4 + 3 and fluorinative 4 + 3 cycloadditions of alkyne 1,4-diether dicobalt complexes

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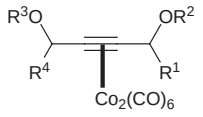
The $BF_3{\cdot}OEt_2$ mediated reactions between alkynyl diether hexacarbonyldicobalt complexes 1 and stannylsilanes 3 or 7 afford cycloheptenyne cobalt complexes 4 or fluorocycloheptyne complexes 8 depending upon the conditions of reaction.

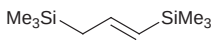
The synthesis of seven-membered carbocyclic compounds is of much interest, due to their presence in a wide variety of natural products and due to the relative paucity of good ways to make the system.[1] The most conceptually attractive routes to the preparation of cycloheptanes are the 4 + 3 cycloaddition approaches, by virtue of the rapid assembly of the ring system and their superficial analogy to [4 + 2] cycloaddition reactions. A number of these cycloadditions have been reported,[2] most extensively those employing oxyallyl cations with dienes[3] and those condensing bis(trimethylsilyl) enol ethers with 1,4-diones.[4]

A potentially valuable variant of the 4 + 3 cycloaddition would be the reaction of sequentially formed cations from alkynyl diether complexes **1** with allyldimetal equivalents **2** or

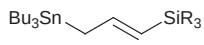


1

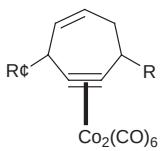
	R^1	R^2	R^3	R^4
a	H	Bn	Bn	H
b	H	Me	Me	H
c	H	Et	Et	H
d	Me	Me	Me	H
e	Ph	Me	Me	H
f	Me	Et	Et	Me
g	Me	TBDMS	Me	H
h	Ph	TBDMS	Me	H
i	Me	Pr^i	Me	H
j	Ph	Pr^i	Me	H



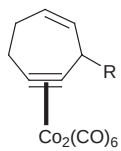
2



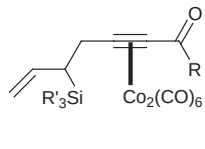
3a R = Me
b R = Et



4



4'



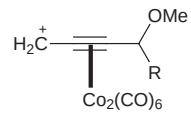
5

a R, R' = H
b R = Me, R' = H
c R = Ph, R' = H
d R, R' = Me

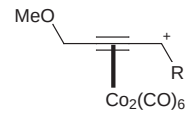
3. The resultant cycloheptyne complexes **4** are known to have good thermal stability,[5,6] and possess an (alkyne)hexacarbonyldicobalt function capable of synthetically important substitution[7] and cycloaddition reactions.[8] This possibility was realized by Takano's group, but they were unable to induce a Lewis acid mediated condensation between disilane **2** and **1a** to form either a cycloheptyne complex, or even useful yields of acyclic products.[9] Recent work in our laboratory has demonstrated the unexpected reactivity pathway of **2** with propargylcobalt cations bearing remote carbonyl functions, and the superiority of stannylsilanes **3** in the formation of acyclic allylation products **5**.[5]† In view of this, we have decided to investigate the viability of 4 + 3 cycloadditions between **1** and **3**.

Addition of 5 equiv. of $BF_3{\cdot}OEt_2$ to a 0 °C CH_2Cl_2 solution of **3a** and **1a** (10^{-1} M) over a period of 0.5 h gave a small amount of cycloadduct **4a** (*ca.* 10%), along with several acyclic allylation and diallylation products. Significantly improved yields of the cyclization product could be realized with methyl ether **1b** and ethyl ether **1c**, and with the triethylsilyl-substituted allyltin **3b**. Under the strictly analogous conditions, these reagent combinations afforded cycloheptenyne complex **4a** in 62 and 72% yields, respectively.

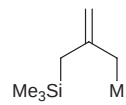
Use of reagent **3b** was investigated under these conditions with substituted alkynyl diether complexes. Methyl substituted **1d** and phenyl substituted **1e** gave cycloheptenyne complexes **4b** and **4c** as regioisomeric double bond mixtures with **4b′** (**4b** : **4b′** = 2.2 : 1) and **4c′** (**4c** : **4c′** = 1.7 : 1), respectively. In both cases, the predominant regioisomer obtained implies the preferential initial formation of the *less* substituted cation **6a**



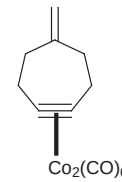
6a



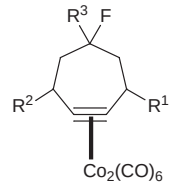
6b



7a M = $SnBu_3$
b M = $SiMe_3$



4e



8

	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	Ph	H	H
d	Me	Me	H
e	H	H	Me

over **6b**. Although a kinetic effect cannot be ruled out at this time, these results are consistent with the reported greater stability of less substituted propargylcobalt cations, as demonstrated by the pK_{R^+} measurements of Nicholas.[10] Dimethyl-substituted substrate **1f** gave the corresponding cycloheptenyne complexes **4d** in a more modest yield, in a 4.0 : 1 mixture of *trans* : *cis* diastereomers.‡ Finally, the isobutene dianion equivalent **7a**[11] reacted with **1c** to give methylenecycloheptyne complex **4e** in 53% yield.

Attempts were made to improve on the regiochemical selectivity for **4b** and **4c** by incorporating a bulkier ether

Table 1 4 + 3 Cycloadditions between alkynyl diether complexes **1** and allyldimetals **3** or **7**

Diether	Allyldimetal	Product	Yield[a] (%)
1b	**3b**	**4a**	62
1c	**3b**	**4a**	72
1d	**3b**	**4b + 4b′**	54 (2.2 : 1)
1e	**3b**	**4c + 4c′**	53 (1.7 : 1)
1f	**3b**	**4d**	42 (4.0 : 1)[b]
1g	**3b**	**4b**	62 (> 30 : 1)
1i	**3b**	**4b**	68 (> 30 : 1)
1h	**3b**	**4c**	37 (> 30 : 1)
1j	**3b**	**4c**	52 (> 30 : 1)
1c	**7a**	**4e**	53

[a] Ratio of regioisomers in parentheses. [b] Ratio of diastereomers *trans*-**4d** : *cis*-**4d**.

Table 2 Fluorinative 4 + 3 cycloadditions between **1** and **3** or **7**

Diether	Allyldimetal	Product	Yield[a] (%)
1c	**3b**	**8a**	**70**
1d	**3b**	**8b**	**57 (2.6 : 1)**
1e	**3b**	**8c**	**55 (2.4 : 1)**
1f	**3b**	**8d**	80 (1.9 : 1 : 0.14)[b]
1c	**7b**	**8e**	48

[a] Ratio of *trans*-**8** : *cis*-**8** in parentheses. [b] Ratio of *trans,trans*-**8d** : *cis,cis*-**8d** : *trans,cis*-**8d**.

function at the more substituted propargylic site. To this end, TBDMS ethers **1g** and **1h** and isopropyl ethers **1i** and **1j** were tested in their reactions with **3b**. Substantial improvements in regioselectivity were observed. Each of these cases resulted in the formation of the 6-substituted isomers (**4b** and **4c**) to the exclusion of the 3-substituted isomers (**4b′** and **4c′**); chemical yields were higher in both systems with the isopropyl ethers.

These cycloadditions were found to take a slightly different pathway under altered reaction conditions. Very slow addition of 5 equiv. of $BF_3{\cdot}OEt_2$ (over 12 h) to a highly dilute CH_2Cl_2 solution of **1c** and **3b** (10^{-3} M) at 0 °C resulted in the formation of fluorinated cycloheptyne complex **8a** (70% yield) to the exclusion of cycloheptenyne complex **4a**. Compound **8a** could also be obtained by rapid $BF_3{\cdot}OEt_2$ addition at 10^{-1} M concentrations, but the yield of this compound (57%) was inferior.

This fluorinative 4 + 3 cycloaddition was also found under the slow addition, high dilution conditions with the substituted diethers **1d**–**f**, giving **8b**–**d** as separable diastereomeric mixtures.[12] In monomethyl substituted **8b** and phenyl substituted **8c**, the *trans* isomers were found to predominate in a *ca.* 2.5 : 1 ratio. Stereoisomer assignments were based on the relatively upfield ^{1}H NMR chemical shift (in *cis*-**8b**) of the axial H atom geminal to fluorine (δ 4.55 in *cis*-**8b** *vs.* δ 5.11 in *trans*-**8b**), the larger vicinal coupling constants for that axial H atom ($J_{ax\text{-}ax}$ (average) = 10.9 Hz in *cis*-**8b** *vs.* $J_{eq\text{-}eq}$ (average) = 7.2 Hz in *trans*-**8b**), and a preferred chair conformation for the complexed cycloheptyne ring.[13]§¶ Dimethyl substituted **8d** was also formed as a mixture of three diastereomers, in a *trans, trans* : *cis, cis* : *trans, cis* ratio of (1.9 : 1 : 0.14). Notably, the ratio of the two diastereomers with *cis* methyl groups to the one with the *trans* orientation of methyl groups corresponds to 21 : 1. The reasons for the preferential formation of *cis*-dimethyl isomers of **8d** in the fluorocycloheptyne series, as opposed to the preferential formation of *trans*-dimethyl **4d** in the cycloheptenyne series, are not understood at this time. Finally, **1c** reacted with isobutene dianion equivalent **7b** under these conditions to afford tertiary fluoride **8e** in fair yield (48%).

In summary, rapid access into cycloheptynecobalt ring systems has been found to occur *via* both fluorinative- and non-fluorinative versions of a 4 + 3 cycloaddition reaction. Work on the preparation of more diversely substituted versions of these compound classes, and studies on the use of these compounds in the preparation of 5,7- and 6,7-ring systems, are in progress and will be reported in due course.

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Notes and references

† These allylation products **5** may also be converted into cycloheptenyne complexes **4** (ref. 5).

‡ Diagnostic for the ^{1}H NMR based assignment of *trans*-**4d** as the major diastereomer is the existence of a 1.7% integrated NOE of the absorption for the pseudoaxial methylene proton (δ 2.00) upon irradiation of the allylic methine resonance (δ 3.75), and a 2.7% integrated NOE of the absorption for the allylic methine proton upon irradiation of the pseudoaxial methylene resonance.

§ MM2 Calculations (PC Model®) predict $J_{ax\text{-}ax}$ values of 11.8 and 11.8 Hz for the proton geminal to fluorine in *cis*-**8b**, and $J_{eq\text{-}eq}$ values of 7.0 and 7.1 Hz for the analogous proton in *trans*-**8b**.

¶ A 4.3% NOE integrated enhancement of the absorption for the propargylic methine H atom (δ 2.89) upon irradiation of the δ 4.55 resonance in *cis*-**8b** also supports the assignment of an axial orientation for these two protons.

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