method for the stereoselective construction of C–C bonds. Much of this methodology is based on the use of chiral quaternary ammonium salts and most commonly these are derived from either cinchona alkaloids, chiral (*atropos*) biaryl fragments, or tartaric acid derivatives.[1] In an effort to expand the range of useful chiral quaternary ammonium salt architectures we have been seeking to develop effective PTCs based on simple commercially-available chiral amines. During the course of these studies we were able to demonstrate that 1 mol% of quaternary ammonium salt **1** (X = Br), derived from α-methyl naphthylamine, was capable of promoting the enantioselective PTC alkylation of glycine imine esters.[2] Follow up studies demonstrated that the same catalyst could also be utilised for the enantioselective Michael addition of glycine imine esters to α,β-unsaturated ketones,[3] and that related PTC salt **2** (X = I, Br) was also capable of delivering high enantioselectivity in these processes.[4]

A key feature of structures **1** and **2** is the conformationally-labile (*tropos*) dihydro-5*H*-dibenz[*c,e*]azepinium ring incorporating the amino group of the chiral amine precursor. This fragment allows the possibility to fine-tune the catalyst by variation of the substituents attached to the aromatic rings and also appears to be essential for high enantioselectivity.[2,5] Given that conformationally-fixed (*atropos*) dihydro-5*H*-dibenz[*c,e*]azepinium salts have proved spectacularly successful in a wide range of PTC processes,[1a–c] it seems likely that catalysts **1** and **2** are effective

because the dihydro-5*H*-dibenz[*c,e*]azepinium ring adopts a single atropisomeric form in the reaction transition state. However, until now we have not been able to provide strong evidence to support this hypothesis. In this paper we describe the development of a synthetic route that allows rapid access to both diastereoisomers of *atropos* analogues of compound **2** and discuss how compounds generated in this way have allowed greater insight into the mode of action of catalysts **1** and **2**.

Discussion

Studies in our group established that catalysts lacking the 4,4′-methoxy and 5,5′-*tert*-butyl substituents in structure **2** were also capable of delivering respectable levels of enantioselectivity (>80% e.e.) in the alkylation of glycine imines.[6] Based on this observation, we initially identified structures **3–6** (Fig. 1) as close analogues of PTC **2**. It was considered that these structures should be accessible from the readily-available racemic biphenol **14** *via* two related approaches. The first of these (Scheme 1) would start with the resolution of biphenol **14**.[7] Regioselective electrophilic substitution of the aryl rings, followed by radical bromination would then allow access to key intermediates **8** and **11**. Conversion into the dihydro-5*H*-dibenz[*c,e*]azepinium salts **3** and **5** could then be achieved by reacting with (*R*)-α-methylbenzylamine followed by introduction of the bis-3,5-trifluoromethylphenyl groups *via* Suzuki–Miyaura coupling and *N*-quaternization.[4] The diastereoisomeric salts **4** and **6** could be prepared simply by taking the other enantiomer of diether **13** through the same sequence of reactions. This approach is analogous to that previously reported by Maruoka[8] and has the advantage that it proceeds *via* a chiral diether **13** with known absolute stereochemistry, consequently the stereochemistry of any resulting dihydro-5*H*-dibenz[*c,e*]azepinium salts would be known with certainty.

The second approach (Scheme 2) would involve generating the tetra-bromide intermediates **8** and **11** as racemates. These

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1, R = 1-naphthyl
2, R = Ph

3, R = H
5, R = t-Bu

4, R = H
6, R = t-Bu

Fig. 1

7, R = H
10, R = t-Bu

8, R = H
11, R = t-Bu

9, R = H
12, R = t-Bu

via resolution

13

14

Scheme 1

3 or 5

7, R = H
10, R = t-Bu

heat

4 or 6

15, R = H
16, R = t-Bu

separate diastereoisomers

8, R = H
11, R = t-Bu

14

Scheme 2

17, X = O; $t_{1/2}$ = 2 h, 101 °C, DMF (ΔE 28 kcal mol^{-1})
18, X = N$^+$Me$_2$; $t_{1/2}$ = 1.5 h, 168 °C, DMF, (ΔE 36 kcal mol^{-1})

Scheme 3

Br$_2$, AcOH
CH$_2$Cl$_2$

14, R = H
13, R = Me

19, R = H, 84%
9, R = Me, 93%

12

Scheme 4

MeI
K$_2$CO$_3$
DMF
74%

20

12
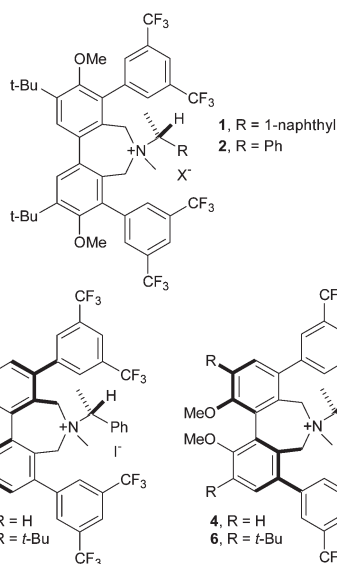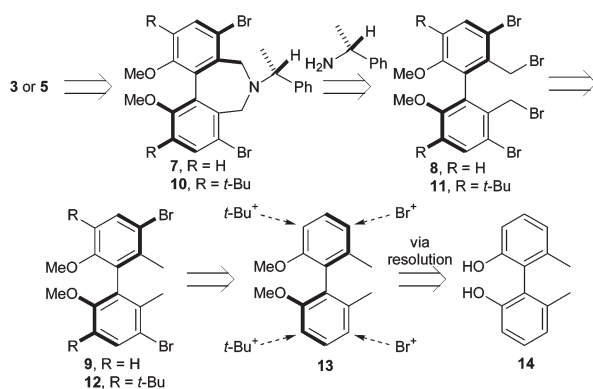
Scheme 5

salts **3–6** could be prepared in fewer steps overall (*e.g.* 8 steps *vs.* 13 steps for compounds **3** and **4**) and eliminates the need for a resolution of the starting biphenol **14**. Clearly this second approach would be more efficient, but in order for it to be useful it would either require kinetic resolution in the formation of the diastereoisomeric dihydro-5*H*-dibenz[*c,e*]azepines **7/15** and **10/16**, or for them to be readily separable.[9]

We also considered that it may also be possible to interconvert the diastereoisomeric dihydro-5*H*-dibenz[*c,e*]azepine intermediates (*e.g.* **7** and **15**) *via* thermal isomerisation. This would open up the possibility of converting a racemic *atropos* biaryl precursor such as **8** into a single diastereoisomeric *atropos* dihydro-5*H*-dibenz[*c,e*]azepine product. With this in mind it was interesting to note that the related dihydro-5*H*-dibenz[*c,e*]oxepine **17** has been reported to undergo thermal isomerisation at >100 °C whereas the corresponding quaternary ammonium salt **18** requires substantially higher temperatures (Scheme 3).[10]

Given these potential advantages we opted to investigate the approach outlined in Scheme 2. Thus this study started with the attempted preparation of the key intermediates **9** and **12**. To this end, racemic biphenol **14** and the corresponding dimethylether **13** were prepared as previously described.[7,8] These were then converted into intermediates **9** and **19** *via* regioselective electrophilic bromination (Scheme 4). We next attempted to introduce the *tert*-butyl substituents *via* Friedel–Crafts alkylation. A range of conditions were investigated (*e.g.* *t*-BuOH–H$^+$, iso-butene–H$^+$),[11,12] but all failed to deliver the desired product. All attempts to reverse the steps and introduce the *tert*-butyl substituents prior to bromination were also unsuccessful.

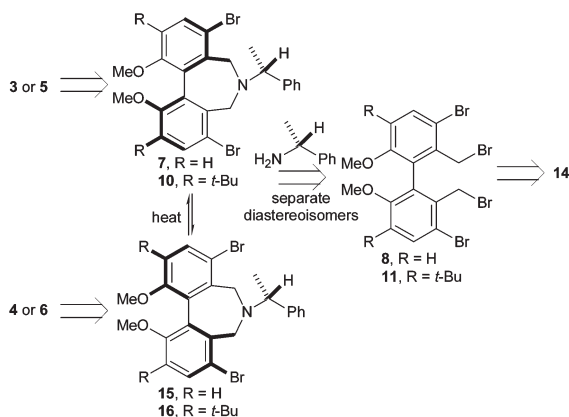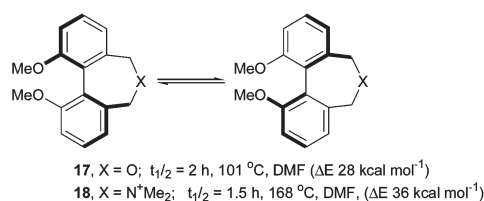In order to circumvent this problem intermediate **12** was prepared from the known biphenol **20**,[13] (Scheme 5).
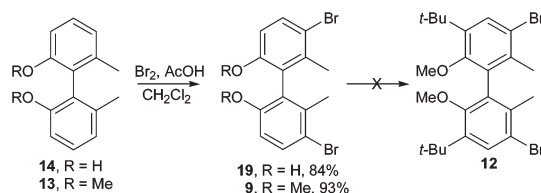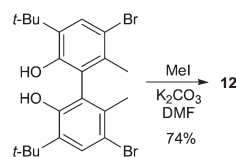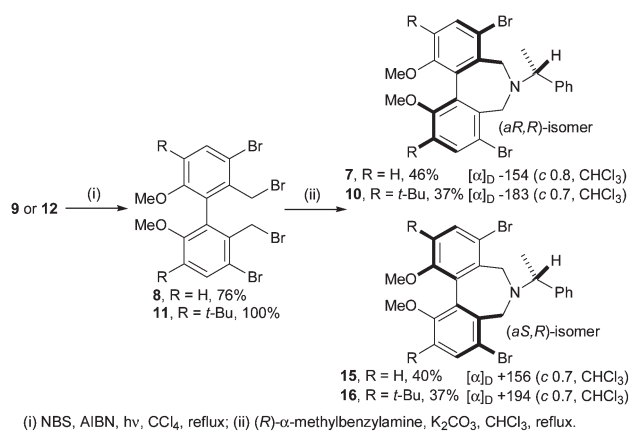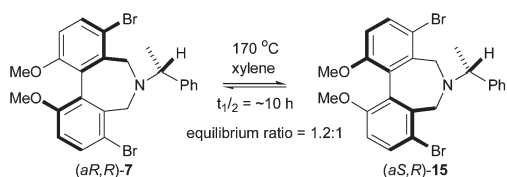
would then be reacted with (*R*)-α-methylbenzylamine to give the dihydro-5*H*-dibenz[*c,e*]azepines **7**, **10**, **15** and **16** which in turn could be converted into the target dihydro-5*H*-dibenz[*c,e*]azepinium salts **3–6** as outlined above. This has the advantage that

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Scheme 6

(i) NBS, AIBN, hv, CCl₄, reflux; (ii) (R)-α-methylbenzylamine, K₂CO₃, CHCl₃, reflux.

Scheme 7

Scheme 8

(i) 3,5-di-CF₃C₆H₃B(OH)₂, Pd(PPh₃)₄, K₂CO₃, dioxane, reflux; (ii) MeI, CH₃CN, 80 °C.

Table 1 Quaternization of **21–24** with CH₃I

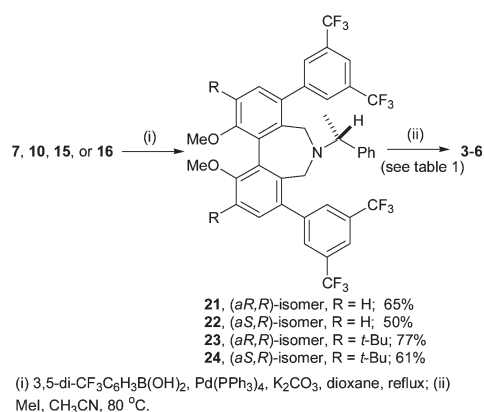| Substrate	Time (h)	Product	Yield (%)
21	9	**3**	36
22	2	**4**	76
23	24	**5**	38
24	3	**6**	74

Intermediates **9** and **12** were then subjected to radical bromination, followed by coupling with (R)-α-methylbenzylamine (Scheme 6). This generated the desired dihydro-5H-dibenz[c,e] azepine intermediates **7**, **10**, **15** and **16** in high overall yield. No kinetic resolution was observed in the second step of this sequence, but gratifyingly the diastereoisomeric pairs **7/15** and **10/16** were readily separated by chromatography on silica gel. The slightly lower isolated yield of compound **15** compared with its diastereoisomer **7** simply reflects the greater difficulty of recovering the more polar diastereoisomer from the silica gel chromatography.

In order to assign the stereochemistry of the diastereoisomeric products, compounds **7** and **15** were also prepared using the approach outlined in Scheme 1. Comparison of ¹H NMR and [α]_D values[14] established that the less polar diastereoisomers had (aR,R)-stereochemistry and the more polar diastereoisomers possess (aS,R)-stereochemistry.

With an efficient route to these key intermediates in hand we next investigated the thermal interconversion of compounds **7** and **15**. Starting with either diastereoisomer, it was found that heating to 170 °C (bath temperature) in xylene was required to effect interconversion. Under these conditions, the equilibrium ratio slightly favoured the (aR,R)-diastereoisomer **7** (Scheme 7). This confirms the *atropos* nature of the dihydro-5H-dibenz[c,e] azepines **7** and **15**, but also offers the possibility of cycling material between these two structures if required. Attempts to interconvert the more highly substituted dihydro-5H-dibenz[c,e] azepines **10** and **16** were unsuccessful.

Conversion of the dihydro-5H-dibenz[c,e]azepines **7**, **10**, **15** and **16** into the target quaternary ammonium salts **3–6** was then effected using procedures analogous to those previously developed for the synthesis of compound **2** (Scheme 8).[4] The 3,5-bis-trifluoromethylphenyl substituents were first introduced via
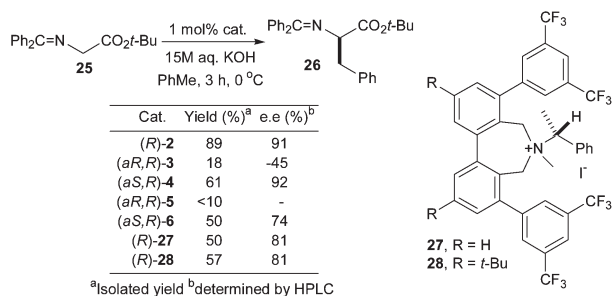
Suzuki–Miyaura coupling. It was found that all four substrates reacted at a similar rate, the lower isolated yields for the (aS,R)-diastereoisomers **22** and **24** again appeared to be a consequence of the fact that these compounds were significantly more polar that the corresponding (aR,R)-diastereoisomers **21** and **23**.

When the quaternization of these products with methyl iodide was attempted, a significant difference in reactivity was observed (Table 1). It was found that the (aS,R)-dihydro-5H-dibenz[c,e] azepines **22** and **24** reacted rapidly with methyl iodide at 80 °C (100% conversion after 2–3 h), whereas the (aR,R)-isomers reacted sluggishly (<40% conversion after 9 h at 80 °C). Attempts to force the latter reactions to completion simply led to substantial decomposition of the products and failed to improve the isolated yields.

The low reactivity of the (aR,R)-dihydro-5H-dibenz[c,e]azepines **21** and **23** towards methyl iodide, coupled with their significantly shorter retention times on silica gel chromatography suggests that the N-lone-pair in these compounds is significantly less accessible than the corresponding N-lone-pair in the (aS,R)-diastereoisomers **22** and **24**.

With *atropos* salts **3–6** prepared we were then able to compare their efficiency as phase-transfer catalysts with the corresponding *tropos* salt **2**. For this purpose we selected the alkylation of glycine imine ester **25** under conditions previously optimised for salts **1** and **2**. The results are shown in Scheme 9. To aid comparison of the structures we have also included results obtained using the related *tropos* salts **27** and **28**.

It was found that all the *atropos* salts (**3–6**) were inferior PTC catalysts compared with the *tropos* salt **2**. In addition, salt **6** exhibited poor solubility in organic solvents such as toluene and chloroform, which further compromised its ability to act as a PTC. After 3 h at 0 °C the alkylation was complete when 1 mol% of catalyst **2** was used, whereas with all the other catalysts

Cat.	Yield (%)[a]	e.e (%)[b]
(R)-2	89	91
(aR,R)-3	18	-45
(aS,R)-4	61	92
(aR,R)-5	<10	-
(aS,R)-6	50	74
(R)-27	50	81
(R)-28	57	81

[a]Isolated yield [b]determined by HPLC

Scheme 9

Fig. 2

Fig. 3

the reaction was incomplete after this time period. Most significantly the reactions involving catalysts with the (aR,R)-stereochemistry (3 and 5) were found to be very sluggish, giving low conversion and low isolated yields. These catalysts also appear to favour the opposite (S) enantiomer of the product 26 as evidenced by the result observed using (aR,R)-3. The difference in reactivity and enantioselectivity between the diastereoisomeric catalysts (aR,R)-3 and (aS,R)-4 seems to confirm the hypothesis that the dihydro-5H-dibenz[c,e]azepinium fragment in these structures plays a key role in influencing both reactivity and enantioselectivity. In this respect these α-methylbenzylamine derived catalysts appear to show similar characteristics to conformationally flexible spirobinaphthyl ammonium salts reported by the Maruoka group.[15] Taken together, these results suggest that reactions involving the *tropos* quaternary ammonium salts 2, 27 and 28 proceed preferentially *via* ion-pair intermediates in which the dihydro-5H-dibenz[c,e]azepinium ring adopts an (aS)-conformation. In this way the stereochemical information in the starting α-methylbenzylamine is amplified to a level that results in high enantioselectivity in the PTC alkylation.

Based on this information, we can now propose a model for how *tropos* quaternary ammonium salts 1 and 2 might interact with the enolate derived from glycine imine 25 (Fig. 2). This model is based on the assumption that the most favourable ion-pair is the one with the greatest electrostatic interaction energy, and that the positive charge in a quaternary ammonium salt resides predominantly on the H-atoms neighbouring the quaternary ammonium centre.[16] Molecular modelling studies on quaternary ammonium salt 2 with the dihydro-5H-dibenz[c,e]azepinium ring in the (aS)-conformation, suggest that the most accessible positive charge lies on a surface comprising four H-atoms (the CH2 indicated, and two H-atoms in the N-CH3 group) adjacent to the quaternary ammonium centre. Modelling of ion-pairs involving this surface suggest that arrangement depicted in Fig. 2 provides the best fit.[17] In this arrangement the *si*-face of the enolate is blocked, which is consistent with the sense of enantioselectivity observed in both alkylation and Michael addition processes involving glycine imine 25 and PTCs 1 and 2.

In contrast, an analogous ion-pair arrangement in which the quaternary ammonium salt 2 has the dihydro-5H-dibenz[c,e]azepinium ring in the (aR)-conformation would have the *re*-face of the enolate blocked (Fig. 3). This is consistent with the observation that *atropos* (aR)-analogues of 2 favour the opposite enantiomer in the glycine imine alkylation (Scheme 9). This ion-pair arrangement is predicted to be >10 kcal mol^{-1} less stable and
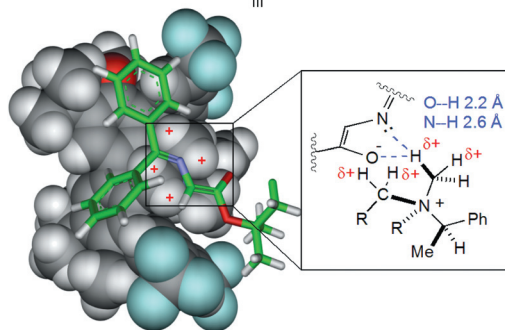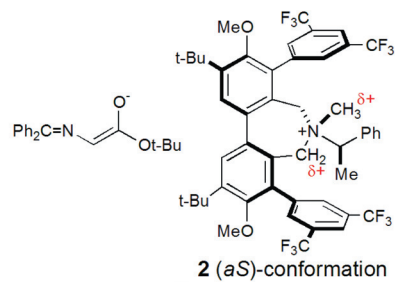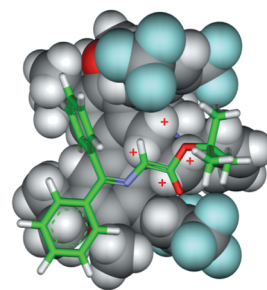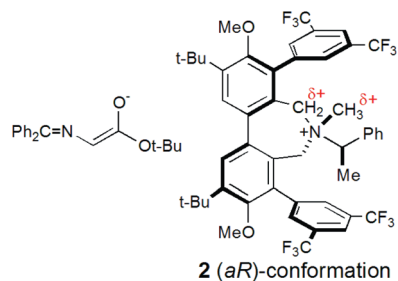
have less favourable overlap of the positive and negative charged surfaces.[17] This is consistent with experimental results which indicate that alkylation *via* this arrangement is highly disfavoured.

Conclusions

In conclusion, we have developed a short synthetic route to diastereoisomeric *atropos* dihydro-5H-dibenz[c,e]azepinium salts *via* reaction of a single enantiomer of (R)-α-methylbenzylamine with racemic *atropos* biphenol derivatives. Compounds prepared

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via this approach have provided strong evidence that structurally related *tropos* dihydro-5*H*-dibenz[*c,e*]azepinium salts preferentially react *via* a single conformation in PTC reactions involving glycine imine enolates. The intermediate *atropos* dihydro-5*H*-dibenz[*c,e*]azepines **7**, **10**, **15**, **16** also have the potential to serve as precursors for a range of other organocatalyst structures (*e.g.* chiral iminium salts for asymmetric epoxidation,[18] chiral secondary and tertiary amines for asymmetric aldol chemistry[19]) and studies into these applications will be reported in due course.

Experimental

General

All solvents and chemicals were used as provided by the supplier. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} pre-coated glass TLC plates, visualized using UV light and then basic potassium permanganate solution. Flash chromatography was performed using Merck silica gel (230–400 mesh) as the stationary phase. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded using either a Perkin-Elmer FT 1600 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV3400 or DPX400 spectrometer at ambient temperature. Chemical shifts are quoted relative to residual solvent and *J* values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br., broad; m, multiplet. Mass spectra were obtained on a Micromass Autospec or Micromass LCT instruments using electron impact (EI) or electrospray (ES) ionization. Specific rotations were measured using a Bellingham and Stanley ADP440 polarimeter at ambient conditions and are given in units of deg cm^2 g^{-1}; *c* is in g per 100 mL of solvent. HPLC analysis was performed on a Hewlett-Packard LC-1100 machine fitted with a diode array detector. All e.e.s were determined by HPLC comparison with racemates using a Chiralcel OD-H analytical column. HPLCs were run in duplicate and the ratio of integrals checked for consistency at four separate wavelengths (220 nm, 232 nm, 254 nm, 280 nm). DFT calculations were performed using B3LYP/6-31G* as implemented in Spartan '10 v1.1.0.[20] Biphenol **14** was prepared and resolved as previously described.[7] Diethers (±)-**9**, (*aS*)-**9**, (*aR*)-**9**, were all prepared from **14** following the procedure previously reported for the (*aS*)-isomer.[8] Biphenol **20** was prepared as previously described.[13]

(±)-5,5′-Dibromo-3,3′-di-*tert*-butyl-2,2′-dimethoxy-6,6′-dimethylbiphenyl, 12

A mixture of 5,5′-dibromo-3,3′-di-*tert*-butyl-2,2′-dihydroxy-6,6′-dimethylbiphenyl **20** (29.7 mg, 0.06 mmol) and anhydrous K_2CO_3 (25.4 mg, 0.18 mmol) in dry DMF (1 mL) was placed under argon. MeI (10 μl, 0.15 mmol) was added and the mixture stirred at room temperature for 18 h. Water (5 mL) was then added and the resulting solution extracted with EtOAc (5 × 5 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether) to give the product (23.4 mg, 74%) as a white solid, m.p. 144–145 °C; R_f 0.5 (98 : 2 petroleum ether–EtOAc); ν_{max}(CHCl$_3$)/cm^{-1} 3011, 1602; δ_H (400 MHz, CDCl$_3$) 7.54 (2H, s, ArH), 3.13 (6H, s, OCH$_3$), 2.09 (6H, s CH$_3$), 1.37 (18H, s, C(CH$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 157.0 (C), 142.7 (C), 135.7 (C), 133.4 (C), 130.4 (CH), 119.4 (C), 59.5 (CH$_3$), 35.0 (C), 30.5 (CH$_3$), 20.6 (CH$_3$); *m/z* (ESI) 537 (M + Na$^+$, ^{81}Br$_2$, 44), 535 (M + Na$^+$, ^{81}Br^{79}Br, 100), 533 (M + Na$^+$, ^{79}Br$_2$, 52%); *m/z* (ESI) found [M + Na]$^+$ 535.0628, $C_{24}H_{32}{}^{81}Br^{79}BrO_2Na^+$ requires 535.0641.

(±)-5,5′-Dibromo-6,6′-bis(bromomethyl)-2,2′-dimethoxybiphenyl, 8

A stirred solution of (±)-5,5′-dibromo-2,2′-dimethoxy-6,6′-dimethylbiphenyl **9** (2.67 g, 6.68 mmol) in CCl$_4$ (25 mL) was placed under a nitrogen atmosphere. NBS (2.73 g, 15.3 mmol) was added followed by AIBN (38 mg). The mixture was stirred at reflux, heated by light bulb irradiation, (100 W bulb, 1 cm from flask) for 2 h. After cooling to room temperature, the mixture was filtered through a short plug of silica, washing through with CCl$_4$ (3 × 60 mL). The solution was concentrated under reduced pressure and the residue purified by chromatography on silica gel (9 : 1 petroleum ether–EtOAc) to give the product **15** (2.82 g, 76%) as a white solid, m.p. 203–206 °C; ν_{max}(neat)/cm^{-1} 3004, 2933, 2835, 1567; δ_H (400 MHz, CDCl$_3$) 7.64 (2H, d, *J* 9.0, ArH), 6.87 (2H, d, *J* 9.0, ArH), 4.26 (2H, d, *J* 10.0, CH$_a$H$_b$Br), 4.24 (d, *J* 10.0, CH$_a$H$_b$Br), 3.71 (6H, s, OCH$_3$); δ_C (100 MHz, CDCl$_3$) 156.4 (C), 135.8 (C), 134.0 (CH), 126.6 (C), 116.3 (C), 112.7 (CH), 56.0 (CH$_3$), 32 (CH$_2$); *m/z* (EI) 560 (M$^+$, ^{79}Br^{81}Br$_3$, 28), 558 (M$^+$, ^{79}Br$_2{}^{81}$Br$_2$, 43), 556 (M$^+$, ^{79}Br$_3{}^{81}$Br, 30), 275 (100), 273 (40), 86 (57), 84 (93%); Found: C, 34.47; H, 2.49, Calc for $C_{16}H_{14}Br_4O_2$: C, 34.45; H, 2.53%.

(±)-5,5′-Dibromo-6,6′-bis-(bromomethyl)-3,3′-di-*tert*-butyl-2,2′-dimethoxybiphenyl, 11

A stirred solution of (±)-biphenyl **12** (1.52 g, 2.97 mmol) in CCl$_4$ (15 mL) was placed under a nitrogen atmosphere. NBS (1.16 g, 6.53 mmol) was added followed by AIBN (17.1 mg, 0.10 mmol). The mixture was stirred at reflux, heated by light bulb irradiation, (100 W bulb, 1 cm from flask) for 3 h. After cooling to room temperature, the mixture was filtered through silica, washing through with Et$_2$O (3 × 30 mL). The solution was concentrated under reduced pressure and the residue purified by chromatography on silica gel (98 : 2 petroleum ether–EtOAc) to give the product (1.99 g, 100%) as a yellow solid, m.p. 67–68 °C; R_f 0.3 (98 : 2 petroleum ether–EtOAc); ν_{max}(neat)/cm^{-1} 2967, 1602; δ_H (400 MHz, CDCl$_3$) 7.68 (2H, s, ArH), 4.35 (2H, d, *J* 10.5, CH*a*HbBr), 4.31 (2H, d, *J* 10.5, CHa*Hb*Br), 3.23 (6H, s, OCH$_3$), 1.40 (18H, s, C(CH$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 156.2 (C), 146.2 (C), 134.2 (C), 132.9 (CH), 131.7 (C), 120.7 (C), 59.9 (CH$_3$), 35.4 (C), 32.4 (CH$_2$), 30.3 (CH$_3$); *m/z* (EI) 672 (M$^+$, ^{79}Br^{81}Br$_3$, 30), 670 (M$^+$, ^{79}Br$_2{}^{81}$Br$_2$, 48), 668 (M$^+$, ^{79}Br$_3{}^{81}$Br, 32), 512 (48), 510 (100), 508 (48%); *m/z* (EI) found [M]$^+$ 669.8945, $C_{24}H_{30}{}^{79}Br_2{}^{81}Br_2O_2{}^+$ requires 669.8932.

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(aR,R)-4,8-Dibromo-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenzo[c,e]azepine, 7 and (aS,R)-4,8-dibromo-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 15

(R)-α-Methylbenzylamine (0.56 g, 4.61 mmol) was added to a solution of (±)-tetrabromide **8** (2.57 g, 4.61 mmol) in CHCl$_3$ (65 mL). Finely ground anhydrous K$_2$CO$_3$ (4.20 g, 30.4 mmol) was added and the mixture placed under an argon atmosphere. After stirring at reflux for 48 h, the mixture was cooled to room temperature, filtered and washed with CHCl$_3$ (30 mL). The solution was concentrated under reduced pressure and the residue purified by chromatography on silica gel (9 : 1 petroleum ether–EtOAc) to give the (aR,R)-isomer **7** (1.09 g, 46%) as a cream solid, m.p. 82–85 °C; [α]$_D$ −154 (c 0.8, CHCl$_3$); R$_f$ 0.2 (9 : 1 petroleum ether–EtOAc); ν$_{max}$(neat)/cm^{-1} 3011, 2938, 2838, 1573; δ$_H$ (400 MHz, CDCl$_3$) 7.60 (2H, d, J 9.0, ArH), 7.59–7.57 (2H, m, ArH), 7.36–7.30 (2H, m, ArH), 7.24 (1H, tt, J 7.5, 1.5, ArH), 6.85 (2H, d, J 9.0, ArH), 4.21 (2H, d, J 12.5, NCHaHb), 3.81 (1H, q, J 6.5, NCHCH$_3$), 3.81 (6H, s, OCH$_3$), 3.00 (2H, d, J 12.5, NCHaHb), 1.34 (3H, d, J 6.5, NCHCH$_3$); δ$_C$ (100 MHz, CDCl$_3$) 155.7 (C), 147.0 (C), 136.2 (C), 132.9 (CH), 128.0 (CH), 127.6 (CH), 127.4 (C), 126.5 (CH), 115.7 (C), 111.8 (CH), 61.2 (CH), 56.0 (CH$_3$), 51.3 (CH$_2$), 22.4 (CH$_3$); m/z (ESI+) 520 (M + H$^+$, ^{81}Br$_2$, 50), 518 (M + H$^+$, ^{81}Br^{79}Br, 100), 516 (M + H$^+$, ^{79}Br$_2$, 48%); m/z (ESI+) found [M + H]$^+$ 518.0135, C$_{24}$H$_{24}$^{81}Br^{79}BrNO$_2$$^+$ requires 518.0147.

Followed by the (aS,R)-isomer **15** (0.96 g, 40%) as a cream solid, m.p. 82–85 °C; [α]$_D$ +156 (c 0.7, CHCl$_3$); R$_f$ 0.1 (9 : 1 petroleum ether–EtOAc); ν$_{max}$(neat)/cm^{-1} 3000, 2934, 2835, 1562; δ$_H$ (400 MHz, CDCl$_3$) 7.58 (2H, d, J 9.0, ArH), 7.43–7.38 (2H, m, ArH), 7.34–7.29 (2H, m, ArH), 7.25 (1H, tt, J 7.5, 1.5, ArH), 4.15 (2H, d, J 13.0, NCHaHb), 3.79 (6H, s, OCH$_3$), 3.61 (1H, q, J 6.0, NCHCH$_3$), 2.87 (2H, d, J 13.0, NCHaHb), 1.70 (3H, d, J 6.0, NCHCH$_3$); δ$_C$ (100 MHz, CDCl$_3$) 155.6 (C), 145.0 (C), 135.9 (C), 132.9 (CH), 128.3 (CH), 127.7 (CH), 127.4 (C), 127.0 (CH), 115.6 (C), 111.9 (CH), 61.6 (CH), 56.0 (CH$_3$), 51.6 (CH$_2$), 23.5 (CH$_3$); m/z (ESI+) 520 (M + H$^+$, ^{81}Br$_2$, 51), 518 (M + H$^+$, ^{81}Br^{79}Br, 100), 516 (M + H$^+$, ^{79}Br$_2$, 48%), m/z (ESI+) found [M + H]$^+$ 518.0143, C$_{24}$H$_{24}$^{81}Br^{79}BrNO$_2$$^+$ requires 518.0147.

(aR,R)-4,8-Dibromo-2,10-di-tert-butyl-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 10 and (aS,R)-4,8-dibromo-2,10-di-tert-butyl-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 16

(R)-α-Methylbenzylamine (0.35 mL, 2.76 mmol) was added to a solution of (±)-tetrabromide **11** (1.68 g, 2.51 mmol) in CHCl$_3$ (65 mL). Finely ground anhydrous K$_2$CO$_3$ (2.29 g, 16.5 mmol) was then added and the mixture placed under an argon atmosphere. After stirring at reflux for 72 h, the mixture was cooled to room temperature and filtered, washing through with CHCl$_3$ (50 mL). The solution was then concentrated under reduced pressure and the residue purified by chromatography on silica gel (1 : 1 petroleum ether–toluene) to give the (aR,R)-isomer **10** (0.58 g, 37%) as a cream solid, m.p. 96–98 °C; [α]$_D$ −183 (c 0.7, CHCl$_3$); R$_f$ 0.2 (98 : 2 petroleum ether–EtOAc); ν$_{max}$(CHCl$_3$)/cm^{-1} 2967, 1450, 1401, 1359, 1245, 1093; δ$_H$ (400 MHz, CDCl$_3$) 7.59–7.56 (4H, m, ArH), 7.34–7.30 (2H, m, ArH), 7.24 (1H, tt, J 7.5, 1.5, ArH), 4.24 (2H, d, J 12.5,

NCHaHb), 3.95 (1H, q, J 6.5, NCHCH$_3$), 3.06 (2H, d, J 12.5, NCHaHb), 3.04 (6H, s, OCH$_3$), 1.41 (18H, s, C(CH$_3$)$_3$), 1.36 (3H, d, J 6.5, NCHCH$_3$); δ$_C$ (100 MHz, CDCl$_3$) 156.9 (C), 147.1 (C), 143.8 (C), 134.0 (C), 132.0 (C), 130.7 (CH), 128.0 (CH), 127.6 (CH), 126.6 (CH), 117.9 (C), 61.3 (CH), 59.9 (CH$_3$), 51.7 (CH$_2$), 35.2 (C), 30.2 (CH$_3$), 22.7 (CH$_3$); m/z (ESI) 632 (M + H$^+$, ^{81}Br$_2$, 50), 630 (M + H$^+$, ^{79}Br^{81}Br, 100), 628 (M + H$^+$, ^{79}Br$_2$, 49%); m/z (ESI) found [M + H]$^+$ 628.1379, C$_{32}$H$_{40}$^{79}Br^{81}BrNO$_2$$^+$ requires 630.1399.

Followed by the (aS,R)-isomer **16** (0.58 g, 37%) as a cream solid, m.p. 96–98 °C; [α]$_D$ +194 (c 0.7, CHCl$_3$); R$_f$ 0.1 (98 : 2 petroleum ether–EtOAc); ν$_{max}$(CHCl$_3$)/cm^{-1} 2965, 1452, 1401, 1359, 1244, 1093; δ$_H$ (400 MHz, CDCl$_3$) 7.54 (2H, s, ArH), 7.44–7.42 (2H, m, ArH), 7.36–7.32 (2H, m, ArH), 7.26 (1H, tt, J 7.0, 1.5, ArH), 4.20 (2H, d, J 13.0, NCHaHb), 3.62 (1H, q, J 6.0, NCHCH$_3$), 3.01 (6H, s, OCH$_3$), 2.92 (2H, d, J 13.0, NCHaHb), 1.70 (3H, d, J 6.0, NCHCH$_3$), 1.40 (18H, s, C(CH$_3$)$_3$); δ$_C$ (100 MHz, CDCl$_3$) 156.9 (C), 145.2 (C), 143.9 (C), 133.8 (C), 132.0 (C), 130.7 (CH), 128.4 (CH), 127.6 (CH), 127.0 (CH), 117.9 (C), 61.7 (CH), 59.9 (CH$_3$), 51.8 (CH$_2$), 35.2 (C), 30.2 (CH$_3$), 21.5 (CH$_3$); m/z (ESI) 632 (M + H$^+$, ^{81}Br$_2$, 54), 630 (M + H$^+$, ^{79}Br^{81}Br, 100), 628 (M + H$^+$, ^{79}Br$_2$, 57%); m/z (ESI) found [M + H]$^+$ 630.1401, C$_{32}$H$_{40}$^{79}Br^{81}BrNO$_2$$^+$ requires 630.1399.

(aR,R)-4,8-Bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 21

(aR,R)-Dibromide **7** (0.75 g, 1.5 mmol), 3,5-bis-trifluoromethylphenylboronic acid (1.81 g, 7.0 mmol) and finely ground anhydrous K$_2$CO$_3$ (1.16 g, 8.4 mmol) were added under an argon atmosphere. Pd(PPh$_3$)$_4$ (80 mg, 0.07 mmol) was added followed by degassed 1,4-dioxane (15 mL). After stirring at reflux for 2 days, the reaction mixture was cooled to room temperature, filtered through Celite and washed with CHCl$_3$ (3 × 15 mL). The solution was concentrated under reduced pressure and the residue purified by chromatography on silica gel (1 : 1 toluene–petroleum ether) to give the product **21** (0.74 g, 65%) as a yellow solid, m.p. 229–231 °C; [α]$_D$ −181 (c 0.7, CHCl$_3$); R$_f$ 0.5 (1 : 1 toluene–petroleum ether); ν$_{max}$(CHCl$_3$)/cm^{-1} 3011, 2940, 2839, 1586, 1491, 1463, 1380, 1279, 1182, 1140; δ$_H$ (500 MHz, CDCl$_3$) 8.60–7.81 (3H, m, ArH), 7.78 (2H, s, ArH), 7.75–7.48 (1H, m, ArH), 7.44 (2H, d, J 8.5, ArH), 7.14 (2H, d, J 8.5, ArH), 7.04–6.97 (3H, m, ArH), 6.80 (2H, d, J 6.5, ArH), 3.94–3.92 (2H, m, NCHaHb), 3.94, (6H, s, OCH$_3$), 3.14–3.12 (1H, m, NCHCH$_3$), 3.13 (2H, d, J 12.5, NCHaHb), 0.97 (3H, d, J 6.5, NCHCH$_3$); δ$_C$ (125 MHz, CDCl$_3$) 156.6 (C), 145.3 (C), 143.2 (C), 133.7 (C), 131.8 (C), 131.3 (C, q, J 33.0), 131.2 (CH), 129.9 (CH), 127.8 (CH), 126.6 (C), 126.1 (CH), 125.7 (CH), 123.4 (C, q, J 273.0), 120.5 (m, CH), 110.5 (CH), 61.1 (CH), 56.0 (CH$_3$), 48.3 (CH$_2$), 23.2 (CH$_3$); m/z (ESI+) 784 (M + H$^+$, 100%); m/z (ESI+) found [M + H]$^+$ 784.2079, C$_{40}$H$_{30}$F$_{12}$NO$_2$$^+$ requires 784.2079.

(aS,R)-4,8-Bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 22

(aS,R)-Dibromide **10** (1.45 g, 2.80 mmol), was reacted with 3,5-bis-trifluoromethyl phenylboronic acid following the procedure

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described above to afford the product **22** (1.09 g, 50%) as a white solid, m.p. 94–96 °C; $[\alpha]_D$ +85 (c 0.7, CHCl$_3$); R_f 0.2 (1 : 1 toluene–petroleum ether); ν_{max}(CHCl$_3$)/cm^{-1} 3012, 2940, 2839, 1587, 1492, 1462, 1380, 1279; δ_H (500 MHz, CDCl$_3$) 7.90–7.81 (6H, m, ArH), 7.34 (2H, d, J 8.5, ArH), 7.09 (2H, d, J 8.5, ArH), 7.01 (1H, tt, J 7.5, 1.5, ArH), 6.94 (2H, dd, J 7.5, 7.0, ArH), 6.82 (2H, dd, J 7.0, 1.5, ArH), 3.92 (6H, s, OCH$_3$), 3.56 (2H, d, J 13.0, NC**H**aHb), 3.07 (1H, q, J 6.5, NC**H**CH$_3$), 2.97 (2H, d, J 13.0, NCHa**H**b), 0.51 (3H, d, J 6.5, NCHC**H**$_3$); δ_C (125 MHz, CDCl$_3$) 156.5 (C), 143.5 (C), 143.4 (C), 134.1 (C), 131.7 (C), 131.4 (C, q, J 33.0), 130.6 (CH), 130.0 (CH), 127.9 (CH), 126.9 (CH), 126.8 (CH), 126.3 (C), 123.4 (C, q, J 273.0), 120.6 (m, CH), 61.3 (CH), 56.0 (CH$_3$), 48.2 (CH$_2$), 19.5 (CH$_3$); m/z (ESI+) 784 (M + H$^+$, 100%); m/z (ESI+) found [M + H]$^+$ 784.2089, C$_{40}$H$_{30}$F$_{12}$NO$_2^+$ requires 784.2079.

(aR,R)-2,10-Di-tert-butyl-4,8-bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 23

(aR,R)-Dibromide **15** (200 mg, 0.32 mmol) was reacted with 3,5-bis-trifluoromethyl phenylboronic acid following the procedure described above to afford the product (218 mg, 77%) as a white solid, m.p. 145–148 °C; $[\alpha]_D$ −122 (c 0.8 in CHCl$_3$); R_f 0.2 (98 : 2 petroleum ether–EtOAc); ν_{max}(CHCl$_3$)/cm^{-1} 2964, 1602, 1452, 1386, 1360, 1257, 1140; δ_H (400 MHz, CDCl$_3$) 7.97 (4H, br s, ArH), 7.80 (2H, br s, ArH), 7.33 (2H, s, ArH), 7.05–6.97 (3H, m, ArH), 6.80–6.78 (2H, m, ArH), 3.94 (2H, d, J 12.5, NC**H**aHb), 3.20–3.13 (3H, m, NCHa**H**b, NC**H**CH$_3$), 3.18 (6H, s, OCH$_3$), 1.50 (18H, s, C(CH$_3$)$_3$), 0.98 (3H, d, J 6.5, NCHC**H**$_3$); δ_C (100 MHz, CDCl$_3$) 158.0 (C), 145.4 (C), 143.6 (C), 142.4 (C), 133.4 (C), 131.5 (C), 131.4 (C), 131.4 (C, q, J 33.0), 129.9 (CH, br s), 128.4 (CH), 127.9 (CH), 126.2 (C), 125.7 (CH), 123.4 (C, q, J 273.0), 120.8–120.5 (CH, m), 61.1 (CH), 59.9 (CH$_3$), 48.5 (CH$_2$), 35.2 (C), 30.4 (CH$_3$), 23.1 (CH$_3$); m/z (ESI) 898 (15), 896 (M + H$^+$, 100%); m/z (ESI) found [M + H]$^+$ 896.3289, C$_{48}$H$_{46}$F$_{12}$NO$_2^+$ requires 896.3331.

(aS,R)-2,10-Di-tert-butyl-4,8-bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepine, 24

(aS,R)-Dibromide **16** (200 mg, 0.32 mmol) was reacted with 3,5-bis-trifluoromethyl phenylboronic acid following the procedure described above to afford the product (173 mg, 61%) as a white solid; m.p. 105–107 °C; $[\alpha]_D$ +74 (c 0.7 in CHCl$_3$); R_f 0.2 (98 : 2 petroleum ether–EtOAc); ν_{max}(CHCl$_3$)/cm^{-1} 2964, 1603, 1454, 1386, 1359, 1280, 1181, 1141; δ_H (400 MHz, CDCl$_3$) 8.00–7.70 (6H, br m, ArH), 7.24 (2H, s, ArH), 7.04–6.95 (3H, m, ArH), 6.89–6.87 (2H, m, ArH), 3.58 (2H, d, J 13.0, NC**H**aHb), 3.17 (6H, s, OCH$_3$), 3.08 (1H, q, J 6.5, NC**H**CH$_3$), 3.03 (2H, d, J 13.0, NCHa**H**b), 1.48 (18H, s, C(CH$_3$)$_3$), 0.53 (3H, d, J 6.5, NCHC**H**$_3$); δ_C (100 MHz, CDCl$_3$) 157.9 (C), 144.0 (C), 143.8 (C), 142.1 (C), 133.4 (C), 132.0 (C), 131.4 (C, q, J 33.5), 131.0 (C), 130.0 (CH, br s), 127.9 (CH), 126.9 (CH), 126.8 (CH), 123.4 (C, q, J 273), 120.8–120.5 (CH, m), 61.3 (CH), 59.8 (CH$_3$), 48.5 (CH$_2$), 35.2 (C), 30.4 (CH$_3$), 20.1 (CH$_3$); m/z (ESI) 896 (M + H$^+$, 100); m/z (ESI) found [M + H]$^+$ 896.3346, C$_{48}$H$_{46}$F$_{12}$NO$_2^+$ requires 896.3331.

(aR,R)-4,8-Bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-methyl-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepinium iodide, 3

A solution of (aR,R)-**21** (91.4 mg, 0.12 mmol) in CH$_3$CN (4 mL) was placed under an argon atmosphere. CH$_3$I (112 μL, 1.80 mmol) was added and the resulting solution stirred at 80 °C for 9 h. The solution was cooled to room temperature, concentrated under reduced pressure and the residue was purified by chromatography on silica gel (19 : 1 CH$_2$Cl$_2$–MeOH) to give the recovered starting material starting material **21** (44.5 mg, 49%), followed by the product **3** (39.0 mg, 36%) as an off white solid, m.p. 148–149 °C; $[\alpha]_D$ +32 (c 0.9, CHCl$_3$); R_f 0.2 (19 : 1 CH$_2$Cl$_2$–MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 2945, 1598, 1494, 1462, 1379, 1280, 1185, 1144; δ_H (400 MHz, CDCl$_3$) 7.95–7.74 (4H, m, ArH), 7.61 (2H, br s, ArH), 7.45 (1H, d, J 8.5, ArH), 7.44 (1H, d, J 8.5, ArH), 7.32–7.22 (3H, m, ArH), 7.29 (1H, d, J 8.5, ArH), 7.28 (1H, d, J 8.5, ArH), 7.12 (2H, dd, J 8.0, 7.5, ArH), 5.38 (1H, d, J 14.5, NC**H**aHb), 5.27 (1H, q, J 7.0, NC**H**CH$_3$), 4.36 (1H, d, J 12.5, NC**H**aHb), 4.18 (1H, d, J 14.5, NCHa**H**b), 3.99–3.93 (1H, m, NCHa**H**b), 3.95 (3H, s, OCH$_3$), 3.93 (3H, s, OCH$_3$), 2.59 (3H, s, NCH$_3$), 1.47 (3H, d, J 7.0, NCHC**H**$_3$); δ_C (100 MHz, CDCl$_3$) 157.8 (C), 157.6 (C), 141.0 (C), 140.7 (C), 133.6 (C), 132.8 (C), 132.7 (C, q, J 33.5), 132.6 (C), 131.9 (CH), 130.5 (CH), 130.1 (CH), 129.8 (br s, C), 128.8 (CH), 128.4 (C), 126.2 (C), 126.1 (C), 124.3 (C), 123.1 (C, q, J 273.0), 122.8 (C, q, J 273.0), 122.7–122.4 (m, CH), 121.5–121.3 (m, CH), 75.3 (CH), 63.5 (CH$_2$), 56.4 (CH$_3$), 56.3 (CH$_3$), 51.3 (CH$_2$), 50.6 (CH$_3$), 15.9 (CH$_3$); m/z (ESI+) 798 (M − I$^+$, 48), 786 (100%); m/z (ESI+) found [M − I]$^+$ 798.2230, C$_{41}$H$_{32}$F$_{12}$NO$_2^+$ requires 798.2235.

(aS,R)-4,8-Bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-methyl-6-(1-phenylethyl)-6,7-dihydro-5H-dibenz[c,e]azepinium iodide, 4

Following the procedure above, (aS,R)-**22** (16.9 mg, 0.02 mmol) was reacted with CH$_3$I (112 μL, 1.80 mmol) at 80 °C for 2 h to give the product **4** (15.2 mg, 76%) as a yellow solid, m.p. 116–118 °C; $[\alpha]_D$ +45 (c 0.85, CHCl$_3$); R_f 0.2 (19 : 1 CH$_2$Cl$_2$–MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 2944, 1594, 1496, 1461, 1380, 1280, 1186, 1144; δ_H (400 MHz, CDCl$_3$) 7.94 (4H, br s, ArH), 7.75 (2H, br s, ArH), 7.53 (1H, d, J 8.5, ArH), 7.45–7.39 (1H, m, ArH), 7.44 (1H, d, J 8.5, ArH), 7.41 (1H, d, J 8.5, ArH), 7.34–7.21 (2H, m, ArH), 7.29 (1H, d, J 8.5, ArH), 7.01 (2H, d, J 7.5, ArH), 4.99 (1H, d, J 14.5, NC**H**aHb), 4.04–3.98 (2H, m, NC**H**CH$_3$, NCHa**H**b), 3.98 (3H, s, OCH$_3$), 3.95 (3H, s, OCH$_3$), 3.47 (1H, d, J 13.0, NC**H**aHb), 3.15 (1H, d, J 13.0, NCHa**H**b), 2.75 (3H, s, NCH$_3$), 0.95 (3H, d, J 7.0, NCHC**H**$_3$); δ_C (100 MHz, CDCl$_3$) 157.6 (C), 157.4 (C), 141.2 (C), 140.8 (C), 132.7 (CH), 132.7 (CH), 132.4 (C), 131.5 (CH), 130.9 (br s, CH), 130.7 (C), 129.9–129.3 (m, CH), 126.5 (C), 126.2 (C), 126.2–119.7 (m, C), 126.1 (C), 124.8 (C), 123.7 (C), 122.7 (C, q, J 273.5), 122.4–122.2 (m, CH), 121.7–121.3 (m, CH), 114.3 (CH), 114.0 (CH), 70.5 (CH), 59.6 (CH$_2$), 58.6 (CH$_2$), 56.5 (CH$_3$), 56.3 (CH$_3$), 43.0 (CH$_3$), 15.8 (CH$_3$); m/z (ESI+) 798 (M − I$^+$, 100%); m/z (ESI) found [M − I]$^+$ 798.2214, C$_{41}$H$_{32}$F$_{12}$NO$_2^+$ requires 798.2235.

(a*R*,*R*)-2,10-Di-*tert*-butyl-4,8-bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-methyl-6-(1-phenylethyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepinium iodide, 5

Following the above procedure (a*R*,*R*)-**23** was reacted with CH$_3$I (112 µL, 1.80 mmol) at 80 °C for 24 h to give the product **5** (31.0 mg, 38%) as a yellow solid, m.p. 194–195 °C; $[\alpha]_D$ +33 (*c* 0.5, (CH$_3$)$_2$CO); R_f 0.2 (19 : 1 CH$_2$Cl$_2$–MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 2958, 1461, 1384, 1362, 1278, 1139, 1058; δ_H (400 MHz, (CD$_3$)$_2$CO) 8.42 (1H, br s, ArH), 8.25 (1H, br s, ArH), 8.07 (2H, br s, ArH), 8.03 (2H, br s, ArH), 7.69 (1H, s, ArH), 7.66 (1H, s, ArH), 7.35 (1H, tt, *J* 7.5, 1.0, ArH), 7.18 (2H, dd, *J* 8.0, 7.5, ArH), 7.05 (2H, dd, *J* 7.5, 1.0, ArH), 5.06 (1H, d, *J* 14.5, NCH*a*Hb), 4.29 (1H, d, *J* 13.5, NCH*a*Hb), 4.82 (1H, q, *J* 7.0, NC*H*CH$_3$), 4.62 (1H, d, *J* 14.5, NCHa*Hb*), 4.47 (1H, d, *J* 13.5, NCHa*Hb*), 3.38 (3H, s, OCH$_3$), 3.26 (3H, s, OCH$_3$), 2.52 (3H, s, NCH$_3$), 1.66 (3H, d, *J* 7.0, NCHC*H*$_3$), 1.52 (9H, s, C(CH$_3$)$_3$), 1.48 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz, (CD$_3$)$_2$CO) 159.3 (C), 159.1 (C), 145.7 (C), 145.5 (C), 142.3 (C), 141.9 (C), 135.9 (C), 135.9 (C), 135.1 (C), 133.6 (C), 131.2 (CH), 130.8 (C), 130.6 (br s, CH), 130.5 (C), 130.4 (CH), 130.1 (CH), 129.9 (CH), 128.8 (CH), 126.7 (C), 123.6 (C), 123.4 (C, q, *J* 272.5), 123.3 (C, q, *J* 272.5), 122.2–122.0 (m, CH), 121.7–121.5 (m, CH), 75.7 (CH), 62.9 (CH$_2$), 60.6 (CH$_3$), 60.4 (CH$_3$), 53.4 (CH$_2$), 48.9 (CH$_3$), 35.3 (C), 35.3 (C), 29.5 (CH$_3$), 29.5 (CH$_3$), 15.9 (CH$_3$); *m/z* (ESI+) 912 (14), 910 (M − I$^+$, 100%); *m/z* (ESI+) found [M − I]$^+$ 910.3484, C$_{49}$H$_{48}$NO$_2^+$ requires 910.3487.

(a*S*,*R*)-2,10-Di-*tert*-butyl-4,8-bis-(3,5-bis-trifluoromethylphenyl)-1,11-dimethoxy-6-methyl-6-(1-phenylethyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepinium iodide, 6

Following the above procedure (a*R*,*R*)-**24** (82.1 mg, 0.09 mmol) was reacted with CH$_3$I (112 µL, 1.80 mmol) at 80 °C for 3 h to give the product **6** (70.7 mg, 74%) as a yellow solid, m.p. 136–138 °C; $[\alpha]_D$ +59 (*c* 0.8, CHCl$_3$); R_f 0.2 (19 : 1 CH$_2$Cl$_2$–MeOH); ν_{max}(CHCl$_3$)/cm^{-1} 2957, 1459, 1385, 1361, 1280, 1186, 1145; δ_H (500 MHz, CDCl$_3$) 8.13 (1H, br s, ArH), 7.98 (2H, br s, ArH), 7.77 (1H, br s, ArH), 7.43–7.39 (2H, m, ArH), 7.32–7.27 (5H, m, ArH), 7.09 (2H, br s, ArH), 5.02 (1H, d, *J* 14.5, NCH*a*Hb), 4.25 (1H, d, *J* 14.5, NCHa*Hb*), 4.07 (1H, q, *J* 7.0, NC*H*CH$_3$), 3.59 (1H, d, *J* 14.5, NCHa*Hb*), 3.36 (3H, s, OCH$_3$), 3.22 (3H, s, OCH$_3$), 3.18 (1H, d, *J* 13.0, NCHa*Hb*), 2.74 (3H, s, NCH$_3$), 1.52 (9H, s, C(CH$_3$)$_3$), 1.48 (9H, s, C(CH$_3$)$_3$), 0.98 (3H, d, *J* 7.0, NCHC*H*$_3$); δ_C (126 MHz, CDCl$_3$) 159.6 (C), 159.0 (C), 147.2 (C), 147.0 (C), 141.7 (C), 141.3 (C), 135.5 (C), 135.1 (C), 132.7 (C, q, *J* 33.5), 131.4 (CH), 131.2 (C), 131.1 (br s, CH), 130.9 (C), 130.1 (C), 130.1 (CH), 130.0 (CH), 129.5 (br s, CH), 124.4 (C), 123.9 (br s, C), 123.0 (C, q, *J* 273.5), 122.9 (C), 122.6 (C, q, *J* 273.0), 122.5–122.3 (m, CH), 121.7–121.5 (m, CH), 70.5 (CH), 61.3 (CH$_3$), 60.8 (CH$_3$), 59.6 (CH$_2$), 59.3 (CH$_2$), 42.8 (CH$_3$), 35.8 (C), 35.7 (C), 30.0 (CH$_3$), 30.0 (CH$_3$), 15.6 (CH$_3$); *m/z* (ESI+) 910 (M − I$^+$, 100%); *m/z* (ESI+) found [M − I]$^+$ 910.3481, C$_{49}$H$_{48}$NO$_2^+$ requires 910.3487.

General procedure for alkylation of benzophenone glycine imine *tert*-butyl ester, 25

The PTC (1 mol%) and benzophenone glycine imine ester (50 mg, 0.17 mmol) were dissolved in toluene (2 mL). The mixture was degassed with nitrogen and cooled to 0 °C. Benzyl bromide (35 mg, 0.20 mmol) was added followed by 15 M aqueous KOH (1 mL) and the mixture stirred vigorously for 3 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organics were dried (Na$_2$SO$_4$), concentrated under reduced pressure, and then purified by chromatography on silica gel. Enantioselectivity was determined by HPLC (Chiralcel OD-H (0.4 × 25 cm) 100 : 1 (hexane–IPA), 0.5 mL min^{-1}, R_t 18 min (*R*)-isomer and 31 min (*S*)-isomer) as previously described.[4]

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