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Cobalt-Catalyzed [4 + 2 + 2] Cycloadditions of Bicyclo[2.2.2]octadienes

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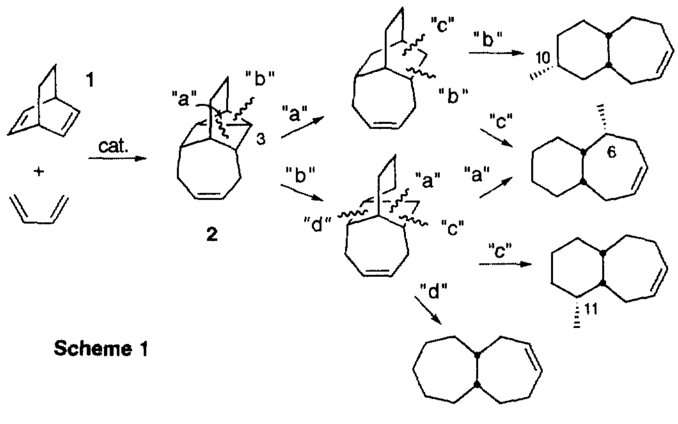
Abstract

The cobalt catalyzed [4 + 2 + 2] cycloadditions of bicyclo[2.2.2]octadiene and several benzobarrelenes are reported, marking the first [4 + 2 + 2] cycloadditions of these homoconjugated dienes. The [2 + 2 + 2] reaction of benzobarrelene with diphenylacetylene was also successful.

Keywords: catalysis, cobalt, cycloadditions, polycyclic aliphatic compounds

The transition metal catalyzed [2 + 2 + 2] homo Diels-Alder (HDA) reactions and [4 + 2 + 2] cycloadditions of norbornadiene are very intriguing reactions in organic chemistry [1-3]. There are few examples, however, of analogous chemistry with other bridged, homoconjugated dienes. Bicyclo[2.2.2]-octa-2,5-diene (1) [4,5], barrelene [6-8], bicyclo[3.2.2]nona-2,5-diene [5], and a few other related bicyclic compounds [9-14] have been shown to participate in uncatalyzed [2 + 2 + 2] HDA reactions with a limited number of dienophiles, but no examples exist of [4 + 2 + 2] reactions of these dienes, nor are there any examples of transition metal catalyzed reactions, [2 + 2 + 2] or [4 + 2 + 2], of these homoconjugated dienes. The successful use of nickel and cobalt catalysts in expanding the scope of norbornadiene HDA chemistry [2] suggested that such catalysts might also be employed in similar chemistry with these dienes. If successful, and if protocols can be developed to open the bicyclooctadiene adducts analogous to the work already accomplished with the norbornadiene adducts [15-18], a new, convergent pathway would be available for accessing a variety of *cis* fused bicyclo-[5.4.0]undecanes. The C-3 carbon from the original adduct could be located at either C-6, C-10 or C-11 on the concave face of the bicycle, or in the *cis* fused bicyclo[5.5.0]dodecane depending upon the regioselectivity of the cleavage reactions (Scheme 1). We now report that the cobalt-catalyzed [4 + 2 + 2] and [2 + 2 + 2] cycloadditions of bicyclo[2.2.2]octadienes proceed in good to excellent yields, thereby achieving the first goal in this project.



Scheme 1

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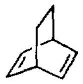
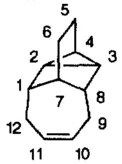
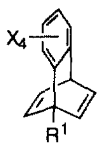
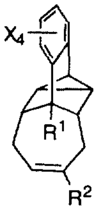
Previous studies established that several catalytic systems employing cobalt are effective in mediating the [4 + 2 + 2] cycloadditions between norbornadiene and 1,3-butadienes [16,19]. Catalysts based on the Lyons [20], Duan [21], and Binger [22] systems were found to be most successful [16], so the present studies began with the Lyons catalytic system. The [4 + 2 + 2] reactions of **1** [23], benzobarrelene (**3**) [24,25], tetrachlorobenzobarrelene (**4**) [24,25], and methoxytetrachlorobenzobarrelene **5** [24,25] with 1,3-butadiene using $Co(acac)_2$/DPPE/Et_2AlCl (1:1.5:10) as the catalytic system (15 mol% Co relative to homoconjugated diene) proceeded smoothly to provde the desired adducts **2**, and **6** - **8** in good yields (Chart 1).[1] The analogous reaction of **5** with isoprene gave the adduct **9** in 48% yield, albeit requiring longer reaction times in comparison to the reactions with butadiene (48 h vs 24 h for 1,3-butadiene).

Chart 1. Cobalt Catalyzed [4 + 2 + 2] Cycloadditions of Bicyclo[2.2.2]octa-2,5-dienes.[a]

Bicyclooctadiene	**Cycloadduct (% Yield)[b]**
 1	 2 (87%)
 3: R^1 = X = H 4: R^1 = H, X = Cl 5: R^1 = OMe, X = Cl	 6: R^1 = R^2 = X = H (80%) 7: R^1 = R^2 = H, X = Cl (95%) 8: R^1 = OMe, R^2 = H, X = Cl (70%) 9: R^1 = OMe, R^2 = CH_3, X = Cl (48%)

a) All reactions were run in toluene, 0.1 - 1.0 M homoconjugated diene, 50 - 55 °C, with $Co(acac)_2$/DPPE/Et_2AlCl (1/1.5/10), 15 mol% based on cobalt, with excess butadiene for 24 - 48 h. b) Isolated yields.

The presence of the desired [4 + 2 + 2] adducts was revealed in the ^1H NMR spectra of the crude product mixtures by the appearance of two key multiplets for the cyclopropyl methines, with the benzylic methine significantly deshielded in the benzobarrelene adducts **6** - **9**. (The H2 and H3 resonances of **2**, and **6** - **9** were chemical shift equivalent at 93.94 kG, hence only two multiplets were observed for the cyclopropyl protons.) In the ^1H spectra of the purified adducts **6** - **9**, a broadened doublet ($J \approx 7.4$ Hz, 2H) for H2 and H3 (δ 1.37 for **6**, δ 1.52 - 1.67 for the chlorinated derivatives **7** - **9**) and a triplet ($J \approx 7.4$ Hz, 1H) for H4 (δ 2.14 for **6**, δ 2.70- 2.80 for the chlorinated derivatives **7** - **9**) were indicative of the adducts. The H2/H3 resonance of **2** also appeared as a broadened doublet (δ 1.02, d, $J = 7.3$ Hz, 2H) while the H4 resonance was further coupled to the H5 methylene protons (δ 0.79, tt, $J = 7.3$, 2.8 Hz, 1H). The location of the methoxyl group at C7 in **8** (rather than C4) was readily apparent from the ^1H and HMQC spectra which confirmed the presence of three cyclopropyl protons and methine carbons (δ 22.2, C2/C3; 19.6, C4). The cyclopropane ring in **8** was further confirmed by the one-bond heteronuclear coupling constants: $^1J_4$ = 166 Hz, and $^1J_{2/3}$ = 175 Hz [26]. The spectra of the isoprene adduct **9** was also in accord with the assigned structure, with the lack of molecular symmetry apparent from the additional nonequivalences of proton and carbon resonances. The location of the methoxyl group in adducts **8** and **9** away from the cyclopropyl ring is consistent with our earlier findings that 2-substituted norbornadienes undergo cobalt-catalyzed [4 + 2 + 2] cycloadditions with butadienes also producing adducts with the original C2 substituent away from the

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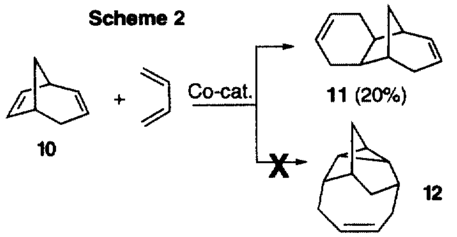
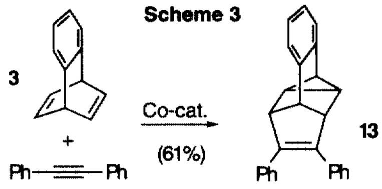
[1] All compounds were characterized by extensive ^1H and ^{13}C NMR studies, HRMS. For typical reaction conditions, see Supporting Material, ref. 16. Characterizing spectroscopic data for **6**: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (bd, J = 7.3 Hz, 1H), 7.11 (ddd, J = 7.3, 7.3, 1.5 Hz, 1H), 7.04 (ddd, J = 7.3, 7.3, 1.0 Hz, 1H), 6.96 (dd, J = 7.3, 1.0 Hz, 1H), 5.52 (m, 2H), 2.60 (bs, 1H), 2.46 (dddd, J = 16.0, 3.8, 3.8, 1.8 Hz, 2H), 2.34 (bdd, J = 16.0, 2.9 Hz, 2H), 2.14 (t, J = 7.4 Hz, 1H), 1.49 (dd, J = 3.8, 3.8 Hz, 2H), 1.38 (dd, J = 7.4, 1.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 135.0, 126.8 (2C), 126.3, 125.7, 124.0, 122.3, 49.9, 38.5 (2C), 33.7 (2C), 20.7 (2C), 20.1; HRMS (EI, 70 eV) *m/z* 208.1250 ($[M]^+$, 28%), calcd for $C_{16}H_{16}$ 208.1252.

cyclopropane ring. Conceivably this regioselectivity minimizes steric clashes between the cobalt with its accompanying ligands and these substituents in an intermediate complex [27].

In contrast to the [4 + 2 + 2] chemistry of the bicyclooctadienes with 1,3-butadiene, bicyclo[3.2.1]octa-2,6-diene (**10**) [28,29] produced only the [4 + 2] adduct **11** in low yield (20%) as a mixture of *endo* and *exo* adducts under these conditions (Scheme 2). No trace of desired cycloadduct **12** was detected.

Scheme 2

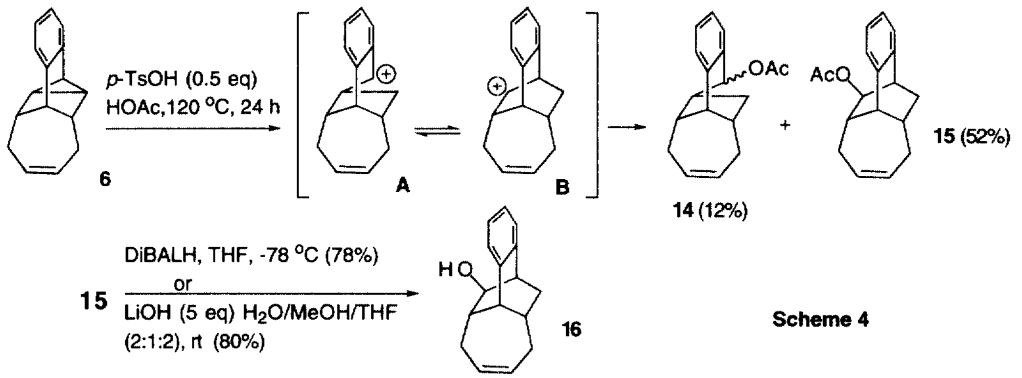




Scheme 3

A [2 + 2 + 2] cycloaddition of **3** was also briefly examined. Using the same cobalt catalyst ($Co(acac)_2/DPPE/Et_2AlCl$, 5 mol% based on Co), cycloadduct **13** was obtained in 61% yield from the reaction with diphenylacetylene (Scheme 3).

With adduct **6** in hand, opening of the cyclopropyl ring to the benzenotricyclo[5.4.0.1^{3,7}]dodecene system using modified Nickon conditions [17] was examined (Scheme 4). Refluxing (120 °C) **6** in *p*-TsOH/HOAc (0.5 eq TsOH relative to **6**) produced tricycle **14** in the early stages of the reaction, but allowing the reaction to proceed for 24 hours produced diastereomerically pure **15** as the dominant product (52%) with lesser amounts of **14** (12%), the latter as a diastereomeric mixture of *endo* and *exo* acetates (1:2.3, *endo*:*exo*). When purified **14** was resubjected to the reaction conditions, rearrangement to **15** was observed (4:1, **15**:**14** after 6 h) indicating that **14** is the kinetic product of the Nickon opening, but **15** is the thermodynamic product.



Scheme 4

Presumably the formation of the benzylic carbocation favors the opening of the cyclopropane to intermediate **A**, but rearrangement to intermediate **B** leads to the thermodynamically more stable **15**. In addition, products resulting from the addition of HOAc to the double bond of **6** were also observed (19%). Cleavage of the acetate in **15** by either DiBALH reduction or basic hydrolysis gave alcohol **16**.[2] The tetrachloroadduct **7** proved to be inert to the Nickon acid-catalyzed opening.

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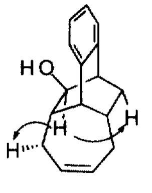
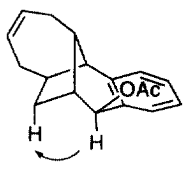
[2] The relative stereochemistry of **16**, and hence it's acetate precursor **15**, was assigned from the NOE's illustrated on the right. The ratio of *endo*:*exo* acetates **14** was also assigned from NOE's obtained on the *exo* acetate, also illustrated to the right. All NOE experiments were DNOE's with the arrows pointing from the proton whose resonance was saturated.



16



14-*exo*

In summary, the first transition metal catalyzed [4 + 2 + 2] and [2 + 2 + 2] cycloadditions of bicyclo[2.2.2]octadienes have been achieved using a cobalt catalytic system initially developed by Lyons. Application of modified Nickon conditions (*p*-TsOH/HOAc) opened the cyclopropane ring of cycloadduct **6** to give a mixture of the kinetic and thermodynamic products **14** and **15**, respectively. Further work on the final fragmentation to the desired bicyclic ring systems is in progress.

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