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Double Cationic Propargylation: From Linear to Polycyclic Ethers

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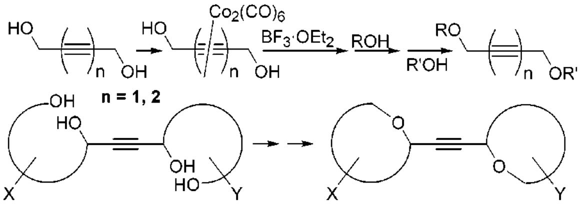
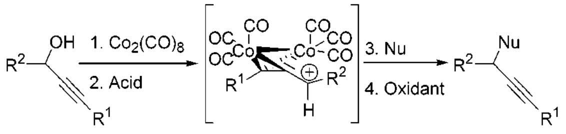
ABSTRACT



The trapping of cations generated from Co$_2$(CO)$_6$-bispropargylic alcohols provided diethers in good yield. The procedure is also valid when two vicinal acetylenes are present. The methodology can be applied to the synthesis of symmetrical or unsymmetrical linear or cyclic propargylic ethers. The use of substrates with a stereochemically defined secondary nucleophilic alcohol provided cyclic ethers with a high degree of stereocontrol.

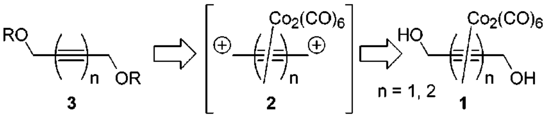
The nucleophilic attack on a Co$_2$(CO)$_6$-propargylic cation is known as the Nicholas reaction.[1] Using this methodology, a propargylic C−O bond (OH, OAc, OR) can be substituted by a wide range of nucleophiles.[1] Particularly interesting for our work is the possibility of producing the substitution of a propargylic alcohol by an alcohol to obtain an ether (Scheme 1). This transformation can be accomplished intramolecularly to afford cyclic oxacycles[2] or using an external alcohol to obtain linear ethers.[3]

Scheme 1. The Nicholas Reaction



We wondered if using an equivalent dicationic species such as **2** could extend our methodology to provide a very efficient and convergent route to highly oxygenated systems **3** (Scheme 2).

Scheme 2. Possible Route to Dipropargylic Ethers



We pondered two possible alternatives that could be adjusted to our basic idea, regarding the use of one or more acetylenes at the starting dipropargylic alcohol (Scheme 2).[4] To probe the viability of our idea we directed our attention to the Co$_2$(CO)$_6$-complexes of 2-butyne-1,4-diol (**1**, $n = 1$) and hexa-2,4-diyne-1,6-diol (**1**, $n = 2$). Satisfactorily, the acidic treatment with BF$_3$·OEt$_2$ followed by the addition of

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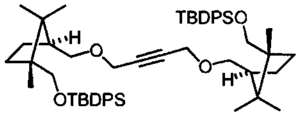
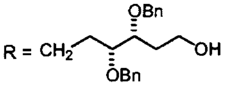
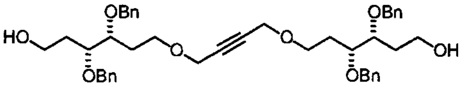
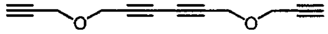
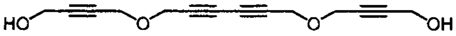
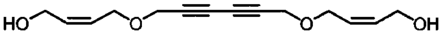
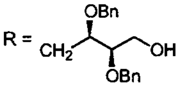
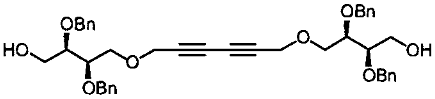
(1) (a) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, Chapter 7.1, pp 685−702. (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809−826.

(2) (a) Palazón, J. M.; Martín, V. S. *Tetrahedron Lett.* **1995**, *36*, 3549−3552. (b) Mukai, C.; Yamaguchi, S.; Sugimoto, Y.-I.; Miyakoshi, N.; Kasamatsu, E.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6761−6765, and references therein. (c) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821−2824, and references therein.

(3) Díaz, D. D.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 9993−9996.

10.1021/ol0164987 CCC: $20.00

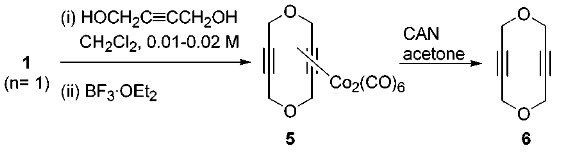
Table 1. Synthesis of Dipropargylic Ethers from Bispropargylic Alcohols

Entry	1 (n)	ROH	3	(%)
1	n = 1	R = $CH_2C{\equiv}CH$		75
2	"	R = $CH_2C{\equiv}CCH_2OH$		71
3	"	R = $CH_2C{=}CCH_2OH$-(*Z*)		72
4	"			80
5	"	 (**4**)		76
6	n = 2	R = $CH_2C{\equiv}CH$		81
7	"	R = $CH_2C{\equiv}CCH_2OH$		71
8	"	R = $CH_2C{=}CCH_2OH$-(*Z*)		64
9	"			69

an excess of propargylic alcohol (ca. 5 equiv) provided in both cases, after demetalation of the acetylenic system,[5] the diether **3** (R = $CH_2C{\equiv}CH$) (Table 1, entries 1 and 6). The procedure can be extended to the use of a wide range of alcohols (Table 1). Thus, even using diols as nucleophiles we were able to obtain the corresponding diether–diols (entries 2–5 and 7–9). Interestingly, the use of chiral diols easily provided the corresponding chiral ethers (entries 4, 5, and 9).[6]

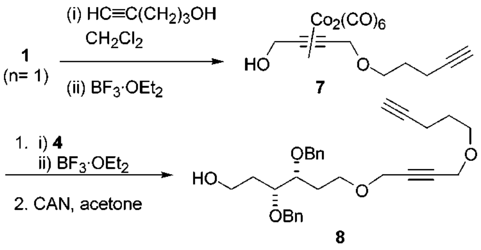
The reaction is sensitive to the concentration. One particularly interesting case was the use of 2-butyne-1,4-diol (**1**, *n* = 1) as the source of the cationic species and as nucleophile (Scheme 3). The use of a low concentration, approximately 0.01 M, provided the complexed cyclic ether **5** that after demetalation yielded 1,6-dioxacyclodeca-3,8-diyne **6** in 76% isolated yield.[7,8]

Scheme 3. Synthesis of 1,6-Dioxacyclodec-3,8-diyne **6**



The possibility of using an additional hydroxy group to form a new ether functionality alerted us to the possible extension of our methodology for the synthesis of linear– and cyclic–mixed ethers. Thus, when the $Co_2(CO)_6$-complex of 2-butyne-1,4-diol (**1**, *n* = 1) was treated with 1 equiv of 4-pentyn-1-ol and 1 equiv of $BF_3{\cdot}OEt_2$, the monocomplexed ether **7** was satisfactorily obtained (77% yield) (Scheme 4). This compound was then treated under similar conditions with the diol **4**, yielding after demetalation the unsymmetrical ether **8** (68% yield).

Scheme 4. Synthesis of Unsymmetrical Dipropargylic Linear Ethers



This finding prompted us to speculate about the possibility of performing a simultaneous cyclization under intramolecu-

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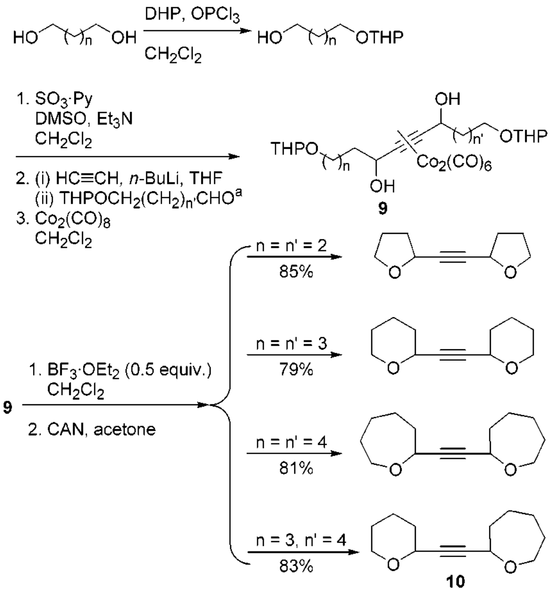
(4) **Typical procedure (Entry 6):** To a stirred solution of hexa-2,4-diyne-1,6-diol (110 mg, 1 mmol) in CH_2Cl_2 (10 mL, 0.1 M) was added dicobalt octadicarbonitrile (855 mg, 2.5 mmol) at room temperature. The reaction was stirred for 1 h, filtered through a silica gel pack, concentrated, and purified by silica gel column chromatography, obtaining the bis-$Co_2(CO)_6$-complex **1** as a dark solid (532 mg, 78% yield). This solid was dissolved again in CH_2Cl_2 (8 mL, ≈0.1 M) under an argon atmosphere at room temperature. To this mixture were consecutively added 5 equiv of propargylic alcohol (ROH) (230 μL, 3.9 mmol) and 2 equiv of $BF_3{\cdot}OEt_2$ (200 μL, 1.56 mmol) at room temperature. The reaction mixture was monitored by TLC. The mixture was poured with vigorous stirring into a saturated solution of $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography to obtain bis-$Co_2(CO)_6{\cdot}$**3** as a dark oil (486 mg, 85% yield). This complex was dissolved in acetone (3 mL), and $Ce(NO_3)_6(NH_4)_2$ (2.9 g, 5 mmol) was added at 0 °C. The mixture was stirred for 10 min, concentrated, diluted with water, and extracted with ether. The organic layers were washed with brine, dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography, obtaining 1,6-bis(2-propynyloxy)-2,4-hexadiyne (**3**) as an oil (117 mg, 95% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 2H), 4.25 (s, 4H), 4.34 (s, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 56.7, 70.8, 74.6, 75.3, 78.5. Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.20; H, 5.51.

lar conditions using a suitable dipropargylic−dihydroxyl system.[9] To probe our idea we synthesized a series of propargylic tetrols **9** in accordance with Scheme 5. Gratifyingly, when **9** was treated with only 0.5 equiv of $BF_3{\cdot}OEt_2$, a concomitant cyclization occurred in all cases, yielding the corresponding five- to seven-membered ring bicyclic ethers. In addition to the significance of the cyclization, two additional facts should be pointed out: (1) the procedure is valid for the synthesis of nonsymmetrical cyclic ethers (ca. **10**) and(2) the reaction works under nonstoichiometric conditions with only 0.5 equiv of Lewis acid, maintaining the nucleophilic oxygen protected as a THPO-ether.[10]

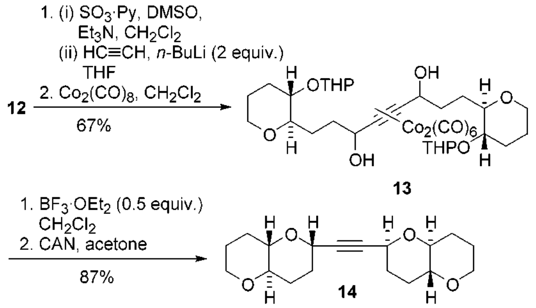
Scheme 5. Synthesis of Symmetric and Unsymmetrical Dipropargylic Cyclic Ethers



[a] The synthesis of **9** (n = 3, n' = 4) was performed in two sequential steps via the monopropargylic alcohol. In all other cases, 2 equiv of the aldehyde was added to dilithium acetylide in one step.

To verify whether our methodology was useful for the stereocontrolled synthesis of cyclic systems, we performed the synthesis of dipropargyl diol **13** in accordance with Scheme 6.[11] In this precursor we have controlled the stereochemistry of both THP-protected secondary alcohols. When **13** was submitted to our standard acidic conditions the tetracyclic system **14** was obtained as the only stereoisomer.[12]

Scheme 6. Simultaneous Stereocontrolled Synthesis of Propargylic Tetracyclic Ethers



In summary, we have described a new and very efficient procedure to synthesize linear or cyclic ethers in a highly efficient and convergent manner. The method permits a high level of control, affording nonsymmetrical compounds. In addition, we have shown that the procedure can be used for the stereocontrolled synthesis of cyclic ethers.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. In addition, NOE studies of compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) In all cases reported in this paper, the $Co_2(CO)_6$-complexes were satisfactorily demetalized in the standard manner (CAN, acetone, 0 °C) to obtain the free acetylenes. See: Seyferth, D.; Nestle, M. O.; Wehman. *J. Am. Chem. Soc.* **1975**, *97*, 7417−7426.

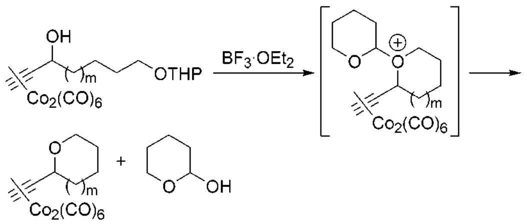
(6) During the formation of **3** it was possible to detect by TLC the transitory formation of the monoether that evolves to the diether. In consequence, the species **2** is a sequentially achieved formalism.

(7) Although **6** is a known compound, the methods for its synthesis reported in the literature provided very poor yields. See: Gleiter, R.; Rittinger, S. *Tetrahedron Lett.* **1988**, *29*, 4529−4532.

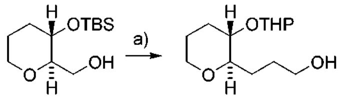
(8) For the synthesis of sulfur macrocycles containing dialkyne units, see: Davies, J. E.; Hope-Weeks, L. J.; Mays, M. J.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **2000**, 1411−1412.

(9) For additional methods to synthesize cyclic ethers, see: (a) Alvarez, E.; Candenas, M. L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980, and references therein. (b) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631−12670. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007, and references therein. (d) Heck, M.-P.; Baylon, C.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2001**, *3*, 1989−1991, and references therein.

(10) A plausible mechanism implies catalytic participation of the Lewis acid, generating the cyclic ether and tetrahydropyran-2-ol:



(11) The THP-protected diol **12** was prepared from known **11**. See: Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64*, 4798−4816. (a) (i) Swern oxidation, (ii) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, (iii) DIBALH, THF, (iv) H_2, PtO_2, MeOH, (v) Ac_2O, DMAP, CH_2Cl_2, (vi) HF, CH_3CN, (vii) DHP, $OPCl_3$, CH_2Cl_2, then NaH, MeOH, 52% overall.



11 **12**

(12) The stereochemistry of **12** was determined by NOE studies (see Supporting Information).