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Arylene Imine Macrocycles of C_{3h} and C_3 Symmetry from Reductive Imination of Nitroformylarenes

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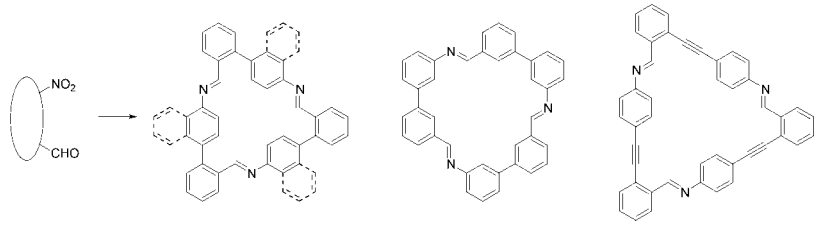
ABSTRACT



Novel C_3-symmetric phenylene imine macrocycles have been synthesized by reductive imination of single nitroformylarenes. Pore size and geometric shape are dictated by the distance between and orientation of the nitro and aldehyde moieties in the precursor backbone. This reaction is facile, requires no purification of the products, and is environmentally friendly.

Shape-persistent macrocycles have become an important class of molecules in several fields, including catalysis,[1] liquid crystals,[2] and supramolecular chemistry.[2a,b,3] By definition these macrocycles have a very small number of available conformations, and this structural rigidity makes them ideal model systems and building blocks for larger nanostructures.[2d,3c,4]

Imines have become an appealing moiety for shape-persistent macrocycles in part because they are easily synthesized, requiring only a minimal number of steps.[5] Furthermore, incorporation of N heteroatoms into the backbone allows for metal chelation and in turn the tuning of the physical and optical properties of the system.[6]

Many methods have been used to synthesize symmetric and unsymmetric imine macrocycles. Among the most common strategies employed is an $[n + n]$ Schiff base condensation between two precursors, one containing two formyl groups and the other having two amine groups.[7] Metal templation or hydrogen bonding favors the formation of macrocycles over linear oligomers. The orientation of the diformyl and diamine groups (i.e., ortho, meta, para) dictates the size and geometric shape of the resulting macrocycle.

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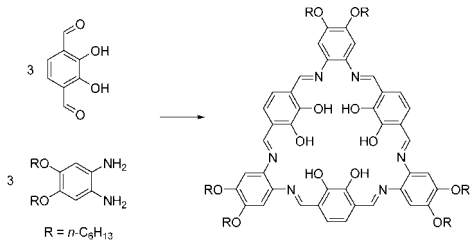
Several groups have made triangular,[7a−d] rhombodial,[6c,8] and hexagonal[9] imine macrocycles via the [n + n] synthetic strategy; an example of a triangular macrocycle is shown in Scheme 1.

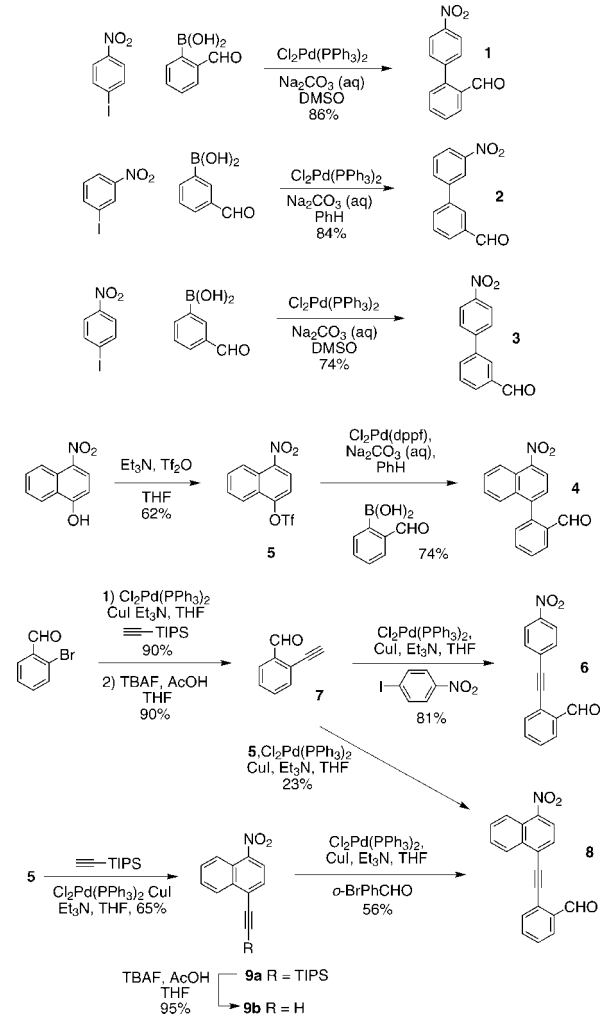
Scheme 1. [3 + 3] Schiff base Strategy[6a]



Few imine macrocycles can be traced back to a single fragment that contains both the amine and the carbonyl moieties.[10] This is most likely due to spontaneous condensation of the amine and carbonyl under a wide variety of conditions that would lead to difficulties in the purification of such a fragment. Difficulties also arise if the single fragment is produced in situ. For example, many of the methods used to reduce nitroarenes to the respective anilines are also used to reduce aldehydes to the primary alcohol.[11] To circumvent this issue we have developed a simple and environmentally friendly one-pot procedure for imine formation from nitroarenes and arylaldehydes. Powdered Fe(0) in an acidic ethanol/water mixture acts as a reducing agent for the nitroarene.[12] The resulting aniline undergoes imine condensation with the desired aldehyde in situ to give the Schiff base. We report the synthesis and structural characterization of novel C_3-symmetric arylene imine macrocycles via this methodology starting from nitroaldehyde precursors.

Suzuki−Miyaura coupling of 2-formylphenylboronic acid and 1-iodo-4-nitrobenzene or 3-formylphenylboronic acid and 1-iodo-3-nitrobenzene gave the corresponding nitroformylarene **1**[13] or **2** in 86% and 84% yields, respectively (Scheme 2). Compound **3**[14] was prepared in 74% yield by cross-coupling 1-iodo-4-nitrobenzene with 3-formylphenylboronic acid. Nitroformylnaphthalene **4** was prepared by triflation of 4-nitro-1-naphthol to afford **5** in 62% yield, followed by coupling of **5** with 2-formylphenylboronic acid under similar condition as before to give **4** in 74% yield. Alkyne precursor **6**[15] was prepared via Sonogashira coupling of 2-bromobenzaldehyde with (triisopropylsilyl)acetylene in 90% yield followed by removal of the TIPS silyl protecting group with TBAF to afford **7** in 90% yield. Subsequent coupling with 1-iodo-4-nitrobenzene yielded **6** in 81% yield, while coupling with **5** gave **8** in 23% yield. The purification of **8** required sublimation because it coeluted with the Hay coupled dimer of **7** during chromatography.

Scheme 2. Synthesis of Nitroformylarene Precursors



Because of the difficulty in isolating **8**, it was also synthesized by cross-coupling of **5** with (triisopropylsilyl)-acetylene to afford **9** in modest 65% yield. Silyl deprotection of **9** in the presence of AcOH occurred smoothly (95% yield), and coupling the terminal ethynylene with 2-bromobenzaldehyde afforded **8** in 56% yield after purification by flash chromatography.

Various nitroarene reduction methods to afford the corresponding imine macrocycles were explored. Hydrogenation of **1** at 65 psi as well as at atmospheric pressure gives a complex mixture of products, presumably because of reduction of both the nitro and aldehyde moieties as well as reduction of the resulting imines. Reduction by first row

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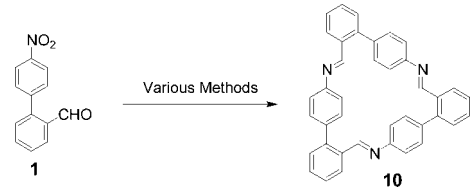
transition metals or main group metals, however, gave the desired imine macrocycle **10** in good yields (Table 1, entries 3−8).

Table 1. Reducing Conditions for Macrocycle **10** Formation



entry	reducing agent	product(s) (yield, %)	ref
1[a]	H_2, Pd−C	complex mixture	11
2[b]	H_2, Pd−C	complex mixture	11
3[c]	Fe, HCl	**10** (56)	12
4[d]	Fe, HCl	**10** (26)	12
5	Al, $NiCl_2$·$6H_2O$	**10** (41)	16
6	Sn, HCl	**10** (47)	17
7	Zn, NaOH	starting material	18
8	Zn, HCl	**10** (23)	19

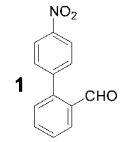
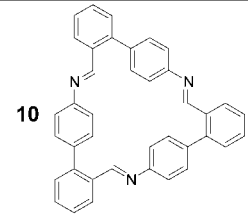
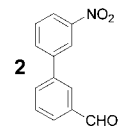
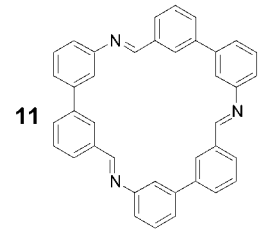
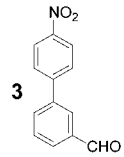
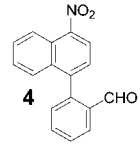
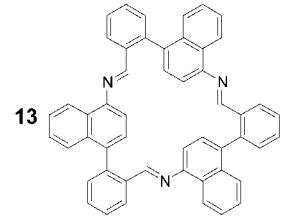
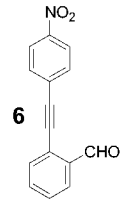
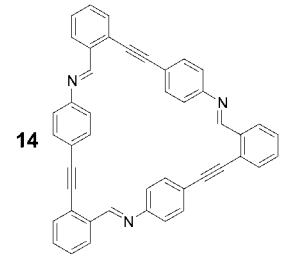
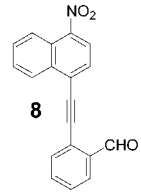
[a] At 65 psi. [b] At atmospheric pressure. [c] 0.003 M in **1**. [d] 0.3 M in **1**.

Fe(0) reduction in acidic aqueous ethanol proceeded smoothly, yielding the macrocycle **10** in 56% yield. Upon treatment of **1** with either Sn and HCl or Al and $NiCl_2$·H_2O, **10** was formed in 47% and 41% yields, respectively. Although the yields are comparable to that of the Fe(0) reaction, isolation and purification of **10** was more difficult with these two methods. Zn reduction of aryl nitro groups has been reported to occur under both basic and acidic conditions.[15,16] However, reduction of **1** under basic conditions returned only starting material, whereas acidic conditions gave the desired macrocycle in 23% after purification.

Macrocycle **10** is formed at both high and low concentrations of nitroformylarene, although the yield of the reaction at 0.3 M is lower than at 0.003 M (entries 3 and 4, Table 1). The mere halving of the yield of a macrocyclic product upon a hundredfold concentration suggests that the imine macrocycle may be formed under thermodynamic conditions, as might be expected of imines in an aqueous medium.

Varying the orientations of the functional groups about the precursor framework (i.e., *ortho-para* in **1** to *meta-meta* in **2**) does not have a drastic affect on reaction yield (Table 2). Macrocycles **10**, **11**, and **14** all possess C_3 symmetry,[20] which is evident by the simplicity of the ^{1}H NMR spectra. These macrocycles are stable in the solid state for months and exhibit only approximately 15% hydrolysis in acidic CH_2Cl_2 at room temperature after 24 h.

Table 2. Reductive Imination of Nitroformylarenes

nitroformylarene	product[a]	yield
		56%
		61%
		0%[b]
		47%
		52%
		0%[b]

[a] Reaction conditions: 1 equiv; 0.003 M; Fe(0) (10 equiv); HCl (6 equiv); EtOH/H_2O (2:1 v/v). [b] Insoluble solid not characterized.

However, attempts to synthesize the larger C_6 hexamer **12** from precursor **3** produced an insoluble solid that did not show any MALDI mass peaks corresponding to a macrocycle but did exhibit an IR band at 1596 cm^{-1} and UV bands at 271 and 332 nm, consistent with imine formation. The formation of a macrocycle from **8** was also unsuccessful, perhaps because the poor solubilities of the larger hexamer expected from **3** and the more hydrophobic backbone of **8**.

Each macrocycle can exist in several different conformations in which the imine nitrogen is either *endo* or *exo* in

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(18) Martin, E. L. *Organic Synthesis*; Wiley: New York, 1943; *Collect. Vol. II*, p 501
(19) Compound **1** (1 equiv; 0.003 M); Zn(0) (10 equiv); HCl (6 equiv); EtOH/H_2O (2:1 v/v) (see Supporting Information).
(20) For other routes to C_3-symmetric imine macrocycles, see ref 10 and Hartley, C. S.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 11682.

relation to the macrocyclic backbone, and in the case of **10**, **13**, and **14**, a simple crankshaft motion allows the interconversion of the *N-exo* and *N-endo* conformations for each imine. The sharpness of the NMR peaks suggests a rapid interconversion of the various conformers at room temperature.

Reduction of **4** gives macrocycle **13**, which is isolated as an inseparable mixture of diastereomers *syn*-**13** and *anti*-**13** (Figure 1). The restricted rotation of the biaryl moieties in **13** prevents interconversion between these diastereomers, which is not observed on the NMR time scale in $CDCl_3$ or C_6D_6 up to 75 °C. HPLC indicates a 1:1 mixture of *syn*- and *anti*-**13**, while MM2, AM1, and HF/6-31(G) calculations indicate *anti*-**13** should be 1.6, 1.2, and 2.4 kcal/mol more stable than *syn*-**13**, respectively.[21]

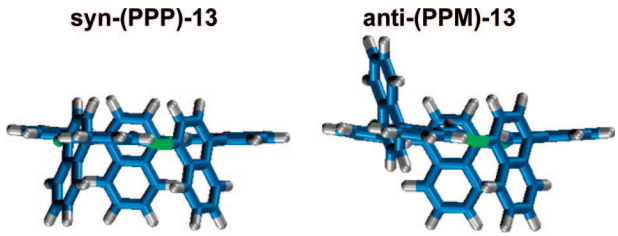

Figure 1. HF/6-31G(d) minimized structures of *syn*-(PPP)-**13** and *anti*-(PPM)-**13**.

Extending the backbone with an alkyne linker affords macrocycle **14** in a modest 52% yield. Interestingly, a significant downfield shift of 0.80 ppm is observed in the ^{1}H NMR for the azomethine proton in **14** when compared to **10**. These protons are different distances from the nearest aromatic ring within their respective macrocycles, but the downfield shift could also be attributed to a weak aromatic ring current arising from the $[4n + 2]$ π-electron circuit present and is consistent with observed NMRs other conjugated shape persistent macrocycles, namely, dehydrobenzo-[*n*]annulenes.[18]

Macrocycles **10** and **11** show absorption spectra similar to that of bistolylimine **16**, having two λ_{max} at ~270 and 315 nm (Figure 2, Table 3) along with an additional λ_{max} at 246 nm. Macrocycle **11** exhibits a greater molar absorptivity than **10** or **16**, which could be the result of the greater planarity of the biphenyl moiety in **11**. The mixture of *syn*-**13** and *anti*-**13** shows two λ_{max} at 297 and 346 nm as well as a short wavelength shoulder at 250 nm. Not surprisingly, **13** and **14** display longer wavelength absorptions compared to **10**, which can be attributed to the extended conjugation of the naphthyl moiety or ethynyl backbone, respectively.

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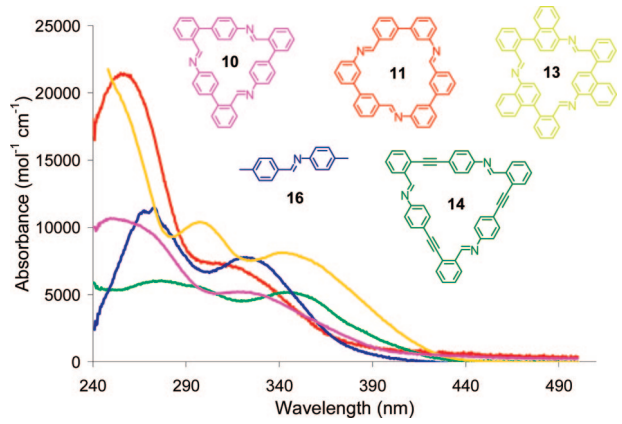

Figure 2. Absorption spectra for macrocycles **10** (pink), **11** (red), **13** (diastereomeric mixture, yellow), **14** (green), and bistolylimine **16** (blue). Spectra were obtained in $CHCl_3$ at concentrations between 0.05 and 0.15 μM.

Table 3. UV-vis Spectroscopy of Macrocycles

compound	λ_{max} (nm) (molar absorptivity, M^{-1} cm^{-1})			
16		268 (10200)	323 (7600)	
10	246 (9100)	275 (3100)	317 (5100)	
11	246 (15000)	268 (8700)	300 (7400)	
13	250 (20200)		297 (6500)	346 (8100)
14		276 (4000)	301 (1200)	342 (5100)

In summary, we have developed an efficient methodology for the synthesis of C_3-symmetric imine macrocycles by reductive imination of nitroformylarenes. This method is simple, inexpensive and environmentally friendly. Solution aggregation and the use of **10**, **11**, **13**, and **14** in dynamic combinatorial chemistry are currently being explored in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds, optimized Cartesian coordinates for *syn*-(PPP)-**13** and *anti*-(PPM)-**13**, and full ref 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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