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(Cycloheptyne)dicobalt Complexes in Organic Synthesis

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Cobalt complexes of cycloheptynes are thermally stable compounds, unlike their metal-free counterparts. The past decade has seen the development of a number of reliable methods for their preparation, and a substantial delineation of the reactions they undergo and tolerate. In turn, these developments have resulted in the exploitation of cycloheptynedicobalt complexes in synthesis. This review details the recent developments in the chemistry of these compounds.

Introduction

Historically, the chemistry of cycloheptynes (**1**, **2**; Figure 1) is mostly of theoretical interest, due to the angle strain at the alkynyl carbon atoms being inconsistent with thermal stability of the ring system.[1] No cycloheptyne is stable at room temperature,[2] while cycloheptyne itself has a $t_{1/2}$ of ca. 1 h at –76 °C. As a result, the synthetic applications of cycloheptynes are limited, and usually involve the generation and in situ trapping reactions during their short lifetime.[3] By contrast, the "natural" bond angle of alkyne–$Co_2(CO)_6$ complexes **3** is ca. 140°. Due to this bending at the nominally sp-hybridized carbon atoms, cycloheptyne–$Co_2(CO)_6$ complexes have a considerably reduced angle strain, and have a far greater stability than their metal-free counterparts. Therefore, they can be stored, handled under standard laboratory conditions, and can be treated as viable isolable synthetic intermediates. Unreported before 1986, the knowledge base of the methods of preparation, decomplexation, reactions tolerated and reactions of the ring system has increased markedly over the past 10 years. This Microreview details the developments in these systems, in our group and those of others. Attention is concentrated on the carbocyclic versions of the ring system; significant developments have also been reported in the corresponding cyclic ether complexes **4**, particularly by the Isobe group.[4] The didehydrooxepane complexes will not be covered explicitly, but many properties and reactions apply to both systems, and in several cases (i.e., decomplexation reactions) the processes under discussion were discovered initially on the cyclic ethers.

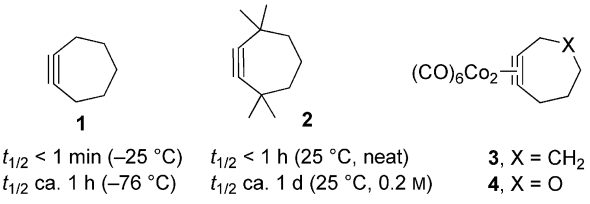

Figure 1. Cycloheptynes vs. cycloheptyne–$Co_2(CO)_6$.

Methods of Preparation

By Nicholas Reaction

The generation of a cation, propargylic to an alkyne–$Co_2(CO)_6$ group, usually by ionization of an oxygen-based function by a Brønsted or Lewis acid, and the trapping of that cation by nucleophiles, is commonly known as the Nicholas reaction.[5] This process features a propargylic cation that is significantly stabilized by the dicobalt function,

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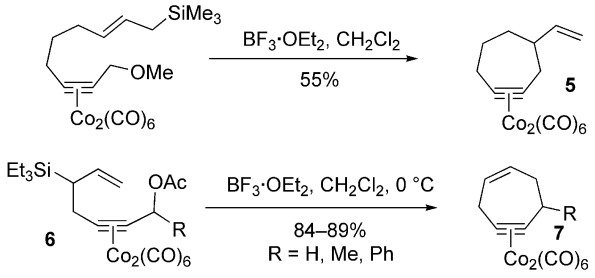
James Green was born in 1960 in Windsor, Ontario, Canada. Following an Honours B.Sc. in Chemistry from the University of Windsor (1982), he worked with Prof. Victor Snieckus at the University of Waterloo (GWC)[2] on amide dienolate chemistry, receiving his Ph. D. in 1987. He subsequent joined the group of Prof. Peter Vollhardt at the University of California, Berkeley (1987–1989), before joining the faculty of the University of Windsor in 1989. His research is focused on the use of organotransition metal compounds in organic synthesis.

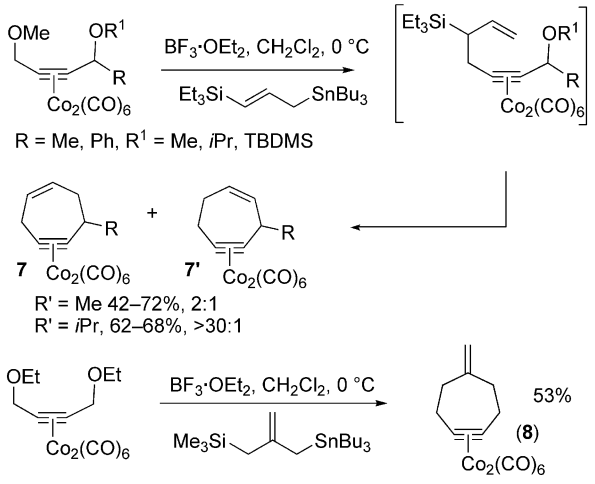
and that is very reliable in its propargyl site reaction with nucleophiles, without intervention of allene by-products. By far, this chemistry has been at the centre of the most common methods of preparation of (cycloheptyne)dicobalt complexes.

The first preparation of this class of compounds employed Nicholas reaction chemistry, in the form of a Lewis acid mediated reaction of propargyl ether complexes with an allylsilane tethered through a three-carbon chain (**5**, Scheme 1).[6] As all the non-alkyne carbon atoms in the cycloheptyne are sp^3-hybridized, there is limited opportunity for further functionalization of such molecules; nevertheless, this original contribution does allow access to the (less commonly encountered) C-4 substitution in the system.



Scheme 1. Allylmetal-based intramolecular Nicholas reactions.

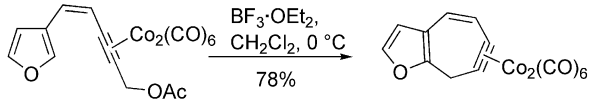
There is no necessity for the allylmetal nucleophile to be in the *exo* position. Our group has demonstrated subsequently that the allylsilane entering into cyclization (**6**) may allow *endo* cyclization to give cycloheptenyne complexes **7**, in good chemical yields.[7] In addition, allylsilane cyclizations onto propargyldicobalt cations can be made to result in the formation of *exo*-methylene systems, by appropriate choice of the allylsilane (see Scheme 2).



Scheme 2. [4+3] Cycloadditions to (cycloheptyne)dicobalt complexes.

The formation of the same cycloheptenyne complexes may be simplified further from an operational standpoint. Subjecting complexes of relatively simple butyne-1,4-diol derivatives to Lewis acid mediated reactions with an allyltin/vinylsilane dinucleophile gives cycloheptenyne–$Co_2(CO)_6$ complexes by way of a [4+3] cycloaddition process. The [4+3] cycloaddition is actually comprised of two allylmetal Nicholas reactions (Scheme 2); initial condensation of the allyltin compound with a propargyl cation complex gives an intermediate closely analogous to **6**, which then undergoes the final bond-forming process by an allylsilane–propargyl cation condensation. The regiochemistry of substitution in such cycloadditions is worthy of note; the predominant product **7** is the one that stems from initial Nicholas reaction that occurs on the *less* substituted end of the butyn-1,4-diol derivative, although the levels of selectivity are only ca. 2:1.[8] Superimposing upon this a larger ether function at the more substituted propargylic site raises this selectivity to near-complete. The 5-methylidene-substituted cycloheptyne complexes **8** are again accessible through this chemistry by the use of 1,3-dimetallo-2-methylenepropanes.[8]

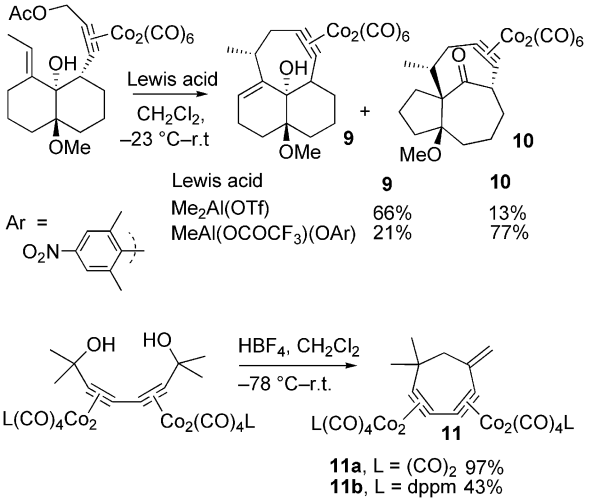
The electrophilicity of simple propargyl–$Co_2(CO)_6$ cation complexes has been investigated carefully,[9] and is such that reliable intermolecular reactivity is likely with nucleophiles as or more nucleophilic than anisole. Consequently, electron-rich aromatic and heteroaromatic ring systems are sufficiently reactive to enter intramolecular reactions with propargyldicobalt cation complexes, and therefore constitute a reliable Friedel–Crafts/Nicholas reaction approach to benzo-fused (cycloheptenyne)dicobalt complexes (Scheme 3).[10,11] Acceptable levels of success in the reaction may be extended to electronically neutral arene nucleophiles; this may be due to the intramolecularity of the process.



Scheme 3. Arene nucleophiles in Friedel–Crafts-based cyclizations.

Alkenes have, on occasion, been shown to undergo ene-type reactions with propargyldicobalt cations to form cycloheptyne complexes, but are less reliably straightforward in their reaction profile. In a contribution significant to the entire area of (cycloheptyne)dicobalt chemistry, the Tanino/Kuwajima group demonstrated that ethylidene-*trans*-decalinols with a pendant (propargyl acetate)–$Co_2(CO)_6$ fragment cyclize to the cycloheptyne-bridged dehydrodecalin complex **9** as a major product. Modestly acidic aluminum-based Lewis acids are required for the success of this reaction (Scheme 4). Rearrangement products were also formed competitively (**10**), to a degree dependent upon the Lewis acid and substrate (vide infra).[12]

To date there is only one report of (cycloheptadiyne)-tetracobalt complexes, and these have been prepared by protic acid ionization of 2,7-dimethyl-3,5-octadiyne-2,7-diol complexes. The cycloheptadiyne complexes **11** are believed to form through a sequence of several steps, beginning with the elimination of one tertiary alcohol to an alkene, which then reacts with propargyldicobalt cation generated by the



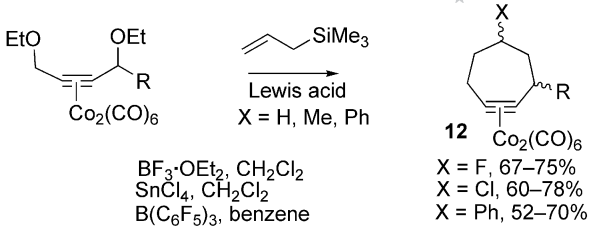
Scheme 4. Alkene nucleophiles in Nicholas reactions.

ionization of the second alcohol function.[13] The cyclization also tolerates replacement of two CO ligands by dppm [dppm = bis(diphenylphosphanyl)methane] on each alkyne–Co_2 unit. In each of the Tanino/Kuwajima and Mays/Woods cases of straightforward cyclization–elimination, the initial cyclization step involves the generation of a tertiary carbocation.

Tandem Nicholas Reaction–Cation Rearrangement/Trapping Processes

In several cases, attack on propargyl cation complexes by alkenes give cycloheptyne complexes by way of processes other than a straightforward nucleophilic attack/deprotonation (ene-type) pathway. Tanino/Kuwajima have found in their ethylidenedecalinol–propargyl acetate complexes that a cyclization/hydroxy-driven electron-deficient rearrangement process is competitive with the cyclization/deprotonation reaction, depending upon the Lewis acid employed, and affords the basic ingenane ring framework (**10**, Scheme 4).[12a] Because Lewis acids at the lower acidity end of the group employed resulted in a greater degree of rearrangement product, formation of an alkoxide may play a critical role in the success of this post cyclization step.

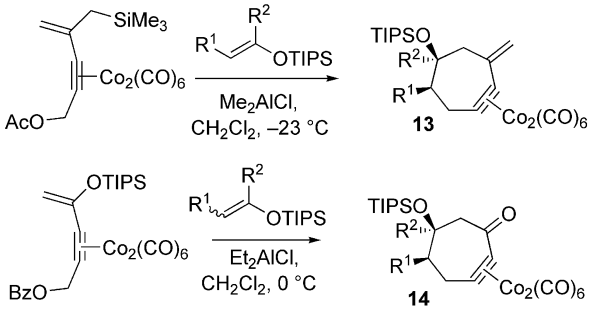
The [4+3] cycloaddition of dicobalt complexes of butyne-1,4-diol derivatives analogous to those described in Scheme 2 may also proceed with allyltrimethylsilane itself (Scheme 5). In these cases the ring-closing step must occur through nucleophilic attack of an alkene to generate a secondary cation, which is in turn trapped by halide from the conjugate base of the Lewis acid in a Prins-type reaction. While this most commonly gives C-5 halo substitution in the (cycloheptyne)dicobalt complex **12**, conducting the reaction in benzene solvent enables arylation as the final step.[14]



Scheme 5. Tandem [4+3] cycloaddition/trapping reactions.

Hosomi–Sakurai/Mukaiyama Reactions

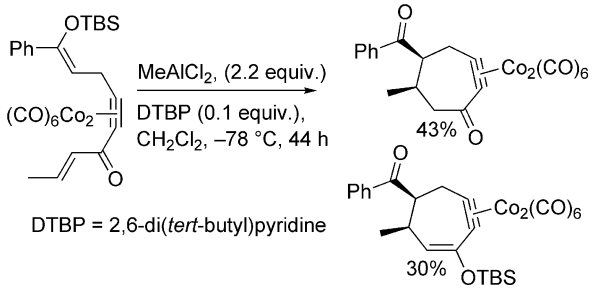
The Tanino group has developed two closely related, stepwise [5+2] cycloaddition protocols that give rapid formation of cycloheptyne–$Co_2(CO)_6$ complexes, in each case with 3,5,6-substitution. In each case, the cycloaddition does involve Nicholas reaction chemistry, but as the initial step, between a propargyl ester complex and a triisopropylsilyl enol ether (TIPS = iPr$_3$Si). In the chronologically earlier case, the siloxyalkyl carbocation resulting from this initial step is in turn attacked by an allylsilane contained in the propargyl ester complexes; this Mukaiyama-type reaction closes the cycloheptyne ring system and gives an *exo*-methylene group at the propargylic site (**13**).[15] In the subsequent report, the second condensation step involves an silyl enol ether; this Hosomi–Sakurai-type process results in a ketone function conjugated to the alkyne of the (cycloheptyne)dicobalt complex (**14**).[16] The [5+2] cycloaddition gives predominant *cis* orientation of the largest C-6 substituent (R^1) and the silyl ether function; this is attributed to an *antiperiplanar* alignment between the intermediate siloxyalkyl carbocation and the silyl enol ether or allylsilane (Scheme 6).



Scheme 6. [5+2] Cycloadditions with silyl enol ethers.

Michael Reaction

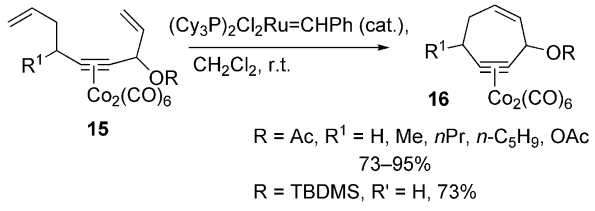
The Iwasawa group has prepared a single example of a cycloheptyn-3-one–$Co_2(CO)_6$ complex by a Lewis acid mediated stereoselective conjugate addition of a 2-alken-5-yn-5-one complex with a remote silyl enol ether (Scheme 7).[17] Although not rigourously assigned, the analogous results on cyclooctyne complexes suggest a *cis* stereochemistry about the newly formed bond.



Scheme 7. Michael reaction affording (cycloheptyne)dicobalt complexes.

Ring-Closing Metathesis

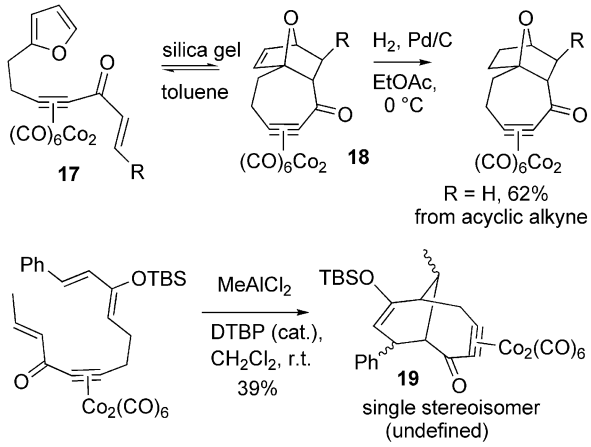
Given the central importance of Nicholas reaction chemistry to the utility of (alkyne)dicobalt complexes, the incorporation of C-3 (propargylic) oxygen functions in (cycloheptyne)dicobalt systems is of particular value. Unfortunately, formation of C-3 oxygen substituted (cycloheptyne)-dicobalt complexes by Nicholas-type chemistry is not facile; our own attempts to form complexes of cycloheptyne propargylic alcohol derivatives by Nicholas reactions of alkynal complexes or their derivatives have been uniformly unsuccessful. Fortunately, the alkyne–$Co_2(CO)_6$ unit is not affected by most metathesis pre-catalysts, and consequently suitably disposed dienes (i.e., **15**) undergo ring-closing metathesis (RCM) cleanly by using the Grubbs I catalyst, to give cycloheptenyne complexes (**16**, Scheme 8).[18,19] Propargylic alcohol complexes themselves do not perform especially well in this process, but once converted into the corresponding acetates or TBDMS ethers (TBDMS = *t*BuMe$_2$Si), cyclization occurs rapidly to give allylic or homoallylic alcohol derivatives. The propargylic oxygen function is not necessary for a successful RCM. It has been proposed that the alkyne–$Co_2(CO)_6$ actually facilitates cyclization by acting as a conformational restraint, but this has not been tested rigourously.



Scheme 8. Ring-closing metathesis based synthesis.

By Diels–Alder Reactions

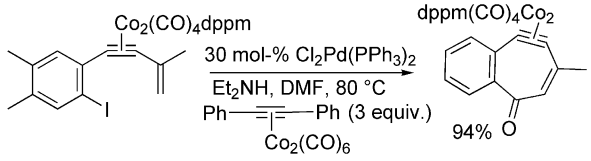
A measure of the degree to which the $Co_2(CO)_6$ unit relieves the angle strain of a cycloheptyne is demonstrated by the report that furan–enynone complex **17** enters an equilibrium with its Diels–Alder adduct **18** when exposed to silica gel (Scheme 9). While the equilibrium is not unilaterally favourable, vinyl ketones predominantly cyclize to the (cycloheptyne)dicobalt-tethered oxabicyclo[2.2.1]heptanes.[20] Hydrogenation of the alkene remnant of the furan in **18** "traps" the cycloheptyne adduct. Iwasawa has also demonstrated one example of an acyclic siloxydiene participating in a Diels–Alder reaction with the alkene of an enynone function to give a bicyclo[4.3.1] system (**19**).[21] The lowered yields of **19** relative to the analogous bicyclo[5.3.1] systems, as well as the variable equilibrium for cycloaddition in the case of **17** → **18**, suggest that this approach is pushing the limits of viability for the ring system.



Scheme 9. Diels–Alder-based syntheses.

Carbonylative Heck Reaction

A unique approach to the preparation of (cycloheptyne)-dicobalt complexes has been reported by Iwasawa and involves the palladium-catalyzed Heck reaction of an iodinated arene or alkene with an enyne complex, with concomitant CO insertion (Scheme 10). As the source for carbonylation is an alkyne–$Co_2(CO)_6$, most efficiently the diphenylethyne complex, this chemistry is not at this time applicable to cycloheptyne–$Co_2(CO)_6$ complexes; instead, the carbonylative Heck process is quite efficient for the $Co_2(CO)_4$(dppm) complexes.[22] The failure of a *cis*-disubstituted iodoalkene complex as a reaction precursor suggests that use of substituents capable of creating some conformational bias is necessary for closing the cycloheptyne ring.



Scheme 10. Carbonylative Heck reaction.

Structural Details

Stability

Hexacarbonyl(cycloheptyne)dicobalt complexes are maroon-coloured oils or solids, darker still when conjugated

Table 1. Reagents tolerated by cycloheptyne–$Co_2(CO)_6$ complexes.

Reagent type	Examples
Reductant	H_2/Pd, H_2/Ni, HN=NH, DIBAL-H, $NaBH_4$
Oxidant	MnO_2
Lewis acid	$BF_3{\cdot}OEt_2$, $SnCl_4$, $RAlCl_2$, R_2AlCl, $RAl(OTf)_2$, R_2AlOTf, $RAl(OTf)(OAr)$, $R_2Al(OAr)$, Et_2AlI, TMSOTf, $(C_6F_5)_3B$
Brønsted acid	*p*TsOH, CSA,[a] HBF_4

[a] CSA = camphorsulfonic acid.

to additional multiple bonds in the ring system. They are sufficiently air-stable to survive traditional chromatographic purification, and may be stored in air at –20 °C. The (cycloheptyne)dicobalt unit survives a number of synthetic transformations on the nucleus; while a comprehensive list of compatible reagents awaits further development, the following are illustrative (Table 1).

A modest number of crystal structures exist of (cycloheptyne)dicobalt complexes.[13,16,22] On the basis of these, the formal C≡C distance is average within the realm of alkyne–$Co_2(CO)_6$ complexes [1.31–1.36 Å, average alkyne–$Co_2(CO)_6$ 1.339 Å[23]], while the bond angles at the formal sp-carbon atoms are towards the lower end of alkyne–$Co_2(CO)_6$ complexes [126.1°–136.0°, average alkyne–$Co_2(CO)_6$ ca. 142°] (Figure 2). Despite the limited amount of crystallographic data on simple members and one clear exception, the ring conformation is best understood in most cases as being in a chair conformation, similar to cycloheptene,[24] and with equatorial substituents thermodynamically preferred. ^{1}H NMR vicinal coupling constants are fairly similar to those of cyclohexanes; selected examples are presented in Figure 2.

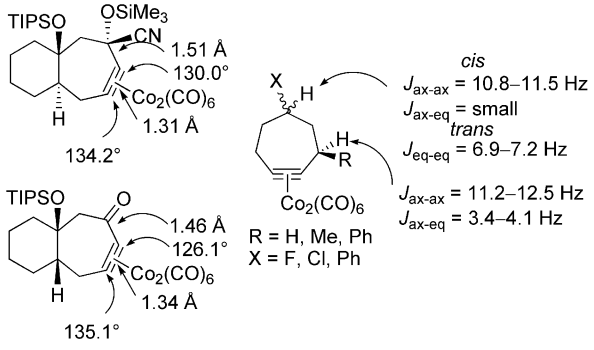
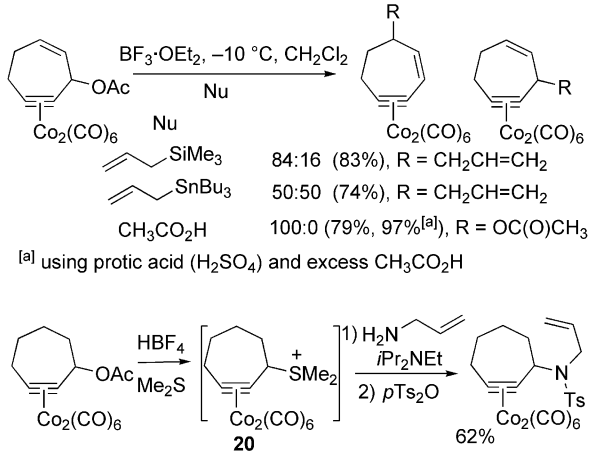


Figure 2. Selected bond lengths and angles, and ^{1}H NMR coupling constants.



Scheme 11. Selected Nicholas reactions on intact (cycloheptyne)dicobalt system.

Assorted data suggest that conjugative stabilization exists between adjacent double bonds and the (alkyne)dicobalt unit, at least to some degree. Single bonds between these functions are slightly reduced in bond length,[13,16,22] and the limited number of reactions reported that could drive the alkene and alkyne–Co_2 functions of cycloheptenyne complexes into conjugation do so (see Scheme 11).[25]

Are Cycloheptynes the Limit?

In most cases, cycloheptyne complexes are the lower limit of cycloalkyne ring sizes that can be prepared readily as $Co_2(CO)_6$ complexes; our group and others have several examples of attempts at the preparation of cyclohexyne–$Co_2(CO)_6$ systems, which have failed. Nevertheless, to the best of our knowledge there are three reports of cyclohexyne–$Co_2(CO)_6$ complexes prepared successfully. The original report of Schreiber on propargyl ether/tethered allylsilane cyclization reactions includes one successful cyclohexyne case (see Scheme 1).[6] During work on the construction of the bicyclo[7.3.0]dodecadiyne ring system, the Magnus group isolated an allene-substituted cyclohexenyne–$Co_2(CO)_6$ complex through an unexpected homologous ene reaction (Figure 3).[26] Recently, the Iwasawa group has adapted the Schreiber methodology to form three naphthalyne–$Co_2(CO)_6$ complexes of limited stability to air.[27]

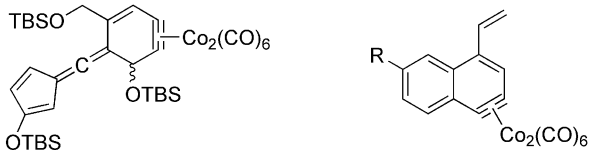


Figure 3. Examples of (cycloheptyne)dicobalt complexes.

Transformations on the Intact Nucleus

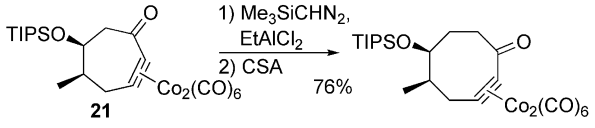
With its good stability and the known use of $Co_2(CO)_6$ complexes as alkyne protecting groups,[28] it is reasonable to expect that the (cycloheptyne)dicobalt unit would be able to survive a number of transformations elsewhere in the molecule concerned. This has proved to be the case.

Nicholas Reactions

As the generation and reactions of cationic propargyldicobalt complexes constitute one of the most popular uses of (alkyne)cobalt complexes,[5] Nicholas reactions on the (cycloheptyne)dicobalt nucleus are a matter of importance. With the requisite leaving group present in the propargylic position, these substitutions are quite facile. The (cycloheptyne)dicobalt has substantial stability to many Lewis and protic acids (see Table 1) and the common nucleophiles known for Nicholas reactions. Consequently, the reaction has been successful for carbon nucleophiles (silyl enol ethers, silyl ketene acetals, allylsilanes, electron-rich arenes), hydride (Et_3SiH), oxygen nucleophiles (alcohols, acetic acid), sulfur nucleophiles (thiols) and nitrogen nucleophiles (CH_3CN) (Scheme 11). By using the propargyl–sulfonium ion (**20**) tactic of Jaouen,[29] the range of N-nucleophiles may be extended to amines themselves.[30] In a manner analogous to other propargyldicobalt cations, cations which are both propargylic and allylic react preferentially at the terminus remote (γ-) to the (alkyne)dicobalt function, both kinetically (predominantly, with less reactive nucleophiles giving greater γ/α ratios) and thermodynamically (exclusively).[25] Finally, in some situations epimerization at the propargylic centre during the substitution is incomplete, suggesting that the fluxional processes known to common propargyldicobalt cations may be slowed in these systems.

Other Nucleophiles – Cyanohydrin Formation

Other reports of nucleophilic chemistry on carbonyl compounds are limited. Lewis acid mediated trimethylsilyl cyanide attack on cycloheptynone complex **21** has been shown to readily result in the formation of the *O*-silylated cyanohydrin, while the same authors have demonstrated clean nucleophilic attack/ring expansion reactions by trimethylsilyldiazomethane and a Lewis acid on the ketone function to give a cyclooctynone complex (Scheme 12).[16] To the best of our knowledge, there are no reports of successful organolithium or Grignard reagent additions to functional groups on the (cycloheptyne)dicobalt system.



Scheme 12. Nucleophilic attack/ring expansion reaction.

Hydrogenation/Reduction

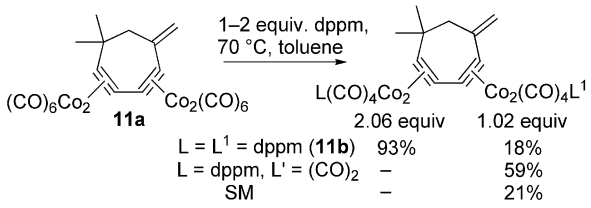
There are several examples of hydrogenation being carried out on intact (cycloheptenyne)dicobalt systems. These examples include both metal-catalyzed hydrogenation (Raney-Ni, Pd/C),[20,31] and transfer hydrogenation (diimide)[32] methods. Reduction of polar functional groups is also often possible. Although instances of $NaBH_4$ reductions of carbonyl groups have had some success, yields are normally higher when a covalent hydride source (DIBAL–H) is employed (see Scheme 18).

Oxidation/Elimination

Oxidation reactions on the intact (cycloheptyne)dicobalt nucleus are rare. Nevertheless, an allylic alcohol has been shown to successfully undergo MnO_2 oxidation to an enone in the presence of a non-reacting alcohol function (see Scheme 18).[33] In the same work, it was demonstrated that a β-hydroxycycloheptenone complex will undergo elimination to form the enone in the presence of HBF_4 or *p*TsOH (Scheme 18). For both oxidation and elimination reactions, it is likely that the full range of compatible reagents and conditions is yet to be explored.

Ligand Exchange

In several reports, one or several of the CO ligands of an alkyne–$Co_2(CO)_6$ complex may be substituted without disrupting the alkyne–Co_2 core of the molecule.[34] Mays and Woods have demonstrated that this possibility applies at least in some cases to cycloheptyne–dicobalt complexes; subjecting cycloheptadiyne–$Co_4(CO)_{12}$ complex **11a** to dppm in warm toluene gives the bis(dppm) complex **11b** in excellent yield (Scheme 13). The use of equimolar amounts of the phosphane affords reasonable amounts of the mono(dppm) complex.[13]



Scheme 13. Ligand exchange in (cycloheptadiyne)tetracobalt complexes.

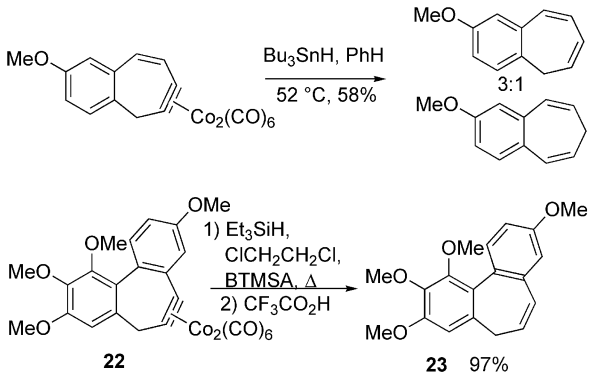
Methods for Removal of the Dicobalt Unit

Simple removal of the $Co_2(CO)_6$ unit from a cycloheptyne complex gives a system with greater ring strain than can be tolerated at ordinary temperatures. As a result, decomplexation of the alkyne–$Co_2(CO)_6$ must be in tandem with another process that transforms the function into one viable within a seven-membered ring system.

Reductive Removal

The most straightforward transformation involving removal of the cobalt atom is decomplexation in conjunction with reduction of the alkyne, normally to a cycloheptene. Bu_3SnH is the most commonly employed reagent for this purpose.[10,16,35] While a detailed mechanism of this transformation is unknown, the critical intermediacy of radicals is proposed. This protocol has been advanced as causing minimal amounts of double-bond migration in the cycloalkene products; nevertheless, our group has observed small amounts of such a migration (Scheme 14). Conjugated

ynone complexes may give overreduction to the cycloheptanone.[16] Alternatively, Birch reduction conditions have been shown to induce this reductive decomplexation effectively (see Scheme 20).[12]



Scheme 14. Reductive removal of $Co_2(CO)_6$ unit.

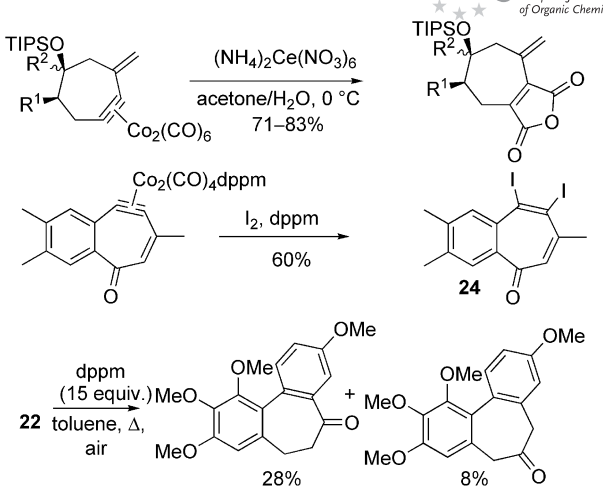
A tactic for overall reduction, which has proven to be particularly effective in our hands, is a tandem hydrosilylation/protodesilylation protocol. Clearly related to, but more convenient than, the Bu_3SnH procedure, exposure of the (cycloheptyne)dicobalt complex **22** to Et_3SiH, in the presence of scavenging alkyne TMS–CC–TMS (BTMSA), converts the complex into a regioisomeric mixture of vinylsilanes in excellent yield.[11,36] Subsequent protodesilylation to give the cycloheptene **23** is similarly efficient.

Finally, sodium hypophosphite[37] and high pressure H_2/Rh (Rh/C or Wilkinson's catalyst),[38] may be considered as potentially useful reagents for reductive decomplexation. While these have not been reported as effecting this transformation on (cycloheptyne)dicobalt complexes, they have been used on the corresponding cyclic ethers, and therefore have a high probability for successful use in the all-carbon ring systems.

Oxidative Removal

There are three separate methods known for oxidative decomplexation of (cycloheptyne)dicobalt complexes. The three give differing reaction outcomes, but each has demonstrated or potential synthetic utility.

Ceric ammonium nitrate (CAN) and molecular iodine are standard reagents for straightforward decomplexation in acyclic (alkyne)dicobalt complexes. In (cycloheptyne)dicobalt complexes, however, decomplexation with CAN occurs in conjunction with CO insertion, ultimately giving the anhydride in good yields (Scheme 15).[15,16,39] Conversely, it has been demonstrated on the $Co_2(CO)_4$(dppm) complexes that treatment with I_2 gives the diiodocycloheptenes **24**;[22] the extension of this procedure to $Co_2(CO)_6$ complexes is a reasonable possibility but unproven.

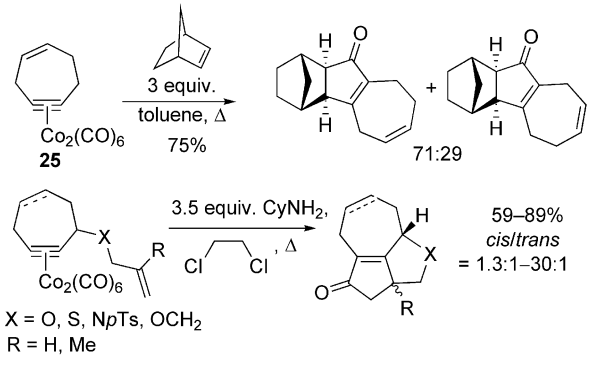


Scheme 15. Oxidative decomplexation reactions.

Finally, subjecting cycloheptyne–$Co_2(CO)_6$ complexes or their dehydrooxepane analogues to heating with dppm and air gives a regioisomeric mixture of cycloheptanones, favouring oxygen incorporation proximal to the sterically most hindered side.[40] Yields are modest, and a significant excess of dppm is necessary, so that procedural improvements are likely required before this protocol sees widespread use in synthesis.

With C–C Bond Formation/Pauson–Khand Reaction

The Pauson–Khand reaction[41] possibilities of (cycloheptyne)dicobalt complexes are particularly exciting ones, as the 7,5-ring system generated by such a transformation is widely encountered in natural products, particularly in many classes of sesquiterpenes.[42] Cycloheptenyne **25** participates in Pauson–Khand reactions, but is a relatively ordinary alkyne–$Co_2(CO)_6$ complex in the process; bridged bicyclic alkenes work well and silyl-substituted allenes work adequately (Scheme 16).[43] Rendering the Pauson–Khand reaction intramolecular by joining the cycloheptyne complex and the alkene with a heteroatom-based tether affords much more consistently successful results.[30] Ether-, thioether-, and sulfonamide-tethered alkenes undergo cycliza-

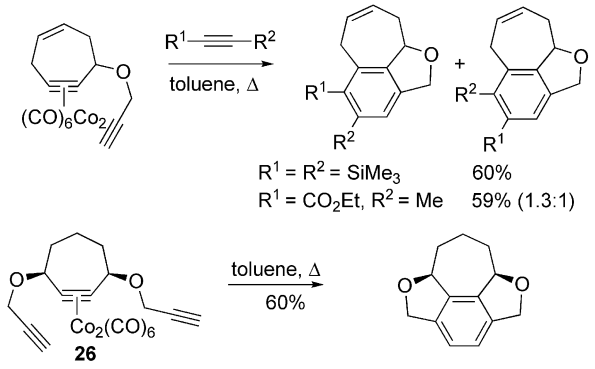


Scheme 16. Pauson–Khand reactions of (cycloheptyne)dicobalt complexes.

tion in reasonable yields, predominantly under the Sugihara conditions;[44] tethers forming both five- and six-membered rings participate well. The *cis* isomers are formed predominantly.

[2+2+2] Cycloaddition

While the most well established form of [2+2+2] cycloadditions involve Co^{I} reagents,[45] there are a number of recorded cases where $Co_2(CO)_8$ may induce the transformation.[46] As a result, we considered it a reasonable possibility that alkyne–$Co_2(CO)_6$ functions of cycloheptyne complexes would be capable of entering into such cycloadditions, therefore giving access to benzocycloheptene systems. This has proved to be feasible in synthetically useful yields, provided that one of the alkyne functions is tethered to the (cycloheptyne)dicobalt complex (Scheme 17).[31] The third alkyne need not be tethered, but in such cases the regioselectivity of incorporation of the third alkyne is poor; consequently, symmetrical alkynes such as bis(trimethylsilyl)ethyne are the best choices for this "third" reaction partner. By tethering two additional alkyne functions to the cycloheptyne complex **26**, it is also possible to render the cycloaddition all-intramolecular.

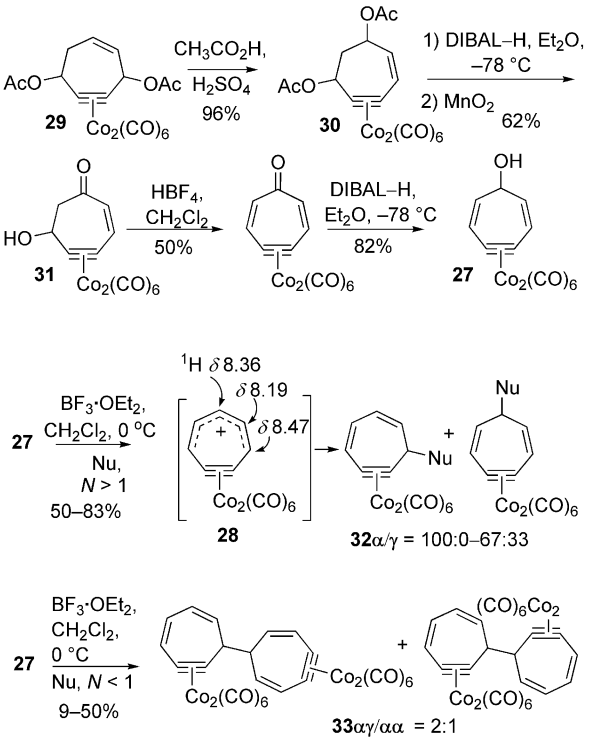


Scheme 17. [2+2+2] Cycloadditions of (cycloheptyne)dicobalt complexes.

Use in Synthesis

Dehydrotropylium–$Co_2(CO)_6$ Ion

The accumulated knowledge of compatible reactions on the (cycloheptyne)dicobalt nucleus has allowed access, in several steps, to the cycloheptadienynol–$Co_2(CO)_6$ precursor **27** to the dehydrotropylium–$Co_2(CO)_6$ ion, and ultimately the ion **28** itself (Scheme 18).[33] RCM adduct **29** underwent rearrangement in acid to give **30**, which in turn afforded **31** by way of nucleophilic cleavage of the acetates and allylic alcohol oxidation. Elimination of the alcohol and reduction of the ketone gave the target alcohol **27**.



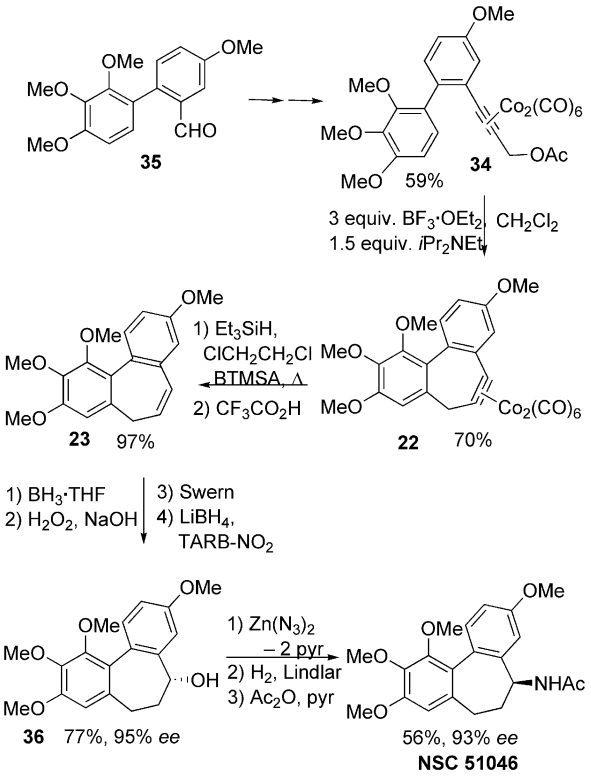
Scheme 18. Synthesis and reactions of dehydrotropylium–$Co_2(CO)_6$.

In subsequent reactions with Lewis acid nucleophile combinations, the generated cation **28** was found to undergo Nicholas reaction chemistry (**32**) with more reactive nucleophiles ($N > 1$ on the Mayr scale[47]), but gave electron transfer/radical dimerization products **33** with less reactive nucleophiles. In the presence of HBF_4, the cation itself **28** precipitated; although limited in lifetime, its ^1H NMR spectrum could be acquired.

Allocolchicine NSC 51046

Our group has applied Lewis acid Nicholas reaction of biaryl-substituted propargyl acetate complex **34** to an enantioselective synthesis of allocolchicine NSC 51046 through the intermediacy of a dibenzocycloheptyne–$Co_2(CO)_6$ complex **22** (Scheme 19). In this case, the electron-rich nature of the A-ring of the allocolchicines provided an excellent handle for the B-ring construction in the tricyclic core.[11] Assembly of **34** was accomplished by way of Suzuki–Miyaura cross-coupling, followed by Corey–Fuchs homologation of the aldehyde **35**. Intramolecular Nicholas reaction mediated by $BF_3{\cdot}OEt_2$ was somewhat more sluggish than expected, likely due to challenges achieving the reactive rotamer of the propargyl cation complex, but nevertheless afforded the tricyclic complex **22** in good yield. Decomplexation by way of the tandem hydrosilylation/protodesilylation protocol gave excellent yields of the dibenzocycloheptene **23** (see Scheme 14), and was converted into the di-

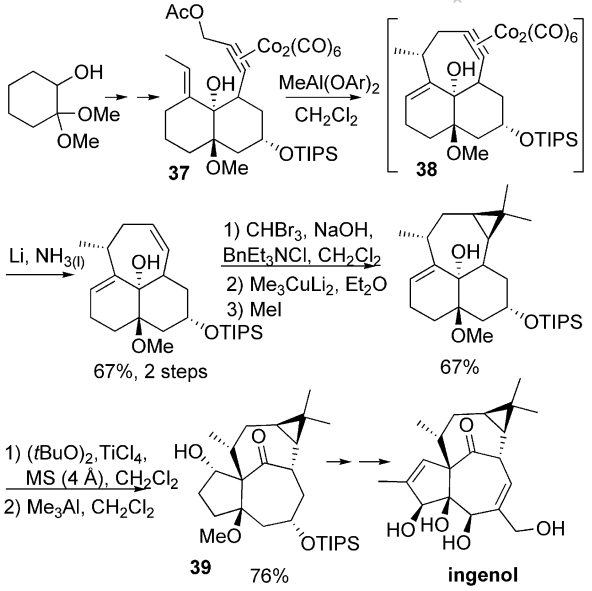
benzosuberone by a conventional hydroboration/oxidation protocol. Enantioselective installation of the benzylamide followed Wulff's method,[48] which involved enantioselective reduction to **36** by using Singaram's TARB-NO_2-modified borohydride,[49] azidation with $Zn(N_3)_2(pyridine)_2$, and azide reduction/acetylation chemistry. NSC 51046 could be recrystallized readily to >99% *ee*.



Scheme 19. Synthesis of NSC 51046.

Ingenol

The Tanino group has employed ene reaction chemistry of ethylidenedecalinols for the total synthesis of ingenol (Scheme 20).[12] The ethylidenedecalinol propargyl acetate complex **37**, built up in several steps from 2-hydroxycyclohexanol dimethyl acetal featuring Claisen rearrangement and intramolecular aluminum enolate alkylation steps, gave solely cyclization/deprotonation product **38** and no cyclization/pinacol rearrangement product upon reaction with $MeAl(OAr)_2$ (Ar = 2,6-dimethyl-4-nitrophenyl). Following Birch-type reductive removal of the alkyne–$Co_2(CO)_6$ function and use of the resultant alkene for *gem*-dimethylcyclopropanation, the 7,5-system **39** was obtained by epoxidation of the cyclohexene and $AlMe_3$-mediated rearrangement. Although several further steps are required to introduce the C-2 methyl and C-6 hydroxymethyl groups and the oxygen functions of ingenol, the appropriate synthetic handles were all installed at this point.



Scheme 20. Synthesis of ingenol.

Conclusions

In addition to being molecules of simple theoretical interest, (cycloheptyne)dicobalt complexes have demonstrated a combination of ready preparation and good stability. By virtue of their ability to survive a reasonable number of synthetic transformations and yet undergo reliable decomplexation reactions when desired, they are proving to be highly useful in synthesis of seven-membered ring containing natural products. As much of the developmental chemistry of these complexes is recent, we expect that the use of these complexes in synthesis will see fuller exploitation in the coming years.

Acknowledgments

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