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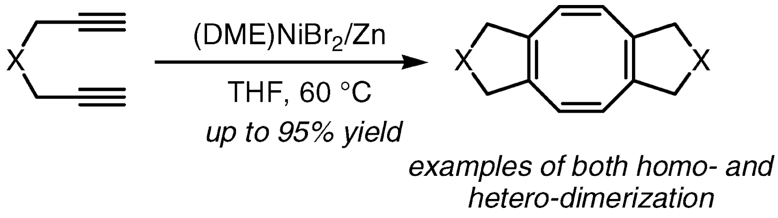

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Nickel(0)-Catalyzed [2 + 2 + 2 + 2] Cycloadditions of Terminal Diynes for the Synthesis of Substituted Cyclooctatetraenes

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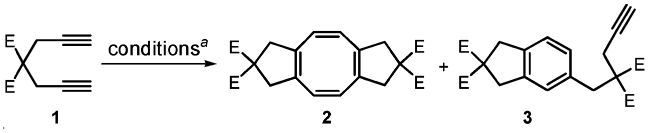
Cyclooctatetraenes (COTs) comprise a fascinating class of molecules that have attracted much theoretical, mechanistic, synthetic, and materials science interest.[1] They have figured as unique ligands in a variety of metal-based catalysts, including most notably lanthanide complexes,[2] and have also been proposed as ligands in bimetallic catalysis.[3] Due to their novel redox properties, substituted COTs have also attracted attention as electron transporting components in organic light-emitting devices.[4] COTs are also important building blocks in synthesis serving as 6π-components in cycloaddition chemistry,[5] precursors to cyclooctane and bicyclooctane derivatives,[6] polyacetylenes,[7] electromechanical actuators,[8] explosives,[9] synthetic sugars,[10] and ingenious approaches to biologically active natural products.[11]

Since the original 10 step synthesis of cyclooctatetraene in 1911,[12] syntheses of COTs have been achieved in various ways.[13] Notable among these and illustrative of the impact of new reactions on step economy,[14] Reppe and co-workers reported in 1948 a single step synthesis of cyclooctatetraene through a remarkable Ni(0)-catalyzed tetramerization of acetylene.[15] To date, however, this industrially useful process has been generally limited to the tetramerization of acetylene itself or simple terminal alkynes. In the latter case, as many as seven constitutional and alkene positional isomers are possible, and many in practice are often formed.[16] To address this limitation, tom Dieck and co-workers creatively showed that 1,4-diazadiene ligands can be used to form 1,2,4,7-tetrasubstituted COTs. However, high yields and selectivities have been reported only with methyl and phenyl propiolate.[17] To date, a general solution for controlling the regioselectivity of alkyne tetramerization has yet to be developed. Our studies to address this problem are reported herein.

An attractive solution to the problem of controlling the regioselectivity of alkyne tetramerization arises through the use of diynes, which in theory would produce only one regioisomer, the 1,2,5,6-tetrasubstituted COT, through a novel four functional component mixed inter- and intramolecular process. This approach is reported to work but only for a specialized case, substituted dipropargyl amines, and requires a significant excess of acrylate or styrene as an additive.[18] Importantly, whether simple mono- or diynes are used, [2 + 2 + 2] cycloadditions compete with and often predominate over COT formation. For example, we (Table 1, entries 1 and 2) and others[19] have found that 1,6-diynes undergo efficient Ni(0)-catalyzed [2 + 2 + 2] cyclotrimerization to produce mainly arenes. Only a trace of COT **2** ($E{=}C(CO_2Me)_2$) is formed from diyne **1** with $NiCl_2(PPh_3)_2$ precatalyst and zinc as a reducing agent (entry 1). Reduction of the precatalyst with $NaBH_4$ favors COT formation, but the reaction proceeds in low yield (entry 3). Significantly, in contrast to phosphine ligands, good selectivity (6.9:1) for COT **2** over arene **3** (entry 10) and an excellent combined yield of cycloadducts (97%) can be obtained by using $(DME)NiBr_2$ conveniently reduced in situ to form Ni(0) by zinc dust in THF (0.1 M) at 60 °C.[20] Of mechanistic and synthetic importance, the formation of arene **3** can be almost completely suppressed (52:1) with high catalyst loading, providing COT **2** in high yield and selectivity (entry 12). It is noteworthy that **2** is a single alkene positional isomer as revealed by alternating single and double bond lengths in its X-ray crystal structure (Figure 1).

Table 1. Effect of Catalyst/Conditions on the [2 + 2 + 2 + 2] Reaction



entry	catalyst	Ni mol %	conditions	time (h)	yield[b] (ratio)[c]
1	**$NiCl_2(PPh_3)_2$**	**20**	**A**	**5**	**89% (1:>20)**
2	$NiCl_2(dppp)$	10	B	24	67% (1:6.3)
3	$NiCl_2(PPh_3)_2$	10	B	9	30% (1.3:1)
4	NiI_2	10	B	2.5	56% 6.3:1)
5	NiI_2	10	A	4	98% (3.7:1)
6	$Ni(cod)_2$	20	C	1	71% (1.7:1)
7	$Ni(acac)_2$	10	B	4.25	50% (3.9:1)
8	$(DME)NiBr_2$	10	B	20	45% (7.7:1)
9[d]	$(DME)NiBr_2$	1	A	24	70% (1:1.2)
10	**$(DME)NiBr_2$**	**20**	**A**	**7**	**97% (6.9:1)**
11[e]	$(DME)NiBr_2$	20	A	1.5	91% (18:1)
12	**$(DME)NiBr_2$**	**40**	**A**	**1.5**	**89% (52:1)**
13[f]	$(DME)NiBr_2$	10	A	4	81% (only **9**)

[a] Conditions A: Ni cat., Zn powder (2:1 with respect to Ni), H_2O (1:1 with respect to Ni), THF (0.1 M), 60 °C. Conditions B: Ni cat., $NaBH_4$ (30 mol %), THF (0.1 M), rt. Conditions C: THF (0.1 M), rt. [b] Combined yield. [c] Ratio determined via ^1H NMR. [d] 2.0 M. [e] 0.5 M. [f] Diyne **8** (slow addition) was used in place of **1**, 0.3 M.

The effects of catalyst loading and concentration on the efficiency and selectivity of the reaction were also investigated. Although the best yields and selectivities are observed at higher catalyst loadings, the reaction still proceeds even with 1 mol % of catalyst (entry 9). Interestingly, the selectivity of this process is dependent on the catalyst concentration. For example, increasing the catalyst loading from 20 to 40 mol % improves the selectivity from 6.9:1 to 52:1 (entries 10 and 12). This is consistent with a mechanism involving dimerization of a metallacycle intermediate as originally suggested by Wilke.[3] It follows that slow addition of the diyne would and indeed does lead to exclusive COT formation (Table 1, entry 13). Finally, the [2 + 2 + 2 + 2] reaction is scalable, allowing for the efficient preparation (77% isolated yield) of **2** on gram scale.

The scope of this process with respect to tether type and length is given in Table 2. The [2 + 2 + 2 + 2] reaction proceeds efficiently with a variety of terminal 1,6- and 1,7-diynes having ester, ketone, aryl, or nitrile substituents. Significantly, in all cases, the [2 + 2 + 2 + 2] reaction is favored over the competing [2 + 2 + 2] process. The reaction proceeds efficiently even without geminal substitution on the diyne tether (entries 2−4). Substrates containing heteroatoms are also tolerated, allowing for the efficient

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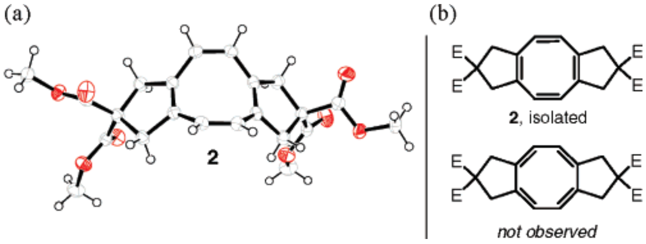
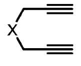
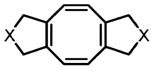
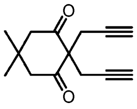
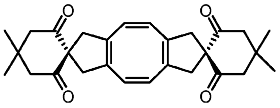
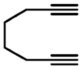
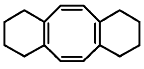
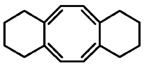
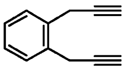
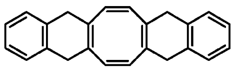


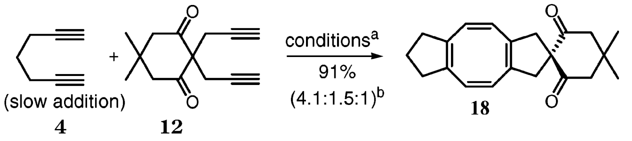
Figure 1. (a) ORTEP diagram of cyclooctatetraene **2**. (b) Line drawing of cyclooctatetraene **2** and its isomer.

Table 2. Substrate Scope of the [2 + 2 + 2 + 2] Reaction[a]

entry	substrate	t (h)	product(s), yield (ratio)[b]
			
1	**1,** $X=C(CO_2Me)_2$	7	**2**, 97% (6.9:1)
2	**4**, $X=CH_2$	4	**5**, 93% (20:1)
3	**6**, X=N-Ts	4	**7**, 90% (5.7:1)
4	**8**, X=O	4	**9**, 84% (9.8:1)
5[c]	**10,** $X=C(CN)_2$	18	**11**, 71% (2.4:1)
6[d]	 **12**	4	 **13**, 59% (17:1)
7	 **14**	4	 +  **15a**, 66% **15b**, 25% (18:1)
8	 **16**	4	 **17**, 95% (>20:1)

[a] Conditions: $(DME)NiBr_2$ (20 mol %), Zn powder (40 mol %), H_2O (20 mol %), THF (0.1 M), 60 °C. [b] Ratio of [2 + 2 + 2 + 2] product(s) to [2 + 2 + 2] product (determined via ^{1}H NMR) unless otherwise noted. [c] Starting material was recovered (20%). [d] 0.5 M.

Scheme 1. Cross Reaction with Two Different Diynes[a]



[a] Conditions: $(DME)NiBr_2$ (20 mol %), Zn powder (40 mol %), H_2O (20 mol %), THF (0.1 M), 60 °C, 1.2 equiv of **12**. [b]Ratio of (**18**:**13**:**5**) determined via ^{1}H NMR; trace [2 + 2 + 2] products also observed.

formation of the corresponding heterocycles **7** and **9** (entries 3 and 4). Additionally, the reaction is completely chemoselective for alkynes over nitriles as demonstrated by formation of **11**. COTs containing spirocyclic ring systems can also be readily constructed (entry 6).

In addition to 5−8−5 ring systems, this method also enables the synthesis of 6−8−6 ring systems in high yields and selectivities. Interestingly, for 1,7-octadiyne **14**, both alkene positional isomers are formed in a 2.6:1 ratio favoring compound **15a** over **15b**. When diyne **16** is used, however, cyclooctatetraene **17** is formed in 95% yield (entry 8) as the only observable product. This methodology also provides a hitherto unexplored strategy for the synthesis of non-symmetrical COTs in cases in which differences in rates of homodimerization exist. For example, when diyne **4** is slowly added to diyne **12**, the cross product **18** is formed preferentially and beyond statistical expectations (Scheme 1).

In summary, catalysts and conditions have been identified that allow for the efficient and selective conversion of a wide range of 1,6- and 1,7-diynes to symmetrical 1,2,5,6-tetrasubstituted COTs. In all cases, the [2 + 2 + 2 + 2] cycloaddition is favored over the [2 + 2 + 2] process, and in all but one case, a single alkene positional isomer is obtained. A hitherto unexplored cross cyclotetramerization is also reported, providing access to differentially substituted COTs. This methodology provides facile access to COTs and to other cyclooctane derivatives, the latter through selective partial hydrogenations or alkene additions. Further studies are in progress.

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Supporting Information Available: Full experimental details are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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