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First Cobalt(I)-Catalyzed [6 + 2] Cycloadditions of Cycloheptatriene with Alkynes

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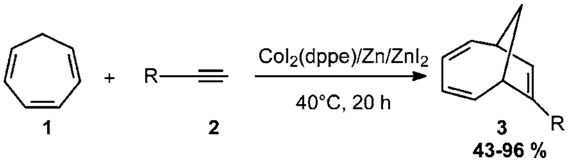
ABSTRACT



The CoI_2(dppe)/Zn/ZnI_2 system effectively catalyzes the [6 + 2] cycloaddition of cycloheptatriene with terminal alkynes to afford 7-alkylbicyclo[4.2.1]nona-2,4,7-trienes in fair to excellent yields. The catalyst proved to be tolerant toward functional groups such as ketone, sulfone, ester, ketal, ether, alcohol, imide, and nitrile. The enantioselective cycloaddition of CHT and phenylacetylene with BINOL phosphoramidite ligand 4 afforded the cycloadduct 3a (R = Ph) in 91% yield and 74% ee.

Transition metal-mediated higher order cycloadditions are important synthetic tools for the construction of medium-sized ring compounds.[1] The photoinduced [6 + 2] cycloaddition of cycloheptatriene (CHT) with internal alkynes was reported first by Pettit[2] using a tricarbonyl(η^4-cycloheptatriene)iron(0) complex to afford bicyclo[4.2.1]nonatriene adducts as tricarbonyl(η^4-triene)iron(0) complexes. A related chromium(0)-mediated [6 + 2] cycloaddition with tricarbonyl(η^6-cycloheptatriene)chromium(0) was demonstrated later by Grevels[3] and thoroughly investigated by Sheridan.[4] In between, Turecek reported the first catalytic procedure with Ziegler catalyst ($TiCl_4$/Et_2AlCl), but the cycloaddition suffered from the competitive cyclotrimerization of the alkyne.[5] Recent efforts focused on the development of $Cr(CO)_nL_{6-n}$ ($n = 2, 3$) complexes bearing labile ligands to perform catalytic processes.[6]

With terminal alkynes, the chromium(0)-promoted cycloadditions are difficult to arrest at the 1:1 alkyne−CHT cycloadduct stage; instead, tetra- and pentacyclic 2:1 alkyne−CHT

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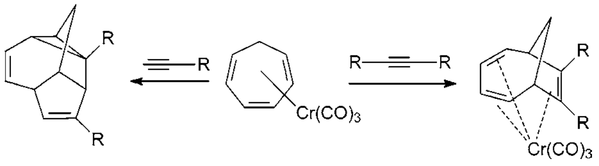
adducts are produced (Scheme 1).[7] These multicomponent reactions are believed to occur through a stepwise [6 + 2] cycloaddition−*homo*[6 + 2] cycloaddition sequence.[7,8] To date, chromium(0)-promoted [6 + 2] cycloadditions with alkynes remain confined to internal alkynes.

Scheme 1. Cycloadditions of [(η^6-CHT)Cr(CO)$_3$] and Alkynes



In continuation of studies into metal-promoted cycloadditions,[9] we have addressed the possibility of effecting a [6 + 2] cycloaddition of cycloheptatriene **1** with terminal alkynes **2** and report in this letter the first cobalt(I)-catalyzed [6 + 2] cycloaddition, which gives 7-alkyl-bicyclo[4.2.1]-nona-2,4,7-trienes **3**.

From the outset, we judged that the makeup of Co-based complexes offered an attractive opportunity for the design, synthesis, and development of effective cycloaddition catalysts. The following cobalt catalytic systems (**A**−**D**) combining CoI$_2$, 1,2-bis(diphenylphosphino)ethane (dppe), and tetrabutylammonium borohydride or zinc metal as a reducing agent with or without ZnI$_2$ in 1,2-dichloroethane (DCE) were selected to test the cycloaddition of **1** with phenylethyne **2a** (Table 1):

Catalyst **A**: CoI$_2$/dppe/Bu$_4$NBH$_4$/ZnI$_2$

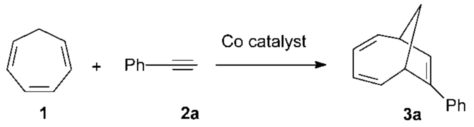
Catalyst **B**: CoI$_2$/dppe/Zn

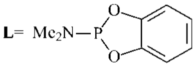
Catalyst **C**: CoI$_2$/dppe/ZnI$_2$

Catalyst **D**: CoI$_2$/dppe/Zn/ZnI$_2$

These catalysts were shown to be effective in homo-Diels Alder cycloadditions (**A**, **B**, and **C**),[9−13] [4 + 2 + 2] cycloaddition of functionalized norbornadienes and butadiene (catalysts **A**−**D**),[14] Diels−Alder-type reactions of 1,3-dienes with terminal or internal alkynes (catalysts **A** and **D**),[10,15] and 1,4-hydrovinylation reactions of 1,3-dienes with functionalized terminal alkenes (catalysts **A** and **D**).[16]

Table 1. Cobalt Catalysts Tested for the [6 + 2] Cycloaddition of Cycloheptatriene **1** with Phenylethyne **2a** to Form **3a**[a]



entry	catalyst (molar ratio)	yield (%)[c]
1	CoI$_2$/dppe/Zn (1/1/5)	39
2	CoI$_2$/dppe/ZnI$_2$ (1/1/5)	5
3	CoI$_2$/PPh$_3$/Zn/ZnI$_2$ (1/2/3/2)	35
4	CoI$_2$/P(OPh)$_3$/Zn/ZnI$_2$ (1/2/3/2)	25
5	**CoI$_2$/L/Zn/ZnI$_2$ (1/2/3/2)** **L**= Me$_2$N—P 	**61**
6	**CoI$_2$(dppe)/Zn/ZnI$_2$ (1/3/2)**	**75**
7	CoBr$_2$(dppe)/Zn/ZnI$_2$ (1/3/2)	40
8	CoI$_2$(dppp)/Zn/ZnI$_2$ (1/3/2)[b]	45
9	**CoI$_2$(dppe)/Bu$_4$NBH$_4$/ZnI$_2$ (1/1/2)**	**74**

[a] All reactions were carried out at a 0.3 M concentration in DCE at 40 °C for 20 h in a Schlenk tube under a nitrogen atmosphere with CHT **1**/**2a**/[Co] in a 1.2/1/0.05 molar ratio. [b] Dppp = 1,3-bis(diphenylphosphino)propane. [c] Yields of isolated **3a**.

When CHT and phenylethyne **2a** were mixed in the presence of CoI$_2$/dppe (5/5 mol %) or preformed CoI$_2$(dppe)[17] in DCE at 40 °C for 20 h, no reaction occurred (not shown in Table 1). Catalysts **B** and **C** afforded the desired cycloadduct **3a** in low yields (entries 1 and 2). The association of a reducing agent and a Lewis acid (catalyst **D**) proved to be beneficial and improved the yield to 75% (entry 6). Ligands such as PPh$_3$, P(OPh)$_3$, or dppp were less effective (entries 3, 4, and 8). Interestingly, the monodentate phosphoramidite ligand proved to be satisfactory, affording **3a** in 61% yield (entry 5). The cycloaddition was also observed by changing CoI$_2$ to CoBr$_2$, giving the cycloadduct in lower yield (entry 7). The efficiency of the cycloaddition was also demonstrated by using Bu$_4$NBH$_4$ as the reducing agent (catalyst **A**) (entry 9). Although catalysts **A** and **D** were similarly effective in promoting the [6 + 2] cycloaddition, the catalyst **D**, which would be expected to be more tolerant to the functional groups of the trienophile **2**, was selected for further studies. The choice of solvent was critical: use

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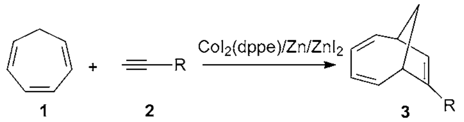
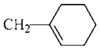
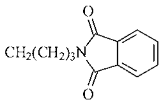
of DCE (75%), trifluoroethanol (TFE) (55%), and toluene (53%) are acceptable; MeCN, THF, dioxane, or DMF afforded no **3a** or trace amounts thereof.

The scope of the [6 + 2] cycloaddition using catalyst **D** was further extended to other terminal alkynes (Table 2).

Table 2. Cobalt-Catalyzed [6 + 2] Cycloaddition of Cycloheptatriene with Terminal Alkynes[a]



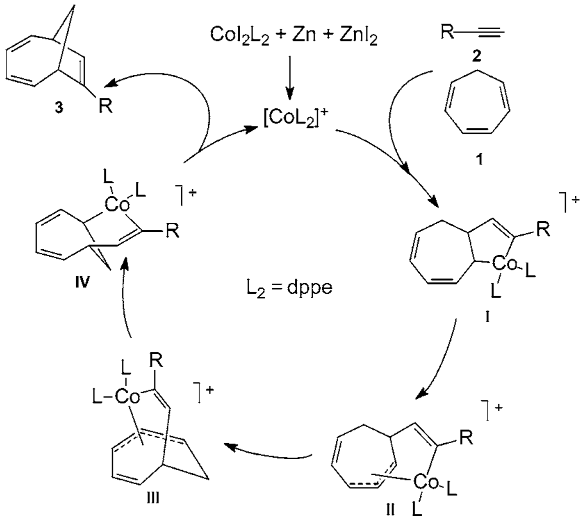
entry	alkyne	R	product	yield (%)[b, c]
1	**2a**	Ph	**3a**	75 (86)
2	**2b**	*n*-Bu	**3b**	74 (95)
3	**2c**	$SiMe_3$	**3c**	92
4	**2d**	CH_2SiMe_3	**3d**	65
5	**2e**		**3e**	43 (68)
6	**2f**	CH_2SO_2Ph	**3f**	50
7	**2g**	$CH_2CH(CO_2Me)_2$	**3g**	55 (83)
8	**2h**	$CH_2C(Me)_2CH_2Ac$	**3h**	96
9	**2i**	CO_2Me	**3i**	21 (43[d])
10	**2j**	$CH(OEt)_2$	**3j**	43 (59)
11	**2k**	CH_2OH	**3k**	19
12	"	"	"	60[d]
13	**2l**	CH_2CH_2OH	**3l**	67[d]
14	**2m**	CH_2CH_2OAc	**3m**	83
15	**2n**		**3n**	82
16	**2o**	$(CH_2)_3CN$	**3o**	90

[a] All reactions were carried out with CHT **1**/alkyne **2**/CoI_2(dppe)/Zn/ZnI_2 in a 1.2/1/0.05/0.15/0.1 molar ratio in DCE at 40 °C for 20 h. [b] Yields of isolated products by column chromatography or distillation. [c] Yields in parentheses are for optimized conditions (slow addition of the alkyne (4 h) using 2.5 mol % CoI_2(dppe)). [d] TFE as the solvent.

This catalytic system tolerates functional groups of **2** such as ketone, sulfone, ester, ketal, ether, alcohol, imide, and nitrile, which are of interest for further transformations. For instance, cycloadducts featuring a vinyltrimethylsilane (**3c**, 92%) or allyltrimethylsilane (**3d**, 65%) (entries 3 and 4) can be involved in a range of reactions of organosilicon compounds.[18] The yields observed depend on both the nature and the position of the functional group on the alkyne. Alkynes **2h**, **2m**, **2n**, and **2o** with the functional group remote from the triple bond afforded the cycloadducts in excellent yields (entries 8, 14, 15, and 16) compared to alkynes **2d**, **2f**, or **2j** with the functionality at propargylic carbon atom (entries 4, 6, and 10). TFE as the solvent proved to be beneficial to promote the cycloaddition of propargyl and homopropargyl alcohols in quite good yields (entries 11−13). Electron-poor alkynes such as methyl propiolate **2i** afforded cycloadduct **3i** in only 21% yield (entry 9), this is likely due to a marked preference of coordination of **2i** to the cobalt species triggering the cyclotrimerization. The efficiency of the cycloaddition was improved by using slow addition of the alkyne (syringe pump, 4 h) and lower catalyst loading (2.5 mol %) (entries 1, 2, 5, 7, 9, and 10).

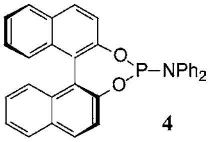
A plausible mechanism is depicted in Scheme 2. As suggested by Snyder, ZnI_2 accelerates the reduction of a CoL_2I_2 by zinc metal.[14a] The coordination of the alkyne and cycloheptatriene to the cationic $[Co(I)L_2]^+$ complex[16c] is followed by an oxidative cyclometalation to give the cobaltacyclopentene **I**.[19] The latter undergoes a 1,5-migration of the $C(sp^3)-Co$ bond through consecutive σ,π-allyl complexes (π-allyl complexes **II** and **III**) to form the bicyclo cobaltacycle **IV**. Subsequent reductive elimination of **IV** releases the cycloadduct **3** and regenerates the cationic $[Co(I)L_2]^+$ species.

Scheme 2. Proposed Mechanism for the Cobalt-Catalyzed [6 + 2] Cycloaddition



On the basis of the above results, a preliminary attempt was made to unravel the catalytic enantioselective [6 + 2] cycloaddition.[20] When phosphoramidite ligand **4**[21] was used (Scheme 3), the cycloaddition[20b] between CHT with **2a** gave rise to **3a** in excellent chemical yield (91%) and good enantioselectivity (74%).[20c]

Scheme 3. Phosphoramidite Ligand for the Enantioselective Cycloaddition



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In conclusion, we have developed the first cobalt-catalyzed [6 + 2] cycloaddition of cycloheptatriene and functional terminal alkynes that proceeds with a non-carbonylmetal catalyst and without irradiation. The reaction proceeded under mild conditions, and the catalyst tolerates a wide range of functional groups. Further optimization of the enantioselectivity with chiral phosphoramidite ligands is underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) To the best of our knowledge, the metal-catalyzed enantioselective [6 + 2] cycloaddition of CHT and alkynes has not yet been reported. (b) The reaction was performed at 40 °C for 20 h in DCE using 5 mol % CoI_2 and CoI_2/L/ZnI_2/Zn in a 1/2/2/3 molar ratio. (c) Determined by HPLC: Chiracel OJ-H, *n*-hexane/2-propanol 97:3, 1 mL/min, 25 °C, t_r = 17.7 min and t_r = 19.2 min.

(21) Phosphoramidite ligands are applied in a large number of a catalytic transformations and allow the production of a true ligand library: Duursma, A.; Boiteau, J. G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045−8052.