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Stereoselective double addition of chiral alkynyl-zincs to cobalt-stabilized acetylenedicarbaldehyde

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Abstract—Acetylenedicarbaldehyde, a desirable but intractable C_4 synthon, can be protected as the Gorgues' dicobalt hexacarbonyl complex. It undergoes chimio-, diastereo- and enantioselective attack of terminal alkynes using zinc triflate and (−)-*N*-methyl-ephedrine to afford stable complexes of chiral secondary carbinol-skipped oligoynes.

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1. Introduction

Acetylenedicarbaldehyde **1** contains as many carbon atoms as unsaturations, and is thus an attractive highly functional C_4 synthon for versatile nucleophilic or pericyclic functionalization. However, its instability has limited its use in organic synthesis.[1] A stable $Co_2(CO)_6$ complex **2**, prepared from a bis(diethylacetal) of compound **1** and dicobalt octacarbonyl, can be used as an alternative synthon.[2] Indeed, double addition of alkyl- and aryl-lithium and -magnesiumbromide reagents to the cobalt complex **2** was recently reported to proceed with moderate diastereoselectivity.[3] Addition of analogous alkynyl nucleophiles was also reported, though in lower yields and undetermined diastereoselectivity.

To the best of our knowledge, the electrophilic reactivity of compound **2** with zinc reagents or under chiral conditions has not been investigated.[4] Both these aspects were tackled while resuming the case of alkynyl nucleophiles;[5] these challenges indeed meet as prerequisites for the stereoselective synthesis of unsubstituted oxy-[*N*]pericyclynes (*carbo*-[*N*]cyclitols, $N = 5$, 6).[6]

As a starting point, we were naturally inspired by the Carreira's methodology for highly enantioselective addition of terminal alkynes to aliphatic, olefinic and aromatic aldehydes.[7,8] Inspection of the literature revealed that less attention had been paid to dicarbaldehyde substrates.[5–8] Moreover, despite mention of a possible application to acetylenic aldehydes, no detail was given for this kind of electrophiles.[9] In a complementary prospect, we herein report on an adaptation of the Carreira's method to the cobalt-stabilized acetylenedicarbaldehyde dielectrophile **2**.

2. Results and discussion

Complex **2** (1.0 equiv) was thus treated with trimethylsilylacetylene (4.2 equiv) in the presence of zinc triflate (4.0 equiv), (−)-*N*-methyl-ephedrine (4.2 equiv) and triethylamine (4.2 equiv) in dichloromethane.[5,7] These conditions allowed for the isolation of the corresponding double adduct **3** and monodesilylated adduct **4** in 38% and 11% yield, respectively (Scheme 1). Control experiments indicated that achievement of significant conversion required such overstoichiometric conditions, and that no reaction occurred in the absence of either zinc triflate or *N*-methyl-ephedrine. In the opposite, further introduction of additional alkyne (6.6 equiv), $Zn(OTf)_2$ (6.0 equiv) and ligand (6.6 equiv), had little effect on the reaction yield and selectivity.

Single crystals of **3** deposited from an ethyl acetate: *n*-heptane mixture, and one of them was submitted to an X-ray diffraction analysis.[10] The relative configuration was demonstrated to correspond to the *threo* bis-adduct **3** (Fig. 1). To our surprise, while the *meso* adducts were predominantly formed (in ca. 80% de) by

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Keywords: Asymmetric addition; Acetylenedicarbaldehyde; Cobalt; Zinc; Ephedrine; Dialkynylcarbinols.

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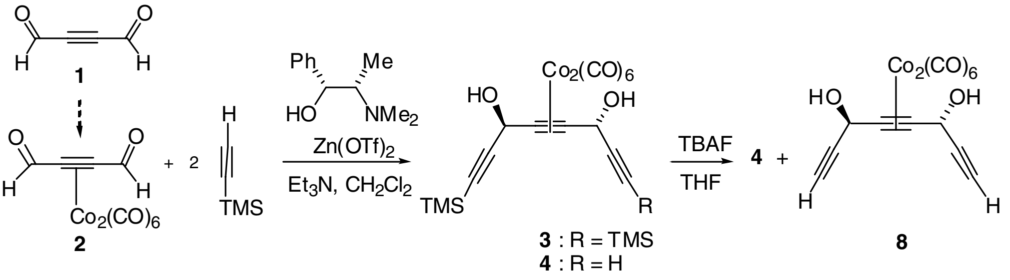


Scheme 1. Zinc-mediated double addition of trimethylsilylacetylene to the cobalt complex of acetylenedicarbaldehyde.

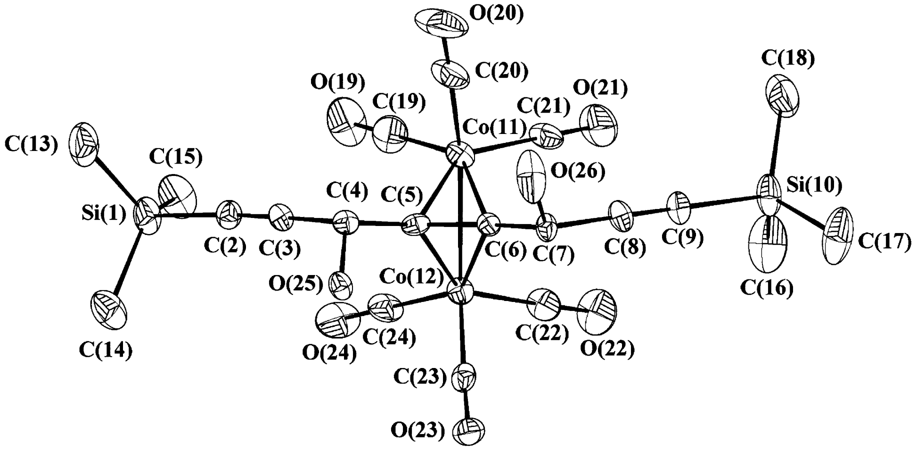


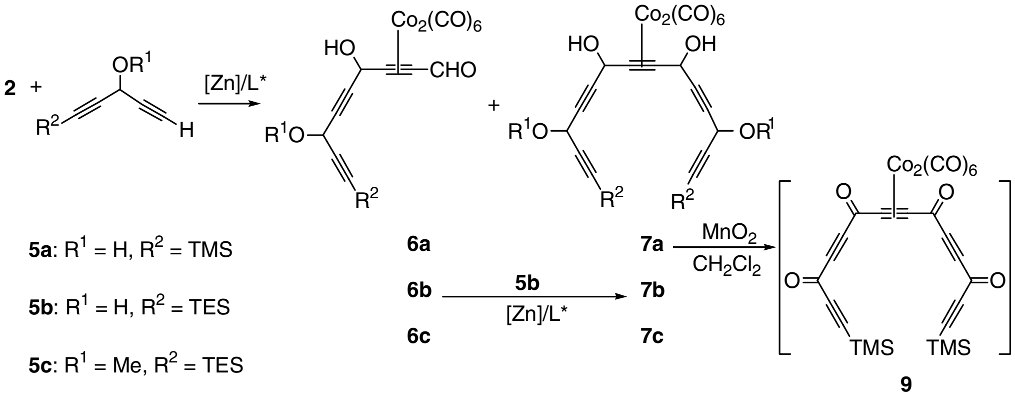
Figure 1. ORTEP view of **3** with atomic numbering.[10] Hydrogen atoms have been omitted for clarity. Selected bond distance (Å) and angles (deg) after averaging over crystallographically non-equivalents units: C(5)–C(6) 1.327(10); C(2,8)–C(3,9) 1.193(9); C(5,6)–Co(11,12) 1.942(6-7); C(2,9)–Si(1,10) 1.841(8); C(4,5)–C(5,6)-C(6,7) 140.933(3-6); C(4,7)–C(5,5)–Co(11,12) 134.42(5); Co(11)–C(5,6)–Co(12) 79.267(2).

the addition of alkyl- and aryl-lithium or -magnesium-bromide reactants,[3] no *meso* adduct **3** here could be detected in the NMR spectra of the crude material. According to NMR analysis, the reaction is thus diastereoselective (de $\geqslant 90\%$). The crystal structure ($P2$ space group) also indicated the presence of a single enantiomer with the *R* absolute configuration at both the carbinol groups of **3**. Since full control of the second attack by the remote first formed carbinolate group is highly unlikely,[3] and since no *meso* (*R*,*S*) isomer was observed (<5 % according to NMR), the *R* configurations of both the carbinol groups are likely independently induced by the sole (−)-*N*-methyl-ephedrine/alkynylzinc reactants.[11] Moreover, the (*R*,*R*) enantiomer observed in the single crystal of **3** shows that (−)-*N*-methyl-ephedrine induced the attack of the *re* face of both the aldehyde groups of **2**. The same sense of induction was observed for a simple ynal substrate (TMS–C$\equiv$C–CHO and H–C$\equiv$C–TES lead to the (*S*)-enantiomer of **5b** in 95% ee),[12] and for all other kinds of aldehyde substrates reported by Carreira et al. (in 90–99% ee).[7a,11]

Encouraged by this result, functional diynes **5a**–**c** were envisioned as terminal acetylenic substrates.[12] The further difficulty introduced by the functionality is actually doubled by the stereogenicity of the substrates, namely by the competition of both reactants for controlling the stereochemistry. Preliminary investigations of this double challenge are reported.

The chiral diynes **5a**–**c** could be prepared from silylpropynals in either racemic (using alkynyl magnesium-bromides) or scalemic forms (via an adapted zinc/*N*-methyl-ephedrine procedure).[7,12] Starting from racemic diynes **5a**–**c**, carbinol-skipped triynal complexes **6a**–**c** and pentayne complexes **7a**–**c** were isolated as mixtures of stereoisomers in moderate yields (Scheme 2). These complexes slowly decompose in air, but despite the expected protecting effect of the ether group, compounds **6c** and **7c** are less stable than **6a**–**b** and **7a**–**b**, respectively. The hydroxyl groups of the diynes had a marked effect on the reactivity as well (Table 1). When diynols **5a** and **5b** were used as the substrates, triynals **6a** and **6b** were the major products (in 46% and 53% yield, respectively), and pentaynes **7a** and **7b** were separated in low yield (Table 1, entries 1–2). By contrast, when the hydroxyl group was protected with a methyl group in **5c**, yield of **7c** increased to 23% (Table 1, entry 3). Nevertheless, the pentayne complex **7c** could not be isolated when the **2**:**5c** ratio was decreased from 1:2 to 1:1.2 (Table 1, entry 5). In general, the second attack is thus much slower than the first one, likely due to deactivation of the remaining carbaldehyde group in [Zn]-**6** aggregates.

We also checked that the double alkynyl addition to both the carbaldehyde groups can be carried out step by step. Reaction of triynal **6b** with diynol **5b** indeed afforded a second sample of pentayne **7c** in 12% yield,



Scheme 2. Generalization of the procedure to diyne reactants for the preparation of secondary carbinol-skipped oligoyne complexes, and a tetraone derivative thereof.

Table 1. Addition of diynes **5** to cobalt complex **2**[a]

Entry	Diyne substrate	Yield of **6** (%)[b]	Yield of **7** (%)[b]	**6**:**7**
1	*rac*-**5a**	46	8	6:1
2	*rac*-**5b**	53	3	18:1
3	*rac*-**5c**[c]	46[d]	23[d]	2:1[d]
4	(+)-(*S*)-**5b**	44	2	22:1
5	*rac*-**5c**[e]	37	Traces	—

[a] All reactions run at rt with the ratio **2**:**5**:Zn(OTf)$_2$:ligand:Et$_3$N = 1:4:8.8:9.6:4.4.

[b] Isolated yield based on cobalt complex **2**.

[c] Ratio **2**:**5c**:Zn(OTf)$_2$:ligand:Et$_3$N = 1:2:4.2:4.4:2.2.

[d] Determined by ^{1}H NMR.

[e] Ratio **2**:**5c**:Zn(OTf)$_2$:ligand:Et$_3$N = 1:1.2:4.2:4.4:2.2.

while unreacted **6b** was recovered in 43% yield (Scheme 2).

The products **6** and **7** appear as single spots on TLC plates under various conditions, and the stereoselectivity of the reaction could not be determined: although slightly divided ^{13}C NMR signals of **6** and **7** suggest the presence of several diastereoisomers (for symmetry reasons, at most two for **6**, and six for **7**), these diastereoisomers could not be fully resolved by NMR spectroscopy. The reaction was also performed from a sample of (+)-(*S*)-**5b** of high enantiomeric purity (>95% ee):[12] whereas ^{13}C NMR analysis suggests that the monoadduct **6b** was now obtained as a single (dia)stereoisomer, the bis-adduct **7b** was still obtained as a mixture of diastereoisomers.[13]

Despite the stereochemical uncertainty, it must be kept in mind that the chemical synthesis of tri- and pentaynes skipped by secondary carbinol vertices has been long considered as challenging.[3,5,6] Moreover, the undetermined stereochemistry of the adducts can also be considered as provisional before oxidation of the carbinol vertices. The pentayne-tetraol **7a** was indeed oxidized to the peculiar tetraone **9** with activated MnO$_2$ at −30 °C (Scheme 2). The tetraone could be isolated in 87% yield by flash chromatography over neutral silica gel, but it turned out to be very instable, even under an argon atmosphere at low temperature. Hence, the tetraone **9** could only be characterized by ^{1}H NMR and IR spectroscopy ($\nu_{CoC\equiv O} = 2105$, 2066, 2035, $\nu_{CH=O} = 1636\ cm^{-1}$).

In view of future application in synthesis of oxy-pericyclynes, desilylation of carbinol-skipped triyne **3** was attempted with TBAF in THF between −80 and −20 °C. To our surprise, while cobalt carbonyl moieties were reported to be easily removed in the presence of TBAF at low temperature,[14] the desilylated complexes **4** and **8** were isolated in 41% and 24% yield, respectively (Scheme 1). When desilylation was performed at 0 °C, triyne **3** was found to decompose in a very short time.

In conclusion, the acetylene dicarbaldehyde complex **2** lends itself to enantioselective transformations of the organic ligand, while preserving the inorganic carbonyl ligands. The procedure applies to highly functional substrates, and affords complexes of novel skipped triynes and pentaynes bearing secondary dialkynyl carbinol functions. Despite their potential tautomeric instability, such functions occur in natural products and some representatives were recently found to exhibit high in vitro antitumoral activity.[15] Before tackling the synthesis of such promising molecules, efforts are in progress to improve yields and extend the procedure to cyclizing versions.

3. Typical experimental procedure (complexes 3 and 4)

A 30 mL flask was charged with Zn(OTf)$_2$ (1.454 g, 4.0 mmol) and (−)-*N*-methyl-ephedrine (0.753 g, 4.2 mmol) and purged with dry argon for 15 min. After the addition of CH$_2$Cl$_2$ (5 mL) and Et$_3$N (0.59 mL, 4.2 mmol), the mixture was vigorously stirred for 2 h at rt, and trimethylacetylene (0.41 g, 4.2 mmol) was syringed in one portion. After stirring for another 20 min, complex **2** (368 mg, 1.0 mmol) in dichloromethane (3 mL) was added. Complete conversion was checked by TLC, and the reaction mixture was quenched with saturated aqueous NH$_4$Cl (10 mL). The mixture was then extracted with diethyl ether (3 × 20 mL). The organic solution was washed with brine (2×10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by column chromatography (neutral silica gel, ethyl acetate/*n*-heptane 1:8) afforded bis-adduct **3** (212 mg, 38% yield) and mono-desilylated bis-adduct **4** (56 mg, 11% yield). Analytical data for **3**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.56 (d, 2H, $J = 6.2$ Hz); 2.81 (d, 2H, $J = 6.1$ Hz); 0.15 (s, 18H). ^{13}C NMR (62.9 Hz, $CDCl_3$) δ 198.6, 103.8, 95.8, 90.9, 63.6, −0.5. FTIR ($CDCl_3$) ν 3590, 3507, 2962, 2928, 2901, 2855, 2252, 2174, 2099, 2062, 2038, 1690, 1252, 1038 cm^{-1}. MS (DCI/NH_3): $m/z = 582$ ($[M+NH_4]^+$), 547 ($[MH-H_2O]^+$).

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Supplementary data

Experimental description and spectroscopical analyses of all new compounds described, X-ray crystal structure determination of complex **3**.

Crystallographic data (excluding structure factors) for the structure in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 279482. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.050.

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10. Crystal data for complex **3**. $C_{20}H_{22}Co_2O_8Si_2$, $(H_2O)_{1/6}$, $M = 567.43$ g mol^{-1}, monoclinic, $a = 12.866(2)$, $b = 11.919(1)$, $c = 14.197(2)$ Å, $\beta = 110.08(1)°$, $V = 2044.8(5)$ Å^3, $T = 180$ K, space group $P2$, $Z = 3$, $\mu(M_o\text{-}K_\alpha) = 1.342$ mm^{-1}, 15,696 reflections measured, 8370 unique ($R_{int} = 0.04$), 3683 reflections used in the calculations [$I > 1.8\sigma(I)$], $R1 = 0.0361$, $wR2 = 0.0348$.
11. The exact overall enantioselectivity could not be determined. Indeed, the strong absorbance of complex **3** precluded comparison of the optical rotation of single crystals with that of the averaged sample.
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13. At least two stereoisomers were detected in the bis-adduct **7b** (2% yield), suggesting that the configuration of (−)-*N*-methyl-ephedrine competes with that of (+)-**5b** or intermediate **6b** in the stereochemical control of the second attack (mismatch).
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