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Authors

Karabiyikoglu, Sedef

Merlic, Craig A

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Transannular [4 + 2] Cycloaddition Reactions of Cobalt-Complexed Macrocyclic Dienynes

Sedef Karabiyikoglu and Craig A. Merlic*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Ⓢ *Supporting Information*

ABSTRACT: The first transannular [4 + 2] cycloaddition reactions of macrocyclic dicobalt hexacarbonyl−dienyne complexes were demonstrated. Complexes were conveniently prepared through palladium(II)-catalyzed intramolecular oxidative cyclization of bis(vinylboronate esters) followed by complexation with dicobalt octacarbonyl. Transannular [4 + 2] cyclo-addition reactions of the complexes occurred at lower temperatures and shorter times than transannular Diels−Alder reactions of metal-free dienynes. Intermolecular control reactions confirmed the effect of cobalt complexation on [4 + 2] cycloaddition reactions of unactivated alkynes and dienes.
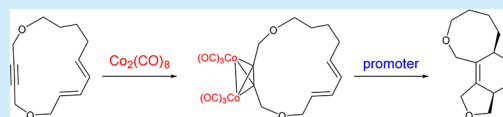
The transannular Diels−Alder (TADA) reaction is a potent synthetic tool for building complex organic scaffolds.[1] TADA reactions are exploited in total syntheses due to their versatility, atom economy, and unique stereoselectivity.[2] Studies on spinosyn A biosynthesis led to the discovery of the first pure Diels−Alderase enzyme that, in fact, catalyzes a transannular Diels−Alder transformation.[3] Although TADA reactions have been widely investigated, utilization of transition metals to promote or catalyze such transformations remains poorly established.[4]

Cobalt−alkyne complexes are versatile species with myriad applications in synthetic chemistry. In addition to operating as protected alkynes[5] and stabilized propargyl cations,[6] dicobalt hexacarbonyl−alkyne complexes participate in several important cycloaddition reactions.[7] In particular, the [2 + 2 + 1] cycloaddition known as the Pauson−Khand reaction (PKR) is the most frequently studied.[8] However, studies on other cycloaddition reactions of alkyne−{Co$_2$(CO)$_6$} complexes, especially the [4 + 2] reaction, are scarce. The only reported examples of [4 + 2] cycloaddition reactions with alkyne−{Co$_2$(CO)$_6$} complexes are (1) intermolecular tandem Diels−Alder/Pauson−Khand reactions of a few terminal alkyne complexes with 1,3-cyclohexadiene[9] and (2) intermolecular Diels−Alder reactions with complexes of otherwise inaccessible strained and reactive cyclic alkynes.[10] Despite this limited precedence, we postulated that [4 + 2] cycloaddition reactions of dicobalt complexes would make structures unattainable via metal-free Diels−Alder reactions accessible and that cobalt-promoted TADA reactions would present a unique entry to both organocobalt and macrocycle chemistry. Herein, we demonstrate the first transannular [4 + 2] cycloadditions of macrocyclic dienyne−{Co$_2$(CO)$_6$} complexes and the advantages over metal-free TADA reactions.

We reported palladium(II)-catalyzed oxidative coupling of bis(vinylboronate esters) as a mild and facile entry to macrocyclic trienes and dienynes.[11] This approach efficiently provided strained cyclic substrates, some of which, such as **2**, readily underwent proximity-induced[12] TADA reactions at room temperature (Scheme 1).[13]
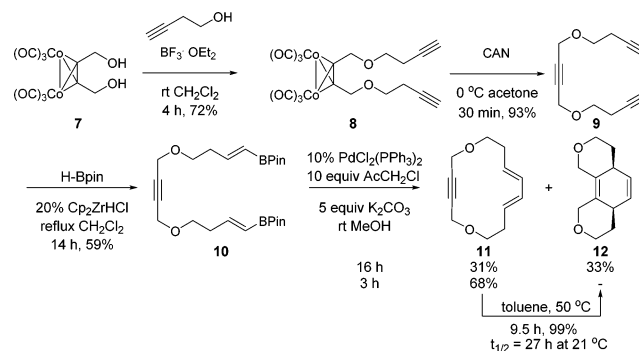
Scheme 1. Previous Work on TADA
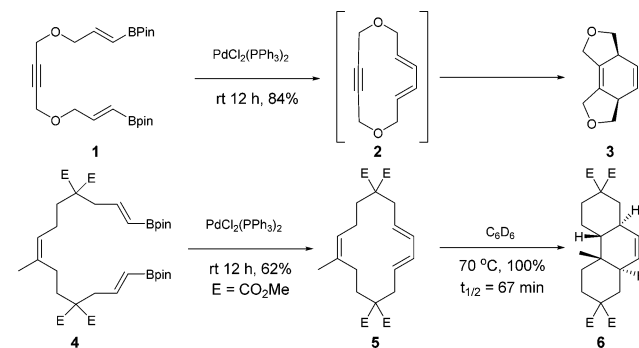
To explore TADA reactivity of 14-membered alkynes, we needed to synthesize dienyne **11** (Scheme 2). Trials to prepare

Scheme 2. Preparation and TADA Reaction of 11

triyne **9** via classical S_N2 reactions with various nucleophiles and electrophiles failed. Therefore, we subjected cobalt complex diol **7** to a double Nicholas reaction.[6,14] The resultant complex **8** was easily converted to novel triyne **9** by $Ce(NO_3)_6(NH_4)_2$ oxidation/decomplexation. Selective bis-hydroboration catalyzed by Schwartz's reagent[15] afforded bis(vinylboronate ester) **10**. A 16 h Pd(II)-catalyzed macrocyclization reaction of **10** formed macrocycle **11** in 31% yield and TADA reaction product **12** in 33% yield, indicating the facility of the room temperature, proximity-induced[12] TADA reaction of 14-membered dienyne **11** (Scheme 2). Decreasing the macrocyclization reaction time to 3 h afforded ring **11** in 68% yield as the principle product. Kinetic studies on isolated macrocycle **11** determined the TADA reaction half-life to be 27 h at 21 °C.[16] Thermal TADA reaction gave complete conversion of **11** to **12** in 9.5 h at 50 °C.

We then shifted our focus to TADA reactions of larger dienyne rings. Hydroboration of triyne **13** produced bis(vinylboronate ester) **14** in good yield, and Pd(II)-catalyzed coupling reaction of **14** smoothly formed macrocycle **15** in 63% yield (Scheme 3).

Scheme 3. Preparation and TADA Reaction of 15
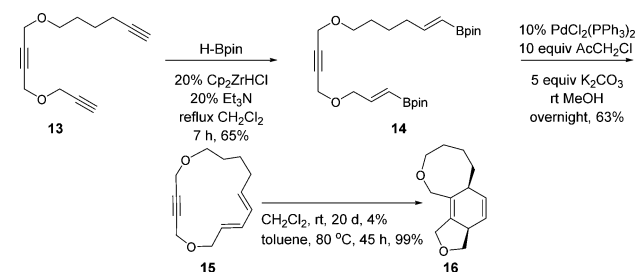
The 15-membered cyclic dienyne was considerably less reactive than 14-membered dienyne **11** as the overnight macrocyclization of **14** did not yield any of the expected TADA product. Stirring **15** at room temperature for 20 days produced tricyclic TADA product **16** in a mere 4% yield. A thermal TADA reaction was more effective as **16** was formed quantitatively upon heating **15** at 80 °C for 45 h (Scheme 3).

As the macrocycle size increases, the TADA reactivity clearly decreases, and thus we investigated alternative transannular [4 + 2] cycloaddition routes. Dicobalt hexacarbonyl complex **17** was prepared via complexation of **15** with $\{Co_2(CO)_8\}$ (Table 1). Dicobalt complex **17** did not form TADA product **16** even after 7 days at rt (Table 1, entry 1). The rate-determining step of the PKR is decoordination of a CO ligand to provide an open coordination site for an incoming alkene. To facilitate this mechanistic step, various promoters are commonly employed.[17] We proposed that PKR promoters might also activate transannular [4 + 2] cycloaddition reactions, thus systems commonly used for PKR substrates were screened.[18] DMSO/THF and TMTU (1,1,3,3-tetramethylthiourea)/toluene systems were ineffective at rt (Table 1, entries 2 and 3), but experiments at 80 °C produced the desired TADA product in 74 and 99% yields, respectively (Table 1, entries 4 and 5). The reaction times indicated that the dicobalt-promoted TADA reaction was considerably more facile than the cobalt-free TADA reaction (Table 1, entry 5, vs Scheme 3). An exceptionally impressive result was obtained when the cycloaddition was performed with the stronger promoter NMO. Although dienyne ring **15** was unreactive at rt (Scheme 3), complex **17** formed product **16** in 80% yield in just 30 min when treated with NMO (Table 1, entry 6). Increasing the reaction time for complete consumption of **17**

**Table 1. Transannular [4 + 2] Reaction of Complex 17**

entry	solvent	temp (°C)	time (h)	promoter[a]	yield (%)[b]
1	CH₂Cl₂	25	168		
2	THF	25	120	DMSO	
3	toluene	25	72	TMTU	
4	THF	80	18	DMSO	74
5	toluene	80	12	TMTU	99
6	CH₂Cl₂	25	0.5	NMO	80
7	CH₂Cl₂	25	4	NMO	90
8	MeCN	25	21	NMO	86

[a]DMSO and NMO were used in 6 equiv, and TMTU was used in 0.6 equiv. [b]Yields are of isolated products. For entries 1−4, unreacted complex **17** and/or decomplexed dienyne **15** was recovered.

increased the yield to 90% (Table 1, entry 7). Acetonitrile solvent, which was the choice of promoter/solvent in reported cycloadditions of dicobalt complexes,[10] did not affect the product yield but dramatically slowed the reaction (Table 1, entry 8).

Next, 16-membered dienyne ring **20** was prepared via hydroboration followed by Pd(II)-catalyzed macrocyclization and tested for transannular [4 + 2] reactivity (Scheme 4). Metal-

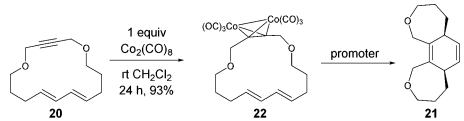**Scheme 4. Preparation and Attempted Metal-Free TADA Reaction of Macrocyclic Dienyne 20**
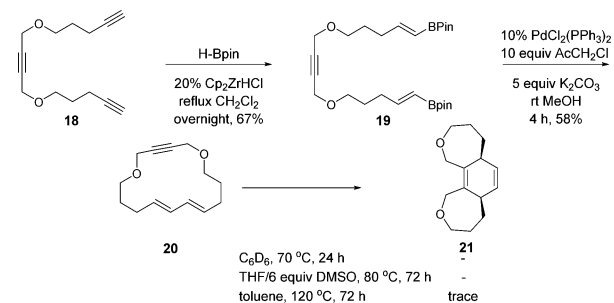
free TADA reaction of **20** was not effective as tricyclic compound **21** was not formed even after heating **20** at 70 °C for 24 h or at 80 °C for 72 h. When macrocycle **20** was heated in toluene at 120 °C for 72 h, only a trace amount of product was observed by TLC. Clearly, this larger system no longer benefits from a proximity effect, and lacking diene or dienophile activating groups, no TADA reactivity was observed.

Dicobalt complex **22** was prepared and subjected to transannular [4 + 2] cycloaddition conditions that were successful but highly dependent on the promoter/solvent composition (Table 2). NMO was ineffective at rt or at 80 °C (Table 2, entries 1 and 2). When heat was used as the sole promoter product, yields were low (Table 2, entries 3 and 4). While toluene/TMTU provided a quantitative conversion of **15** to tricycle **16** (Table 1, entry 5), it failed to promote formation of tricycle **21**. Higher yields of **21** were achieved with TMTU and benzene solvent (Table 2, entry 6).[19] Finally, product **21** was successfully synthesized in an 86% yield with a THF/DMSO system (Table 2, entry 7).

Products **16** and **21** were obtained from the cobalt-promoted reactions as single diastereomers, and they were predicted to

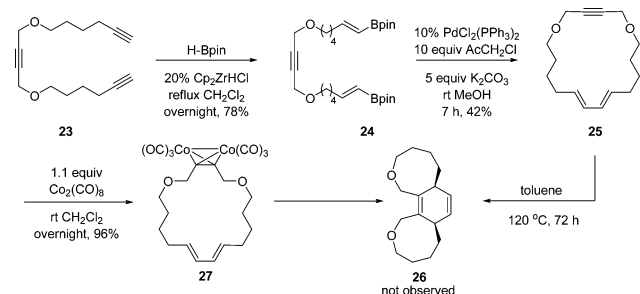## Table 2. Transannular [4 + 2] Reaction of Complex 22

entry	solvent	temp (°C)	time (h)	promoter[a]	yield (%)[b]
1	CH₂Cl₂	25	48	NMO	14
2	DCE	80	48	NMO	17
3	toluene	80−100	96		21
4	(n-Bu)₂O	140	17		25
5	toluene	100	24	TMTU	
6	benzene	70	12	TMTU	51
7	THF	80	18	DMSO	86

[a]NMO and DMSO were used in 6 equiv, and TMTU was used in 0.6 equiv (entry 5) and in 2 equiv (entry 6). [b]Yields are of isolated products. For entry 1, unreacted complex **22** and decomplexed **20** were recovered. For entries 2−6, recovered **22** and **20** were detected with unidentifiable decomposition products.

have *cis* stereochemistry. ¹H NMR analysis determined that thermal metal-free TADA reaction of dienyne **15** and transannular [4 + 2] cycloaddition reaction of dicobalt complex **17** formed the same diastereomer of **16**. Thus, the stereochemistry of tricyclic products **16** and **21** from cobalt-promoted reactions were assigned as *cis*.

We next turned to a transannular cycloaddition of a larger dienyne ring. The 18-membered ring **25** was synthesized from bis(vinylboronate ester) **24** in 42% yield by Pd(II)-catalyzed macrocyclization (Scheme 5). Like dienyne **20**, **25** was inert in a

Scheme 5. Preparation and Attempted TADA Reactions of Macrocyclic Dienyne 25

thermal TADA reaction; after heating at 120 °C for 72 h, no desired tricycle **26** was formed. Complex **27** was prepared and subjected to a transannular [4 + 2] reaction with various promoters, but no product was observed. The lack of reactivity may be due to steric interference by the extended methylene chains.

One reason for the paucity of dicobalt-promoted [4 + 2] cycloaddition examples is the high propensity for PKR to occur. {Co₂(CO)₆}−alkyne complexes are known to undergo facile intermolecular PKR with dienes.[9,20] Moreover, acyclic dienyne dicobalt hexacarbonyl complexes were shown to prefer PKR over dicobalt-promoted intramolecular [4 + 2] cycloadditions.[21] In our studies, dicobalt promoted *transannular* [4 + 2] cycloaddition reactions showed impressive selectivity, and no transannular PKR products **28**, **29**, or **30** were detected (Scheme 6). This may be due to conformational effects and a propensity for the intermediate cobaltocycle resulting from alkene insertion

## Scheme 6. Possible Transannular PKR Products
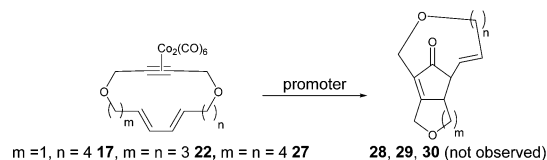
into the dicobalt−alkyne moiety to undergo a 1,3-shift and subsequent reductive elimination faster than CO insertion.

Since tricycles **12**, **16**, and **21** bear 1,4-cyclohexadiene rings, aromatization might be anticipated, especially when heated with oxidants. However, aromatization products derived from **12** and **21** were not observed. The aromatized form of **16** was detected by ¹H NMR only in trials involving heating with cobalt and oxidizing promoters. Since **16** is synthesized via dicobalt-promoted [4 + 2] reaction at rt, aromatization can be avoided.

Finally, we tested intermolecular dicobalt-promoted [4 + 2] cycloadditions. These control reactions used dienes and dienophiles not activated with electron-donating or -withdrawing components similar to TADA substrates **11**, **15**, **20**, and **25**. Dienophiles 3-hexyne and 1,4-dipropoxybut-2-yne (**35**) were reacted with 2,3-dimethylbuta-1,3-diene, but thermal Diels−Alder products were not formed (Scheme 7). However, dicobalt

Scheme 7. Dicobalt-Promoted Intermolecular [4 + 2] Reactions
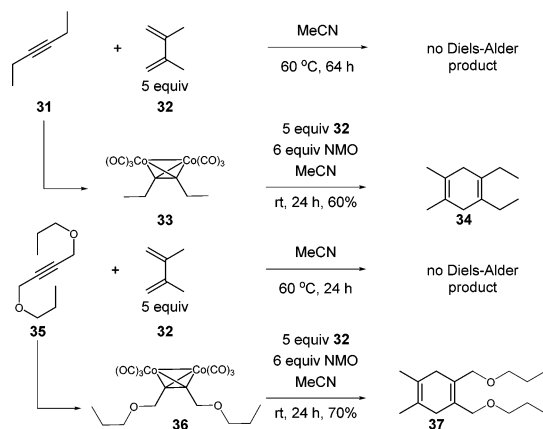
complexes **33** and **36** were reactive, and [4 + 2] adducts **34** and **37** were formed at rt (Scheme 7). A competing PKR was not observed from **36**, and only a trace was detected from **33**.[16] Mechanistically, a 1,3-shift from a 5-membered to a 7-membered cobaltocycle leading to [4 + 2] adducts should be favored by converting the carbon bonded to cobalt from tertiary to primary. Key to the success of these reactions was incorporation of the mild promoter MeCN as reaction solvent and slow addition of NMO. Under these conditions, we could avoid using high equivalents of diene. These results suggest that dicobalt-promoted [4 + 2] cycloaddition reactions may be more feasible than previously thought and deserve further exploration.

In conclusion, we demonstrated the first transannular [4 + 2] cycloaddition reactions of dicobalt hexacarbonyl alkyne complexes. Transannular Diels−Alder reactions of 14-, 15-, 16-, and 18-membered cyclic dienynes, efficiently synthesized via Pd(II)-catalyzed macrocyclizations, were investigated. Dicobalt-promoted transannular cycloadditions were significantly more effective than metal-free thermal TADA reactions, and competing PKRs were not observed. Intermolecular control

reactions confirmed the ability to select [4 + 2] cycloaddition reactions over PKR.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01984.

Experimental details and spectral data for isolated products (PDF)
NMR Spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: merlic@chem.ucla.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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