

# The Dicobalt Hexacarbonyl(alkyne) Moiety as a Stereocontrol Element in Intramolecular Friedel–Crafts Alkylations<sup>1</sup>

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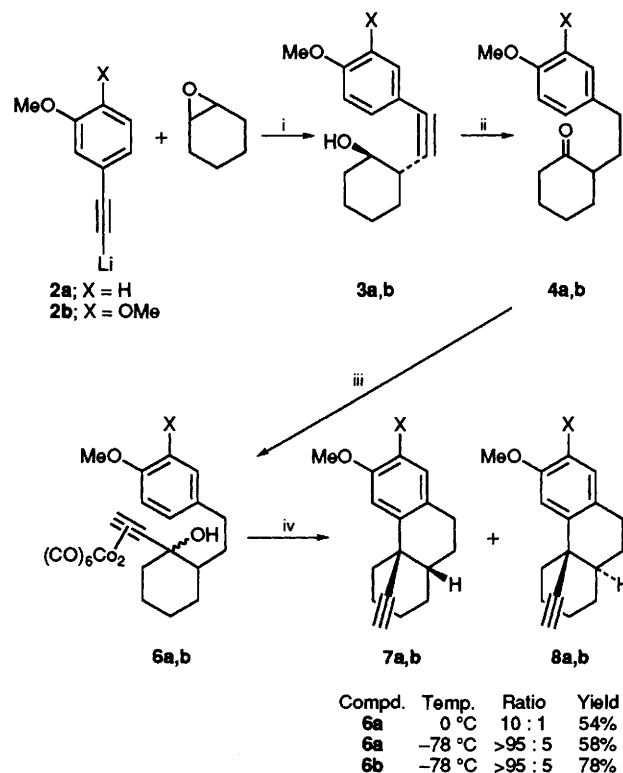
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A dicobalt hexacarbonyl(alkyne) moiety is used as a stereocontrol element in Friedel–Crafts cycloalkylation reactions that deliver *cis*-4a-ethynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrenes exclusively.

As part of an effort to develop a new, general synthesis of the medicinally important morphinans<sup>2</sup> (Fig. 1), we have been investigating intramolecular Friedel–Crafts reactions as a way of preparing ethynyloctahydrophenanthrenes, e.g. **1a**. These previously unknown compounds contain the entire carbon skeleton necessary to generate the morphinan nucleus. The issue of paramount importance here is the stereochemistry at the *B*–*C* ring structure; we need to be able to synthesize **1a** with *cis*-stereochemistry. This stereochemical issue has been well-studied in cycloalkylations of this type, largely in the context of diterpenoid synthesis;<sup>3</sup> in general the phenanthrene with *trans*-stereochemistry predominates. Under certain conditions, however, significant amounts of the *cis*-isomer can be obtained. For example, Coxon and Steel<sup>4</sup> have shown that the cycloalkylation of 2-methyl-1-(2-phenylethyl)cyclohexanol, when initiated with superacids at  $-78^\circ\text{C}$ , delivers the *cis*-isomer **1b** ( $X = \text{H}$ ) predominantly. It is clear from these studies that the *cis*-stereoisomer is the kinetic product. The 75:25 ratio of *cis/trans*-**1b** obtained by these investigators appears to be the highest achieved in an intramolecular Friedel–Crafts reaction that gives a 4a-substituted-1,2,3,4,4a,9,10,10a-octahydrophenanthrene. For our purposes we required a cyclization reaction that produced a much higher *cis*:*trans* ratio.

Our recent experience with cobalt-stabilized prop-2-ynyl cations in intramolecular Friedel–Crafts reactions<sup>5</sup> coupled with an appreciation for the conformational tendencies in the decalin series<sup>6</sup> led us to consider employing the dicobalt hexacarbonyl(alkyne) moiety as a stereo-directing group.<sup>7</sup> It was felt that the organocobalt cluster would not only permit cation generation and subsequent ring closure at low temperatures, *i.e.* under kinetic control, but through simple steric interactions or possibly template effects, would promote the formation of *cis*-**1a**, perhaps to the exclusion of the *trans*-isomer. To test our proposal, the chemistry depicted in Scheme 1 was carried out.

The lithium anions **2a,b**, generated from the corresponding alkynes with butyllithium, were first treated with boron trifluoride–diethyl ether at  $-78^\circ\text{C}$ , and then with cyclohexene oxide to give, after quenching, alkynols **3a,b** in acceptable yield.<sup>8†</sup> Hydrogenation of the triple bond in **3a,b** followed by oxidation with pyridinium chlorochromate (PCC) gave ketones **4a,b** in excellent yields for the two steps. Reaction of **4a,b** with ethynylmagnesium bromide produced the corresponding prop-2-ynyl alcohols **5a,b** (74–86%) as *ca.* 1:1 mixture of diastereoisomers. Admixture of the alcohols with dicobalt octacarbonyl afforded good yields of the cyclization substrates **6a,b**. Treatment of a solution of **6a** in dichloro-



**Scheme 1** Reagents and conditions: i,  $\text{BF}_3\cdot\text{OEt}_2$ , tetrahydrofuran (THF),  $-78^\circ\text{C}$ , then  $\text{NH}_4\text{Cl}$  (aq.); **3a**, 65%; **3b**, 85%; ii,  $\text{H}_2$ , Pd/C, hexanes, then PCC,  $\text{CH}_2\text{Cl}_2$ , 80–85% overall; iii,  $\text{HC}\equiv\text{CMgBr}$ , THF,  $0^\circ\text{C}$ , 74–86%, then  $\text{Co}_2(\text{CO})_8$ ,  $\text{CH}_2\text{Cl}_2$ , 81–84%; iv,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$ , then  $\text{Fe}(\text{NO}_3)_3$ , MeOH,  $0^\circ\text{C}$

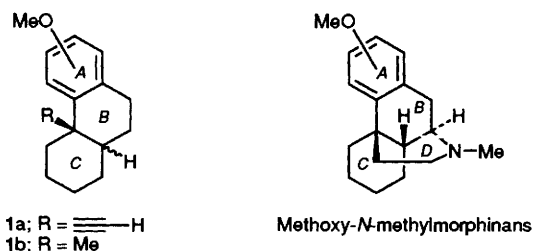


Fig. 1

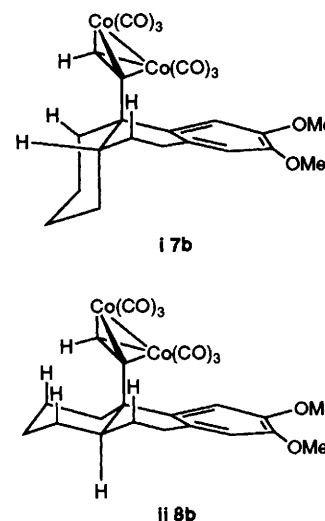


Fig. 2 *i*, *cis*, and *ii*, *trans*, cobalt-complexed ethynylphenanthrenes **7b** and **8b** respectively

methane at 0 °C with boron trifluoride–diethyl ether, followed by immediate decomplexation with iron(III) nitrate in methanol at 0 °C, gave a 10:1 mixture of ethynyloctahydrophenanthrenes **7a** and **8a** in an overall yield of 54% for the two steps. When this reaction was performed at –78 °C, a single regio- and stereo-isomer was obtained as ascertained by high-field <sup>1</sup>H NMR spectroscopy (58% yield, mp 70–72 °C). This compound was tentatively assigned structure **7a**. Subjecting **6b** to the same conditions again produced a single regio- and stereo-isomer of the phenanthrene product as a white solid (mp 103–106 °C) in 78% yield. A single crystal of this material was obtained and an X-ray analysis performed.‡ The results of this study clearly showed the *cis*-stereochemistry at the ring juncture, thereby confirming our assignments of **7** and **8**. Interestingly, reaction of the cobalt-free prop-2-ynyl alcohol **5b** under conditions identical to those above does not give any of the phenanthrene products. Thus, use of the cobalt-stabilized prop-2-ynyl cations appears to be essential if these Friedel–Crafts reactions are to proceed in good yield.

The cobalt-mediated cycloalkylation reactions described appear to be the first to give a 4a-substituted-octahydrophenanthrene with exclusive *cis*-stereochemistry. The reasons for this stereochemical outcome are not clear; given the fluxional nature of the cobalt-stabilized prop-2-ynyl cation,<sup>9</sup> and its unknown conformation in this particular system, any explanation given for the stereochemical result must be considered tentative. We offer the following simple rationale as a beginning, however. Molecular models show that steric interactions exist between the axial organocobalt cluster and the three axial hydrogens in the dicobalt hexacarbonyl complex of **8** (ii, Fig. 2). In the cobalt complex of the *cis*-isomer **7** (i, Fig. 2), these interactions should be less severe since in the most stable conformation, of the two possible, there is only a single interaction between the cobalt moiety and an axial hydrogen. To the extent that these interactions are reflected in the transition states leading to the  $\sigma$ -complexes of the respective cyclization products, one would expect a stereochemical bias in favour of cobalt-complexed **7**. Note that this explanation is essentially a product-based analysis and does not take into account any conformational preferences of the cobalt-stabilized cations; these may play an important role in determining stereochemistry. Experimental and computational studies are currently being pursued that should help to sort out the various features responsible for the particular stereochemical processing observed during these cycloalkylation reactions.

In summary, we have used the dicobalt hexacarbonyl-(alkyne) moiety as a stereocontrol element in intramolecular Friedel–Crafts alkylations. The products, methoxy-substituted, *cis*-ethynyloctahydrophenanthrenes **7a,b**, are obtained in good yield from the cobalt-complexed prop-2-ynyl alcohols **6a,b**. Conversion of **7a,b** to morphinans is currently being pursued.

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## Footnotes

† All new compounds, except **6a,b**, were characterized by <sup>1</sup>H NMR, IR, and mass spectral data. Cobalt complexes **6a,b** were characterized by IR spectroscopy only.

‡ *Crystal data*: triclinic, space group  $P\bar{1}$ ,  $a = 7.911(3)$ ,  $b = 8.894(2)$ ,  $c = 10.694(2)$ ,  $\alpha = 94.01(2)$ ,  $\beta = 98.78(2)$ ,  $\gamma = 94.55(3)^\circ$ ,  $Z = 2$ , Mo-K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ),  $F(000) = 790$ , Siemens R3m/V diffractometer, 2538 reflections with  $F > 4\sigma(F)$ ,  $R = 0.051$ ,  $R_w = 0.068$ . Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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