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Cobalt π-Cations in Carbocyclic Ring Constructions

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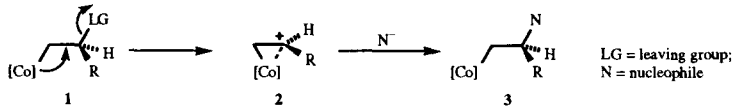
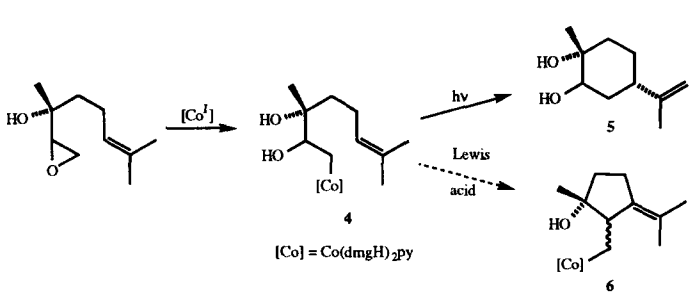
Abstract: In a combination of cobalt-mediated cationic and free radical chemistry, treatment of the allyl silane substituted β-hydroxycobaloxime **13** with *p*TSA led predominantly to the *trans*-disubstituted cyclopentane **14**, which on irradiation with TEMPO produced **15**. In a similar manner, the cobaloxime **18** was cyclised to **19** in the presence of *p*TSA which, on irradiation with a sunlamp then underwent radical mediated cyclisation to the substituted indane **20**. Copyright © 1996 Elsevier Science Ltd

The term "cobalt π-cation" has been used to describe those intermediates involved in nucleophilic substitution reactions at β-centres in organocobalt compounds. During fundamental studies of the mechanism of action of coenzyme B_{12} dependent enzymes, Golding *et al.*,[1] and others,[2] have shown that these S_N1 like reactions (Scheme 1) proceed with retention of configuration at the β-centre, implying a double inversion sequence orchestrated by the neighbouring cobalt centre *via* a cobalt π-cation species **2**, *i.e.* **1**→**2**→**3**. Over the



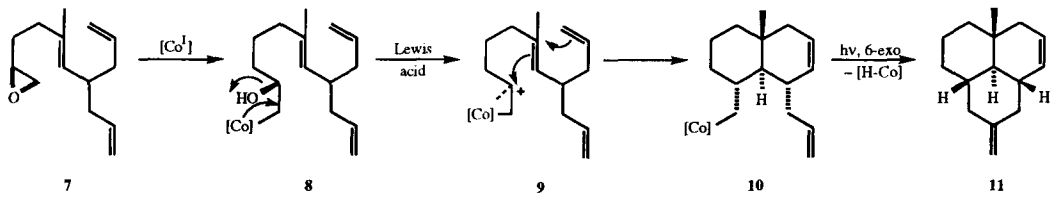
Scheme 1

past few years we have described the application of a wide range of carbon-centred free radical reactions in synthesis, based on homolysis of the carbon-cobalt bond in organocobalt compounds.[3] Thus we have exploited the reactions of alkyl, acyl, aryl, vinyl and carbamoyl organocobalt species, and applied them in the synthesis of functionalised cyclic and acyclic compounds, including polycycles[4] and target natural products *e.g.* thienamycin[5] and forskolin.[6] We have also shown that β-hydroxycobaloximes *e.g.* **4** are smoothly produced when epoxides are treated with cobalt(I) oxime, and that these reagents undergo radical-mediated cyclisations onto proximal olefin bonds leading to carbocycles, *e.g.* **4**→**5** (Scheme 2).[7]



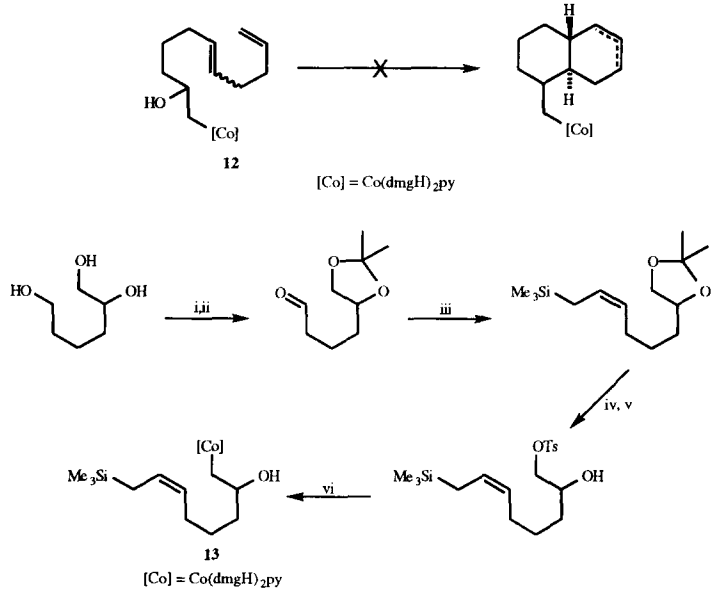
Scheme 2

These interests in radical-based organocobalt chemistry, together with our other contemporaneous interests in both electrophilic[8] and radical-based biomimetic syntheses[9] of polycyclic terpenes and steroids begged the question: is it possible to complement the free radical and the cationic chemistry associated with alkylcobalt reagents and design a new approach to the stereocontrolled synthesis of polycyclic structures based on:(i) cobalt(I) mediated ring opening of an epoxide, *viz.* **7**→**8**, followed by (ii) generation of a cobalt π-cation intermediate **9** and intramolecular electrophilic (poly)cyclisation of this species with an adjacent nucleophilic alkene bond, leading to **10**; and finally (iii) complete the cascade of ring constructions by carbon→cobalt bond homolysis in **10** and subsequent cyclisation, *i.e.* **10**→**11** (Scheme 3)? The studies described in this *Letter* summarise the outcome of our initial foray with this proposal.[10]



Scheme 3

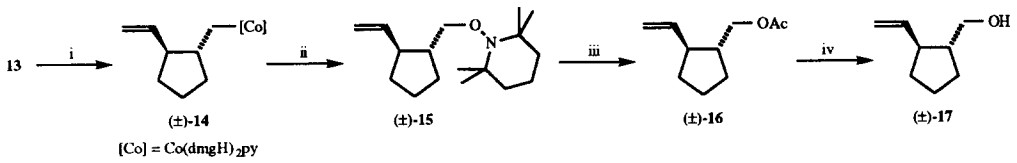
Thus, we began our study by examining the ability of the alkene bond in the β-hydroxycobaloxime **4** we had described earlier, to participate in a cobalt π-cation induced cyclisation. Much to our chagrin treatment of **4** with a range of protic and Lewis acids, *i.e.* *p*TSA, $BF_3.OEt_2$, *p*PTS, under a variety of conditions failed to provide any evidence of the formation of the expected cyclic product **6**; instead only starting material was recovered in these reactions. A similar result was obtained with the analogous diene alcohol **12** as a substrate, when a complex mixture of acyclic materials was formed, leaving us with the early conclusion that the alkene bonds in **4** and **12** were probably insufficiently nucleophilic (or the cobalt π-cation was insufficiently electrophilic) to allow the reaction partners to participate in an intramolecular S_N process. We decided therefore to examine the scope for the more nucleophilic allyl silane group in the aforementioned cyclisations and, with this in mind, we prepared the β-hydroxycobaloxime **13**, as summarised in Scheme 4.[11]



Reagents: i. *p*TSA, acetone, 100%; ii. PDC, CH_2Cl_2, 77%; iii. "$Ph_3P{=}CHCH_2SiMe_3$",[12] 62%; iv. conc. HCl, H_2O, MeOH, $CHCl_3$, 47%; v. *p*TsCl, py, CH_2Cl_2, 70%; vi. $NaCo^I(dmgH)_2py$, 40%

Scheme 4

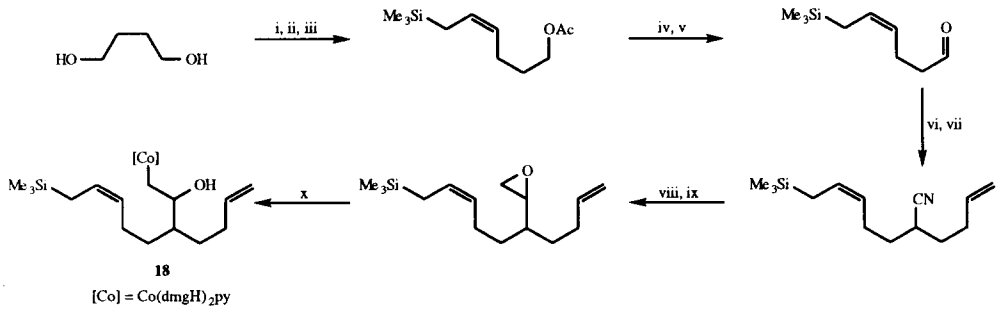
Gratifyingly, when a solution of the alkylcobaloxime **13** was treated with either $BF_3.OEt_2$ in dichloromethane or with *p*TSA in tetrahydrofuran at –78 °C it underwent a smooth cyclisation, presumably *via* the cobalt π-cation intermediate and produced predominantly the *trans*-disubstituted cyclopentane **14** (*trans*:*cis* 5:1) in 65% yield. The *trans*-geometry assigned to **14** followed as a result of complementary radical chemistry leading to a synthesis of the known alcohol **17**.[13] Thus, irradiation of a solution of the cobaloxime **14** in benzene containing TEMPO, with a sunlamp resulted in its smooth conversion into the substituted hydroxylamine **15** in 96% yield. Reductive cleavage of **15** using Zn/HOAc, followed by saponification of the resulting acetate **16** then produced the known *trans*-carbinol **17** which displayed spectroscopic data identical with those published in the literature (Scheme 5).[13]



Reagents: i. $BF_3.OEt_2$, CH_2Cl_2 or *p*TSA, THF, –78 °C, 65%; ii. TEMPO, PhH, hν, rt, 96%; iii. Zn, AcOH, 100 °C, 49%; iv. K_2CO_3, MeOH, 61%

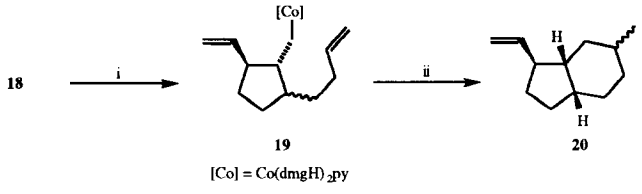
Scheme 5

Encouraged by this result, we next prepared the diene substituted β-hydroxycobaloxime **18**, in order to examine its anticipated cascade (cationic - radical) cyclisation to the substituted perhydroindane **20**. The cobaloxime **18**, produced as a mixture of diastereoisomers, was prepared starting from 1,4-butanediol, as summarised in Scheme 6. Treatment of **18** with *p*TSA in tetrahydrofuran, once again resulted in smooth cationic cyclisation involving the allyl silane double bond to produce a mixture of but-3-enyl side chain epimers of the *trans*-vinyl/methylcobaloxime substituted cyclopentane **19**, in 60% yield. Irradiation of a solution of **19** in benzene, using light from a conventional sunlamp, then led to a mixture of diastereoisomers of the corresponding indane (**20**, 45%).[14]



Reagents: i. NaH, AcCl, 71%; ii. PDC, CH_2Cl_2, 71%, iii. "$Ph_3P{=}CHCH_2SiMe_3$", 60%; iv. K_2CO_3, MeOH, 62%; v. PDC, CH_2Cl_2, 55%; vi. Mg, 4-bromobut-1-ene, 55%; vii. $MeSO_2Cl$, Et_3N then NaCN, DMSO, 60 °C, 60%; viii. DIBAL, –78 °C, H_3O^+, 67%; ix. $Me_3S^+I^-$, *n*BuLi, 50%; x. $NaCo^I(dmgH)_2py$, 45%

Scheme 6

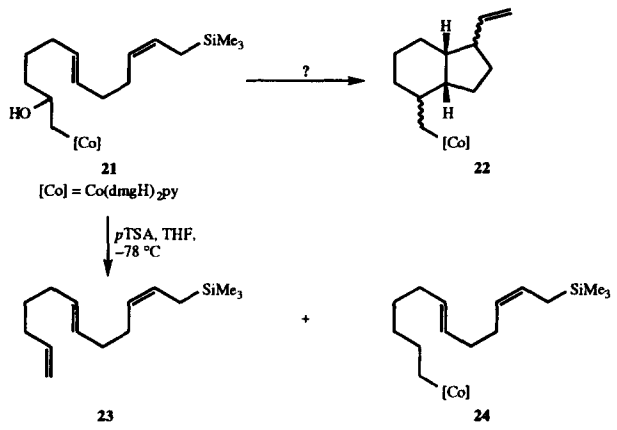


Reagents: i. *p*TSA, THF, –78 °C, 60%; ii. hν, PhH, rt, 45%

Scheme 7

In an attempt to form a perhydroindane in one step *via* a cobalt π-cation, using an allyl silane and a β-hydroxycobaloxime separated by an additional alkene bond, we also synthesised the substrate **21**. However, treatment of **21** with *p*TSA did not lead to the hoped-for substituted perhydroindane **22**, but instead led only to the products **23** (28%) and **24** (34%) resulting from β-elimination (also termed "alkene decomplexation")[10] and from hydride quench respectively in the cobalt π-cation intermediate produced from the starting material (Scheme 8).

Similar to the substrates **4** and **12** it therefore seems that an unactivated alkene is not able to participate in cobalt π-cation mediated carbocyclic ring constructions of the type depicted in Scheme 3, whereas allyl silanes and presumably other activated alkenes are perfectly acceptable partners. Further studies are now in progress with alternate carbon nucleophiles directed towards alternative ring constructions.



Scheme 8

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14. We presume that the modest yield of 45% reflects the fact that only the major but-3-enyl side chain epimer of **19** undergoes cyclisation to the *cis*-ring fused perhydroindane **20**. The reductive termination of this radical cyclisation reaction, **19**→**20**, was somewhat surprising, but is not unprecedented (see under ref. 3 above).

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