previously in a more tedious manner.[15] Base-induced cyclization of the 1,6-diketone resulting from hydrolysis of 8 yields a pair of diastereomeric aldols (18, eq 7) that would be expected[16] to be capable of dehydration to an enone which is an intermediate in Paquette's synthesis of (±)-silphinene.[16]

Thiophenol can be added to enones generated in this way leading to iterative cyclizations. This aspect is being explored as well as methods of controlling stereochemistry in some of the reactions of homoenolate equivalents with electrophiles.

Acknowledgment. We thank the National Institutes of Health for financial support.

Supplementary Material Available: Characteristic procedures, spectral data, and ^{1}H NMR spectra of new compounds (43 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Cobalt-Catalyzed Intramolecular Homo Diels–Alder Reactions

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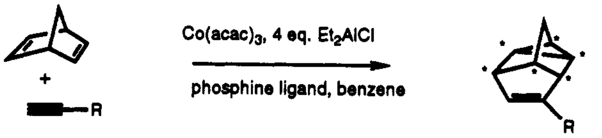
Received November 6, 1991

Summary: Norbornadienes bearing a tether at C-2 which contains an acetylene have been found to undergo a cobalt-catalyzed intramolecular homo-Diels–Alder reaction creating pentacyclic cycloadducts.

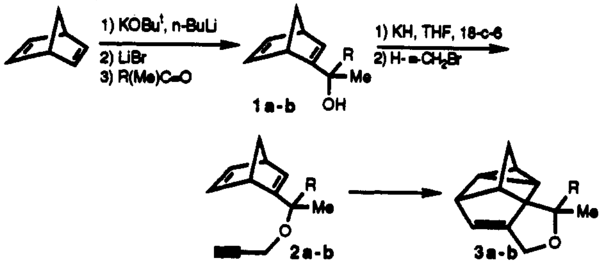
There is considerable interest in metal-catalyzed cycloaddition processes, in particular those between dienes and unactivated olefins, dienes, or acetylenes.[2,3] We have recently reported the cobalt-catalyzed [2 + 2 + 2] homo-Diels–Alder cycloaddition (HDA) between norbornadiene and a variety of unactivated acetylenes.[3a] An asymmetric version has also been developed.[3b] This reaction is very efficient for the construction of complex polycycles, eq 1.



(1)

We were interested in examining the facility of the intramolecular variant of this reaction. The decrease in entropy associated with tethering the two reactive components suggests that the reaction will be significantly more facile than the intermolecular reaction.[4] However, this likely rate enhancement is compromised by the dramatic decrease in rate associated with intermolecular cycloadditions with substituted norbornadienes.[5] In fact, prior to this study, there were no reported examples of successful intramolecular HDA reactions.[6] In this report, we detail the first examples of a transition metal catalyzed intramolecular homo-Diels–Alder reaction.

Efficient routes to the cycloaddition precursors were developed starting with norbornadiene. Deprotonation of norbornadiene with n-BuLi/KOBu^t occurred smoothly at −78 °C in THF.[7] Treatment of this anion with lithium bromide followed by acetaldehyde or acetone gave alcohols **1a** (R = H, 1.5:1 mixture of diastereomers) and **1b** (R = Me). Treatment with KH, THF, −50 to 0 °C and reaction of the alkoxide (in the presence of 18-crown-6) with propargyl bromide gave **2a** (R = H) and **2b** (R = Me) in 96% and 39% yield, eq 2.



(2)

Thermal cycloaddition of **2a** was attempted. No reaction was observed after heating **2a** for 24 h in toluene at 110 °C; however, in mesitylene at 170 °C for 24 h, a 3% yield of **3a** (6:1 diastereomeric mixture of cycloadducts) was isolated.[8]

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[5] Substituents reduce the rate of the cycloaddition, see: Lautens, M.; Edwards, L. G. *J. Org. Chem.* **1991**, *56*, 3761.

[6] In one instance a competing ene reaction occurred, see: Kelly, T. R. *Tetrahedron Lett.* **1973**, *14*, 437.

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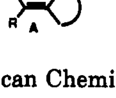
[8] *A priori* there are two possible modes of cyclization to consider: A or B. The structure of the cycloadduct was determined by examination of the ^{13}C APT spectrum. In all cases we have examined, the cycloadducts observed are of general structure A.



A

B

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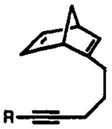
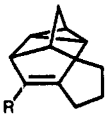
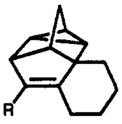
Table I. Intramolecular Cycloaddition of Dienynes Using Cobalt Catalysts

entry	dienynes	conditions[a] (% Co)	cycloadduct	yield[b]
1				
	4a (R=H)	A		N.R.
	4a (R=H)	B (7%)		**5a** 78%
	4a (R=H)	C (7%)		**5a** 64%
	4b (R=Me)	B (8%)		**5b** 69%
	4c (R=TMS)	B (10%)		**5c** 63%
	4d (R=Ph)	B (11%)		**5d** 70%
2				
	6a (R=H)	B (5%)		**7a** 64%
	6b (R=Me)	B (8%)		**7b** 43%
	6c (R=TMS)	B (10%)		**7c** 48%

[a] A = 140–170 °C. B = Co(acac)$_3$, dppe, 6 equiv of Et$_2$AlCl. C = Co(acac)$_2$, dppe, 3–4 equiv of Et$_2$AlCl. [b] Isolated yields of pure material.

Metal catalysis proved to be milder and more efficient than the thermal process. Treatment of **2a** with 8 mol % Co(acac)$_3$, 4 equiv of Et$_2$AlCl, and dppe in benzene at *room temperature* for 5 h increased the yield of the cycloadduct 5-fold to 15% (**3a**, 3.5:1 mixture of diastereomers).[9] The same diastereomer was produced as the major product from the thermal and metal-catalyzed reaction. Cycloaddition of dienyne **2b** under similar conditions afforded **3b** in 22% yield.[10]

Though the yield of the cycloadditions were modest, these initial results were extremely encouraging since we had previously shown that *intermolecular* cycloaddition between norbornadiene and methyl propargyl ether failed to give any cycloadduct and in fact the propargyl ether acted as a poison towards the catalyst.[3a] The Lewis acidic character of the reducing agent, Et$_2$AlCl, was also of concern since the starting materials **2a,b** and the cycloadducts **3a,b** contained sensitive functional groups. We concluded that a significant improvement in the yields of the cycloaddition would be realized if the oxygen within the tether were replaced by a carbon. This supposition proved to be accurate.

The all-carbon dienynes **4a–d** and **6a–c** were prepared and their intramolecular cycloadditions studied (Table I).[11] No reaction was observed upon treatment of **4a** at 150 °C in the absence of the catalyst. However, cobalt catalysts derived from treatment of Co(acac)$_3$/dppe *or* Co(acac)$_2$/dppe with 4–6 equiv of Et$_2$AlCl were very effective.[12] Cycloadducts **5a–d** and **7a–c** were obtained in 45–78% yield; a substantial increase compared to **3a,b**. The cycloadditions were carried out at 0.15–1.0 M in dienyne thus avoiding the use of syringe pumps or high-dilution reaction conditions. This concentration is significantly higher than for many intramolecular reactions and is feasible due to the sluggishness of competing intermolecular coupling reactions.

In general, cycloadditions which formed a cyclopentane or cyclohexane ring were very facile with the yields of the former higher than the latter.[13] A variety of substituents were tolerated on the acetylene including an alkyl, aryl, or silyl group. Our previous studies had established that *intermolecular* cycloadditions with disubstituted acetylenes were very poor.[3a] Thus, there is a significant improvement in reactivity by tethering the two reactive partners in this reaction.

In conclusion, we have shown that cobalt catalysts promote the intramolecular homo-Diels–Alder reactions of unactivated dienynes. Three bonds and a pentacyclic framework are created in one step. Little or no cycloaddition occurs in their absence. The ease of preparation of the starting materials and the efficiency by which the construction of rigid, highly strained polycyclic compounds is achieved are important features of this methodology.

Acknowledgment. We thank the A. P. Sloan Foundation, the Natural Science and Engineering Research Council (NSERC) of Canada, Bio-Mega Inc., the Merck Frosst Centre for Therapeutic Research, and the University of Toronto for financial support.

Supplementary Material Available: General and specific procedures and characterization for the compounds reported (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) All new compounds for which structures are shown were fully characterized (IR, ^{1}H NMR, ^{13}C NMR, and HRMS). Some of the starting dienynes and all the cycloadducts proved to be too unstable for satisfactory microanalyses.

(10) We had anticipated improved yields due to a *gem*-dialkyl effect. For a recent discussion, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224 and references cited therein.

(11) **6a–c** were prepared by trapping the anion of norbornadiene with an excess of 1,4-dibromobutane and subsequent displacement of the bromide with an acetylide anion. The first step of this sequence was inefficient for the synthesis of **4a–d** due to the formation of 2-allylnorbornadiene. A more efficient route (55% vs 10% overall yield) involved treatment of the norbornadiene anion with 3-bromopropan-1-ol, conversion of the primary alcohol to the tosylate (TsCl, pyridine, CH$_2$Cl$_2$), and displacement of the tosylate with an acetylide anion.

(12) (a) Cobalt(II) as well as cobalt(III) salts, following reduction with Et$_2$AlCl, promote the cycloaddition reaction; details to be published. (b) A typical procedure is as follows: DEAC (12–60 mol %, 1.8 M in toluene) was added to a flask containing Co(acac)$_3$ (2–10 mol %), dppe (1.6–8 mol %), the dienyne (1 mmol), and benzene (6 mL). The mixture was stirred at room temperature for 3–36 h. The reaction was quenched by the addition of 20 drops of 2-propanol. Addition of 10 mL hexane and filtration through a plug of silica using hexane or ether (100 mL) as eluant removed the metal salts. Further purification was achieved by bulb-to-bulb distillation or flash column chromatography on silica gel.

(13) Attempted cycloaddition to form a four-membered ring failed to occur regardless of the reaction conditions. Cycloaddition to form a seven-membered ring gave a complex mixture of products in very low yield.