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# Totally Chemo- and Regioselective Cobalt(I)-Mediated Formal Intermolecular Cyclotrimerization of Alkynes

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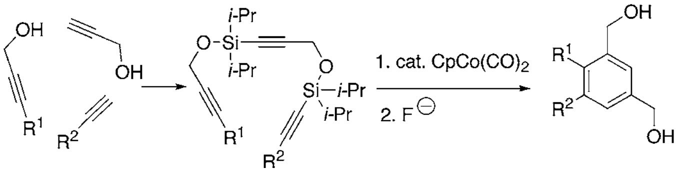
## ABSTRACT



**The first examples of totally chemo- and regioselective formal intermolecular cobalt(I)-catalyzed [2 + 2 + 2] cyclizations of three different alkynes are reported. The use of disposable silylated tethers in the sequence cyclization followed by the displacement of the silicon group led to polysubstituted arenes as a unique cycloadduct in high yields.**

Transition metal mediated cyclotrimerizations of alkynes have been recognized to be one of the most powerful and general methods to synthesize substituted arenes.[1] Despite intensive research in this field, the intermolecular version of this process suffers from poor chemo- and regioselectivity. Various transition metal complexes have been used to overcome this problem; however, the selectivity of catalytic intermolecular reactions of two or three alkynes has remained a crucial issue.[1,2] Different alternative approaches have been proposed to circumvent the lack of selectivity. Indeed, intramolecular or partially intramolecular reactions of $\alpha,\omega$-diynes with excess of monoynes have been successfully employed to solve the selectivity problems and have been elegantly used in the total synthesis of complex natural and unnatural compounds.[3] In addition, more recently, formal [2 + 2 + 2] cyclizations of alkynes via a palladium homo- and cross-coupling/[4 + 2] benzannulation were demonstrated to occur also in a highly regioselective manner.[4]

In this context, we turned our attention to the silylated tethers that allow the transformation of intermolecular reactions into intramolecular ones.[5] Indeed, we thought that

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[1] For reviews, see: (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1129−1162. (b) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 741−770. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662. (e) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915. (f) Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Georg Thieme Verlag: Stuttgart, 2001; Vol. 1, pp 439−530.

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[3] (a) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549−4552. (b) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 536−556. (c) Vollhardt, K. P. C. *Pure Appl. Chem.* **1985**, *57*, 1819−1826. (d) Slowinski, F.; Aubert, C.; Malacria, M. *Adv. Synth. Catal.* **2001**, *343*, 64−67. (e) Petit, M.; Chouraqui, G.; Phansavath, P.; Aubert, C.; Malacria, M. *Org. Lett.* **2002**, *4*, 1027−1029. (f) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143−12160 and references therein.

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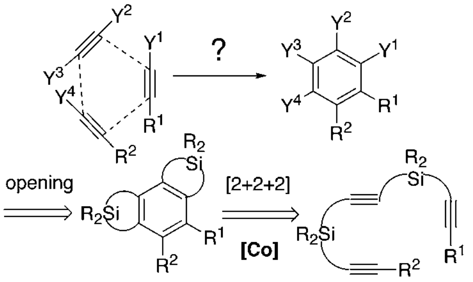
**Scheme 1**



the intramolecular cobalt(I)-catalyzed cyclotrimerizations of silicon-linked triynes (Scheme 1) would be highly attractive alternatives based upon the fact that the cyclizations would be catalytic in metal and chemo- and regioselective. Finally, the tethers could be selectively removed after the reaction, leading easily to functionalized arenes. Here we present the first examples of cobalt(I)-catalyzed formal inter- and partially intermolecular [2 + 2 + 2] cyclizations of three different alkynes and diynes with 1 equiv of monoyne with a complete control of selectivity.

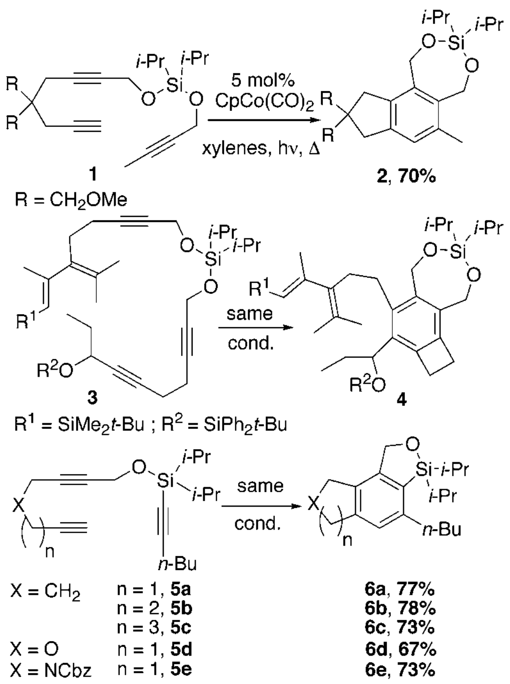
Silicon linkers, which are generally ethers, have been applied to many types of reactions:[5] radical cyclizations, [4 + 2] cycloadditions, nucleophilic additions, Pauson−Khand reactions,[6] and metathesis.[7] As far as we are aware, only one cobalt-mediated [2 + 2 + 2] cycloaddition of an enediyne having a silyl ether linkage between the triple and double bonds has been reported.[8]

From a practical point of view, we have recently disclosed a new and efficient one-pot procedure for the preparation of unsymmetrical silaketals that completely avoids the formation of the undesired symmetric compounds. High yields were obtained particularly when diisopropylchlorosilane was employed, and this method could also be extended to the preparation of unsymmetrical silyl ethers and silanes.[9]

Having in hand a series of silicon-tethered triynes **1**, **3**, **5a**−**e**, **7**, **8**, and **11**, which were produced following our previously reported procedure, we checked their behavior in the presence of 5 mol % of $\eta^5$-cyclopentadienyldicarbonyl cobalt(I) [CpCo(CO)$_2$] in boiling xylenes under irradiation.

Our initial findings showed that the cyclizations of **1**, **3**, and **5a**−**e** exhibiting only one silylated linker furnished the corresponding benzenic derivatives **2**, **4**,[10] and **6a**−**e** in good yields (Scheme 2). All of the cycloadducts were quite stable and easy to handle under standard conditions.

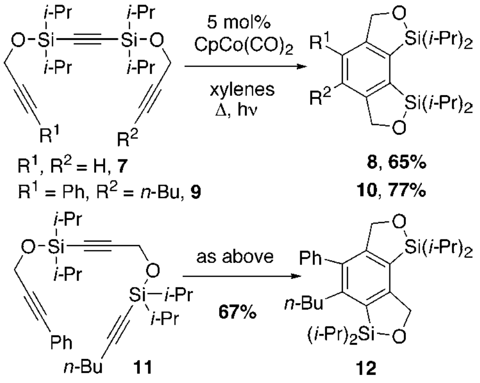
**Scheme 2**



It is noteworthy that such cycloadditions are fully compatible with the presence of silaketal O−Si−O or silyl ether O−Si−C in addition to a dienic moiety or heteroatomic tether.

An additional silicon linker, as well as the steric hindrance of the four isopropyl substituents, did not alter the course of the cyclization. Indeed, the cycloadducts **8**, **10**, and **12** were obtained in good yields regardless of the substitution of the terminal triple bonds (Scheme 3).

**Scheme 3**



By treatment with *n*-tetrabutylammonium fluoride (TBAF) in THF at low (−78 to 0 °C) or refluxing temperature, the

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(5) For reviews, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813−854. (c) Gauthier, D. R. J.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338. (d) White, J. D.; Carter, R. G. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Vol. 4, pp 371−412. (e) Skrydstrup, T. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Vol. 4, pp 439−530.

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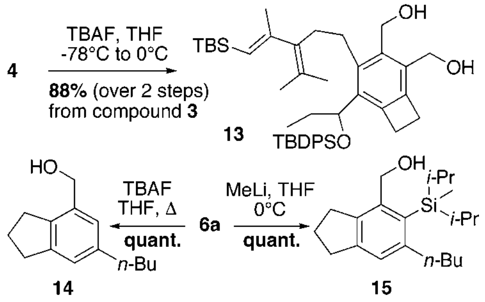
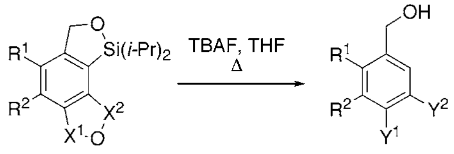
(10) Compound **4** was used without further purification in the next step; see Scheme 4.

**Scheme 4**



**Scheme 5**



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|---|---|
| $X^1 = CH_2$, $X^2 = Si(i\text{-}Pr)_2$ | $Y^1 = CH_2OH$, $Y^2 = H$ |
| $R^1$, $R^2$ = H, **8** | **16**, **60%** |
| $R^1$ = Ph, $R^2$ = *n*-Bu, **10** | **17**, **62%** |
| $X^1 = Si(i\text{-}Pr)_2$, $X^2 = CH_2$ | $Y^1 = H$, $Y^2 = CH_2OH$ |
| $R^1$ = Ph, $R^2$ = *n*-Bu, **12** | **18**, **76%** |

cycloadduct **4** led to the corresponding diol **13**, which was obtained from the triyne **3** in 88% overall yield (Scheme 4).

The opening of the silylated adduct **6a** can occur either with TBAF or MeLi to furnish quantitatively **14** and **15,** which formally arise from a totally chemo- and regioselective semi-intermolecular [2 + 2 + 2] reaction between octa-2,7-diyn-1-ol and hex-1-yne or silylated hexyne, respectively.

The displacement of the silylated linkers of the adducts **8**, **10**, and **12** required 4 equiv of TBAF and led to the diols **16**, **17**, and **18** in 60%, 62%, and 76% yield, respectively (Scheme 5). The overall sequence is quite remarkable, because it led to di- or tetrasubstituted arenes, which formally originate from a [2 + 2 + 2] cyclization between two propargylic alcohol units and an alkyne moiety that, in the case of **16**, can be acetylene. Note that, depending on the substitution of the internal triple bond by one or two silylated groups (**9** vs **11**), we were able to reach either 1,2,3,4-tetrasubstituted arene **17** or its 1,2,3,5-regioisomer **18**.

In summary, we have reported the first examples of totally chemo- and regioselective formal intermolecular cobalt(I)-mediated [2 + 2 + 2] cyclizations of triynes or diynes with monoynes via the judicious use of disposable silylated tethers. This represents a major improvement since the intermolecular cyclotrimerization of three different alkynes gave an untractable mixture of all accessible arenes derivatives. On the contrary, the cyclotrimerization followed by the displacement of the silylated groups led to functionalized polysubstituted arenes in high yields.

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

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