Chem. Soc. Rev., 1988, **17**, 361–382

SIMONSEN LECTURE *

Cobalt-mediated Radical Reactions in Organic Synthesis

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Cobalt is the 'core' transition metal in vitamin B_{12}, or cyanocobalamin (1a), which is without doubt one of the most complex naturally occurring co-ordination compounds found in nature.[1] Vitamin B_{12} is essential in the nutrition of humans, and it plays a crucial role in the fascinating biochemical reactions whereby fats, proteins, and carbohydrates are used to produce energy in living cells. The 'biochemically active' form of B_{12} is adenosylcobalamin or coenzyme B_{12} (1b), which contains an adenosyl moiety bonded covalently through its 5′-carbon

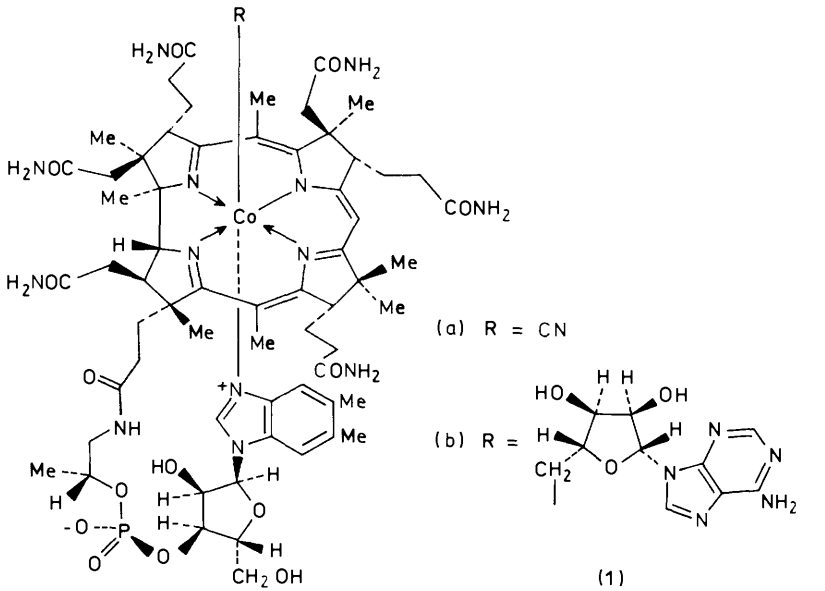
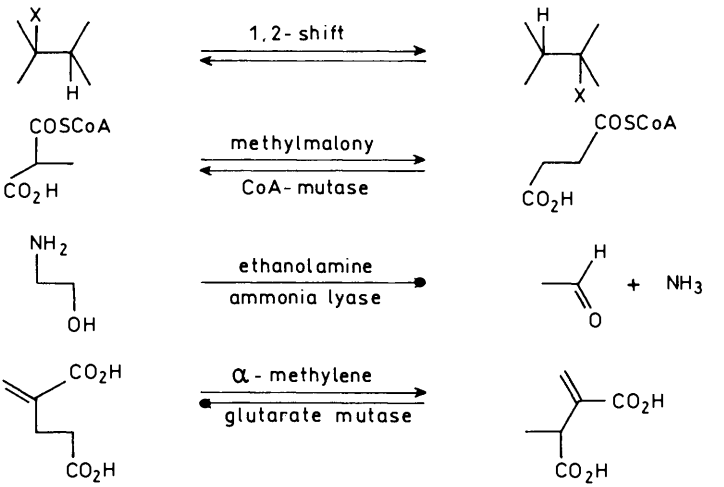


Figure 1

* Delivered at a Symposium, 'Contemporary Organic Synthesis', at the Scientific Societies' Lecture Theatre, London on 23rd November, 1987, and on other occasions at the Universities of Aberdeen, Cambridge, Cardiff, Leeds, and Reading.

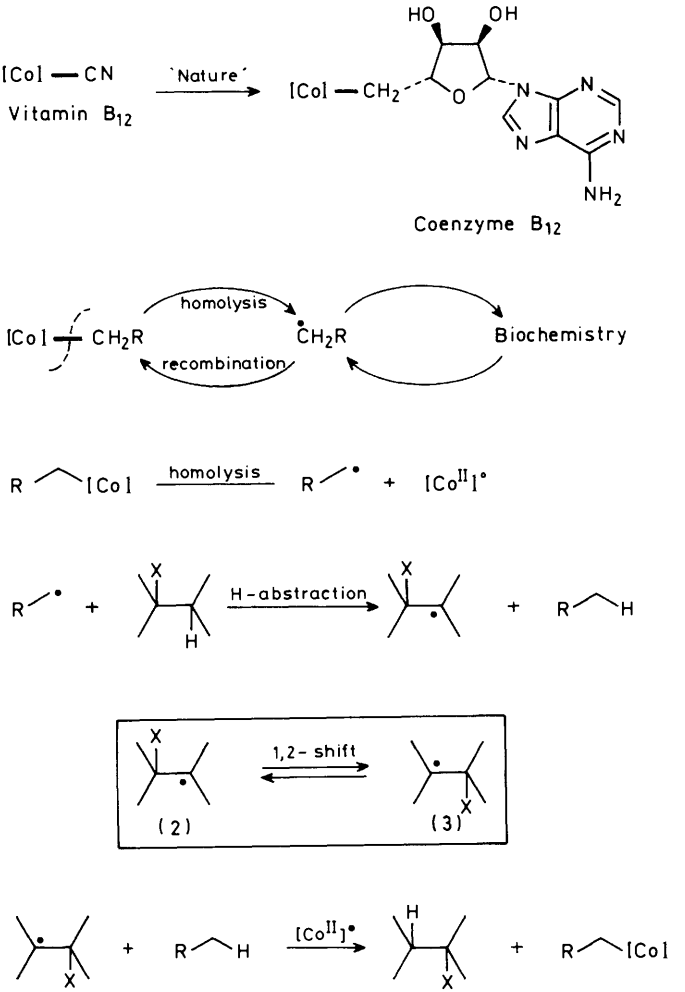
[1] 'B_{12}', Volumes 1 and 2, ed. D. Dolphin, Wiley Interscience, New York, 1982.

to the cobalt atom in the corrinoid. Coenzyme B_{12} orchestrates a range of important and subtle molecular rearrangements, in which a group X in a substrate migrates to an adjacent carbon centre at the same time as a H-atom migrates from the adjacent carbon to the one where the X-group was originally bonded (Scheme 1). Several kinds of coenzyme B_{12}-dependent molecular rearrangements have been discovered, according to the nature of the migrating group X, which can be thioester *e.g.* methylmalonyl-CoA mutase, hydroxyl *e.g.* diol dehydratase, amino *e.g.* ethanolamine ammonia lyase, glycyl *e.g.* glutamate mutase, or acrylate *e.g.* α-methyleneglutarate mutase (Scheme 1).



Scheme 1

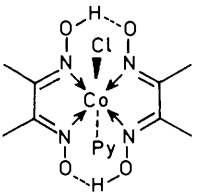
The mechanisms of the coenzyme B_{12}-dependent reactions depicted in Scheme 1 have been studied in immense detail. These investigations have demonstrated that the enzyme reactions are triggered by homolysis of the C→Co bond in the coenzyme B_{12}, leading initially to a methylene radical of deoxyadenosine together with a Co^{II} species. The adenosyl radical is then thought to abstract an H-atom from the substrate producing a new carbon-centred free radical and deoxyadenosine. Rearrangement of (2) to (3) (Scheme 2), followed by re-abstraction of an H-atom from deoxyadenosine, finally completes the sequence of events resulting in overall '1,2-shift' *via* radical intermediates.



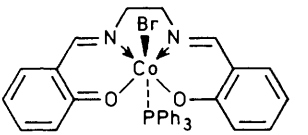
Scheme 2

The implication of the involvement of radical intermediates in the reactions catalysed by coenzyme B_{12} has received strong support, not only from labelling, stereochemical, and theoretical studies, but also from electron spin resonance spectroscopy investigations and from studies of the properties of the C→Co bond in model compounds of the coenzyme like alkyl cobaloximes (4), salens (5), and

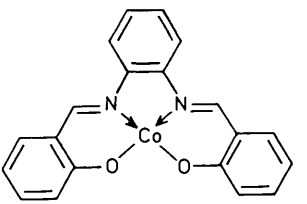
salophens (6). The reader is referred to a review, by Golding and Rao,[2] for a comprehensive summary of the recent literature pertaining to the mechanistic features of coenzyme B_{12}-dependent reactions.



(4) Cobaloxime



(5) $BrCo^{III}(salen)PPh_3$

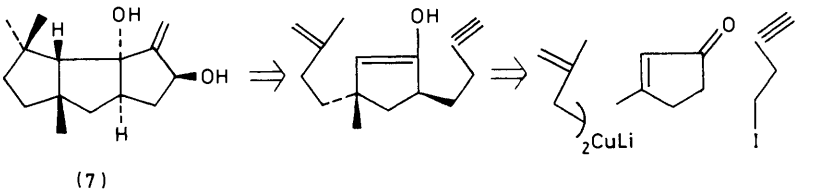


(6) Co^{II}(salophen)

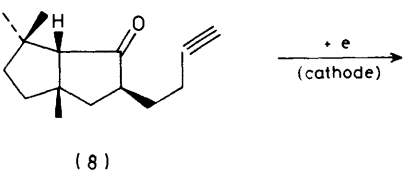
The special ability of vitamin B_{12} and its analogues to form alkyl cobalt derivatives, in combination with the ease of homolysis of the C→Co bonds in these molecules, leading to alkyl radicals, has led a number of researchers to examine some of the free-radical chemistry of organocobalt complexes. Particularly prominent in this area, before our own studies, was the work of Schrauzer, Johnson, Tada, Kochi, and Scheffold.[3] About five years ago, we became interested in the possibilities for organocobalt compounds as all purpose 'radical-in-bottle-reagents' for general organic synthesis. The motivation came as a result of our contemporaneous work in the area of total synthesis of complex polycyclic natural products. In some of this work we had investigated a range of photochemical, electrochemical, and stannane-based free-radical C→C bond-forming reactions to elaborate specific portions of the unusual ring systems present in the secondary metabolites capnellenediol (7), alliacolide (10), and

[2] B. T. Golding and D. N. R. Rao. 'Adenosylcobalamin-dependent Enzyme Reactions' in 'Enzyme Mechanisms', ed. M. I. Page and A. Williams. Royal Society of Chemistry. 1987. p. 404.

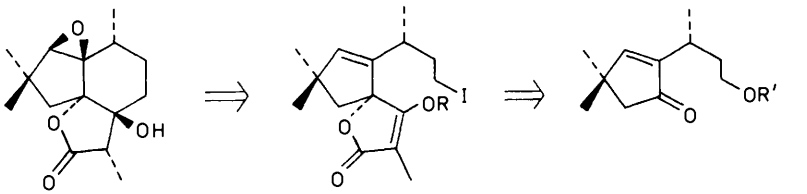
[3] For some reviews see: (*a*) D. Dodd and M. D. Johnson. *Organomet. Chem. Rev.*. 1973. **52**. 1; (*b*) J. M. Pratt and P. J. Craig, *Adv. Organomet. Chem.*. 1973. **11**. 331; (*c*) E. Langer. *Methoden der Organischen Chemie*. 1984. 13.9b; (*d*) R. Scheffold. *Modern Synthetic Methods*. 1981–2, **3**, 362; (*e*) P. J. Toscano and L. G. Marzilli. *Prog. Inorg. Chem.*. ed.. S. J. Lippard. Wiley-Intersciences, London, 1984, **31**, 105; (*f*) G. Costa. *Coord. Chem. Rev.*. 1972, **8**, 63; (*g*) D. G. Brown. *Prog. Inorg. Chem.*. 1973, **18**. 177; (*h*) B. T. Golding in '*Comprehensive Organic Chemistry*'. Vol. 5. ed. D. H. R. Barton and W. D. Ollis. Pergamon. Oxford. 1979, Ch. 24.4.



(7)



(8) (9)



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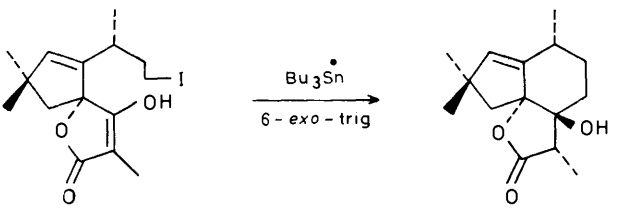
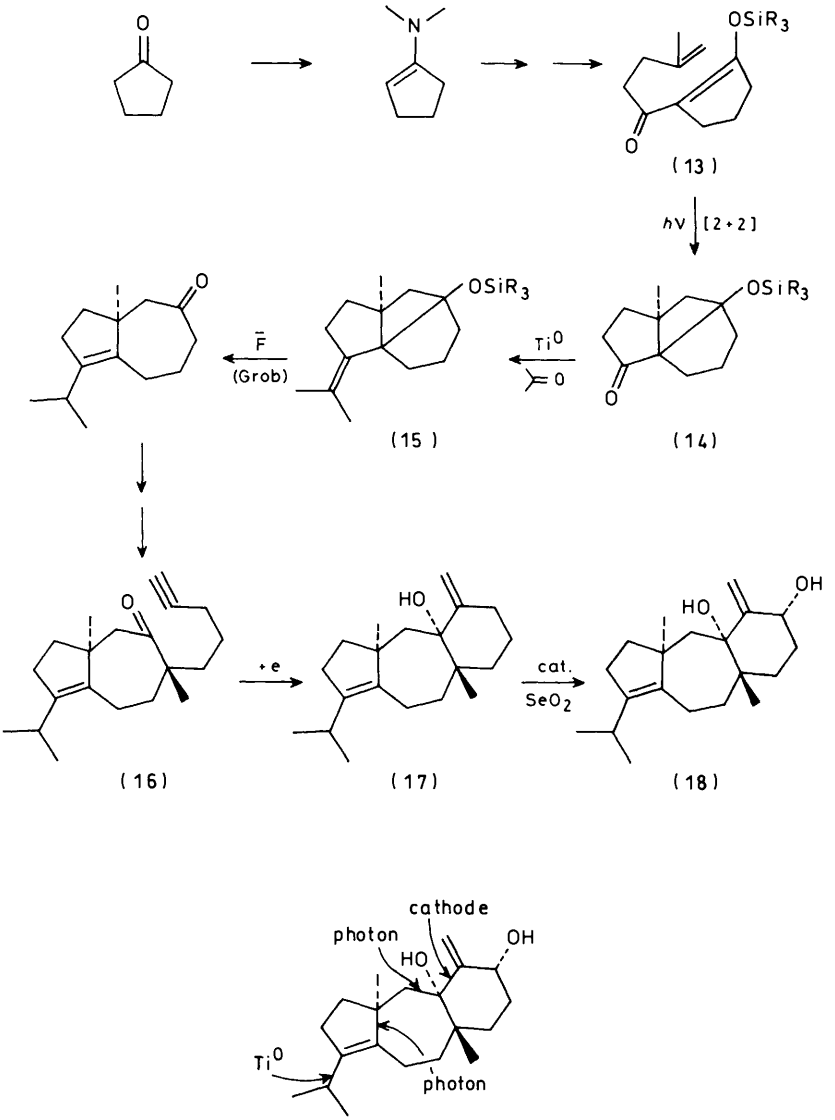


(11) (12)

isoamijiol (18). In the case of capnellenediol (7), for example, we were able to highlight the use of intramolecular reductive coupling between acetylenes and ketones *viz.* (8) ⟶ (9), to elaborate the sensitive allylic alcohol functionality



Scheme 3

associated with ring C in the structure.[4] With alliacolide (10), we showed how useful the 6-*exo*-trigonal cyclization (11) ⟶ (12), of a radical onto an enolic

[4] G. Pattenden and S. J. Teague, *Tetrahedron Lett.*, 1982, **23**, 5471; *J. Chem. Soc., Perkin Trans. 1*, 1988, 1077.

C=C bond could be to set up the three contiguous chiral centres in the substituted lactone portion in this unique metabolite.[5] Finally, in our synthesis of the dolastane diterpene isoamijiol (18), summarized in Scheme 3, we used only seven C→C bond-forming reactions to elaborate the entire ring system starting from cyclopentanone, and no less than four of these reactions involved free-radical intermediates *i.e.* (13) ⟶ (14); (14) ⟶ (15); (16) ⟶ (17).[6]

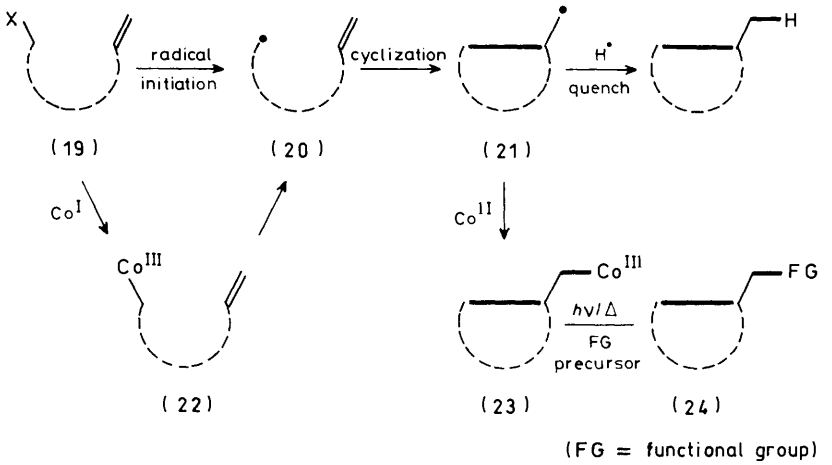
The foregoing total syntheses of capnellenediol, alliacolide, and isoamijiol certainly highlighted for us the enormous scope for free-radical reactions in complex natural product synthesis. Furthermore, these studies were carried out at a time (1980—1985) when the whole area of free-radical mediated C→C bond-forming reactions was undergoing a renascence of interest from some of the foremost synthetic chemists, and many other spectacular applications of free-radical reactions to complex synthetic problems were emerging.[7] Perhaps nowhere else were these applications being better exploited than in the synthesis of carbo- and hetero-cyclic molecules. Spectacular as many may have been however, the overwhelming majority of these free-radical cyclization reactions were performed under reductive conditions with the result that ring formation was invariably accomplished at the expense of two functional groups *i.e.* the radical precursor group X, and the radical acceptor *e.g.* a C=C bond, as shown in Scheme 4.

The mode of action of coenzyme B_{12}, briefly summarized above, had told us two important things: (i) cobalt forms weak (~20—30 kcal/mole) covalent bonds to carbon, leading to relatively stable organocobalt compounds, and (ii) homolysis (Δ or hν) of these organocobalt molecules provides a rich source of carbon radicals. With this information, it was our contention that single electron-transfer from a nucleophilic Co^{I}-reagent to the C→X in substrate (19) (Scheme 4), should lead to the carbon-centred radical (20) or possibly the organocobalt precursor molecule (22). The radical (20) would then undergo the anticipated *exo*-cyclization onto the proximate C=C bond, leading to the new product-radical centre (21). This product-radical centre might then be 'trapped' by Co^{II} (generated in the initial redox reaction) leading to the cobalt-functionalized cyclic molecule (23). Subsequent homolysis of the C→Co bond in (23), in the presence of radical trapping agents, could then be used to introduce a variety of functionality at the product radical centre, thereby enhancing still further the use

[5] M. Ladlow and G. Pattenden. *Tetrahedron Lett.*, 1985, **26**, 4113; *J. Chem. Soc., Perkin Trans. 1*, 1988, 1107.

[6] G. Pattenden and G. M. Robertson. *Tetrahedron Lett.*, 1986. **27**, 399; M. J. Begley, G. Pattenden, and G. M. Robertson. *J. Chem. Soc., Perkin Trans. 1*, 1988, 1085.

[7] For selected examples see: B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds', Pergamon Press, 1986; G. Stork, 'Radical-Mediated Cyclisation Processes', in 'Selectivity – A Goal for Synthetic Efficiency', ed., W. Bartmann and B. M. Trost, Verlag Chemie, Basel, 1984, pp. 281- 99; D. J. Hart, *Science*, 1984, **223**, 883; D. J. Hart and H.-C. Huang, *Tetrahedron Lett.*, 1985, **26**, 3749; K. Sharikaran, C. P. Sloan, and V. Sniekus, *Tetrahedron Lett.*, 1985, **26**, 6001; L. Van Hijfte and R. D. Little. *J. Org. Chem.*, 1985, **50**, 3940; E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821; G. Stork and N. H. Baine. *Tetrahedron Lett.*, 1985, **26**, 5927; D. P. Curran and S.-C. Kuo, *J. Am. Chem. Soc.*, 1986, **108**, 1107; D. P. Curran and M.-H. Chen, *Tetrahedron Lett.*, 1985, **26**, 4991; D. P. Curran, M. H. Chen, and D. Kim, *J. Am. Chem. Soc.*, 1986, **108**, 2489; D. A. Burnett, J.-K. Choi, D. J. Hart, and Y.-M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8201; M. Tokuda, Y. Yamada, T. Takai, and H. Suginome. *Tetrahedron Lett.*, 1985, **26**, 6085; see also refs. 8 and 9.



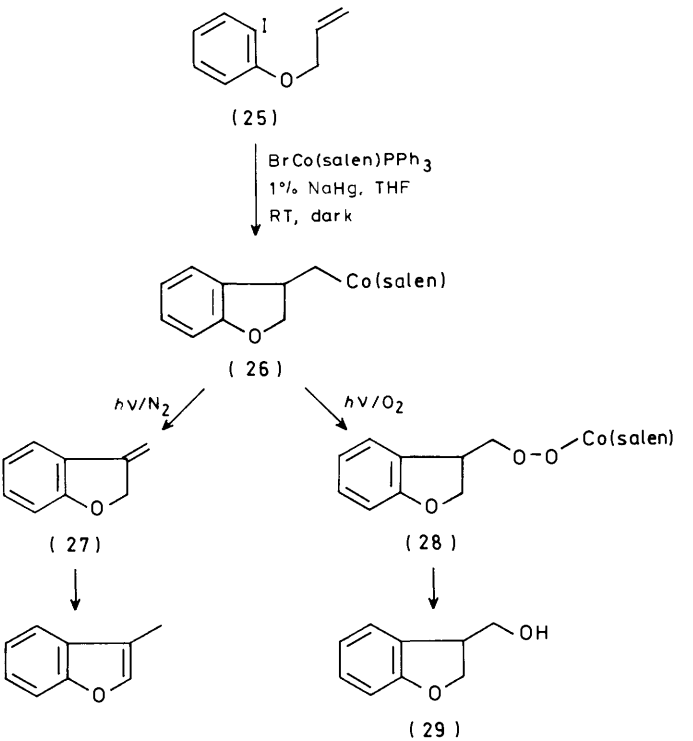
Scheme 4

of free-radical cyclization reactions, in the synthesis of *functionalized* carbo- and hetero-cyclic molecules [*viz.* (24)].

The feasibility of this simple proposition, the outcome of which constitutes the basis of this article, was first investigated using the simple model substrate (*O*-allyl)iodophenol (25). After initial disappointment with cobaloxime(I) and reduced vitamin B_{12} itself, it was gratifying to find that when the iodide (25) was added to an emerald green solution of the cobalt(I) reagent produced from cobalt(III) salen (5) (1% NaHg in THF under argon), a 65% yield of the hoped-for organocobalt compound (26) was smoothly secured.[8] Brief exposure of a degassed solution of (26) in dichloromethane to light from a 100W sunlamp then resulted in facile dehydrocobaltation (β-elimination) leading to the alkene (27), which on chromatography was isomerized quantitatively to 3-methylbenzofuran. In a separate experiment, a similar irradiation of (26) in the presence of molecular oxygen, led to the corresponding peroxy cobalt complex (28) which could be reduced by sodium borohydride to produce the carbinol (29) in 25% overall yield.

It was evident from this preliminary study that the proposition to use nucleophilic Co^{I} complexes, together with knowledge of the weakness of the C→Co bond to: (a) initiate radical formation, (b) effect cyclization and trap the product radical centre with Co^{II}, and finally (c) use the C→Co bond to introduce functionality (*i.e.* C=C and OH) into the cyclized product, was fully vindicated. Indeed, several other examples, summarized in Scheme 5, demonstrated the wide applicability of this new cobalt-initiated–cyclization–trap-functional group inter-

[8] V. F. Patel, G. Pattenden, and J. J. Russell, *Tetrahedron Lett.*, 1986, **27**, 2303.



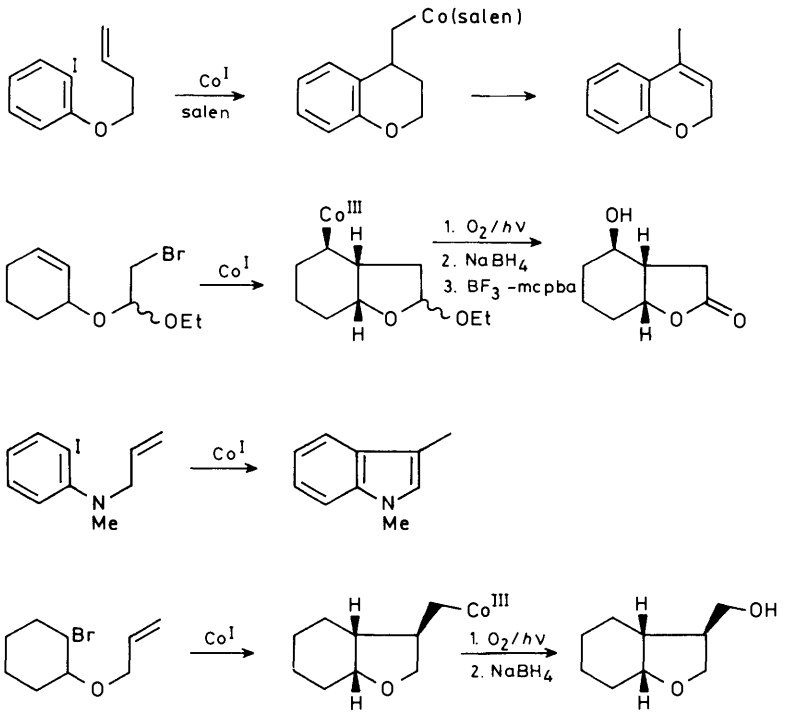
conversion strategy for the synthesis of a very wide range of OH-substituted aromatic and heterocyclic molecules.[8,9]

Encouraged by these results, and using the easily available organocobalt salen compound (26) as a model compound, we next examined further uses of the C→Co bond in preparative organic chemistry. A more practical procedure for inserting oxygen at the product radical centre resulting from cyclization of (25), was by irradiation of the isolated organocobalt complex (26) in the presence of tetramethylpiperidino oxide (TEMPO), followed by reduction of the resulting adduct (30) using zinc in acetic acid. In this manner overall yields of 75% were realized for the conversion of (26) into the carbinol acetate (31).[10]

In a similar manner, irradiation of solutions of (26) in the presence of diphenyldisulphide or diphenyldiselenide produced the corresponding substituted sulphide (85%) and selenide (75%) respectively, and halogen could be introduced at the product radical centre from cyclization of (25) by treatment of the

[9] H. Bhandal, G. Pattenden, and J. J. Russell, *Tetrahedron Lett.*, 1986, **27**, 2299; see also: M. Ladlow and G. Pattenden, *ibid.*, 1984, **25**, 4317; M. J. Begley, M. Ladlow, and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1095.

[10] V. F. Patel and G. Pattenden, *Tetrahedron Lett.*, 1987, **28**, 1451.



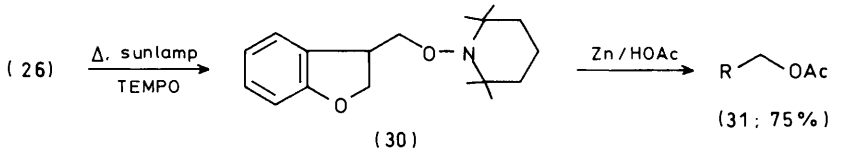
Scheme 5

organocobalt intermediate (26) with either methanesulphonyl chloride (78%), bromotrichloromethane (79%), or iodine (42%). A less practical way to introduce sulphur at the product radical centre was by dissolution of (26) in liquid sulphur dioxide, followed by acid work-up of the intermediate cobalt sulphone (32); in this manner low yields ($\sim$20%) of the sulphinic acid (33) were realized.

The incorporation of nitrogen at the product radical centre resulting from cyclization of (25) was readily accomplished when a solution of the intermediate (26) in dimethylformamide containing triethylamine was irradiated in the presence of nitrogen monoxide. This procedure led to a 1:1 mixture of *Z*- and *E*-isomers of the oxime (34; 78%) which could then be reduced to the corresponding amine (35) using lithium aluminium hydride.[10]

We also examined the chemistry of the 'salophen' complex corresponding to (26), and of the cobalt salophens (36a) and 36b), obtained from 2-iodopropane and 1-iodo-2-phenylethane respectively. This chemistry was unexceptional, and by similar methodologies to those described for (26) we were able to access the corresponding oxygen, sulphur, selenium, halogen, and nitrogen functionalized products from these reagents.[11]

[11] V. F. Patel, Ph. D. Thesis. University of Nottingham. Nov. 1987.



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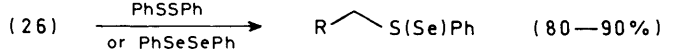

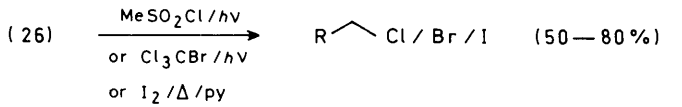

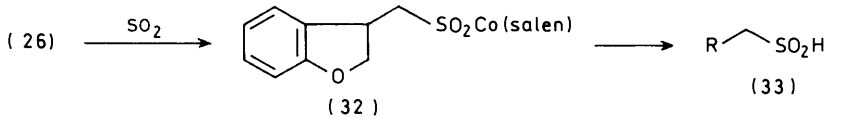

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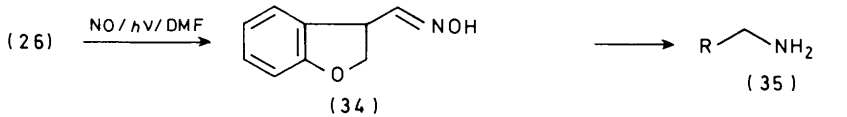

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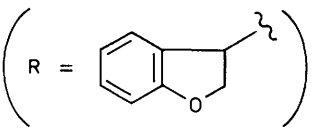
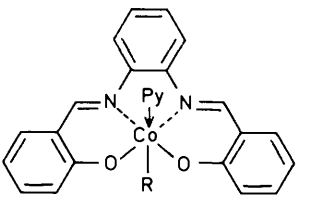
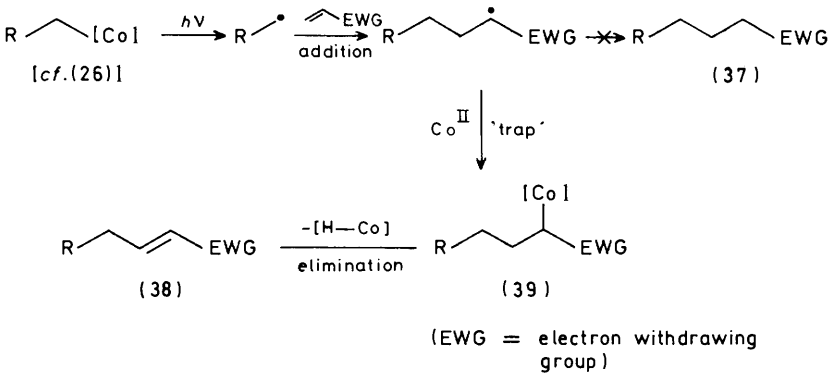




(36)

(a) R = Me_2CH —
(b) R = $PhCH_2CH_2$ —
(c) R =



Scheme 6

The addition of carbon radicals to alkenes is well known to be one of the most powerful methods for the formation of C–C bonds, and a number of publications attest the preparative value of these reactions in synthesis.[12] Accordingly, we decided to examine the intermolecular addition reactions between our organocobalt reagents *viz.* (26), (36a), (36b), *etc.*, and a variety of deactivated C=C bonds (simple alkenes, like cyclohexene, and activated alkenes, like enol ethers, were shown to be inert to the organocobalt reagents). These reactions proved to be quite novel. Instead of leading to the products (37) of straightforward addition followed by H-quench of the product radical centre, the reactions led to new *alkene* products [*viz.* (38)], which resulted from radical (Michael) addition to the C=C bonds followed by 'dehydrocobaltation' from the presumed organocobalt intermediates (39) (Scheme 6).[13]

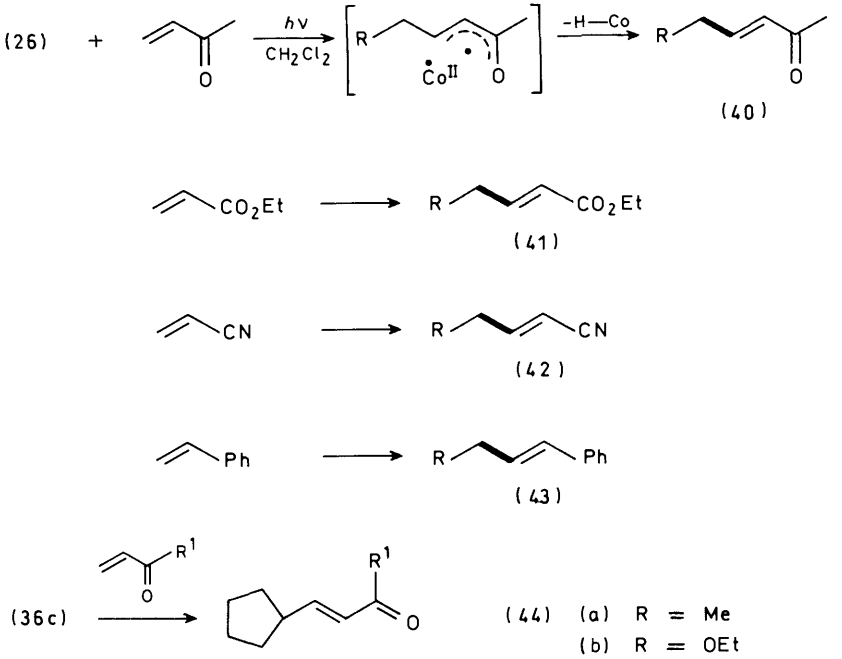
Thus, when a solution of (26) in methylene dichloride was irradiated (300 W, sunlamp, 36 h) in the presence of methyl vinyl ketone (5 equiv.), work-up led to the separation of a single adduct corresponding to the *E*-enone (40). In a similar manner, irradiation of (26) in the presence of ethyl acrylate or acrylonitrile, led to the corresponding adducts (41; 65%) and (42; 30%) respectively. Significantly higher yields in the addition–elimination sequence (26) ⟶ (39) ⟶ (38) (Scheme 6), were realized when styrene was used as the 'Michael' acceptor. Thus, yields of 75—80% of the adduct (43) were produced when the organocobalt compound (26) was irradiated in the presence of styrene. This latter result may reflect the ease of elimination of H–Co in the second step of the sequence, over those cases involving methyl vinyl ketone, ethyl acrylate, and acrylonitrile.

Secondary alkyl radicals were found to behave in a similar manner to primary radicals in the alkene addition–elimination sequence, as evidenced by studies

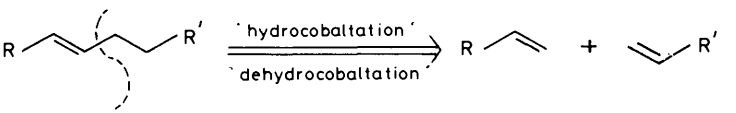
[12] G. E. Keck, E. J. Enholm, and D. F. Kachensky, *Tetrahedron Lett.*, 1984, **25**, 1867; D. H. R. Barton and D. Crich, *ibid.*, p. 2787; J. E. Baldwin, R. M. Adlington, and A. Basak, *J. Chem. Soc., Chem. Commun.*, 1984, 1284.

[13] V. F. Patel and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1987, 871.

with the organocobalt salophen (36c) derived from bromocyclopentane. Like (26) the organocobalt (36c) underwent photolytic homolysis in the presence of both methyl vinyl ketone and ethyl acrylate producing the corresponding *E*-adducts (44a) and (44b) in 45% and 55% yield, respectively.[13]



The single step synthesis of new alkene products from the addition of organocobalts to deactivated C=C bonds, involving 'dehydrocobaltation' as the key, second step was most interesting. Fortuitously for us, some years ago, Schrauzer *et al.*[14] had described the reverse of this sequence *i.e.* the preparation of alkylcobalt reagents by the 'hydrocobaltation' of deactivated C=C bonds! This

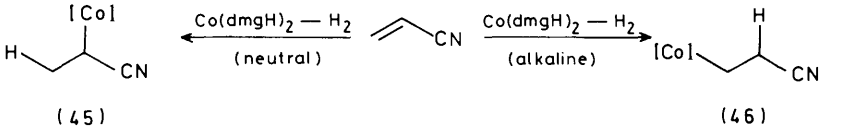


Scheme 7

[14] G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, 1967, **89**, 1999.

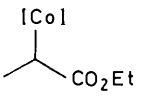
observation, together with our own work, suggested that we could draw together the principles of 'hydrocobaltation' of alkenes and 'dehydrocobaltation' of organocobalt complexes to provide a new and interesting approach to the controlled cross-coupling between sp^2 carbon centres leading to functionalized alkenes, as shown in Scheme 7. This proved to be the case.[15]

The regiospecificity of hydrocobaltation of alkenes is critically dependent on the pH of the medium.[14] Thus, treatment of acrylonitrile with cobalt dimethylglyoximato in the presence of hydrogen, followed by work-up with pyridine, led to the crystalline α-substituted cobaloxime (45). The same reaction under alkaline conditions (aq. NaOH) instead leads to the β-substituted cobaloxime (46). In a similar manner, hydrocobaltations of ethyl acrylate led to (47) and (48a) under neutral and alkaline conditions, respectively. Using a range of pH conditions, we were only able to secure the β-substituted cobaloximes (48b), (49a), (49b), (50), and (51) from hydrocobaltation reactions of methyl vinyl ketone, methyl acrylonitrile, methyl methacrylate, acrolein, and itaconic anhydride, respectively.

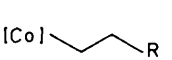


(45) (46)

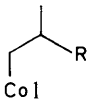
[Co] = $Co(dmgH)_2py$



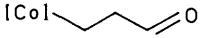
(47)



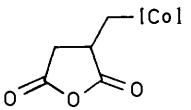
(48) (a) R = CO_2Et
(b) R = COMe



(49) (a) R = CN
(b) R = CO_2Me



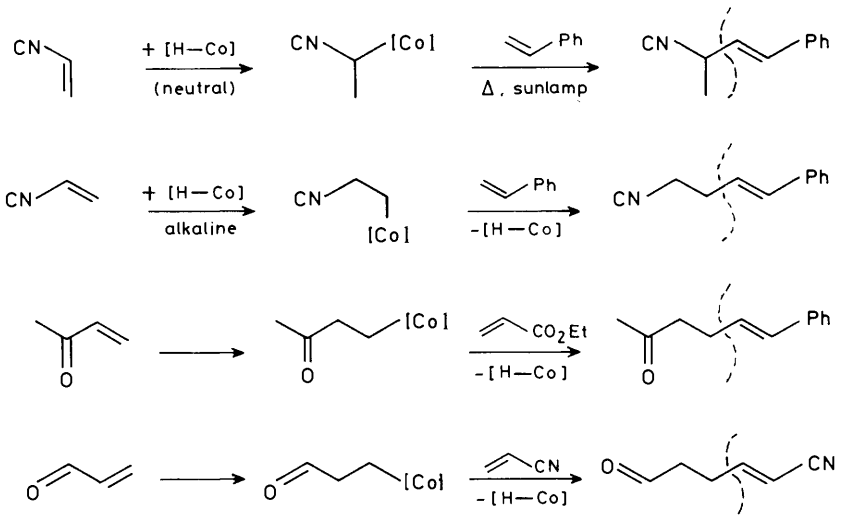
(50)



(51)

Irradiations of solutions of either of the alkylcobaloximes (45) ⟶ (51) in dichloromethane in the presence of the deactivated alkenes styrene, ethyl acrylate, acrylonitrile, or methyl vinyl ketone, then led to the anticipated alkene products shown in Scheme 8. The foregoing results illustrate a new approach to the cross-coupling of sp^2 carbon centres which is complementary to the

[15] H. Bhandal and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1988, 1110.



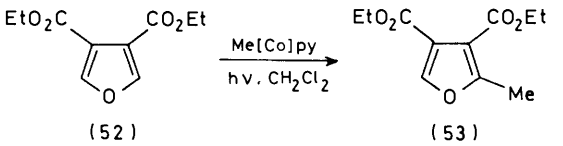
Scheme 8

ubiquitous Heck reaction. Furthermore, in principle, the hydrocobaltation–radical addition–dehydrocobaltation sequence should be amenable to fine 'tuning' to allow the coupling of any alkene to a second alkene at either of their α- or β-sites leading to several types of cross-coupled products. This remains to be investigated.

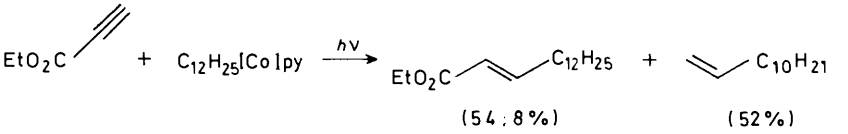
A number of other possibilities exist for the addition of organocobalt reagents to deactivated C→C multiple bonds. For example, the addition of methylcobaloxime to the furan (52) provides a useful yield of the 2-methyl furan (53).[16] Furthermore, although the additions of alkylcobalt reagents to ethyl propiolate and to phenylacetylene lead to only poor yields of the addition products (54) and (57) respectively, with phenylacetylene a very high yield of the vinylcobalt reagent (56) is produced concurrently. The vinylcobalt (56), which is derived *via* dehydrocobaltation of (55), followed by hydrocobaltation of phenylacetylene, could offer further scope in synthesis, but this chemistry has not yet been explored.[16]

In further investigations of the opportunities for stable organocobalt reagents in synthesis we have also prepared a range of acylcobalt salophen compounds, precursors to the corresponding acyl radicals. The acylcobalt salophens are conveniently synthesized from carboxylic acid chlorides or the mixed anhydrides with 2,6-dichlorobenzoic acid, following treatment with sodium cobalt(I) salophen. In this manner we have prepared a range of the primary, secondary, tertiary, allyl, vinyl, aryl, and arylmethyl acylcobalt salophens (58), all of which are brightly coloured, stable crystalline materials.[17]

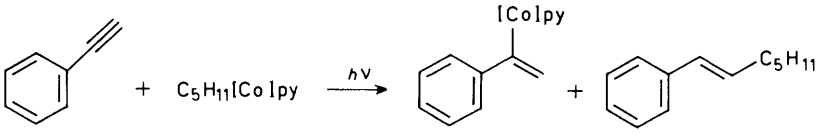
[16] K. Carr and G. Pattenden, unpublished work.
[17] D. J. Coveney, V. F. Patel, and G. Pattenden. *Tetrahedron Lett.*, 1987. **28**, 5949.



(52) (53)

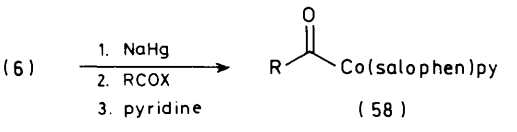


(54 ; 8%) (52%)



(55) (56 ; 66%) (57 ; 10%)

Irradiation of de-aerated, refluxing solutions of the acylcobalt salophens (58) in methylene dichloride, in the presence of deactivated C=C bonds, similar to the

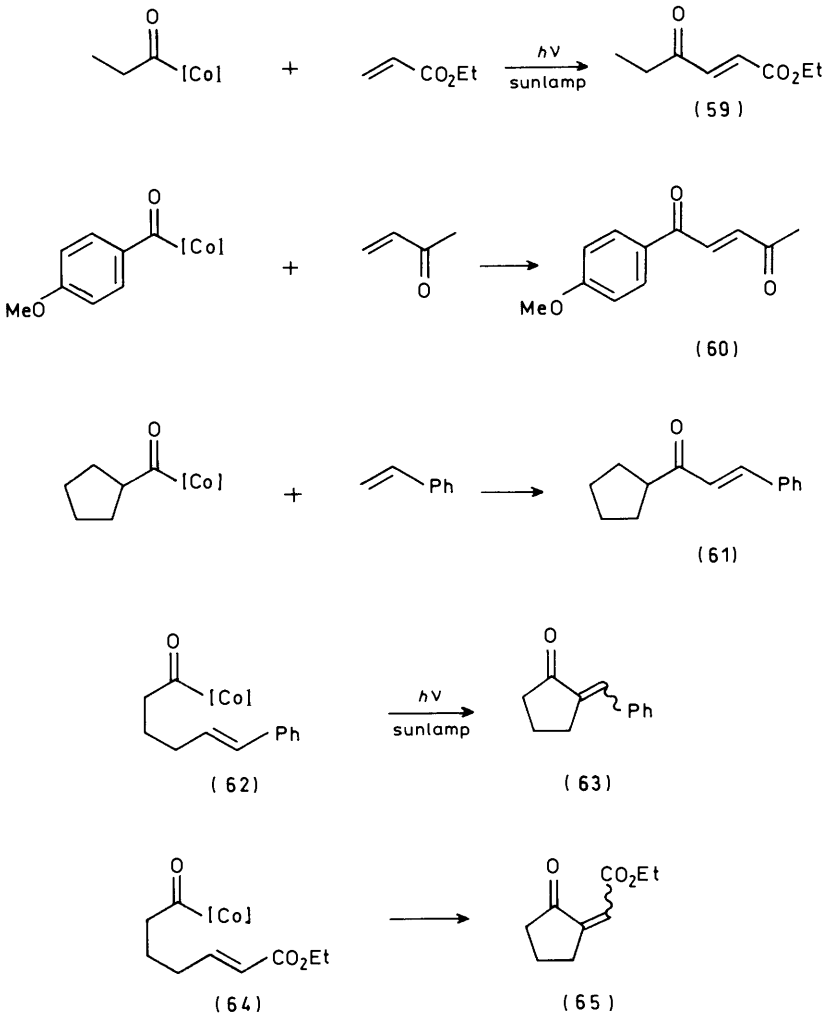


(58)

R = 1°, 2°, 3°, allyl, vinyl, aryl, OR′, NR_2' *etc.*

reactions with alkylcobalt compounds, led to good yields of the corresponding highly functionalized alkene products (59 ⟶ 61) resulting from the now familiar: homolysis (to $R\dot{C}O$)–addition–elimination (dehydrocobaltation) sequence (Scheme 9). Similar reactions involving acyl radical intermediates, could be carried out in an intramolecular sense leading to ring synthesis. Thus, irradiation of either of the acylcobalt salophen compounds (62) and (64) led to good yields of *Z*-*E*-mixtures of the corresponding cyclopentanones (63) and (65), respectively.[17]

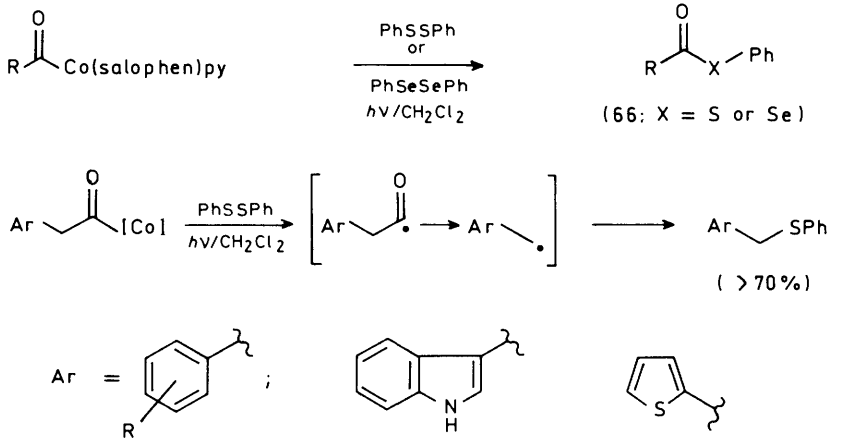
The acylcobalt salophen compounds (58) all reacted with diphenyldisulphide and diphenyldiselenide (CH_2Cl_2 solutions, sunlamp, 18 h) producing the



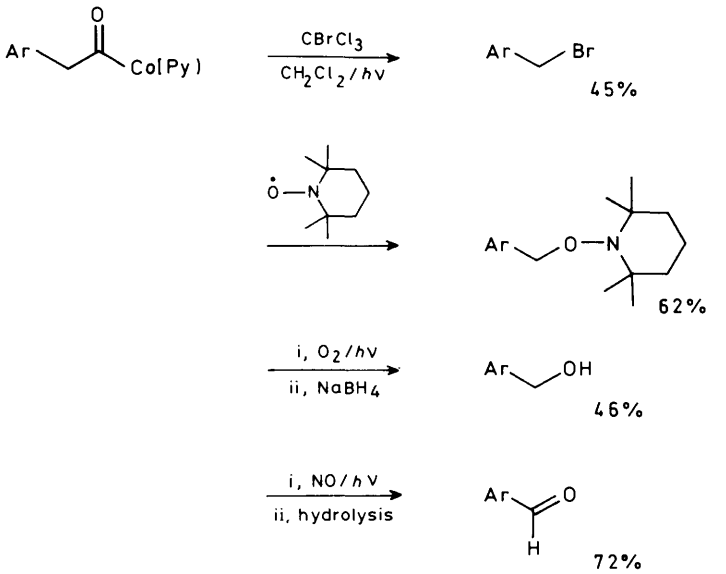
Scheme 9

corresponding phenylthio and phenylseleno esters (66) in high yields (70—80%). By contrast, both allyl- and arylmethyl-substituted acylcobalt salophen reagents, under identical conditions, underwent facile C→Co bond homolysis and *in situ* decarbonylation, producing new (alkyl) radical centres which were then intercepted by the $PhS^{\bullet}$ and $PhSe^{\bullet}$ radicals, leading to functionalized nor-alkanes (Scheme 10).[18]

[18] V. F. Patel and G. Pattenden, *Tetrahedron Lett.*, 1988, **29**, 707.

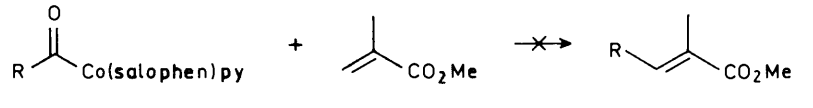


Scheme 10



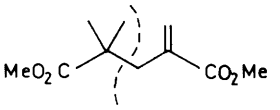
Scheme 11

A range of similar reactions, using arylmethyl-substituted acylcobalt salophens and bromine-, oxygen-, and nitrogen-containing radical trapping agents demonstrated the generality of this new method for the degradation of carboxylic acids to functionalized nor-alkanes *via* acylcobalt salophen intermediates (Scheme

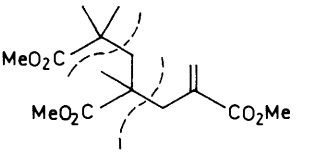


(67) MMA (68)

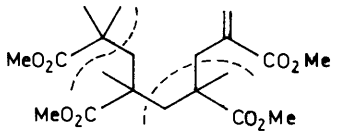
(a) R = 4-$OMeC_6H_4$
(b) R = $PhCH_2$, Et, Pr^i, Bu^t



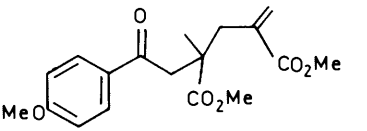
(69)



(70)



(71)



(72)

11). The overall sequence amounts to a cobalt 'equivalent' of the Barton radical decarboxylation reaction of carboxylic acids *via* the corresponding thiohydroxamic ester, which is of course related to the classic Hunsdiecker reaction.[18]

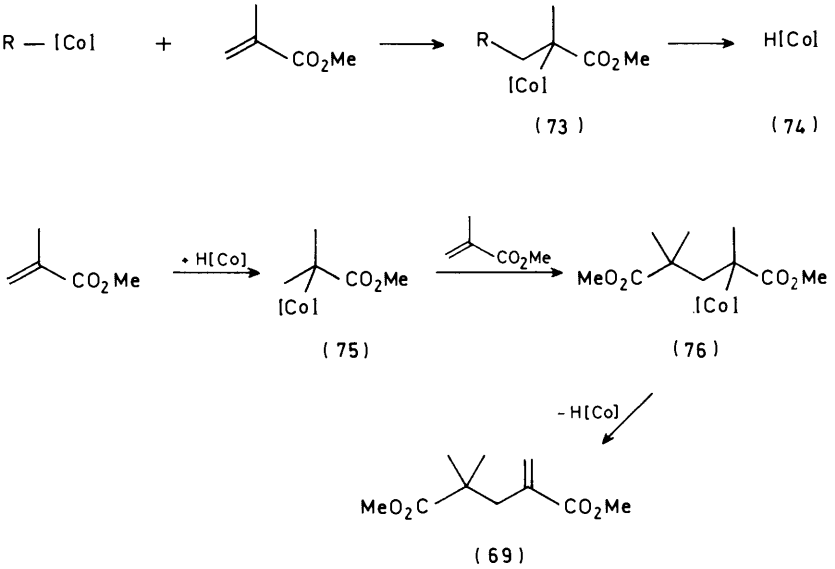
One of the most interesting and synthetically useful reactions to emerge from our studies of alkyl- and acyl-cobalt compounds was their 'oxidative additions' to deactivated C=C bonds leading to new substituted alkene products. In attempts to expand the scope of this sequence, we have also examined a number of corresponding reactions using methyl methacrylate (MMA), together with other, more substituted (both α- and β-) alkene substrates. Although these reactions were found to be uniformly less efficient in the synthesis of 1:1 adducts of the type (68), interestingly, in the special case of MMA the reactions led largely to the formation of oligomers of MMA by way of an unusual photoinduced catalytic 'hydrocobaltation – dehydrocobaltation' sequence.[19]

Thus, irradiation of the acylcobalt salophen (67a) with MMA in methylene dichloride led largely to a mixture of the dimer (69; 25%), trimer (70; 20%) and tetramer (71; 20%) of MMA, accompanied by small amounts of the 1:2 adduct (72). Similar reactions, with a range of alternative acylcobalt salophens (67b), and also alkylcobalt salophen reagents led to comparable yields of the oligomers

[19] W. M. Bandaranayake and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 1988, 1179.

(69), (70), and (71) of MMA. Conversely, irradiation of MMA in the presence of cobalt salophen *alone*, produced no detectable amounts of obligomers.

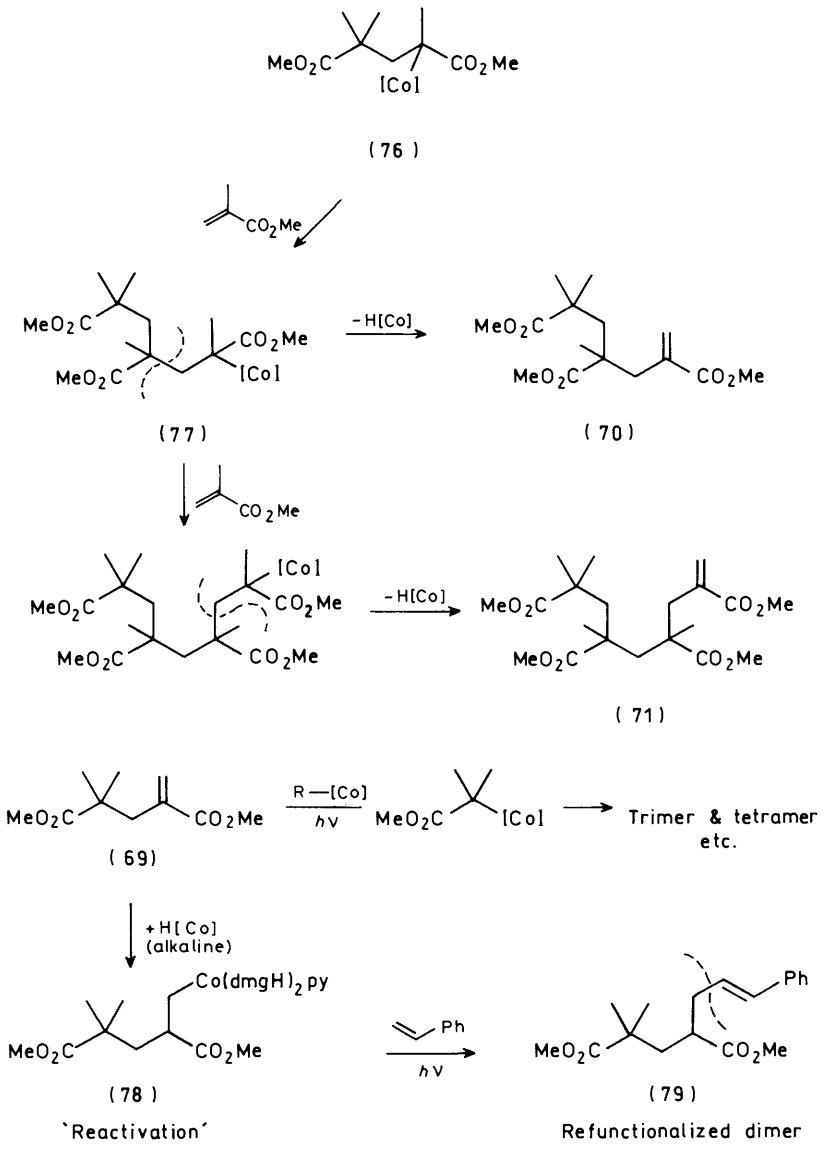
It seems likely that the oligomerizations of MMA in the presence of acyl and alkyl cobalt salophens, are orchestrated by a unique series of controlled 'hydrocobaltation–dehydrocobaltation' reactions involving the 1:1 adduct (73) as key intermediate. Thus, initial homolysis of the starting acyl (or alkyl) cobalt reagent, followed by carbon radical addition to the β-centre of MMA, first leads to the 1:1 adduct (73). 1,2-Elimination (dehydrocobaltation) from (73) next produces an alkene together with 'hydridocobalt salophen' (74) which is the effective catalyst for the oligomerization. Hydrocobaltation of MMA by (74),



under neutral pH conditions is regioselective (see previous discussion, p. 374[14]), and leads to the reactive organocobalt intermediate (75). Michael-type radical additon of (75) to MMA followed by dehydrocobaltation from the adduct (76), then leads to the dimer (69) of MMA. In alternative sequences, addition–elimination reactions between (76) and MMA, and between (77) and MMA produce the trimer (70) and tetramer (71), respectively, of MMA.[19]

In separate experiments, we were able to initiate further polymerization of the dimer (69) by simple irradiation of (69) in methylene dichloride in the presence of an alkyl- or acyl-cobalt salophen; thus the dimer (69) with (67) led to a 2:1:1 mixture of (69), (70), and (71) (total yield, 76%).

Finally, we have also demonstrated that it is possible to 'reactivate' the oligomers of MMA for further chemical studies, by applying the principle of hydrocobaltation, highlighted elsewhere. Thus, treatment of the dimer (69) with



hydridodimethylcobaloxime under alkaline conditions in the presence of hydrogen, first led to the crystalline cobaloxime (78). Irradiation of (78) with styrene then led to the novel 1:1 adduct (79) resulting from the now familiar C–Co bond homolysis–addition–dehydrocobaltation sequence.[19]

The scope for alkyl- and acyl-cobalt reagents in general preparative organic

chemistry is considerable. The reagents are valuable precursors of the corresponding alkyl and acyl radical intermediates, under mild (Δ, sunlamp), neutral conditions, which are of widespread use in a variety of functional group transformations, C→C bond-forming reactions, and in ring synthesis. In addition, using the principles of hydrocobaltation of, and dehydrocobaltation to, C=C bonds, the facile cross-coupling of sp^2 carbon centres can be achieved, together with the controlled oligomerization of methacrylates and the 'reactivation' of methacrylate oligomers. The opportunities for organocobalt reagents in synthesis could be enhanced still further if, for example, modified ligands would permit their use in asymmetric synthesis, and also if they could be used to access other radical intermediates like the aminyl- and iminyl-centred radicals. The impetus for our present work came from studies of strategy and design for the synthesis of biologically significant natural products. Organocobalt reagents also have a role to play in this demanding and important endeavour, and although some progress has already been made,[20] much more is anticipated from our contemporaneous studies.

Acknowledgements. It gives me immense pleasure to have this opportunity to thank my co-workers, who are named in the references, for all their hard work and enthusiastic collaboration over the past few years. I am also grateful for the encouragement and financial support this work has received from Glaxo Group Research, Rhône-Poulenc, and the S.E.R.C.

[20] J. H. Hutchinson, P. L. Myers, and G. Pattenden, *Tetrahedron Lett.*, 1987, **28**, 1313.