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The Nicholas reaction: the use of dicobalt hexacarbonyl-stabilised propargylic cations in synthesis

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1. Scope of the review

This report sets out to summarise important advances in the chemistry and synthetic utility of dicobalt hexacarbonyl-stabilised propargylic cations. Two excellent reviews have already been published that cover this topic in detail.† The influential review written by Nicholas[1] in 1987 brought this relatively unknown area of organometallic chemistry to the attention of a much wider audience. Over the following few years, an increasing number of research groups wrote articles describing how the chemistry could be exploited to achieve a variety of different synthetic goals. In 1995, a second review was published as part of Comprehensive Organometallic Chemistry II.[2] This provided a thorough update on the rapid advances taking place in the chemistry during this period. Our review seeks to build on this, and to bring readers up-to-date with recent accomplishments in the area. Went[3] has written a more general review on the synthesis, structure and reactivity of polynuclear cobalt–alkyne complexes and this contains a little of the chemistry discussed here. Christie and Fletcher[4] have recently reviewed the area of cobalt-mediated cyclisations and part of their review discusses some of the same material mentioned here.

This review will concentrate on where complexation of an alkyne to dicobalt hexacarbonyl, $Co_2(CO)_6$, has been used to help stabilise carbocationic charge generated at the

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† During the preparation of this report Green published an equally authoritative review of the area.[115]

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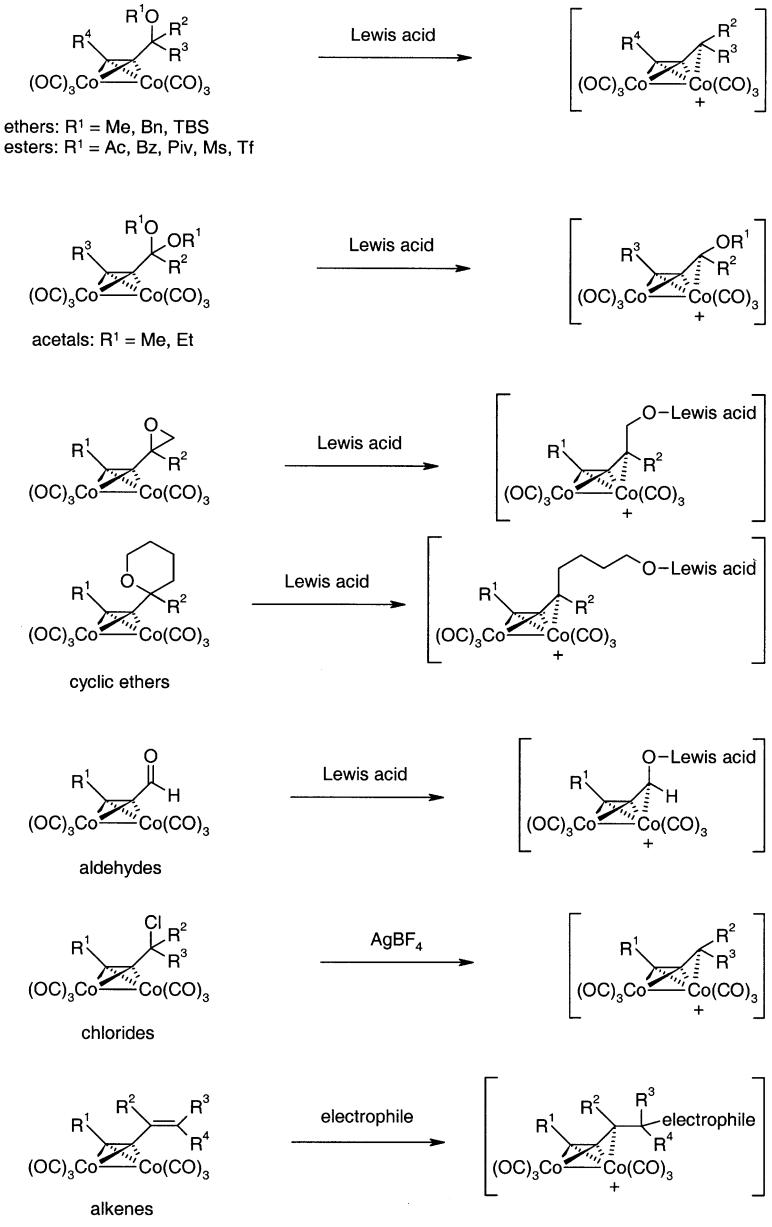
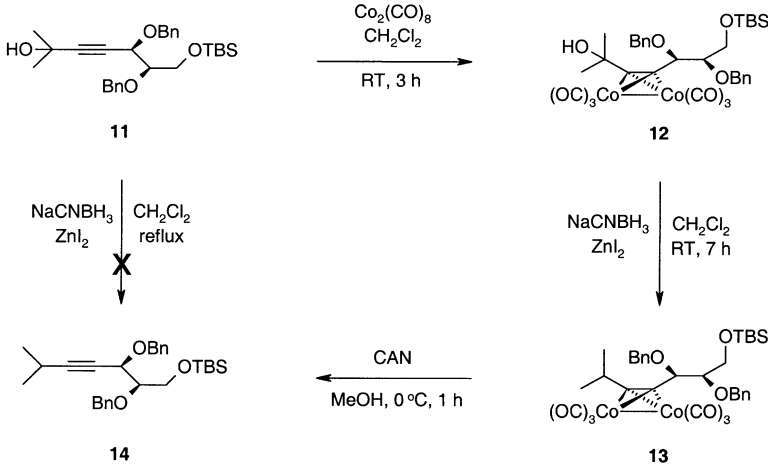
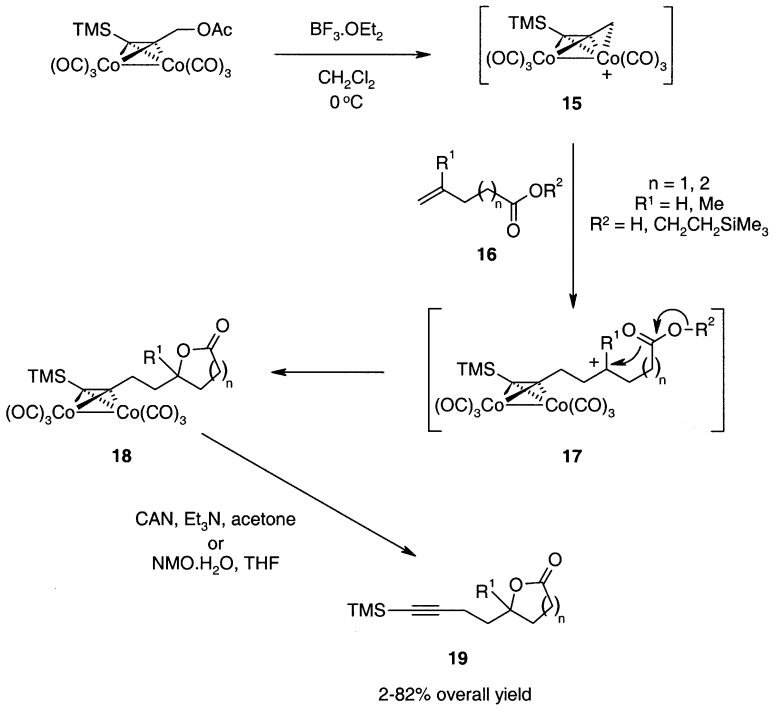


Scheme 1.



Scheme 2.

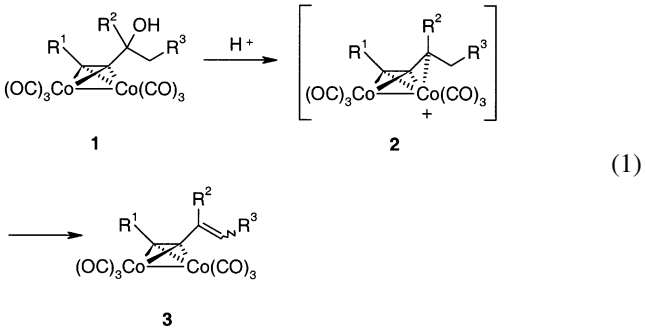


Scheme 3.

carbon α- to the alkyne moiety, prior to treatment with a nucleophile, the Nicholas reaction. Reactions of $Co_2(CO)_6$-stabilised alkynyl radicals will also be discussed. Applications where complexation of an alkyne to $Co_2(CO)_6$ has been used to enable the synthesis of cyclopentenones via the Pauson–Khand reaction will not be considered here. A chapter of Comprehensive Organometallic Chemistry II[5] has been dedicated to the Pauson–Khand reaction and Christie and Fletcher's[4] review provides a recent update on this topic. Similarly, cyclotrimerisation reactions of alkynes bound to $Co_2(CO)_6$ used to generate highly substituted benzene rings,[4] or examples where the $Co_2(CO)_6$ unit has been used merely as a sterically demanding 'blocking' group, or as a protecting group for the alkyne, will not be mentioned.

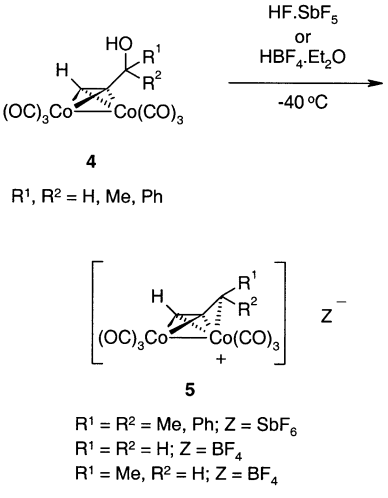
2. Introduction

In 1972, Nicholas and Pettit[6] reported the facile nature of acid-catalysed dehydration of dicobalt hexacarbonyl-complexed propargyl alcohols **1** to the corresponding 1,3-enyne derivatives **3** (Eq. (1)).



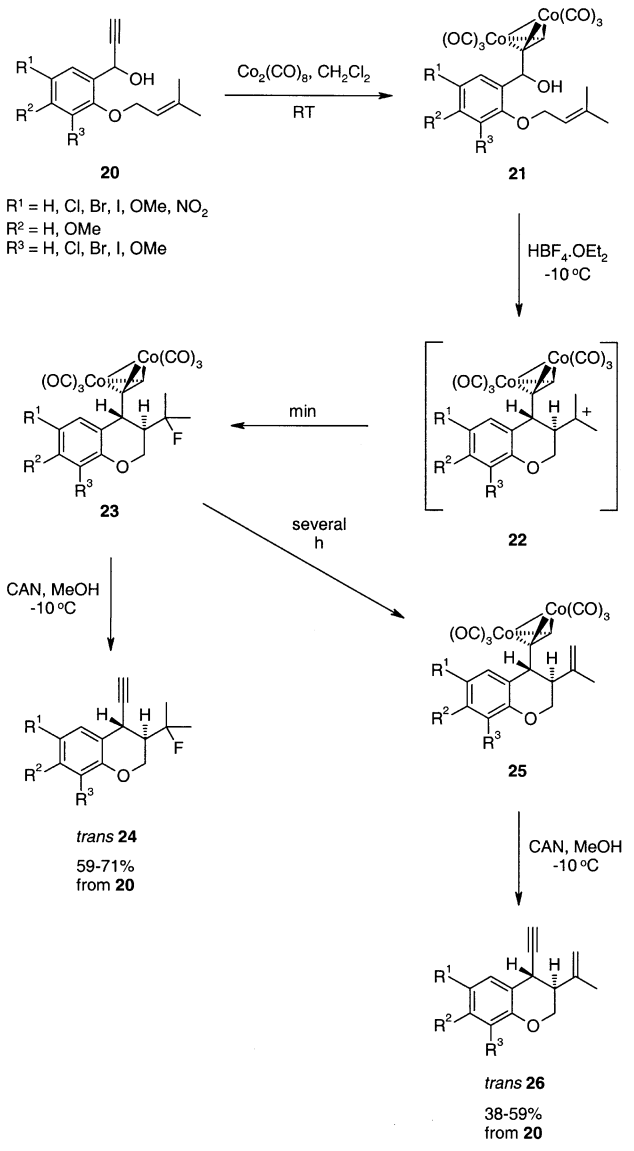
(1)

Propargyl alcohols not complexed to $Co_2(CO)_6$, however, failed to react under the same conditions. It had already been shown[7] that identical 1,3-enyne complexes **3** could be readily hydrated under similar mildly acidic conditions. These findings suggested that the likely intermediates in the reactions, $[(propargylium)Co_2(CO)_6]^+$ cations **2**, possessed considerable stability. It was, in fact, possible to observe these cations by ^1H NMR at 10°C when generated using *d*-trifluoroacetic acid.[6] Later, Connor and Nicholas[8] were able to isolate salts of such cations **5** as stable, dark red solids by treatment of the $Co_2(CO)_6$-complexed propargyl alcohols **4** with excess $HF{\cdot}SbF_5$ or tetrafluoroboric acid etherate (Eq. (2)).



(2)

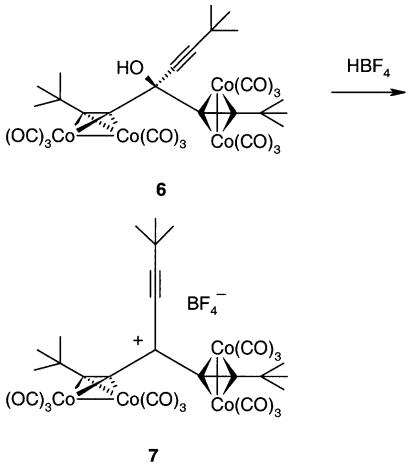
The reason that these complexes are so remarkably stable is due to significant delocalisation of the cationic charge onto



Scheme 4.

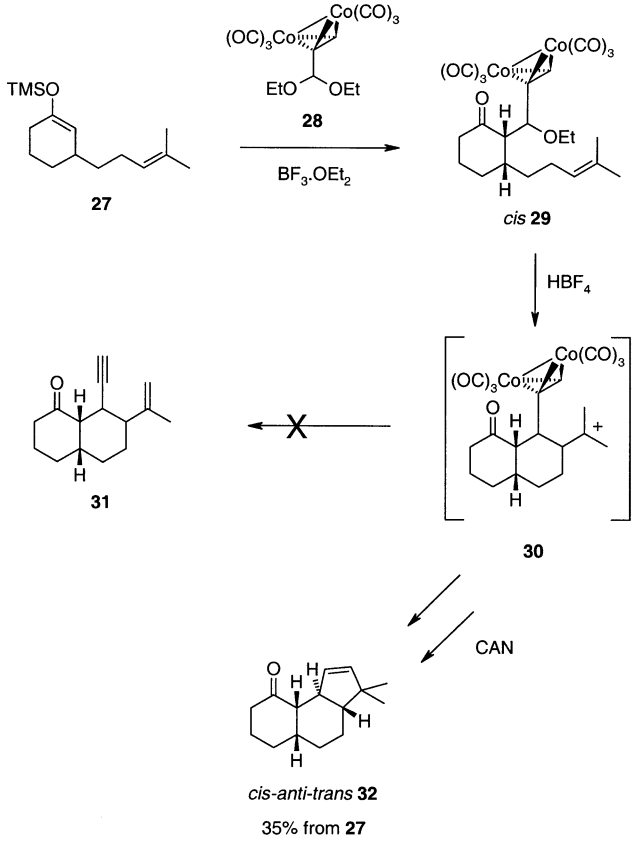
the $Co_2(CO)_6$ moiety. Experimental evidence[8] for this charge delocalisation takes the form of an increase in the IR absorption frequencies of the C≡O ligands present in the cations compared with those present in the parent alcohols. This increase, 40–60 cm^{-1}, is consistent with greater C–O bonding as a result of decreased $d(Co) \rightarrow \pi^*(CO)$ donation in the electron-deficient cations. ^1H NMR resonances of alkyl groups α- to the newly generated cationic centre experience smaller than expected deshielding effects relative to the neutral complexes, as do the ^{13}C NMR resonances of the co-ordinated C≡C–C system. Additionally, the ^{13}C NMR resonances of the C≡O ligands show small shielding effects.[9] These observations all support the idea of significant charge dispersal in such systems.

Recently, Melikyan et al.[10] published the first X-ray crystal structure of a $Co_2(CO)_6$-complexed propargyl cation. The compound chosen for their study **7** (Eq. (3)) contained two stabilising $Co_2(CO)_6$ groups, thus imparting extra thermal stability and greater crystallinity to the cation.



(3)

When comparing the crystal structures of **7** and the parent alcohol **6** several observations can be made. Generation of the cation leads to rehybridisation of the central sp^3 carbon atom to sp^2, with an almost ideal trigonal planar arrangement of atoms. The covalent bonds around the central carbon in the cation all shorten, as expected, due to greater *s*-character in the hybridisation of their orbitals. The orientation of the C≡C and Co–Co bonds in each of the metal complexes in neutral **6** is essentially perpendicular, with angles very close to 90°. In charged **7**, however, the metal complexes become non-equivalent with one adopting a twist of 7.7° away from perpendicular. A shift of the central

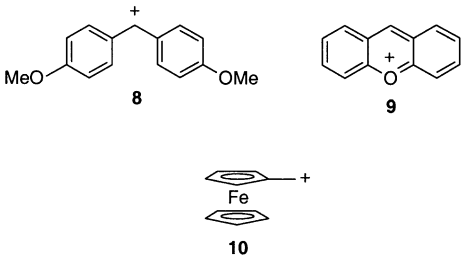


Scheme 5.

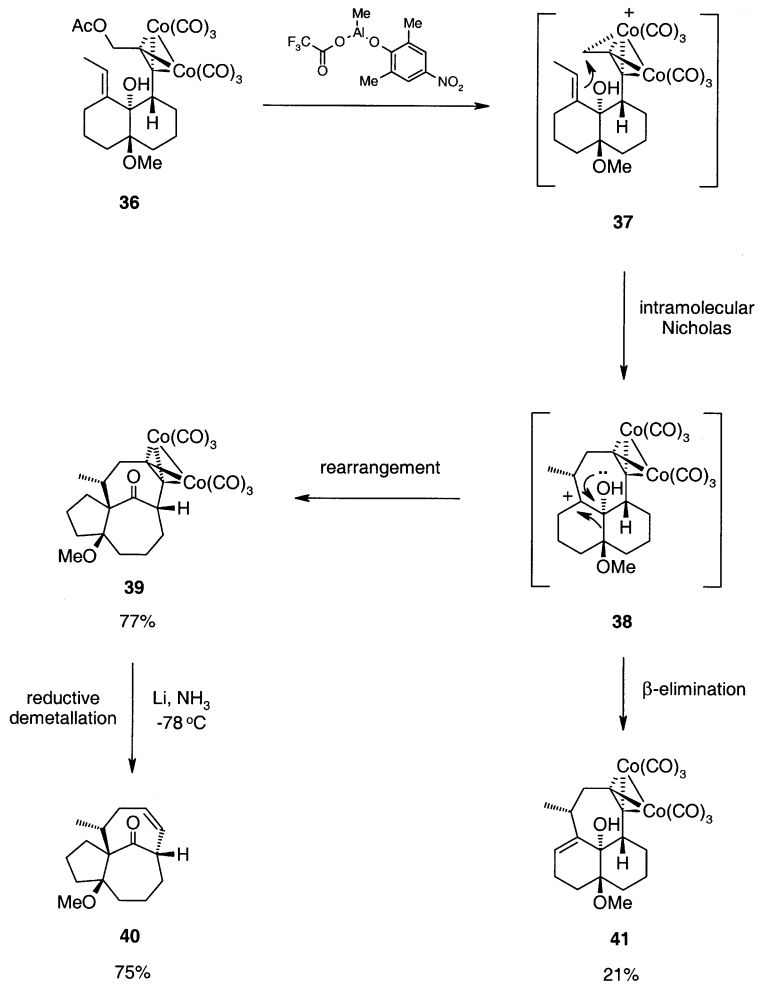
carbon atom closer towards one of the metal atoms in each Co–Co pair is also apparent in **7**, whereas in **6** it lies essentially equidistant from them. These fascinating observations begin to illustrate, for the first time, the physical changes at the atomic level that result from carbocationic charge stabilisation by the $Co_2(CO)_6$ group.

In addition to protonation of the precursor alcohols discussed above (Eq. (1)), the stabilised carbocations can be generated in a variety of other ways (Scheme 1). $Co_2(CO)_6$-complexed propargyl ethers, esters or aldehydes, when treated with Lewis acids, liberate carbocations—a method often used for the in situ preparation of carbocations prior to further reaction. The ethers can be alkyl, benzyl or silyl[11] and they can be cyclic or part of an acetal. Esters most often used include acetate, benzoate and pivaloate. Sulphonic acid esters such as mesylate[12] or triflate[13,14] can also be used. Related to this method of carbocation generation is the action of silver tetrafluoroborate on a suitable propargyl chloride.[15] Finally, electrophiles can be added to 1,3-enyne complexes.

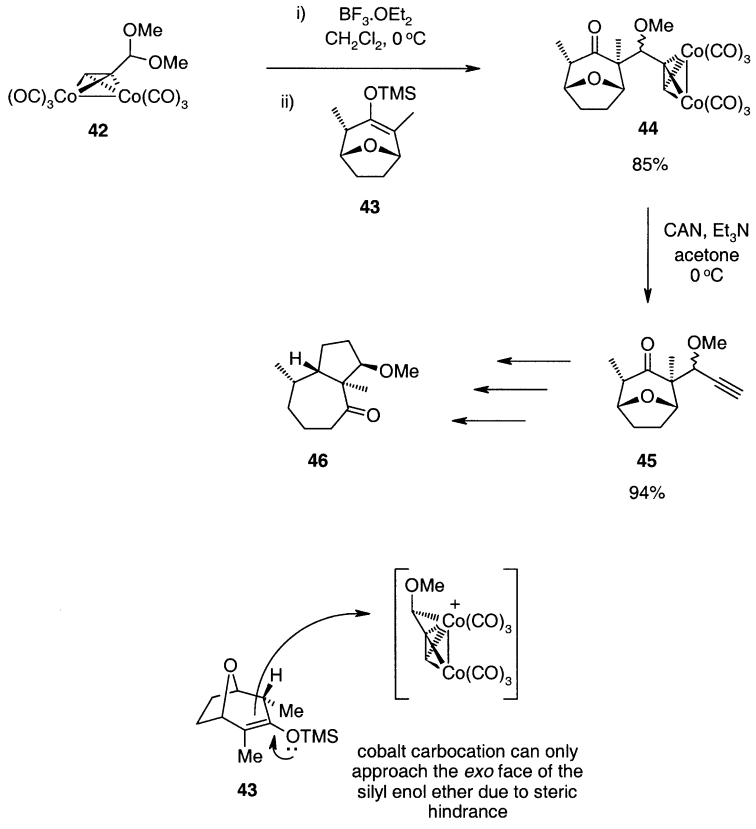
Once the stabilised carbocations have been generated, they can be reacted with a whole host of different nucleophiles. Mayr et al.[16] have studied the reaction kinetics of some simple $Co_2(CO)_6$-stabilised propargyl cations with a variety of π-nucleophiles and hydride donors. The corresponding electrophilicity parameters can be calculated for the cations and compared with those of other electrophiles. This allows $Co_2(CO)_6$-stabilised propargyl cations to be ranked, in terms of their reactivity, alongside other known electrophiles. Predictions can then be made as to what kind of nucleophiles should react with them. These authors concluded that dicobalt hexacarbonyl-stabilised propargyl cations are slightly less electrophilic than the dianisylmethylium ion **8** and behave in a similar manner to the xanthylium **9** and ferrocenylmethylium **10** ions.



Mayr et al. also predicted that the cations should react with numerous π-nucleophiles including electron-rich aromatics, simple alkenes, allylsilanes, allylstannanes, enol ethers and silylketene acetals. These predictions



Scheme 6.



Scheme 7.

are in good agreement with the experimental observations (vide infra).

The $Co_2(CO)_6$-complexed alkyne precursors used to generate the stabilised carbocations are easily prepared by the reaction of the alkyne with $Co_2(CO)_8$ in a suitable solvent.[17] Solvents that have been used include pentane, hexane, heptane, benzene, toluene, diethyl ether, tetrahydrofuran, dichloromethane and ethyl acetate. The products are usually obtained in high yields as red, brown or purple solids or oils, which are stable, and are easily purified by chromatography on silica or alumina.

After the Nicholas reaction, the cobalt complexes can be decomplexed in numerous ways, either oxidatively to yield the parent alkyne, or reductively to yield an alkene or a substituted alkene. Some of the oxidative methods that have been used for decomplexation are:

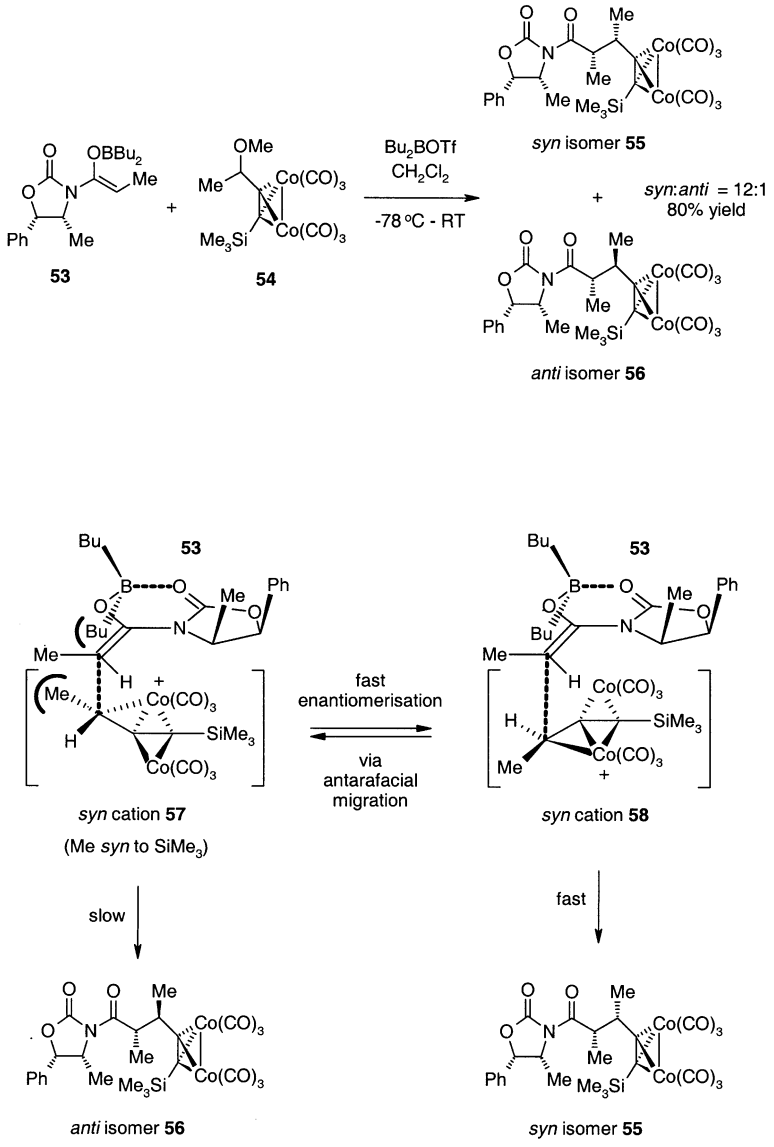
1. ferric nitrate used in alcohols, alcohol/tetrahydrofuran, or dichloromethane;
2. ceric ammonium nitrate or ceric sulphate, often in conjunction with a tertiary amine such as triethylamine or 2,6-di-*tert*-butyl-4-methylpyridine, used in acetone, methanol, methanol/water, methanol/ether, or acetonitrile; iodine used in tetrahydrofuran or benzene;
3. trimethylamine *N*-oxide used in tetrahydrofuran, methanol or chloroform;
4. *N*-methylmorpholine *N*-oxide, often in conjunction with 1,4-cyclohexadiene, used in tetrahydrofuran, dichloromethane, 2-propanol, *N*,*N*-dimethylformamide or carbon tetrachloride/*t*-butanol;
5. tetrabutylammonium fluoride used in tetrahydrofuran;
6. sodium methanethiolate used in *N*,*N*-dimethylformamide;
7. pyridine used in ether/air; and
8. dimethylsulphoxide/water used in benzene;

and some of the reductive methods that have been used for decomplexation to give alkenes are:

1. lithium used in liquid ammonia;
2. hydrogenation over rhodium–charcoal catalyst used in ethanol;
3. hydrogenation over Wilkinson's catalyst used in benzene;
4. tributyltin hydride used in benzene;
5. tributyltin hydride and *N*-bromosuccinimide used in 1,4-cyclohexadiene; and
6. triethylsilane or triphenylsilane used in benzene—forms the respective vinylsilane.

3. Hydride as nucleophile

In their synthesis of (+)-bengamide E, Hanaoka et al.[18] describe the deoxygenation of the tertiary propargyl alcohol **11** to the isopropyl derivative **14**, using sodium cyanoborohydride in the presence of zinc iodide (Scheme 2). These conditions, developed by Lau,[19] are known to reduce allylic and benzylic alcohols readily at room temperature. The propargyl alcohol **11** failed to react, however, even under reflux, but its $Co_2(CO)_6$ complex **12** reduced smoothly at room temperature to give **13**. The proposed mechanism of the reduction using sodium cyanoborohydride/zinc iodide is



Scheme 8.

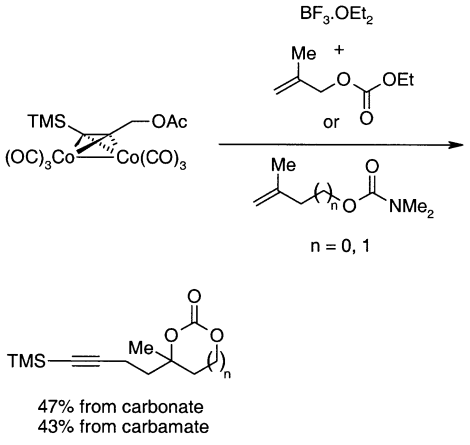
thought to involve single electron-transfer processes giving rise to radical intermediates.[19] The $Co_2(CO)_6$ group could therefore be helping to stabilise a radical rather than a cation in this example (vide infra).

4. Carbon as nucleophile

4.1. Alkenes

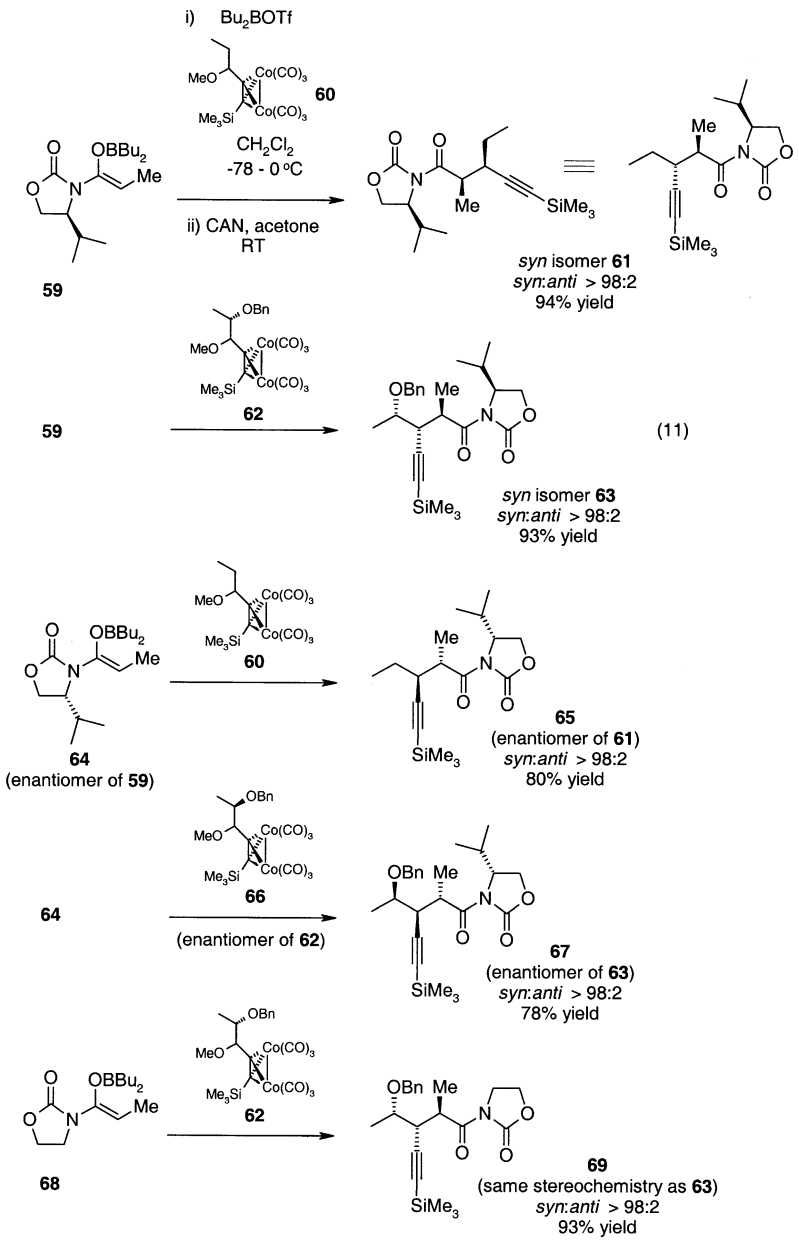
Krafft and co-workers[20] have studied the Nicholas reaction between the carbocation **15** and a terminal alkenyl acid or ester **16** (Scheme 3). The carbocation formed after initial intermolecular reaction **17** is trapped intramolecularly by the acid/ester moiety to give a lactone **18**, which is then decomplexed to give **19** in poor to good overall yield. The sequence works best for generation of five-membered lactones (i.e. n=1) and when **17** is a tertiary carbocation (i.e. R^1=Me).

Cyclic carbonates can be synthesised in an analogous fashion using alkenyl carbonates or carbamates (Eq. (4)).



(4)

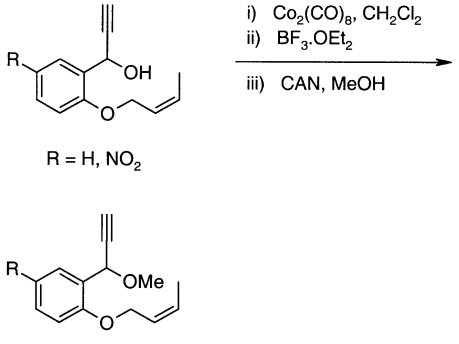
Tyrrell et al.[21,22] have used a tethered trisubstituted alkene as a nucleophile to effect ring closure onto a benzylic Nicholas cation in a new one-pot synthesis of benzopyrans (Scheme



Scheme 9.

4). The propynyl alcohol **20** is complexed to cobalt, cyclised under Lewis acid conditions and finally decomplexed to give the product, with each step taking place in situ. The carbocation **22**, formed after cyclisation of the complex **21**, is quenched by fluoride ion from the tetrafluoroboric acid to give the fluoride **23**, which is decomplexed to afford the fluorinated benzopyran **24** exclusively as the *trans* isomer in good yield. Furthermore, if the fluoride **23** is kept several hours prior to treatment with ceric ammonium nitrate, the alkene **25** can be obtained, perhaps via cobalt-assisted elimination of HF, which gives the isopropenyl benzopyran **26** in moderate to good yield after decomplexation. The nature of the substituents around the aromatic ring has little effect upon the reaction, unlike the substitution of the tethered alkene.

Attempts to try and cyclise disubstituted alkenes failed (Eq. (5)). This reinforces the findings of Krafft[20] namely that when cyclisation leads to generation of a secondary rather than a tertiary carbocation the yields are drastically



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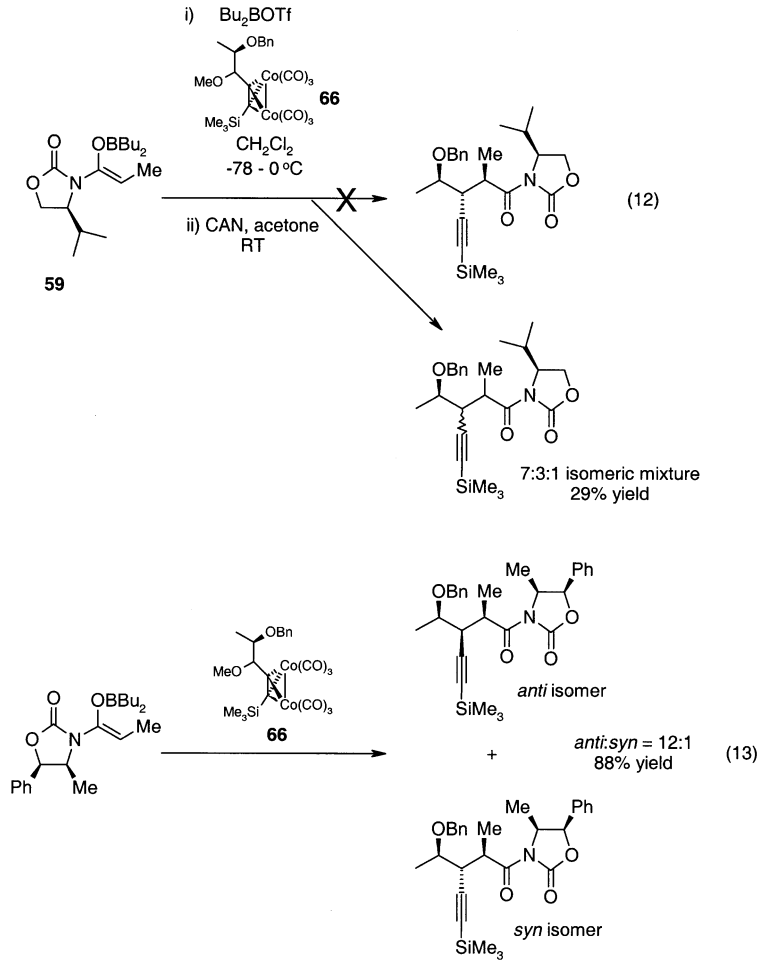
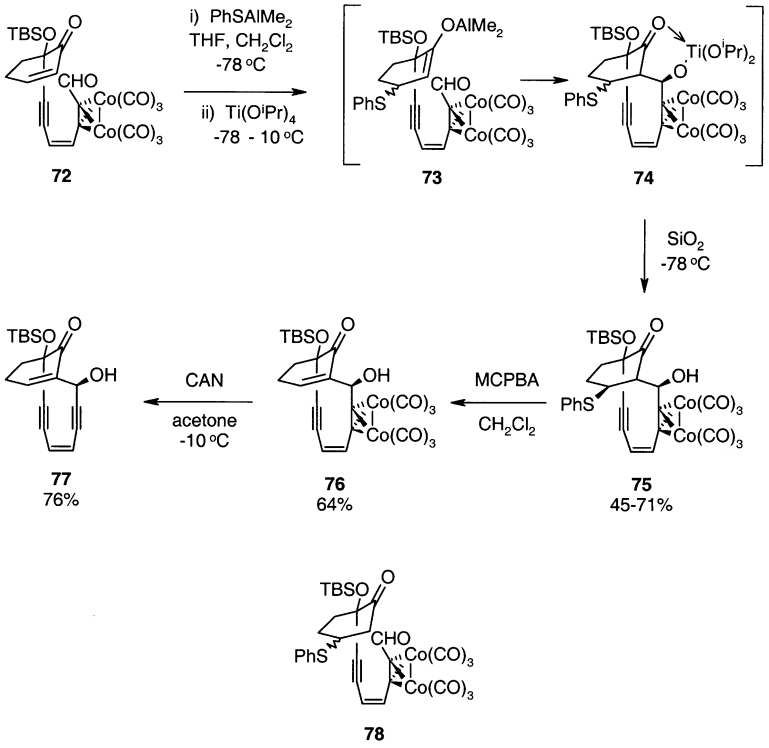
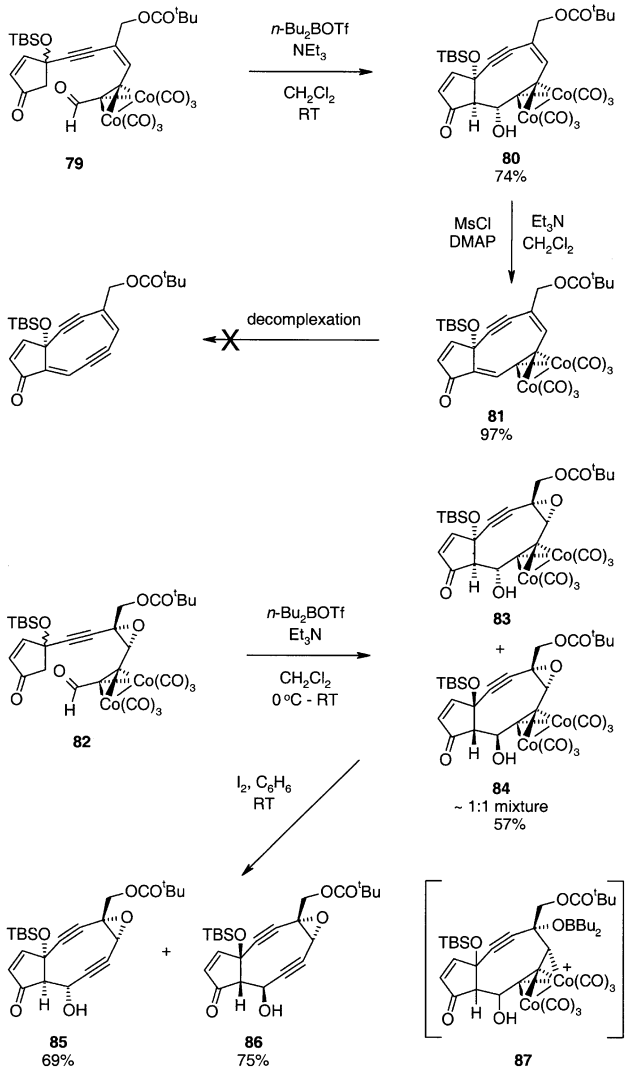


Scheme 10.



Scheme 11.

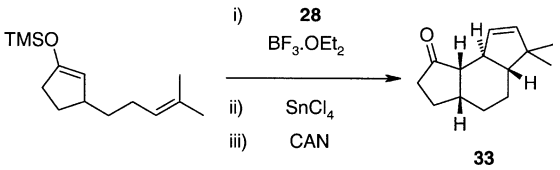


Scheme 12.

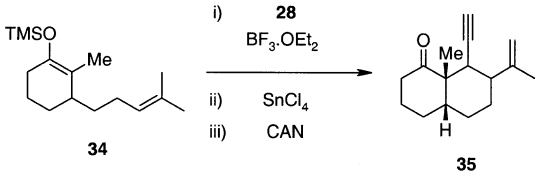
reduced. A number of other Lewis acids were examined in the reaction and found to be equally proficient, albeit in some instances giving mixtures of halogenated and alkenyl benzopyrans. The Lewis acids can even be used in sub-stoichiometric quantities.

Tyrrell[23] has extended this work to the cyclisation of non-aromatic precursors in an attempt to synthesise substituted decalins (Scheme 5). Use is again made of a one-pot method, this time including an initial intermolecular Nicholas reaction between the silyl enol ether **27** and the cobalt complex **28** used to prepare the cyclisation precursor **29** exclusively as the *cis* isomer. Upon treatment with more Lewis acid, **29** reacts as expected, presumably to form a carbocation **30**, which when decomplexed with ceric ammonium nitrate, or a range of other decomplexing reagents, fails to give any of the predicted decalone **31**. Instead, and quite surprisingly, the tricycle **32** is formed as a single product, with *cis–anti–trans* relative stereochemistry, in an overall yield of 35%. The exact nature of the intermediates that give rise to this second cyclisation is the subject of further study by the authors.

A 5-6-5 tricycle **33** can be synthesised in an analogous fashion (Eq. (6)), but the incorporation of an α-methyl substituent prevents the second cyclisation from taking place so that the silyl enol ether **34** gives the decalone **35** (Eq. (7)).



(6)



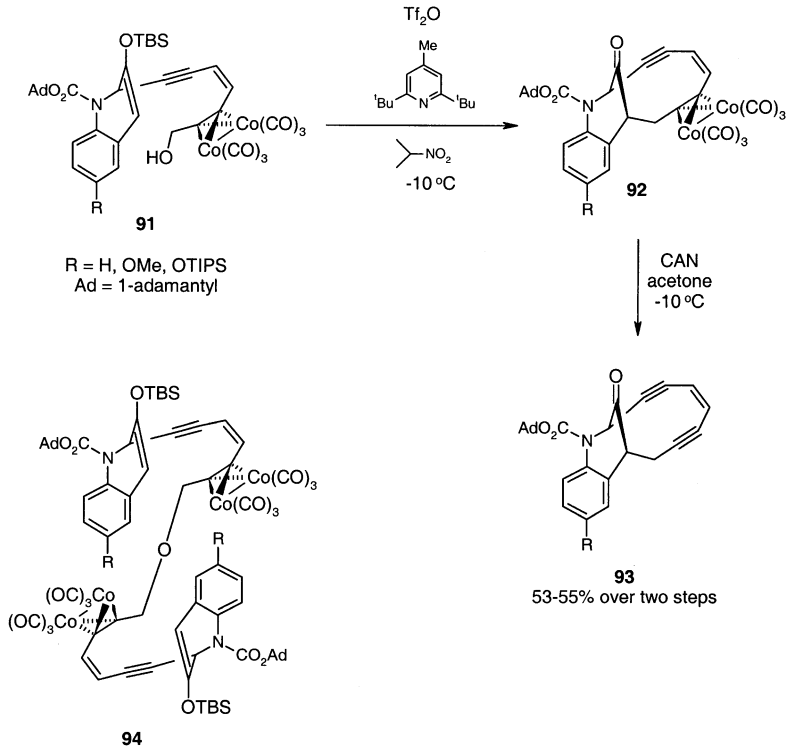
(7)

Tanino and co-workers[24] have developed a novel approach to the highly strained ingenane skeleton based upon a tandem Nicholas cyclisation–rearrangement strategy (Scheme 6). When treated with a suitable Lewis acid, the cobalt complex **36** formed a stabilised carbocation **37**, which was trapped intramolecularly by the adjacent alkene to form the tertiary carbocation **38**. The carbocation **38** then underwent a pinacol-type rearrangement to give the ingenane core **39**. A number of different Lewis acids were examined, with attention quickly focusing on substituted aluminium reagents, which combine low Lewis acidity with the ability to form an alkoxide from the tertiary alcohol, thus promoting the rearrangement pathway. The reagent of choice appeared to be $CH_3Al(OCOCF_3)[2,6\text{-}(CH_3)_2\text{–}4\text{-}NO_2\text{–}C_6H_2O]$, which gave a 77% yield of **39** together with 21% of the allyl alcohol **41** resulting from β-elimination. Finally, the cobalt complex **39** was reductively cleaved using Birch conditions to give the alkene **40** in 75% yield.

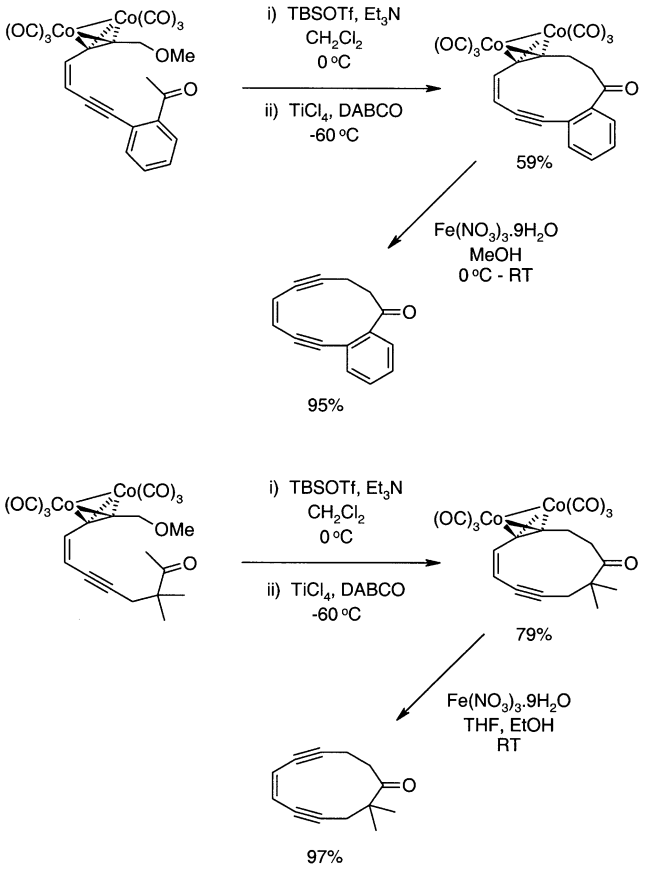
4.2. Enol derivatives

Montaña et al.[25,26] have used the nucleophilic attack by the silyl enol ether **43** upon the $Co_2(CO)_6$-stabilised carbocation derived from the acetal **42** to introduce a C_3 subunit which ultimately becomes the five-membered ring in their enantioselective synthesis of the *trans*-fused bicyclo[5.3.0]decane ring **46** (Scheme 7). The bulkiness of the cobalt cluster directs the attack at only the *exo* face of the silyl enol ether, as shown, thereby forming a single isomer at the position of attachment. A 1:1 mixture of epimers is produced at the adjacent methoxy position, which is of little consequence in the subsequent synthetic protocol. The cobalt complex **44** was readily demetallated using ceric ammonium nitrate to give the alkyne **45**, which was transformed into the *trans*-bicyclo[5.3.0]decane **46** in seven steps.

In their studies of the synthesis of carbocyclic rings, Tyrrell and co-workers[27] have used the intramolecular reaction between a silyl enol ether and a Nicholas carbocation to effect the synthesis of cyclic β-alkynyl ketones (Eqs. (8) and (9)). The keto group can be formed *endo*-cyclic **47** or

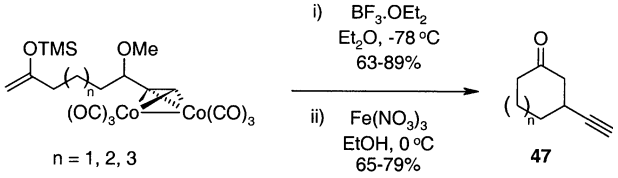


Scheme 13.



Scheme 14.

exo-cyclic **48**, depending upon which enol ether is used. *exo*-Cyclic keto groups are formed with *trans* stereochemistry relative to the alkyne moiety, in full agreement with the transition state model of Schreiber.[28]



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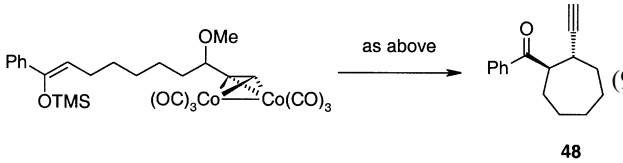
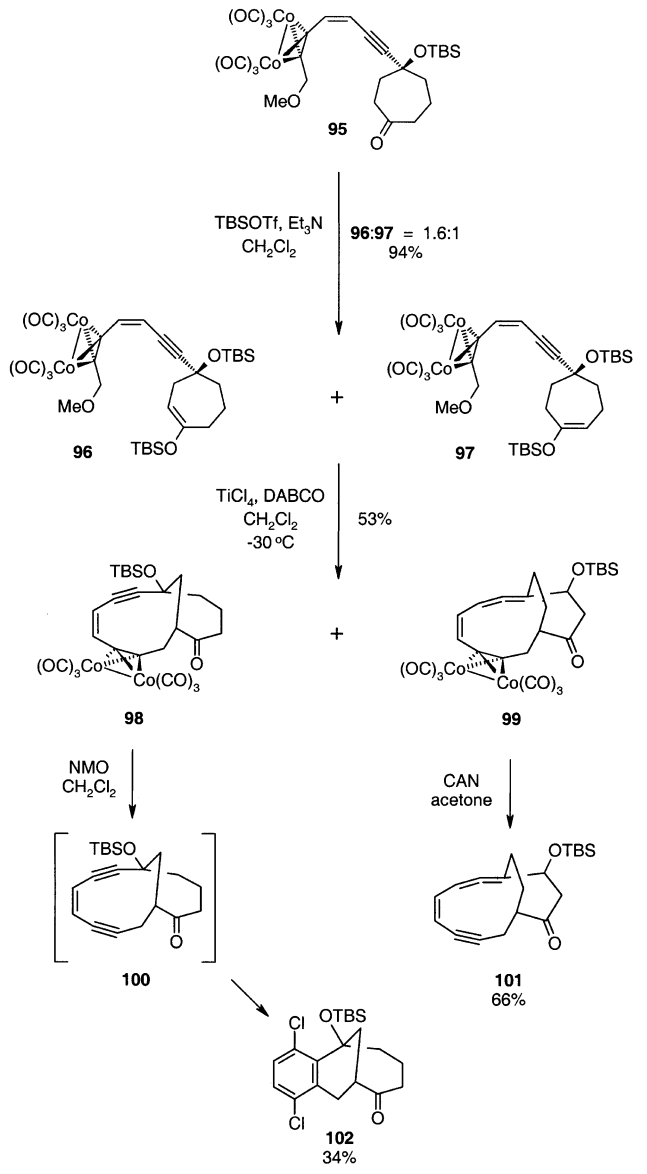


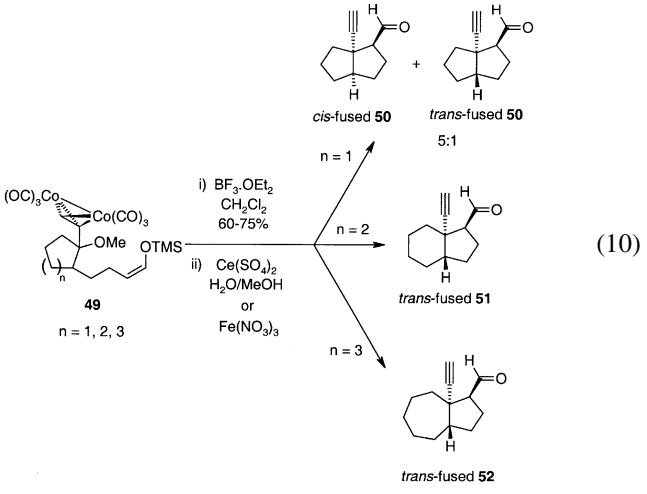
(9)

Tyrrell[29] has extended this work to the synthesis of bicyclic rings (Eq. (10)). When the cyclopentane derivative **49** (n=1) is treated with boron trifluoride etherate to effect cyclisation followed by cerium ions to effect decomplexation, a 5:1 mixture of the rather unstable *cis*-fused/*trans*-fused bicyclic aldehydes **50** is obtained. In contrast, the cyclohexane derivative **49** (n=2) and the cycloheptane derivative **49** (n=3) both exclusively afford the *trans*-fused bicyclic aldehydes **51** and **52**, respectively. As reported above, the relationship between the pendant aldehyde on the newly formed



Scheme 15.

ring and the alkyne moiety at the ring junction is *trans* in each case.



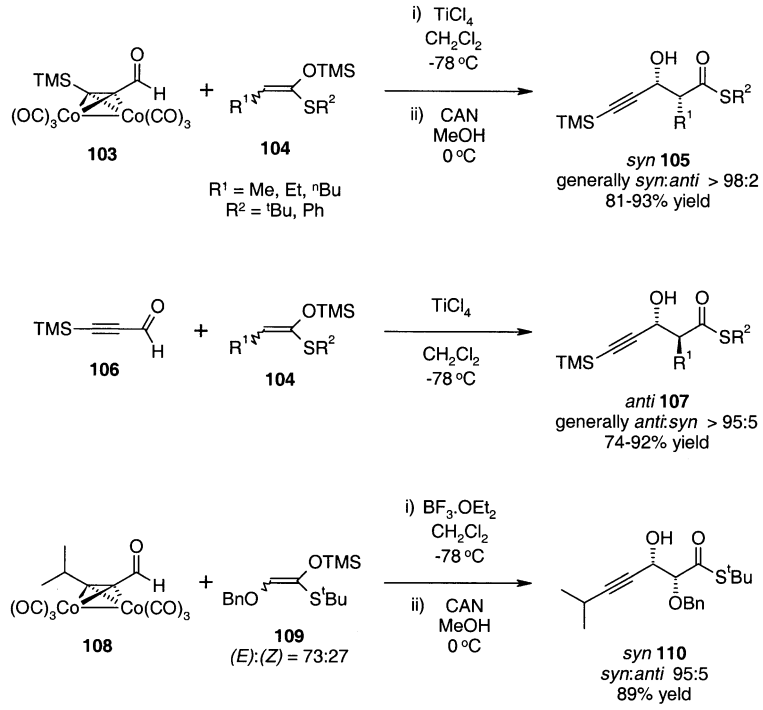
(10)

In 1987, Schreiber et al.[30] showed that boron enolates derived from Evans' chiral oxazolidinones would react with $Co_2(CO)_6$-stabilised carbocations to afford chiral products in good yield. The chiral enolate **53** and the cobalt complex **54**, for example, react in the presence of dibutylboron triflate to give a chiral 12:1 mixture of the *syn*/*anti* products **55** and **56**, respectively, in 80% yield (Scheme 8). Schreiber elegantly rationalised this result by postulating a novel double stereodifferentiating process in which the $Co_2(CO)_6$-stabilised cation rapidly interconverts via enantiomerisation at a rate that is faster than the alkylation reaction.

If two of the four possible stereoisomeric cobalt-stabilised cations, the *syn* enantiomers **57** and **58**, approaching the chiral enolate **53** along the Seebach[31] synclinal transition state, are considered, the cation **57**, which would react to give the *anti* alkylation product **56**, experiences a steric interaction between its methyl group and one of the pendant butyl groups on the boron of the enolate. Reaction between this 'mismatched' cation/enolate pair is therefore expected to be slow. The cation **58**, on the other hand, which would react to give the *syn* alkylation product **55**, does not experience this steric interaction. Reaction between this 'matched' cation/enolate pair is therefore expected to be fast. It has already been shown by NMR studies that $Co_2(CO)_6$-stabilised cations, e.g. **57** and **58**, can rapidly interconvert via an antarafacial migration[30] and if this process takes place at a faster rate than the alkylation reaction, the cation **57** will be converted to **58** and react to form the *syn* alkylation product **55** exclusively.

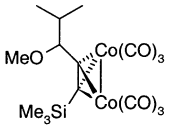
More recently, Jacobi and co-workers[32–38] have used the enolate **53** and other chiral and non-chiral oxazolidinone enolates, e.g. **59**, **64**, and **68**, to alkylate a host of dicobalt hexacarbonyl-stabilised cations, e.g. **60**, **62** and **66**, many containing chiral substituents (Scheme 9). The chiral products from these reactions, e.g. **61**, **63**, **65**, **67**, and **69**, were then used to prepare intermediates for tetrapyrrole and β-lactam syntheses. In most examples, the enolate/cation pair appears to be 'matched' and to produce good levels of diastereo- and enantioselectivities with *syn*/*anti* ratios >98:2. The chirality of the cation alone can even completely control the reaction, as shown by the excellent diastereo- and enantioselectivity obtained between the achiral enolate **68** and the chiral cobalt complex **62**.[34,35,37]

There are, however, exceptions such as the cobalt complex **70** which generally gives poor yields in these reactions probably due to a combination of steric effects and a tendency for the intermediate stabilised carbocation to undergo β-elimination.[34,37] Benzylthio ethers, e.g. **71**, appear not to be compatible with the reaction,[36] although the corresponding benzyloxy ethers, e.g. **62** and **66** (Scheme 9), react well. In addition, if the enolate/cation pair happens to be 'mismatched', i.e. if, in the transition state, the chirality of the enolate interferes with the chirality of the cation, poor yields and poor selectivities can then result. The reaction can even transpose its normal *syn* selectivity and produce the *anti* isomer as the major product[35–37] (compare the outcome of Eqs. (12) and (13) in Scheme 10 with Eq. (11) in Scheme 9). At present, there appears to be no way to predict which enolate/cation pairings will be

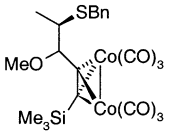


Scheme 16.

'matched' and which will be 'mismatched'. More research into possible transition state models for these fascinating reactions is eagerly awaited.



70



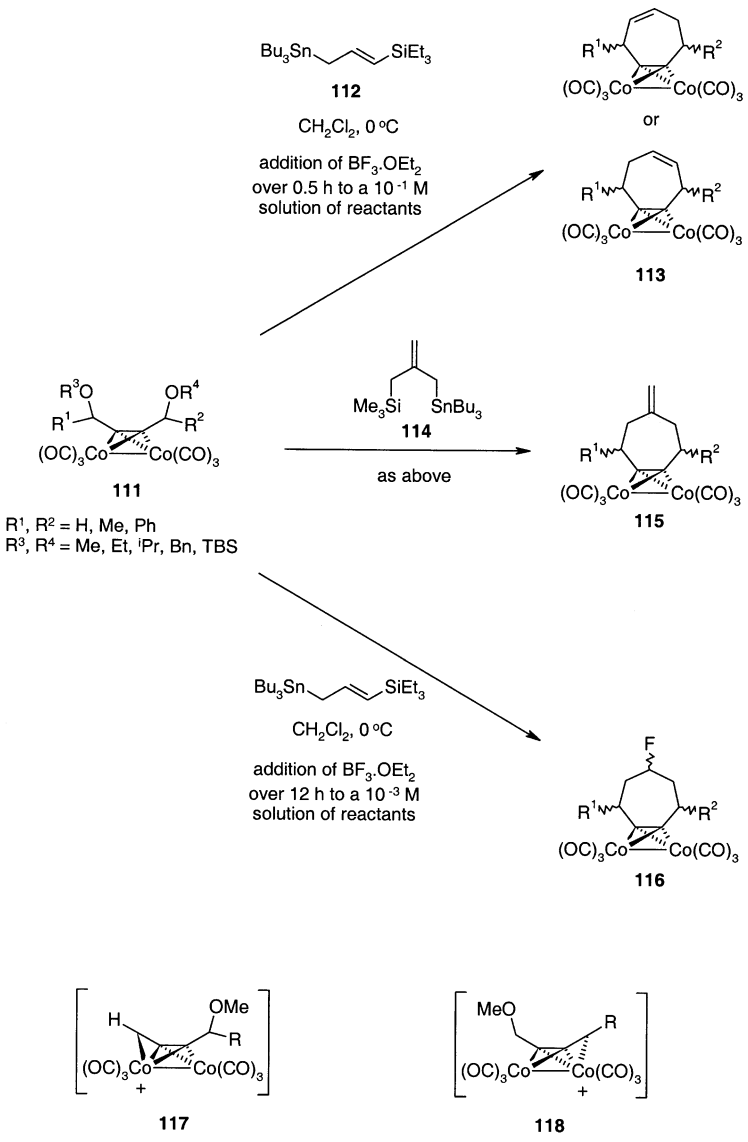
71

One of the largest areas of research that has used the Nicholas reaction to a supreme effect has been directed towards the synthesis of the enediyne antibiotics. This chemistry, largely dominated by the Magnus group, has exploited the coupling of silyl enol ethers or boron enolates with $Co_2(CO)_6$-stabilised carbocations, generated via Lewis acid treatment of the appropriate propargyl ethers or aldehydes (aldol reaction), to obtain large, highly strained, ring ketones.

In his protected calicheamicinone synthesis, Magnus[39] has used a combination of aluminium and titanium reagents to effect the key intramolecular aldol reaction used to prepare the bicyclo[7.3.1]tridecadienediyne ring core **77** (Scheme 11). The reagent, $PhSAlMe_2$, rapidly adds to the cobalt complex **72** to form two diastereomeric β-sulphides, presumably **73**. When treated with titanium tetraisopropoxide, only one of these β-sulphides cyclises to form the product **75**, most probably via a chelate **74**. The reaction is worked up by quenching with silica gel at −78°C to prevent a retro-aldol reaction to give **78**. The unstable sulphide **75** is rapidly oxidised and eliminated to give the stable unsaturated ketone **76**, which cannot now undergo a retro-aldol reaction, and then decomplexed to the bicyclo[7.3.1]tridecadienediyne ring **77** using ceric ammonium nitrate. This route supersedes a previously reported aldol cyclisation to form the bicyclo[7.3.1]tridecadienediyne ring system using dibutylboron triflate/DABCO,[40] and other cyclisations involving silyl enol ethers that use titanium tetrachloride/DABCO or triflic anhydride/2,6-di-*tert*-butyl-4-methylpyridine.[40–43]

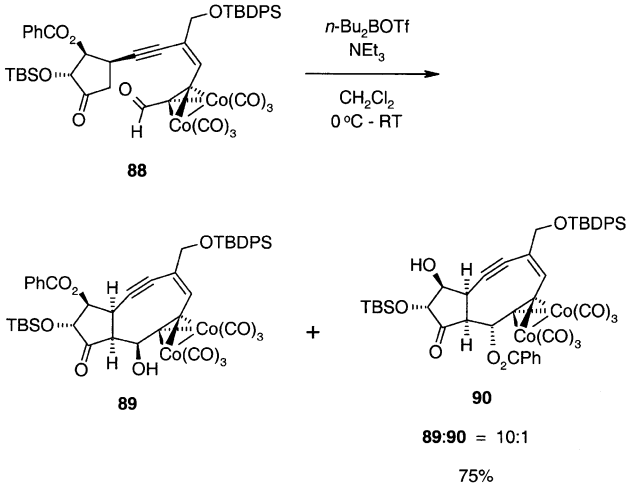
In the synthesis of the bicyclo[7.3.0]dodecadienediyne cores of kedarcidin and neocarzinostatin, Magnus and co-workers[44–46] used dibutylboron triflate/triethylamine to effect the crucial intramolecular aldol reaction (Scheme 12). The cyclisation appears to produce a 1:1 mixture of diastereomers that, for compound **79** at least, equilibrate on silica during work-up to give a single isomer **80** as the sole product. The successful cyclisation of the epoxide **82** is surprising, since it was anticipated that the epoxide moiety might spring open to relieve ring strain under the Lewis acid conditions of the aldol reaction, thus producing another cobalt-stabilised carbocation, e.g. **87**. Whilst the alcohol **80** could be readily dehydrated to the triene **81**, subsequent demetallation only led to decomposition. Removal of the $Co_2(CO)_6$ moiety from the complexes **83** and **84**, however, was successfully accomplished using iodine in benzene to afford the diynes **85** and **86**, respectively, in good yield.

Using an almost identical strategy to synthesise the same bicyclo[7.3.0]dodecadienediyne ring system, Caddick et al.[47,48] employed dibutylboron triflate/triethylamine to cyclise the keto aldehyde **88** (Eq. (14)). This aldol reaction produced a 10:1 mixture of products, identified as the alcohols **89** and **90**. Interestingly, the major product in this case, **89**, had the hydroxyl group in the opposite orientation to that observed by Magnus, presumably as a result of the extra, rather bulky, substitution around the cyclopentane ring. The minor product, **90**, appeared to be the hydroxy



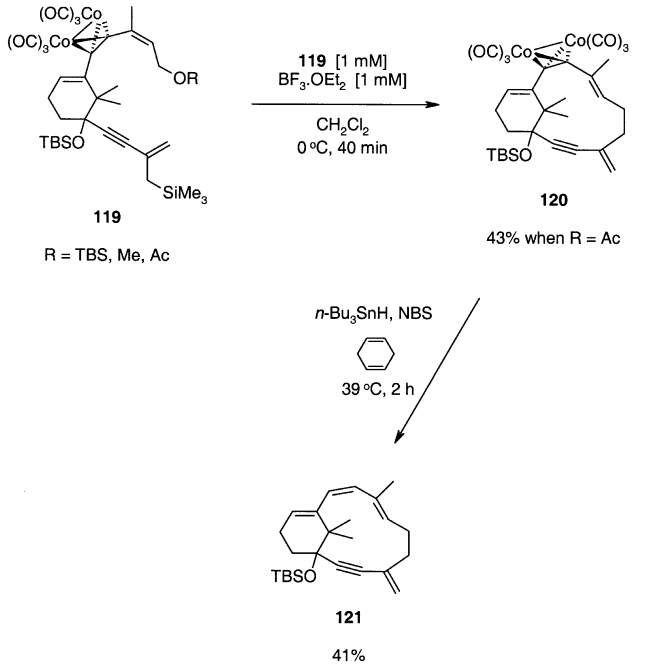
Scheme 17.

epimer of **89** with a concomitant benzoate migration.



(14)

For the preparation of the 10-azabicyclo[7.3.1]tridecaenediyne ring system found in dynemicin A, Magnus et al.[13,14,49] used the intramolecular trapping of a Nicholas cation with a silyl enol ether (Scheme 13). The stabilised cation was generated using triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in 2-nitropropane as the solvent. When the reaction was conducted in dichloromethane, only the symmetrical ether **94** was obtained. Magnus rationalised that, in a non-polar, poorly solvating environment such as dichloromethane, the alcohol **91** could hydrogen bond with itself, intermolecularly. Consequently, as soon as any carbocation was generated, it was immediately trapped by a neighbouring molecule of **91** to give **94**. The answer would be to create a much more polar, better solvating environment to help stabilise the $Co_2(CO)_6$-propargylic cation long enough to enable it to react intramolecularly with the silyl enol ether. 2-Nitropropane (or nitromethane[13]) provides just that environment. The cyclised product **92** is quite unstable and is decomplexed immediately using ceric ammonium nitrate to give the required azabicyclo[7.3.1]tridecaenediyne ring **93**.



Scheme 18.

In 1994, Magnus[50] reviewed his general strategy for using dicobalt hexacarbonyl–acetylene complexes and the Nicholas reaction for the synthesis of enediyne antibiotics.

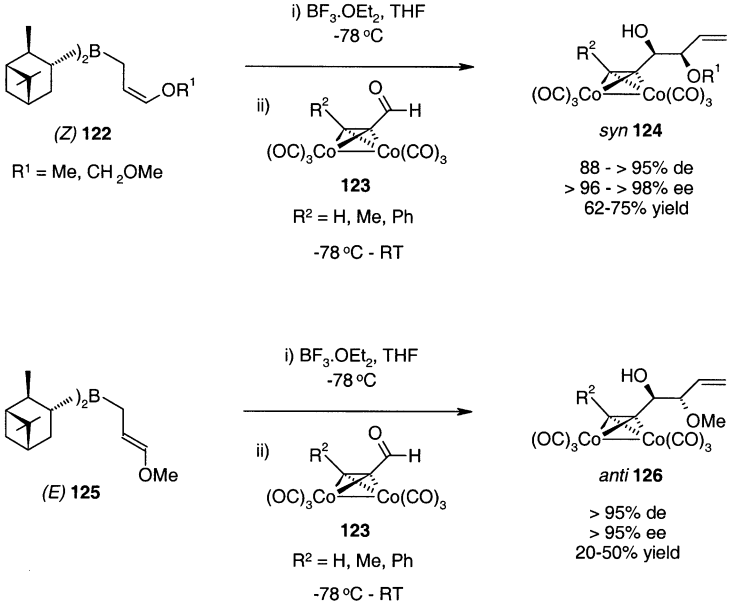
Maier and co-workers[51,52] have used the titanium tetrachloride/DABCO conditions of Magnus (vide supra) to effect ring closure of a silyl enol ether onto a $Co_2(CO)_6$-stabilised carbocation during the synthesis of model enediyne ring systems (Schemes 14 and 15). The cyclic ketone **95** (Scheme 15) formed two isomeric silyl enol ethers, **96** and **97**, one of which, **96**, cyclised to form the predicted product **98**. The other silyl enol ether, **97**, cyclised to form the unusual allene **99**, probably via a dyotropic rearrangement of the product that was formed initially. Bizarrely, whilst demetallation of the cobalt complex **98** with *N*-methylmorpholine *N*-oxide led to the formation of the aromatic **102**, presumably via a Bergman cyclisation of the enediyne **100**, the allene **99** could be demetallated using ceric ammonium nitrate to give the *stable* eneyne–allene ring system **101**.

Hanaoka and co-workers[53–55] had previously reported that the aldol reaction between the cobalt complex **103** and *O*-silylketene *O*,*S*-acetals **104** in the presence of titanium tetrachloride proceeded to give the *syn* stereoisomer **105** selectively, whereas the free alkyne **106** reacted to give the *anti* stereoisomer **107** (Scheme 16). Both the (*E*)- and (*Z*)-isomers of the *O*-silylketene *O*,*S*-acetals react to give the same product and, with one or two exceptions, the stereoselectivity of the reactions was >98:2. More recently, in his total synthesis of bengamide E, Hanaoka[56,57] reported that the isopropyl-substituted cobalt complex **108** reacted analogously with an *O*-silylketene *O*,*S*-acetal that carried an extra oxygen substituent **109**. Changing the Lewis acid to boron trifluoride etherate greatly improved the reaction, and gave the *syn* product **110** in 89% yield with 95:5 stereoselectivity.

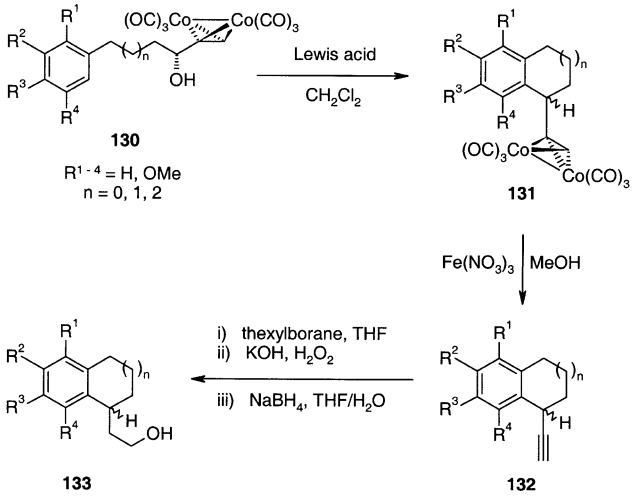
Hanaoka and Mukai[58] have reviewed their development and exploitation of the reactions of alkyne–$Co_2(CO)_6$ complexes. Part of their review discusses in detail the *syn*-selective aldol reaction mentioned above, and its application to the synthesis of bioactive molecules.

4.3. Allylmetals

Green[59] has successfully carried out the synthesis of the $Co_2(CO)_6$-complexed cycloheptyne derivatives **113**, **115** and **116** (Scheme 17) by employing a double Nicholas reaction between the alkynyl diether complexes **111** and the allyldimetals **112** and **114**. Despite an earlier report disclosing the failure of an analogous reaction,[60] Green



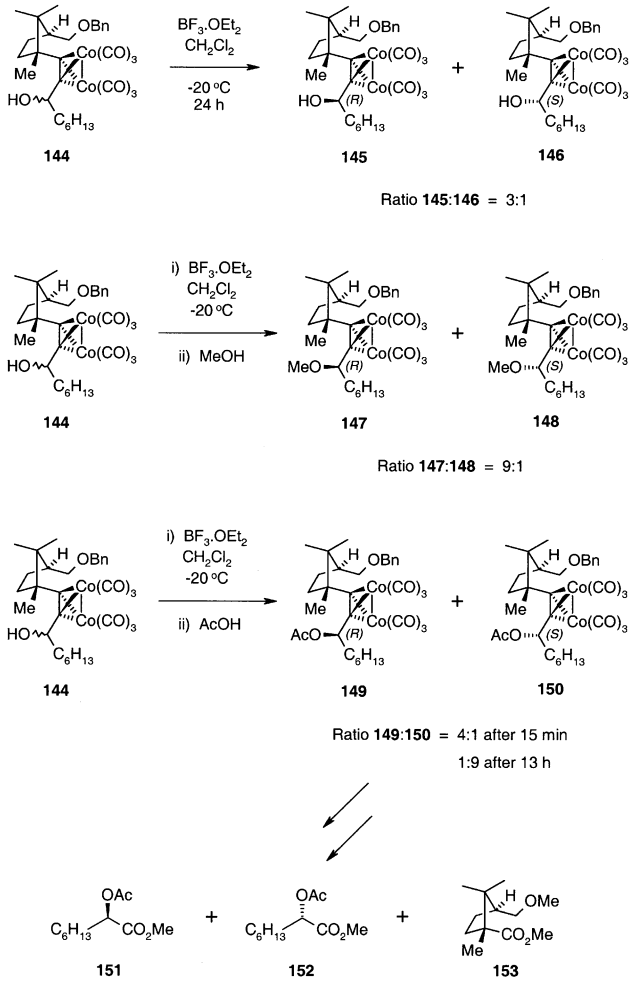
Scheme 19.



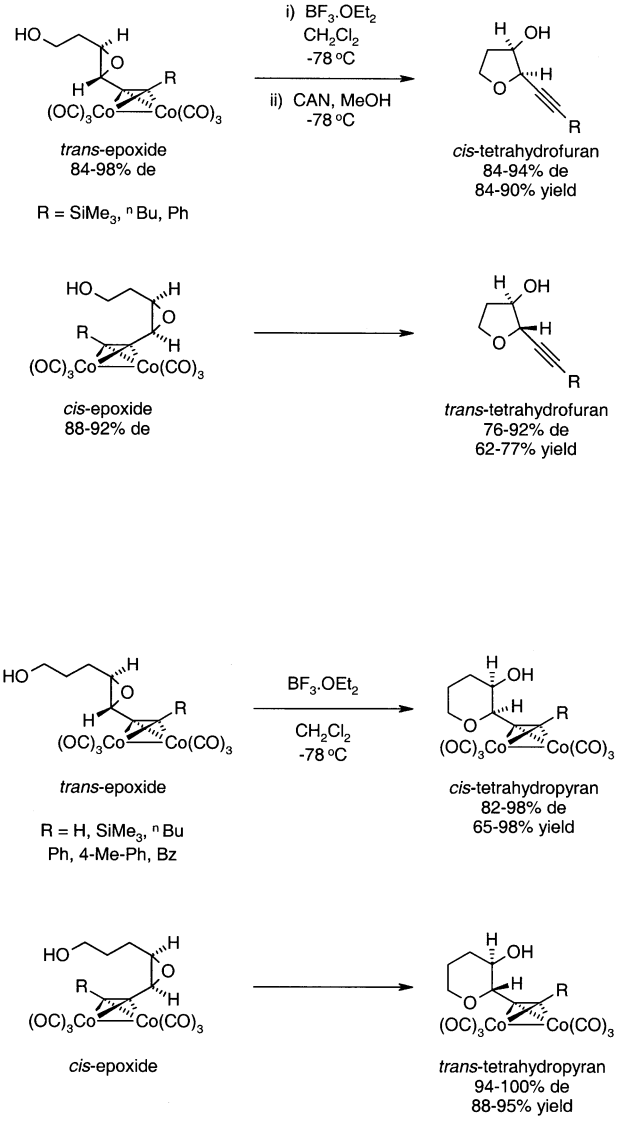
Scheme 20.

discovered that moderately slow addition of a Lewis acid to a solution of the silylstannane and the diether complex at 0°C gave the cycloheptyne derivatives in 37–72% yield. A brief study varying the substituents R^1–R^4 concluded that the double bond regioisomer of the product that is derived from initial formation of the less substituted carbocation, e.g. **117** rather than **118**, predominates, and that the *trans* diastereomer of the product predominates over the *cis* diastereomer. In addition, and quite surprisingly, much slower addition of the Lewis acid to a more dilute solution of the reactants afforded the fluoride **116** in 55–80% yield. These single-step procedures supersede the author's earlier work describing the synthesis of cycloheptyne derivatives in three steps.[61]

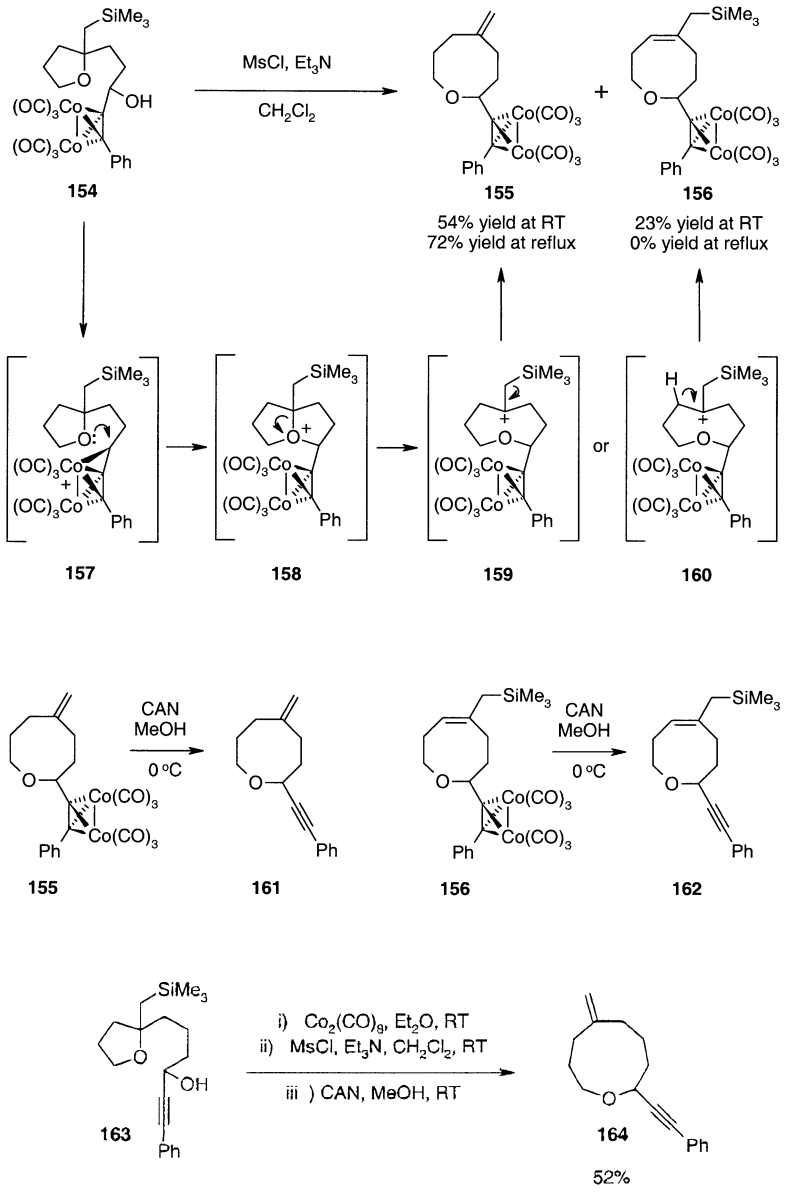
In his synthesis of the bicyclo[9.3.1]pentadecane skeleton **121**, common to a series of taxoid diterpenoids, Isobe[11,62] has used an intramolecular Nicholas reaction between a vinylogous $Co_2(CO)_6$-stabilised carbocation and an allylsilane (Scheme 18). When a dilute solution of the cobalt complex **119** was treated with a Lewis acid, the bicycle **120** was obtained. The cyclisation proceeded to give a single regioisomer with *trans* stereochemistry as described by Nicholas.[63] An examination of three different leaving groups (silyl ether, methyl ether, acetate) and two Lewis acids (boron trifluoride etherate, triflic acid) concluded that the best cyclisation conditions were those shown in Scheme 18, affording the product in 43% yield from the



Scheme 21.



Scheme 22.



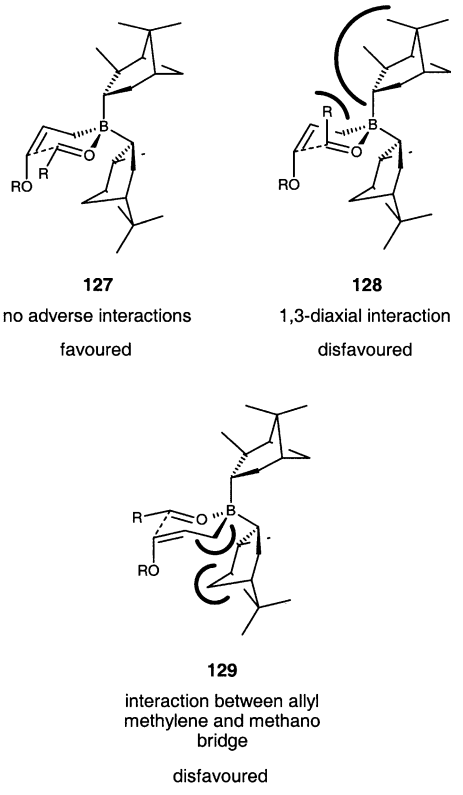
Scheme 23.

acetate. The bicycle **120** could not be oxidatively decomplexed to the free diyne, presumably because of the increase in strain energy in the diyne system, and only degradation products were observed. Instead, the cobalt complex was cleaved reductively using tribuyltin hydride and catalytic *N*-bromosuccinimide in 1,4-cyclohexadiene to give the *cis*-tetraene **121** in 41% yield.

Nicholas[64,65] has studied the reaction of the chiral (*Z*)- and (*E*)-(γ-alkoxyallyl)diisopinocampheylboranes **122** and **125** with $Co_2(CO)_6$-complexed alkynyl aldehydes **123** (Scheme 19). Whereas the free alkynyl aldehydes reacted with poor efficiency (5–15% yield) and limited enantioselectivity (65–89% ee) with **122** and **125**, the corresponding cobalt complexes underwent efficient regio-, diastereo- and enantioselective reaction, producing the (3-alkoxy-4-hydroxy-1-ene-5-yne)$Co_2(CO)_6$ complexes in moderate to good yield. The (*Z*)-borane **122** reacted to give the *syn*-diol derivatives **124** whilst the (*E*)-borane **125** gave the diol derivatives with *anti* stereochemistry **126**. The complexes **124** and **126** were readily demetallated without loss of enantiomeric purity upon treatment with ceric ammonium nitrate in acetone (40–72% yield).

The diastereoselectivities observed in these reactions can be explained satisfactorily by the six-membered chelation transition state model for allylmetal additions to carbonyl compounds. Consider the putative transition states **127** and **128** involving the ((*Z*)-alkoxyallyl)borane. That which leads to the *syn* adduct, i.e. **127**, avoids a 1,3-diaxial interaction between the bulky (alkynyl)$Co_2(CO)_6$ and isopinocampheyl units, an interaction which is clearly present in **128**, the transition state leading to the *anti* adduct. Similar transition states can be drawn using the ((*E*)-alkoxyallyl)borane which help to explain its *anti*-selectivity.

The origin of the enantioselectivities in these reactions, however, is less apparent. A tentative explanation provided

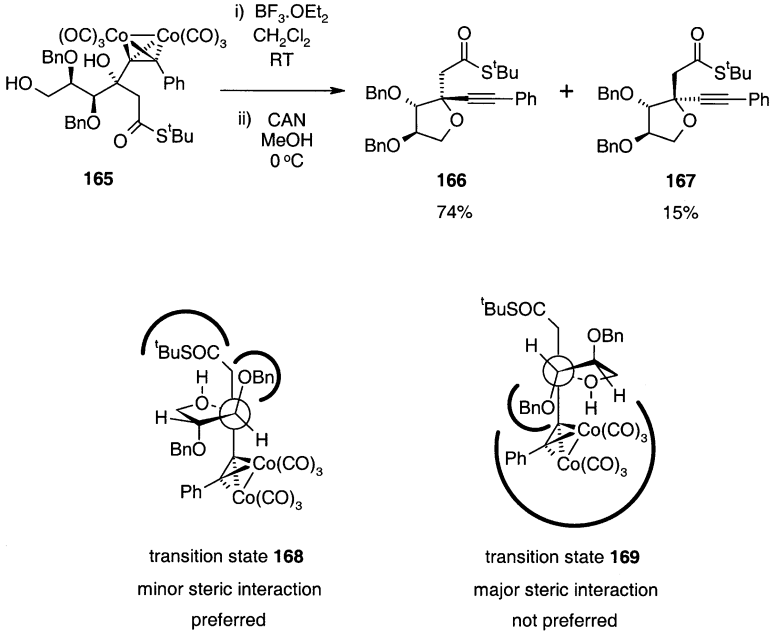


by Nicholas involves a comparison of the putative transition states **127** and **129**. A minimisation of the steric interactions between the two isocampheyl units bound to the boron creates a chiral pocket around the site at which the reacting allyl and aldehyde fragments are assembled. The methano bridge of the pseudoequatorial isocampheyl unit appears to have a greater steric/electronic interaction with the nearby allyl methylene group in **129** than with the aldehyde oxygen in **127**. Consequently, the aldehyde approaches the allylborane from only one of its two available faces, and a chiral product results. The greater bulk of the cobalt complexes compared with the free aldehydes may help to enhance this effect by distorting the transition state and magnifying the interactions, thus increasing the observed enantioselectivity.

4.4. Aromatics

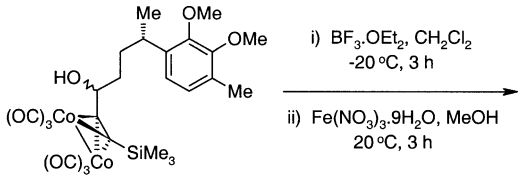
Muehldorf et al.[66] examined the reactions of $Co_2(CO)_6$-complexed chiral secondary propargyl alcohols tethered to electron-rich aromatic rings **130** to probe whether they would cyclise enantiospecifically to give chiral products **131** (Scheme 20). Unfortunately, the tetrahydronaphthalenes **131** and **132** proved to be thermolabile, and rapid conversion to the alcohol **133** was necessary before the enantiomeric purity of the products could be measured. The absolute stereochemistry of the products, however, was not established. The cyclisation reactions were conducted at as low a temperature as practically possible, typically between −65 and 0°C, to balance reasonable reaction times with the need to maintain the carbocation configuration. Three parameters were varied to assess their effect upon enantioselectivity: the Lewis acid, the size of the newly formed ring, and the pattern of aromatic substitution. Boron trifluoride etherate proved to be the best Lewis acid, whilst only formation of six-membered rings gave chiral products. With regard to the pattern of aromatic substitution, there is a requirement to activate the ring towards cyclisation electronically without hindering it sterically. 3,4-Dimethoxy-substitution in **130** gave the best results, leading to the corresponding product **133** (R^1, R^4=H; R^2, R^3=OMe; n=1) in 72% yield and 97% ee.

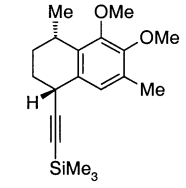
Broadly speaking, it is the reaction temperature that controls the degree of enantioselectivity: at temperatures above −50°C, racemisation of the $Co_2(CO)_6$-stabilised carbocation intermediate[30] begins to compete with ring formation.



Scheme 24.

Kocienski and co-workers[67] have used a similar ring closure in their approaches to pseudopterosin G aglycone. A methyl substituent on the alkyl chain tether provides the controlling chiral centre in this example, and the stereochemistry of the propargyl alcohol is therefore unimportant (Eq. (15)).

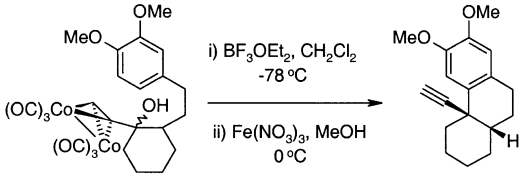




90% de
86% yield from
uncomplexed alkyne

(15)

Grove et al.[68] have prepared a *cis*-fused octahydrophenanthrene system using an intramolecular Nicholas reaction similar to those discussed above. When the cobalt complex **134** was treated with boron trifluoride etherate at −78°C, followed by ferric nitrate at 0°C, a 78% yield of the tricycle **135** was obtained (Eq. (16)).

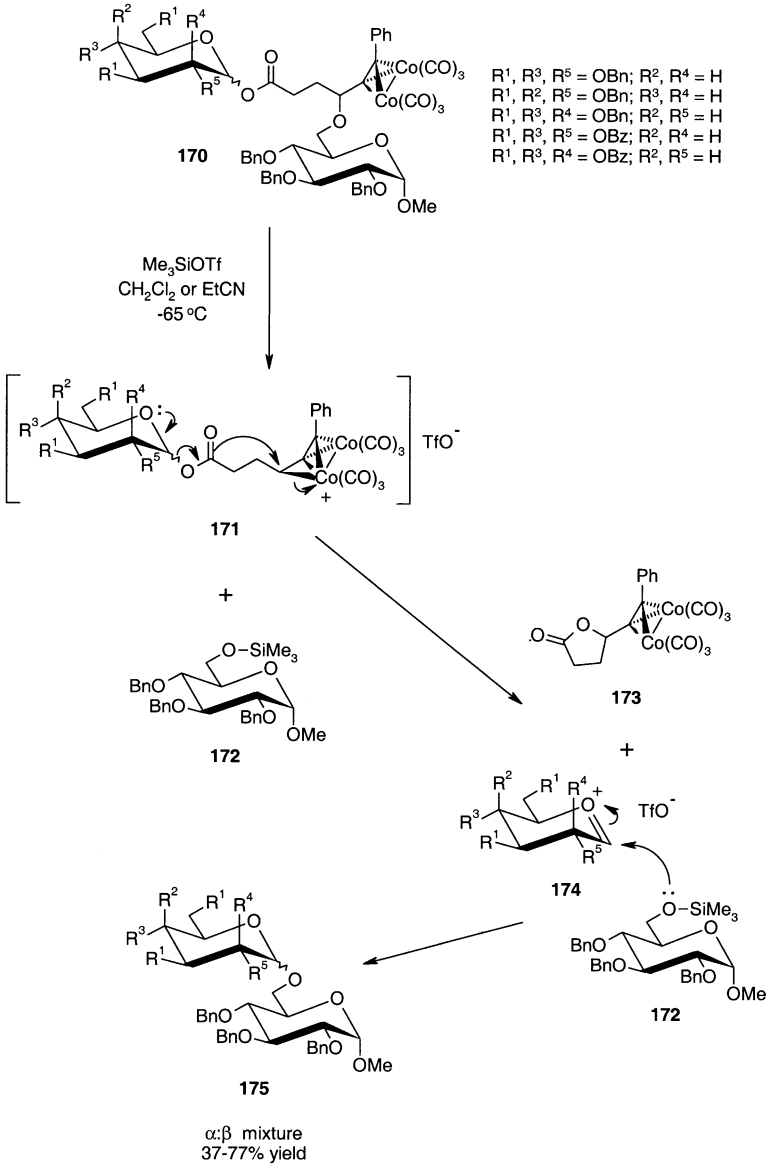


134

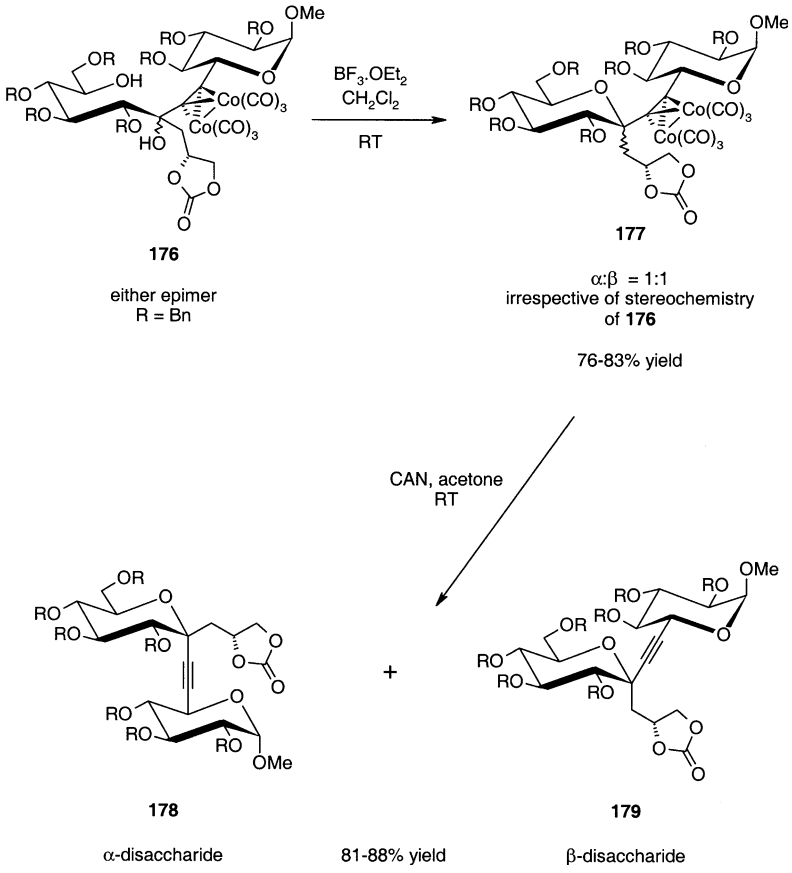
135

78%
> 95:5 *cis*:*trans*

(16)

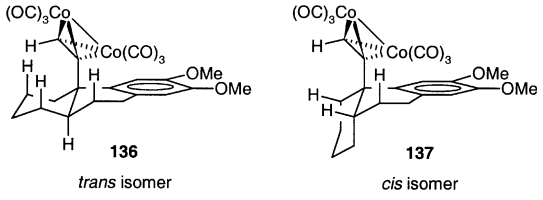


Scheme 25.



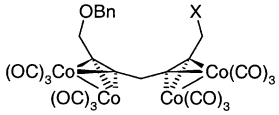
Scheme 26.

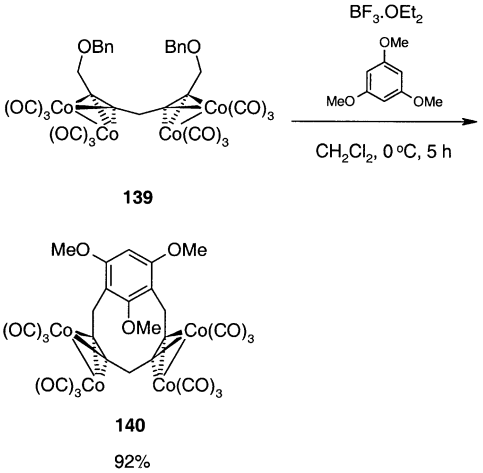
A tentative explanation for the resulting *cis* stereochemistry is provided by the structures **136** and **137**.



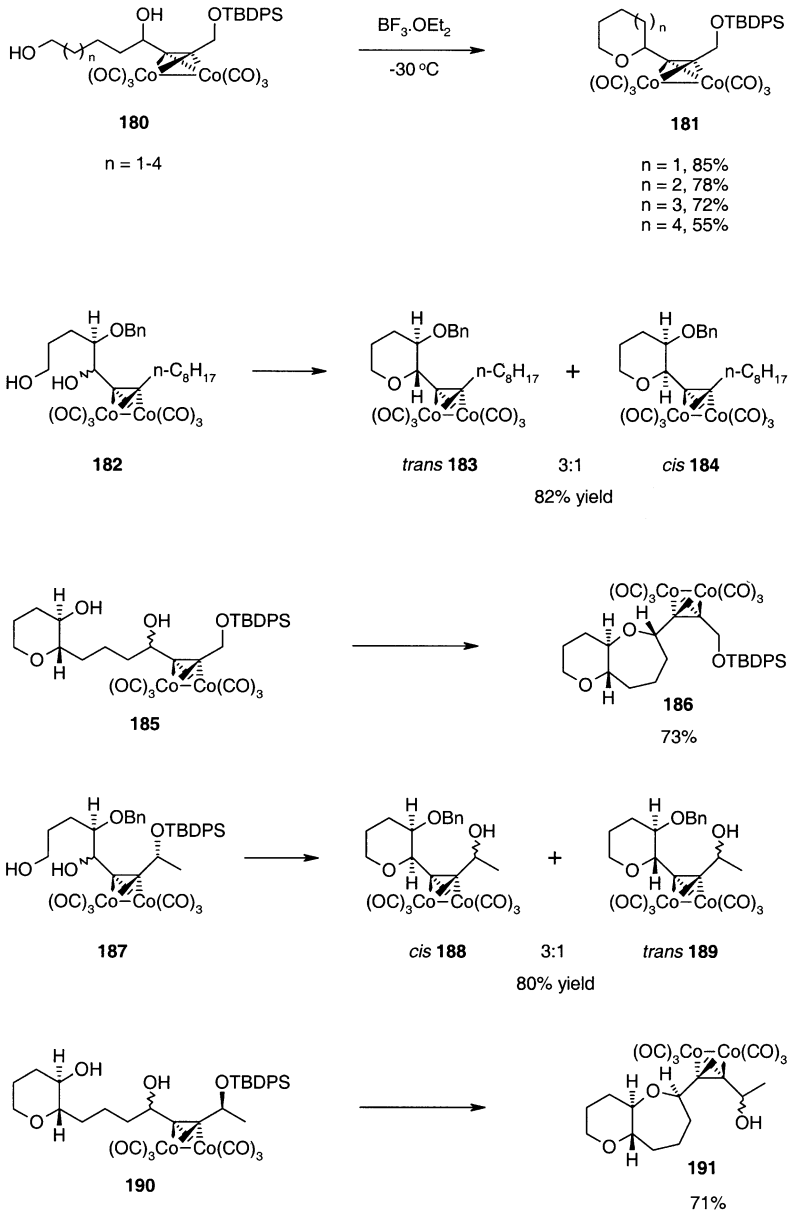
In the most stable conformation of the *trans* isomer **136**, steric interactions exist between the axial $Co_2(CO)_6$ moiety and three axial hydrogens, whereas in the most stable conformation of the *cis* isomer **137** there is only steric interaction with one axial hydrogen. If the transition states leading to these two products contain similar interactions, then a bias towards producing the less congested *cis* isomer would be expected. This product-based analysis does not, of course, take into account conformational preferences of the $Co_2(CO)_6$-stabilised cation, which ultimately may provide the controlling stereochemical influence.

Guo and Green[69] have examined the chemistry of cobalt complexes of hepta-2,5-diynyl-1,7-diol derivatives **138** to establish whether carbocation generation and subsequent Nicholas reaction would take place selectively at the different terminal ether/ester sites. This is indeed found to occur and provides a method for independently varying the two ends of the molecule, the site bearing the methoxy or acetoxy group reacting first.





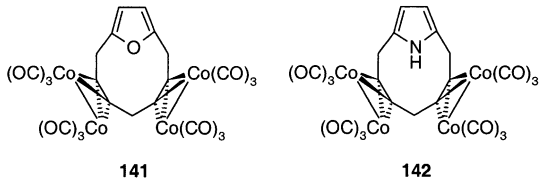
(17)



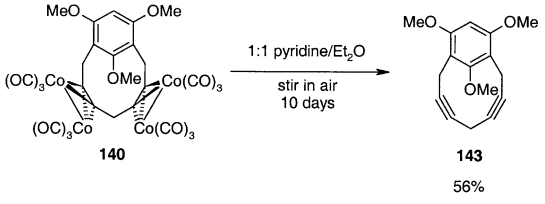
Scheme 27.

Related to this work, the same authors[70] have shown that the dibenzyl derivative **139** will react with electron-rich aromatics in good yields to form the [7]metacyclophanediyne complexes **140** (Eq. (17)).

Furan reacts to give **141** in 43% yield, whilst pyrrole reacts in two separate steps to give **142** in 20% overall yield. Thiophene, however, does not react with **139**.



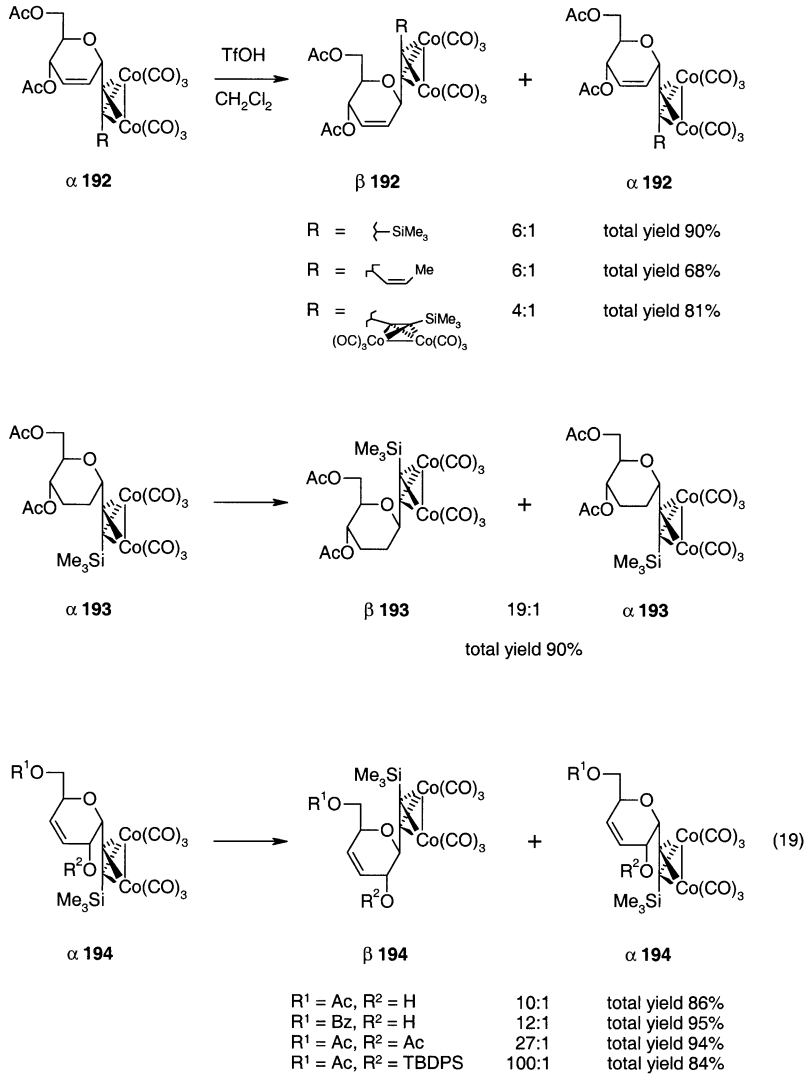
Amazingly, **140** can be decomplexed under mild conditions to give the strained, but thermally stable, [7]metacyclophanediyne parent molecule **143** (Eq. (18)), the smallest [*n*]metacyclophane containing a triple bond reported so far.



(18)

5. Oxygen as nucleophile

Martín and co-workers[71] have recently shown that the chiral cobalt complex **144** produces a 3:1 mixture of diastereomers **145** and **146** upon treatment with boron trifluoride etherate at −20°C for 24 h (Scheme 21). Additionally, in the



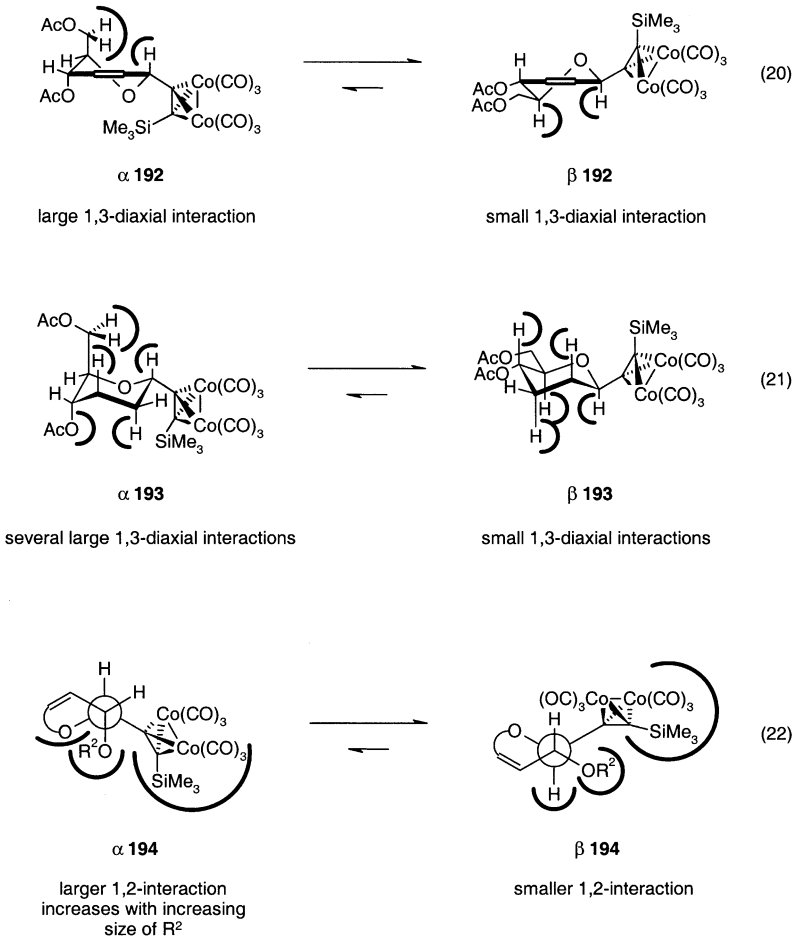
Scheme 28.

presence of external oxygen nucleophiles such as methanol or acetic acid, the methyl ethers **147** and **148** or acetates **149** and **150** can be obtained with good diastereoselectivity after only 15 min. Interestingly, when methanol is used and the reaction time is extended to 13 h, no change is observed in the diastereomeric ratio, whilst when acetic acid is used and the reaction time is extended, a complete reversal of the diastereomeric ratio occurs. The authors suggest that, over time, the better leaving-group ability of acetate compared with methoxy allows equilibration from the kinetic to the thermodynamic product. The major product can be easily purified by flash chromatography, demetallated to the alkyne, reduced to the alkene and then cleaved by a number of different methods to give enantiomerically pure α-hydroxy acid derivatives, such as **151** and **152**. The chirality used in the starting material derives from camphoric acid and is easily recovered as the ester **153**, after cleavage of the product.

With regard to the use of an oxygen nucleophile to trap a $Co_2(CO)_6$-stabilised carbocation in an intramolecular sense, several research groups have independently developed identical, or very similar, methodologies to solve closely related synthetic problems.

Of the major contributors in this area, Mukai and Hanaoka have been instrumental, not only in developing novel approaches for the preparation of cyclic ethers, but also in the synthesis of natural products. As an example, they have used the Lewis acid-catalysed opening of a $Co_2(CO)_6$-complexed α-epoxy-alkyne followed by intramolecular trapping with a pendant hydroxyl group to generate tetrahydrofuran[72] and tetrahydropyran[73,74] rings (Scheme 22). This *endo*-mode ring closure reaction is highly stereoselective, presumably by virtue of a cobalt-assisted double inversion process,[74] with *trans*-epoxides giving *cis* products and *cis*-epoxides *trans* products. Additionally, the outcome of the reaction is little influenced by the nature of the substituent at the terminal position of the alkyne. Of the Lewis acids studied, boron trifluoride etherate and trifluoroacetic acid were found to be the most effective.

Mukai and Hanaoka[58] describe these *endo*-mode cyclisations in more detail in a review of their work on



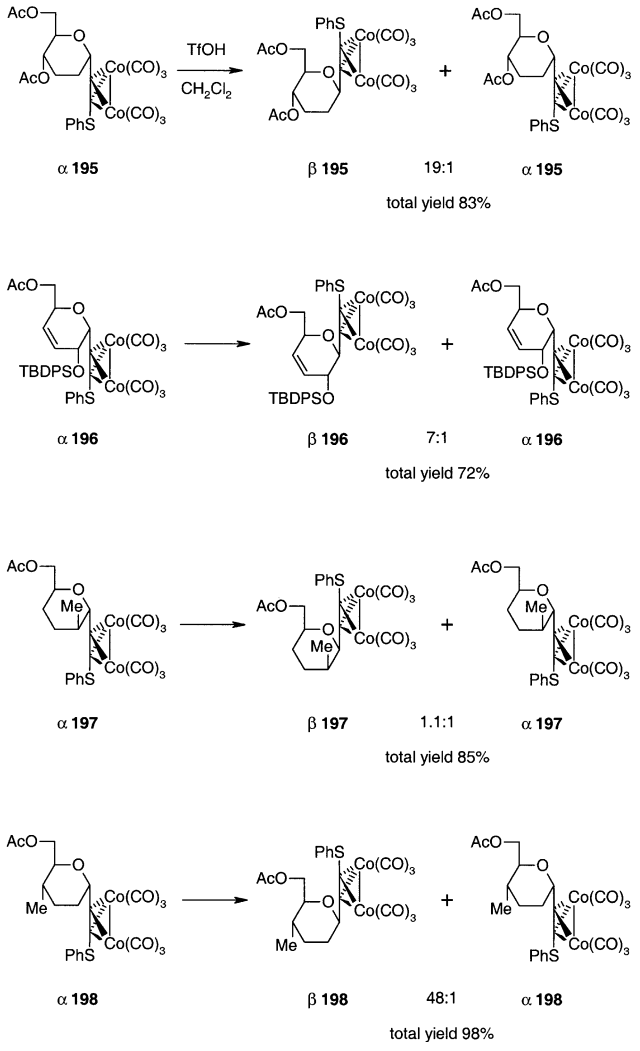
Scheme 29.

stereoselective and regioselective reactions of alkyne–$Co_2(CO)_6$ complexes.

More recently,[12] workers from the same group have developed a method for generating eight- and nine-membered oxacycles using a different approach. Ingeniously, the oxygen atom of the tetrahydrofuran ring is persuaded to act as a nucleophile by an adjacent trimethylsilylmethyl substituent. When the tetrahydrofuran **154** was treated with mesyl chloride and triethylamine in dichloromethane at room temperature, a mixture of the oxocanes **155** and **156** was obtained (Scheme 23). When the reaction was conducted at reflux, however, oxocane **155** was obtained as the sole product in 72% yield. The reaction is thought to proceed as depicted in Scheme 23, with the mesylate group leaving to generate the stabilised carbocation **157**, which is trapped by the oxygen of the nearby tetrahydrofuran to give the oxonium ion **158**. The more stable carbocation **159** can then form because of β-stabilisation by the trimethylsilyl group. Finally, elimination of the trimethylsilyl group gives the oxocane **155**, whilst elimination of a β-hydrogen **160** gives the oxocane **156**. Interestingly, when boron trifluoride etherate or other Lewis acids were used, no oxocane derivatives were obtained. The products were easily decomplexed to the alkynes **161** and **162** using ceric ammonium nitrate. An identical methodology was used to synthesise the oxonane **164** from the tetrahydrofuran **163**.

In the synthesis of (+)-secosyrins 1 and 2, Mukai and Hanaoka[75,76] have used the stereoselective nucleophilic attack by a hydroxyl group onto a cobalt-stabilised carbocation to prepare a substituted tetrahydrofuran (Scheme 24). The alcohol **165** was treated with boron trifluoride etherate to induce cyclisation, followed by ceric ammonium nitrate to demetallate, to give a 5:1 mixture of the tetrahydrofurans **166** and **167**. The authors explain the stereoselectivity by considering the two proposed transition states for cyclisation. The transition state **168**, which leads to the desired stereoisomer **166**, suffers only a small steric interaction between the eclipsed benzyloxy and thioacetate groups. In contrast, the transition state **169**, which leads to the undesired stereoisomer **167**, suffers a very serious steric interaction between the eclipsed benzyloxy and bulky $Co_2(CO)_6$–alkyne groups. Transition state **168** would therefore be expected to be preferred over transition state **169**, and hence tetrahydrofuran **166** to predominate over tetrahydrofuran **167**.

Finally, Mukai and Hanaoka[77] have developed a new glycosylation reaction, which makes elegant use of the cobalt-complexed 6-phenyl-hex-5-ynoic acid moiety as a leaving group. When the glucopyranoside esters **170** were treated with trimethylsilyl triflate at −65°C, the disaccharides **175** were obtained (Scheme 25). The reaction proceeds by initial Lewis acid-catalysed elimination of the glucosyl silyl ether **172** to give the cobalt-stabilised carbocation **171**,



Scheme 30.

collapse of the carbocation to give the oxonium ion **174** with simultaneous expulsion of the lactone **173** and, finally, capture of the oxonium ion by the glucosyl ether **172**. The ratio of the α- to β-isomers in the final products **175** was dependent upon the reaction solvent (dichloromethane or propionitrile), the stereochemistry of the R^4 and R^5 substituents, and whether *O*-benzyl ethers or *O*-benzoyl esters were used as protecting groups.

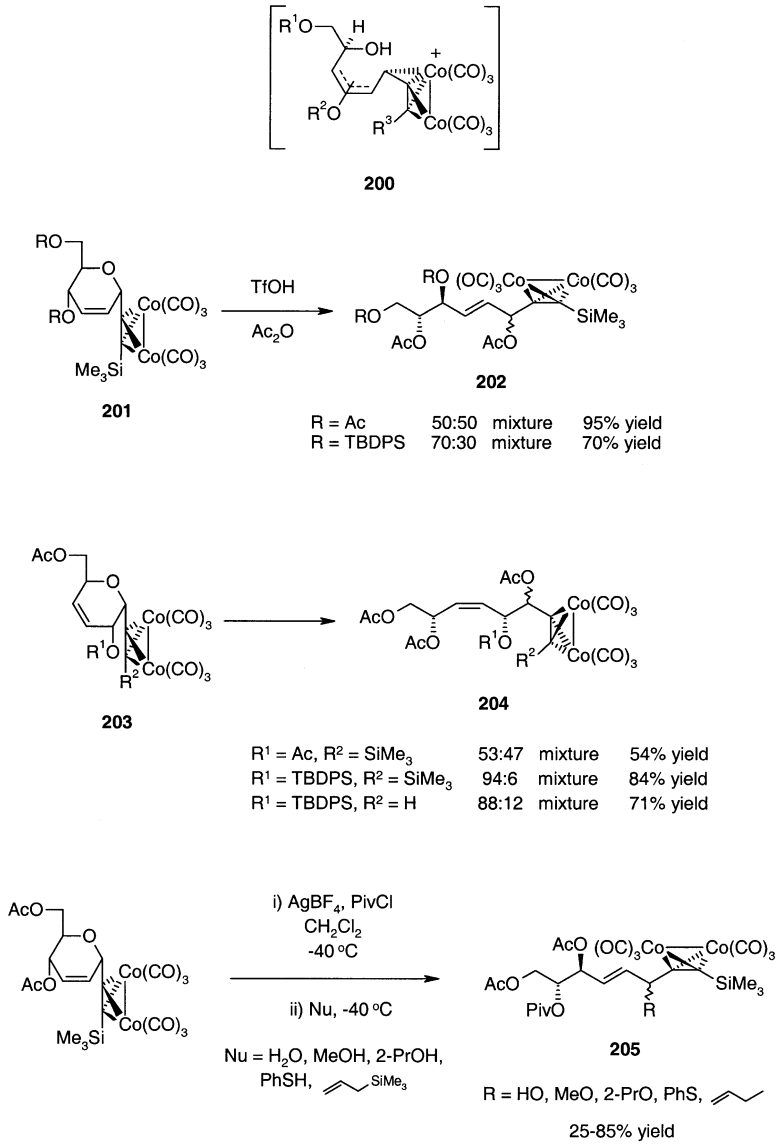
Staying with disaccharide formation, an intramolecular Nicholas reaction was used by Schmidt and co-workers[78] for the synthesis of carbon-bridged disaccharides (Scheme 26). Either epimer of the diol **176** could be treated with boron trifluoride etherate to give a 1:1 mixture of the α- and β-disaccharides **177**, which were then decomplexed with ceric ammonium nitrate to give the two separate α- and β-isomers **178** and **179**.

Martín and Palazón[79] have developed a method of synthesising medium-sized monocyclic and fused bicyclic ethers which is highly stereoselective when chiral substituents are present in the precursors. When the linear diols **180** were treated with boron trifluoride etherate at −30°C, the corresponding cyclic ethers **181** were obtained in good yield (Scheme 27). The reaction is regiospecific, i.e. cyclisation occurs at only one of the propargylic positions, giving the cyclic ether that contains an *exo*-$Co_2(CO)_6$–alkyne moiety; no *endo*-$Co_2(CO)_6$–alkyne products were observed. Additionally, it was noted that the silyl protecting group is unaffected by the reaction. The chiral diol **182** cyclised under similar conditions to give a mixture of the tetrahydropyrans **183** and **184**, with the *trans* isomer **183** predominating, whilst the tetrahydropyran **185** cyclised to give the fused oxepane **186** exclusively, a compound with *trans* stereochemistry at the new ring junction.

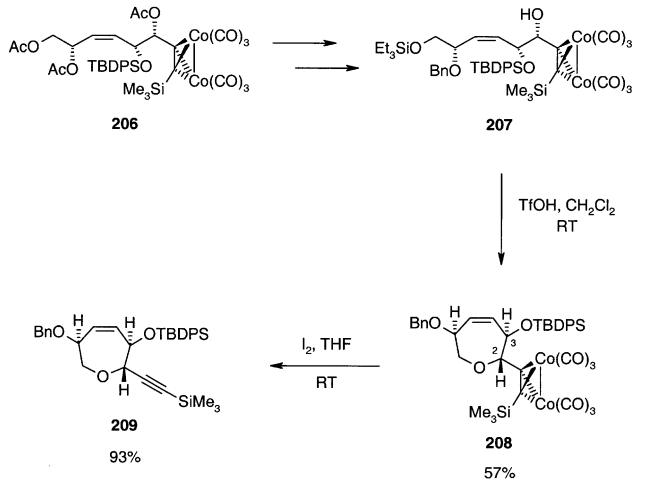
The addition of a second stereocentre in the starting material at the other propargylic position, however, somewhat complicates matters. The chiral diol **187** cyclised to give a mixture of the tetrahydropyrans **188** and **189**, with the *cis* isomer **188** predominating, whilst the tetrahydropyran **190**, with the opposite configuration at the second stereocentre compared with **187**, gave the fused oxepane **191** exclusively, a compound with *cis* stereochemistry at the new ring junction. It is noteworthy that, in both of these examples, the silyl protecting group was lost, together with the chirality at that position. This is presumably as a consequence of the $Co_2(CO)_6$-stabilised *secondary* carbocation that can form from the diols **187** and **190** by loss of the *O*-silyl group being more stable than the *primary* carbocation that would form via *O*-silyl loss from the diols **180** and **185**. It is therefore clear that the presence of a second stereocentre influences the cyclisation reaction, cf. **186** and **191**, even though the stereochemical information at that position is ultimately lost.

Isobe is the other major contributor to the area of intramolecular Nicholas reactions using oxygen nucleophiles. In the early 1990s, his research group disclosed[80,81] that an alkynyl substituent at the C-1 position of a pyranose ring could be epimerised from the α- to the β-position via its dicobalt hexacarbonyl complex. The α-substituted-$\Delta_{2,3}$-pyranose derivatives **192**, for example, were epimerised to ≥4:1 β/α mixtures in good yield by using trifluoromethanesulphonic acid in dichloromethane at room temperature (Scheme 28). The saturated pyranose derivative **193** was analogously epimerised to a 19:1 β/α mixture, whilst α-substituted-$\Delta_{3,4}$-pyranoses carrying a C-2 substituent **194** could be epimerised to 10–100:1 β/α mixtures, depending upon the nature of the C-2 substituent (Eq. (19)).

Apparently, the driving force for forming the β-isomer in preference to the α-isomer in the pyranoses **192** and **193** is the minimisation of 1,3-diaxial steric interactions in the lowest energy boat-form conformation of the compounds (Scheme 29). The saturated pyranose **193** has more 1,3-diaxial interactions to minimise than the unsaturated pyranose **192** (Eqs. (20) and (21)), and hence there is a greater energy difference between the α- and β-isomers of **193** compared with **192**, a better β/α ratio therefore being obtained from **193** than **192**. For the C-2 substituted pyranoses **194**, a 1,2-steric interaction becomes important. By comparing the Newman projections of the α- and β-isomers of **194** looking along the C-2 to C-1 bond (Eq. (22)), there will be greater steric interactions in the α-isomer than the β-isomer. Moreover, these interactions will be dependent upon the size of the C-2 substituent, i.e.



Scheme 31.

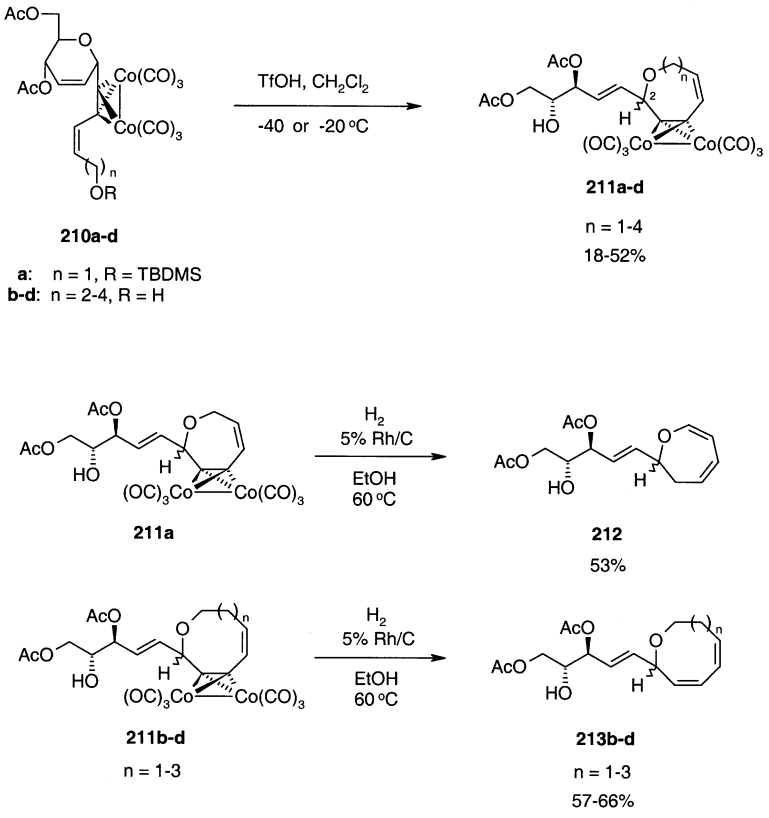


Scheme 32.

as R^2 increases in bulk the steric interactions increase and there is a greater driving force for the compound to adopt a β-stereochemistry. This explains the trend in β/α ratios shown in Eq. (19), Scheme 28. An examination of a variety of different decomplexing agents[80] concluded that the best reagent to use was iodine in tetrahydrofuran, which gave the free alkynylpyranoses in 82–100% yield.

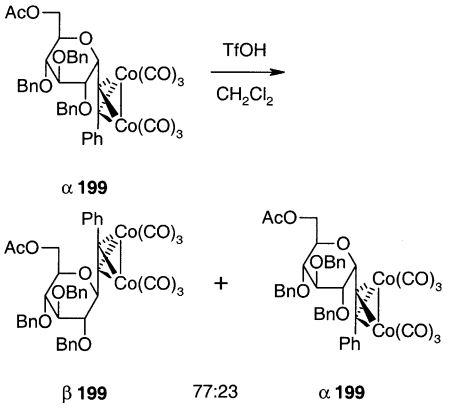
This epimerisation strategy was used by Isobe and co-workers to epimerise the phenylthioalkynylpyranoses **195–198** (Scheme 30), in synthetic studies towards,[82,83] and in a synthesis of,[84,85] segment C of tautomycin.

Désiré and Veyrières[86] have used the same epimerisation conditions on the pyranose **199** to obtain a 77:23 β/α mixture of isomers (Eq. (23)). This demonstrates that the technique can be applied to fully-substituted pyranose derivatives. Unfortunately, however, the resulting β/α ratio seems to be much lower than that obtained by Isobe



Scheme 33.

from the partially-substituted pyranoses.



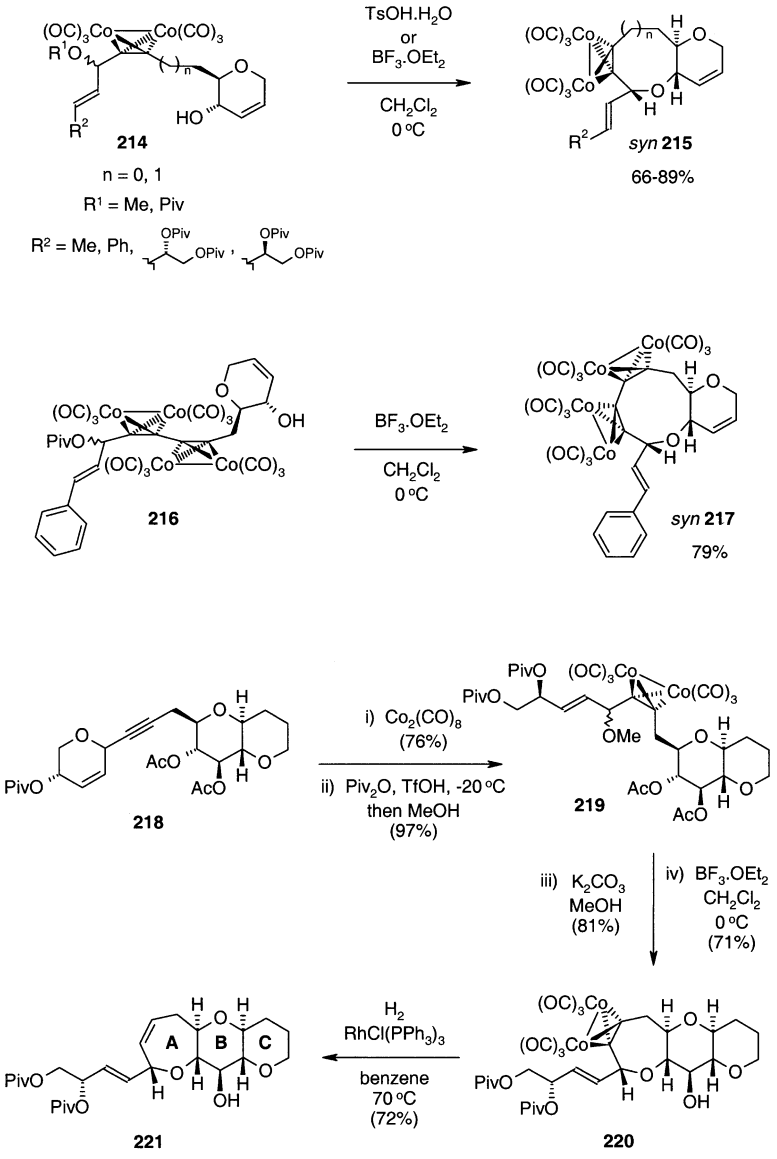
(23)

Realising that, for epimerisation to occur, a ring-opened form of the pyranose, e.g. **200** (Scheme 31), must be generated, Isobe et al.[87,88] wondered whether such an intermediate could be trapped, manipulated and then re-cyclised to a give a substituted oxepane. By treating the pyranose derivatives **201** and **203** with trifluoromethanesulphonic acid in acetic anhydride, linear derivatives **202** and **204** were indeed obtained, generally in good yield. The products **202** derived from the $\Delta_{2,3}$-pyranoses **201** were isolated as the more stable *trans*-olefins and not the *cis* products. This olefinic isomerisation implies that the cationic intermediate derived from $\Delta_{2,3}$-pyranoses is not only stabilised by the dicobalt hexacarbonyl moiety, but also by delocalisation of the adjacent π-system. In the $\Delta_{3,4}$-pyranoses **203**, however, this π-delocalisation cannot occur and the *cis* stereochemistry of the double bond is therefore maintained in the products **204**.

All of the ring-opened products were obtained as diastereomeric mixtures at the original anomeric position, but the diastereomeric ratios obtained from the $\Delta_{3,4}$-pyranoses containing a bulky C-2 substituent were surprisingly high. The authors provide an explanation[88] for this diastereoselectivity based upon conformational analysis of the proposed transition states for the cobalt-assisted ring-opening reaction using mechanistic arguments similar to those first proposed by Schreiber.[30]

If the ring-opening reaction was conducted using silver tetrafluoroborate/pivaloyl chloride, followed by addition of a nucleophile, a more synthetically useful, differentially protected, linear product **205** could then be obtained.[89]

With a suitably trapped linear *cis*-olefin in hand, Isobe and co-workers[87,88] turned their attention towards re-cyclisation to an oxepane derivative. The triacetate **206** was quickly transformed into the alcohol **207** and then treated with trifluoromethanesulphonic acid to give the oxepane **208** as the sole cyclisation product (Scheme 32). Apparently, the high stereoselectivity observed in this reaction is a result of thermodynamic control: the two extremely bulky substituents at the C-2 and C-3 positions of **208** prefer to adopt a *trans* relationship in order to minimise steric strain. Finally, the oxepane **208** was easily demetallated with iodine to give the free alkyne **209**.

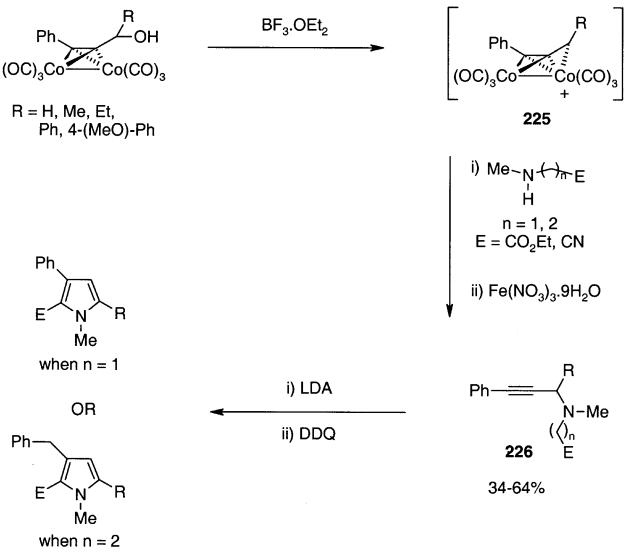


Scheme 34.

Isobe[90,91] has extended this cyclisation reaction to generate medium-sized rings from alkynyl-substituted pyranoses in one simple operation. Recognising that the linear *trans*-olefins obtained from the ring opening of $\Delta_{2,3}$-derivatives could not cyclise back to the starting material because of the change in olefin stereochemistry, Isobe et al. prepared the $\Delta_{2,3}$-pyranoses **210a–d** (Scheme 33). Upon treatment with trifluoromethanesulphonic acid, these ring opened to give the *trans*-olefins, as before, but the $Co_2(CO)_6$-stabilised carbocations could then readily cyclise onto a new hydroxyl group, held in position by a *cis*-olefin tether, and thus generate the seven- to 10-membered rings **211a–d** in moderate yield. The cyclic products were all obtained as 1:1 mixtures of diastereomers at the C-2 position.

Attempted oxidative demetallation of the products with iodine in tetrahydrofuran was unsuccessful, presumably due to the high ring strain that would be present in the free cyclic alkynes. Instead, the compounds were reductively demetallated by high-pressure hydrogenation over a 5% rhodium on charcoal catalyst at 60°C using ethanol as the solvent. Whilst the eight-, nine- and 10-membered rings **211b–d** were reduced to the corresponding cyclic dienes **213b–d** without complication, the oxepane **211a** was reduced and then isomerised to give a cyclic vinyl ether **212**.

Finally, in synthetic studies towards the ciguatoxin and gambiertoxin 4b molecules, Isobe[92] has combined all of this ring-opening and ring-closing methodology to synthesise fused 7–6, 8–6 and 9–6 bicyclic ethers similar to those prepared by Martín and Palazón (vide supra). This has culminated in the synthesis of the left-hand A/B[93,94] and A/B/C[94–96] rings of ciguatoxin (Scheme 34). *trans*-Alkenes carrying a six-membered ring alcohol on a $Co_2(CO)_6$–alkyne tether **214**, for example, were cyclised using tosic acid or boron trifluoride etherate to give the 7–6 and 8–6 bicycles **215**, with predominant or exclusive formation of the *syn* stereoisomer. Similarly, a compound containing a



Scheme 35.

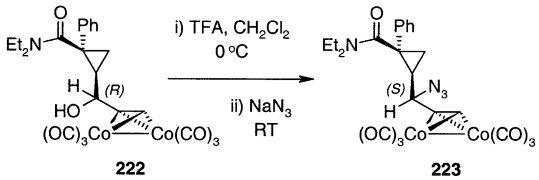
tether comprising two $Co_2(CO)_6$-complexed alkynes **216** was cyclised to give the 9–6 bicycle **217**. In order to prepare the A/B/C rings of ciguatoxin, a $\Delta_{2,3}$-pyranose suitably substituted with an alkyne-tethered 6–6 bicyclic ether **218** was treated with dicobalt octacarbonyl and then ring opened using pivalic anhydride/trifluoromethanesulphonic acid/methanol to give the fully-protected *trans*-alkene **219**. Following acetate hydrolysis, **219** was cyclised to the tricycle **220** using boron trifluoride etherate, and then reductively demetallated with high-pressure hydrogenation over Wilkinson's catalyst in hot benzene to give the desired product **221**.

Isobe et al.[97] have recently reviewed their work in the field of sugar acetylene chemistry. Part of their review describes, in more detail than given above, the authors' excellent use of the Nicholas reaction when applied to $Co_2(CO)_6$-complexes of sugar acetylenes and their derivatives.

6. Nitrogen as nucleophile

6.1. Azide

There has been one report of an azide being used in the Nicholas reaction. Shuto et al.[98] treated the alcohol **222** successively with trifluoroacetic acid and sodium azide to give the azide **223** as the sole product, which was then transformed into the NMDA receptor antagonist **224** (Eq. (24)).



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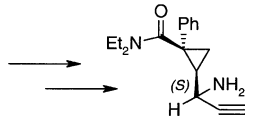

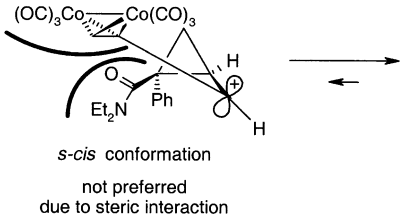

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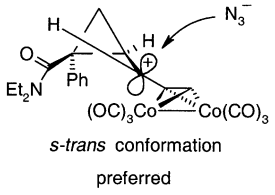
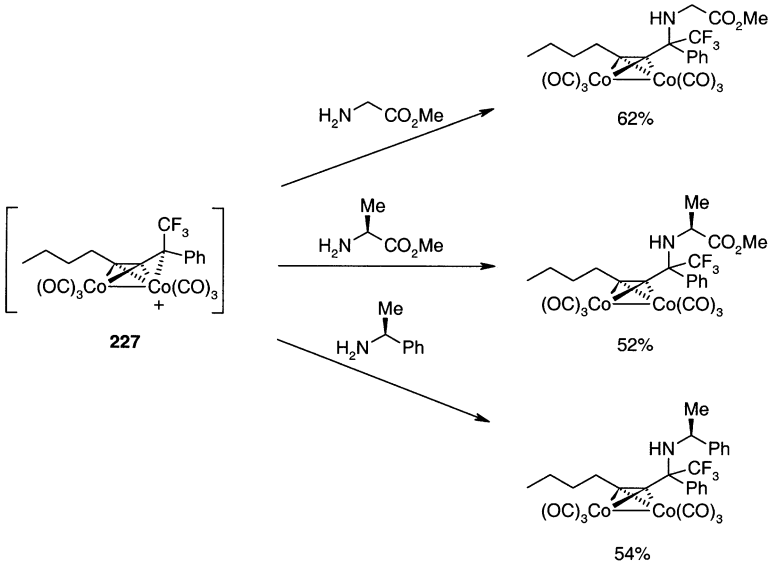
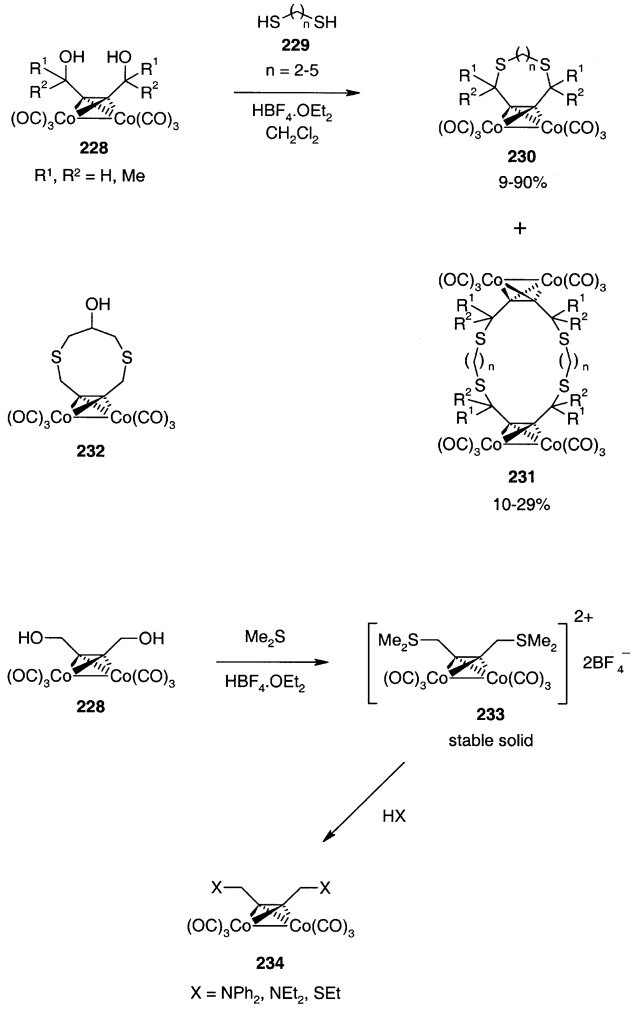




Scheme 36.



Scheme 37.

In this system, the intermediate carbocation is not only stabilised by the $Co_2(CO)_6$ moiety, but also by the α-cyclopropyl group. The observed stereochemistry derives from nucleophilic attack by the azide on the least-hindered face of the preferred *s-trans* conformation of the carbocation (Eq. (25)).

6.2. Amines

Yeh et al.[99] have reacted the $Co_2(CO)_6$-stabilised cations **225** with α- and β-amino acid derivatives to give, after decomplexation, the alkynes **226** in moderate to good yields (Scheme 35). The alkynes were then cyclised to give pyrroles.

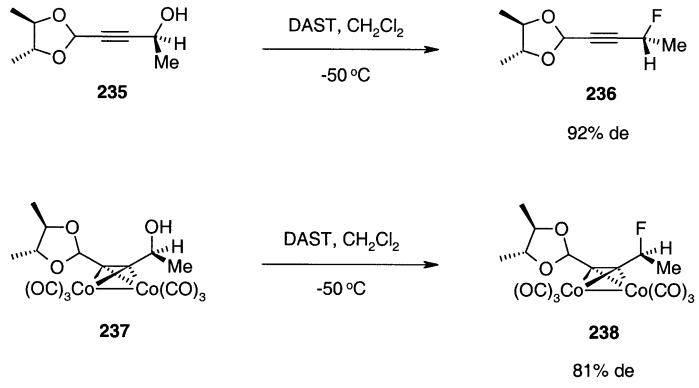
On a similar theme, Bonnet–Delpon and co-workers[100] have generated the α-trifluoromethyl-carbocation **227** and treated it in dichloromethane at −10°C with simple amino acid esters and chiral α-methylbenzylamine (Scheme 36). Its reaction with a carbon nucleophile is also described. This is the first report disclosing the synthesis and reactions of a $Co_2(CO)_6$-stabilised α-trifluoromethyl-propargylium cation, and demonstrates its potential as a synthon for preparing compounds containing a CF_3-substituted quaternary carbon.

Went et al.[101] have prepared the diamines **234** from a dimethylsulphide-stabilised dication **233** (Scheme 37) (vide infra).

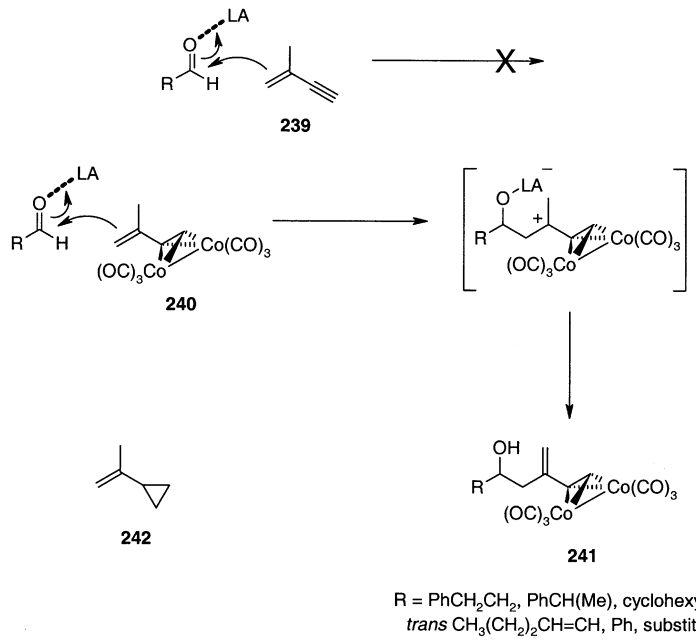
7. Sulphur as nucleophile

Apart from the occasional reports in the literature of thiophenol being used as a nucleophilic trap for $Co_2(CO)_6$-stabilised propargylic cations, the only chemistry of note that uses sulphur nucleophiles in Nicholas reactions is that reported by Went et al.[102] A series of cyclic dithia–alkyne complexes **230** were prepared by treating the diols **228** with simple alkyl dithiols **229** in the presence of tetrafluoroboric acid etherate (Scheme 37). The dimeric compounds **231** were also obtained as by-products from the reaction and, in some instances, even trimers were isolated. This is an extension of earlier work[103] in which the diol **228** (R^1, R^2=H) was treated with alkylthiols to produce dithioethers. A cyclic compound containing a pendant hydroxyl group **232** and its corresponding dimer were also prepared. Interestingly, these were the only products isolated from the reaction, indicating a preference for *S*- rather than *O*-alkylation.

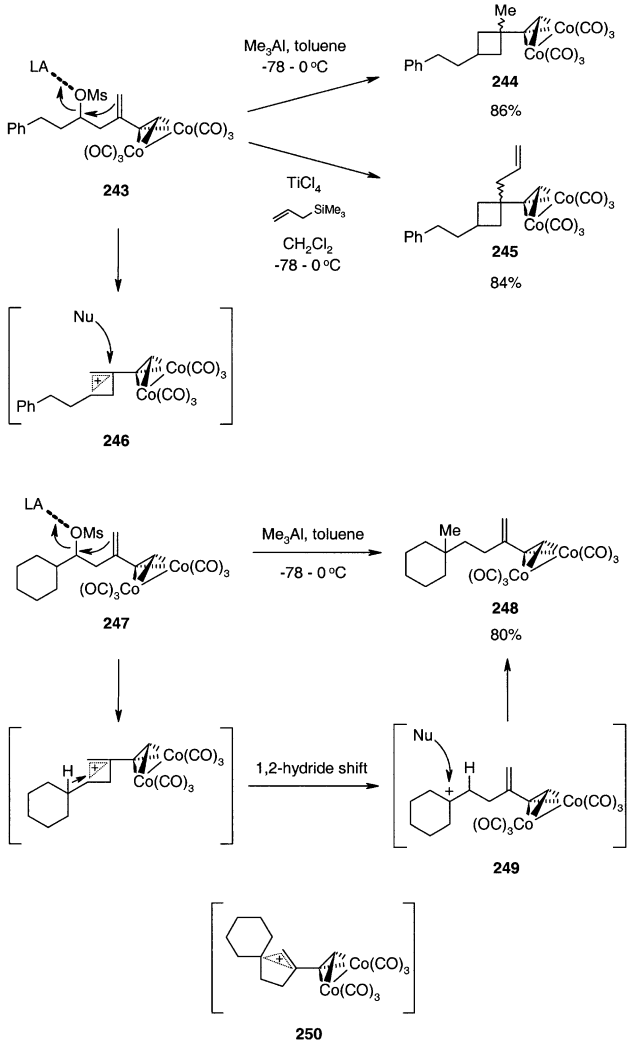
Went and co-workers[101] have used dimethyl sulphide to produce a stable form of the dication obtained from protonation of the diol **228** (R^1, R^2=H). The product **233**, which



Scheme 38.



Scheme 39.



Scheme 40.

is obtained in high yield, is a thermally stable orange solid that can be stored in air for over a year! It is, however, still reactive with respect to nucleophiles, and gave the predicted products **234** when treated with secondary amines or a thiol.

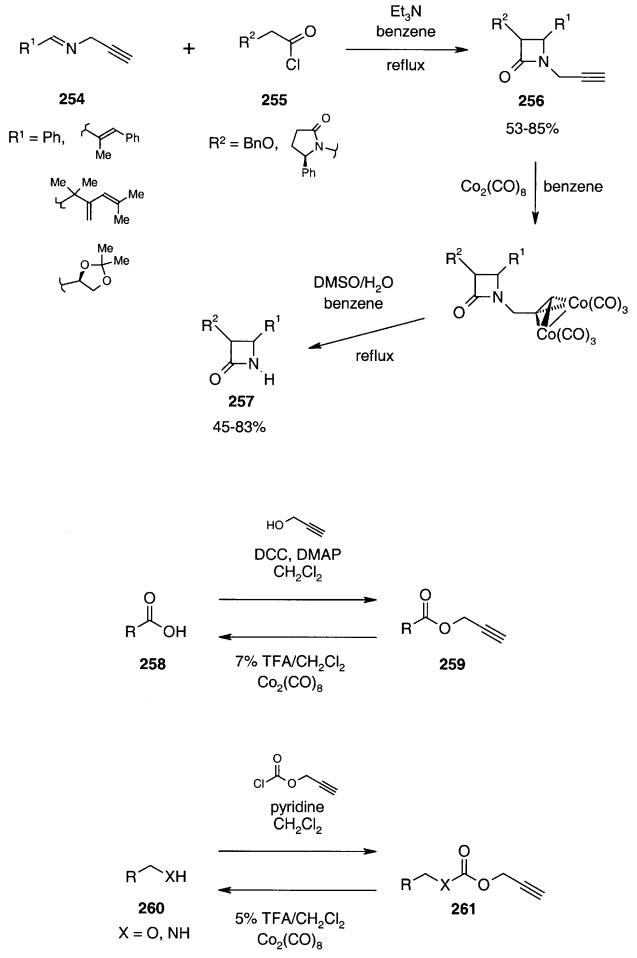
8. Fluoride as nucleophile

Grée et al.[104] reported the first Nicholas reaction using fluoride as the capturing nucleophile (Scheme 38). They discovered that, whilst treatment of the chiral propargyl alcohol **235** with diethylaminosulphur trifluoride (DAST) at −50°C gave the predicted fluoride **236**, the product resulting from inversion of configuration, the cobalt complex **237** gave the fluoride **238**, the product resulting from retention.

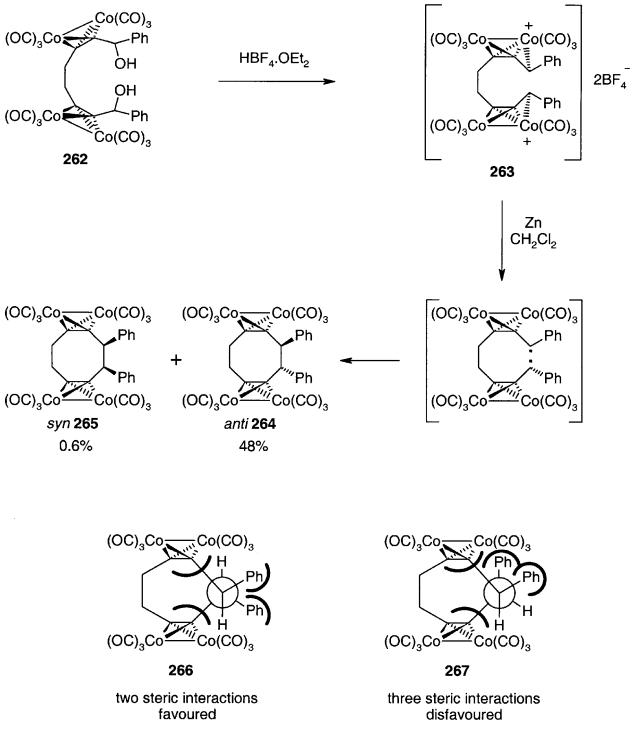
Additionally, the diastereoselectivity of the reaction of **237** with DAST was dependent upon the temperature: at −80°C the de was 86% and, at +20°C, it was only 40%. This is entirely consistent with the known dynamic behaviour of $Co_2(CO)_6$-stabilised propargyl cations.[30] The diastereoisomerisation of the cation derived from **237** must be slow at −80°C, compared to the rate of fluorination, and so retention of configuration is observed. As the temperature increases, the cation begins to isomerise, and a reduction in the diastereoselectivity is observed.

The exact nature of the fluorinating agent in these reactions has yet to be established. It is interesting to note that fluoride ion in the form of tetrabutylammonium fluoride has been shown to be an efficient reagent for decomplexing $Co_2(CO)_6$–alkyne complexes.[28,105,106]

Fluoride ion has been shown to trap carbocation intermediates which are formed from the reaction between $Co_2(CO)_6$-stabilised cations and alkenes.[21,59,61]



Scheme 41.



Scheme 42.

9. Miscellaneous reactions

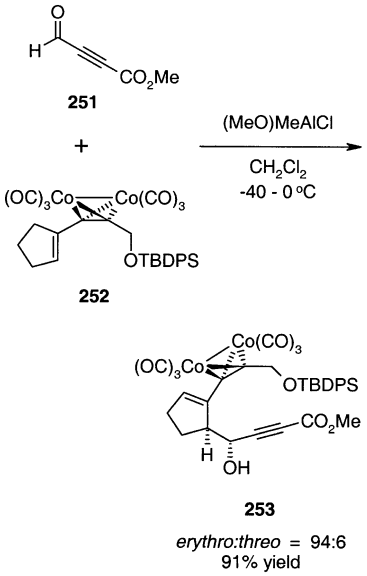
9.1. Carbonyl-ene reaction

Recently, two different research groups have reported the carbonyl-ene reaction between an aldehyde and a $Co_2(CO)_6$-complexed eneyne.

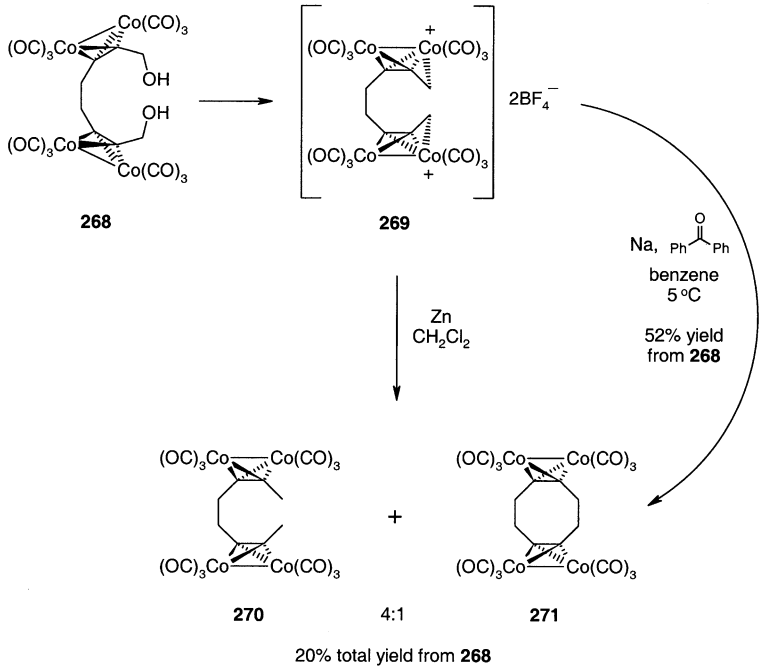
Suzuki and co-workers[107] established that, whilst the parent eneyne **239** would not react with unactivated aldehydes in the presence of a Lewis acid, its cobalt complex **240** reacted smoothly to give a series of secondary alcohols **241** (Scheme 39). The authors comment that, although the $Co_2(CO)_6$ group does activate the eneyne towards electrophilic attack by stabilising the developing positive charge, this activation appears not to be as efficient as that provided by an adjacent cyclopropyl group, such as in **242**, for example. Nevertheless, a wide range of alcohols **241** could be prepared in good yield and, where diastereomers could be formed, these were obtained as 1:1 mixtures.

Suzuki[108] extended this work to the preparation of cyclobutanes (Scheme 40). The secondary alcohol obtained by the carbonyl-ene reaction was mesylated and treated with a Lewis acid/nucleophile combination to induce cyclisation and trap the newly-formed carbocation. When the substituent on the mesylate was a primary alkyl group, as in the cobalt complex **243**, the cyclobutanes **244** and **245** could be obtained in good yield via the stabilised carbocation **246**. When the substituent was a secondary or tertiary alkyl group, however, as in the mesylate **247**, a cyclobutane was not formed. Instead, a 1,2-hydride or alkyl shift occurred, giving a new carbocation **249**, which was then trapped by the nucleophile to give an acyclic product, such as **248**. There is some evidence that a delocalised cationic form such as **250** may participate in stabilising the carbocation **249**.

Mikami et al.[105] have meanwhile, used a carbonyl-ene reaction between the aldehyde **251** and the cobalt complex **252** to generate an enediyne intermediate, the alcohol **253** (Eq. (26)). Unlike the examples from Suzuki's work, this



(26)



Scheme 43.

reaction proceeded with good diastereoselectivity, affording the *erythro* product **253** in 88% de.

9.2. Protecting-group methodology

Two research groups have disclosed the use of the Nicholas reaction as part of a novel protecting-group strategy. Alcaide and Sierra et al.[109] prepared a series of *N*-prop-2-ynyl-β-lactams **256** by the reaction of the *N*-prop-2-ynyl imines **254** with different acid chlorides **255** (Scheme 41). The *N*-prop-2-ynyl protecting group was then removed by treatment of a benzene solution with dicobalt octacarbonyl, followed by in situ reaction with dimethylsulphoxide and water, to give the free β-lactams **257** in moderate to good yield. The exact mechanistic pathway for this deprotection is unclear as the usual protic or Lewis acid conditions required for the Nicholas reaction appears to be absent.

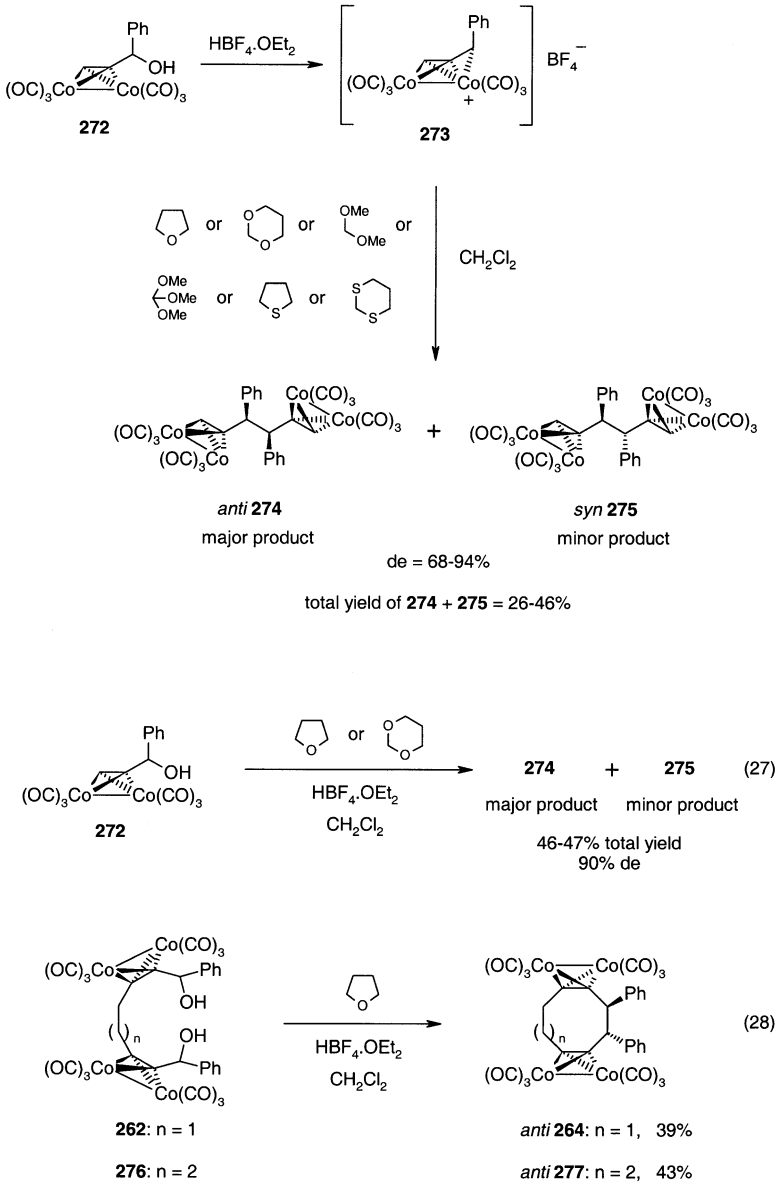
Fukase et al.[110] have recently introduced the propargyl and propargyloxycarbonyl (Proc) groups as new protection agents for carboxy, hydroxy and amino functions. Carboxyl groups **258** could be esterified to the propargyl esters **259** with propargyl alcohol, dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine, whilst hydroxy and amino functions **260** could be protected with the Proc group **261** by using propargyl chloroformate and pyridine. The propargyl ester and Proc groups were stable to neat trifluoroacetic acid at room temperature, conditions that would easily cleave a Boc group. They were removed in excellent yield by successive treatment with 5 or 7% trifluoroacetic acid/dichloromethane followed by the addition of dicobalt octacarbonyl, conditions that did not cleave a Boc group.

10. Radical reactions

As stated at the outset of this review, complexation to $Co_2(CO)_6$ appears to help stabilise alkynyl radicals as well as alkynyl carbocations. Melikyan[111] has used these stabilised radicals, generated by the reduction of the corresponding carbocations, to effect inter- and intramolecular carbon–carbon bond coupling reactions. When the dication salt **263**, for example, obtained from the diol complex **262**, was treated with zinc dust in dichloromethane, a moderate yield of the *anti*-cyclooctadiyne complex **264** was obtained, together with a trace of the *syn* diastereomer **265** (Scheme 42). The remarkably high stereoselectivity observed in this reaction can be explained by conformational analysis of the putative diradical intermediates **266** and **267**. The intermediate **266**, which gives rise to the *anti* diastereomer, experiences two gauche interactions between bulky groups, whilst the intermediate **267**, which gives rise to the *syn* diastereomer, experiences three such interactions. The intermediate **266** is therefore favoured over intermediate **267** and the *anti* diastereomer predominates.

When the same reaction was applied to the primary dication salt **269**, obtained from the diol complex **268**, only a small amount of the desired product **271** was obtained, along with significant quantities of the acyclic **270**, obtained via hydrogen atom abstraction (Scheme 43). In order to overcome this serious side reaction, a new reducing system was developed that would not provide a hydrogen atom source. Treatment of the dication salt **269** with sodium and benzophenone in benzene successfully gave the cyclooctadiyne complex **271** in much improved yield.

The major drawback with these reactions is the modest yields that are attainable, mainly due to the poor solubility of the cationic intermediates and the heterogeneous nature of the zinc reducing agent. Any improvements gained by using the sodium/benzophenone protocol are offset by the experimental inconveniences of conducting this reaction, together with its incompatibility with reducible functional



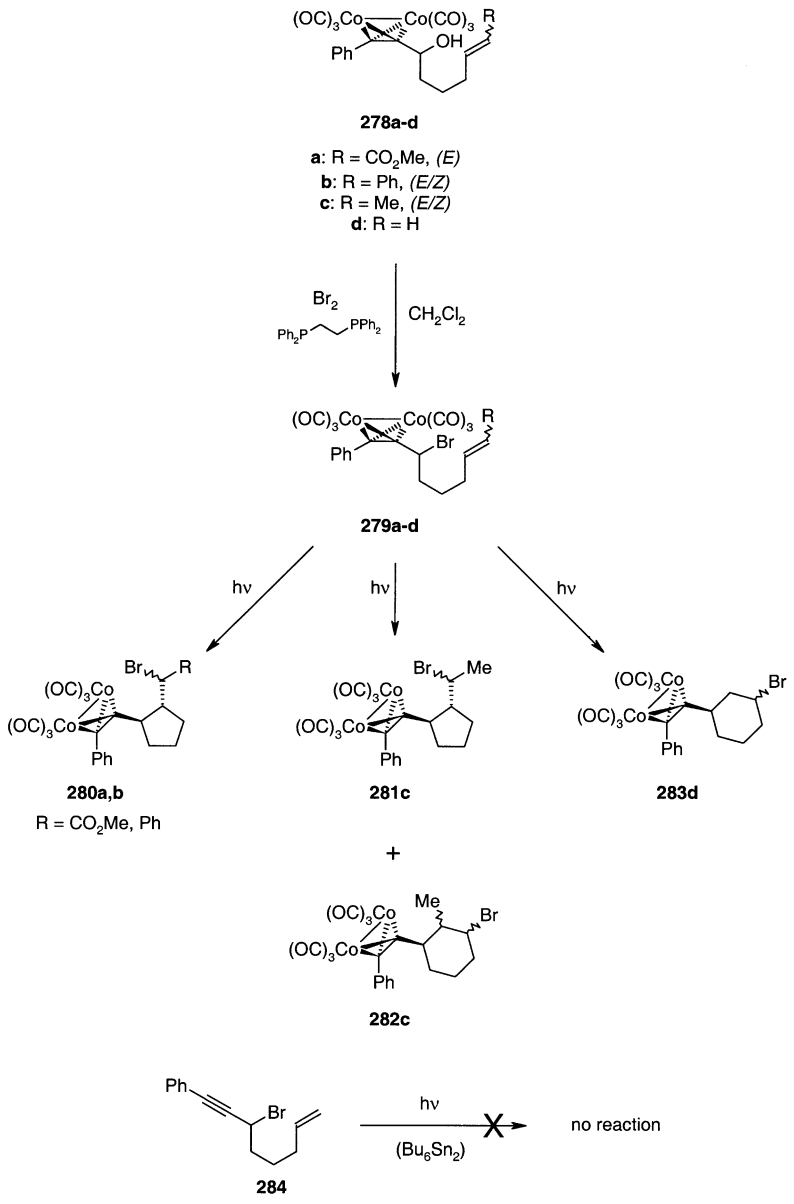
Scheme 44.

groups. Some of these problems have been solved by the recent discovery[112] that a variety of *O*- and *S*-containing organic compounds can act as homogeneous, one-electron reducing agents in this reaction.

When the cation salt **273**, for example, was treated in dichloromethane with any of the reagents shown in Scheme 44, varying yields of the *anti* and *syn* dimers **274** and **275** were produced, with the *anti* diastereomer **274** predominating as before. The reaction can be further simplified to a one-step process, without the need to first isolate the cation salt **273**. When the cobalt complex **272** in dichloromethane was treated with tetrafluoroboric acid etherate and either tetrahydrofuran or 1,3-dioxolane, the dimers **274** and **275** were produced in 46–47% total yield with 90% de (Eq. (27)).

Currently, the exact mechanism of this reaction and the nature of the one-electron donating species is not well understood, and is being investigated by the authors. The stereoselectivity of the reaction can be understood, however, using similar conformational arguments to those discussed earlier (see Scheme 42). Finally, this one-step radical coupling reaction has been applied to the cobalt complexes **262** and **276** to synthesise the eight- and nine-membered carbocycles **264** and **277**, which are analogous to those prepared previously (Eq. (28)).

Nicholas[113,114] has followed a different approach by exploring cyclisation reactions involving the addition of a $Co_2(CO)_6$-stabilised radical to a carbon–carbon double bond, in a manner analogous to the well-characterised 5-hexenyl radical cyclisation. The radicals were generated from the rather unstable propargyl bromide complexes **279a–d**, which were, in turn, obtained from the corresponding propargyl alcohol complexes **278a–d** by treatment with

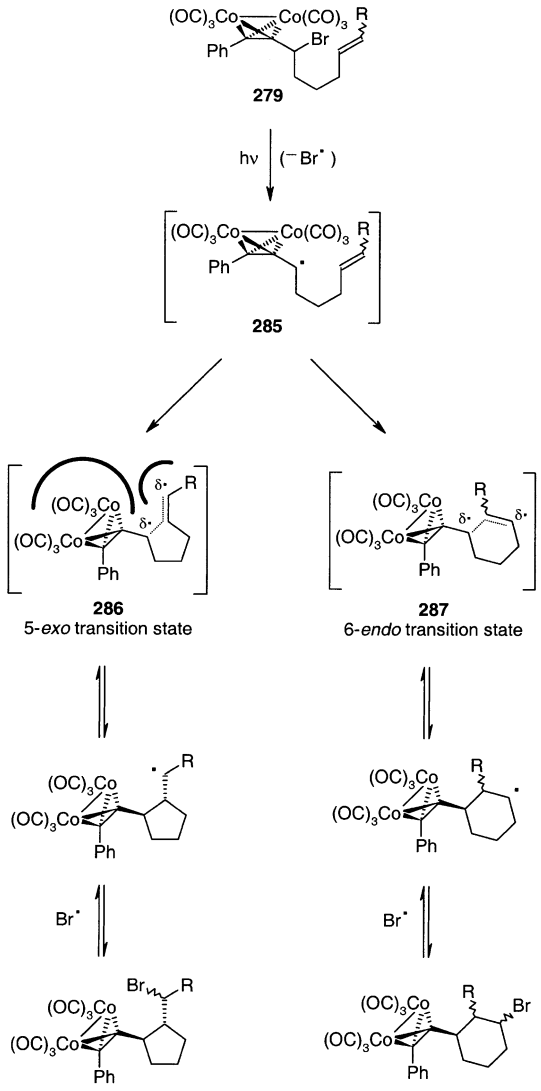


Scheme 45.

bromine and 1,2-bis(diphenylphosphino)ethane (Scheme 45). When the bromide complexes were left in direct sunlight or irradiated with a 300 W sunlamp for 1 h, they were converted to the cyclic products in good yields. The regiochemical course of these cyclisations was found to depend dramatically upon the alkene substituent, the bromoester (*E*)-**279a** and the phenyl derivative (*E*/*Z*)-**279b** giving the *trans*-cyclopentanes **280a**,**b** exclusively, the products of 5-*exo* cyclisation. The methyl derivative (*E*/*Z*)-**279c**, however, afforded a mixture comprising the *trans*-cyclopentane **281c** and the cyclohexane **282c**, the product arising from 6-*endo* cyclisation. Finally, the unsubstituted bromoalkene **279d** gave the 6-*endo* product exclusively, the cyclohexane **283d**.

Irradiation was not the only radical initiation method used, and cyclic products could also be obtained chemically, by treatment of a benzene solution of the bromide complexes with triethylborane/oxygen and a hydrogen atom donor such as tributyltin hydride or diphenylsilane. In these examples, mixtures of products arising from hydrogen atom abstraction and bromine atom transfer were obtained. It is interesting to note that the free eneyne bromide **284** remained unchanged when exposed to irradiation, either in the presence or absence of hexabutylditin.

The regio- and stereoselectivity of these radical cyclisation reactions can be explained by consideration of a reaction mechanism that has a late, product-like, transition state. Photolytic homolysis of the carbon–bromine bond in **279** would generate the $Co_2(CO)_6$-stabilised propargyl radical **285** (Scheme 46). In a product-like, transition state for cyclisation **286** or **287**, there would be significant carbon–carbon bond making (and breaking) as well as development of radical character at the original olefinic carbon atoms. With a strongly radical-stabilising group at the olefinic



Scheme 46.

terminus, e.g. when R=CO_2Me or Ph, the 5-*exo* transition state **286** would be favoured because it would allow delocalisation at the developing radical centre. For an unsubstituted olefin, R=H, the 6-*endo* transition state **287** would be preferred because it would allow the development of a radical at a secondary-carbon centre, rather than at a primary centre. When the olefin terminates in a methyl group (R=Me), the choice would be between two similarly energetic secondary radicals, and a mixture of products would therefore be obtained. With regard to the stereoselectivity that is observed in the cyclisation, steric interaction between the bulky $Co_2(CO)_6$–alkyne unit and the –CHR group would be very significant in a late transition state. The effect would be felt most strongly during the formation of the 5-*exo* products **286** and this may explain the preference for the reaction to form *trans*- rather than *cis*-cyclopentanes.

Attempts to extend the cyclisation reaction to 6-heptenyl systems met with failure. Upon irradiation, no appreciable quantities of cyclic products were detected, although the presence of small amounts of dimeric material did imply that radical intermediates had been generated.

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Biographical sketch

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