# Reactions of Cobalt-Complexed Acetylenic Aldehydes with Chiral (γ-Alkoxyallyl)boranes: Enantioselective Synthesis of 3,4-Dioxy 1,5-Enynes

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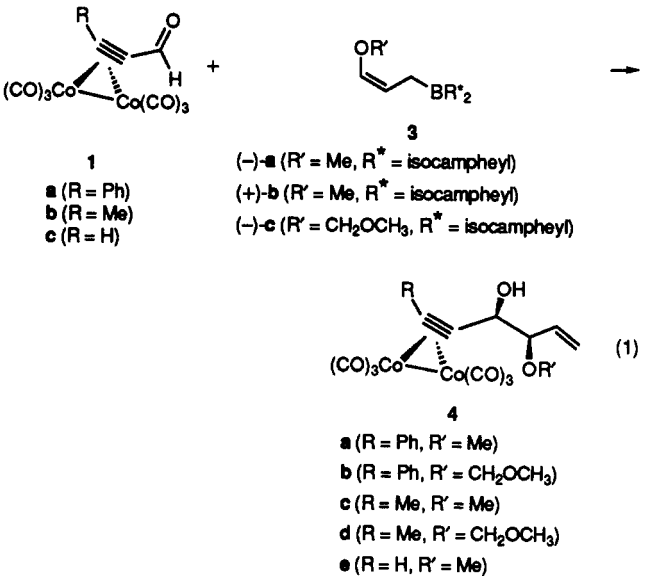
*Summary:* Whereas free acetylenic aldehydes react with (γ-alkoxyallyl)diisocampheylboranes **3** with poor efficiency (<10% yield) and limited enantioselectivity, the corresponding $-Co_2(CO)_6$ complexes **1** undergo efficient (65–76% yield), diastereoselective (88–>95% de), and enantioselective (>96% ee) coupling reactions with **3**, producing (3,4-dioxy 1,5-enyne)$Co_2(CO)_6$ **4**.

The stereocontrolled construction of acyclic structures containing multiple asymmetric centers is critical for the efficient synthesis of highly functionalized, biologically active molecules.[1] Previous studies in our laboratory[2] and others[3] have demonstrated that dicobalt hexacarbonyl complexes of acetylenic aldehydes and acetals, (RC≡C-CHO)$Co_2(CO)_6$ (**1**) and [RC≡CCH(OR)$_2$]$Co_2(CO)_6$ (**2**), undergo highly diastereoselective aldol reactions with silyl enol ethers. In a related development of Roush and Park[4] found enhanced *enantioselectivity* in the asymmetric allyl- and crotylboration of **1** and homologous 3-yn-al complexes relative to reactions of uncomplexed acetylenic aldehydes. Toward the goal of developing enantioselective routes to polyfunctional building blocks using Co-based technology, we report herein the results of a preliminary study of the reactions of (γ-alkoxyallyl)diisocampheylboranes **3**[5] with acetylenic aldehydes and their $-Co_2(CO)_6$ complexes. Whereas the free acetylenic substrates react with poor efficiency and limited enantioselectivity with **3**, the corresponding Co derivatives undergo efficient regio-, diastereo-, and *enantio*selective reactions, producing 3,4-dioxy 1,5-enynes (after demetalation). The latter are attractive chiral building blocks for the asymmetric synthesis of natural products possessing multiple adjacent stereocenters.

[(*Z*)-γ-Alkoxyallyl]diisocampheylboranes **3a–c** were prepared by metalation of the corresponding allyl ethers and subsequent treatment with *B*-methoxy-(+)- or -(−)-diisopinocampheylborane.[5] The reactions of 2-butynal and 3-phenylpropynal with borane **3a** were carried out by treatment of the borane with 1.3 equiv of $BF_3{\cdot}Et_2O$ in THF at −78 °C (5 min) followed by addition of the aldehyde. After 3–4 h at −78 °C and warming to room temperature, workup with ethanolamine or aqueous ammonium chloride and flash chromatography gave the expected 3,4-dioxy 1,5-enyne derivatives but in very poor yields (5–10%). This appears to be the result of polymerization of the acetylenic aldehydes under the reaction conditions. NMR and GC/MS analysis suggested the presence of single diastereomers, but chiral GC[6] and Mosher ester[7] analysis of the products indicated only a moderate enantioselectivity for the reactions (ca. 65% ee).

Reactions of the corresponding $-Co_2(CO)_6$ derivatives of the aldehydes provided a dramatic improvement in efficiency and selectivity. The aldehyde complexes **1a–c** were prepared in good yield by complexation of the readily available acetylenic acetals ($Co_2(CO)_8$/20 °C) followed by Amberlyst 15-catalyzed hydrolysis (acetone/$H_2O$) at room temperature. The reactions of **1** with allylboranes **3a–c**, when carried out as for the free aldehydes, gave dark red (3-alkoxy-4-hydroxy 1-en-5-yne)$Co_2(CO)_6$ complexes **4** in good yield[8] (eq 1, Table I).




The $^1H$ and $^{13}C$ NMR spectra of the product complexes **4a–d** indicated the presence of a single diastereomer (>97%) in all but one case (entries 1–5) which was tentatively assigned the *syn* stereochemistry based on literature precedent.[9] This assignment was confirmed by an X-ray structure determination of the major isomer of **4e**[10] (entry 6). The somewhat lower diastereoselectivity obtained with complex **1c** appears to reflect its lesser steric demand derived from the bent geometry of the coordinated

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(6) Cyclodextrin B column (30 m), 70 °C (5 min) → 220 °C 5°/min.

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(8) Appropriate spectroscopic and analytical data were obtained for new compounds; these are included along with representative procedures as supplementary materials.

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**Table I. Preparation of (*syn*-3,4-Dioxy 1,5-enyne)$Co_2(CO)_6$**

| entry | aldehyde complex | borane | product complex | % yield[a] | % de[b] | % ee |
|---|---|---|---|---|---|---|
| 1 | PhC≡CCHO, $Co_2(CO)_6$ | 3a | 4a | 75 | >95 | >98[c] |
| | 1a | | | | | |
| 2 | 1a | 3b | 4a[d] | 75 | >95 | >98[c] |
| 3 | 1a | 3c | 4b | 62 | >95 | >96[e] |
| 4 | $CH_3C$≡CCHO, $Co_2(CO)_6$ | 3a | 4c | 73 | >95 | >96[e] |
| | 1b | | | | | |
| 5 | 1b | 3c | 4d | 65 | >95 | >96[e] |
| 6 | HC≡CCHO, $Co_2(CO)_6$ | 3a | 4e | 76 | 88 | >96[e] |
| | 1c | | | | | |

[a] Yield after chromatography. [b] Determined by $^1H$ and $^{13}C$ NMR. [c] Determined by chiral GC on cyclodextrin. [d] Enantiomer of product 4a from reaction of 1a with 3a. [e] Determined by $^{19}F$ NMR of Mosher ester derivative.

alkyne.[11] Similar findings in the reactions of silylenol ethers with 1 and 2[2,3] and the related $[(RC{\equiv}CCR_2)Co_2(CO)_6]^+$ complexes[12] have been noted. Moreover, analysis of 4 using chiral NMR shift reagent Eu(hfacam)$_3$ pointed to formation of a single enantiomer (≥95%) in each case. This conclusion was confirmed by a combination of Mosher ester $^{19}F$ NMR characterization and chiral GC (cyclodextrin B) studies of the demetalated compounds (*vide infra*). Treatment of (+)- or (−)-borane **3a,b** with **1a** (entries 1 and 2) gave opposite enantiomers of comparable optical purity. Although the reactions with MOM-derivative **3c** resulted in somewhat lower yields, the high *syn* selectivity and enantioselectivity were still preserved. It is perhaps noteworthy that the enantioselectivities found in the present study are somewhat higher than those reported by Roush and Park for the corresponding reactions of 1 with tartrate-derived crotylboranes.[4a] However, whether this modest effect is derived from differences in the chiral group of the borane, the γ-alkoxy vs alkyl group, or the differing acetylenic substituents is unclear.

Decomplexation of the adducts 4 was accomplished conveniently in high yield (73–78%) and with no loss in enantiomeric purity following their treatment with $(NH_4)_2Ce(NO_3)_6/Et_3N$/acetone (−78 to +20 °C).[8] The resulting 3,4-dioxy 1-en-5-ynes are very attractive synthetic intermediates for subsequent regio- and stereocontrolled transformation by virtue of their differentiated unsaturated C–C units and O-functions.

In conclusion, we note the key roles played by the $-Co_2(CO)_6$ moiety in these transformations. First, it serves a protective function for the triple bond, blocking potential competing addition/polymerization reactions. Second, there is a considerable stereocontrolling effect of complexation which presumably reflects the greatly increased steric demand of the bulky, bent $-(alkynyl)Co_2(CO)_6$ moiety relative to the linear, "skinny" alkyne. Efforts to expand the scope of this reaction and to demonstrate the synthetic potential of the derived 3,4-dioxy 1-en-5-ynes in natural products synthesis are under investigation.

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**Supplementary Material Available:** Experimental procedures and compound characterization data (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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