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Synthesis of chiral nonracemic polyimine macrocycles from cyclocondensation reactions of biaryl and terphenyl aromatic dicarboxaldehydes and 1*R*,2*R*-diaminocyclohexane

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Dedicated to Professor Angela Danil de Namor on the occasion of her 65th birthday

Abstract—The synthesis of biaryl and terphenyl dicarboxaldehydes using Suzuki coupling methodology and their macrocyclisation reactions with 1*R*,2*R*-diaminocyclohexane yielding novel polyimine macrocycles derived from the [2+2] and [3+3] cyclocondensation reactions is presented. The ratio of products was found to depend on the overall geometry of the dicarboxaldehydes.

The development of supramolecular chemistry has been mainly driven by the availability of suitable macrocyclic receptors. Once a class of macrocyclic receptors with a unique shape, distinct architecture and set of functional groups becomes widely available from natural or synthetic sources, they start to inspire the imagination of supramolecular chemists to devise and synthesise novel sophisticated receptors, molecular machines and devices.[1–3] Following initial work by Gawronski et al.,[4] we have recently reported the synthesis of large polyimine *meta*- and *para*-cyclophane type macrocycles using a [3+3] cyclocondensation strategy, in which six imine bonds are formed.[5–8] We have named these compounds trianglimines due to their characteristic triangular geometry. In a modular approach, macrocycles of various ring sizes including different functionalities in enantiomerically pure form were obtained. Other groups have also reported on the use of the [3+3] cyclocondensation strategy.[9–13]

In this communication, we report a detailed and systematic study of the [*n*+*n*] cyclocondensation concept using a selection of biaryl and terphenyl dicarboxaldehydes. Both types of dicarboxaldehyde building blocks should allow a modular approach for the synthesis of fascinating macrocycles with ring sizes between 30 and 60 in a highly efficient way. As model substrates, we chose a series of differently substituted biaryl dicarboxaldehydes, which we obtained by the palladium catalysed Suzuki coupling reactions using formyl boronic acids **1**–**3** and aromatic bromobenzaldehydes **4** and **5**. All biaryl dicarboxaldehydes **6a**–**e** could be obtained in good to excellent yield using a modification of the literature procedure (Scheme 1)[14] with $Pd(dppf)Cl_2$ as the catalyst. Compounds **6b**–**e** are novel compounds and the yields are given in Table 1.

We then extended our Suzuki coupling approach by reacting 2 equiv of 4-formyl boronic acid **2** with a series of aromatic dibromides **7a**–**g** to obtain a series of substituted terphenyl dialdehydes **8a**–**g** in moderate to good yields. For the terphenyl series, slightly modified Suzuki conditions were required using $Pd(PPh_3)_4$ as the catalyst in toluene (Scheme 2). All compounds, with the exception of **8g**, which has been reported by Gawronski and co-workers during the course of this investigation[13] are novel and were fully characterised. The yields are summarised in Table 1.

All the dicarboxaldehydes were subjected to the [*n*+*n*] cyclocondensation reaction with 1*R*,2*R*-diamino-cyclohexane **9** using the conditions reported by us previously (Scheme 3).[5–8] The crude reaction mixtures were

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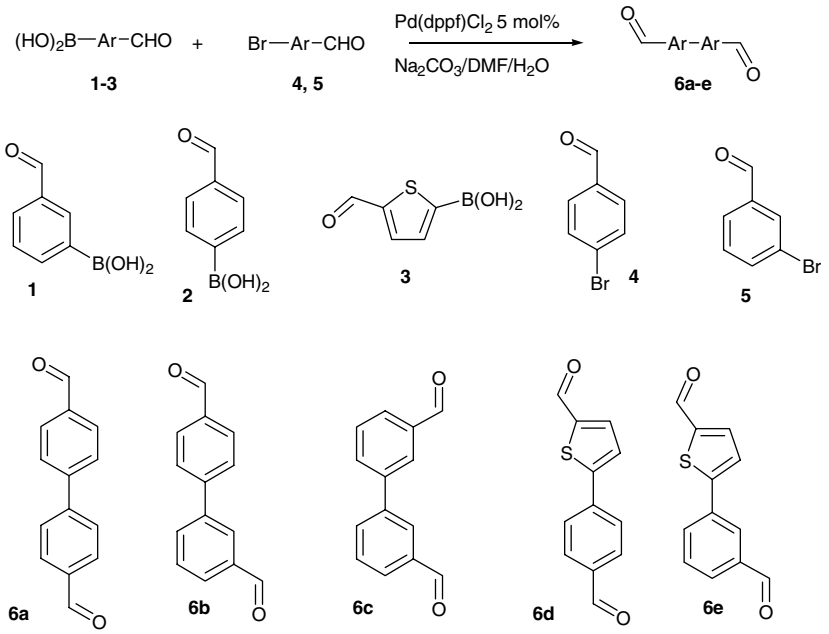


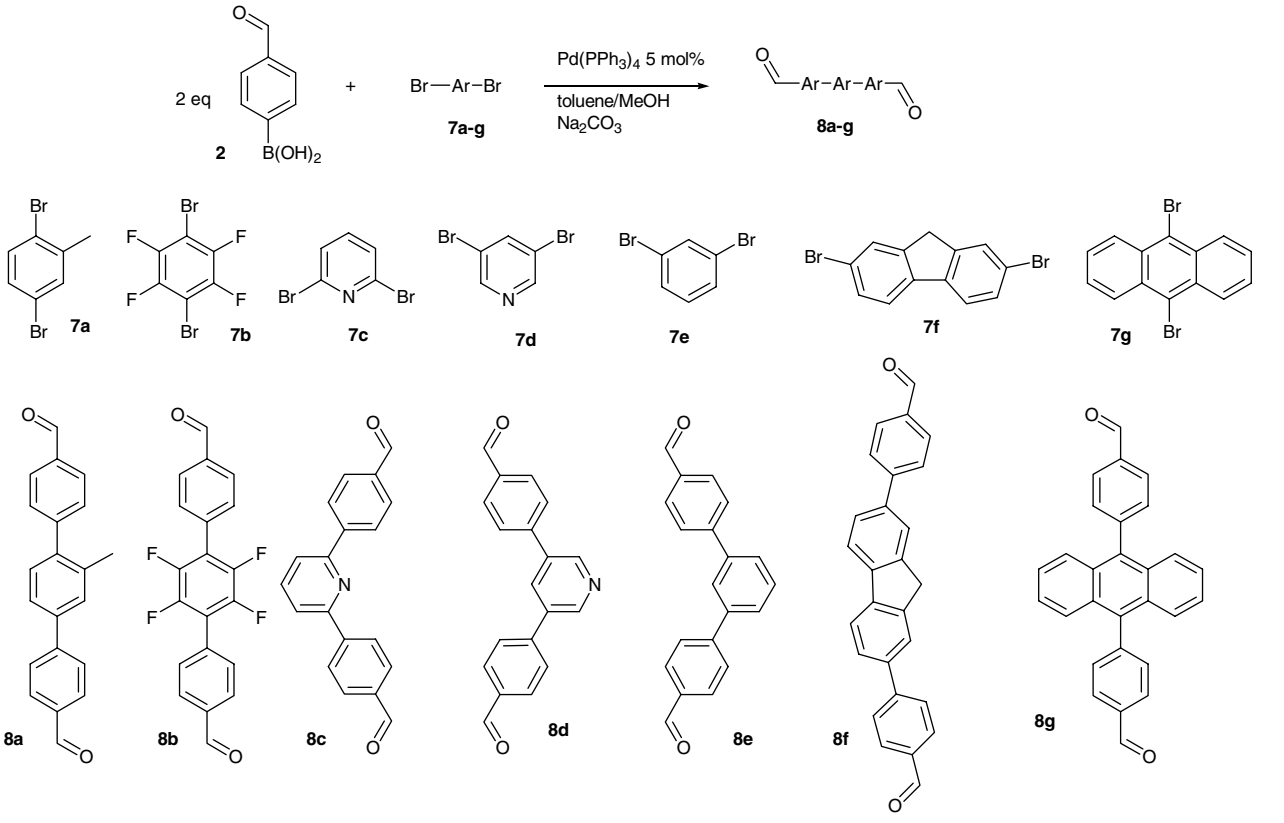
Scheme 1. Synthesis of biaryl dicarboxaldehydes.

Table 1. Yields of aromatic dicarboxaldehydes **6a–e** and **8a–g**

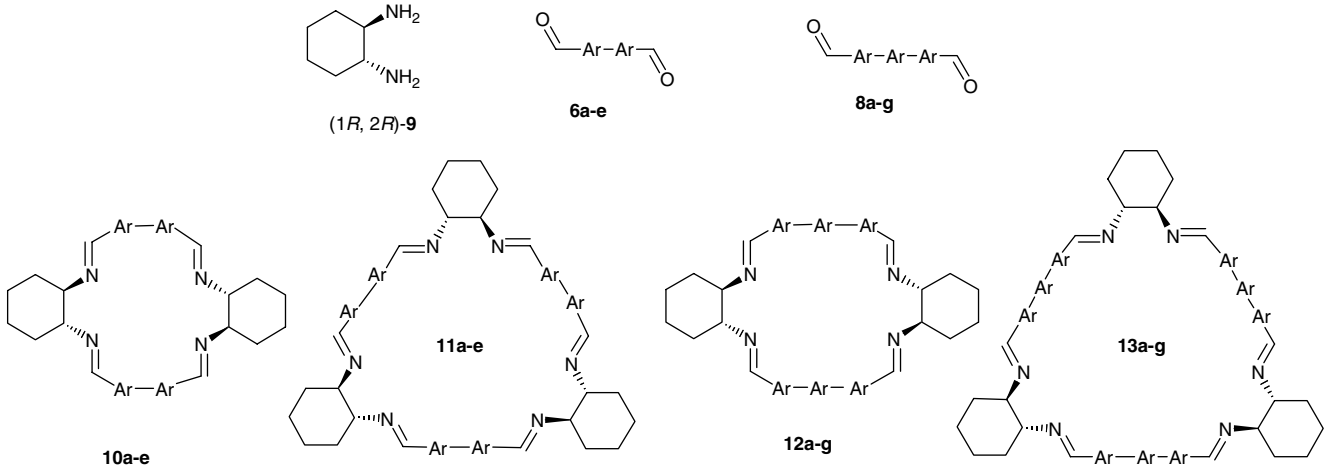
Starting materials	Product	Yield (%)
2 and **4**	**6a**	31
1 and **4** or **2** and **5**	**6b**	12/84
1 and **5**	**6c**	71
3 and **5**	**6d**	98
3 and **4**	**6e**	86
1 and **7a**	**8a**	81
1 and **7b**	**8b**	23
1 and **7c**	**8c**	90
1 and **7d**	**8d**	75
1 and **7e**	**8e**	70
1 and **7f**	**8f**	51
1 and **7g**	**8g**	48

analysed by ^{1}H NMR spectroscopy and FAB and ESI mass spectrometry after 12 and 48 h of reaction time in dichloromethane at room temperature and the ratios of [2+2] and [3+3] cyclocondensation reaction products were determined (representative results in Table 2). In all cases macrocyclic products were observed exclusively as opposed to alternative polymeric oligoimine products. Both reaction products display, due to their inherent symmetry only one set of NMR signals for the two or three repeating units but can be unambiguously identified according to their unique m/z of their molecular ions. It has to be noted that the ratio of products determined by integration of the crude ^{1}H NMR spectra and the mass spectra differ greatly.[10] To allow unambiguous assignment of the minor and major products in the ^{1}H NMR spectra diffusion, NMR spectra of the crude mixtures were obtained. The macrocyclic polyimine compound displaying a smaller diffusion coefficient was assigned to the [3+3] cyclocondensation product, whereas the compound with the larger diffusion coefficient was assigned as the [2+2] cyclocondensation product.[15–17]

As expected mass spectrometry overestimates the formation of the lower molecular weight product in all cases. If FAB and ESI mass spectrometry are directly compared, FAB was found to overestimate the amount of the lower molecular weight compound formed. All compounds with a linear arrangement of the two O=C carbons and the biaryl axis form trianglimines as the product of a [3+3] cyclocondensation reaction (see **8a**,**b**,**g**). In some instances, small amounts of [2+2] cyclocondensation products are observed after 12 h of reaction time. In all of these cases, the trianglimine macrocycles could be isolated in pure form and characterised. Interestingly, the ^{1}H NMR spectra were characterised by broad bands presumably due to rapid rotation around the C–C biaryl axes. In the case of dicarboxaldehydes displaying a nonlinear arrangement of the two O=C carbons and the biaryl axes mixtures of [2+2] and [3+3] cyclocondensation products were always observed after 12 h of reaction time. After 48 h of reaction time it was observed that the reaction mixture had equilibrated and in case of, for example, compounds **8c**,**f** the [2+2] cyclocondensation products **12c**,**f** were obtained exclusively. It appears that in these cases the [2+2] cyclocondensation products **12c**,**f** are the products of thermodynamic control as suggested earlier.[7] In the case of dicarboxaldehydes **6b**,**d** and **6e** two alternative regioisomeric tetraimine macrocycles **10a**,**d**,**e** are expected to form in the [2+2] cyclocondensation reaction. Detailed ^{1}H,^{1}H-NOESY experiments showed that in each case, the regioisomer with a C_2-axis along the centre of the macrocyclic cavity is formed exclusively as the only product of the [2+2] cyclocondensation reaction (see Scheme 4 for representative structures). Representative analytical data are given in reference section.[17–20]



Scheme 2. Synthesis of terphenyl dicarboxaldehydes.



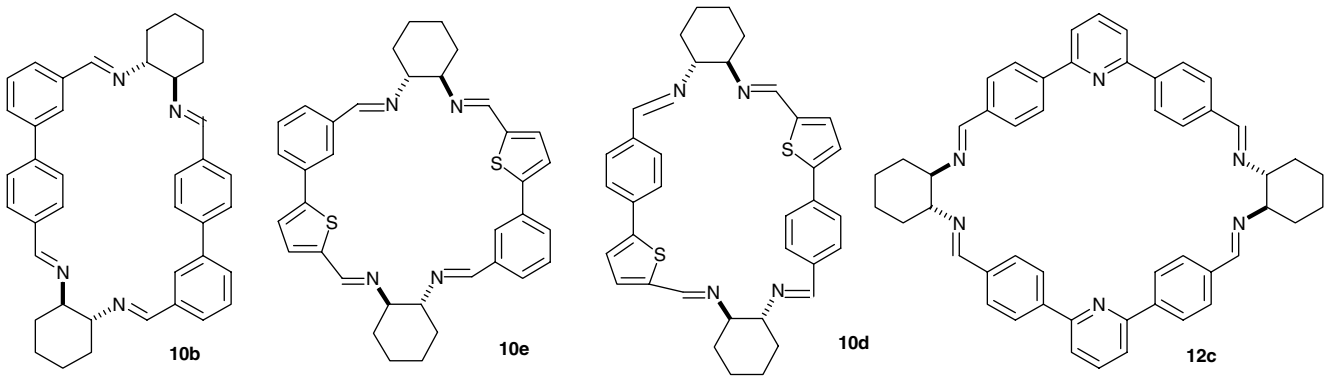
Scheme 3. Synthesis of polyimine macrocycles.

In conclusion, we have shown that extended rigid aromatic dicarboxaldehydes can be obtained in good yields using Suzuki coupling reactions. This class of compound represent valuable building blocks in polymer chemistry and macrocyclic chemistry. The [*n*+*n*] cyclocondensation strategy using an aromatic dialdehyde and 1*R*,2*R*-diaminocyclohexane can be applied to biaryl and terphenyl dicarboxaldehydes to yield fascinating enantiomerically pure polyimine macrocycles. The nature of the cyclocondensation product depends strongly on the overall geometry of the dicarboxaldehyde building block. For a linear arrangement of carbonyl–biaryl axes trianglimine [3+3] cyclocondensation products were obtained exclusively, whereas in all cases of nonlinear carbonyl biaryl axes geometries, [2+2] cyclocondensation products were obtained. All novel macrocycles synthesised maybe useful in organic synthesis, for chiral recognition and applications in supramolecular chemistry.

Table 2. Ratio of products formed from the [*n*+*n*] cyclocondensation reaction

Starting materials	Products[a]	Ratio after 12 h by ^{1}H NMR[b]	Ratio after 12 h by ESI[c]	Ratio after 48 h by ^{1}H NMR	Ratio after 48 h by ESI	Isolated yield (%)
6a	**10a+11a**	6:94	12:88[d]	>2:98	>2:98	90 (**11a**)
6b	**10b+11b**	97:3	95:5	—	—	67 (**10b**)
6c	**10c+11c**	>98:2	98:2	—	—	72 (**10c**)
6d	**10d+11d**	95:5	95:5	—	—	72 (**10d**)
6e	**10e+11e**	98:2	98:2	—	—	66 (**10e**)
8a	**12a+13a**	2:98	2:98	2:98	2:98	66 (**13a**)
8b	**12b+13b**	2:98	2:98	2:98	2:98	55 (**13b**)
8c	**12c+13c**	90:10	70:30[e]	95:5	90:10	78 (**12c**)
8d	**12d+13d**	78:22	58:42	95:5	88:12	81 (**12d**)
8e	**12e+13e**	90:10	75:25	98:2	95:5	79 (**12e**)
8f	**12f+13f**	85:15	60:40	90:10	80:20	34 (**12f**)
8g	**12g+13g**	>2:98	2:98	2:98	2:98	71 (**13g**)

[a] Products assigned by diffusion NMR.
[b] Crude mixture in $CDCl_3$ at 500 MHz using the HC=N signal.
[c] In MeOH positive ion mode 0.0001 M ratio of intensities of *m*/*z*.
[d] FAB measurement shows 35:65 ratio.
[e] FAB measurement shows 90:10 ratio.



Scheme 4. Selected products of macrocyclisation reaction.

Acknowledgements

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17. Analytical data for compound **6c**: Mp (98–98.2 °C); IR ν_{max} (Nujol)/cm^{-1} 1698 (C=O), 1600–1463 (CAr=CAr), 783, 690; ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 10.12 (2H, s, CH=O), 8.15 (2H, s, Ar–H), 7.93 (4H, m, Ar–H), 7.68 (2H, d, *J* 8.1 Hz, Ar–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 192.9, 140.9, 137.3, 133.2, 130.02, 129.2, 128.2; CHN calcd: 79.90 C, 4.70 H; found: 79.83 C, 4.72 H; GC–MS $C_{14}H_{10}O_2$ (*m*/*z* 210, M+H).
18. Analytical data for compound **10c**: Mp 197.8–198 °C; $[\alpha]_D^{25}$ −113.75 (*c* 0.4, $CHCl_3$); IR ν_{max} (Nujol)/cm^{-1}: 1629 (C=N), 1463–1377, 723 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 8.37 (4H, s, N=CH), 8.15 (4H, s, Ar), 7.66 (12H, m, ArH), 3.74 (4H, m, NCH), 2.17–1.56 (16H, m, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$): δ_C 162.4, 154.6,

145.9, 141.4, 137.2, 134.2, 131.5, 129.8, 128.6, 126.8, 124.8, 74.8, 72.2, 65.8, 33.1, 32.1, 24.65, 15.29; FAB: $C_{40}H_{40}N_4$ (*m*/*z* 576, M+H).

19. Analytical data for compound **8c**: Mp over 163–166 °C; IR ν_{max} (Nujol)/cm^{-1}: 1687 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 10.11 (s, 2H, CHO), 8.32 (d, 4H, *J* 8.1, ArH), 8.03 (d, 4H, *J* 8.1, ArH), 7.93 (t, 1H, *J* 7.8, pyrH), 7.84 (d, 2H, *J* 7.8, pyrH); CHN calcd: 79.43 C, 4.56 H, 4.88 N; found: 79.6 C, 4.51 H, 4.80 N; MS (CI): $C_{19}H_{13}NO_2$ (*m*/*z* 287.1, M+H).

20. Analytical data for compound **12c**: Mp over 200 °C; $[\alpha]_D^{25}$ −182 (*c* 0.1, $CHCl_3$); IR ν_{max} (Nujol)/cm^{-1}: 1637 (C=N); ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 8.35 (s, 4H, HC=N), 7.97 (d, 8H, *J* 8.1, ArH), 7.61 (d, 8H, *J* 8.1, ArH), 7.57 (t, 2H, *J* 7.9, pyrH), 7.39 (d, 4H, *J* 7.9, pyrH), 3.39 (m, 4H, NCH), 1.96–1.52 (m, 16H, CH_2); ^{13}C NMR (125 MHz; $CDCl_3$): δ_C 161.7, 156.5, 141.5, 137.7, 136.9, 128.5, 127.5, 120.1, 74.4, 32.9, 24.7; CHN calcd: 82.16 C, 6.34 H, 11.5 N; found: 82.50 C, 6.05 H, 11.31 N; MS (LSIMS): $C_{50}H_{46}N_9$ (*m*/*z* 731, M+H).