JOC*Note*

Synthesis of 1-Substituted Benzo[*c*]isoxazol-3(1*H*)-imines via Tandem Nitroso-Ene/Intramolecular Cyclizations of 2-Nitrosobenzonitrile

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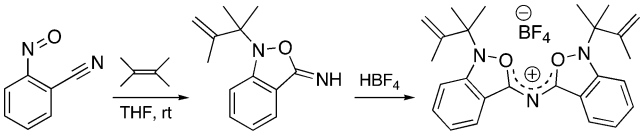
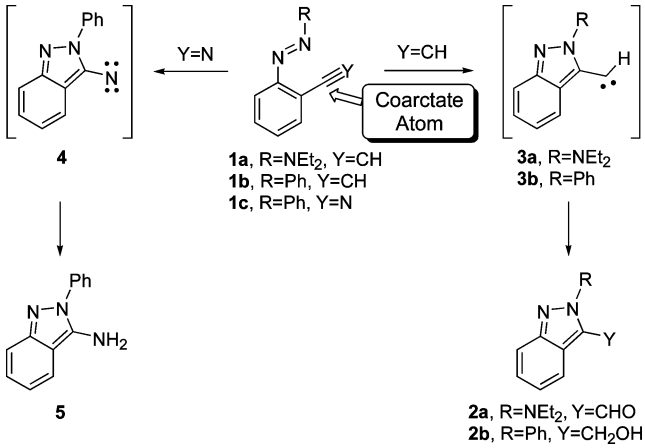


Instead of reacting via the expected coarctate cyclization pathway, 2-nitrosobenzonitrile undergoes a tandem nitroso-ene/intramolecular cyclization to form benzo[*c*]isoxazol-3(1*H*)-imines in very good yields under neutral conditions and at moderate temperatures. Treatment of three of the imines with HBF_4 results in dimerization/condensation to furnish unusual, delocalized cationic systems.

Nitrogen-containing heterocycles have diverse applications, from drugs used as antitumor agents and enzyme inhibitors[1−3] to optical materials used in light-emitting diodes and conducting polymers.[4] Exploration of the properties of heterocyclic systems requires efficient, facile, and high-yielding syntheses of these molecules. Our group,[5] among others,[6] has explored novel synthetic routes to heterocycles based on thermal, photochemical, transition metal or Lewis acid mediated cyclizations of conjugated hetero-"ene-ene-yne" moieties (e.g., **1a**−**c**, Scheme 1).[7] Formation of the five-membered isoindazole rings (**2a,b**) proceeds via carbene (carbenoid) intermediates (**3a,b**), which may be trapped using typical methods. We recently expanded the synthetic viability of this cyclization methodology to include the nitrile functionality (**1c**).[5d] The conjugated azo-ene-nitrile moiety reacts in a manner analogous to the aforementioned cyclizations (e.g., **4**) in very good to excellent overall yield, with the resultant nitrogen-based functionality at the 3-position of **5** permitting for additional synthetic manipulation.

SCHEME 1. Cyclization of Conjugated Hetero-Ene-Ene-Yne Systems



These cyclizations are proposed to follow "coarctate" reaction pathways. Coarctate reactions are characterized by simultaneous formation of two bonds and breakage of two bonds in a single reaction step at the coarctate atom.[8] Incorporation of heteroatoms into the ene-ene-yne skeleton provides the potential for lone pair participation, giving rise to a "pseudocoarctate" reaction pathway. The amount of lone pair participation is determined computationally.[9]

To further explore the applicability of the hetero-ene-ene-yne cyclization methodology, we replaced the azo portion of the conjugated system with a nitroso functionality (e.g., **6**). Density functional theory (DFT) calculations of the nitroso-ene-nitrile cyclization (see Supporting Information) suggest that the reaction has activation energies comparable to the azo-ene-yne and azo-ene-nitrile cyclizations previously investigated in our laboratory. Anisotropy of the current-induced density (ACID)[9] calculations reveal such a pathway to be a true coarctate reaction with no lone pair participation. On the basis of our previous studies, we envisioned that the coarctate cyclization of **6** would proceed via a nitrene (nitrenium) intermediate, reacting in a similar manner as the azo-ene-nitrile system.[5d]

Synthetic trials began with the preparation of cyclization precursor **6**. Oxidation of commercially available 2-aminobenzonitrile using oxone in a 1:4 mixture of CH_2Cl_2 and water

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SCHEME 2. Synthesis and Cyclization of Nitrile 6

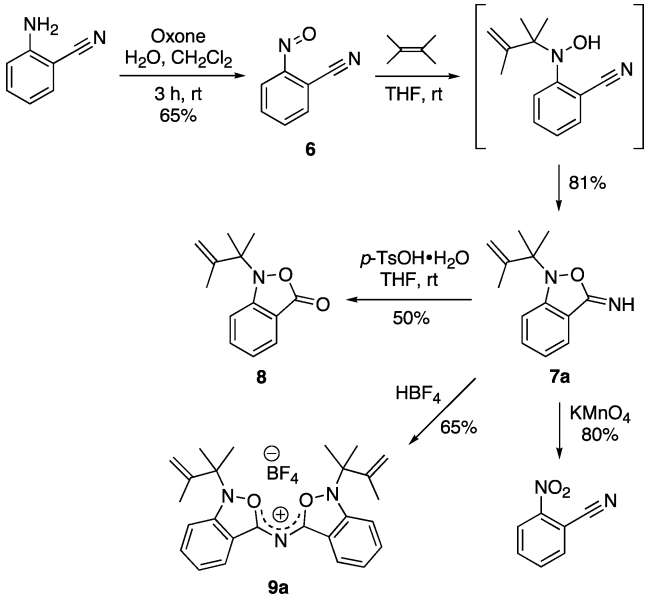

TABLE 1. Reactions Conditions for Cyclization of 6[a]

solvent	Lewis acid (equiv)	temp (°C)	yield **7a** (%)
DCE[b]	CuCl (10)	rt	9
DCE	BF_3·OEt_2 (1)	rt	15
DCE	BF_3·OEt_2 (10)	rt	15
THF	BF_3·OEt_2 (10)	rt	75
Et_2O	BF_3·OEt_2 (10)	rt	16
THF	BF_3·OEt_2 (10)	100	72
THF	$ZnCl_2$ (10)	rt	60
THF	*p*-TsOH·H_2O (10)	rt	78
THF	**none**	**rt**	**81**
PhH	none	100	80
Et_2O	**none**	**rt**	**81**

[a] 2,3-Dimethyl-2-butene (10 equiv) used as trapping agent. [b] 1,2-Dichloroethane.

afforded **6** in 65% yield (Scheme 2).[10] Nitrile **6** could be synthesized in multigram quantities with only filtration over a pad of silica gel necessary to obtain the desired product in pure form.

Initial studies utilizing 2,3-dimethyl-2-butene (nitrene/nitrenium trap) and $SnCl_2$·$2H_2O$, which was successful at inducing cyclization of **1c**, only resulted in reduction of the nitroso group of **6**, affording a complex mixture of products. Switching to CuCl, which worked for **1a,b**, furnished a cyclized product (**7a**, 9%) that incorporated the alkene trap (Table 1). Use of BF_3·OEt_2 at room temperature in DCE with excess 2,3-dimethyl-2-butene also afforded **7a** (15%). The yield could be increased significantly (75%) using THF as solvent. A trial employing *p*-TsOH·H_2O in place of a Lewis acid also resulted in cyclization. Surprisingly, when a control reaction was run in the absence of any type of acid, cyclization also occurred and the highest yield of product (81%) was attained. While the exact structure of the cyclization product and the specific arrangement of the nitrene trap were not readily obvious, 1D and 2D NMR experiments implicated the basic benzisoxazole skeleton. Subsequent experiments (vide infra) confirmed the cyclization product to be benzo[*c*]isoxazol-3(1*H*)-imine **7a**.

(10) Priewisch, B.; Rück-Braun, K. *J. Org. Chem.* **2005**, *70*, 2350−2352.

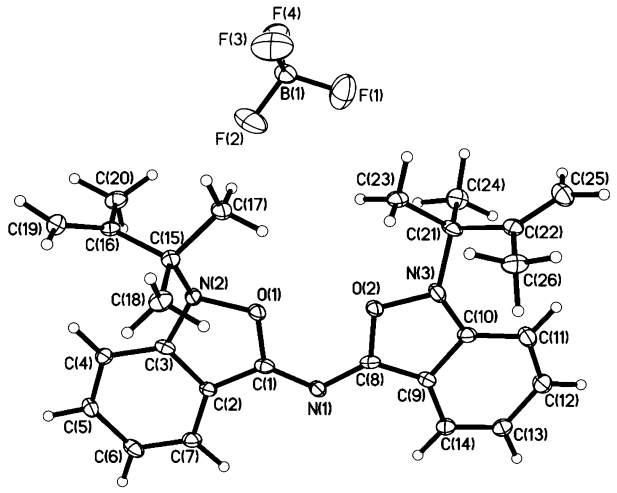

FIGURE 1. Molecular structure of cation **9a**; ellipsoids drawn at the 30% probability level. Selected bond lengths (Å): N2−O1 1.438, O1−C1 1.352, C1−N1 1.313, N1−C8 1.337, C8−O2 1.357, O2−N3 1.413.

Repeated attempts to crystallize **7a** were unsuccessful; thus, we opted to protonate the compound with acid to hopefully induce crystallization. Treating **7a** with HBF_4 in CH_2Cl_2 and allowing the solution to stand in the dark for 24 h afforded pale green needles. X-ray crystallographic analysis of the material (Figure 1) confirmed formation of the benzisoxazole skeleton but surprisingly showed the alkene trap attached to the ring nitrogen and not to the exocyclic nitrogen as would be expected for a coarctate cyclization. Even more surprising, the X-ray data revealed that the green needles were an unusual U-shaped cationic compound (**9a**) formed by the acid-catalyzed dimerization/condensation of **7a**.

As shown in Figure 1, the cationic portion of **9a** adopts a U-shaped geometry that is essentially planar (mean deviation of 2.1°). Bonds O1−C1 and O2−C8 are essentially identical in length (1.352 and 1.357 Å, respectively). The C1−N1 and N1−C8 bonds are also of similar length but slightly shorter (1.313 and 1.337 Å, respectively). These data indicate a nearly uniform distribution of charge across the five atoms. This structural motif closely resembles the 1,3-dialkoxy-2-azapropenylium salts studied by Würthwein et al.[11] These latter cationic systems have been used in the synthesis of 2,6-disubstituted 4-aminopyridines[11e] and are proposed to occur in two geometries: a linear, orthogonal 2-azaallenium form[11a,b] or a bent, planar 2-azaallylium form.[11c−e] Electron-donating groups tend to favor the bent, planar geometry, while the linear, orthogonal structure is preferred in the presence of aliphatic and aromatic substituents. The solid state conformation of **9a** supports this trend, as the benzisoxazole substituent functions as an electron donor.

In contrast to the U-type structure of **9a**, the Würthwein systems typically adopt a W-type geometry. DFT calculations confirm that, of the three possible conformations shown in Figure 2, the planar U-shape of **9a** is the lowest in relative

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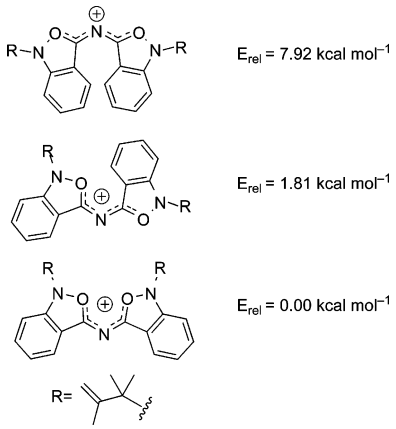


FIGURE 2. Possible conformations of **9a** and calculated relative energies (B3LYP/6-31G).

energy. Instead, the W-shaped geometry has the highest relative energy (7.92 kcal mol^{-1}) due to steric crowding of the aromatic rings, which results in twisting of the cation by 66° (see Supporting Information).

The delocalized nature of the positive charge on **9a** is corroborated by the ^{1}H NMR data. Only one signal is seen for each of the four distinct aromatic hydrogen atoms, which give rise to signals that are shifted downfield from those of **7a** by as much as 0.47 ppm for the hydrogen atoms nearest the cation: ($\Delta\delta_{\mathbf{7a\rightarrow12a}}$ = 0.47, 0.46, 0.44, 0.32 ppm for the aromatic hydrogen atoms). The signals for the alkene and methyl hydrogen atoms of **9a** also are shifted downfield from those of **7a** by 0.25 and 0.40 ppm, respectively. NMR signals of **9b,c** are similarly shifted downfield from their respective monomeric units **7b,c** (see Supporting Information).

The confirmed structure of **9a** (and thus inferred structure of **7a**) clearly shows that instead of reacting via the expected coarctate reaction, precursor **6** preferentially undergoes a tandem nitroso-ene/intramolecular cyclization to form cyclization product **7a** (Scheme 2). The nitroso functionality represents one of many electrophilic enophiles capable of undergoing the heteroatom variant of the ene reaction.[12] Due to the low energy of their LUMO, nitroso compounds are among the most reactive enophiles. Analogously, electron-rich alkenes (such as 2,3-dimethyl-2-butene) represent the most reactive alkenes in the nitroso-ene reaction; electron-deficient alkenes do not readily participate in the analogous reaction. The resultant hydroxylamine intermediate, while so far eluding detection, readily cyclizes to furnish **7a**. Although the calculated energy profile (see Supporting Information) indicates that **6** could undergo a coarctate cyclization, the tandem nitroso-ene/intramolecular cyclization must represent a lower-energy, more favorable reaction pathway.

Several attempts were made to determine the reactivity of **7a**. $KMnO_4$-mediated oxidation yielded multiple products, one of which was identified as 2-nitrobenzonitrile. When stirred at room temperature with *p*-TsOH·H_2O in THF, **7a** converted into a carbonyl-containing compound, which was later identified as **8** (Scheme 2).

Using the optimal conditions for cyclization of **6** with 2,3-dimethyl-2-butene (Table 1), a variety of alkenes was tested for reactivity in the tandem nitroso-ene/cyclization with **6**

SCHEME 3. Tandem Nitroso-Ene/Cyclizations of 6 with Tri- and Tetrasubstituted Alkenes

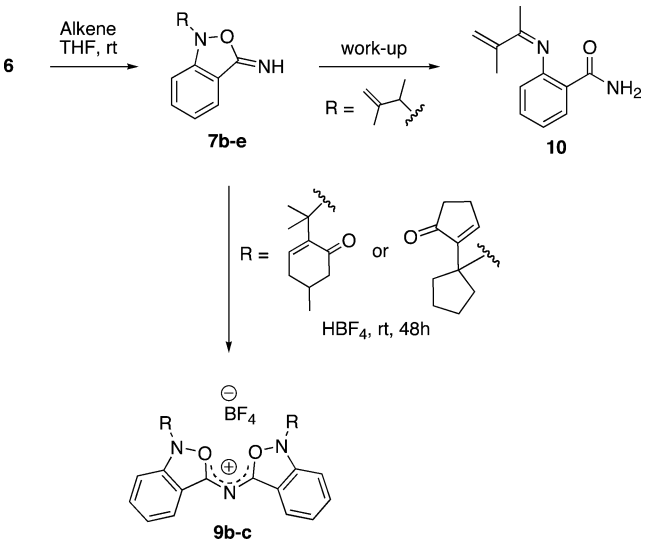
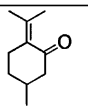
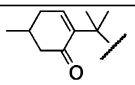
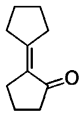
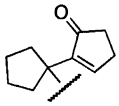
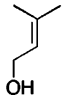
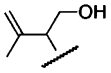


TABLE 2. Yields of Benzo[*c*]isoxazol-3(1*H*)-imines

Alkene	Product (% Yield)	R
	**7b** (78%)	
	**7c** (55%)	
	**7d** (77%[a])	
	**7e** (83%[a])	

[a] Yield is approximate due to facile rearrangement of product.

(Scheme 3 and Table 2). Disubstituted alkenes (not shown) required elevated temperatures (100 °C) and afforded poor yields of cyclization products that proved to be unstable and/or inseparable from multiple side products. In the case of trisubstituted alkenes, the initial cyclization product underwent an irreversible rearrangement to yield the more stable imine upon workup. For example, **7d** readily afforded **10** when treated with aqueous acid or base, with silica gel, or when left standing at room temperature for 1 h. Only when tetra-substituted alkenes were employed did the reaction proceeded in good yield under neutral conditions at room temperature. Analogous to **7a**, subjecting **7b** and **7c** to HBF_4 in CH_2Cl_2 afforded dimers **9b** and **9c** in 49% and 53% yields, respectively.

In conclusion, our studies have shown that **6** reacts via an unanticipated tandem nitroso-ene/intramolecular cyclization, as opposed to a coarctate cyclization pathway. A novel route for the selective cyclization of **6** in the presence of electron-rich, tetra-substituted alkenes has been developed. HBF_4-promoted dimerization of cyclization products provides delocalized cationic salts. We are currently working on extending this new methodology to the synthesis of novel heterocyclic compounds and we continue to investigate the anion-binding ability of salts **9**.

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Experimental Section

General Methods. These are described in ref 5c.

General Cyclization Procedure. Nitrile **6** (50 mg, 0.38 mmol) was dissolved in freshly distilled THF (15 mL, 0.03 M), and alkene (2−10 equiv) was then added to the solution. The reaction was stirred at room temperature until TLC indicated complete consumption of the starting material (7−24 h). Removal of the solvent in vacuo furnished the crude product. The material was dissolved in CH_2Cl_2 (15 mL) and filtered through a pad of deactivated silica gel (1:1 EtOAc/CH_2Cl_2). Removal of the solvent in vacuo furnished the pure imines **7a**−**e**.

Imine 7a. Nitrile **6** and 2,3-dimethyl-2-butene (0.23 mL, 1.89 mmol) were reacted for 7 h, affording **7a** (65 mg, 81%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 5.06 (m, 2H), 2.02 (m, 3H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.6, 148.5, 132.5, 124.0, 123.8, 113.7, 113.5, 104.1, 68.3, 29.7, 23.0, 19.4; IR (NaCl) 3302, 2924, 2854, 1688, 1666, 1462, 1148 cm^{-1}. HRMS (EI) for $C_{13}H_{16}N_2O$: calcd 216.1263, found 216.1261.

Imine 7b. Nitrile **6** and (+)-pulegone (0.62 mL, 3.78 mmol) were reacted for 8 h, affording **7b** (84 mg, 78%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.14 (m, 2H), 7.00 (d, J = 8.1 Hz, 1H), 2.54 (m, 2H), 2.23 (m, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.0, 146.9, 141.1, 132.5, 124.4, 124.2, 114.2, 67.4, 48.4, 34.8, 30.3, 23.9, 23.8, 21.2; IR (NaCl) 3297, 2955, 1677, 1461, 1364, 1312, 1234, 1153, 1023, 757 cm^{-1}. HRMS (EI) for $C_{17}H_{20}N_2O$: calcd 284.1524, found 284.1524.

Imine 7c. Nitrile **6** and 2-cyclopentylidenecyclopentanone (0.057 mL, 3.78 mmol) were reacted for 9 h, affording **7c** (59 mg, 55%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.15 (m, 2H), 2.76 (s, 1H), 2.44 (m, 3H), 2.28 (m, 2H), 2.19 (m, 2H), 1.86 (m, 2H), 1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 207.5, 163.5, 163.4, 152.9, 143.6, 132.7, 124.5, 123.8, 119.3, 114.6, 74.7, 40.0, 35.6, 34.4, 32.7, 29.7, 26.1, 25.4, 23.4; IR (NaCl) 2958, 2874, 1700, 1684, 1653, 1636, 1609, 1464, 1310, 1240, 1170, 1001, 758 cm^{-1}. HRMS (EI) for $C_{17}H_{18}N_2O_2$: calcd 282.1368, found 282.1376.

Imine 7d. Nitrile **6** and 2-methyl-2-butene (1.89 mL, 3.78 mmol, 2.0 M in THF) were reacted for 8 h, affording **7d** (59 mg, 77%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 1H), 7.56 (m, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 5.08 (d, J = 6.0 Hz, 1H), 5.00 (s, 1H), 4.25 (q, J = 6.3 Hz, 1H), 1.07 (d, J = 10.5 Hz, 3H), 1.30 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 145.9, 133.8, 124.5, 124.1, 114.7, 113.2, 112.0, 113.6, 67.2, 66.1, 21.2, 14.1; IR (NaCl) 3301, 3210, 3091, 2978, 2941, 2920, 2877, 1678, 1611, 1597, 1467, 1310, 1238, 1151, 1101, 1029, 904, 756 cm^{-1}. HRMS (EI) for $C_{12}H_{14}N_2O$ calcd 202.1106, found 202.1100.

Imine 7e. Nitrile **6** and 3-methyl-2-buten-1-ol (0.045 mL, 0.454 mmol) were reacted for 24 h, affording **7e** (83 mg, 83%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 4.92 (d, J = 12.6 Hz, 2H), 4.19 (m, 1H), 4.11 (m, 1H), 3.88 (m, 1H), 1.66 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 154.1, 139.8, 133.5, 124.2, 124.1, 117.2, 112.0, 73.0, 61.2, 59.2, 25.9, 22.0; IR (NaCl) 3341, 2924, 1660, 1613, 1509, 1450, 1378, 1319, 1155, 1042, 914, 752, 629 cm^{-1}. HRMS (EI) for $C_{12}H_{14}N_2O_2$: calcd 218.1055, found 218.1050.

General Dimerization Procedure. Imine (**7a**−**c**) (0.378 mmol) was dissolved in CH_2Cl_2 (0.8 mL) and aqueous HBF_4 (0.01 mL, 48−50% by weight) was added. The mixture was aged in the dark, open to air for 48 h, allowing the dimer salt (**9a**−**c**) to crystallize from the reaction mixture.

Salt 9a. 65%; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 9 Hz, 2H), 7.88 (m, 2H), 7.49 (m, 4H), 5.32 (d, J = 9.3 Hz, 4H), 2.03 (s, 6H), 1.74 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 152.2, 145.7, 139.2, 138.3, 126.3, 125.8, 116.1, 115.4, 112.3, 71.8, 25.0, 24.8, 19.3; IR (NaCl) 3501, 3094, 2987, 1755, 1643, 1611, 1515, 1462, 1379, 1332, 1151, 1074, 1017, 911 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 494 (3.33). Em λ_{max} 229 (3.34). HRMS (EI) for $C_{26}H_{30}N_3O_2$ [M]$^+$: calcd 416.2332, found 416.2330.

Salt 9b. 49%; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 8.1 Hz, 2H), 7.75 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.17 (m, 2H), 6.77 (s, 2H), 2.63 (m, 4H), 2.22 (t, J = 11.1 Hz, 6H), 1.76 (s, 6H), 1.69 (s, 6H), 1.07 (d, J = 5.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 198.2, 169.0, 151.8, 149.7, 149.5, 138.4, 138.3, 125.8, 112.2, 109.4, 69.1, 47.8, 34.6, 30.0, 25.6, 21.0; IR (NaCl) 3194, 2957, 2875, 1677, 1457, 1153, 1066, 1027, 755 cm^{-1}; HRMS (ESI) for $C_{34}H_{38}N_3O_4$ [M]$^+$: calcd 552.2857, found 552.2862.

Salt 9c. 53%; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 2H), 7.86 (t, J = 2.4 Hz, 2H), 7.82 (m, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 2.62 (m, 9H), 2.26 (m, 6H), 1.84 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 169.6, 166.5, 152.9, 141.4, 138.2, 126.3, 125.5, 113.5, 110.4, 100.2, 75.7, 35.8, 35.5, 34.0, 33.9, 26.5, 22.7; IR (NaCl) 3277, 3190, 2959, 2880, 1701, 1617, 1457, 1309, 1069, 756 cm^{-1}. HRMS (ESI) for $C_{34}H_{36}N_3O_4$ [M]$^+$: calcd 548.2544, found 548.2549.

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Supporting Information Available: Experimental details for **6**, **8**, and **10**; computed energy diagram for coarctate cyclization of **6**; copies of ^{1}H and ^{13}C NMR spectra for **6**, **7a**−**e**, **8**, **9a**−**c**, **10**; X-ray structure of **9a** in CIF format, structure refinement details, tables of atomic coordinates, thermal parameters, bond lengths, and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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