Chemistry of Propargyldicobalt Cations: Recent Developments in the Nicholas and Related Reactions

James R. Green*

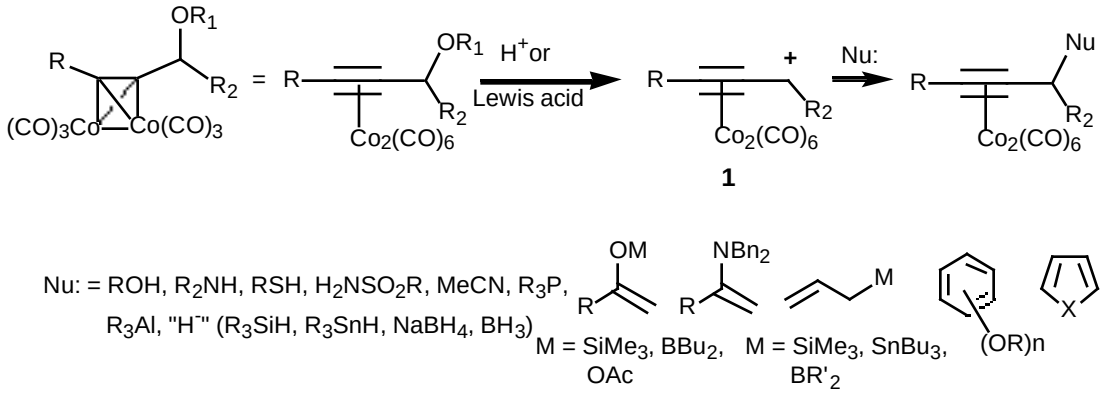
Department of Chemistry and Biochemistry, School of Physical Sciences, University of Windsor, Windsor, Ontario, N9B 3P4, Canada

Abstract: The chemistry of propargyldicobalt cations, also known as the Nicholas reaction, is reviewed, with a focus on the developments since 1995. Advances in the understanding of the fundamental properties, such as structure, stability, and reactivity, of both the hexacarbonyl complexes and those bearing other ligands are discussed. All reactions involving propargyl cation dicobalt complexes are covered, including those stemming from ionization of propargylic leaving groups and those created by electrophilic addition to enyne complexes. Migration reactions involving either initiation or termination by propargyl cation complexes are included, as are the generation and reactions of propargyldicobalt radicals. Cyclization reactions employing these cations have received much attention, in cases with the alkynedicobalt unit located in both exocyclic and endocyclic positions, and these reports are described. Particular attention is paid to preparation of medium ring cycloalkyne complexes and their heterocyclic analogues. In addition, there is discussion of the progress in the in selectivity of these reactions, especially in terms of introduction of asymmetry at the propargylic site. Finally, recent applications of Nicholas reaction chemistry in the synthesis of natural products and related compounds are reported.

INTRODUCTION

The Nicholas reaction, or chemistry of hexacarbonyl(μ-propargylium)cobalt cations, has been known since 1972 [1]. The reactions of complexes of this type have seen much attention since this time, and the area was reviewed by Nicholas in 1987 and 1995 [2]. Research on the fundamental characteristics, reactions, and synthetic applications has continued unabated since the 1995 review of Nicholas and Caffyn, and this review is therefore intended to focus on developments from 1995 on, with reference to earlier work if useful for completeness sake. Some authors active in this field have written accounts of their own work [3,4]. In additions, more comprehensive reviews have appeared which contain sections on propargyl cation cobalt complexes [5,6,7].

The attention paid to these compounds is understandable. The cations (**1**) may be generated from hexacarbonyldicobalt complexes of propargylic alcohols, ethers, or acetates reliably using either protic or Lewis acids (Equation 1). These complexes themselves are soluble in CH_2Cl_2, but normally either insoluble or sparingly soluble in ether, and may in many instances be precipitated out from the latter solvent and characterized spectroscopically. Reaction with these cations is highly predictable in regiochemistry. Nucleophiles attack at the propargylic site exclusively; allene formation without prior loss of the $Co_2(CO)_6$ unit has never been reported, to our knowledge. Elimination of H^+ to an enyne complex can compete, but normally can be overridden by the nucleophilic attack process. Cations also conjugated to a double bond normally react at the remote end of the alkene, on the other hand, giving conjugated enyne complexes.



Equation 1. Nicholas reaction - transformation and common nucleophiles.

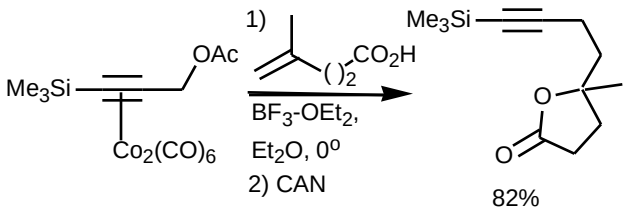
*Address correspondence to this author at the Department of Chemistry and Biochemistry, School of Physical Sciences, University of Windsor, Windsor, Ontario, N9B 3P4, Canada

1385-2728/01 $20.00+.00

The range of nucleophiles capable of attacking these cations is extensive. Oxygen centred nucleophiles include water and various alcohols, incorporating hydroxy- and alkoxy functions, respectively. Nitrogen based nucleophiles include amines, sulfonamides, and (less reliably) acetonitrile. Thiols are also capable of attack on these cations. Pyridine, thioethers, and phosphines give the corresponding salts [8]; the thioether adducts themselves can be used as propargyl cation complex surrogates in some cases.

In the realm of carbon based nucleophiles, ketones themselves can react with propargydicobalt cations through the enol form, but are not efficient unless present as solvent or possessing a high enol content (i.e., β-dicarbonyls). Enol derivatives such as enol silanes, enol boranes, and (occasionally) enamines are much more reliable nucleophiles. Allylmetal derivatives such as allylsilanes, allylstannanes, allylboranes and allylborinates are commonly employed nucleophiles. Arenes will attack these complexes if they are electron rich (including heterocycles); benzene itself is not nucleophilic enough to react efficiently unless present as solvent. Alkenes do react with the propargyl cation, but the product carbocations eliminate to give a mixture regioisomeric alkenes. If a remote carbonyl function (ester, acid, O-linked carbamate, acetate) is present, this then attacks the 'product' carbocation to give incorporation of an oxygen based substituent (Equation 2) [9].

The attack of organometallic reagents on these cations is less routinely applied. Some success has been reported for methyl, 1º alkyl, and acetylenic alanes, and for cyano incorporation with Et_2AlCN, but these have not seen extensive use, and appear to have limited generality. Consequently, study into the viability of Nicholas chemistry employing other organometallic alkyl/aryl reagents warrants further examination. Hydride attack is much more reliable, and many reagents may accomplish this overall reduction. Examples of reactions with these common nucleophiles are present in the earlier reviews by Nicholas [2], and the reader is directed to these for specific literature cases.

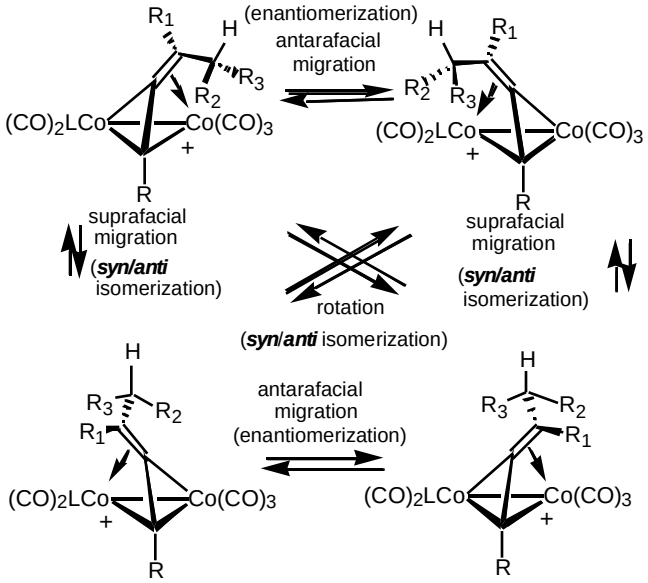


Equation 2. Tandem alkene attack-cation trapping.

FUNDAMENTAL PROPERTIES

The accepted model for the structure of propargylcobalt cobalt complexes was proposed by Schreiber [10]. The model features a bending of the propargylic carbon towards one of the cobalt atoms, and is fluxional by two processes. Antarafacial migration is the lower energy process (undetected for a 1º cation, 11.5 kcal/mol for a 2º cation, 10.1 kcal/mol for a 3º cation), with a higher energy *syn/anti* interconversion process which is either rotation orsuprafacial migration (12.9 kcal/mol for a 3º cation) (Scheme 1).

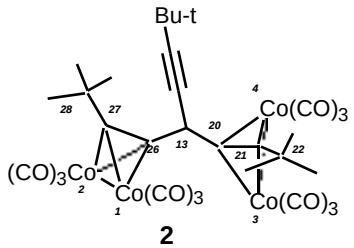
The analogous mono(triphenylphosphine) complexes have since been prepared and studied, and the analogous processes in the complexes found to have higher energy barriers. The *syn/anti* barrier (either rotation or antarafacial migration in tandem with suprafacial migration) is ca. 17-20 kcal/mol (for 2º and 3º cations), whereas the antarafacial migration itself could not be measured, due to exclusive formation (within detection limits) of the cation bent towards the phosphine bearing cobalt atom [11].



Scheme 1. Fluxional processes in propargyl dicobalt cations.

Reprinted with permission from Reference 11 Copyright 1992 American Chemical Society.

Confirmation of the structure of the propargylium hexacarbonyldicobalt cation has been sought since the proposal of Schreiber. Unfortunately, these compounds have generally not possessed enough long term stability for X-ray crystallographic study. Conversely, derivatives with suitable stability for such studies, such as those stabilized as



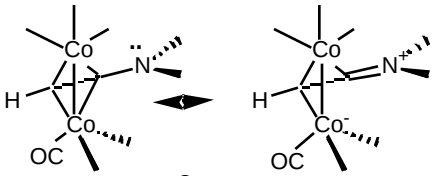
2

C(13)-C(26)-C(27)-C(28) = 55º
C(13)-C(20)-C(21)-C(22) = 43º
C(13)-Co(1) = 3.07 Aº
C(13)-Co(2) = 2.81 Aº
C(13)-Co(3) = 3.27 Aº
C(13)-Co(4) = 2.89 Aº

Fig. (1). Crystal structure of cobalt stabilized propargyl cation.

Adapted with permission from Reference 14. Copyright 1998 Wiley-VCH.

iminium ions [12], pyrilium salts [13], pyridinium, phosphonium, or sulfonium salts [8] show little structural change at the propargylcobalt unit, although some shifts in infrared CO stretching frequencies (to higher frequency) are observed in some of the complexes. Fortunately, the Melikyan group has been successful in isolating and performing X-ray crystallographic structural analysis on **2** [14], which supports most of the assertions of Schreiber (Fig. (**1**)). Relevant structural features of **2** include distinct differences in each of the sets of the two C_{α}^{+}-Co distances (0.26 and 0.36 Å) for the two $Co_2(CO)_6$ units, substantial dihedral angles about the C_{α}-CC-$C_{\alpha'}$ bonds (43º and 55º), and a nearly perfect sp^2 hybridized, trigonal planar orientation at the propargylic carbon. Curiously, DFT optimized geometries neutral ynamine-$Co_2(CO)_6$ complexes have a complementary effect, showing a lengthening of one alkynyl C-Co bond and a planar N atom, evidence of contribution of resonance form **3** (Fig. (**2**)) [15].



3

Fig. (2). Resonance form description of ynamine dicobalt complexes.

The reactivity of propargyliumcobalt complexes has been empirically established by the types of nucleophiles with which these systems would (or would not) react. Measures of pK_{R+} values have been determined, variously reported as –7.40 - -6.80 [16a] and as –5.50 [16b]. Mayr's group has quantified the reactivity of propargylium cobalt complexes **4**, using their electrophilicity parameters E (Fig. (**3**)) [17]. The values of E determined show a relatively narrow range of reactivity, over a factor of ca. 10 (E = -1.22 and –2.22) for the hexacarbonyl complexes, and shows them to be roughly equivalent in reactivity to ferrocenylmethylium ion and xanthylium ion. These also confirm the suitability of reactivity of these cations with electron rich arenes (i.e., anisole), alkenes, or alkynes, marginal reactivity with toluene, and (normally) insufficient reactivity with benzene.

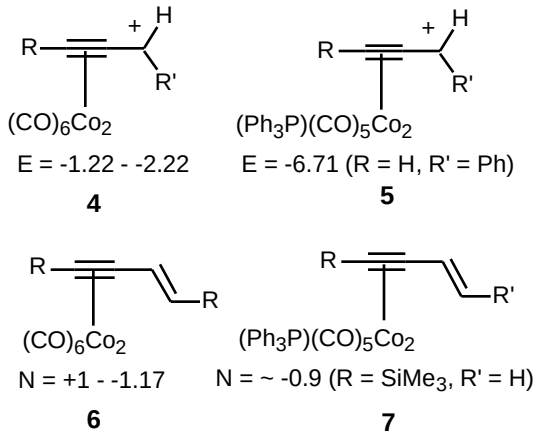


Fig. (3). Mayr's electrophilicity/nucleophilicity parameters.

The mono(triphenylphosphine) complexes **5**, by contrast are ca. 10^5 times less reactive (E = -6.71), indicating insufficient reactivity with the less reactive allylsilanes and all but the most electron rich arenes. The reactivity of dppm complexes is less certain, as pK_{R+} values (-11.0) suggest a cation less stable than the hexacarbonyl complexes [18], while work on CF_3 substituted propargylium complexes suggest greatly enhanced cation stability with this ligand [19]. Propargyl cations with one and two tris(pyrrolyl)phosphine ligands have also been generated [20]; although these cations are attacked by one of the pyrrole ligands, it is not possible at this time to evaluate cation's properties in electrophilicity or pK_{R+} terms.

Mayr has given an analogous reactivity treatment to the reactions of vinyl substituted alkynedicobalt complexes (**6**) with electrophiles in order to generate the propargyl cation [21]. Here, there is *not* a good correlation between the stability of the ultimately formed propargylium cation and the reactivity of the precursor alkene. While a modest increase in reactivity is seen upon addition of an alkyl substituent and modestly more so with an aryl group, the overall nucleophilicity of these enynes (N = +1 - -1.17) roughly approximate their all-organic analogues missing the alkynedicobalt unit (Fig. (**3**)). Most strikingly, the monophosphine complexes **7** give only a tiny (1.8x) increase in nucleophilicity relative to the hexacarbonyls. The group's conclusions that only electrophiles with E > 0 initiating reaction with these enyne complexes (excepting the more reactive phenyl substituted case) is consistent with most literature examples.

There is no experimental evidence at this point to suggest an analogous stabilization of silylium ions (**8**, Fig. (**4**)) by the $Co_2(CO)_6$ unit; migration barriers on indene and rates of allyl protonation show no sizeable differences from the metal free systems [22]. EHMO calculations suggest a modest stabilization is possible [23].

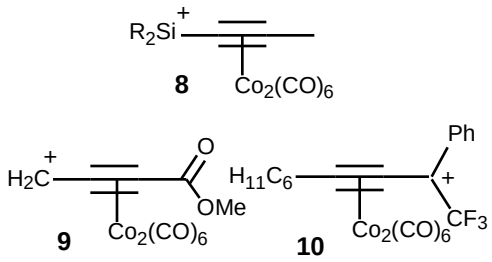


Fig. (4). Electron withdrawing group bearing propargyldicobalt complexes.

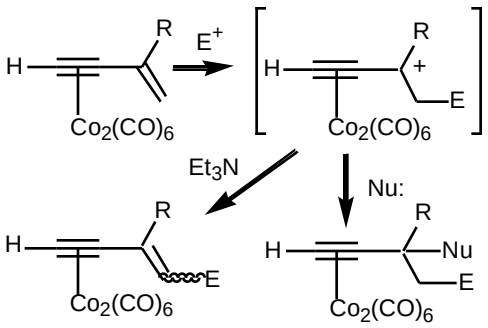
REACTIVITY

Consistent with Nicholas' work on pK_{R+} values, the effect of substituents at the propargylic centre on reactivity are quite minimal. In fact, the nature of the substituent on the remote terminus appears to have a greater, although still small effect. As a result, it is expected that Nicholas reactions should be feasible, even with strongly electron withdrawing groups on the organic unit of the cation. In fact, electron withdrawing groups on the remote alkyne terminus

(**9**) have been found to allow Nicholas reactions with the normal nucleophiles with careful choice of leaving group and Lewis acid [24]. In many of these cases use of a precursor propargyl chloride complex and $AgBF_4$ are the recommended choices for generation of these formally umpolung, carbonyl γ-cation equivalents. Strongly electron-withdrawing CF_3 groups have been tolerated at the propargylic centre (**10**), most reliably when the centre also possesses an aryl substituent [19,25]. Without the aryl groups, attempted cation formation fails, but replacement of one CO by triphenylphosphine or two CO's by a dppm ligand allows cation formation in these cases.

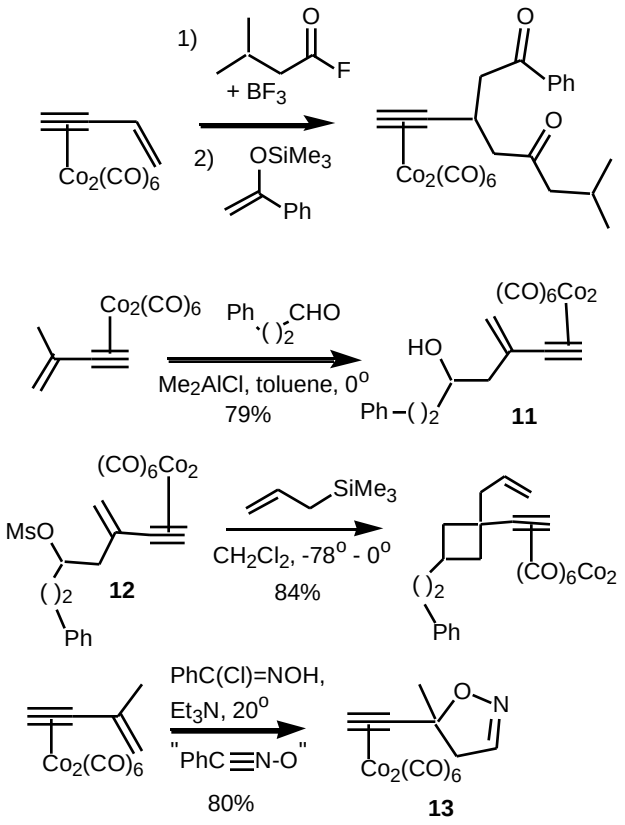
REACTIONS OF ENYNE COMPLEXES

An alternative method of generating propargyl cobalt cations is the attack of electrophilic species by the double bond of a conjugated enyne-$Co_2(CO)_6$ complex (Scheme 2). Smit and Caple have investigated this process extensively, and found that a number of carbocations, and arenesulfenium and nitronium ions are able to initiate this process [26]. Among carbocations, the majority of attention has been paid to a wide variety of acylium ions, but 3º alkyl carbenium ions (*t*-butyl, adamantyl), α-arylthio carbenium ions, and even another propargylcobalt cation have been employed to initiate this process. The nucleophiles employed in the subsequent propargylium ion trapping have mostly been hydroxide or alkoxide type, but instances of most of the common propargylium ion compatible nucleophiles (allylsilanes, silyl enol ethers) also have been reported (Scheme 3). Elimination over substitution is a more commonly encountered side reaction in these processes, particularly with acylium ion electrophiles and with 3º propargyl cation intermediates; this may be accomplished intentionally by the addition of Et_3N.



Scheme 2. Electrophilic attack initiated reactions of enyne dicobalt complexes.

More recently, Suzuki's group has extended this chemistry to that initiated by aldehydes in the presence of Me_2AlCl [27]. Due to the relatively elevated reaction temperature and 3º propargyl cation formed, elimination occurs subsequently, giving an ene reaction type product (**11**). No attempt to trap the cation was reported. Mikami has demonstrated the possibility of high *erythro* (R*,S*) diastereoselectivity in these transformations, and has applied the chemistry the preparation of bicyclic enediyne analogues [28].



Scheme 3. New reactions of enyne dicobalt complexes.

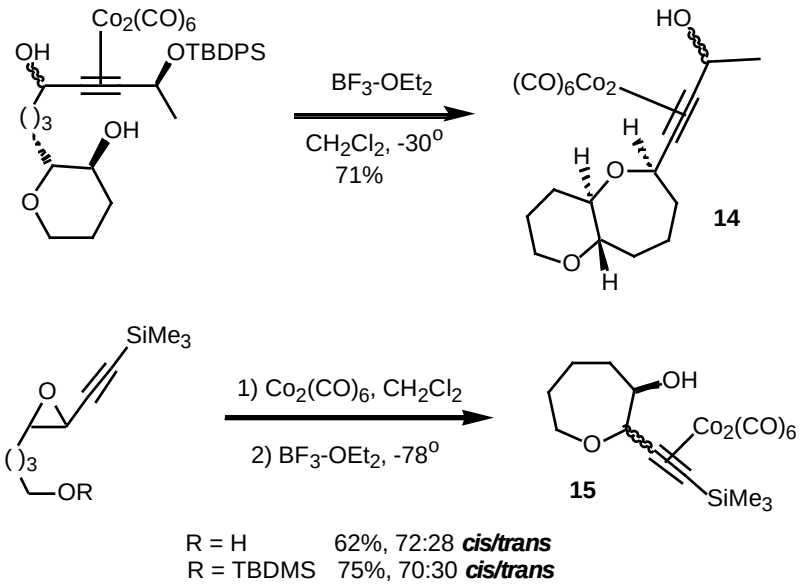
Suzuki has subsequently taken the mesylate derivatives of the product alcohols and found that in some cases (1º alkyl substituents, **12**), a Lewis acid mediated ionization followed by a 4-*endo* trig attack of the alkene occurs; the process ultimately may be terminated by nucleophilic trapping of the resultant propargyl cation [29]. Even in more highly substituted cases, where other migration pathways overwhelm this trapping reaction, a mesylate departure anchimerically assisted by the alkene unit is proposed.

Finally, nitrile oxides have been found to undergo dipolar cycloaddition with the double bond of enyne complexes [30]. Although these cycloadditions are likely concerted, the regiochemistry (**13**) does reflect that expected based on polarization of the double bond.

CYCLIZATION REACTIONS - EXOCYCLIC ALKYNES

A considerable amount of recent work has been focussed on the cyclization reactions between an alcohol function and a propargyl alcohol or ether function to give cyclic ethers bearing an alkyne-$Co_2(CO)_6$ unit (Scheme 4). Boron trifluoride etherate has been found to induce this cyclization, giving cyclic ethers of 5 [31] and 6-9 members [32]; an unusual feature of this process finds the oxepanes (i.e., **14**) apparently forming more rapidly than the 6-membered cases.

Mukai and Hanoaka have paid much attention to cyclization reactions between a pendant alcohol function and alkynyl epoxide functions, catalyzed by BF_3 [33]. These

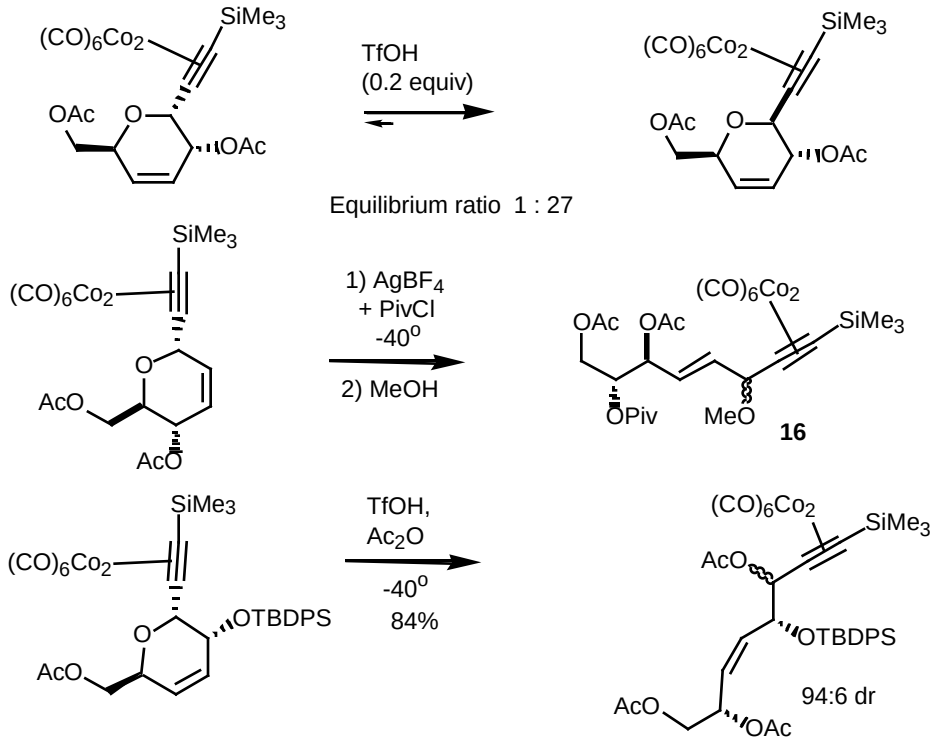


Scheme 4. Cyclic ether formation reactions.

ring closing reactions occur exclusively in an endo fashion at the propargylic site, giving 5-, 6-, or 7- membered ethers (**15**), with the facility for formation of the propargyl cation overriding normal relative ring closing rates in the 6- and 7-membered cases (Scheme 4). TBDMS ethers may be used to some advantage over the alcohols in the oxepane cases. In an unusual adaptation using a related approach, Mukai and Hanoaka have employed a propargyl ether with a remote pyranosidic ester function as a source for a glycosylation, using formation of propargylic lactone complex as the trigger [34].

Once closed, ready generation of the propargylic cation species from the cyclic ether alkyne complexes could be expected to provide a ready route to epimerization at this site, and this has proven to be the case in the pyran ring systems. Under equilibrating conditions with CF_3SO_3H, the large size of the alkyne-$Co_2(CO)_6$ unit [35,36] results in equilibria featuring this unit predominantly in the β-(equatorial) orientation (Scheme 5) [37]. These β-/α- ratios are often quite high (4:1 – 100:1). Since the metal free alkynyl function is normally incorporated with high α-selectivity, total flexibility in its orientation is normally possible.

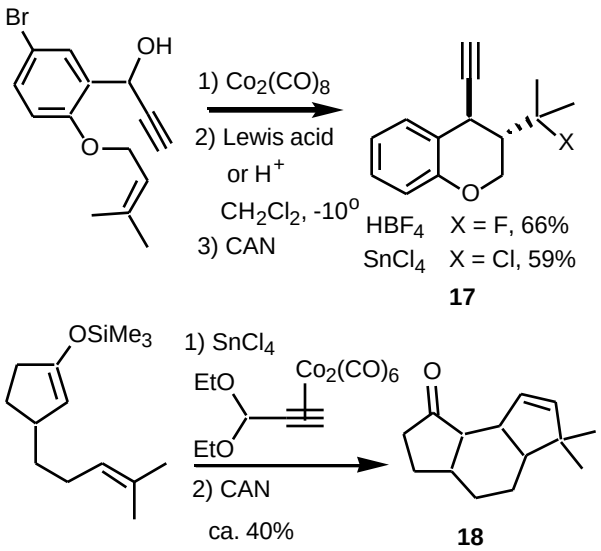
Under suitable conditions, these pyran ring systems may be induced to undergo ring opening. Protonation of the pyran with TfOH in the presence of acetic anhydride to both



Scheme 5. Cyclic ether epimerization and ring opening.

trap the resultant OH and attack the propargyl cation gives protected acyclic polyols [38]. In the $\Delta_{2,3}$ cases, (*Z*)- to (*E*)-isomerization of double bond and incorporation of the nucleophile at the propargyl site of a vinylogous system is observed (**16**); this regiochemistry of nucleophile incorporation is unusual in Nicholas reaction chemistry. Use of pivaloyl tetrafluoroborate to initiate the ring opening allows incorporation of other nucleophiles such as water, alcohols, thiophenol, and allyltrimethylsilane. The same stereochemical and (predominantly) regiochemical patterns are observed such cases.

Cyclization reactions onto non-activated alkenes have been studied by Tyrrell. Propargylcobalt cations undergo reactions with suitably disposed trisubstituted alkenes to give either benzocyclohexane rings or benzopyran ring systems, depending on the tether [39]. In some cases these eliminate to form an alkene unit, but with judicious choice of conditions, the resulting 3° cation may be trapped with halide ion from the Lewis (or protic) acid to form 3° fluorides, chlorides, or (less successfully) bromides (**17**, Scheme 6). In a few instances, decomplexation of the crude reaction mixtures give further cyclization onto the alkyne unit. The starting materials themselves are prepared by an enol silane/propiolaldehyde-$Co_2(CO)_6$ Nicholas reaction, and in some cases the one pot tandem Nicholas reaction-Nicholas cyclization-decomplexative cyclization is possible (**18**). In other cases, the Tyrrell group has employed a more conventional enol silane to cyclize onto the cation derived from a propargyl ether complex. Cycloalkanones and cycloalkyl ketones of 5-, 6-, 7-, and 8- members may be formed efficiently in this process [40]. Tyrrell has also applied this chemistry in the ring fusion of cyclopentane-carboxaldehydes onto existing cycloalkanes.

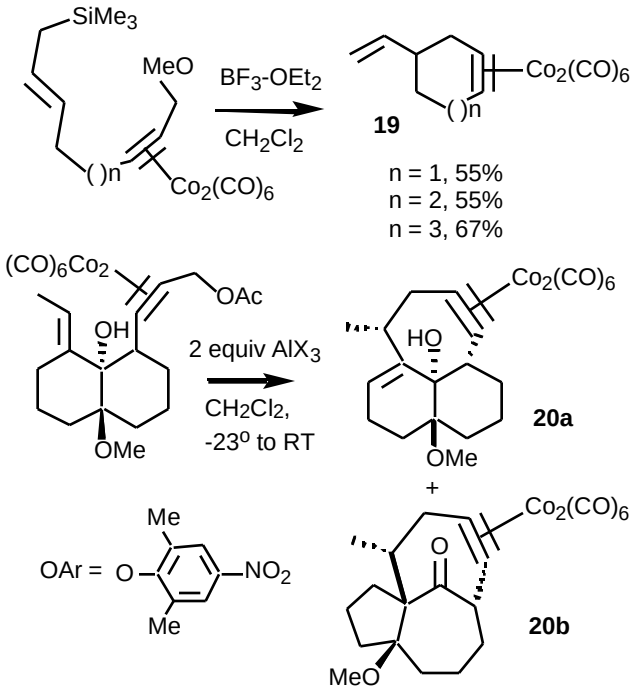


Scheme 6. Carbocyclizations-exocyclic alkyne complexes.

CYCLOALKYNE RING FORMING REACTIONS

The synthesis of cycloalkyne cobalt complexes of medium ring sizes has been the subject of much recent activity. The source of attention stems the instability of metal free cycloalkynes of small or even medium ring sizes due to angle strain upon the sp hybridized C atoms [41]. As the 'natural' bond angles of alkynecobalt complexes are ca. 140°, the reduced ring strain and therefore the viability of medium ring cycloalkyne cobalt complexes is logical. This is made further attractive by the common occurrence of fused 7,5- and 8.5- ring systems in many naturally occurring compounds, and the ability of the Pauson-Khand reaction [42] to convert alkynecobalt complexes into cyclopentenones. In several instances, variants of the Nicholas reaction have shown the ability to form cycloheptyne and cyclooctyne complexes readily. The synthetic utility of these cycloalkyne complexes has also been aided by the recent development of methods of removal of the cobalt unit in tandem with carboxylation [43], reduction [44,45], or hydrosilylation [43c] of the triple bond.

The initial report in this area from the group of Schreiber described the *exo* trig cyclization reactions of allylsilanes onto propargyl cation complex, a process which succeeds for six-, seven-, and eight membered ring systems (**19**, Scheme 7) [46]. To date this is still the only successful report of a cyclohexyne-$Co_2(CO)_6$ complex. More recently, Tanino and Kuwajima have reported that a *trans*- decalin system bearing an exocyclic alkylidene and a propargyl acetate –$Co_2(CO)_6$ complex undergoes cyclization, followed by one of two processes [44]. Highly Lewis acidic organoaluminum reagents give cyclization followed by a proton loss to form a 7,6,6-system (**20a**). Less Lewis acidic organoaluminums give cyclization followed by a pinacol-type rearrangement to afford 7,7,5-system of the ingenane skeleton (**20b**).

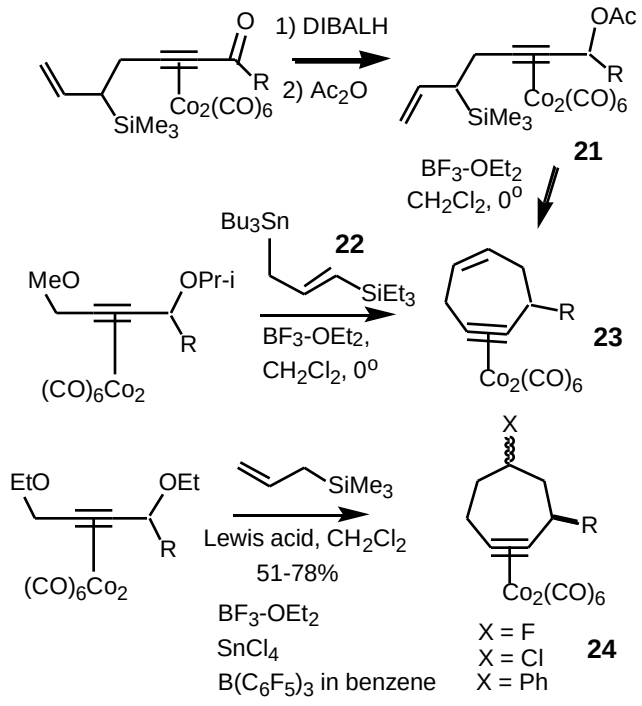


	20a	20b
$Me_2Al(OTf)$	69%	13%
$MeAl(OCOCF_3)(OAr)$	21%	77%

Scheme 7. Ring closure reactions giving cycloheptyne complexes.

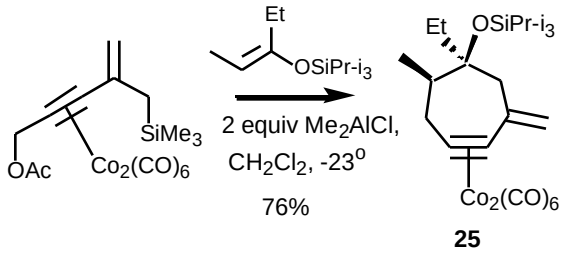
The Green group has demonstrated that the suitably constructed allylsilanes (**21**), derived themselves from intermolecular Nicholas reactions with silylated allylstannanes (**22**) [24] undergo 7-*endo* trig cyclization to afford cycloheptenyne complexes (**23**) in excellent yield (Scheme 8) [47]. A version of this cyclization may also afford *exo* methylene complexes. The application of the same allyldimetal equivalent in reaction with butyne-1,4-diether complexes gives cycloheptenyne complexes by two sequential allylmetal Nicholas reactions, by way of an overall 4+3 cycloaddition process [48]. These cycloadditions show interesting reaction selectivity at with substrates with differing propargyl site substitution; initial condensation occurs selectively at the less substituted site. This selectivity is modest (70:30), but may be increased to high levels by also incorporating ether functions of differing bulk at the two sites. Oxygen substituted cases are made by other methods [49].

This 4+3 cycloaddition process can take a slightly different course under high dilution, slow addition conditions, affording fluorocycloheptynes. This product was determined to be resulting from initial destannylation of the silylstannane, such that the ultimate product results from a 4+3 cycloaddition occurring on the allylsilane, giving a 2° cycloalkyl cation trapped by halide from the Lewis acid source. Employing allyltrimethylsilane itself and different Lewis acids, fluorination, chlorination, bromination termination steps can be induced (**24**). In benzene solvent, the 2° cycloalkyl cation can be made to arylate in the one pot process [50,51]



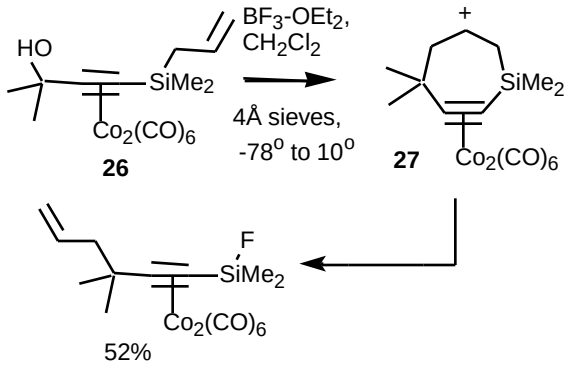
Scheme 8. 4+3 Cycloaddition routes to cycloheptyne complexes.

Tanino has developed an alternative tandem condensation involving a Nicholas reaction of a triisopropylsilyl (TIPS) enol ether, followed by trapping of the α-siloxy cation with an allylsilane [52]. This overall 5+2 cycloaddition process gives *exo* methylene cycloheptyne complexes (**25**), and gives good to excellent diastereoselection of the newly formed vicinal chiral centres (Equation 3). The observed diastereomer is rationalized in terms of an antiperiplanar relationship between the intermediate oxonium ion and the allylsilane π- system.



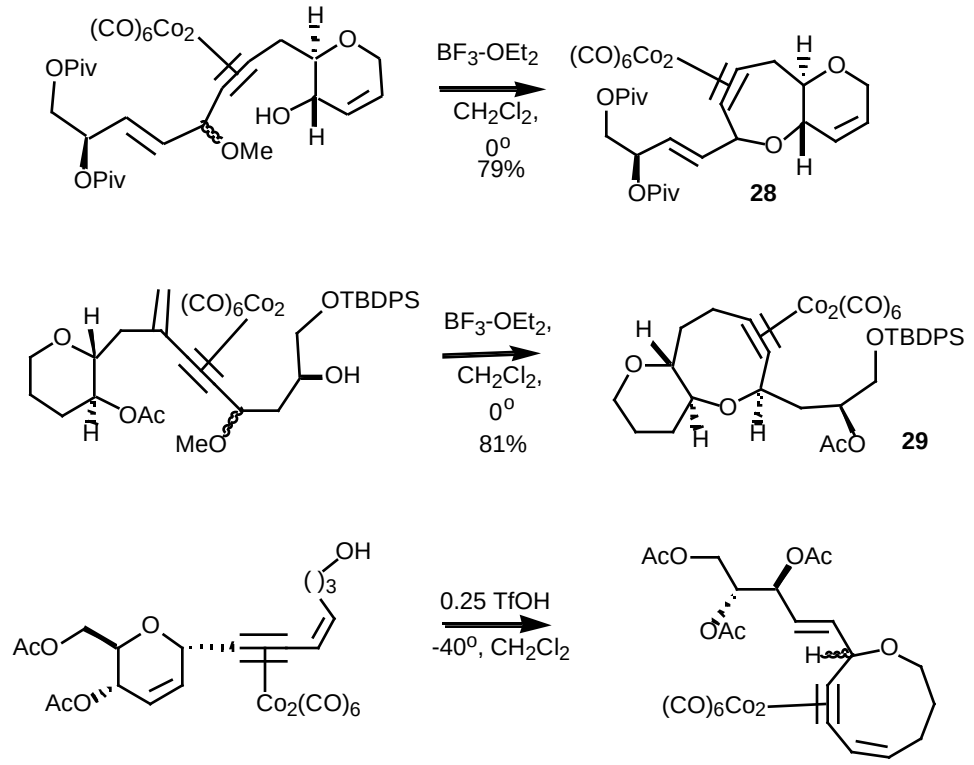
Equation 3. 5+2 Cycloaddition approach to cycloheptyne complexes.

A process related to the above cycloheptyne forming reactions, but not resulting in a cycloalkyne complex, occurs in the allyl migration reactions of acetylenic allylsilane complexes (**26**) (Equation 4) [53]. Here a silacycloheptyne complex containing a β-silyl cation (**27**) is implicated, but it is ring opened by fluoride induced elimination in the final step.



Equation 4. Intramolecular allyl transfer via silacycloheptyne carbenium ion.

In heterocyclic medium ring cycloalkynes [54], recent work has been dominated by the reports of Isobe [3]. The principal strategy of this work involves the protic or Lewis acid induced cyclization of a remote alcohol function onto a propargyl methyl ether complex. By choice of the length of the tether, 7,8, or 9- membered rings can be formed in good yield (Scheme 9). Stereoselection is normally excellent at the epimerizable propargylic ether carbon. In the case of the seven membered ring compounds (i.e., **28**), there is mounting evidence in both oxepane and cycloheptyne complexes of a preferred extended chair conformation for the ring and axial/equatorial preferences for substituents strongly analogous to the traditional cyclohexane situation [47,48,55]. In the larger ring systems, the conformational properties are less clearly understood, but a *cis* relationship at the two ether α-sites is favoured (i.e., **29**). In more moderate yield, the ring systems may even be prepared by a one-pot tandem C-1 alkynylcobalt dihydropyran ring opening-cyclization protocol (Scheme 9) [56].



Scheme 9. Cycloalkynyl ether formation.

Isobe has made extensive use of these cycloalkynyl ether and alkynyl substituted cyclic ether complexes in synthesis, particularly in work towards ciguatoxin (Fig. (**5**)) and the related gambietoxin. More specifically, the group has employed the oxepane ring forming protocol for formation of the (A)BC ring system of the (5*S*)-enantiomer of ciguatoxin and the (A)B system of gambietoxin [54,57]. The oxocane cyclization, followed later by the oxepane protocol, have been employed for the I and K rings of the HIJK system [58]. Finally, the oxepane and oxinin cyclizations have been employed for the E and F rings, respectively, of the DEF system [59].

Larger ring alkyne complexes have also been prepared by intervention of propargylcobalt cations (see also **Synthesis**). Isobe has prepared the taxane type bicyclo[9.3.1] system (**30**) by macrocyclization of a remote allylsilane unit in moderate yield; this case appears to be a rather difficult cyclization (Scheme 10) [60]. The more commonly encountered substitution at remote end of the vinylogous system is also found here.

Green and co-workers have found that bis(propargyl ether) tetracobalt complexes are capable of reacting with electron rich arenes and some π-excessive heterocycles by way of two successive Nicholas reactions. These give [7]metacyclophanediynes (**31**) in one synthetic step [61]. In some cases, the macrocyclization step is apparently very facile, and the yields for the transformation are excellent.

In heterocyclic examples, Mays has applied methodology originally employed by Went for medium ring ether and thioether alkyne complexes [62] to macrocyclic diyne cases. Treatment of a diynediol tetracobalt complex with catalytic

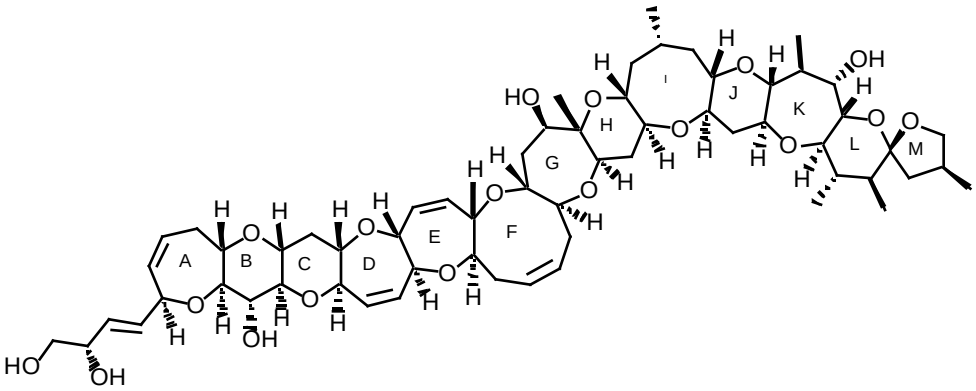
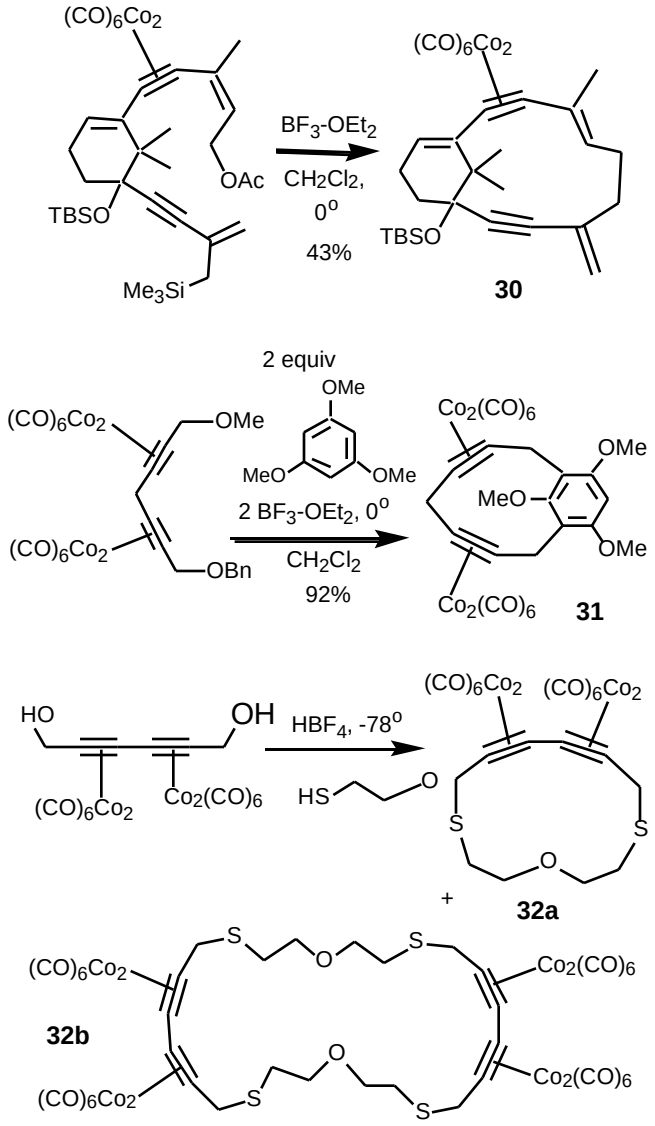


Fig. (5). Ciguatoxin (CTX1B).



Scheme 10. Macrocyclic cycloalkynes.

HBF_4 and a dithiol results in formation of both a 13-membered ring sulfur containing macrocycle (**32a**) its 26-membered ring dimer (**32b**), in excellent total yields [63]. In one case, one of the CO ligands on one Co atom is substituted by a sulfur ligand.

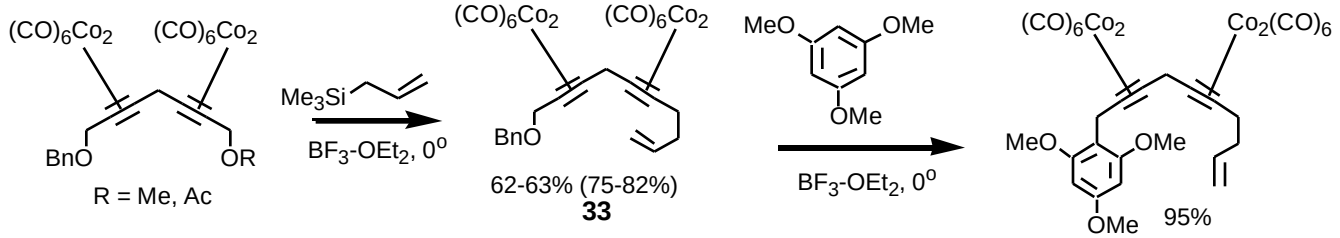
SELECTIVITY IN NICHOLAS REACTIONS

Several literature reports have implied that selectivity is possible when two possible sites for propargyl cation formation exist; almost invariably kinetic factors are employed in this process. This is implied in the in the cyclic ether formation reactions of Martín, as remote propargylic OTBDPS groups often remain undisturbed in the process (see Scheme 4) [32]. Regioselective ionization of the less sterically hindered propargyl ether is also apparent in the 4+3 cycloaddition chemistry of the Green group (see Scheme 8) [47]. The ability to ionize a less sterically hindered or better leaving group has been demonstrated more directly by this group, in the monocondensation reactions of 1,4-diyne tetracobalt complexes (**33**, Scheme 11) [64]. Selectivity is good, but not outstanding, for ionization of MeO or OAc groups over a benzyloxy group. Finally, Schreiber's epoxydictymene synthesis contains a highly selective ionization of the less sterically hindered oxygen atom of an unsymmetrical acetal (see **Synthesis**) [65].

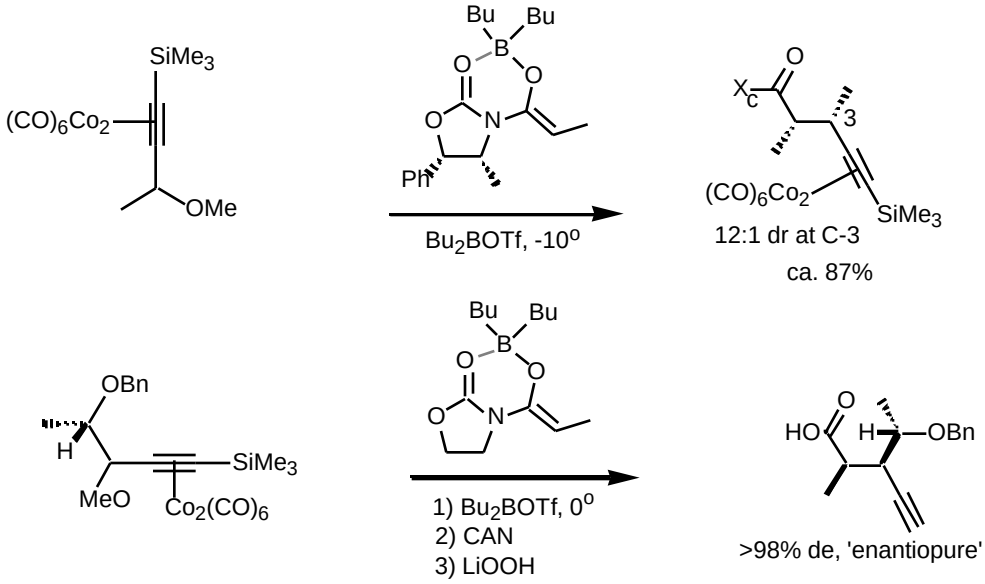
SELECTIVITY-ASYMMETRIC SYNTHESIS

The rapid antarafacial migration (enantiomerization or epimerization) process which occurs at the propargylic centre of these cations is both an advantage and a drawback for asymmetric synthesis using these complexes. On the plus side, chiral nucleophiles should be able to discriminate between enantiofaces (or diastereofaces) at the propargyl site, and react selectively to form diastereomerically and enantiomerically enriched products. This has been demonstrated in many cases, with silyl enol ethers [9,45] and particularly with the enol boranes derived from N-acyl oxazolidinones, which give high *syn* de's about the newly formed bond. In the cases of enantiopure enol boranes, high de's are induced by the auxiliary in the condensation reactions (Scheme 12). A synclinal orientation of the enol C=C and the alkynyl carbon-propargyl carbon bond has been proposed to rationalize the stereoselection and the increased diastereoselectivity with increased size of the remote alkynyl R group (for chiral boron enolates **34a**, and enol silanes **34b**, Fig. (**6**)). In at least some cases in this type of condensation, even a chiral centre adjacent to the propargyl site is capable is inducing high diastereoselectivity in the condensation reactions [66].

The addition of many nucleophiles with propiolaldehyde-$Co_2(CO)_6$ complexes also occurs with levels of simple diastereoselectivity which ranges from good to excellent. Silyl enol ethers (regardless of geometry) and cyclic silyl ketene acetals give *syn* diastereomers with ca. 80% de's; acyclic silyl ketene acetals derived from thioesters give outstanding *syn* diastereoselection (Scheme 13) [67]. The comparison between the propynal complexes and the corresponding acetal complexes (i.e., **35**) [68] is difficult due



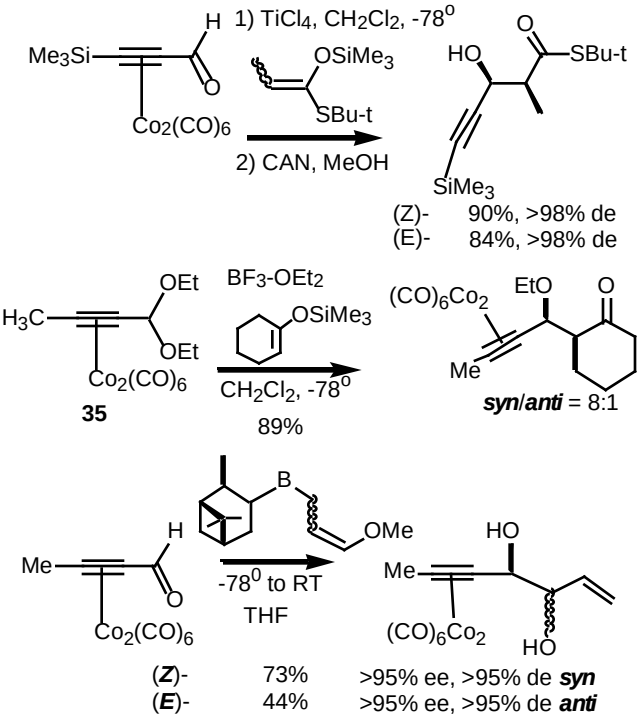
Scheme 11. Selective Nicholas reactions on 2,5-diyne-1,7-diol derivative complexes.



Scheme 12. Asymmetric Nicholas condensation reactions.

the differences in cases investigated. In the case of the acetal complexes, the normally encountered relationship between the remote alkyne terminus R group and stereoselection is not apparent. Allylboronates [69] and allylboranes [70] give excellent diastereoselectivity in favour of the (Z)-crotylmetal to *syn*- and (E)-crotylmetal to *anti*- pair of results; in addition the enantioselectivity of addition is substantial with the tartrate derived chiral boronates and excellent with the diisopinocamphenylboranes.

Other asymmetric transformations are possible on carbonyls conjugated to alkyne-$Co_2(CO)_6$ complexes. In ketones, the large size of the alkyne-$Co_2(CO)_6$ unit allows enantioselective hydroboration in the presence of chiral oxazaborolidines (Equation 5) [71]. Despite the fact that this most often requires one of the less sterically hindered oxazaborolidines, and the fact that the oxazaborolidines normally do not work well in catalytic amounts, excellent ee's can be obtained in most cases where substituents reside on the remote alkyne terminus.



Scheme 13. Asymmetric condensations of propynal derivatives.

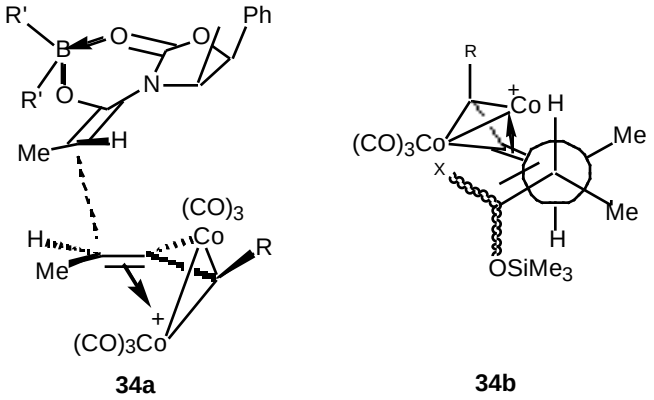
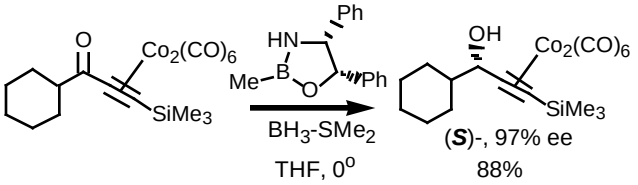


Fig. (6). Proposed condensation transition state.

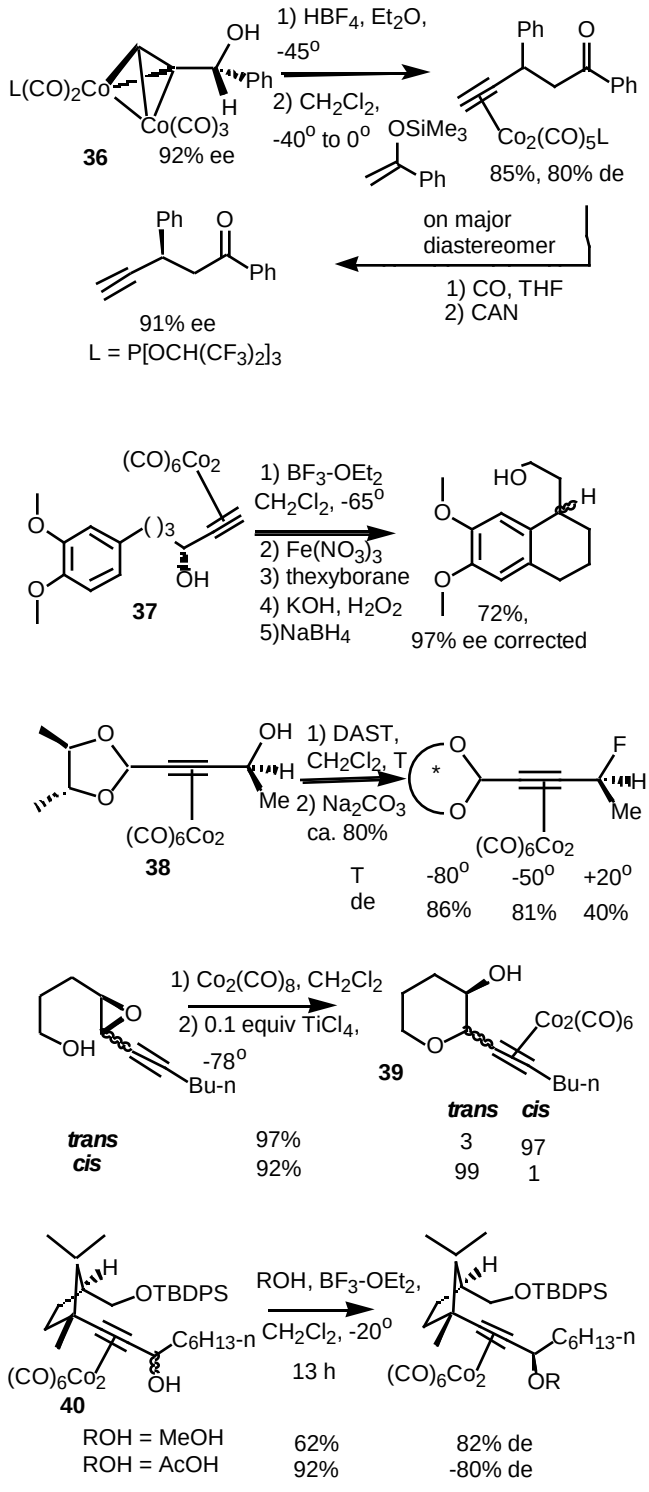
Reprinted with permission from Reference 10. Copyright 1987 American Chemical Society.

Otherwise, the rapid enantiomerization process of propargyldicobalt cations puts restrictions on the ability to create chiral centres enantioselectivity at the propargylic site. This can be overcome in selected cases. Nicholas has shown that replacing a CO ligand with a tris(hexafluoroisopropyl) phosphite [$P(OCH(CF_3)_2)_3$] ligand (**36**, Scheme 14) is a



Equation 5. Enantioselective reduction of alkynone complexes.

compromise which allows sufficient reactivity with silyl enol ethers and allylsilanes, giving variable de's, but slowing the enantiomerization process such that the condensation occurs in at least one case with essentially complete retention of configuration at the propargyl site [72]. In the hexacarbonyl substrates, Muehldorf has demonstrated that enantioenriched propargyl alcohol complexes bearing a three carbonyl tether to an electron rich aromatic ring (i.e., **37**) undergoes low temperature cyclization to give cyclohexanes with varying degrees of enantiomerically enrichment at the benzylic site [73]. Grée has been able to fluorinate propargyl alcohol complexes **38** with 86% de in favour of retention at –80 ºC [74]. Since the remote chiral auxiliary has no effect on the de's, and the metal free complexes fluorinate with inversion, the most straightforward interpretation features a fluorination of the propargyl cation that competes well with the antarafacial migration process. A similar successful 'competition' has been seen in Lewis acid catalyzed cyclization of alcohols onto alkynyl epoxides, giving hydroxy- substituted cyclic ether complexes (**39**, Scheme 14, and Scheme 4). In the tetrahydrofuran and tetrahydropyran cases, attack of the alcohol function occurs with high degrees of retention for both the *cis* and *trans* epoxide precursors, presumably by a double inversion mechanism [33b,c]. This stereospecific feature does *not* extend to the oxepane systems. These results suggest that other very rapid *in situ* cation formation/trapping reactions may be able to give high levels of retention of configuration at the propargylic site.

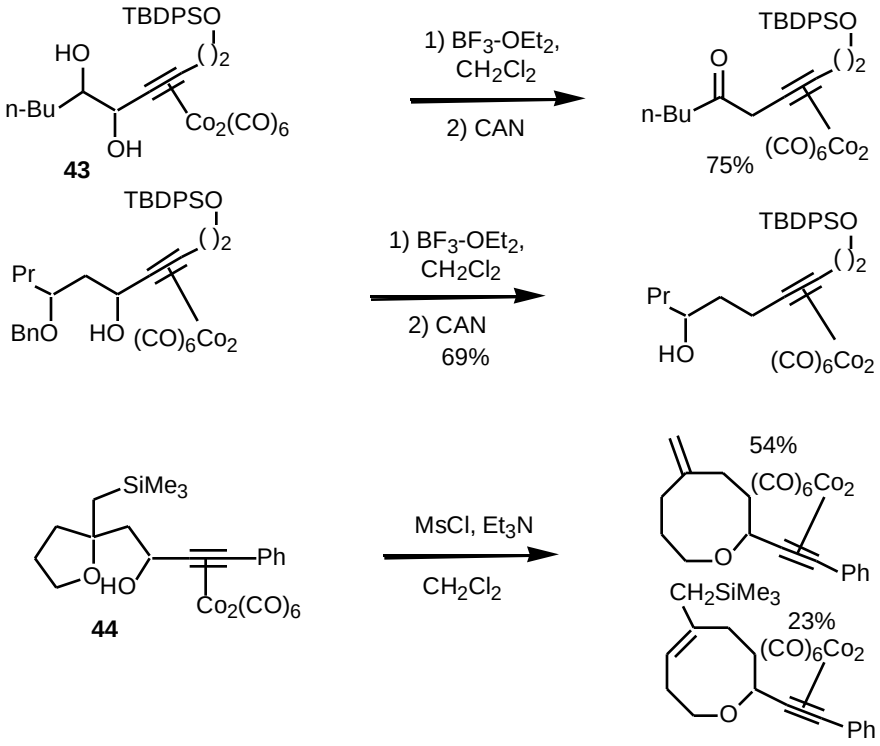


Scheme 14. Asymmetric induction at propargylic centres.

The group of Martín has employed a still different approach at enantiomeric enrichment at the propargylic site in Nicholas reactions. Attachment of a camphoric acid derived chiral auxiliary (**40**) allows alcoholysis of the remote propargylic alcohol site in ca. 80% de's, and acetoxylation in more limited de's under kinetic control, but with complete reversal of stereoselection (up to –82% de) under thermodynamic control [75]. Although these complexes are convertible to α-hydroxy ester, aldehyde, and *vic*-alcohol derivatives, the 'auxiliary' is not readily removable while keeping the acetylene function intact.

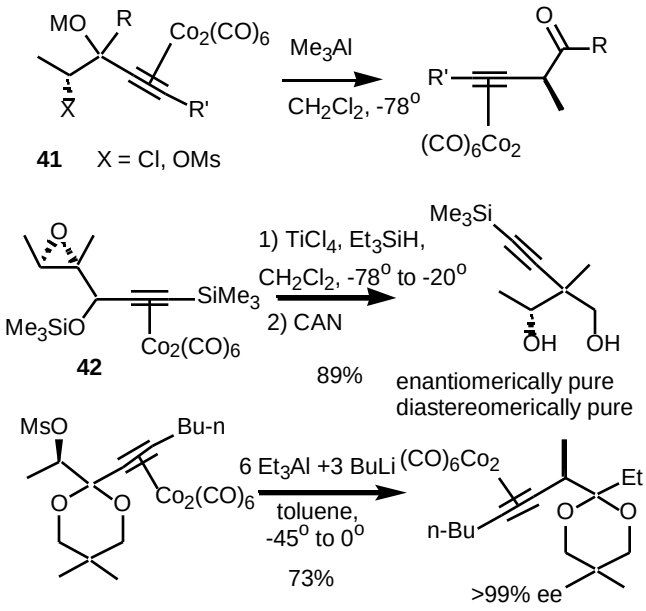
MIGRATIONS

Several recent developments in methods of generation of chirality at the propargylic centre in alkyne-cobalt complexes involve migration of the alkyne-cobalt unit. If a cation is generated at the centre homopropargylic to the unit, the alkyne-cobalt complex has demonstrated a very high aptitude for 1,2-migration, which is > alkyl, aryl and even 4-MeOPh, and comparable to Me_3Si-vinyl. These migrations have taken several manifestations. β-Chloro-α-hydroxy alkyne complexes or β-mesyloxy-α-hydroxy alkyne complexes (**41**, Scheme 15) rearrange to a α-hydroxy carbenium ion, which in turn deprotonates to give the homopropargylic ketone [76]. The β,γ-epoxy-α-trimethylsiloxy alkyne complexes (**41**) also rearrange, to give α-trimethylsiloxy carbenium ions, which lose the formal Me_3Si^+ to give homopropargylic ketones containing an additional hydroxy function, or are reduced *in situ* to give the diol. Finally, the β-mesyloxy propargyl acetal complexes rearrange to give α,α-dialkoxy carbenium ions, which may be trapped by hydride, alkyl, or alkynyl nucleophiles to give the corresponding ketals [77]. In each of these cases, when the original leaving group is on a chiral centre, the migration occurs with complete inversion of stereochemistry at this migration terminus. Suzuki's group has employed the epoxide fragmentation/migration protocol to incorporate the dihydrofuran and side-chain chirality in the synthesis of several furaquinocins [74b].



Scheme 16. Alkynyl-cobalt migrations. Non asymmetric examples.

One noteworthy feature of the above nucleophilic rearrangement processes is how the straightforward formation of the propargylcobalt cation is apparently not a competitive process. Nevertheless, if there is a simple change of the group in the homobenzylic position to a poorer leaving group, a different rearrangement pathway is followed. When diol complex **43**, for instance, is subjected to BF_3-OEt_2, ionization of the propargylic OH, followed by hydride migration to the propargyl site, and final deprotonation gives the homopropargylic ketone which has undergone reduction at the propargylic site (Scheme 16) [78]. If 1º or 2º bishomopropargylic benzyl ethers are present, the propargylium cation undergoes hydride transfer from the benzylic carbon, and the resultant reduction at the propargylic site is coupled with debenzylation at the bishomopropargylic site [79]. MOM ethers perform similarly, but less cleanly. Finally, Mukai and Hanoaka have extended their cyclic ether forming reactions to 8-membered cases by employing a trimethylsilylmethyl substituted tetrahydrofuran (**44**), which uses a propargyl cation that induces ring opening a C-O bond of an oxolane to form a β-silyl cation; the latter then loses H^+ or "Me_3Si^+" [80]. Rather than employing a Lewis acid for propargyl cation formation however, conversion of the propargyl alcohol function to the mesylate was the only protocol found to be efficient in inducing this process.

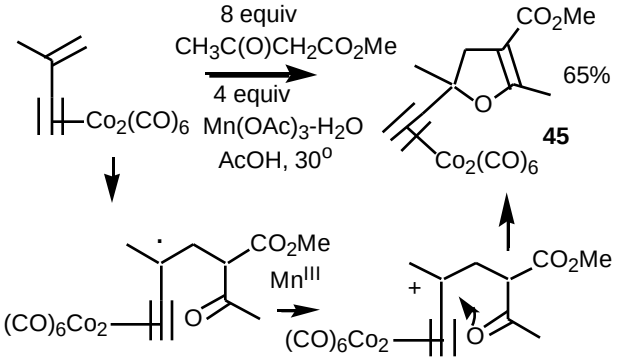


Scheme 15. Alkyne-cobalt migrations. Asymmetric versions.

Finally Wagner-Meerwein rearrangements have been observed in the propynyl-$Co_2(CO)_6$ substituted fenchyl (but not bornyl) cation [81]. Propargylsteroidal cations also give products of methyl group migration [82].

PROPARGYL RADICAL REACTIONS

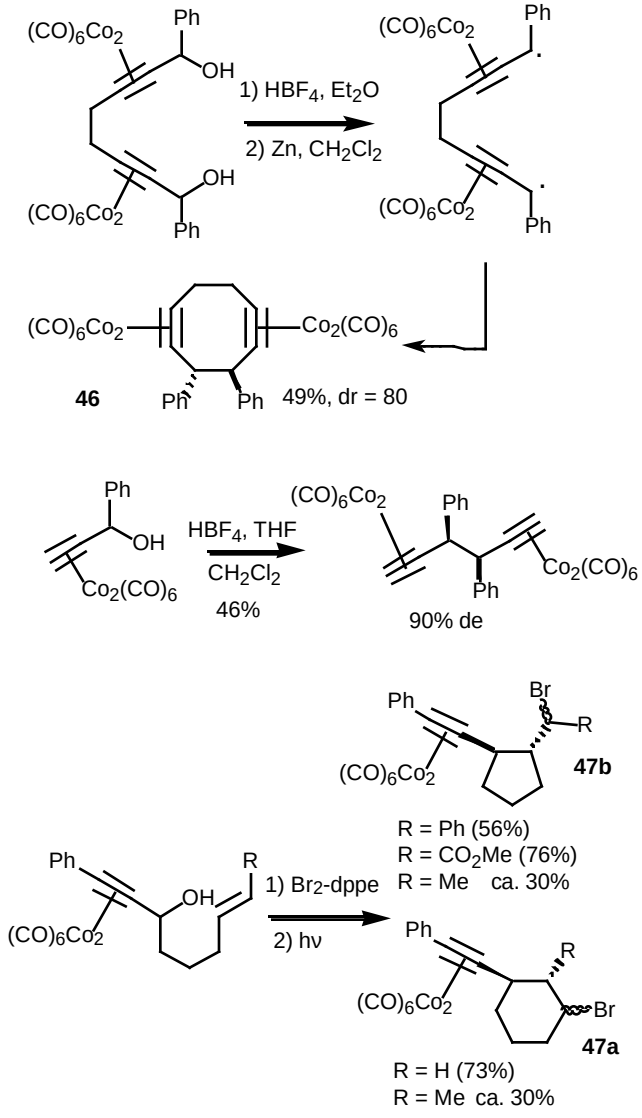
Propargylcobalt free radicals have for many years been postulated as the source of dimerized side products in propargyl cation chemistry. Interest in this area was spurred on, however, by the reported reaction of β-dicarbonyl compounds with 1,3-enyne-$Co_2(CO)_6$ complexes induced by $Mn(OAc)_3$, affording dihydrofuran-alkyne complexes (**45**) in variable yields (Scheme 17) [83]. These impressive transformations were postulated to occur by addition of a β-dicarbonyl 'radicloid' to the alkene unit to give a



Scheme 17. Mn^{III} induced cyclization reactions.

propargylcobalt radical, followed by oxidation of that radical to a propargylcobalt cation, and intramolecular attack of the ketone oxygen atom on that cation.

Since this report, it has become clear that free radicals at the site propargylic to an alkyne-$Co_2(CO)_6$ are readily made,



Scheme 18. Propargyldicobalt radical reactions.

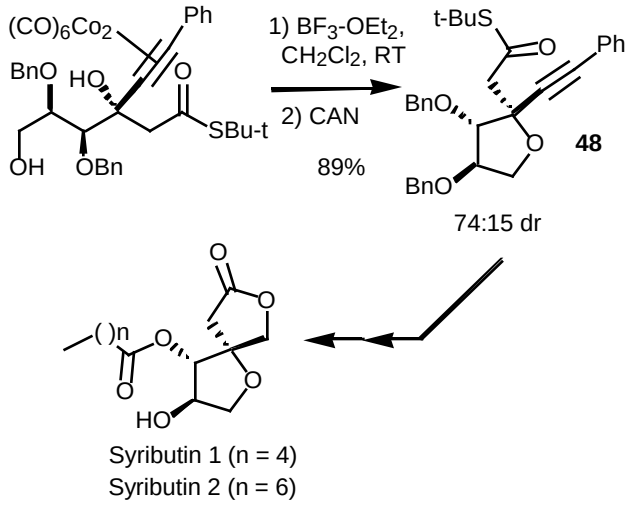
despite there being little data on their structure, absolute stability, or lifetime. Most commonly, they have been prepared by reduction of the propargyl cations by Zn metal [84]. Under such conditions, the so-generated radicals tend to dimerize, at the propargylic site, to give 1,5-diyne complexes in both acyclic and medium sized (8-10) cyclic cases (**46**, Scheme 18). These homocouplings are noteworthy for their good to excellent *syn*- (acyclic)/*trans*-(cyclic) diastereoselectivity about the newly formed bond in 2° cases. Exceptions to the homocoupling reactions are found the tertiary radicals and those bearing CF_3 groups [19], which decompose by H-atom abstraction and other routes [85]. In the absence of detailed mechanistic work, it is best to regard propargylcobalt radicals as nucleophilic radicals.

More recently, propargyl radical cobalt complexes have been formed by other methods. Single electron transfer to propargyldicobalt cations from cyclic ethers and thioethers, cyclic and acyclic acetals, (cyclic) dithioacetals, and ortho esters gives these radicals; THF is apparently the best of these in term of dimerization yields [86]. Added reductants such as Bu_3SnH are capable of overriding the dimerization, giving overall reduction.

Recently, the Nicholas has looked at radical cyclizations of the propargyl radical cobalt complexes from the modestly stable propargyl bromides [87]. These cyclizations are unusual in there is a high tendency to undergo radical atom transfer cyclizations, a high preference for forming *trans*-disubstituted cyclopentanes, and (in the absence of radical stabilizing groups) an increased tendency to prefer the 6-*endo* cyclization mode (**47a**) as opposed to the more common 5-*exo* mode (**47b**).

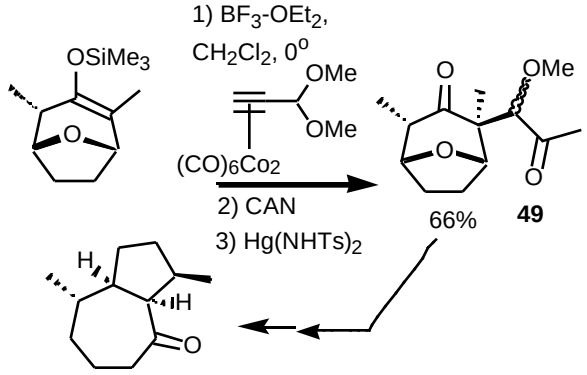
SYNTHESIS

Several research group have made extensive use of Nicholas reaction chemistry in the synthesis of natural products or related targets. Particularly heavy use has been made of ether cyclization reactions and asymmetric enol borane condensations.



Scheme 19. Application to syributin synthesis.

Among syntheses featuring propargyl dicobalt mediated ether forming steps, Isobe's extensive work has been addressed previously (see Scheme 9, Fig. (**5**)). Mukai and Hanoaka have made synthetic use of the exo alkynyl tetrahydrofuran forming reactions by cyclization of alcohol functions onto propargyl alcohol complexes [31]. As the source of enantiomeric enrichment is already present in benzyl ethers, only diastereoselectivity is necessary in this cyclization. The major diastereomer from this cyclization (**48**, Scheme 19) was converted into (+)-secosyrins 1 and 2, and (+)-syributins 1 and 2 by converting the alkynyl unit into the CH_2O unit of the lactone by reduction and oxidative cleavage steps.



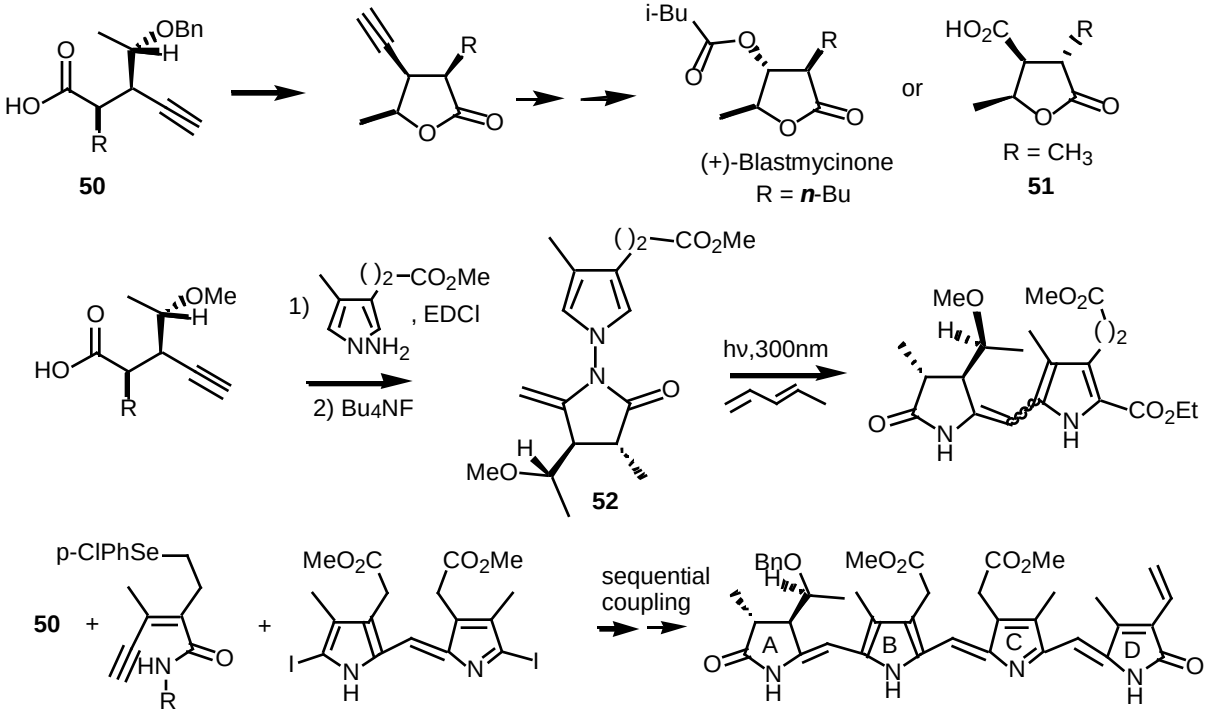
Scheme 20. Construction pseudoguaiane-type skeleton.

In the chemistry of Nicholas reactions of enolate equivalents, Montaña has employed an acyclic enol silane/alkynyl acetal Nicholas reaction for incorporation an α-methoxyacetone surrogate (**49**, Scheme 20) onto a bicyclic cycloheptanone. Excellent *exo* facial selectivity was obtained in this attack by the bicyclic system. The ketone was employed to fuse a cyclopentane onto the system, ultimately affording the bicyclo[5.3.0]decane framework of the pseudoguaiane type [88].

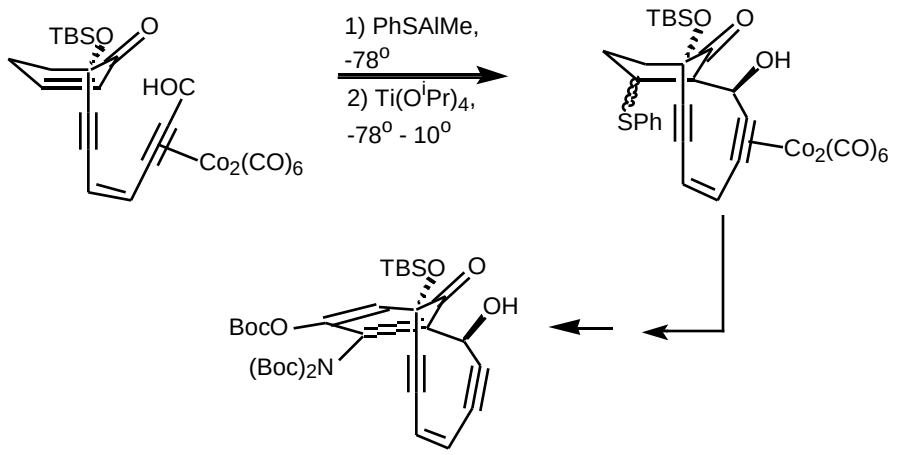
Jacobi has made extensive use of asymmetric Nicholas reactions of enol boranes with substituted propargyl cation complexes in synthesis (Scheme 21, see also Scheme 12). Application of decomplexed alkynyl ketones such as **50** in the preparation of chiral lactones, including blastmycinone and blastmycinolactol, was accomplished by alkyne hydration followed by epimerization of the ketone and Baeyer Villiger oxidation at C-3 [89]. Oxidation of the alkyne unit to a carboxylic acid allows synthesis of several of the paraconic acids (i.e., **51**), including both enantiomers of phaseolinic acid, depending upon timing of the epimerization at the lactone α-carbon [64].

Application of the enol borane condensation chemistry in tandem with a photolytic N-pyrrolo enamide 3,5-sigmatropic rearrangment of **52** has be used to prepare AB ring synthons of both phytochrome and the related phycocyanin [90]. Although the relative stereochemistry is destroyed in the process, the enol borinate condensation chemistry in tandem with iodopyrrole-alkyne cross coupling (Sonogoshira) chemistry has been used to give the CD ring system of phytochrome [91,92]. The enol borinate Sonogoshira coupling protocol has also been employed recently to construct the ABCD framework onto a bis-iodopyrrin ring system [93], and to prepare ^{13}C labelled enantiopure phytochomobilin dimethyl ester [94].

In related chemistry, Jacobi has employed the alkyne amides of type **50** in tandem with cross coupling reactions on cyclic iminoyl derivatives and intramolecular N atom addition the alkyne to sequentially build up hexahydropyrrins, tripyrrolines, and secocorrins [95].

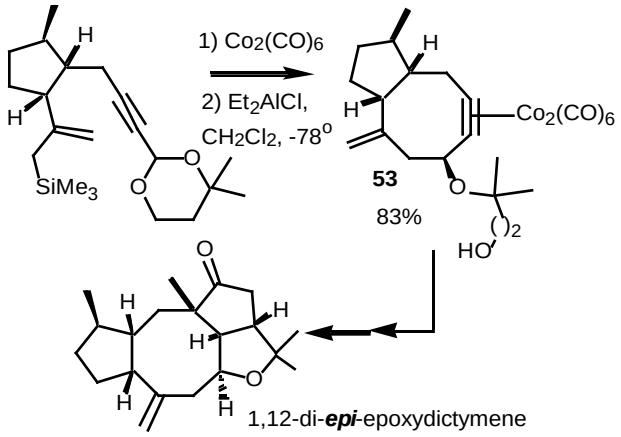


Scheme 21. Application of enol borinate condensation reactions in synthesis of δ-lactone, δ-lactam, and polypyyrole natural targets.



Scheme 23. Tandem conjugate addition-Nicholas condensation approach to bicyclo[7.3.1]enediynes.

Finally, Jacobi's use of a Curtius rearrangement/ alkyne oxidative cleavage/ DCC coupling approach to β-lactam synthesis has been outlined in a previous review on the area [2a]. The use of this approach in a formal total synthesis of thienamycin has appeared in full paper form, and has been extended to a formal total synthesis of carbapenem PS 5 [96].



Scheme 22. Application of cyclooctyne -$Co_2(CO)_6$complex to epoxydictymene syntheses.

Schreiber has made use of allylsilane 8-*exo* trig cyclization chemistry onto unsymmetrical alkynyl acetal complexes in order to set up fused 8,5-ring systems (**53**, Scheme 22) [63]. The product cyclooctyne-$Co_2(CO)_6$ complex may be elaborated further into a tetracyclic system by employing the remaining ether function (from the acetal) in intramolecular Pauson-Khand chemistry. This framework has been converted readily into an epimer of (+)-epoxydictymene; (+)-epoxydictymine itself has been obtained in several steps via an oxidative ring opening, and ultimately a Michael-type reclosure process [63].

The application of Nicholas chemistry and the stability of alkyne cobalt complexes in cyclic enediyne complexes has been discussed in a previous review [2] and only a limited amount of new work on this chemistry has appeared [97]. The Magnus' group's work on synthesis of the azabicyclo[7.3.1]enediyne core of dynemicin A has appeared in full paper form [98]. In addition, the group has reported a tandem enone conjugate addition-Lewis acid mediated cyclization strategy for the core bicyclo[7.3.1]enediyne of calicheamicinone (Scheme 23) [99]. Finally, Caddick has prepared more highly oxygenated versions of the bicyclo[7.3.0]core of the neocarzinostatin and kedarcidin class of enediynes via boron mediated aldol type closure on an alkynal-$Co_2(CO)_6$ complex [100].

MISCELLANEOUS

The ready formation of cations in the site propargyl to alkynedicobalt complexes has been used by Martín to prepare acyclic propargyl ethers and by Fukase and Kusumoto to remove propargyl and propargyloxycarbonyl protecting groups from alcohols, amines and esters [101]. Yeh has employed amination reactions of propargyl cation complexes to give propargyl amine precursors to highly substituted pyrroles [102].

REFERENCES

[1] Nicholas, K. M., Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21.

[2] a) Caffyn, A. J. M., Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Ed., Hegedus, L. S., Vol. Ed., Pergamon, Oxford, 1995, vol. 12, ch. 7.1; b) Nicholas, K. M., *Acc. Chem. Res.* **1987**, *20*, 207

[3] Isobe, M., Nishizawa, R., Hosokawa, S., Nishikawa, T. *Chem. Commun.* **1998**, 2665, and references therein.

[4] Jacobi, P. A., Zheng, W. In *Enantioselective Synthesis of β-Amino Acids;* Juaristi, E., Ed., Wiley-VCH, New York, N. Y. , 1997; pp 359-372.

[5] Melikyan, G. G., Nicholas, K. M. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds., VCH, Weinheim, 1995, Ch. 4.

[6] McGlinchey, M. J., Girard, L., Ruffolo, R.. *Coord. Chem. Rev*. **1995**, *143*, 331.

[7] Went, M. J. *Adv. Organomet. Chem.* **1997**, *41*, 69.

[8] a) El-Amouri, H., Gruselle, M., Jaouen, G., Daran, J. C., Vaissermann, J. *Inorg. Chem.* **1990**, *29*, 3238; b) Bennett,

S. C., Phipps, M. A., Went, M. J. *J. Chem. Soc, Chem. Commun.* **1994**, 225, and references therein.

[9] Krafft, M. E., Cheung, Y. Y., Wright, C., Cali, R. *J. Org. Chem.* **1996**, *61*, 3912.

[10] Schreiber, S. L., Klimas, M. T., Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

[11] Bradley, D. H., Khan, M. A., Nicholas, K. M. *Organometallics* **1992**, *11*, 2598.

[12] Maas, G., Rahm, R., Mayer, D., Baumann, W. *Organometallics* **1995**, *14*, 1061.

[13] Caro, B., Robin-Le Guen, F., Sénéchal-Tocquer, M.-C., Prat, V., Vaissermann, J. *J. Organomet. Chem.* **1997**, *543*, 87.

[14] Melikyan, G. G., Bright, S., Monroe, T., Hardcastle, K. I., Ciurash, J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 161; *Angew. Chem.* **1998**, *110*, 170.

[15] Balsells, J., Vázquez, J., Moyano, A., Pericàs, M. A., Riera, A. *J. Org. Chem.* **2000**, *65*, 7291.

[16] a) Connor, R. E., Nicholas, K. M. *J. Organometal. Chem.* **1977**, *125*, C45; b) Gruselle, M., Cordier, C., Salmain, M., El Amouri, H., Guerin, C., Vaissermann, J., Jaouen, G. *Organometallics* **1990**, *9*, 2993.

[17] a) Kuhn, O., Rau, D., Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900; b) Mayr, H., Patz, M. *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 938; *Angew. Chem.* **1994**, *106*, 990.

[18] Osella, D., Ravera, M., Nervi, C., Cavigiolo, G., Vincent, M., Vessières, A., Jaouen, G. *Eur. J. Inorg. Chem.* **2000**, 491.

[19] Gruselle, M., Malézieux, B., Andrés, R., Amouri, H., Vaissermann, J., Melikyan, G. G. *Eur. J. Inorg. Chem.* **2000**, 359.

[20] Castro, J., Moyano, A., Pericàs, M. A., Piera, A., Maestro, M. A., Mahía, J. *Organometallics* **2000**, *19*, 1704.

[21] Mayr, H., Kuhn, O., Schlier, C., Ofial, A. R. *Tetrahedron* **2000**, *56*, 4219.

[22] a) Ruffolo, R., Kainz, S., Gupta, S., Brook, M. A., McGlinchey, M. J. *J. Organomet. Chem.* **1997**, *547*, 217. b) Stradiotto, M., Brook, M. A., McGlinchey, M. J. *Inorg. Chem. Commun.* **1998**, *1*, 105.

[23] Ruffolo, R., Decken, A., Girard, L., Gupta, H. K., Brook, M. A., McGlinchey, M. J. *Organometallics* **1994**, *13*, 4328.

[24] Vizniowski, C. S., Green, J. R., Breen, T. L., Dalacu, A. V. *J. Org. Chem.* **1995**, *60*, 7496.

[25] Amouri, H., Bégué, J.-P., Chennoufi, A., Bonnet-Delpone, D., Gruselle, M., Malézieux, B. *Org. Lett.* **2000**, *2*, 807; b) Kondratenko, M. A., Malézieux, B., Gruselle, M., Bonnet-Delpone, D., Bégué, J.-P. *J. Organomet. Chem.* **1995**, *487*, C15.

[26] Smit, W. A., Caple, R., Smoliakova, I. P. *Chem. Rev.* **1994**, *94*, 2359, and references therein.

[27] Nagasawa, T., Kitamura, M., Suzuki, K. *Synlett* **1995**, 1183.

[28] Mikami, K., Feng, F., Matsueda, H., Yoshida, A., Grierson, D. S. *Synlett* **1996**, 833.

[29] Kitamura, M., Ohmori, K., Suzkui, K. *Tetrahedron Lett.* **1999**, *40*, 4563.

[30] Dare, S., Ducroix, B., Bernard, S., Nicholas, K. M. *Tetrahedron Lett.* **1996**, *37*, 4341.

[31] Mukai, C., Moharram, S. M., Azukizawa, S., Hanoaka, M. *J. Org. Chem.* **1997**, *62*, 8095.

[32] Palazón, J. M., Martín, A. S. *Tetrahedron Lett.* **1995**, *36*, 3549.

[33] a) Mukai, C., Sugimoto, Y., Ikeda, Y., Hanoaka, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1161; b) Mukai, C., Ikeda, Y., Sugimoto, Y., Hanoaka, M. *Tetrahedron Lett.* **1994**, *35*, 2179; c) Mukai, C., Sugimoto, Y., Ikeda, Y., Hanoaka, M. *Tetrahedron* **1998**, *54*, 823; d) Mukai, C., Yamaguchi, S., Sugimoto, Y., Miyakoshi, N., Kasanatsu, E., Hanoaka, M. *J. Org. Chem.* **2000**, *65*, 6761.

[34] Mukai, C., Itoh, T., Hanoaka, M. *Tetrahedron Lett.* **1997**, *38*, 4595.

[35] Malisza, K. L., Girard, L., Hughes, D. W., Britten, J. F., McGlinchey, M. J. *Organometallics* **1995**, *14*, 4676.

[36] To our knowledge, no exact measure of the 'size' of an alkyne-Co2(CO)6 unit has been reported. Available literature suggests conformational A values in between *i*-Pr and *t*-Bu: see Ref. 35 and Deschamps, N. M., Kaldis, J. H., Britten, J. F., Lock, P. E., McGlinchey, M. J. Presented at the 83rd Canadian Society for Chemistry Conference, Calgary, May 2000; paper IN3 157.

[37] a) Isobe, M., Jiang, Y. *Tetrahedron Lett.* **1995**, *36*, 567; b) Tanaka, S., Isobe, M. *Tetrahedron* **1994**, *50*, 5633; c) For an epimerization on a steroid nucleus, see: Luu, D. H., Nguyen, T. D. *Tap Chi Hoa Hoc* **2000**, *38*, 40; *Chem. Abstr*. *134*:56834.

[38] Tanaka, S., Tatsuta, N., Yamashita, O., Isobe, M..*Tetrahedron* **1994**, *50*, 12883; b) Tanaka, S., Isobe, M. *Synthesis* **1995**, 859.

[39] a) Mann, A., Muller, C., Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427; b) Berge, J., Claridge, S., Mann, A., Muller, C., Tyrrell, E. *Tetrahedron Lett.* **1997**, *38*, 685; c) Tyrrell, E., Tillett, C. *Tetrahedron Lett.* **1998**, *39*, 9535.

[40] a) Tyrrell, E., Heshmati, P., Sarrazin, L. *Synlett* **1993**, 769; b) Tyrrell, E., Claridge, S., Davis, R., Lebel, J., Berge, J. *Synlett* **1995**, 714.

[41] For discussion of bond angles and strain energies in cyclic alkynes, see: a) Krebs, A., Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189; b) Meier, H. *Adv. Strain Org. Chem.* **1991**, *1*, 215.

[42] a) Fletcher, A. J., Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657; b) Geis, O., Schmalz, H.-G. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 911; *Angew. Chem.* **1998**, *110*, 955; c) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Ed., Hegedus, L. S. Vol. Ed., Pergamon: Oxford, 1995; Vol. 12, Chapter 7.2; d) Schore, N. E., *Org. React.* **1991**, *40*, 1; e) Schore, N. E. In *Comprehensive Organic Synthesis;* Trost, B. M, Ed., Paquette, L. A. Vol. Ed., Pergamon: Oxford, 1991; Vol. 5, Chapter 9.1; f) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.

[43] Schottelius, M. J., Chen, P. *Helv. Chim. Acta* **1998**, *81*, 2341; Sugihara, T., Okada, Y., Yamaguchi, M., Nishizawa, M. *Synlett* **1999**, 768.

[44] a) Isobe, M. Yenjai, C., Tanaka, S. *Synlett* **1994**, 916; b) Hosokawa, S., Isobe, M. *Synlett* **1995**, 1179; c) Hosokawa, S., Isobe, M. *Tetrahedron Lett.* **1998,** *39*, 2609.

[45] Nakamura, T., Matsui, T., Tanino, K., Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032.

[46] Schreiber, S. L., Sammakia, T., Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

[47] Green, J. R. *Chem. Commun.* **1998**, 1751.

[48] Patel, M. M., Green, J. R. *Chem. Commun.* **1999**, 509.

[49] Green, J. R. *Synlett* **2001**, 353.

[50] Lu, Y., Green, J. R. *Synlett* **2001**, 245.

[51] A related process has been observed in the reactions of 4-alkoxyalkynones and alkynal acetals with the silylstannanes gives cycloheptadienyne complexes; Mohamed, A., Green, J. R., unpublished results.

[52] Tanino, K., Shimizu, T., Miyama, M., Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 6116.

[53] Ruffolo, R., Brook, M. A., McGlinchey, M. J. *Organometallics* **1998**, *17*, 4992.

[54] Schore, N. E., Najdi, S. D. *J. Org. Chem.* **1987**, *52*, 5296.

[55] Hosokawa, S., Isobe, M. *J. Org. Chem.* **1999**, *64*, 37.

[56] Yenjai, C., Isobe, M. *Tetrahedron* **1998**, *54*, 2509.

[57] For the (5R)-ABC fragment, see: Saeeng, R., Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911.

[58] a) Liu, T.-Z., Isobe, M. *Tetrahedron* **2000**, *56*, 5391; b) Liu, T.-Z., Isobe, M. *Synlett* **2000**, 266; c) Liu, T.-Z., Kirschbaum, B., Isobe, M. *Synlett* **2000**, 587.

[59] Kira, K., Isobe, M. *Tetrahedron Lett.* **2000**, *41*, 5951.

[60] a) Shibuya, S., isobe, M. *Synlett* **1998**, 373. b) Shibuya, S., Isobe, M. *Tetrahedron* **1998**, *54*, 6677.

[61] Guo, R., Green, J. R. *Chem. Commun.* **1999**, 2503.

[62] a) Demirhan, F., Gelling, A., Irisli, S., Jeffery, J. C., Salek, S. N., Senturk, O. S., Went, M. J. *J. Chem. Soc, Dalton Trans.* **1993,** 2765; b) Bennett, S. C., Jeffery, J. C., ., Went, M. J. *J. Chem. Soc, Dalton Trans.***1994**, 3171.

[63] Davies, J. E., Hope-Weeks, L. J., Mays, M. J., Raithby, P. R. *Chem. Commun.* **2000**, 1141.

[64] Guo, R., Green, J. R. *Synlett* **2000**, 746.

[65] a) Jamison, T. F., Samayati, S., Crowe, W. E., Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353; b) Jamison, T. F., Shambati, S., Crowe, W. E., Schreiber, S. L. *J. Am. Chem. Soc***. 1994**, *116*, 5505.

[66] Jacobi, P. A., Herradura, P. *Tetrahedron Lett.* **1996**, *37*, 8297.

[67] Mukai, C., Hanoaka, M. *Synlett* **1996**, 11, and references therein.

[68] Tester, R., Varghese, V., Montana, A. M., Khan, M., Nicholas, K. M. *J. Org. Chem.* **1990**, *55*, 186.

[69] a) Roush, W. R., Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143; b) Roush, W. R., Park, J. C. *Tetrahedron Lett.* **1991**, *32*, 6285.

[70] Ganesh, P., Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737.

[71] a) Corey, E. J., Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153; b) Bach, J., Berenguer, R., Garcia, J., Loscertales, T., Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.

[72] Caffyn, A. J. M., Nicholas, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6438.

[73] Muehldorf, A. V., Guzman-Perez, A., Kluge, A. F. *Tetrahedron Lett.* **1994**, *35*, 8755.

[74] Grée, D., Madiot, V., Grée, R. *Tetrahedron Lett.* **1999**, *40*, 6399.

[75] Betancourt, J. M., Rodríguez, C. M., Martín, V. S. *Tetrahedron Lett.* **1999**, *39*, 9773.

[76] a) Nagasawa, T., Taya, K., Kitamura, M. Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949; b) Saito, T., Suzuki, T., Morimoto, M., Akiyama, C., Ochiai, T., Takeuchi, K., Matsumoto, T., Suzuki, K. *J. Am. Chem. Soc.* **1998**, *120*, 11633.

[77] Taya, K., Nagasawa, T., Suzuki, K. *Synlett* **1997**, 304.

[78] Soler, M. A., Martín, V. S. *Tetrahedron Lett.* **1999**, *40*, 2815.

[79] Díaz, D., Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 743.

[80] Mukai, C., Yamashita, H., Ichiryu, T., Hanoaka, M. *Tetrahedron* **2000**, *56*, 2203.

[81] Kondratenko, M., El Hafa, H., Gruselle, M., Vaissermann, J., Jaouen, G., McGlinchey, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 607.

[82] Cordier, C., Gruselle, M., Jaouen, G., Bakhmutov, V. I., Galahov, M. V., Troitskaya, L. L., Solokov, V. I. *Organometallics* **1991**, *10*, 2303.

[83] Melikyan, G. G., Vostrowsky, O., Bauer, W., Bestmann, H. J., Khan, M., Nicholas, K. M. *J. Org. Chem.* **1994**, *59*, 222.

[84] a) Melikyan, G. G., Combs, R. C., Lamirand, J., Khan, M., Nicholas, K. M. *Tetrahedron Lett.* **1994**, *35*, 363; b) Melikyan, G. G., Khan, M. A., Nicholas, K. m. *Organometallics* **1995**, *14*, 2170.

[85] It is possible that the tandem proparyl alcohol reduction/Pauson-Khand chemistry of Periasamy proceeds through a propargyl radical that is ultimately reduced: Periasamy, M., Lakshimi M., Rao, N., Rajesh, T. *J. Organomet. Chem.* **1998**, *571*, 183.

[86] a) Melikyan, G. G., Deravarakian, A. *J. Organomet. Chem.* **1997**, *544*, 143; b) Melikyan, G. G., Deravakian, A., Myer, S., Yadegar, S., Hardcastle, K. I., Ciurash, J., Toure, P. *J. Organomet. Chem.* **1999**, *578*, 68.

[87] a) Salazar, K. L., Khan, m. A., Nicholas, K. M. *J. Am. Chem. Soc.* **1997**, *119*, 9053; b) Salazar, K. L., Nicholas, K. M. *Tetrahedron* **2000**, *56*, 2211.

[88] a)Montaña, Á. M., Fernández, D., Pagès, R., Filippou, A. C., Kociok-Köhn, G. *Tetrahedron* **2000**, *56*, 425; b) Montaña, Á. M., Fernández, D., *Tetrahedron Lett.* **1999**, *40*, 6499.

[89] Jacobi, P. A., Herradura, P. *Tetrahedron Lett.* **1997**, *38*, 6621.

[90] Jacobi, P. A., Buddhu, S. C. ; Fry, D., Rajeswari, S. *J. Org. Chem.* **1997**, *62*, 2894.

[91] Jacobi, P. A., Guo, J., Rajeswari, S., Zheng, W. *J. Org. Chem.* **1997**, *62*, 2907.

[92] Jacobi, P. A., DeSimone, R. W., Ghosh, I., Guo, J., Leung, S. H., Pippin, D. *J. Org. Chem.* **2000**, *65*, 8478.

[93] Jacobi, P. A., Coutts, L. D., Guo, J., Hauck, S. I., Leung, S. H. *J. Org. Chem.* **2000**, *65*, 205.

[94] Jacobi, P. A., Pippin, D. *Org. Lett.* **2001**, *3*, 827.

[95] a) Jacobi, P. A., Brielmann, H. L., Hauck, S. I. *Tetrahedron Lett.* **1995**, *36*, 1193; b) Jacobi, P. A., Liu, H. *Org. Lett.* **1999**, *1*, 341; c) Jacobi, P. A., Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958; d) Jacobi, P. A., Liu, H. *J. Org. Chem.* **1999**, *64*, 1778.

[96] Jacobi, P. A., Murphee, S., Rupprecht, F., Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413.

[97] For reviews, see: a) Magnus, P. *Tetrahedron* **1994**, *50*, 1397; b) Magnus, P. In *Organometallic Reagents in Organic Synthesis*; Bateson, J. H., Mitchell, M. B., Eds., Academic Press: London, 1994, Chapter 1; c) Maier, M. E. *Synlett* **1995**, 13.

[98] Magnus, P., Eisenbeis, S. A., Fairhurst, R. A., Iliadis, T., Magnus, N. A., Parry, D. *J. Am. Chem. Soc.* **1997**, *119*, 5591.

[99] Magnus, P., Miknis, G. F., Press, N. J., Grandjean, D., Taylor, G. M., Harling, J. *J. Am. Chem. Soc.* **1997**, *119*, 6739.

[100] a) Caddick, S., Delisser, V. M., Doyle, V. E., Khan, S., Avent, A. G., Vile, S. *Tetrahedron* **1999**, *55*, 2737; b) Caddick, S., Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 2355.

[101] a) Diaz, D. D., Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 9993; b) Fukase, Y., Fukase, K., Kusumoto, S. *Tetrahedron Lett.* **1999**, *40*, 1169.

[102] Wang, J.-L., Ueng, C.-H., Yeh, M.-C. P. *Tetrahedron Lett.* **1995**, *36*, *2823*.