Tetrahedron Letters, Vol. 33, No. 20, pp. 2851-2854, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Cascade Cobalt Group Transfer - Radical Trapping - Tandem Radical Cyclisation Reactions in Synthesis

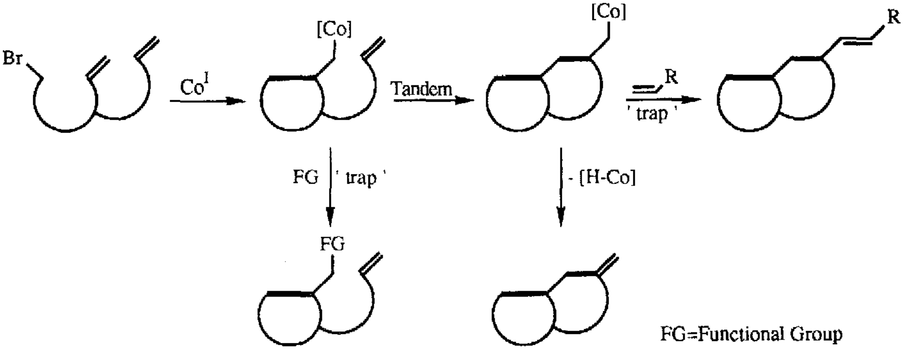
Amjad Ali, David C. Harrowven and Gerald Pattenden*

Department of Chemistry, The University, Nottingham NG7 2RD

Key Words: Organocobalt compounds; radical cyclisation reactions; cascade tandem processes.

Abstract: *Cobalt mediated tandem radical cyclisations, viz* ***(1)*** *→* ***(3)****,* ***(5)*** *→* ***(7)****,* ***(10)*** *→* ***(13)****, can be carried out in sequence with isolation of intermediate organocobalt reagents, i.e.* ***(2)****,* ***(6)****,* ***(11)****, or alternatively in a 'one-pot' operation. In the presence of reactive radical trapping agents (e.g.* $^3O_2$*, TEMPO) the intermediate organocobalt reagents undergo functional group exchange, [e.g.* ***(11)*** *→* ***(15)*** *and* ***(14)*** *respectively], whereas in the presence of less reactive styrene, a cascade of cobalt group transfer-radical trapping-tandem radical cyclisation - dehydrocobaltation reactions result allowing, for example, the five step 'one-pot' synthesis of* ***(12)*** *from* ***(10)*** *in 20% overall yield.*

Current literature bears ample witness to the explosive development that has taken place over the past decade in the applications of a wide array of radical centred reactions in modern synthesis. Although several contemporary issues address aspects of stereoselectivity in radical carbon-to-carbon (and other) bond forming reactions,[1] an equally large amount of attention is currently being given to the demanding problem of effecting consecutive radical carbon-to-carbon bond forming reactions, in a controlled manner leading, for example, to functionalised ring-fused carbo- and heterocyclic systems.[2] In recent publications, we have described the development and use of a wide range of alkyl, acyl, vinyl and carbamoyl cobalt reagents in radical carbon-to-carbon and carbon-to-heteroatom bond forming reactions, including ring synthesis.[3] One of the special features that distinguishes these cobalt-mediated radical carbon-to-carbon bond forming reactions from most other radical based methods (*e.g.* using Bu_3SnH, R_3SiH) is that they proceed with transfer of the cobalt group from the precursor molecule to the product molecule leading to a new cobalt-functionalised molecule. This molecule is then available for further use in synthesis, *e.g.* by dehydrocobaltation leading to an alkene product, or by interception with an external radical trapping agent. We now show how we have developed this chemistry to effect consecutive cobalt-mediated radical cyclisation reactions, in a controlled manner, allowing trapping and interception of intermediate organocobalt intermediates, leading to functionalised mono and bicyclic systems (see Scheme 1).

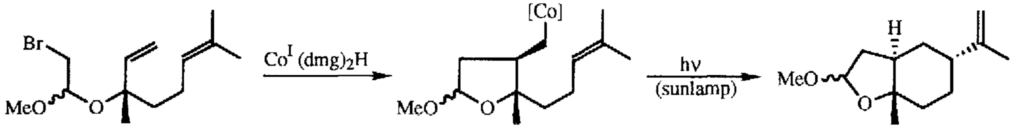


FG=Functional Group

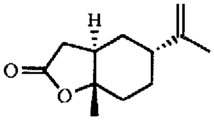
Scheme 1

We first examined the cobalt-mediated tandem radical cyclisation of the bromoacetal (**1**) derived from (±)-linalool.[4] Thus, treatment of a mixture of diastereoisomers of (**1**) with cobalt (I) dimethylglyoxime (from $CoCl_2$, dimethylglyoxime, in $MeOH$-$NaOH$-C_5H_5N, under N_2) at 0 - 25°C for 3h resulted in exclusive 5-*exo*-trig cyclisation leading to the tetrahydrofuranyl methyl cobaloxime (**2**), as a stable orange powder in 60% yield.[5,6] When a solution of (**2**) in dry, degassed benzene was irradiated with an ultraviolet sunlamp for 18h, it was then found to undergo a second, equally smooth, 6-*exo*-trig cyclisation, which was accompanied by dehydrocobaltation, producing the *trans*-ring fused bicycle (**3**) in a satisfying 85% yield.[7] The sequence leading from the bromoacetal (**1**) to the bicycle (**3**) can also be carried out in a 'one-pot' operation, although the overall yield is lower. Hydrolysis and *in situ* oxidation of (**3**) in the presence of Jones' reagent then provides the bicyclic lactone (**4**; 66%).

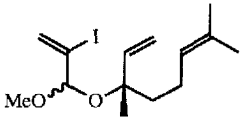
In a similar manner, treatment of a solution of the vinyl iodide (**5**)[8] in tetrahydrofuran, with cobalt (I) salophen (from Co(II) salophen, 1% NaHg; THF, N_2, 25°C) led to the formation of the intermediate cobalt salophen (**6**; 50%) which on irradiation gave the corresponding bicycle (**7**;85%).



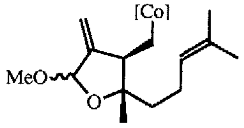
1 **2** **3**



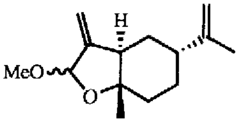
4



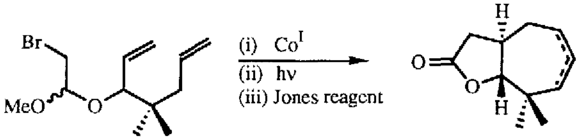
5



6



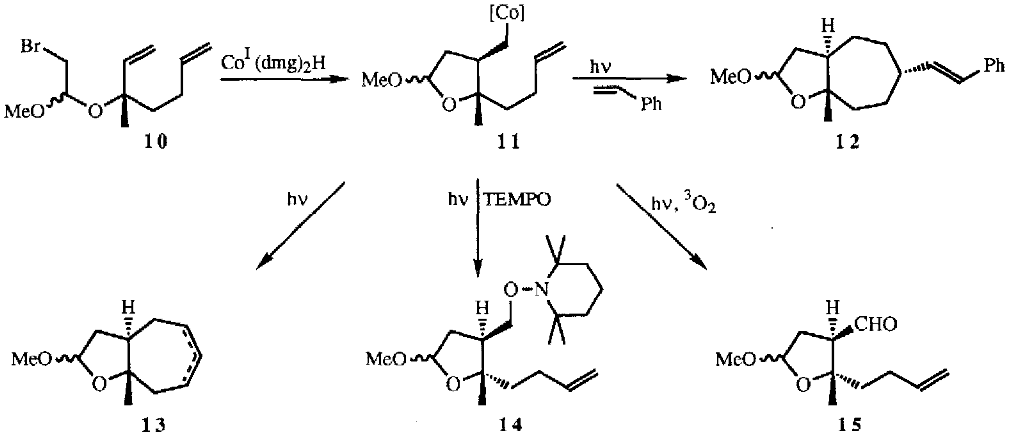
7



8 **9**

In order to explore further synthetic applications and examine stereochemical features of the reaction sequence (**1**) → (**2**) → (**3**) in more detail, we next investigated the tandem cyclisation and radical trapping possibilities of the substrate (**10**) which incorporates only mono-substituted carbon-to-carbon double bonds. Thus, treatment of the bromo-acetal (**10**) derived from hepta-1,6-dien-3-ol with cobalt (I) dimethylglyoxime in MeOH at 0-25°C, similar to (**1**), first led to the corresponding furan cobaloxime (**11**) in a pleasing 80% yield. Furthermore, when a solution of (**11**) in benzene was irradiated with a conventional sunlamp it underwent smooth cyclisation and dehydrocobaltation leading to a mixture of alkene positional isomers of a bicyclic product in a combined yield of 58%. Spectroscopic data quickly established that this bicycle had structure (**13**), showing that the second ring, surprisingly, had been formed as a result of exclusive 7-*endo* trig cyclisation.[9] As in the earlier examples, the tandem cyclisation of (**10**) to (**13**) could be carried out in a one-pot sequence, simply by treating the bromoacetal (**10**) with Co(I) cobaloxime, allowing the formation of (**11**), and then irradiating the same solution. A similar sequence of tandem 5-*exo* then 7-*endo* trig cobalt mediated radical cyclisations from the bromodiene (**8**), in the presence of cobalt (I) dimethylglyoxime led to the analogous 5,7-fused bicyclic lactone (**9**) (50% overall).

Interestingly, when a solution of the tetrahydrofuranylmethyl cobaloxime (**11**) in benzene was saturated with oxygen and then irradiated with a sunlamp, the only product isolated (~30%) was the aldehyde (**15**), which is presumably formed by oxidative elimination involving a peroxycobalt intermediate. Likewise, irradiation of (**11**) in the presence of the equally potent radical trapping agent tetramethylpiperidine oxide (2 equivs) led to the substituted hydroxylamine (**14**; ~25%) as an unstable yellow oil.



Scheme 2

Finally, in order to demonstrate a sequence of tandem cyclisation **followed** by radical trapping, we generated the cobaloxime (**11**), and then irradiated it *in situ* in the presence of the less reactive radical trapping agent styrene. This 'cascade' reaction, led in one pot, to the product (**12**) resulting from tandem 5-*exo*-7-*endo* cyclisation,[*cf.* to (**13**)], with *in situ* product radical trapping by styrene terminating in dehydrocobaltation, in an overall 30-50% yield. Further work is now in progress to develop this cascade cobalt group transfer-radical trapping-tandem radical cyclisation sequence, with more elaborate ring-fused carbo and heteropolycycles.

Acknowledgements

We thank the S.E.R.C. for a CASE award studentship (to A.A.) and Rhône-Poulenc Rorer for generous financial support.

References and Notes

1. (a) Beckwith,A.L.J.; Chai,C.L.L. *J.Chem.Soc., Chem.Comm.*, **1990**, 1087. (b) Beckwith, A.L.J.; Davison, I.G.E. *Tetrahedron Lett.*, **1991**, *32*, 49. (c) Curran,D.P.; Shen,W.; Zhang,J; Heffner,T.A. *J.Am.Chem.Soc.*, **1990**, *112*, 6738. (d) Porter,N.A.; Lacher,B.; Chang,V.H.-T.; Magnin,D.R. *J.Am.Chem.Soc.*, **1989**, *111*, 8309. (e) Porter,N.A.; Scott,D.M.; Lacher,B. *J.Am.Chem.Soc.*, **1989**, *111*, 8311. (f) Porter,N.A.; Wu,W-X; McPhail,A.T. *Tetrahedron Lett.* **1991**, *32*, 707. (g) Porter,N.A.; Scott,D.M.; Rosenstein,I.J.; Giese,B.; Veit,A; Zeitz,H.G. *J.Am.Chem.Soc.*, **1991**, *113*, 1791. (h) Guindon,Y.; Lavallee,J.-F.; Boisvert,L.; Chabot,C.; Delorme,D.; Yoakim,C.; Hall,D.; Lemieux,R.; Simoneau,B. *Tetrahedron Lett.* **1991**, *32*, 27.

(i) Scott,D.M.; McPhail,A.T.; Porter,N.A. *Tetrahedron Lett.* **1990**, *31*, 1679. (j) Porter,N.A.; Swann,E.; Nally,J.; Mcphail,A.T *J.Am.Chem.Soc.*, **1990** , *112*, 6740. (k) Giese,B.; Zehnder,M.; Roth,M.; Zeitz,H.-G. *J.Am.Chem.Soc.*, **1990** , *112*, 6741. (l) Giese,B.; Bulliard,M.; Zeitz,H.-G. *Synlett* , **1991**, 425 (m) Hamon,D.P.G.; Massey-Westropp,R.A.; Razzino,P. *J.Chem.Soc. Chem.Comm.*,**1991**, 722; *idem, ibid*, **1991**, 332

2. (a) Jasperse,C.P., Curran,D.P.; Fevig,T.L. *Chem. Rev.*, **1991**, *91*, 1237. (b) Stork,G.; Sher,P.M. *J.Am.Chem.Soc.*, **1986**, *108*, 303. (c) Jasperse,C.P.; Curran,D.P. *J.Am.Chem.Soc.*, **1990**, *112*, 5601. (d) Schwartz,C.E.; Curran,D.P. *J.Am.Chem.Soc.*, **1990**, *112*, 9272. (e) Curran,D.P.; Fevig,T.L.; Totleben,M.J. *Synlett*, **1990**, 773.
3. (a) Bhandal,H.; Patel,V.F.; Pattenden,G.; Russell,J.J. *J.Chem.Soc., Perkin Trans. 1*, **1990**, 2691. (b) Patel,V.F.; Pattenden,G. *J.Chem.Soc., Perkin Trans. 1*, **1990**, 2703. (c) Bhandal,H.; Howell,A.R.; Patel,V.F.; Pattenden,G. *J.Chem.Soc., Perkin Trans. 1*, **1990**, 2709. (d) Howell,A.R.; Pattenden,G. *J.Chem.Soc., Perkin Trans. 1*, **1990**, 2715. (e) Coveney,D.J.; Patel,V.F.; Pattenden,G. *J.Chem.Soc., Perkin Trans. 1*, **1990**, 2721. (f) Patel,V.F.; Pattenden,G.; Thompson,D.M. *J.Chem.Soc., Perkin Trans. 1*, **1990**, 2729. (g) Gill,G.B.; Pattenden,G.; Reynolds,S.J. *Tetrahedron Lett.*, **1989**, *30*, 3229. (h) Harrowven,D.C.; Pattenden,G. *Tetrahedron Lett.*, **1991**, *32*, 243. (i) Pattenden,G.; Reynolds,S.J. *Tetrahedron Lett.*, **1991**, *32*, 259.
4. (a) Stork,G.; Mook,R. *J.Am.Chem.Soc.*, **1983**, *105*, 3741. (b) Bhandal,H.; Pattenden,G.; Russell,J.J. *Tetrahedron Lett.*, **1986**, *27*, 2299.
5. The '*trans*' stereochemistry is drawn for the cobaloxime (2) in line with the Beckwith model for the cyclisation of hexenyl radicals *i.e.* the alkyl groups align themselves in a preferred pseudo-equatorial orientation in the transition state, see: Beckwith,A.L.J.; Easton,C.J.; Lawrence,T.; Serelis,A.K. *Aust. J. Chem.*, **1983**, *36*, 545.
6. All new compounds showed satisfactory spectroscopic data, together with microanalytical and / or mass spectrometry data.
7. Only one positional isomer of the olefin was detected in the crude reaction mixtures. *i.e.* dehydrocobaltation involves the least (alkyl) substituted carbon centre see :- Duong,K.N.V.; Ahond, A.; Merienne, C.; Gaudemer, A. *J. Organometal. Chem.* **1973**, *55*, 375.
8. Prepared by treating a solution of linalool in carbon tetrachloride with methoxyallene in the presence of *N*-iodosuccinimide (25°C, 2h) (51%).
9. The *endo*-selectivity in this cyclisation is no doubt facilitated by having the reactive centres in the *trans* (*anti*)-orientation, with preferred cyclisation occurring at the least substituted carbon centre in the alkene acceptor.

(Received in UK 11 February 1992)