Novel Templating Effect in the Macrocyclization of Functionalized Diynes by Zirconocene Coupling[**]

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Functionalized macrocycles are useful chemical species for many applications, but their syntheses can present a considerable challenge. The synthesis of a pure macrocycle often involves lengthy separations and low isolated yields.[1] Much of the difficulty encountered in macrocycle synthesis relates to the lack of stoichiometric control typically associated with combining a specified number of monomer units into the macrocycle. Approaches that address this issue include preassembly of the monomer units by templating strategies[2] or the use of covalently attached "tethers" that control the stoichiometry of macrocyclization.[3]

We have been exploring the use of the zirconocene-coupling of rigid diynes for the high-yield synthesis of macrocycles.[4] With silyl-substituted diynes, zirconocene coupling is reversible in the presence of donor solvents, such that a low-energy pathway exists for the formation of a single thermodynamic product. We have shown that this method allows for a high degree of selectivity in the macrocyclization stoichiometry, which can be controlled by the diyne geometry. Linear, rigid diynes lead to trimeric macrocycles, while bent or somewhat flexible diynes produce dimeric macrocycles.[4]

The importance of diyne geometry in defining the course of zirconocene macrocyclization suggests that the templating of functionalized diynes might represent a useful extension of this method. In perhaps the simplest variation of this approach, zirconocene itself would serve as both the coupling and templating reagent. The electronic structure of 2,2′-bipyridine (bpy) is known to change substantially on coordination to a electron-rich early transition metal center.[5a] Chelation of zirconocene was expected to force the bpy into the *syn* conformation, and strong π donation from zirconium to bpy leads to disruption of aromaticity in the rings and distortions that should change the geometry of the $[Cp_2Zr(bpy)]$-based spacer group (Cp = cyclopentadiene). To investigate this possibility, we determined the crystal structure for $[Cp_2Zr(bpy)]$,[5b–d] which was synthesized as described previously.[4a] This compound features a highly bent bpy ligand, as can be seen in the ORTEP diagram in Figure 1. In this structure, the bending of the bpy ligand may be described by the angle between the C1, C2, C3 and C8, C9, C10 planes (Figure 1). For $[Cp_2Zr(bpy)]$, this angle is 143°, which is 37° less than that for the planar, uncoordinated bpy.

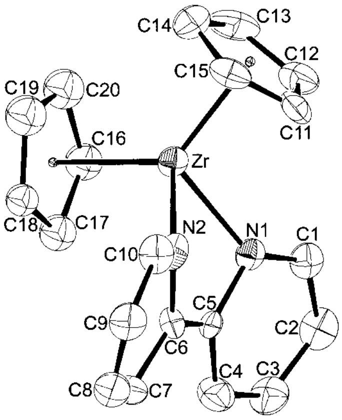
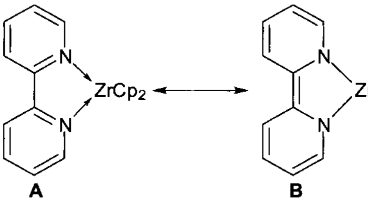


Figure 1. ORTEP diagram of $[Cp_2Zr(bpy)]$. Thermal ellipsoids are set at the 50% probability level.

Inspection of bond distances within the bpy ligand of $[Cp_2Zr(bpy)]$ reveals regular bond alternations consistent with partial dearomatization of the rings, which results from donation of electron density from zirconium to antibonding π* levels of the bpy unit. These distortions represent a strong contribution from resonance form **B**, with the single C−C bonds in this structure being an average of 0.04 Å longer, and C−C double bonds 0.05 Å shorter, than the corresponding distances in bpy.[7]



The influence of the d^2 configuration of zirconium on the structure of the bpy ligand of this complex is further revealed by comparison with the d^0 analog $[Cp_2Zr(bpy)OTf]OTf$,[5e] ($OTf = OSO_2CF_3$, triflate) which has a less bent bpy ligand (164°) and no discernible bond alternation within the rings. Also, $[Cp_2Ti(bpy)]$ has a much less bent bpy ligand (169°) and no evidence of bipyridine bond alternation.[5f] This is likely to be a result of weaker donation of π electron density from the metal into the π* orbitals of the bpy ligand.[5g]

Since bent diynes are observed to give dimeric macrocycles under zirconocene-coupling conditions, it seemed that diynes containing a bent $[Cp_2Zr(bpy)]$ group might be coupled to give dimeric products. As shown in Scheme 1, addition of one equivalent of $[Cp_2Zr(py)(Me_3SiC{\equiv}CSiMe_3)]$[4a, 6] (py = pyridine) to the linear, bpy-containing diynes **1** and **2** gives excellent yields of triangular, trimeric macrocycles.[4a,b] However, reaction of two equivalents of the zirconocene reagent with the same diynes gives excellent yields of the dimeric macrocycles **3** and **4**. Crystalline **3** was obtained from the

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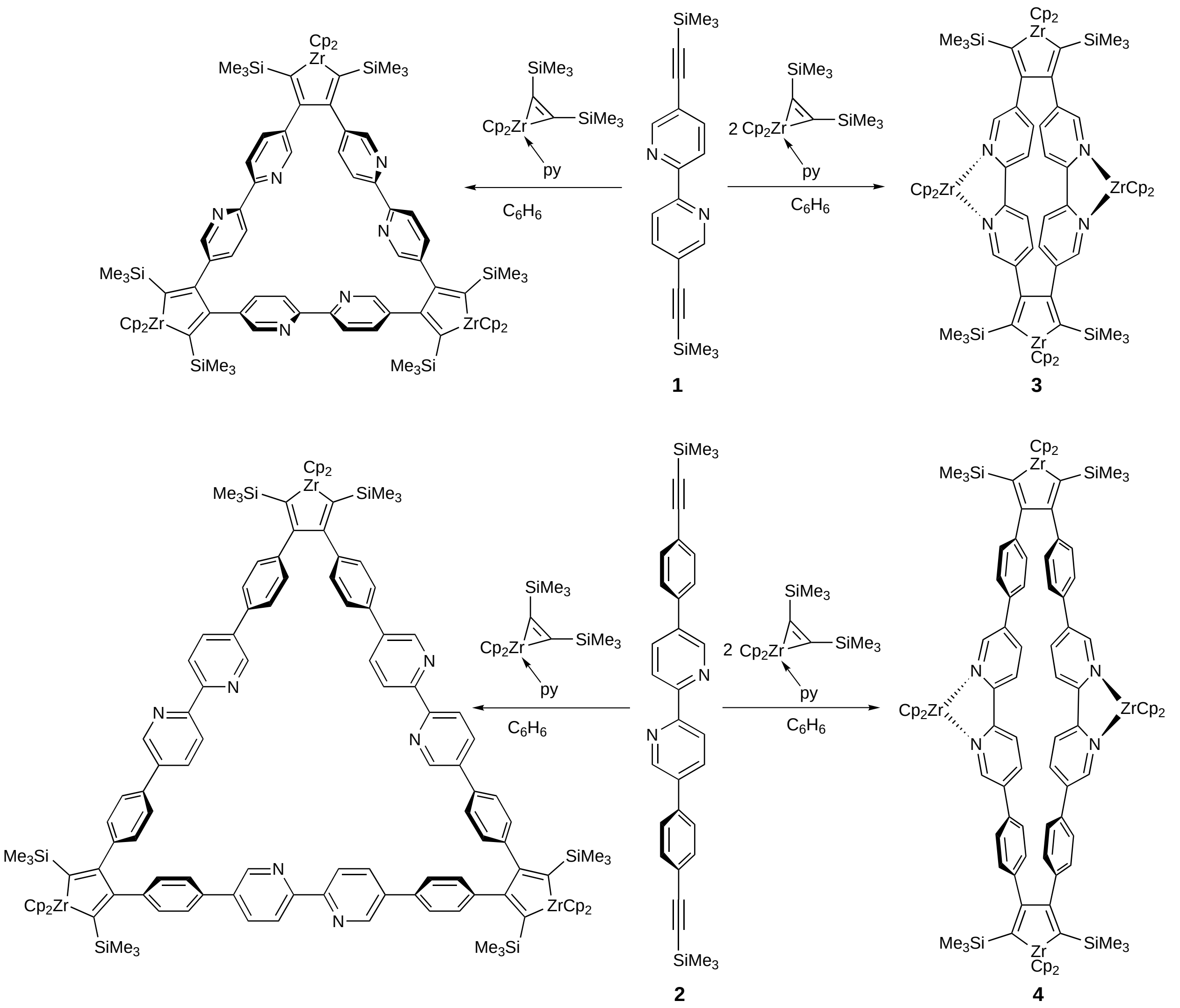

Scheme 1. The reported syntheses of trimeric macrocycles from bpy-containing diynes[4a,b] and the syntheses of **3** and **4** from the same starting materials.

reaction of [$Cp_2Zr(py)(Me_3SiC{\equiv}CSiMe_3)$] and diyne **1** (2:1 ratio) in benzene. This reaction is complete after seven days at 40 °C, giving **3** in 96 % yield as black crystals, some of which were of X-ray quality. Crystalline **4** was obtained under identical conditions in 95 % yield. The use of zirconocene as both templating and macrocyclization reagent thus allows a high level of control over the macrocyclization stoichiometry, based simply on the ratio of reagents employed.

The ready formation of trimeric macrocycles in the absence of a second equivalent of [$Cp_2Zr(py)(Me_3SiC{\equiv}CSiMe_3)$] suggests that the alkyne groups are the first site of zirconocene complexation. Numerous species are likely to be present in the reaction mixtures which yield **3** and **4**, but the equilibrating nature of the zirconocene-coupling reaction results in the eventual formation of a single product.

An ORTEP diagram of **3** is given in Figure 2. The bpy units in this molecule are bent to an even greater degree than in [$Cp_2Zr(bpy)$] (angle between the planes of 125°), suggesting that this macrocycle may be strained. Macrocycle **4** (Figure 3) has an analogous angle across bpy of 135°, intermediate between those of **3** and [$Cp_2Zr(bpy)$]. The range of angles observed for bpy in complexes [$Cp_2Zr(bpy)$], **3**, and **4** indicates that the energy required to bend the bpy unit is greatly reduced by its coordination to the Cp_2Zr fragment. Both **3** and **4** exhibit bond alternations in the bpy rings that are similar in magnitude to those observed in [$Cp_2Zr(bpy)$].

The diamond-shaped central cavity of the larger macrocycle **4** contains a benzene guest molecule. Based on examination of the crystal structures, the largest sphere that could be accommodated in the cavity of **3** would have a van der Waals radius of 1.15 Å, while a sphere of radius 2.83 Å would fit into the cavity of **4**. However, larger, more elongated objects could fit readily into these cavities.

The ^1H and ^{13}C NMR spectra of **3** exhibit resonance signals for three distinct Cp groups in a

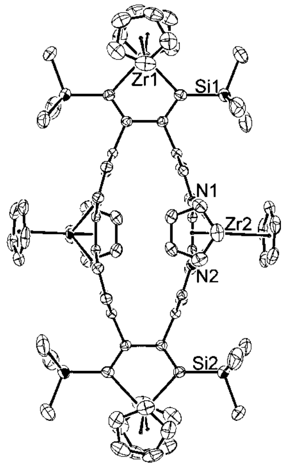

Figure 2. ORTEP diagram of **3**. Thermal ellipsoids are set at the 50 % probability level and the heteroatoms of the asymmetric unit are labeled.

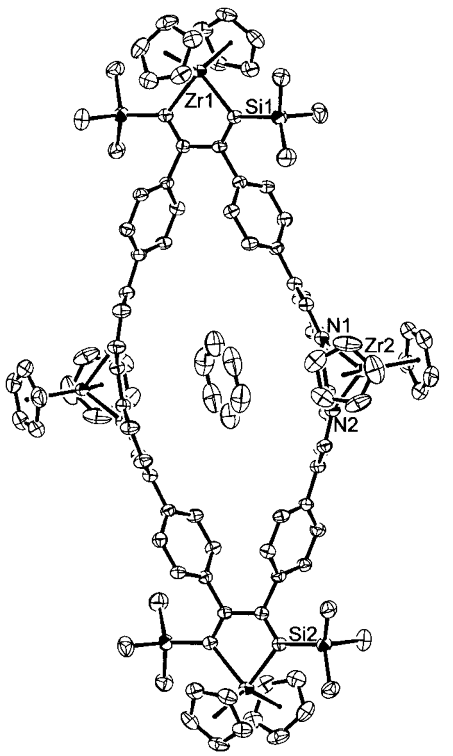

Figure 3. ORTEP diagram of **4** showing the benzene guest molecule. Thermal ellipsoids are set at the 50 % probability level and the heteroatoms of the asymmetric unit are labeled.

2:1:1 ratio. This indicates that in toluene and THF solution as well as in the solid state the two Cp rings of the $[Cp_2Zr(bpy)]$ fragment are distinct (chemically inequivalent). This situation appears to result from the compact and constrained geometry of **3**. The bpy rings of this molecule may not readily rotate past one another, as would be required to interconvert the Cp rings. Heating a solution of **3** in $[D_8]$toluene results in decomposition to multiple products within minutes at 110 °C, before any coalescence of the Cp resonances. Decomposition of **3** occurs more rapidly in $[D_8]$THF, with the resonances assigned to **3** disappearing within one minute at 60 °C as resonance signals from multiple unidentified products appear.

In contrast, the ^1H NMR spectrum of **4** at 25 °C in $[D_8]$THF exhibits only two resonance signals for the Cp rings, indicating that the $[Cp_2Zr(bpy)]$ fragments are freely rotating in the more open structure of **4**. Cooling a $[D_8]$THF solution of **4** at −20 °C results in decoalescence of one of the Cp resonance signals ($\delta = 5.69$ at room temperature). At −40 °C these Cp groups give two resonance signals at $\delta = 5.29$ and 6.15, which sharpen further as the temperature is lowered. This corresponds to a barrier to Cp ring exchange of 11.5 kcal mol^{-1}.[8]

This work demonstrates a new means for precisely controlling the stoichiometry of macrocyclization through the use of a single zirconocene reagent as both templating and macrocyclization reagent. We are currently investigating methods for selectively derivatizing the two distinct zirconocene sites in these macrocycles and exploring the potential of this templating approach in controlling macrocycle size and shape.

Experimental Section

$[Cp_2Zr(bpy)]$ was synthesized as previously described.[4a] X-ray quality crystals were obtained through vapor diffusion of pentane into a benzene solution.

Macrocycle **3**. Diyne **1**[4b] (0.370 g, 1.06 mmol) and $[Cp_2Zr(py)(Me_3SiC{\equiv}C\text{-}SiMe_3)]$[6] (1.00 g, 2.12 mmol) were loaded into a 100 mL Schlenk flask, which was then charged with dry benzene (50 mL). The flask was sealed, and the reaction mixture was sonicated at room temperature for 10 min. The reaction mixture was then heated to 40 °C for 7 days. Black crystals of the product, some of which were of X-ray quality, precipitated from solution over this time. The solvent was removed by cannula filtration, and the product was dried under vacuum. The isolated yield was 0.806 g, 96 %; ^1H NMR (500 MHz, $[D_6]$benzene, 298 K): $\delta = 0.20$ (s, 18 H, $Si(CH_3)_3$), 5.40 (s, 5 H, Cp), 5.82 (d, $J = 9$ Hz, 2 H, bpy), 5.86 (s, 5 H, Cp), 6.10 (s, 10 H, Cp), 6.50 (d, $J = 9$ Hz, 2 H, bpy), 6.89 (s, bpy); (300 MHz, $[D_8]$toluene, 298 K): $\delta = 0.18$ (s, 18 H, $Si(CH_3)_3$), 5.33 (s, 5 H, Cp), 5.78 (d, $J = 9$ Hz, 2 H, bpy), 5.85 (s, 5 H, Cp), 6.08 (s, 10 H, Cp), 6.47 (d, $J = 9$ Hz, 2 H, bpy), 6.84 (s, bpy); (300 MHz, $[D_8]$THF, 298 K): $\delta = 0.06$ (s, 18 H, $Si(CH_3)_3$), 5.18 (s, 5 H, Cp), 5.82 (d, $J = 9$ Hz, 2 H, bpy), 5.92 (s, 5 H, Cp), 6.33 (s, 10 H, Cp), 6.64 (d, $J = 9$ Hz, 2 H, bpy), 6.77 (s, bpy); $^{13}C\{^1H\}$ NMR (125 MHz, $[D_6]$benzene, 298 K): $\delta = 3.6$ ($Si(CH_3)_3$), 102.5 (Cp), 106.4 (Cp), 111.4 (Cp), 116.2, 122.6, 127.5, 135.5, 145.3, 149.5, 206.8 (C-Zr); elemental analysis (%) calcd for $C_{80}H_{88}N_4Si_4Zr_4$: C 60.71, H 5.60, N 3.54; found: C 60.57, H 5.32, N 3.39.

Macrocycle **4**. Diyne **2**[4a] (0.500 g, 0.998 mmol) and $[Cp_2Zr(py)(Me_3SiC{\equiv}C\text{-}SiMe_3)]$[6] (0.945 g, 2.01 mmol) were loaded into a 100 mL Schlenk flask, which was then charged with dry benzene (90 mL). The flask was sealed, and the reaction mixture was sonicated at room temperature for 10 min. The reaction mixture was then heated to 40 °C for 7 days. Black crystals of the product, some of which were of X-ray quality, precipitated from solution over this time. The solvent was removed by cannula filtration, and the product was dried under vacuum, yield was 0.895 g, 95 %. The product is extremely air-sensitive, and has very low solubility in hydrocarbon solvents and diethyl ether. Decomposition was observed in THF solution at room temperature over several hours, but proton NMR spectra could be obtained if the sample was frozen for transit to the spectrometer. ^1H NMR (300 MHz, $[D_8]$THF, 298 K): $\delta = -0.18$ (s, 18 H, $Si(CH_3)_3$), 5.69 (s, 10 H, Cp), 6.44 (s, 10 H, Cp), 6.58 (d, $J = 9$ Hz, 4 H, phenylene), 6.74 (d, $J = 8$ Hz, 2 H, bpy), 6.99 (d, $J = 9$ Hz, 4 H, phenylene), 7.11 (d, $J = 8$ Hz, 2 H, bpy), 7.86 (s, bpy); (300 MHz, $[D_8]$THF, 203 K): $\delta = -0.21$ (s, 18 H, $Si(CH_3)_3$), 5.29 (s, 5 H, Cp), 6.18 (s, 5 H, Cp), 6.49 (s, 10 H, Cp), 6.56 (br d, 4 H, phenylene), 6.96 (br, 6 H, phenylene and bpy), 6.23 (br d, 2 H, bpy), 8.02 (s, 2 H, bpy); elemental analysis (%) calcd for $C_{104}H_{104}N_4Si_4Zr_4$: C 66.19, H 5.55, N 2.97; found: C 65.96, H 5.32, N 2.93.

Crystal data for $[Cp_2Zr(bpy)] \cdot (C_{20}H_{18}N_2Zr)$: crystal dimensions $0.21 \times 0.20 \times 0.14$ mm, orthorhombic, space group $P2_12_12_1$, $a = 8.9433(8)$, $b = 9.6960(9)$, $c = 18.728(2)$ Å, $V = 2176.94(2)$ Å^3, $\rho_{calcd} = 1.54$ g cm^{-3}, $2\Theta_{max} = 51.1°$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å), ω scans, $T = -113$ °C, of 7331 measured reflections, 1664 were unique, and 1189 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPREP with an empirical absorption correction using SADABS ($T_{max} = 0.86$, $T_{min} = 0.63$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 204; H atoms were calculated but not refined; $R = 0.039$, $R_w = 0.044$, GOF = 1.30.

Crystal data for **3** ($C_{46}H_{50}N_2Si_2Zr_2$): crystal dimensions $0.40 \times 0.30 \times 0.32$ mm, monoclinic, space group $P\bar{1}$, $a = 13.8846(1)$, $b = 14.0501(1)$, $c = 14.2032(1)$ Å, $\alpha = 61.385(1)°$, $\beta = 87.029(1)°$, $\gamma = 65.559(1)°$, $V = 2176.94(2)$ Å^3, $\rho_{calcd} = 1.33$ g cm^{-3}, $2\Theta_{max} = 52.1°$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å), ω scans, $T = -109$ °C, of 10481 measured reflections, 7292 were unique, and 6416 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPREP with an empirical absorption correction using SADABS ($T_{max} = 0.90$, $T_{min} = 0.80$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 469; H atoms were calculated but not refined; $R = 0.028$, $R_w = 0.042$, GOF = 1.80.

Crystal data for **4** ($C_{76}H_{76}N_2Si_2Zr_2$): crystal dimensions $0.20 \times 0.18 \times 0.15$ mm, monoclinic, space group $P\bar{1}$, $a = 14.6211(2)$, $b = 15.0342(2)$, $c = 17.7675(1)$ Å, $\alpha = 65.455(1)°$, $\beta = 66.895(1)°$, $\gamma = 88.621(1)°$, $V =$

$3222.32(8)$ Å^3, $\rho_{\text{calcd}} = 1.29\ \text{g cm}^{-3}$, $2\Theta_{\max} = 52.3°$, Mo$_{K\alpha}$ radiation ($\lambda = 0.71069$ Å), ω scans, $T = -115\,°\text{C}$, of 15644 measured reflections, 10891 were unique, and 8247 were observed (with $I > 3.00\sigma(I)$), data corrected for Lorentz and polarization effects, analyzed for agreement and absorption using XPREP with an empirical absorption correction using SADABS ($T_{\max} = 0.78$, $T_{\min} = 0.71$). The structure was solved by direct methods (SIR92) and developed by least-squares refinement against $|F|$. No. of parameters, 739; H atoms were calculated but not refined; $R = 0.032$, $R_w = 0.039$, GOF = 1.61.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-153030 (**3**), CCDC-153031 (**4**), and CCDC-153749 ([Cp$_2$Zr(bpy)]). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[1] D. Parker, *Macrocycle Synthesis: A Practical Approach*, Oxford University Press, Oxford, **1996**.

[2] a) *Templated Organic Synthesis* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **2000**; b) M. Nakash, Z. Clyde-Watson, N. Feeder, J. E. Davies, S. J. Teat, J. K. M. Sanders, *J. Am. Chem. Soc.* **2000**, *122*, 5286–5293, and refs therein; c) S. Anderson, H. L. Anderson, J. K. M. Sanders, *Acc. Chem. Res.* **1993**, *26*, 469–475.

[3] a) S. Höger, *J. Polym. Sci. Part A* **1999**, *37*, 2685–2698, and refs therein; b) C. R. Woods, J. P. Bourgeois, P. Seiler, F. Diederich, *Angew. Chem.* **2000**, *112*, 3971–3974; *Angew. Chem. Int. Ed.* **2000**, *39*, 3813–3816, and refs therein.

[4] a) J. R. Nitschke, S. Zürcher, T. D. Tilley, *J. Am. Chem. Soc.* **2000**, *122*, 10345–10352; b) J. R. Nitschke, T. D. Tilley, *J. Org. Chem.* **1998**, *63*, 3673–3676; c) F. Q. Liu, G. Harder, T. D. Tilley, *J. Am. Chem. Soc.* **1998**, *120*, 3271–3272; d) S. S. H. Mao, T. D. Tilley, *J. Am. Chem. Soc.* **1995**, *117*, 7031–7032; e) S. S. H. Mao, T. D. Tilley, *J. Am. Chem. Soc.* **1995**, *117*, 5365–5367.

[5] a) E. Uhlig, *Pure Appl. Chem.* **1988**, *60*, 1235–1240; b) L. A. Bishop, M. A. Turner, L. B. Kool, *J. Organomet. Chem.* **1998**, *553*, 53–57; c) R. Beckhaus, K. H. Thiele, *J. Organomet. Chem.* **1986**, *317*, 23–31; d) P. C. Wailes, H. Weigold, *J. Organomet. Chem.* **1971**, *28*, 91–95; e) U. Thewalt, W. Lasser, *J. Organomet. Chem.* **1989**, *363*, C12–C14; f) R. Gypes, P. T. Witte, M. Horácek, I. Císarová, K. Mach, *J. Organomet. Chem.* **1998**, *551*, 207–213; g) A. M. McPherson, B. F. Fieselmen, D. L. Lichtenberger, G. L. McPherson, G. D. Stucky, *J. Am. Chem. Soc.* **1979**, *101*, 3425–3430.

[6] U. Rosenthal, A. Ohff, W. Baumann, A. Tillack, H. Görls, V. V. Burlakov, V. B. Shur, *Z. Anorg. Allg. Chem.* **1995**, *621*, 77–83.

[7] A. Almenningen, O. Bastiansen, S. Gundersen, S. Samdal, *Acta Chem. Scand.* **1989**, *43*, 932–937.

[8] J. Sandström, *Dynamic NMR Spectroscopy*, Academic Press, New York, **1982**, p. 182.

Rapid Access to Complex Molecular Architectures via *o*-Azaquinones**

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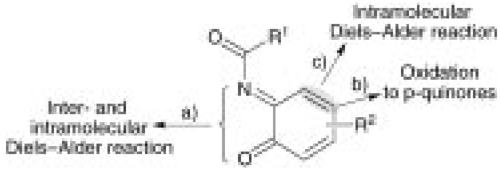
We have recently reported a number of new synthetic technologies[1] based on the use of the hypervalent iodine reagent DMP and its precursor IBX (for abbreviations of reagents, see legends to schemes). Despite their similar structures and ability to oxidize alcohols to carbonyl compounds, IBX and DMP exhibit distinctly different reactivity profiles towards a multitude of organic substrates. The facile generation of *o*-azaquinone-type structures from anilides and DMP, and their demonstrated ability to undergo inter- and intramolecular Diels–Alder reactions as heterodienes (Scheme 1, path a)[1a,f] or to undergo further oxidation to *p*-quinones[1f] (Scheme 1, path b) prompted us to investigate them further. Close inspection revealed the potential of utilizing these quinones to construct rapidly complex mimics of known natural products and potential protein ligands. Herein we report a new mode of reactivity of these underexplored molecular entities in which the double bond adjacent to the imide moiety (Scheme 1, path c) is richly exploited by means of cascade reactions. Initiated by DMP, this pathway proceeds through an intramolecular Diels–Alder reaction of the generated *o*-azaquinone–diene constructs and leads, via ketohydroxyamides, to a multitude of molecules (e.g. **1**, **2a**, and **3a**, Scheme 2), which resemble the pseudopterosin natural products.[2] Alternatively, further



Scheme 1. Reactivity of *o*-azaquinones as versatile chemical entities. a) Participation in inter- and intramolecular Diels–Alder reactions (ref. [1a,f]), b) oxidation to *p*-quinones (ref. [1f]), and c) proposed intramolecular Diels–Alder reactions.

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