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Preparation of C2-Symmetric Biaryl *bis*-Iminium Salts and Their Use as Organocatalysts for Asymmetric Epoxidation

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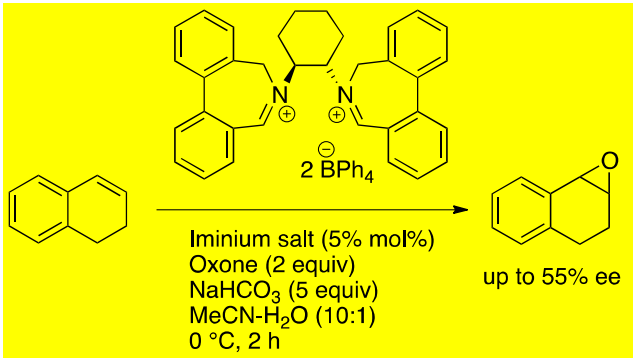

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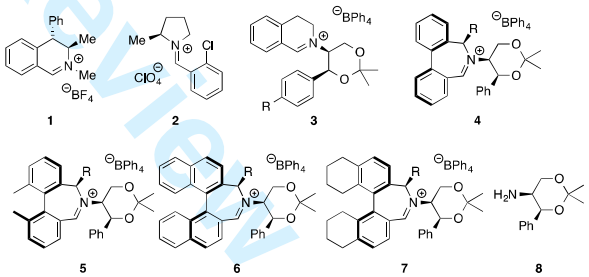
Abstract: Two C2-Symmetric *bis*-iminium salt species containing biphenylazepinium units and derived from two chiral diamines were prepared and tested as organocatalysts for asymmetric epoxidation.

Key words Iminium, Diamine, Organocatalysis, Epoxidation, Biaryl

Introduction

Oxaziridinium salts generated *in situ* from iminium salts with oxone were first shown by Lusinchi to be effective electrophilic oxidants for epoxidation of alkenes, rendering the development of a catalytic process possible.[1] The first enantiomerically pure iminium salt to be used in this way was **1**, with the controlling asymmetric centres sited in the saturated ring of a dihydroisoquinolinium salt, and it was shown to catalyse epoxidation of alkenes with ees of up to about 40% (Figure 1).[2] Even exocyclic iminium salts such as **2**, derived from condensation of enantiopure pyrrolidine moieties with aromatic aldehydes, can afford moderate ees (up to 22%) with relatively high catalyst loadings (up to 100 mol%), necessary perhaps due to *in situ* hydrolysis of the iminium units.[3] Our own contribution has been to design chiral iminium salts that contain asymmetric centres in the exocyclic nitrogen substituent, based upon the reasoning that such designs would bring the enantiocontrolling asymmetric centres closer to the site of oxygen transfer, and hence potentially increase enantioselectivity. We have shown that iminium salts such as **3**-**7** provide ees of up to 99% in epoxidation under our standard conditions using Oxone as stoicheiometric oxidant in aqueous acetonitrile,[4] or using tetraphenylphosphonium monoperoxysulfate (TPPP)[5] under non-aqueous conditions,[6] as well as other oxidants.[7]

Figure 1: Examples of chiral iminium salts



Catalysts incorporating an azepinium structure are highly reactive, inducing complete epoxidation of alkenes within 1–10 minutes in aqueous acetonitrile at 0 °C; they are the most reactive iminium salt epoxidation catalysts discovered to date, and among the most reactive known organocatalysts, effective at loadings of as low as 0.1 mol%. We have applied the chemistry to the synthesis of several natural products including lomatin[8] and scuteflorin A.[9]

Related chiral secondary amines have also been shown to catalyse the asymmetric epoxidation of alkenes, giving up to 66% ee.[10] We have reported that amines corresponding to a number of our iminium salts, such as **4** and **6** (R= H), are indeed effective epoxidation catalysts under our standard conditions, giving yields and ees very similar to the corresponding iminium

species. We have postulated that the amine catalysts are oxidized *in situ* to the corresponding iminium salts, which in turn epoxidize the alkenes *via* the oxaziridinium salts.[11] Yang has examined a range of chiral secondary amines for catalytic activity;[12] these studies revealed the presence of an electron-withdrawing substituent (such as hydroxyl or fluorine groups) at the β-position to the amine group to be beneficial for catalytic activity.

The design of chiral iminium salt catalysts in our group has often centred on the use of (+)-(*S,S*)-L-acetonamine **8** (Figure 1) and its derivatives as chiral appendages, which are effective presumably due to the electronic and steric roles played by the 1,3-dioxane ring and the phenyl group. Studies performed in the group have confirmed that the aromatic C4 substituent in the 1,3-dioxane is vital to obtain high enantioselectivities. Other chiral appendages used for the synthesis of biphenyl-derived iminium salt catalysts, for example *N*-(−)-isopinocampheylamine (IPC), gave lower enantioselectivities.

In the past 20 years, optically active *trans*-1,2-diaminocyclohexane (DACH) has been extensively used as a chiral ligand and as a chiral appendage in catalysts for use in diverse asymmetric reactions.[13] For example, DACH has been used in the synthesis of highly efficient salen ligands used in the asymmetric epoxidation of alkenes,[14] chiral thioureas used as hydrogen-bonding catalysts,[15] and ligands used in palladium-catalysed allylic alkylations.[16] Crystallisation of DACH-binol diastereoisomeric complexes have allowed the resolution of racemic binol.[17] Medicine has also used derivatives of DACH as drugs: notably, complexes with platinum have been developed as anticancer drugs,[18] and water-soluble salen ligands have been used as antibiotics.[19]

We envisaged that a catalyst incorporating DACH or its derivatives might be a potent chiral inducer with the potential to enhance enantioselectivities induced by iminium salt catalysts. With this in mind, we initially aimed to prepare iminium salt catalyst **9**, depicted in Figure 2.

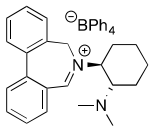


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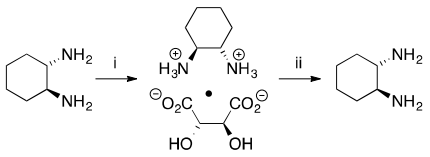
Figure 2: An iminium salt catalyst with a DACH-derivative chiral appendage

We obtained enantiopure (1*S*,2*S*)-DACH **10** from the resolution of racemic *trans*-DACH **10** with D-tartaric acid and subsequent liberation of the monotartrate salt **11** using aqueous sodium hydroxide (Scheme 1).[20] Other methodologies have been developed to resolve the DACH enantiomers, including using the corresponding citrate salts,[21] and high pressure.[22]



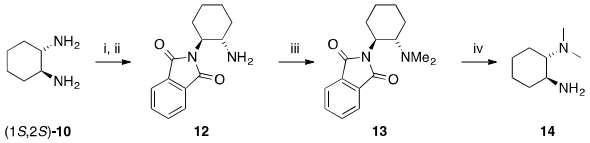
(±)-**10** **11** (1*S*,2*S*)-**10**

Reagents and Conditions: i: D-Tartaric acid (1.0 equiv.), H_2O, CH_3COOH, r.t., 2h, 40%; ii: 4M NaOH, 10 min.

Scheme 1

Using the procedure developed by Gawroński and Kaik,[23] monophthaloylation of (1*S*,2*S*)-**10** was achieved in excellent yield by heating a solution of (1*S*,2*S*)-**10**, phthalic anhydride, and *p*TSA in xylenes under reflux for one hour. The resulting salt was liberated using saturated sodium hydrogen carbonate overnight to give compound **12**. Eschweiler-Clark methylation of **12** using *para*-formaldehyde and formic acid as the hydrogen donor afforded the *bis*-methylated product **13** in 85% yield. Subsequent deprotection of the phthaloyl protecting group using hydrazine monohydrate gave the desired compound **14** in 50-60% yield (Scheme 2).

Reagents and Conditions: i: *p*TSA (1 equiv.), phthalic anhydride



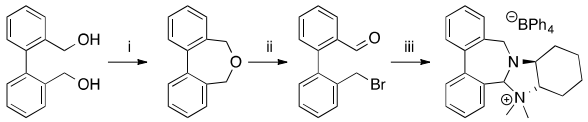
(1*S*,2*S*)-**10** **12** **13** **14**

(1 equiv.), xylenes, reflux, 2 h, 95%; ii: Saturated $NaHCO_3$, CH_2Cl_2, r.t., 16 h, 80%; iii: CH_2O (2.5 equiv.), HCOOH, reflux, 16 h, 85%; iv: $NH_2NH_2.H_2O$ (3 equiv.), EtOH, reflux, 1 h, 50-60%.

Scheme 2

The biphenyl portion was conveniently prepared from 2,2-biphenyl dimethanol **15**, which, after treatment with aqueous hydrobromic acid (24%) at 100 °C for 40 min, gave the oxepine **16**. Subsequent treatment of **16** with molecular bromine in carbon tetrachloride under reflux for one hour led to carboxaldehyde **17** in 60% yield. Cyclocondensation of amine **14** with bromoaldehyde **17** followed by cation exchange, however, furnished quaternary ammonium salt **18** in 70% yield, rather than iminium salt **9** (Scheme 15). We assume that the formation of iminium salt **9** is followed by an intramolecular addition of the nitrogen lone pair at the iminium carbon atom, leading to the formation of the thermodynamically more stable product **18**. We have recently used a similar process to prepare tetracyclic oxazolidines.[24]

Reagents and Conditions: i: HBr (24% in water), 100 °C, 40 min,



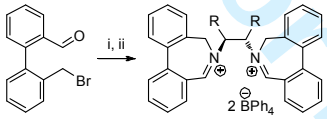
15 **16** **17** **18**

85%; ii: Br_2 (1.1 equiv.), CCl_4, reflux, 1 h, 60%; iii: **14** (1 equiv.), EtOH, r.t., 16 h; then $NaBPh_4$ (1.1 equiv.), EtOH, CH_3CN, r.t., 5 min, 70%.

Scheme 3

Ammonium salt **18** was subsequently tested in the epoxidation of 1-phenylcyclohexene under standard conitions (Ammonium salt (5 mol%), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN:H_2O (10:1), 0 °C), but failed to mediate any epoxidation of the alkene substrate at a catalyst loading of 10 mol%, perhaps suggesting that the potential equilibrium of **18** with iminium salt **9** is unfavourable.

We conjectured that cyclocondensation of two equivalents of bromoaldehyde **17** with the parent (1*S*,2*S*)-diaminocyclohexane might generate an interesting C2-symmetric *bis*-iminium salt species **19**, which, we reasoned, might provide improved enantioselectivity through a more ordered transition state resulting from higher steric crowding. We were successful in preparing *bis*-iminium catalysts **19** and **20**, by condensation of bromoaldehyde **17** with (1*S*,2*S*)-**10** and (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine, respectively, followed by treatment with sodium tetraphenylborate, and recrystallization (Scheme 4).



17 **19**: ($CH_2CH_2CH_2CH_2$)
20: Ph

Reagents and Conditions: i: amine (0.5 equiv.), EtOH, r.t., 48 h; ii: $NaBPh_4$ (1.1 equiv.), EtOH, CH_3CN, r.t., 5 min, **19**: 55%; **20**: 52%.

Scheme 4

We subsequently utilized these catalysts in the epoxidation of a number of prochiral alkenes (Table 1).

Table 1 Asymmetric epoxidation of alkenes using *bis*-iminium salts **19** and **20**.[a]

Catalyst	19			20		
Alkene	Conv.[b]	ee[c]	Conf.[d]	Conv.[b]	ee[c]	Conf.[d]
	100%	22%	(−)-1*S*,2*S*	100%	26%	(−)-1*S*,2*S*
	94%	55%	(−)-1*S*,2*R* [e]	100%	18%	(−)-1*S*,2*R* [e]
	100%	4%	(−)-1*S*,2*S*	100%	6%	(−)-1*S*,2*S* [f]
	100%	17%	(+)-1*R*,2*R*	55%	12%	(+)-1*R*,2*R* [f]

[a] Epoxidation conditions: Iminium salt (5 mol%), Oxone (2 equiv.), $NaHCO_3$ (5 equiv.), MeCN:H_2O (10:1), 0 °C, 2 h. [b] Conversions were evaluated from the ^{1}H-NMR spectra by integration of alkene versus epoxide signals. [c] Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column, or by chiral GC on a Chiraldex B-DM column. [d] The absolute configurations of the major enantiomers were determined by comparison with literature values except where indicated. [e] Epoxidation conditions: iminium salt (5 mol %), Oxone (2 equiv.), Na_2CO_3 (4 equiv.), MeCN:H_2O (1:1), 0 °C, 4 h. [f] 5 h.

Interestingly, catalyst **19** was more reactive than **20**. This catalyst provided 90-95% isolated yields for all four epoxides; it induced complete epoxidation of *trans*-α-methylstilbene and *trans*-stilbene in two hours, while catalyst **20** required prolonged reaction times of up to five hours to achieve 100% conversion of *trans*-α-methylstilbene, and gave a moderate 55% epoxide conversion with *trans*-stilbene in five hours. Both catalysts induced similar enantioselectivities for most substrates, except for 1,2-dihydronaphthalene, typically a challenging substrate for chemical asymmetric epoxidation processes, with catalyst **20** giving higher enantioselectivity than **19** (55% *vs.* 18% ee). The difference in enantioselectivities for this substrate may result from changes in the transition state geometry arising from π-stacking between the aromatic groups of catalyst **20** and the alkene substrate. The reactions are remarkably clean, with only the alkene substrate, epoxide, and catalyst evident in the ^{1}H NMR spectra of the product mixtures.

Conclusion

C2-symmetric *bis*-iminium salts derived from (1*S*,2*S*)-diaminocyclohexane **10** are successful organocatalysts for asymmetric epoxidation, providing enantioselectivities of up to 55%, in the epoxidation of 1,2-dihydronaphthalene. A related ammonium salt **18**, arising from iminium salt **9** by *in situ* intramolecular conjugate addition of the nitrogen atom to the iminium unit failed to mediate epoxidation.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(25) **General procedure for the synthesis of 5*H*-dibenzo[*c,e*]azepinium salts from 2-[2-(bromomethyl)phenyl]benzene carbaldehyde and primary amines:** A solution of the amine (1 equiv) in ethanol (10 mL per gram of amine), was added dropwise to an ice cooled solution of 2-[2-(bromomethyl)-phenyl]benzene carbaldehyde **17** (1.1 equiv) in ethanol (10 mL per gram of **17**). The reaction mixture was stirred overnight while attaining ambient temperature. Sodium tetraphenylborate (1.1 equiv) in the minimum amount of acetonitrile was added in one portion to the reaction mixture and after 5 minutes of stirring, the organic solvents were removed under reduced pressure. Ethanol was added to the residue, followed by few drops of water. The resulting solid was collected by filtration and washed with additional ethanol followed by diethyl ether. If no solid materialises after the addition of the water the suspension is allowed to settle and the ethanol/water phase is decanted off. The gummy residue was macerated in hot ethanol or methanol. The organic salt may then precipitate but in some rare cases it does so upon slow cooling of the hot alcoholic solution. If solubility problems do arise, small amounts of acetonitrile may be added during this process. For catalyst **19**: Prepared according to the general procedure using (1*S*,2*S*)-diaminocyclohexane **10** (0.10 g, 0.88 mmol) and 2-[2-(bromomethyl)-phenyl]benzene carbaldehyde **17** (0.51 g, 1.85 mmol, 2.1 equiv). The product **19** was isolated as yellow powder (0.51 g, 52%); m.p. 145-147 ºC; $[\alpha]^{20}_{D}$ −170.2 (*c* 0.59, CH_3CN); ν_{max}(film)/cm^{-1} 3052, 2933, 1639, 1597, 1552, 1480, 1445, 1425, 1332, 1265, 1208, 761, 731, 705; ^{1}H-NMR (400 MHz, DMSO-d$_6$, 100 °C): δ 1.77 (2 H, d, *J*= 12.0 Hz), 2.01 (2 H, d, *J*= 8.0 Hz), 2.30 (2 H, d, *J*= 8.0 Hz), 2.49–2.53 (2 H, m), 4.71 (2 H, d, *J*= 12.0 Hz), 5.06 (2 H, d, *J*= 12.0 Hz), 5.71 (2 H, s), 6.83 (8 H, t, *J*= 7.2 Hz), 6.97 (16 H, t, *J*= 7.2 Hz), 7.17–7.26 (18 H, m), 7.52 (4 H, br s), 7.73–7.79 (4 H, m), 7.87–8.06 (8 H, m); ^{13}C-NMR (100 MHz, DMSO-d$_6$, 100 °C): δ 24.0, 32.1, 55.0, 72.1, 121.9, 125.1, 125.6, 126.7, 127.0, 128.7, 129.0, 129.5, 130.4, 130.4, 133.8, 135.9, 136.2, 136.8, 141.5, 171.2; *m/z* (FAB) 468.2560; $C_{34}H_{32}N_2$ (cation) requires 468.2566.

(26) **General procedure for epoxidation reactions:** The alkene (1 equiv) and the catalyst (5 mol%) were dissolved in a mixture of acetonitrile and water (10:1, 3 mL per mmol of alkene) and the mixture was cooled to 0 °C. A mixture of Oxone (2 equiv) and sodium hydrogenocarbonate (5 equiv) was added as a solid in one portion to the mixture with vigorous stirring. The mixture was stirred at 0 °C until complete conversion of the alkene was observed by TLC. Diethyl ether (30 mL per mmol of alkene) was added and the reaction mixture was filtered through a pas of mixed anhydrous magnesium sulfate and sodium bisulfite. The

solvents were removed under reduced pressure and the residue was purified using silica gel column chromatography using hexanes as the eluent.

Checklist (have these on hand for manuscript submission in ScholarOne):

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- email address for each author
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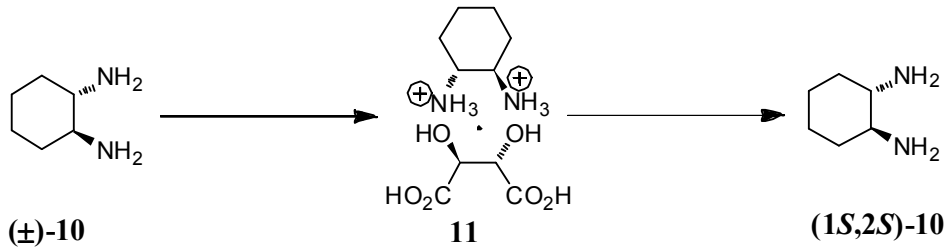
- original graphics files zipped into one zip file
- eye-catching graphical abstract as an individual file
- 5–8 key words
- separate Supporting Information file
- separate zipped Primary Data files including cover sheet (optional)

Useful links:

- SYNLETT homepage
- SYNLETT information and tools for authors
- Graphical abstract samples (PDF file download)
- What is "Primary Data"?
- ScholarOne (manuscript submission)

Supplementary information

Resolution of *trans*-1,2-diaminocyclohexane 10 [1]

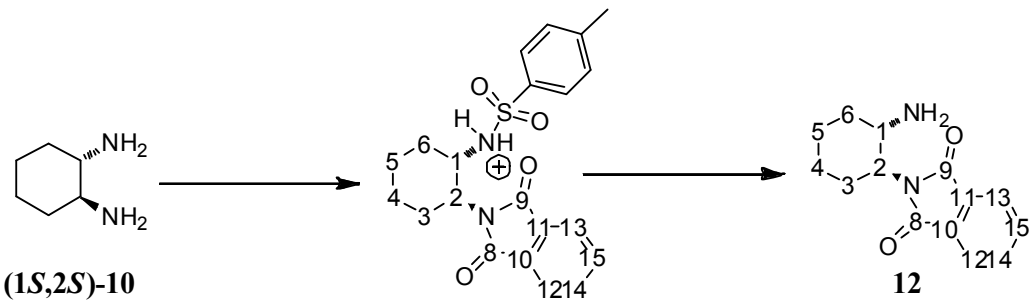


(±)-10 **11** **(1*S*,2*S*)-10**

A 250 mL beaker equipped with a large magnetic stirrer bar was charged with D-(−)-tartaric acid (8.56 g, 57.03 mmol) and distilled water (25 mL). The mixture was stirred at room temperature until complete dissolution was achieved, at which point a mixture of racemic *trans*-1,2-diaminocyclohexane **10** (14.00 mL, 114.14 mmol) was added at a rate such that the reaction mixture reached 60 ºC. Glacial acetic acid (6 mL) was added to the resulting mixture at such a rate that the reaction temperature reached 65 ºC. The resulting heterogeneous white slurry was vigorously stirred as it was cooled to room temperature over 2 h. The reaction mixture was then cooled to 5 ºC in an ice bath for over 2 h and the precipitate was collected by vacuum filtration. The wet white cake was washed with ice cooled water (6 mL) and rinsed with ice cooled methanol (5 × 6 mL). The white crude product was then recrystallized from water (1: 10 w/v) by heating to 90 ºC and cooling it to 5 ºC overnight. The product was then dried under reduced pressure (40 ºC) to yield the desired compound (*S,S)*-1,2-diammoniumcyclohexane mono tartrate salt **11** as a white crystalline solid (10.63 g, 40%); m.p. 170-173 °C; [Lit.[2] 252-255 °C]; $[\alpha]^{20}_{D}$ −12.4 (*c* 4.00, H_2O); [For the (*R*,*R*)-diammonium (*R*,*R*)-tartrate salt: Lit.[2] $[\alpha]^{20}_{D}$ +12.5 (*c* 4.00, H_2O)].

The salt was liberated by washing with 4 M NaOH (20 mL) and extraction into dichloromethane (3 × 30 mL). The combined organic extracts was dried (Na_2SO_4) and the solvent removed *in vacuo* to afford (1*S,*2*S*)-1,2-diaminocyclohexane (1*S,*2*S*)-**10** as colourless crystals.

(1*S*,2*S*)-*N*-Phthaloyl-1,2-diaminocyclohexane 12 [3]

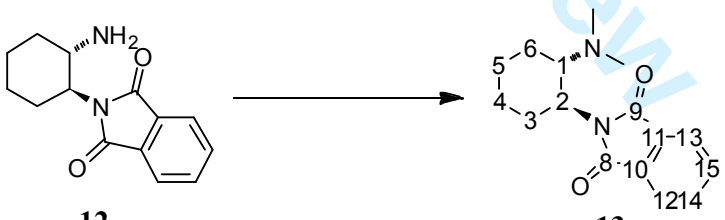


(1*S*,2*S*)-10 **12**

(1*S*,2*S*)-Diaminocyclohexane **10** (2.04 g, 17.90 mmol) was dissolved in in xylenes (50 mL) and *p*TSA (3.40 g, 17.90 mmol) and phthalic anhydride (2.65 g, 17.90 mmol) were added at room temperature. The reaction mixture was then heated under reflux with vigorous stirring until a homogeneous solution was obtained and the product begun to crystallize (2 h). After cooling the mixture to room temperature, the colourless solid product was collected by filtration, washed with xylenes, hexanes and dried under vacuum to give the sulfonate salt of desired product **12** (6.79 g, 95%); m.p. 250-251 °C; [Lit.[3] 249-252 °C]; $[\alpha]^{20}_D$ +18.2 (*c* 1.00, $CHCl_3$); [Lit.[3] $[\alpha]^{20}_D$ −15.8 (*c* 1.0, $CHCl_3$)]; ν_{max}(film)/cm^{-1} 3384, 3027, 2930, 2885, 1770, 1703, 1495, 1389, 1219, 809, 680; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22 (2 H, m), 1.43-1.51 (1 H, m), 1.67-1.70 (3 H, m), 2.34 (3 H, s), 3.92 (1 H, m), 4.18 (1 H, dt, *J*= 11.7 Hz, 3.9 Hz), 7.00 (2 H, d, *J*= 8.0 Hz), 7.31 (2 H, d, *J*= 8.1 Hz.), 7.42 (2 H, dd, *J*= 7.4 Hz, 4.4 Hz), 7.42 (2 H, dd, *J*= 7.4 Hz, 3.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.3, 23.7, 24.5, 29.0, 30.0, 50.7, 52.4, 122.9, 125.9, 128.6, 132.0, 133.3, 139.9, 141.0, 168.5.

A solution of the sulfonate salt (6.70 g, 16.80 mmol) in dichloromethane (30 mL) was stirred overnight with saturated sodium hydrogen carbonate solution (10 mL). The organic phase was separated, dried (Na_2SO_4) and the solvent removed *in vacuo* to give the product **12** as a colourless solid (3.65 g, 89%); m.p. 126-127 °C; [Lit.[3]123-125 °C]; $[\alpha]^{20}_D$ +78.5 (*c* 1.00, $CHCl_3$); [Lit.[3] $[\alpha]^{20}_D$ −79.3 (*c* 1.00, $CHCl_3$)]; ν_{max}(film)/cm^{-1} 3426, 1695, 1652, 1457, 1397, 1372, 1127, 1067, 956, 892, 725; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.08–1.41 (5 H, m), 1.66–1.77 (3 H, m), 1.94–2.00 (1 H, m), 2.06–2.18 (1 H, m), 3.34 (1 H, dt, *J*= 11.1 Hz, 4.1 Hz), 3.72 (1 H, dt, *J*= 10.5 Hz, 3.9 Hz), 7.63 (2 H, dd, *J*= 5.4 Hz, 3.2 Hz), 7.75 (2 H, dd, *J*= 5.5 Hz, 3.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.1, 25.6, 29.3, 36.7, 50.8, 58.5, 123.1, 131.9, 133.9, 168.8; *m/z* (EI) 244.1208; $C_{14}H_{16}N_2O_2$ $(M)^+$ requires 244.1212.

(1*S*,2*S*)-*N*,*N*-Dimethyl-*N*'-Phthaloyl-1,2-diaminocyclohexane 13 [3]

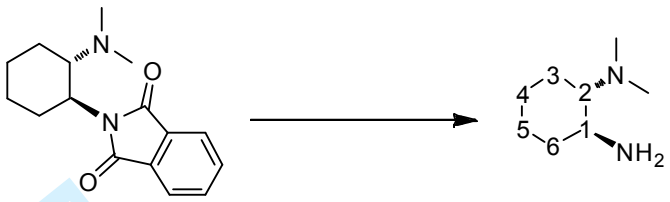


12 **13**

A mixture of (1*S*,2*S*)-*N*-Phthaloyl-1,2-diaminocyclohexane **12** (2.28 g, 9.32 mmol), 90% formic acid (5 mL) and 37% formaldehyde solution (1.60 mL, 20.50 mmol) was heated under reflux overnight. The solvents were removed *in vacuo* and the resulting residue was dissolved in dichloromethane (40 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 × 30 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the desired product **13** as a yellow powder (2.18 g, 86%); m.p. 123-124 °C; [Lit.[3] 123-125 °C]; $[\alpha]^{20}_D$ +31.5 (*c* 1.00, $CHCl_3$); [Lit.[3] $[\alpha]^{20}_D$ −32.5 (*c* 1.00, $CHCl_3$)]; ν_{max}(film)/cm^{-1} 2926, 2358, 1759, 1701, 1500, 1385, 1136, 1077, 715; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.10–1.27 (3 H, m),

1.71–1.78 (3 H, m), 1.84–1.89 (1 H, m), 2.08 (6 H, s), 2.10–2.15 (1 H, m), 3.24 (1 H, dt, *J*= 11.2 Hz, 3.2 Hz), 4.04 (1 H, dt, *J*= 11.2 Hz, 4.0 Hz), 7.61 (2 H, dd, *J*= 5.2 Hz, 2.8 Hz), 7.73 (2 H, dd, *J*= 5.2 Hz, 3.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7, 24.1, 24.7, 29.2, 39.3, 51.2, 61.1, 121.9, 131.2, 132.5, 167.7; *m/z* (EI) 272.1529; $C_{16}H_{20}N_2O_2$ $(M)^+$ requires 272.1525.

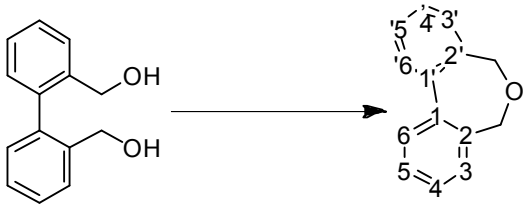
(1*S*,2*S*)-*N*,*N*-Dimethyl-1,2-diaminocyclohexane 14 [3]



13 **14**

(1*S*,2*S*)-*N*,*N*-Dimethyl-*N*'-Phthaloyl-1,2-diaminocyclohexane **13** (0.64 g, 2.35 mmol) was dissolved in ethanol (5 mL) and hydrazine hydrate (0.29 mL, 2.20 mmol) was added at room temperature. The reaction mixture was then heated under reflux until complete disappearance of the starting material was observed (typically 1 h). After cooling the reaction mixture to room temperature, diethyl ether (30 mL) was added to the mixture and the resulting precipitate filtered. The filtrate was then evaporated to dryness to give the product **14** as pale-yellow oil (0.20 g, 60%); $[\alpha]^{20}_D$ +32.0 (*c* 1.00, $CHCl_3$); [Lit.[4] $[\alpha]^{20}_D$ −36.0 (*c* 1.00, $CHCl_3$)]; ν_{max}(film)/cm^{-1} 3360, 2926, 2778, 1574, 1450, 1376, 1338, 1268, 1167, 1098, 1057, 1035, 942, 871, 819; ^{1}H-NMR (400 MHz, $CDCl_3$): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.91–1.08 (4 H, m), 1.51–1.65 (3 H, m), 1.79–1.83 (1 H, m), 1.89 (1 H, dt, *J*= 10.0 Hz, 3.2 Hz), 2.09 (6 H, s), 2.33 (2 H, br s), 2.43 (1 H, dt, *J*= 10.4 Hz, 4.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.4, 24.8, 25.3, 34.7, 39.9, 51.1, 69.4.

5,7-Dihydro-dibenzo[c,e]oxepine 16 [5]

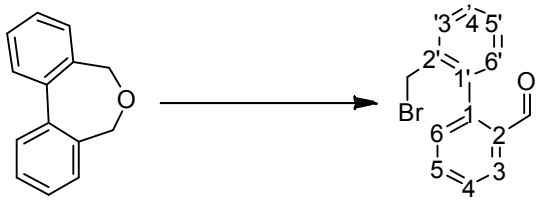


15 **16**

A suspension of 2,2'-biphenyl dimethanol **15**, (4.22 g, 19.5 mmol), in hydrobromic acid (60 mL, 24% in water), was heated to 100 ºC for 40 min. The cloudy solution was allowed to cool and the aqueous phase extracted with diethyl ether (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), saturated aqueous sodium hydrogen carbonate (50 mL), dried (Na_2SO4) and the solvent removed under reduced pressure to afford the product **16** as a colourless solid (3.25 g, 85%); m.p. 69-71 ºC; ν_{max}(film)/cm^{-1}

2852, 1652, 1558, 1447, 1376, 1198, 1072, 1046, 997, 903, 891, 753, 668; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.21 (4 H, s), 7.23–7.48 (8 H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 67.8, 127.6, 128.5, 129.0, 129.9, 135.2, 141.4; *m/z* (EI) 196.0884; $C_{14}H_{12}O$ (M^+) requires 196.0888.

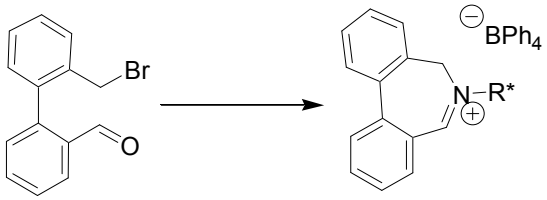
2'-Bromomethyl-2-formyl-1,1'-biphenyl 17 [5]



16 **17**

A solution of bromine (1.44 mL, 11.0 mmol) in carbon tetrachloride (6 mL) was added dropwise over 5 min to an ice-cooled solution of 5,7-dihydrodibenzo[*c,e*]oxepine **16** (5.00 g, 25.48 mmol) in carbon tetrachloride (50 mL); the reaction mixture turned a deep red colour. The cooling bath was removed and the reaction mixture heated under reflux for 2 h. The solvent was evaporated under reduced pressure, and then diluted with diethyl ether (80 mL). The organic layer was washed with saturated aqueous sodium carbonate (2 × 50 mL), brine (2 × 30 mL), dried (Na_2SO4) and the solvents removed under reduced pressure to yield an orange oil. Recrystallization from ethyl acetate/light petroleum afforded the product **17** as colourless crystals. (4.20 g, 60%); m.p. 57-58 ºC; ν_{max}(nujol) /cm^{-1} 3188, 1667, 1590, 1391, 1248, 1198, 774, 722, 632; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.30 (2 H, dd, *J*= 40.0, 10.4 Hz), 7.21 (1 H, dd, *J*= 7.4 Hz, 1.2 Hz), 7.38 (1 H, ddd, *J*= 7.4 Hz, 7.4 Hz, 1.4 Hz), 7.40–7.47 (2 H, m), 7.54–7.47 (2 H, m), 7.67 (1 H, ddd, *J*= 7.4 Hz, 7.4 Hz, 1.4 Hz), 8.07 (1 H, ddd, *J*= 7.8 Hz, 1.4 Hz, 0.6 Hz), 9.73 (1 H, d, *J*= 0.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.4, 127.6, 128.4, 128.5, 129.1, 130.67, 130.71, 131.0, 133.6, 134.1, 136.0, 137.8, 143.3, 191.7; *m/z* (EI) 275.9979; $C_{14}H_{11}BrO$ (M^+) requires 275.9974.

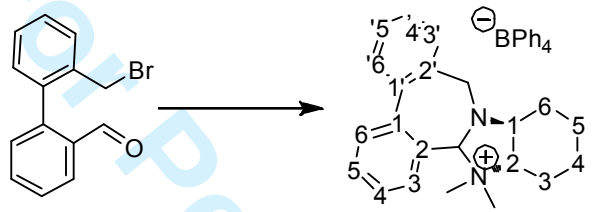
General procedure for the synthesis of 5*H*-dibenzo[*c,e*]azepinium salts from 2-[2-(bromomethyl)phenyl]benzene carbaldehyde and primary amines



A solution of the amine (1 equiv) in ethanol (10 mL per gram of amine), was added dropwise to an ice cooled solution of 2-[2-(bromomethyl)-phenyl]benzene carbaldehyde **17** (1.1 equiv) in ethanol (10 mL per gram of **17**). The reaction mixture was stirred overnight while attaining ambient temperature. Sodium

tetraphenylborate (1.1 equiv) in the minimum amount of acetonitrile was added in one portion to the reaction mixture and after 5 minutes of stirring, the organic solvents were removed under reduced pressure. Ethanol was added to the residue, followed by few drops of water. The resulting solid was collected by filtration and washed with additional ethanol followed by diethyl ether. If no solid materialises after the addition of the water the suspension is allowed to settle and the ethanol/water phase is decanted off. The gummy residue was macerated in hot ethanol or methanol. The organic salt may then precipitate but in some rare cases it does so upon slow cooling of the hot alcoholic solution. If solubility problems do arise, small amounts of acetonitrile may be added during this process.

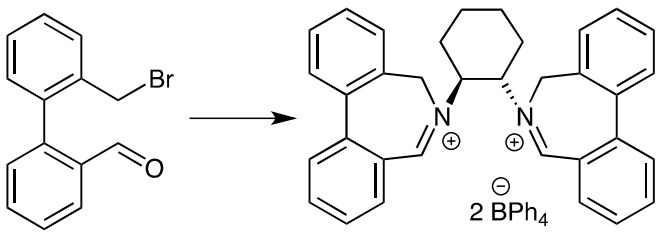
(1*S*,2*S*)-14,14-Dimethyl-9b,10,11,12,13,13a,14,14a-octahydro-9H-9a-aza-14-azonia-tribenzo[a,e,g]azulene tetraphenylborate 18



17 **18**

Prepared according to the general procedure from (1*S*,2*S*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **14** (0.04 g, 0.28 mmol). Ammonium salt **18** was isolated as a yellow powder (0.13 g, 70%); m.p. 186-187 ºC; $[\alpha]^{20}_{D}$ +60.8 (*c* 1.00, CH_3CN); Found: C, 85.99; H, 7.39; N, 4.34. $C_{46}H_{47}BN_2$ requires C, 86.50; H, 7.42; N, 4.39%; ν_{max}(film)/cm^{-1} 3049, 2940, 1642, 1579, 1473, 1450, 1425, 1265, 1208, 1141, 736, 706, 612; ^{1}H-NMR (400 MHz, acetonitrile-d_3, −40 °C): δ 1.06–1.25 (4 H, m), 1.66–1.92 (4 H, m), 2.46 (6 H, s), 2.71 (1 H, bs), 3.15 (1 H, t, *J*= 9.2 Hz), 3.58 (1 H, bs), 3.81 (1 H, d, *J*= 15.2 Hz), 5.57 (1 H, bs), 6.74 (4 H, t, *J*= 7.2 Hz), 6.90 (8 H, t, *J*= 7.2 Hz), 7.17–7.20 (8 H, m), 7.26–7.35 (2 H, m), 7.38–7.54 (4 H, m), 7.67–7.71 (2 H, m); ^{13}C-NMR (100 MHz, acetonitrile-d_6): δ 22.1, 23.1, 23.7, 29.9, 41.5, 49.6, 64.7, 70.4, 101.7, 121.7, 125.3, 126.3, 128.4, 128.6, 129.0, 129.3, 129.5, 131.2, 133.5, 134.2, 135.2, 135.4, 138.6, 141.8; *m/z* (EI) 320.2257; $C_{22}H_{27}N_2$ (cation) requires 320.2253.

(1*S*,2*S*)-*Bis*-Iminium salt 19



Prepared according to the general procedure using (1*S*,2*S*)-diaminocyclohexane **10** (0.10 g, 0.88 mmol) and 2-[2-(bromomethyl)-phenyl]benzene carbaldehyde **17** (0.51 g, 1.85 mmol, 2.1 equiv). The product **19** was isolated as yellow powder (0.51 g, 52%); m.p. 145-147 ºC; $[\alpha]^{20}_{D}$ −170.2 (*c* 0.59, CH_3CN); ν_{max}(film)/cm^{-1} 3052, 2933, 1639, 1597, 1552, 1480, 1445, 1425, 1332, 1265, 1208, 761, 731, 705; ^{1}H-NMR (400 MHz, DMSO-d_6, 100 °C): δ 1.77 (2 H, d, *J*= 12.0 Hz), 2.01 (2 H, d, *J*= 8.0 Hz), 2.30 (2 H, d, *J*= 8.0 Hz), 2.49–2.53 (2 H, m), 4.71 (2 H, d, *J*= 12.0 Hz), 5.06 (2 H, d, *J*= 12.0 Hz), 5.71 (2 H, s), 6.83 (8 H, t, *J*= 7.2 Hz), 6.97 (16 H, t, *J*= 7.2 Hz), 7.17–7.26 (18 H, m), 7.52 (4 H, br s), 7.73–7.79 (4 H, m), 7.87–8.06 (8 H, m); ^{13}C-NMR (100 MHz, DMSO-d_6, 100 °C): δ 24.0, 32.1, 55.0, 72.1, 121.9, 125.1, 125.6, 126.7, 127.0, 128.7, 129.0, 129.5, 130.4, 130.4, 133.8, 135.9, 136.2, 136.8, 141.5, 171.2; *m/z* (FAB) 468.2560; $C_{34}H_{32}N_2$ (cation) requires 468.2566.

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