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Synthetic Methods

The Synthesis of Highly Substituted Cyclooctatetraene Scaffolds by Metal-Catalyzed [2+2+2+2] Cycloadditions: Studies on Regioselectivity, Dynamic Properties, and Metal Chelation**

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Cyclooctatetraenes (COTs) are a fascinating class of molecules with great potential utility as building blocks for synthesis,[1] scaffolds for drug discovery, designed carbohydrate mimics,[2] ligands for d- and f-block metals[3] including those for asymmetric catalysis,[4] and components for molecular detection devices (e.g. dynamic molecular tweezers)[5] and novel materials.[6] For many applications including the use of COTs in fluxional materials,[7] conducting polymers,[8] and light emitting devices,[9] the type and degree of COT substitution play a critical role in controlling the redox and electronic properties of the system. For other applications, substitution determines COT topological chirality and the rate of COT racemization by tub-to-tub ring inversion.[10] Notwithstanding their considerable potential, highly substituted and functionalized COTs have received limited attention partly due to the relative paucity of methods for their general and efficient synthesis.[11]

While Reppe's Ni^0-catalyzed tetramerization of acetylene provides cyclooctatetraene itself,[12] related cyclo-tetramerizations of terminal alkynes lead to complex mixtures and those of internal alkynes encounter reactivity problems.[13] Two classes of alternative methods for the synthesis of hexa- and octa-substituted COTs have been developed, those based on the metal-mediated coupling of two dienes,[14] and high-temperature rearrangement of semibullvalenes,[15] barrelenes,[16] or cyclobutadiene dimers.[17] However, these approaches have been limited mainly to the construction of simple alkyl and/or aryl substituted COTs. Recently, we reported that the favored metal-catalyzed [2+2+2] cycloaddition of diynes can be completely reversed with certain nickel catalysts to produce [2+2+2+2] cycloaddition products.[18] However, key issues related to the applications of COTs such as the formation of hexa- and octa-substituted COTs, reaction regioselectivity, and tolerance of heteroatom substitution are unexplored. We now report that the lack of reactivity of internal alkynes can be overcome through a mixed inter/intramolecular nickel(0)-catalyzed [2+2+2+2] cycloaddition of commercially or readily available 1,6-diynes, providing access to hexa- and octa-substituted COTs with a variety of functionalities. We also report the first study of the regioselectivity of this process, the first example of a fully intramolecular [2+2+2+2] cycloaddition, and the initial study of the use of these novel ligands in metal complexation.

Our studies initially focused on diynes which incorporate both an internal and a terminal alkyne, which provide hexasubstituted COTs in good yields (Table 1). Only trace amounts of [2+2+2] products were observed. Significantly, the regioselectivities of the process range from 4.6:1 when the substituent is CH_2OCH_3 (entry 2) to >20:1 when it is aromatic or heteroaromatic (entries 3–6). It is noteworthy, both synthetically and mechanistically, that the corresponding fully intermolecular reactions of propyne and propargyl alcohol proceed with minimal regioselectivity to provide complex and difficult to separate mixtures of regio- and other isomers.[19] A wide variety of functional groups are tolerated in this process including an ether (entry 2), an ester (entry 5), a Boc-protected nitrogen heterocycle (entry 6) and even a free phenolic group (entry 4). The rapid increase in molecular complexity attending this four-component cycloaddition process is noteworthy and rare as four carbon–carbon bonds and three rings are formed in a single operation.

Diynes containing two internal alkynes were next studied (Table 2). Alkyl- (entry 4), functionalized alkyl- (entries 2 and 3), and aryl substituted alkynes, the last with both electron donating (entry 5) and withdrawing groups (entry 6), work well. X-ray structures were obtained for COTs **2** and **14**, which verified the double bond isomer in both cases, as well as the regiochemistry of COT **2** (Figure 1).[20]

While the preceding studies provide access to fully substituted and 1,2,3,5,6,7-hexa-substituted COTs, the first study of a fully intramolecular [2+2+2+2] cycloaddition involving tetrayne **25** was explored for the synthesis of 1,2,3,4,5,6-hexa-substituted COTs (Scheme 1). This mechanistically and synthetically intriguing process proceeds in 66% yield with the formation of four carbon–carbon bonds and four rings, an uncommon bond and ring-forming event.

Our interest in this methodology is prompted partly by the potential use of highly substituted COTs as tunable ligands for catalysis, fluxional scaffolds for drug discovery and conformational switches for functional devices. These applications could further benefit from the topological chirality of

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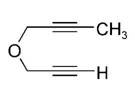
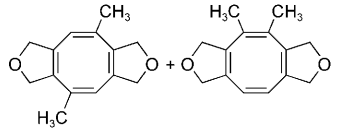
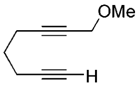
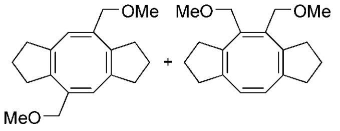
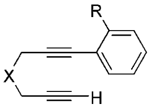
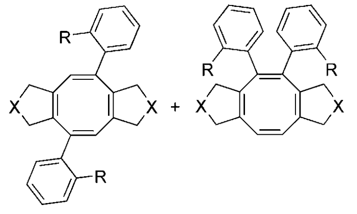
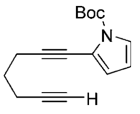
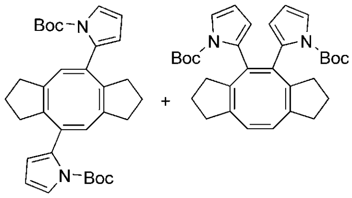
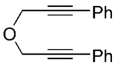
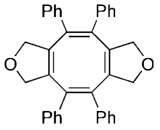
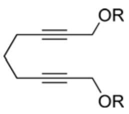
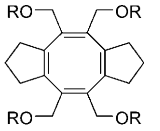
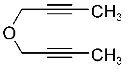
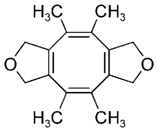
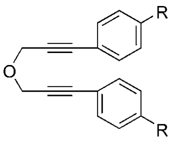
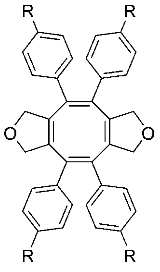
Table 1: Mixed internal/terminal diyne [2+2+2+2] cycloadditions.[a]

Entry	Diyne	t [h]	Product(s), yield[b] (ratio)[c]
1[d]		1	
	1		**2**, 80% (10:1)
2		2	
	3		**4**, 73% (4.6:1)
			
3[e]	**5**	0.5	**6**, X=O, R=H, 56%(>20:1)
4	**7**	2	**8**, $X=CH_2$, R=OH, 51%(>20:1)
5	**9**	0.5	**10**, $X=CH_2$, $R=CO_2CH_3$, 68% (>20:1)
6[e]		0.5	
	11		**12**, 90% (>20:1)

[a] Conditions: [(dme)$NiBr_2$] (20 mol%) (dme = dimethoxyethane), Zn powder (40 mol%), H_2O (20 mol%), THF (0.1 M), 60°C. [b] Yield of isolated products. [c] Determined by ^1H NMR spectroscopy. [d] [(dme)$NiBr_2$] (40 mol%), Zn powder (80 mol%), H_2O (40 mol%). [e] 0.5 M.

Table 2: [2+2+2+2] Cycloadditions with internal diynes.[a]

Entry	Diyne	t [h]	Product, yield[b]
1		2	
	13		**14**, 78%
			
2[c,d]	**15**	0.25	**16**, $R=CH_3$, 76%
3[c]	**17**	2	**18**, R=PMB, 72%
4[c]		1	
	19		**20**, 64%
			
5	**21**	18	**22**, R=OMe, 69%
6	**23**	2	**24**, $R=CO_2CH_3$, 52%

[a] Conditions: [(dme)$NiBr_2$] (20 mol%), Zn powder (40 mol%), H_2O (20 mol%), THF (0.1 M), 60°C. [b] Yield of isolated compounds. [c] 0.5 M. [d] [(dme)$NiBr_2$] (40 mol%), Zn powder (80 mol%), H_2O (40 mol%). PMB = p-methoxybenzyl.

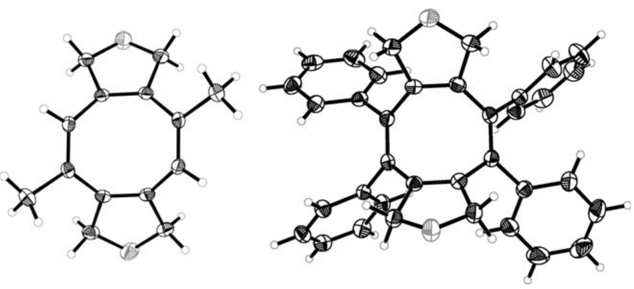
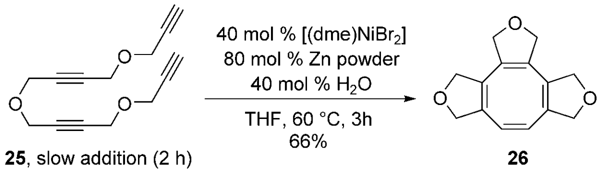


Figure 1. ORTEP diagrams of COTs **2** and **14** (C black; O light gray; H small circles).



25, slow addition (2 h)

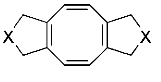
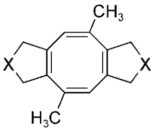
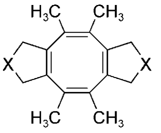
26

Scheme 1. Fully intramolecular [2+2+2+2] cycloaddition.

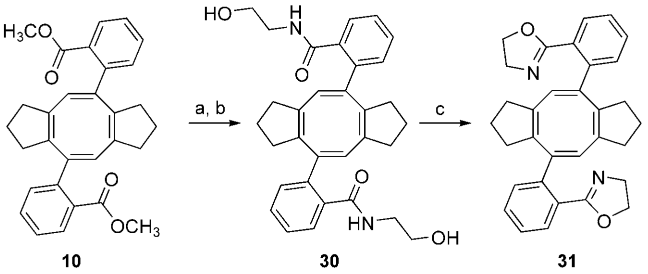
certain COTs as well as their ability to “epimerize” through ring inversion. To explore their fluxional behavior, we measured the ring-inversion barriers of selected COTs by variable-temperature ^1H NMR spectroscopy. While the activation energy for COT itself is ca. 10–11 kcal mol^{-1},[21] the activation energies for these cycloadducts can be “tuned” by altering the degree of COT substitution (Table 3).[10]

The availability of heteroatom-substituted COTs coupled with their controllable dynamic behavior opens opportunities for their use as ligands for metal sensing and catalysis. Toward

Table 3: Ring-inversion barriers of cycloadducts with varying substitution ($X=C(CO_2CH_3)_2$) as determined by VT-NMR spectroscopy.

		
27, $\Delta G^{\neq}$ [kcal mol^{-1}] = calculated: 12.0 experimental: 11.3	**28**, $\Delta G^{\neq}$ [kcal mol^{-1}] = calculated: 20.9 experimental: 20.0	**29**, $\Delta G^{\neq}$ [kcal mol^{-1}] = calculated: 45.2 experimental: ND

this end, we have examined the use of COT **10** as a diversification point for accessing metal complexing ligands. The initial compound targeted was bis-oxazoline[22] **31**, which was synthesized in three steps from COT **10** (Scheme 2).



Scheme 2. Synthesis of bis-oxazoline COT **31**. a) LiOH, MeOH/THF, 17 h, reflux, 96%; b) glycinol, HBTU, HOBt, DMF, *i*Pr$_2$NEt, RT, 24 h c) MsCl, NEt$_3$, CH$_2$Cl$_2$, 5 h, 86% over 2 steps. HBTU = *O*-(benzotriazol-1-yl)-tetramethyluronium hexafluorophosphate, HOBt = 1-hydroxybenzotriazole, Ms = mesyl.

Treatment of **31** with ZnBr$_2$ in CDCl$_3$ results in a single, well-defined NMR-observable metal complex (**32**). The solution structure, based on ROESY measurements of **32**, is shown in Figure 2. This is the first example of a topologically chiral racemic COT used to coordinate metals through appended nitrogen-containing functionality.[23]

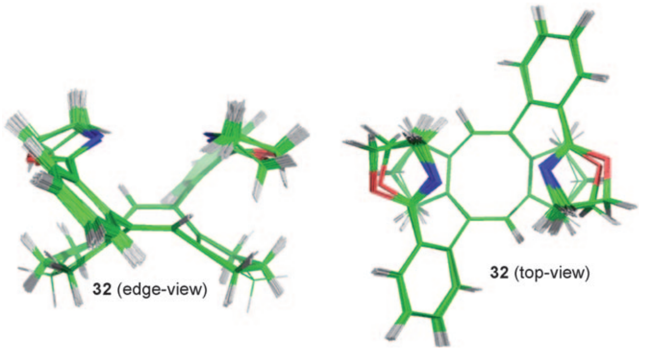


Figure 2. Solution structure of ZnBr$_2$/COT complex **32** (Zn and Br atoms not shown). The 50 lowest energy conformers are overlaid (within ca. 8 kcal mol^{-1} of minimum). C green, O red, N blue, H gray.

In summary, [2+2+2+2] cycloadditions with internal and highly functionalized alkynes have been achieved allowing for the first and efficient synthesis of highly functionalized hexa- and octa-substituted COTs based on Ni^0-catalyzed [2+2+2+2] cycloadditions of readily available 1,6-diynes. Furthermore, the first study of the regioselectivity of this process is described and is shown to proceed with high levels of control. Additionally, the initial example of a fully intramolecular [2+2+2+2] cycloaddition, a remarkable process proceeding with the formation of four new rings, is reported. Finally, the initial use of COTs as metal complexing ligands is shown in the formation of a Zn^{II} complex with bis-oxazoline ligand **31**.

Experimental Section

Representative procedure: Under N$_2$, THF (2.8 mL) was added in one portion by syringe through a septum to an oven-dried round bottom flask, that had been flushed with N$_2$ for 10 min, containing 1,6-diyne **1** (300 mg, 2.77 mmol), [(dme)NiBr$_2$] (342 mg, 1.10 mmol), zinc powder (144 mg, 2.20 mmol) and a stir bar. Water (20 μL, 1.10 mmol) was added in one portion and the reaction was placed into a 60 °C oil bath. After 2 h no starting diyne was observed by TLC. The reaction was allowed to cool to RT and then filtered through celite (Et$_2$O eluent). The solvent was removed under reduced pressure and the brown residue was purified by column chromatography (5% EtOAc/pentane) yielding **2** (240 mg, 2.22 mmol, 80%) as a yellow solid.

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[20] CCDC 726958 726959 (**2** and **14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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