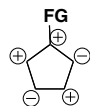


Cyclopentane Synthesis

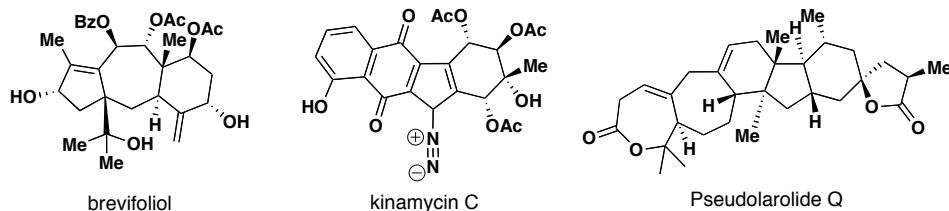
Dan O'Malley

Baran Group Meeting

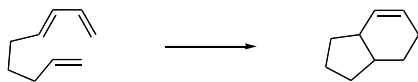
Students of organic chemistry are taught a number of reactions for the synthesis of cyclohexanes at a very early stage of their careers. Techniques for the creation of cyclopentanes, however, are generally taught at a much later stage and are rarely given the same detailed treatment. This may be the result of the fact that there are no equivalents of reactions such as the Diels-Alder and Robinson Annulation in terms of generality, extent of use, and historical importance. This may, in turn, be caused by the fact that the cyclopentane is an inherently "unpoled" functionality, as illustrated below.



This situation is further exacerbated by the general lack of cheaply available cyclopentane compounds in the chiral pool; whereas a number of cyclohexane terpenes are readily available for elaboration, there are no analogous cyclopentane natural products. Cyclopentanes are however, present in many molecules which represent unanswered challenges at the forefront of organic synthesis.



Although there may not be as many well-known "general" methods for the construction of cyclopentanes as there are for 3,4, or 6 membered rings, there are in fact an enormous number of methods that have been applied to their synthesis, so this review is by no means comprehensive. As cyclopentadienes, cyclopentadienes, and fulvenes are generally highly unstable and are generally synthesized to be used immediately in a reaction rather than as a target in and of themselves, their synthesis is not covered here. Also, this review focuses on "active" methods of cyclopentane synthesis, wherein the ring is being created directly, rather than being formed from the tether of another ring formation. For example an intramolecular Diels-Alder reaction could create a cyclopentane as shown below, but this would be a "passive" formation of the cyclopentane and therefore outside the scope of this review.



Even within these restrictions, there are still a prohibitively large number of cyclopentane syntheses. The ones included here have been selected base upon their novelty, effectiveness, usefulness, and ease of use.

This presentation is broken down into the following categories. Some reactions either fit more than one category or do not fit easily into any of them. Efforts have been made to place all such reactions in the most appropriate category.

- I. General Information
- II. Ionic Reactions
- III. Metal Mediated Reactions
- IV. Radical Reactions
- V. Pericyclic and Pseudo-pericyclic Reactions
- VI. Ring Expansion and Contraction Reactions

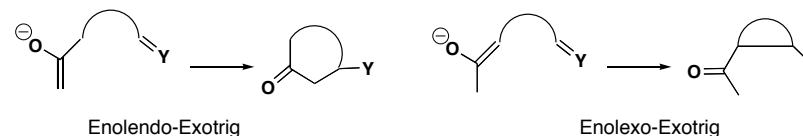
I. General Information

Baldwin's rules

Baldwin has divided ring closure reactions into those that are "favored" and those that are "disfavored". Those that are disfavored are not always impossible, but are frequently much more difficult to effect. The classifications are based upon groups connected by a chain of methylene groups. Replacement of these groups with atoms other than carbon, changing their hybridization, and placing substitution upon them will alter the readiness of ring closure.

The rules relevant to the closure of cyclopentanes and the competing reactions are as follows:
 five-*exo-tet* is favored
 five-*exo-trig* is favored; four-*endo-trig* is disfavored
 five-*endo-trig* is disfavored; six-*exo-trig* is favored
 five-*exo-dig* is favored; six-*endo-dig* is favored
 five-*endo-dig* is favored; four-*exo-digo* is disfavored

Separate rules for enolate reactions have been created. These are explained below.



five-*enlendo-exo-tet* is disfavored
 five-*enloexo-exo-tet* is favored
 five-*enloexo-exo-trig* is favored
 five-*enlendo-exo-trig* is disfavored

The Thorpe-Ingold Effect

As noted above, the nature of the substituents on the chain which is to form a ring affects the rate of ring closure. Transannular interactions of CH_2 groups contribute to ring strain, so replacement of one or more methylene groups with heteroatoms or sp^2 carbons can eliminate some transannular strain. Although this effect is most pronounced in the closure of medium-sized rings, many methods of five membered ring formation, particularly passive ones, function more effectively when creating tetrahydrofurans or pyrrolidenes than when generating cyclopentanes. Thus, passive methods for the formation of these rings are not always effective for the synthesis of carbocycles.

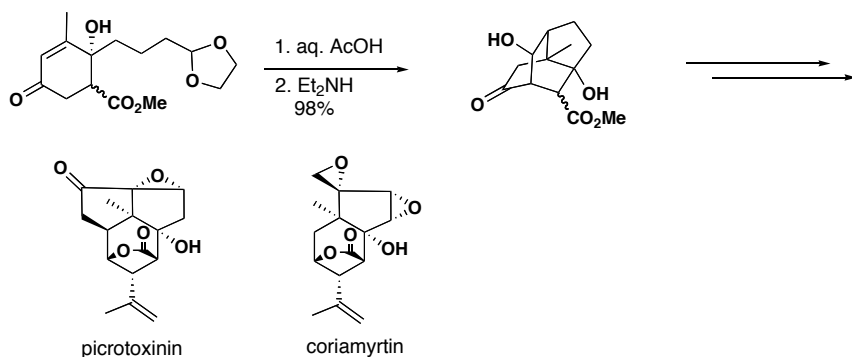
A similar effect is the Thorpe-Ingold or gem-dimethyl effect. The placement of quaternary carbon at the center of chain can substantially enhance its rate of ring formation. This occurs for several reasons. The quaternary carbon has a smaller C-C-C bond angle, so a smaller reduction in this angle is necessary to effect ring formation. Also, the increased number of *gauche* interactions destabilizes open form more than the closed ring, further reducing the energy gap. From an entropic standpoint, the quaternary carbon greatly reduces the flexibility of the open chain and thus its entropy but has little effect upon the entropy of the ring. As a result, many annulation procedures are tested upon chains bearing a quaternary center. Readers are warned that reaction rates and yields may decrease if this carbon is replaced with a methylene unit.

II. Ionic Reactions

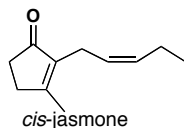
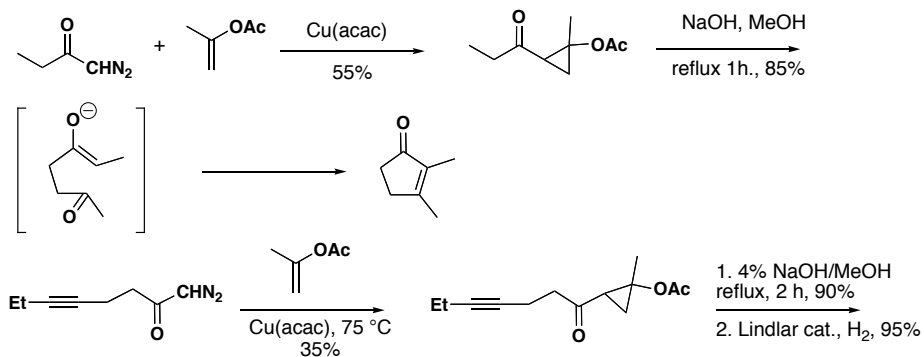
Many traditional ionic reactions, such as aldol condensations and enolate alkylations, can be applied to the synthesis of cyclopentane derivatives. There are also a number of special protocols for the sequential addition of the necessary appendages to common functional groups followed by immediate ring closure, often in a single pot.

A. Enolate Reactions

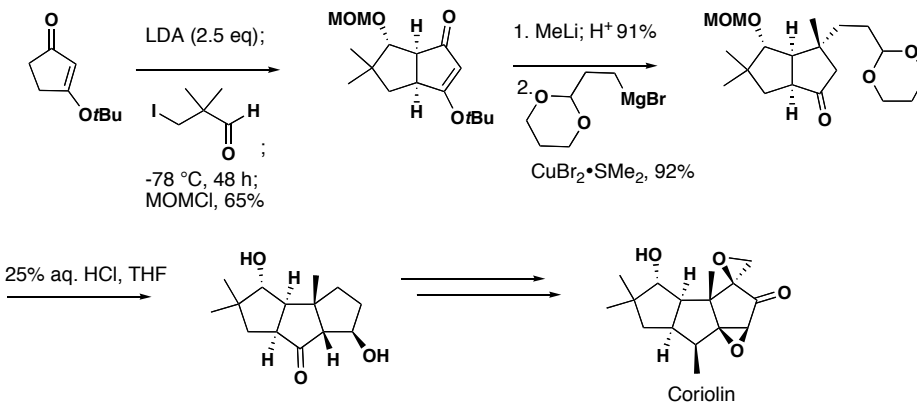
Hata and coworkers used a Michael addition to establish a cyclopentane ring in their synthesis of (–)-Picrotoxinin and (+)-Coriamyrtin. (*JACS*, **1984**, *106*, 4547-4552)



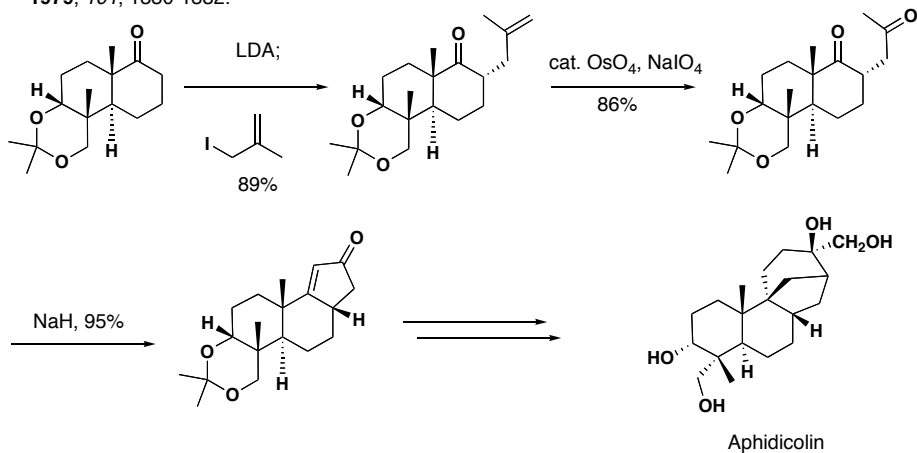
McMurray has developed a simple procedure for generating a specific aldol product of a 1,4-diketone by generating it from an acetoxy cyclopropanone. (*Tet. Lett.*, *27*, 2575-2578, **1971**.)



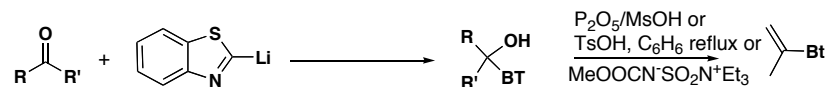
Koreeda and Mislankar have developed an annulation procedure using a dianion and a β -iodoaldehyde and applied it to a synthesis of racemic coriolin. (*JACS*, **1983**, 7203-7205.)



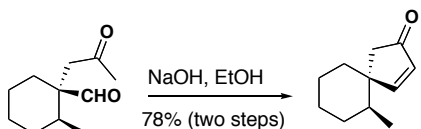
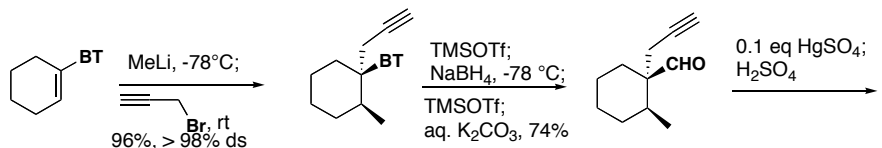
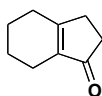
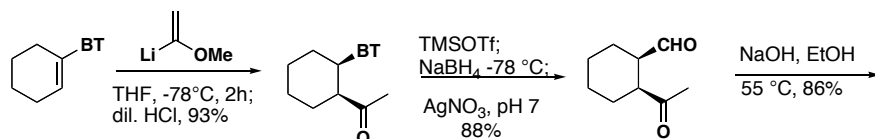
Isobutenyl groups can be used as a surrogate for a CH₂COCH₃ group, enabling a three-step annulation from a ketone to a cyclopentenone. McMurry used this approach in his synthesis of Aphidicolin. (*JACS*, **1979**, *101*, 1330-1332.)



Boger and Corey have developed a procedure to use the benzothiazole group as a masked aldehyde, giving access to fused and spiro cyclopentanes. *Tet. Lett.*, **1979**, 5-8, 9-12, 13-16.



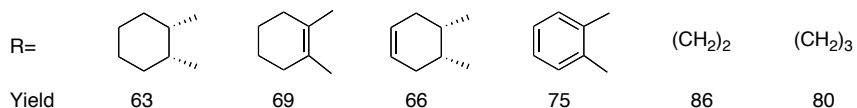
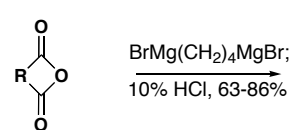
Provides alternative to enals, which are poor Michael acceptors.



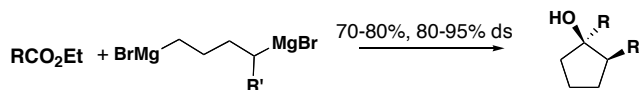
Similar strategies have been developed which use the Saegusa oxidation instead of mercury.

B. Grignard-Type Reactions

Canonne and Belanger developed a simple and direct method to spirocyclopentanes using bis-Grignard reagents. *J. Chem. Soc. Chem. Comm.* **1980**, 125, 125-6.

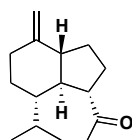
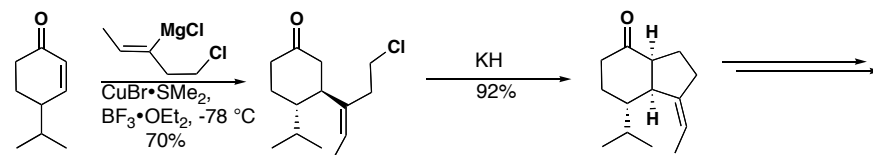


High diastereoselectivity is obtained when the grignard includes an alkyl group. *JOC*, **1987**, 52, 4025-4031.



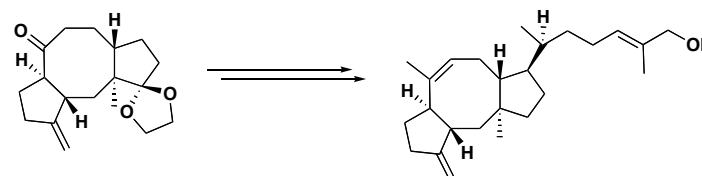
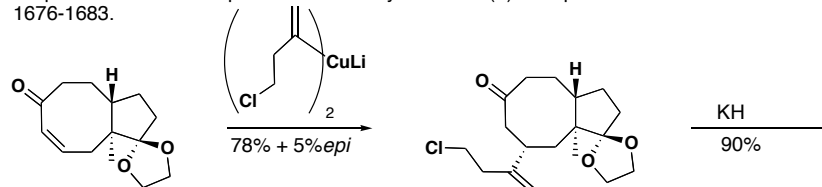
The use of 3-halo organocuprates or grignard reagents for a Michael addition followed by an enolate alkylation has been used several times for the construction of cyclopentanes.

Piers and Gavai used a two step procedure in their synthesis of racemic oplopanones. *J. Org. Chem.* **1980**, 55, 2380-2390.

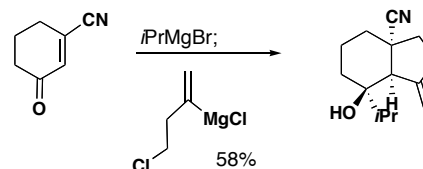


Anhydrooplopanone

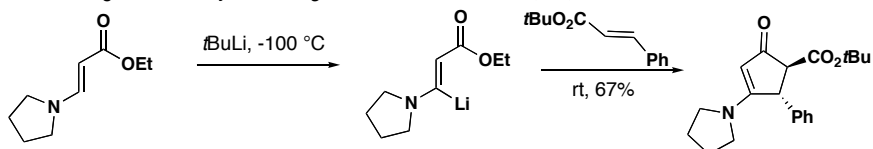
Paquette used a similar procedure in his synthesis of (+)-Ceroplastol. *J. Am. Chem. Soc.* **1993**, 115, 1676-1683.



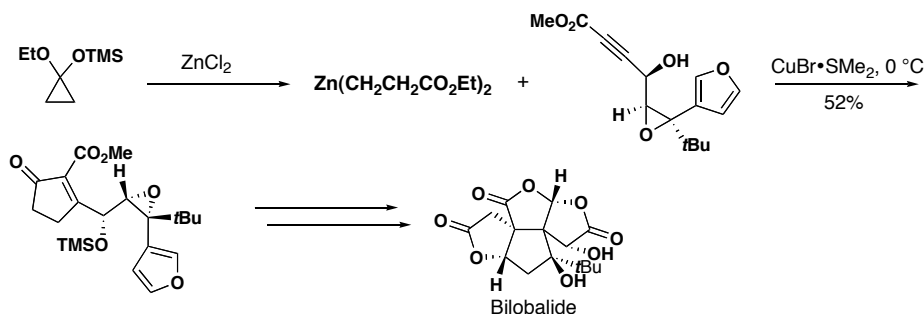
Fleming has developed an efficient multicomponent version using chelation control. *Angew. Chem. Int. Ed.* **2004**, 43, 1126-1129.



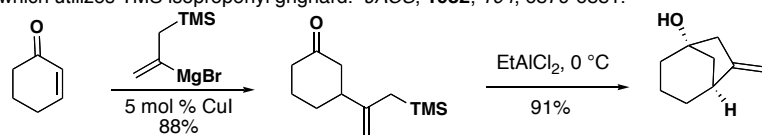
Several methods based on the conjugate addition of homoenolates to alkenes and alkynes followed by condensation of the resulting enolate have been developed. Talbiersky has developed a method using 3-aminoacrylates. *Angew. Chem. Int. Ed.* **1978**, *17*, 204-205.



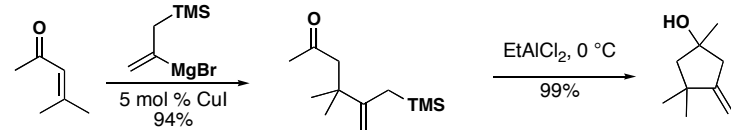
Crimmins used a Zinc homoenolate in his synthesis of (±)-Bilobalide. *JACS*, **1993**, *115*, 3146-3155.



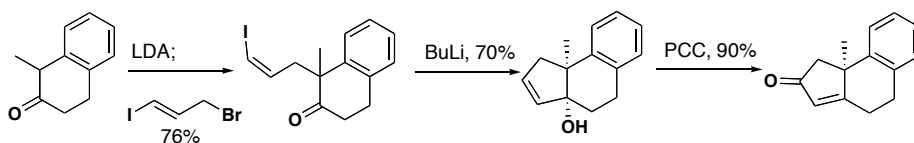
Methods have also been developed which include a Michael addition, followed by activation of the new appendage and cyclization to the carbonyl of the Michael acceptor. Trost has published such a procedure which utilizes TMS isopropenyl grignard. *JACS*, **1982**, *104*, 6879-6881.



3-methyl cyclopentene gives 88 and 84% yields

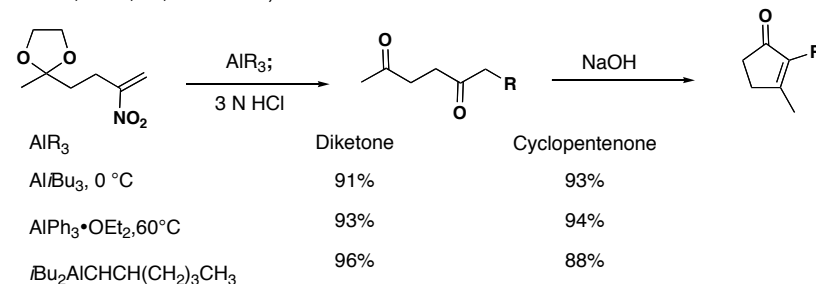


Piers has produced a method which encompasses enolate alkylation of ketones, α -ketoesters, and dimethyl hydrazones with (Z)-3-bromo-1-iodopropene, followed by grignard lithium-halogen exchange and condensation. (*Tet. Lett.* **1994**, *35*, 8573-8576.)



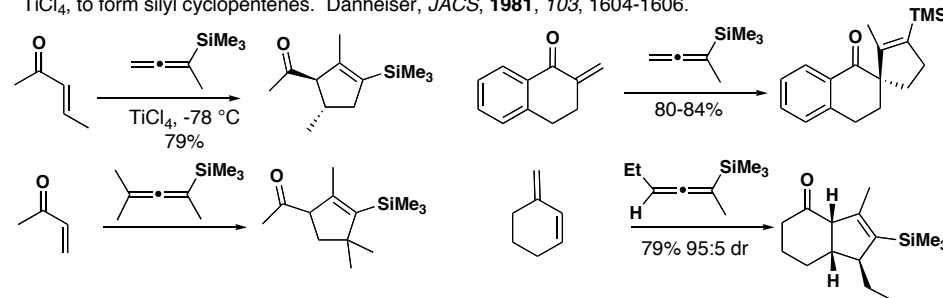
Compound	Yields	Yields	Yields	Yields
	78%	77%	83%	93%
	73%	85%	66%	68%
	86%	61%	88%	68%

Conjugate addition of alkyl, alkenyl, or aryl aluminum compounds to nitroalkenes is effective for generating 1,4-diketones, which can be condensed to cyclopentenones. (Pecunioso and Menicagli, *JOC*, **1988**, *53*, 2614-2617)

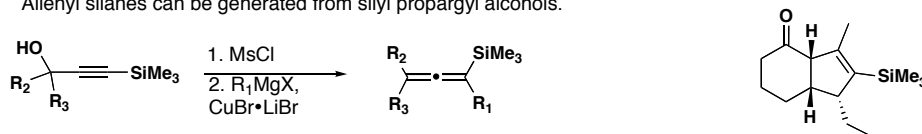


Addition of allyl and allenyl silanes to α,β -unsaturated carbonyls

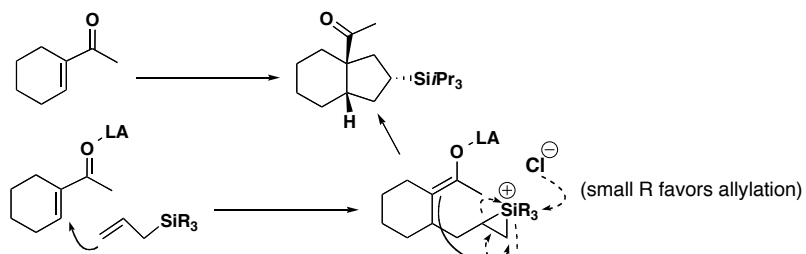
The Danheiser Annulation is the treatment of enones and allenyl silanes with a Lewis acid, frequently TiCl₄, to form silyl cyclopentenones. Danheiser, *JACS*, **1981**, *103*, 1604-1606.



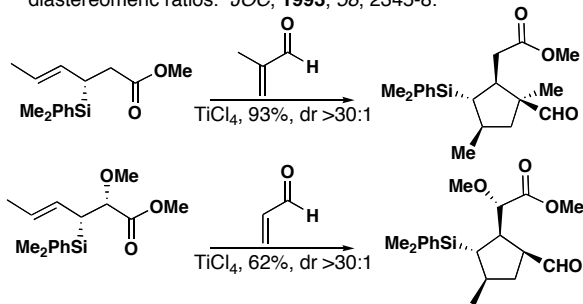
Allenyl silanes can be generated from silyl propargyl alcohols.



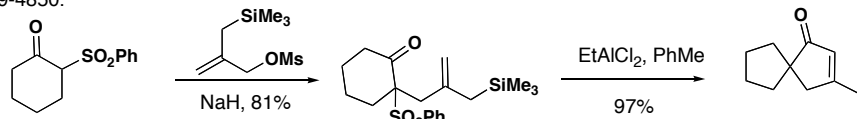
Depending on the choice of Lewis Acid and allyl silane, the Sakurai allylation can be modified to produce silyl cyclopentanes. The use of enantiopure allyl silanes can give good to excellent *ee*'s. Knölker *et al.*, *Tet. Lett.*, **1999**, 40, 3557-3560.



Panek has applied Chiral crotylsilanes to the generation of highly substituted cyclopentanes in excellent diastereomeric ratios. *JOC*, **1993**, 58, 2345-8.

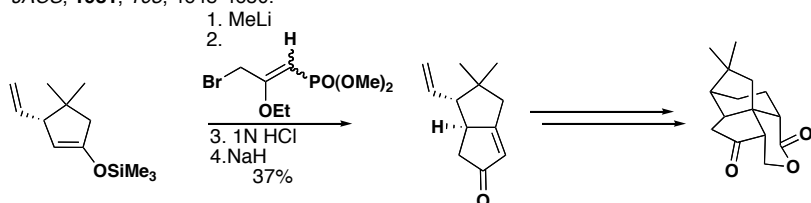


Trost has developed bisfunctional allylsilanes for the annulation of spiro cyclopentenones. *JACS*, **1983**, 4849-4850.

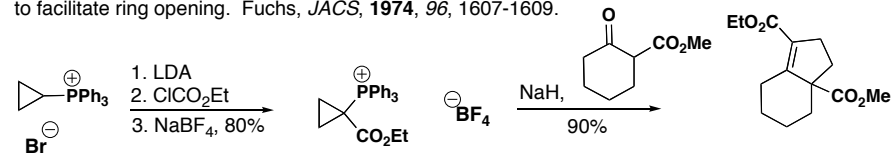


Wittig/ Horner-Wadsworth-Emmons Type Reactions

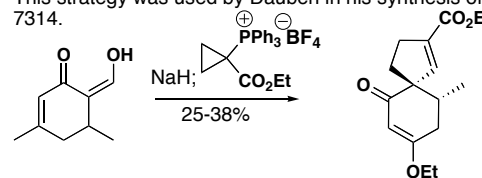
Helquist used a bromo HWE reagent to effect a cyclopentenone annulation in his synthesis of quadrone. *JACS*, **1981**, 103, 4648-4650.



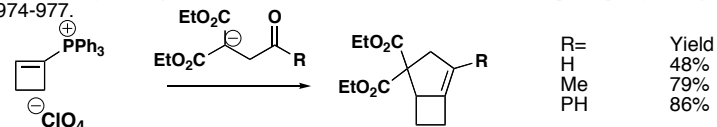
Cyclopropyl phosphonium salts have been used with enolates to generate cyclopentanes, but require forcing conditions for the ring opening step. This drawback has been avoided by adding an ester group to facilitate ring opening. Fuchs, *JACS*, **1974**, 96, 1607-1609.



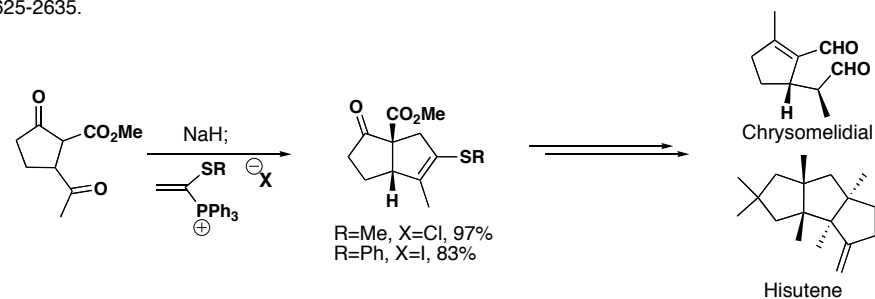
This strategy was used by Dauben in his synthesis of Spirovetivane sesquiterpines. *JACS*, **1977**, 99, 7307-7314.



Cyclobutenyl Phosphonium salts have been used by Minami to [2.3.0] bicycloheptanes. *JOC*, **1989**, 54, 974-977.

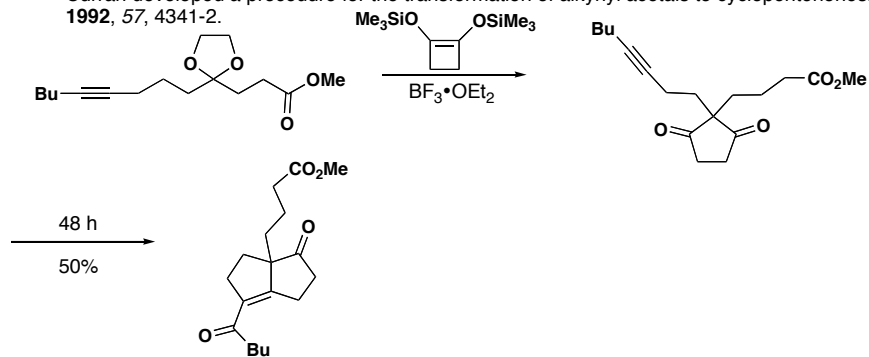


The principle of using conjugate addition to activate Wittig reagents has been applied to acyclic reagents by Hewson in his synthesis of several cyclopentanoid natural products. *J. Chem. Soc. Perkin 1*, **1985**, 2625-2635.



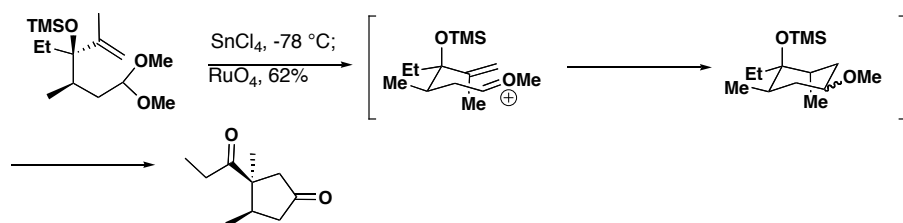
Prins and Prins-Pinacol Cyclizations

Curran developed a procedure for the transformation of alkynyl acetals to cyclopentenones. *JOC*, **1992**, *57*, 4341-2.

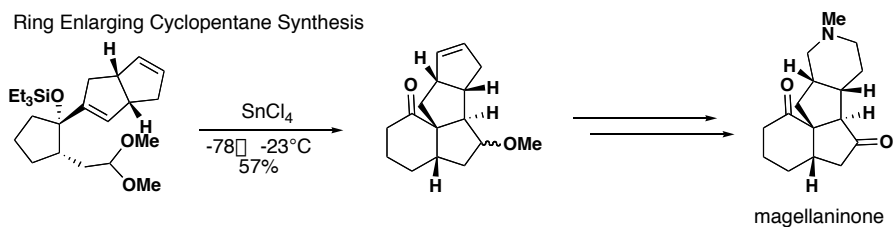


Overman has made extensive use of a number of different Prins-Pinacol rearrangements in the synthesis of natural products. For a review, see *JOC*, **2003**, *68*, 7143-7157.

Cyclopentane synthesis

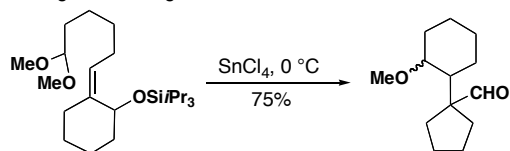


Ring Enlarging Cyclopentane Synthesis

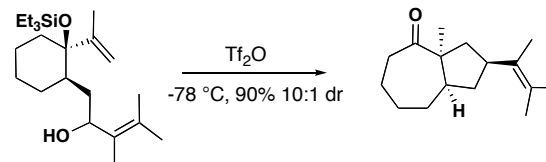


This reaction also works with dithioacetals in place of acetals (dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) is used as the promoter. This reaction can also be used to create medium sized rings. The use of alkynes for the Prins reaction gives cyclopentene products.

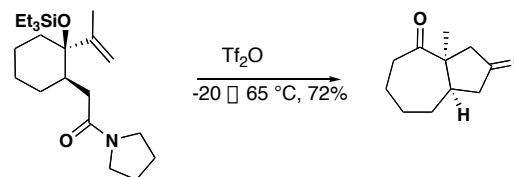
Ring Contracting Annulations



Allyl cations formed from allyl alcohol and triflic anhydride can also initiate the reaction.

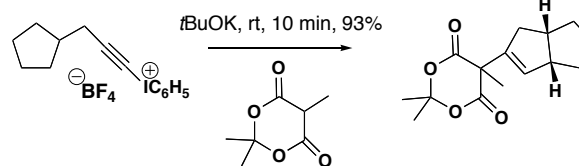


Keteniminium ion initiated reactions can be used to form cyclopentanones

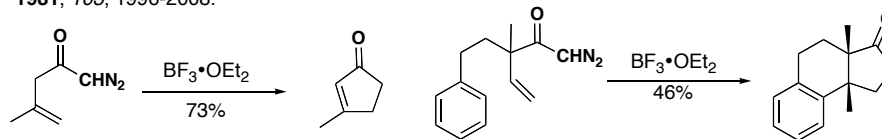


Carbene Insertion Reactions

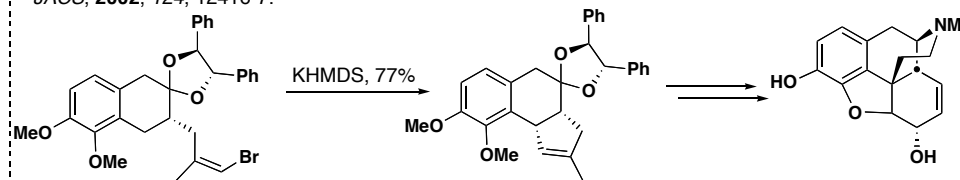
Michael addition to alkynylidonium salts can be used to generate carbenes which then undergo C-H insertion to form a cyclopentene. Ochai *et al.*, **1986**, *108*, 8281-8283.



Lewis acid promoted decomposition of diazo ketones can also lead to cyclopentenone formation. *JACS*, **1981**, *103*, 1996-2008.

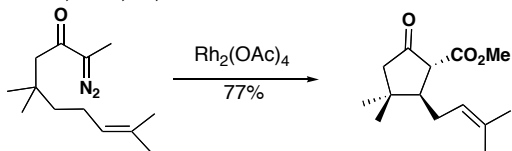
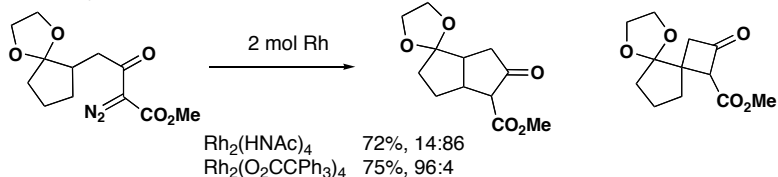


Taber used C-H insertion of a carbene derived from an alkenyl bromide in his synthesis of morphine. *JACS*, **2002**, *124*, 12416-7.

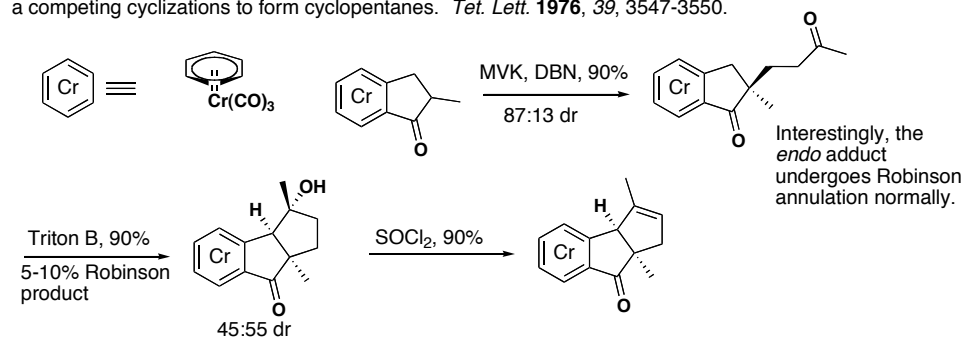


III. Organometallic Reactions

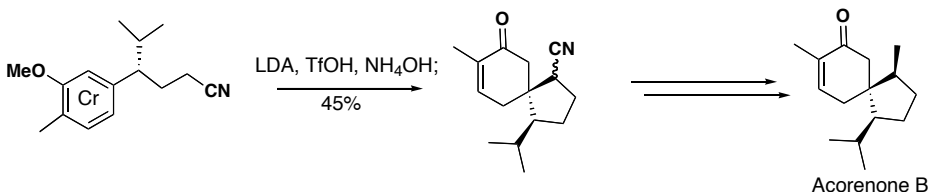
Carbene C-H insertion reactions.

Taber has observed that Rhodium can induce C-H insertion of diazo α -ketoesters to form cyclopentenes. *JOC*, **1982**, 47, 4808-9.Ikegami has discovered that the choice of ligand for Rhodium can profoundly affect the methylene/methine selectivity of carbene insertions. *Tet. Lett.* **1992**, 33, 2709-2712.

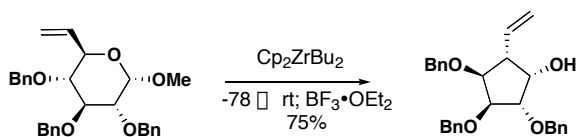
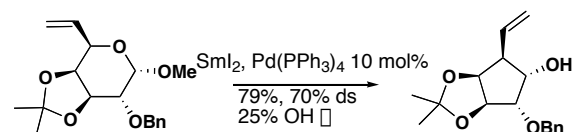
Reactions of Chromium-Arene complexes

Meyer found that indanones complexed to chromium do not undergo Robinson annulation, but instead a competing cyclizations to form cyclopentanes. *Tet. Lett.* **1976**, 39, 3547-3550.

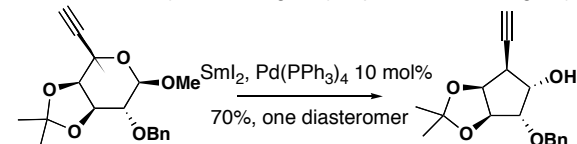
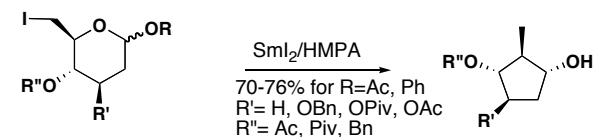
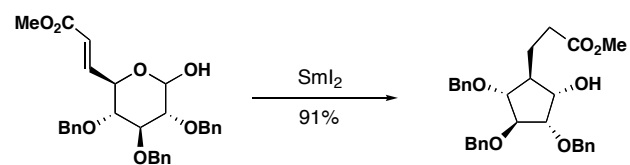
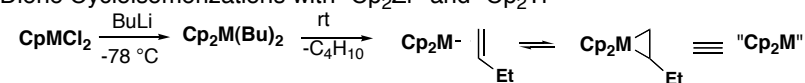
Spiro annulation of arene chromium complexes was used in Semmelhack's synthesis of Acorenone B



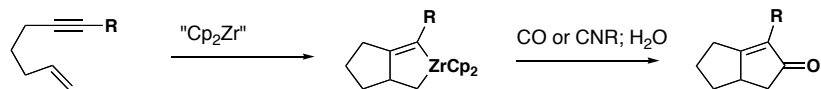
Samarium and Zirconium mediated synthesis of cyclopentanes from carbohydrates

Taguchi has reported the use of "Cp₂Zr" to convert pyranoses into cyclopentanes with excellent diastereoselectivity. *JACS*, **1993**, 115, 8835-6.Aurrecoechea has used the Sml₂-Pd(0) system to effect similar transformations, but diastereoselectivity was often problematic. *JOC*, **2000**, 65, 6493-6501.

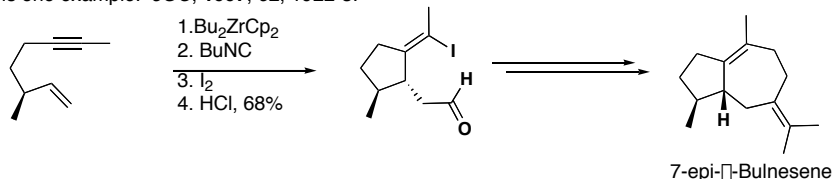
Diastereoselectivity was often greatly improved when using alkyne derivatives.

Holzapfel has developed a procedure for the use of Sml₂ with iodo pyranoses. *Tet. Lett.* **1996**, 37, 5817-5820.Matsuda has applied Sml₂ to conjugated systems. *Angewandte*, **2000**, 39, 355-357.Diene Cycloisomerizations with "Cp₂Zr" and "Cp₂Ti"

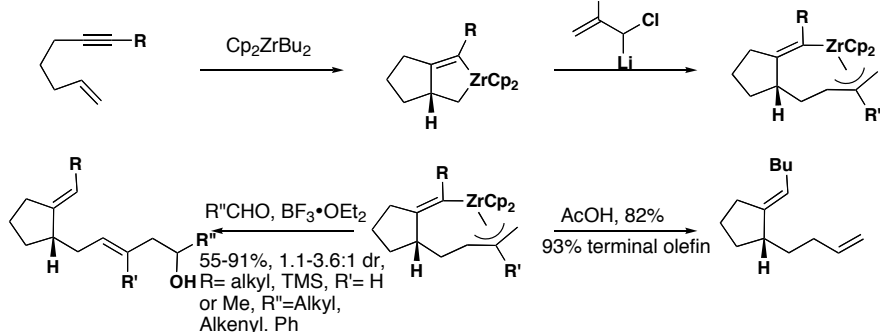
Typical form of reaction:



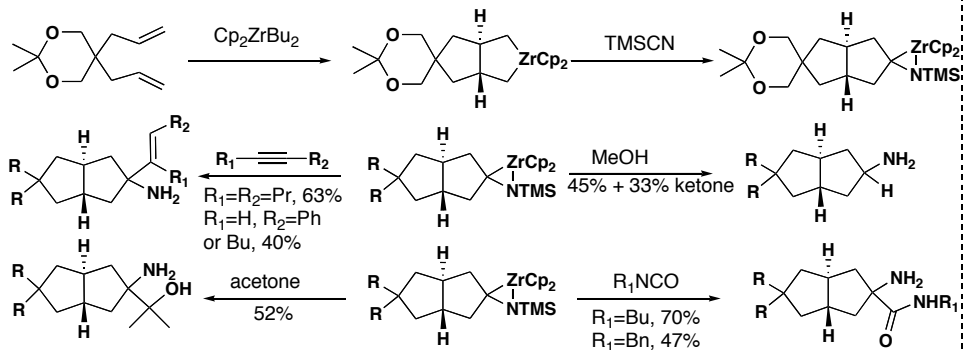
Many other reactions can be performed on the Zirconocycle. Negishi's synthesis of 7-epi- β -Bulnesene is one example. *JOC*, **1997**, 62, 1922-3.



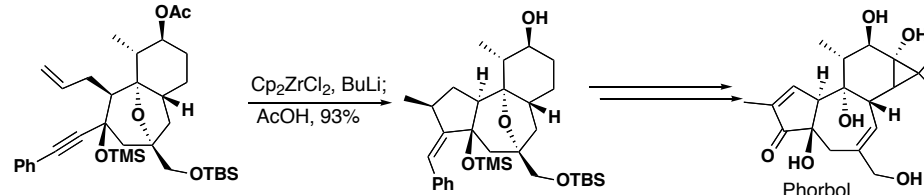
The zirconocycle can also react with lithium chlorallylide reagents, resulting in chain extension. Gordon and Whitby, *Synlett*, **1995**, 77-8.



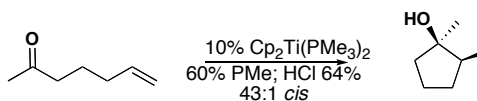
Reaction of the zirconocycle with TMS creates an intermediate capable of inserting a variety of additional groups. Whitby and coworkers, *Tet. Lett.* **1995**, 36, 4113-6.



The Zirconocycle can also be removed by AcOH, resulting in a reductive cyclization, as Wender did in his synthesis of Phorbol. *JACS*, **1997**, 119, 7897-8.

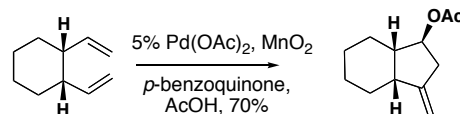


β -Enones can also be cyclized using titanocene and zirconocene. Buchwald has discovered a catalytic method for this transformation. *JACS*, **1996**, 118, 3182-3191.

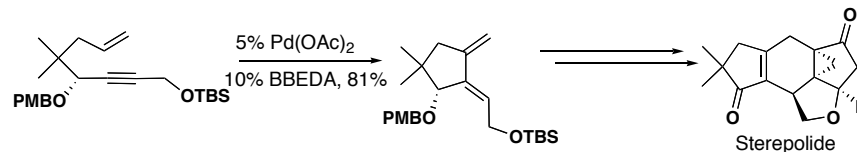


Palladium catalyzed reactions

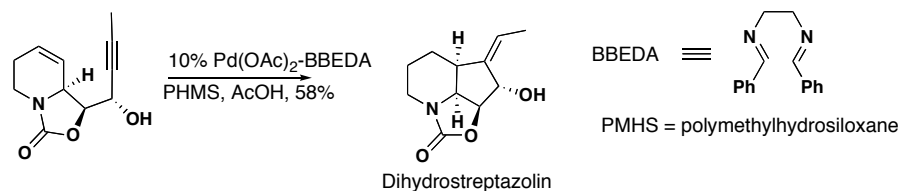
Palladium catalyzes the cycloisomerization of 1,5-dienes and enynes to cyclopentanes in a number of different manners. Moberg and Heuman discovered a procedure which induces attack of a nucleophile. *JOC*, **1989**, 54, 4914-4929.



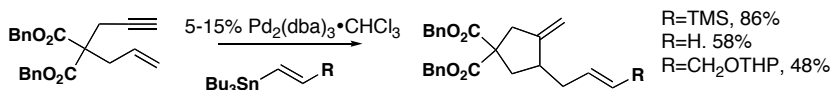
Trost used a similar method to create a diene in his synthesis of sterepolid. *Angewandte*, **1989**, 28, 1502-4



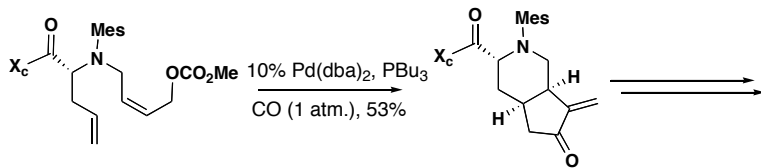
Kibayashi used a reductive version of this reaction in his synthesis of Dihydrostreptazolin. *Tet. Lett.* **1996**, 37, 8787-8790.



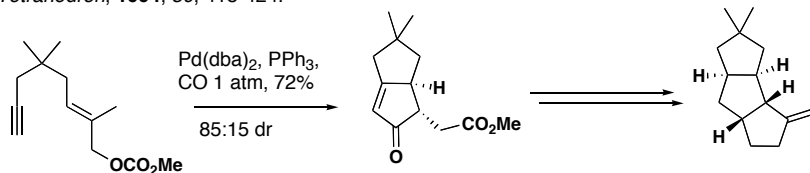
Kibiyashi has also developed a version of this reaction which is terminated by coupling with an organotin reagent. *Tet. Lett.* **1997**, *38*, 3027-3030.



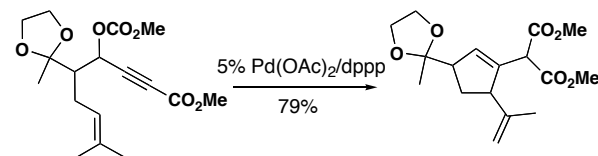
1,6-enynes and dienes also undergo cycloisomerization in the so-called palladium-ene reaction. However, this reaction requires an allylic or propargylic leaving group and is often coupled with carbonylation. Oppolzer used this reaction in his synthesis of Isoaunicine. *JACS*, **1991**, *113*, 9660-1.



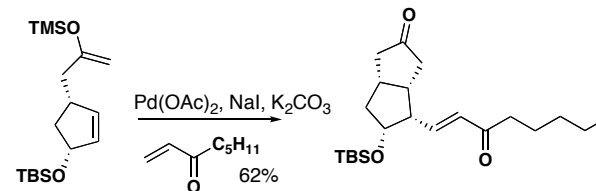
This reaction can also be used to create [3.3.0] systems, as in Oppolzer's synthesis of hirsutene. *Tetrahedron*, **1994**, *50*, 415-424.



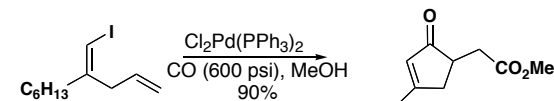
Mandai demonstrated that propargylic leaving groups will also initiate this reaction. *Tet. Lett.*, **1994**, *35*, 5701-5704.



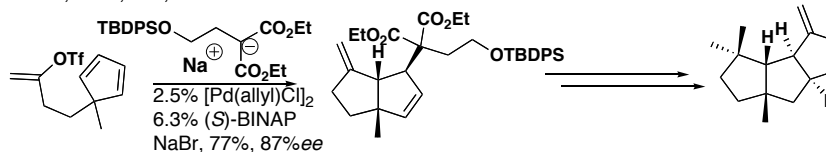
Pd can also induce cyclopentenone formation from alkenes and silyl enol ethers. Larock used a cascade reaction of this type in his synthesis of carbacyclin. *Tet. Lett.* **1991**, *32*, 5911-4.



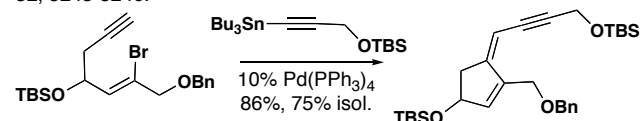
Carbonylative Heck reactions can also be used to form cyclopentenones. Tour and Negishi developed a catalytic procedure for the reaction. *JACS*, **1985**, *107*, 8289-8291.



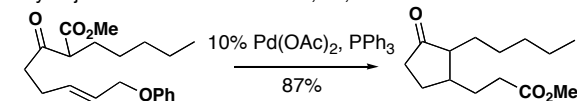
Shibasaki used an asymmetric Heck reaction/carbanion capture reaction in his synthesis of capnellene. *JACS*, **1996**, *118*, 7108-7116.



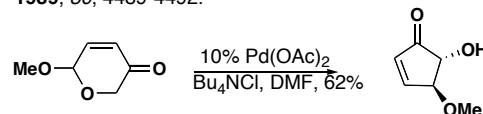
Heck reactions can also set up cascades terminated with organotin reagents. Nuss *et. al.* *Tet. Lett.* **1991**, *32*, 5243-5246.



□-Allyl substitution reactions can be used to form cyclopentanes, as in Tsuji's synthesis of dihydrojasmonate. *Tet. Lett.* **1980**, *21*, 1475-1478.

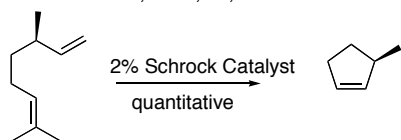


Dihydropyranones can be converted to cyclopentenones by palladium. Mucha and Hoffmann, *Tet. Lett.* **1989**, *30*, 4489-4492.

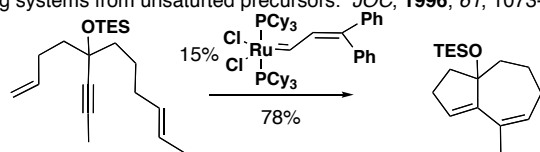


Olefin and Alkyne Metathesis Reactions

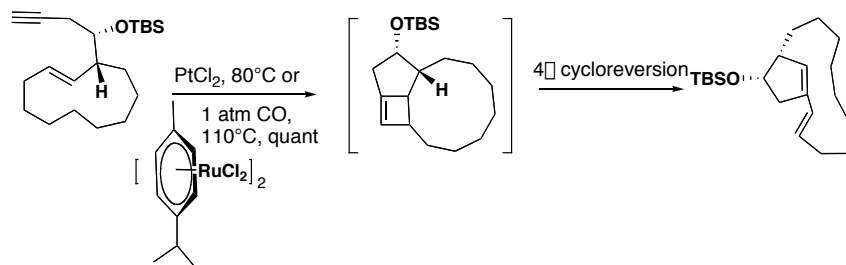
Ring closing metathesis reactions generally function well for the closure of cyclopentenes. Sita, *Macromolecules*, **1995**, *28*, 656-7.



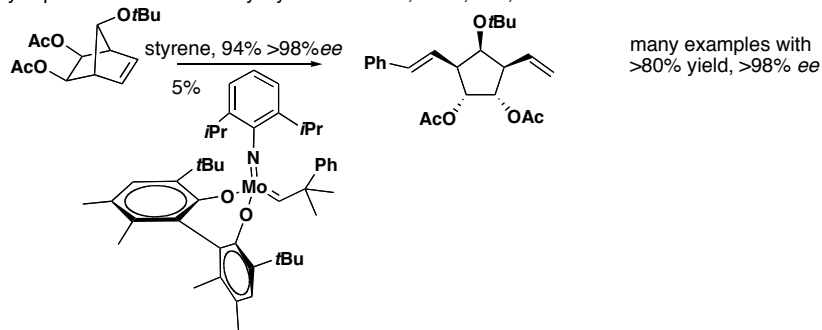
Grubbs has found that enyne Methathesis cascades are useful for the synthesis of a variety of fused ring systems from unsaturated precursors. *JOC*, **1996**, *61*, 1073-1081.



Enyne methathesis can be used to perform a simultaneous annulation and macrocycle expansion. Trost and Doherty, *JACS*, **2000**, *122*, 3801-3810.

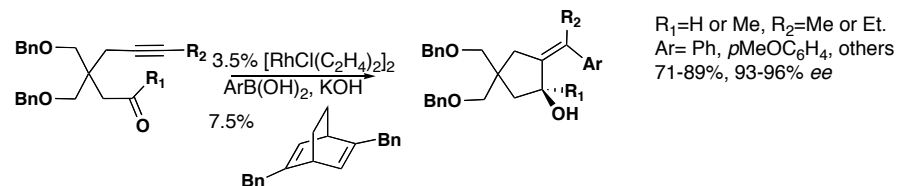


Schrock and Hoveyda have used tandem ring opening metathesis and cross methathesis to form chiral cyclopentanes from norbornyl systems. *JACS*, **2001**, *123*, 7767-7777.

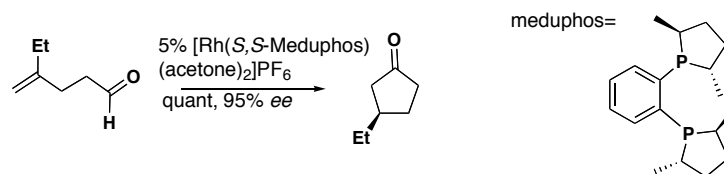


Miscellaneous Organometallic Reactions

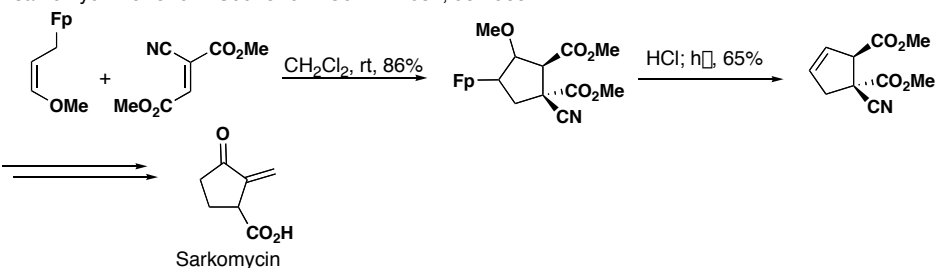
Hayashi has found that chiral rhodium complexes can induce alkynes to undergo cyclization with excellent enantioselectivity. *JACS ASAP*.



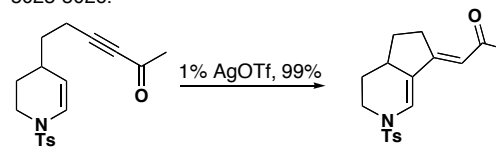
Bosnich found that pentenals can be induced to cyclize in quantitative yield and excellent enantioselectivity. *J. Chem. Soc. Chem. Comm.* **1997**, 589-590.



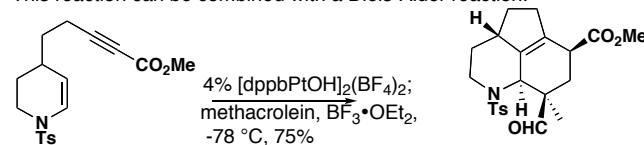
Allyliron complexes readily undergo [3+2] cycloadditions. Baker used this reaction in his synthesis of sarkomycin. *J. Chem. Soc. Chem. Comm.* **1984**, 987-988.



AgOTf and PtCl_2 have been found to promote cycloisomerization. Harrison and Dake, *Org. Lett.* **2004**, *6*, 5023-5026.

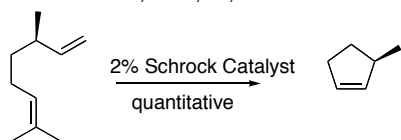


This reaction can be combined with a Diels-Alder reaction.

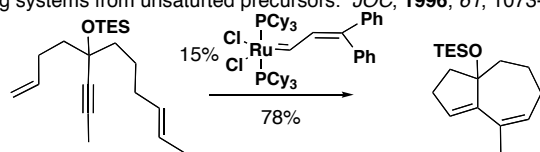


Olefin and Alkyne Metathesis Reactions

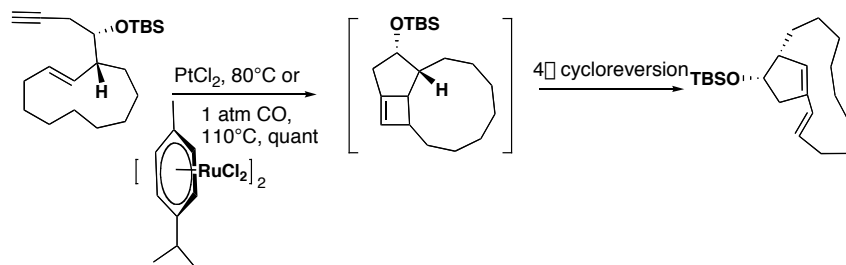
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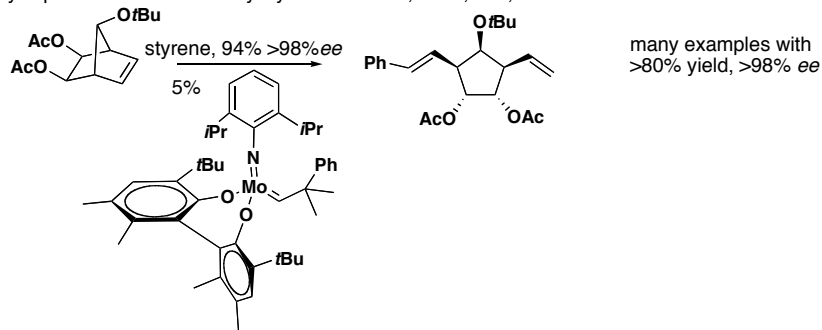
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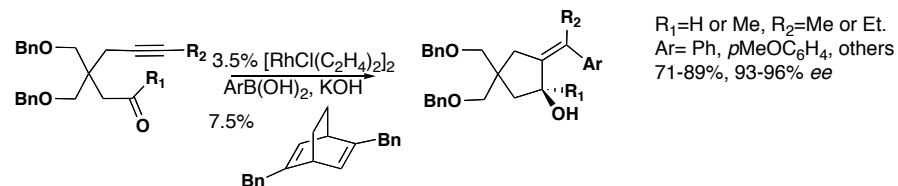


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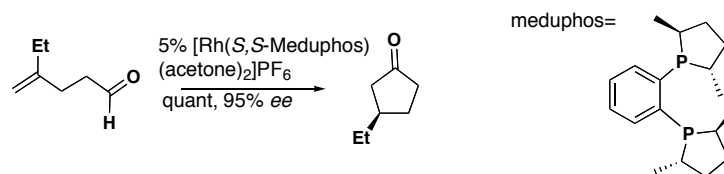


Miscellaneous Organometallic Reactions

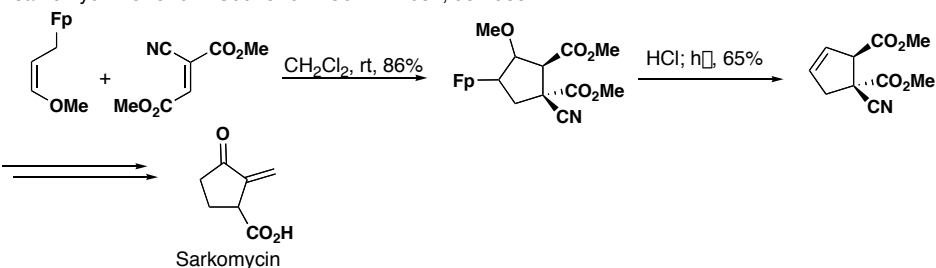
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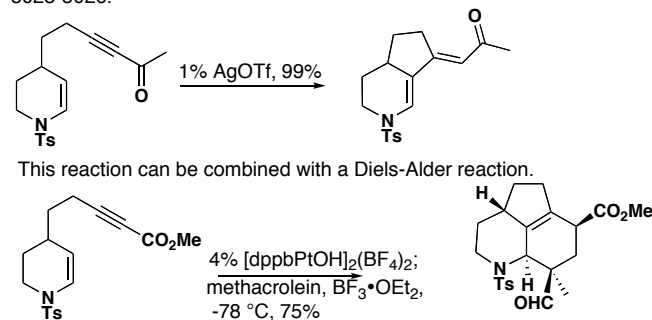
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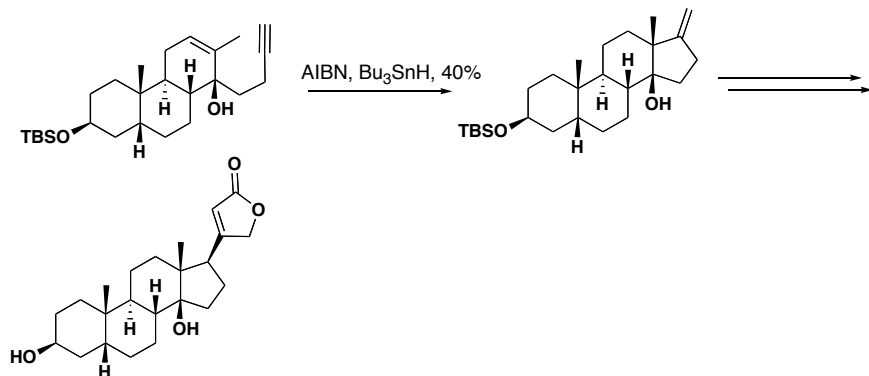
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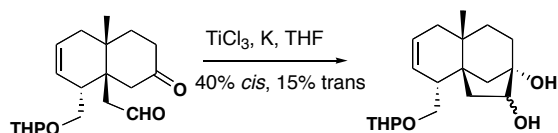


Stork utilized a simple radical closure of a cyclopentane in his synthesis of Digitoxigenin. *JACS*, **1996**, *118*, 10660-1.

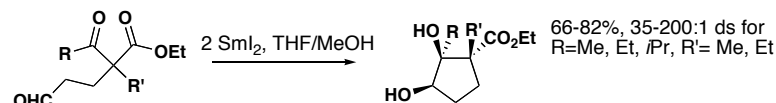


Generation of Radicals from Carbonyls

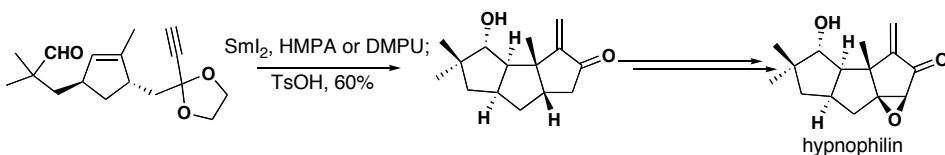
The McMurry coupling is a radical coupling between two carbonyls, usually initiated by Ti(0) generated *in situ*. This reaction was used to form the difficult CD ring system in Corey's initial route to Gibberellic Acid. *JACS*, **1978**, *100*, 8031-8034.



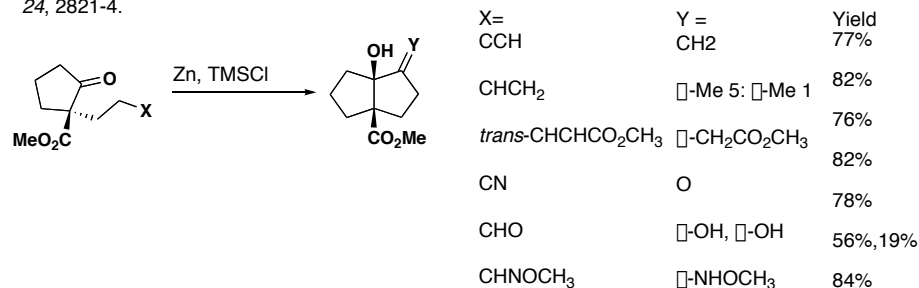
SmI_2 can also be used to induce pinacol coupling to form cyclopentanes. Molander and Kenny, *JOC*, **1988**, 2132-4.



Curran used SmI_2 to initiate a radical cascade in his synthesis of hypnophilin and coriolin. *JACS*, **1988**, *110*, 5064-7.

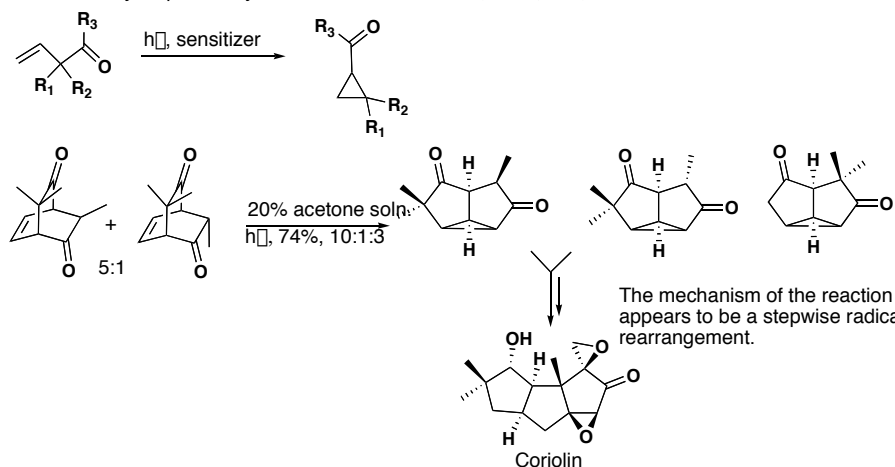


Corey has developed a procedure for the generation of radicals from carbonyls using Zn. *Tet. Lett.* **1983**, *24*, 2821-4.

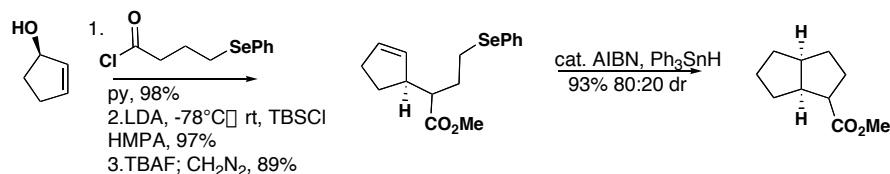


Miscellaneous Radical Reactions

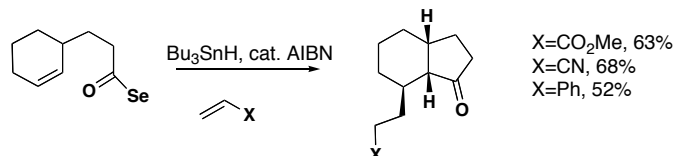
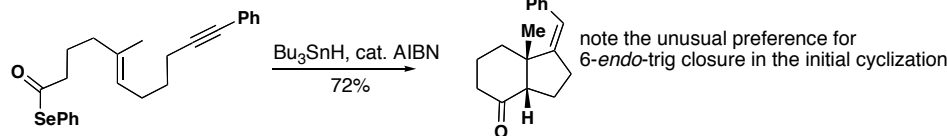
The Oxo-di- α -methane rearrangement is the rearrangement of a α - β -enone to an acyl cyclopropane. It is reviewed in *Comprehensive Organic Synthesis* (Demuth, volume 2 215-237). Unlike the regular di- α -methane rearrangement, it has been employed in several syntheses. For example, Demuth used it as a key step in his synthesis of Coriolin. *JACS*, **1986**, *108*, 4149-4154.



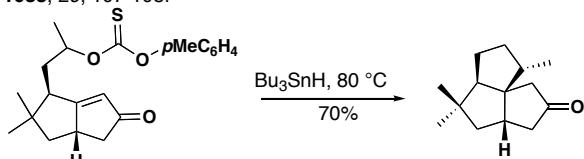
Clive has developed an annulation procedure that converts cyclopentenols into [3.3.0]octanes. *J. Chem. Soc. Chem. Comm.* **1986**, 588-9.



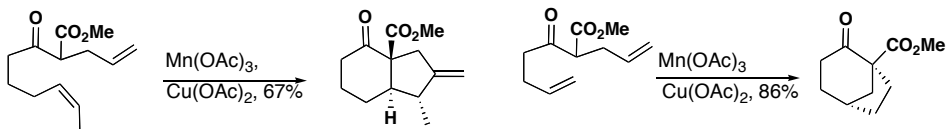
Boger has developed a protocol for the generation of acyl radicals from selenesters. These radicals can be induced to undergo a variety of cascades to form cyclopentanes. *JACS*, **1990**, *112*, 4003-8.



Nagarajan used a thioncarbonate to initiate a radical cyclization in his synthesis of silphinene. *Tet. Lett.* **1988**, *29*, 107-108.



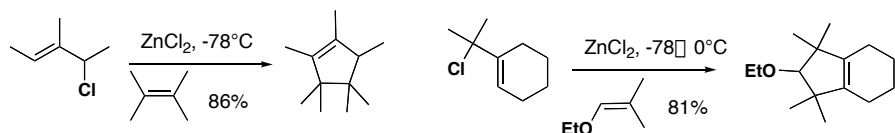
Oxidative radical reactions initiated by Mn(III) also do not follow the normal rules for radical cyclization, but can form cyclopentanes as part of a radical cascade. Snider and Dombroski, *JOC*, **1987**, *52*, 5489-5491.



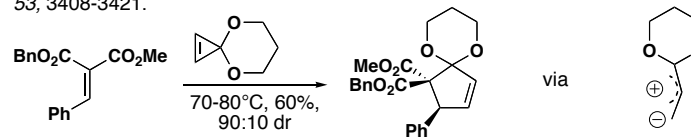
V. Pericyclic and Pseudo-pericyclic Processes

[3+2] cycloadditions

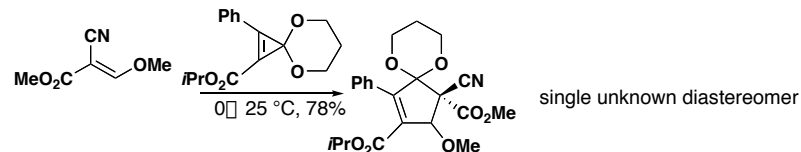
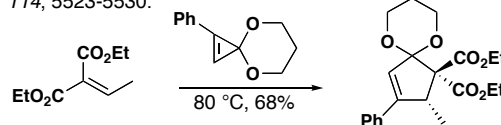
Although [3+2] cycloadditions are among the most common procedures for the synthesis of five membered heterocycles, very few examples of their use in carbocycle synthesis exist. Mayr has found that allyl cations will undergo cycloaddition with substituted alkenes. This reaction is believed to proceed via a stepwise mechanism, and regioselectivity is governed by cation stability. *Angewandte*, **1981**, *20*, 1027-9.



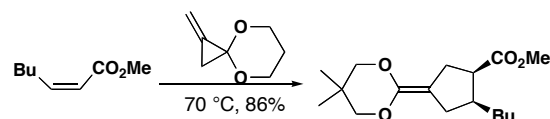
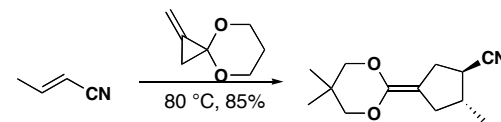
Boger discovered that cyclopropene ketals undergo thermolytic opening and will form [3+2] adducts with olefins bearing two electron withdrawing groups. This is known as the Boger cycloaddition. *JOC*, **1988**, *53*, 3408-3421.



Nakamura applied this cycloaddition to the synthesis of highly functionalized cyclopentenes. *JACS*, **1992**, *114*, 5523-5530.

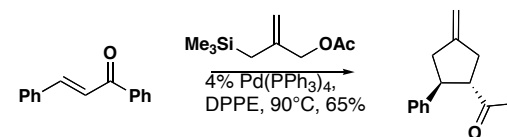
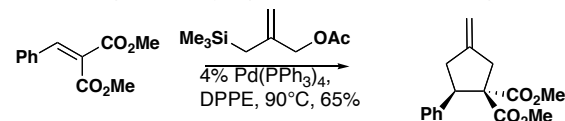


Nakamura also found that methylene cyclopropene ketals will undergo [3+2] cycloaddition in good yield with olefins with only a single electron withdrawing group. *JACS*, **1989**, *111*, 7286-7.

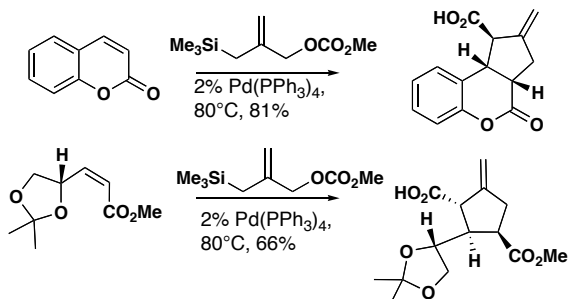


Palladium-Catalyzed Trimethylene Methane Reactions

Studies by Trost and Others have uncovered a variety of substituted isobutenes which act as trimethylene methane equivalents cyclopentane annulations in the presence of Pd(0). *JACS*, **1979**, *101*, 6429-6432.

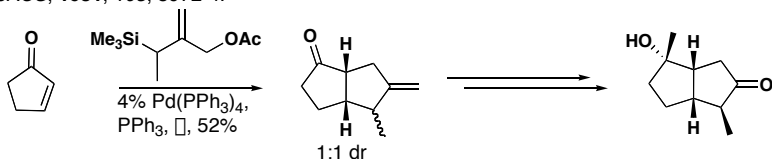


The use of allylic carbonates instead of acetates led to the unexpected incorporation of carboxylic acid moieties in the product. Trost *et. al.*, *JACS*, **1988**, *110*, 1602-8.



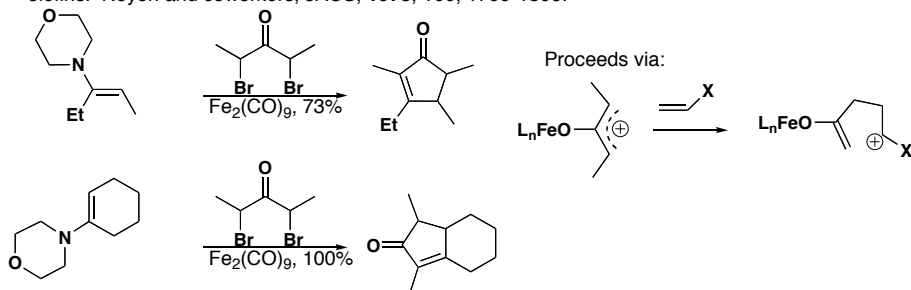
The use of *trans* olefins generally leads to a mixture of epimeric acids, favoring a *trans* orientation to the proximal appendage.

Substitution can also be introduced on the isobutene, but this frequently leads to a mixture of epimers. This strategy is therefore often used when the *exo*-methylene is oxidized to a ketone, which allows epimerization of the β -substituent. Trost used this approach in a formal synthesis of chrysomelidial. *JACS*, **1981**, *103*, 5972-4.



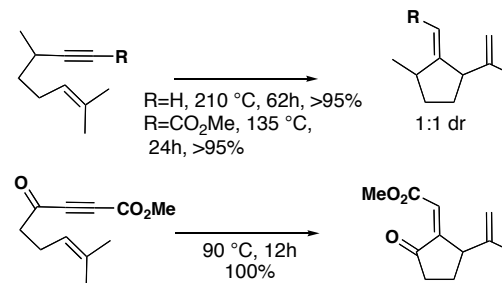
Iron Carbonyl induced cyclization of dibromoketones

Iron Carbonyl can induce a formal [3+2] cyclization between β,β' dibromo ketones and electron rich olefins. Noyori and coworkers, *JACS*, **1978**, *100*, 1799-1806.



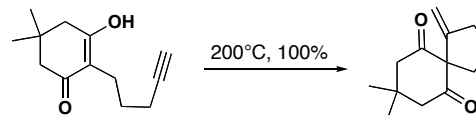
Ene reactions

Ene reactions are generally effective for the closure of cyclopentanes. Snider noted that significant rate acceleration could be achieved by placing carbonyl groups in conjugation with the enophile in Alder ene reactions. *JOC*, **1978**, *43*, 2161-4.



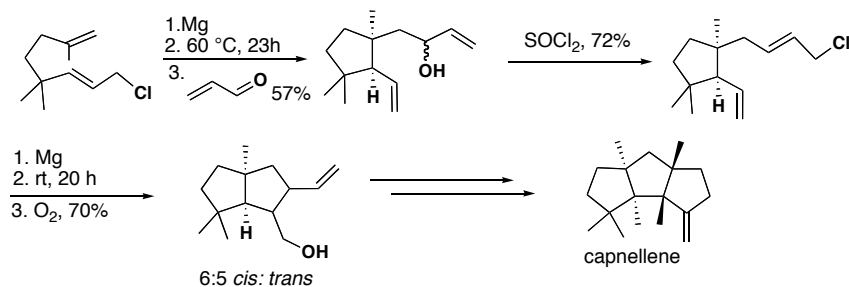
Conia Ene reactions are also useful for annulation of cyclopentenes. However, they often require temperatures in excess of 300 °C, which limits their usefulness in the synthesis of complex targets. Nonetheless, this reaction can be useful in the synthesis of molecules without thermally sensitive functionality. Conia and Percec, *Synthesis*, 1975, 1-19.

β,β' -Diketones already possess a pronounced enol character and therefore undergo Conia ene reactions at much lower temperatures.

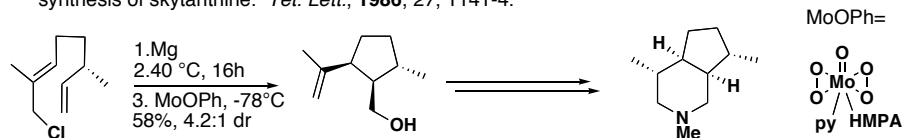


Allyl Grignard reagents with appropriately situated alkenes may undergo a reaction known as the magnesium ene reaction, in which MgX is transferred instead of a hydrogen atom. These reagents then can undergo further reactions typical of Grignard reagents.

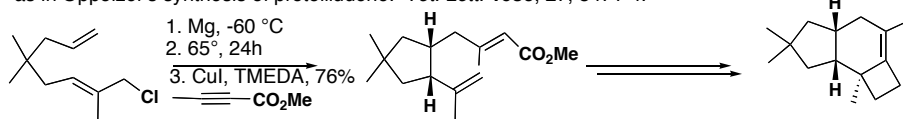
Oppolzer used dual magnesium ene reactions in his synthesis of capnellene. *Tet. Lett.*, **1982**, *23*, 4669-4672.



Oppolzer demonstrated that a pre-existing chiral center can provide diastereoselectivity in the magnesium ene reaction and that the resulting Grignard can be hydroxylated using MoOPh in his synthesis of skyanthine. *Tet. Lett.*, **1986**, 27, 1141-4.

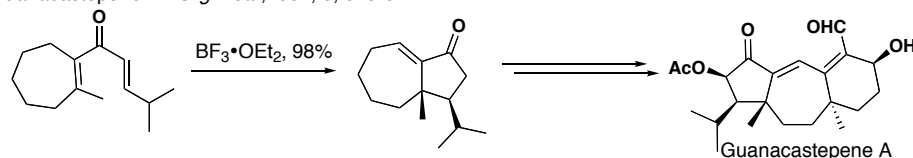


The addition of copper salts can induce a Grignard formed in this reaction to perform a Michael addition, as in Oppolzer's synthesis of protoilludene. *Tet. Lett.* **1986**, 27, 5471-4.

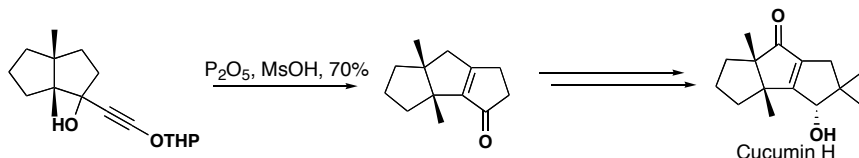


The Nazarov Cyclization

The Nazarov cyclization is Bronstead or Lewis Acid catalyzed cyclization of divinyl cations, most often generated from divinyl ketones, to cyclopentanes. Chiu used this reaction in his synthesis of Guanacastepene A. *Org. Lett.*, **2004**, 6, 613-6.

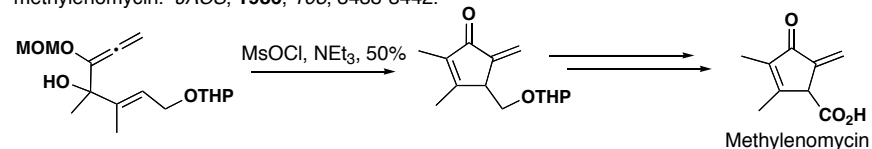


Another common precursor to the Nazarov cyclization is a 2-alkyn-1,4-diol. Reaction with strong acid or a dehydrating agent initiates a Rupe rearrangement (rearrangement of 3° propargylic alcohols to α,β -unsaturated ketones). Elimination then furnishes the divinyl ketone. Srikrishna used this protocol in his synthesis of Cucumin H. *Org. Lett.*, **2003**, 5, 2295-8.



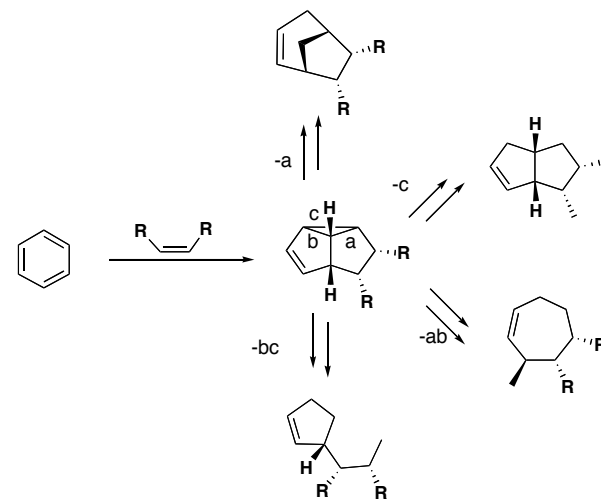
A large number of other precursors and initiation procedures for the Nazarov cyclization, including Hg(II) catalyzed hydration of enynes, TMSI induced elimination of 4-pyranones, opening of α,β -vinyl cyclobutanones, opening of *gem*-dichlorocyclopropyl methanols, and epoxidation of vinyl allenes. The presence of a silicon group on one alkene can help direct the reaction, and work has been done on asymmetric variants. The reaction has been reviewed. Hyatt and Reynolds, *Org. React.*, **1994**, 45, 1-158.

Although not exactly a Nazarov cyclization, Tius used a similar methodology in his synthesis of methylenomycin. *JACS*, **1986**, 108, 3438-3442.

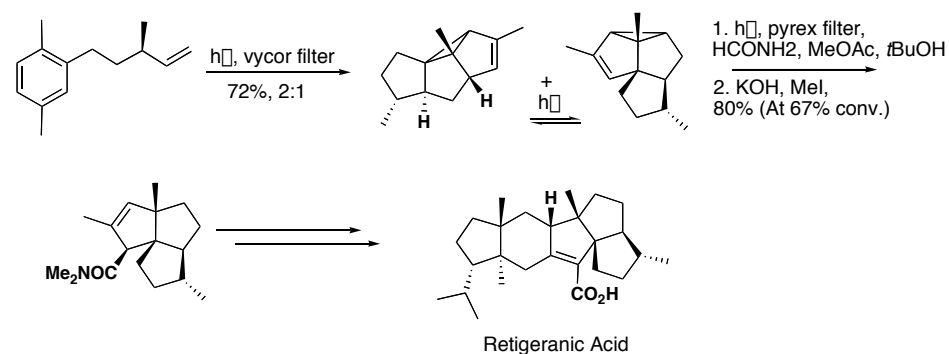


Arene-Olefin Cycloaddition

Irradiation of arenes and alkenes with properly matched electronics results in a *meta* cycloaddition through either a concerted or a radical process to give a tricyclic structure. This reaction has been reviewed. Wender, Siggel, Muss. *Comprehensive Organic Synthesis*, 5, 645-673.



Wender has used this reaction in a number of syntheses, including Retigeranic Acid. *Tet. Lett.* **1990**, 31, 2517-2520.

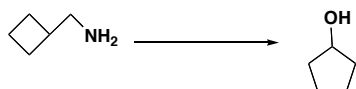


VI. Ring Expansion and Contraction Approaches

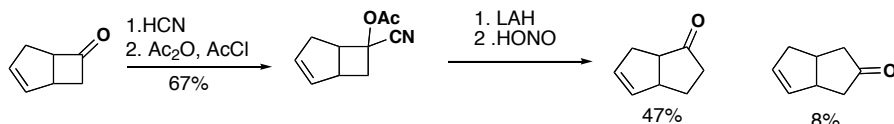
Demjanov and Tiffenau-Demjanov Ring Expansion

The Demjanov ring contraction is the reaction of a cycloalkyl methyl amine with HONO to form a diazonium ion, which then rearranges to form a cycloalkanol homologated by one carbon. This reaction is unfortunately often hampered by other cationic rearrangements and side reactions. The Tiffenau variant employs an alcohol on the ring carbon bearing the aminomethyl group, and the expansion occurs in a pinacol sense. These reactions have been reviewed. Smith and Baer. *Organic Reactions*, 11, 157-189.

The original Demjanov ring expansion was conducted on cyclobutylmethyl amine. Demjanov and Luschnikov, *J. Russ. Phys.-Chem. Soc.*, 1901, 33, 279.

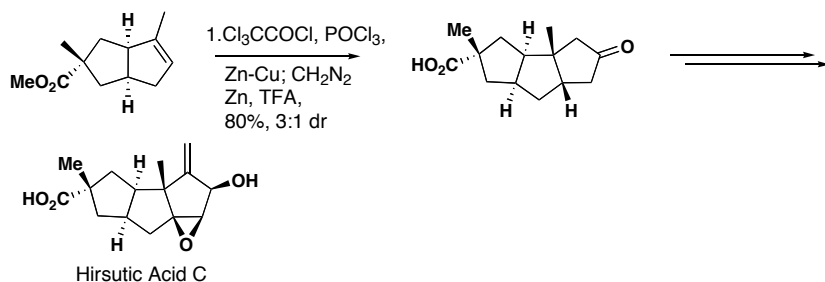


Smith *et. al.* used the Tiffenau-Demjanov ring expansion in the synthesis of bicyclo [3.3.0]octanes. *JACS*, 1952 74, 2278-2282.

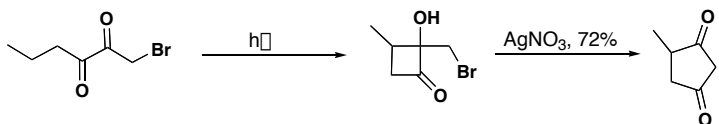


"Explanation of the course of the ring expansion reaction is difficult without knowledge of the stereochemical relationship between the aminomethyl group and the *cis*-hydrogens at the ring junctions.... It would be particularly interesting if [the two products] were each obtained from a different stereoisomer."

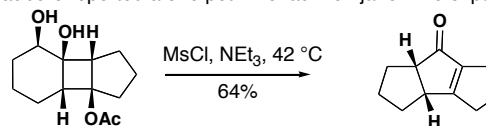
The Tiffenau-Demjanov has now largely been supplanted by other methods of cationic rearrangement. A one-pot procedure involving attack of diazomethane on ketones has been developed. Greene combined this reaction with a [2+2] cycloaddition to quickly form a cyclopentanone in his synthesis of Hirsutic Acid C. *JACS*, 1983, 105, 2435-9.



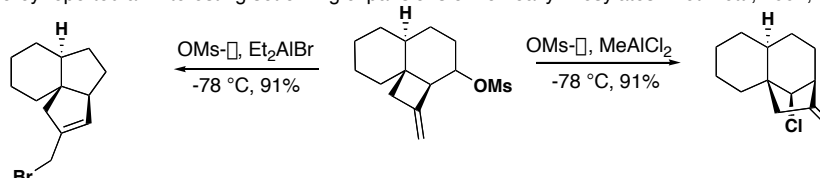
Hamer has also developed a Tiffenau-Demjanov-like ring expansion using Ag(I) initiated removal of a bromine substituent. *Tet. Lett.*, 1986, 27, 2167-8.



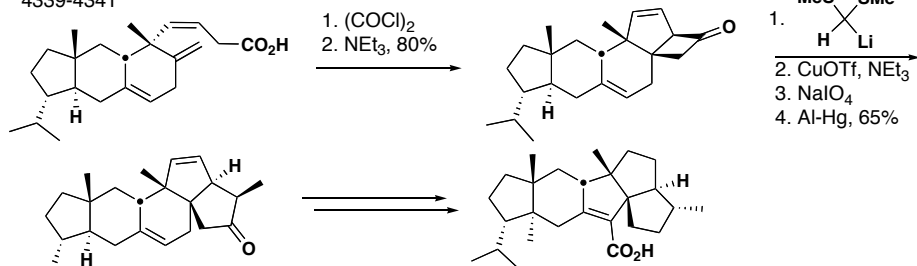
Caubere reported a one pot Tiffenau-Demjanov like expansion of pinacols. *JOC*, 1993, 48, 4572-8.



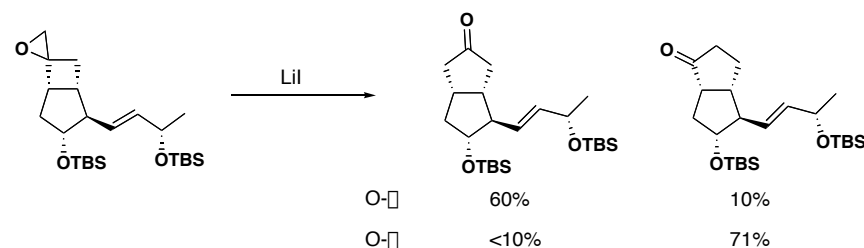
Corey reported an interesting set of ring expansions of homoallyl mesylates. *Tet. Lett.*, 1997, 38, 7491.



Corey used a ring expansion of a cyclobutanone in his synthesis of retigeranic acid. *JACS*, 1985, 107, 4339-4341

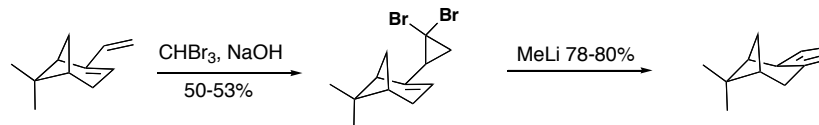


Spiro cyclobutene oxides also undergo ring expansion to cyclopentanones. Hart reported a procedure for this reaction using LiI, which intercepts a Tiffenau-Demjanov like intermediate. *Tet. Lett.* 1985, 26, 2713-6.



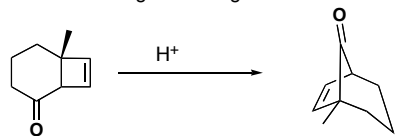
The Skattebol rearrangement

Paquette has used the Skattebol rearrangement to synthesize cyclopentadienes from butadienes.

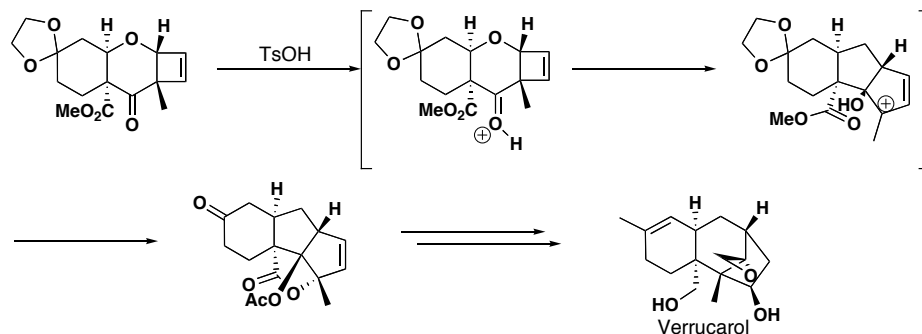


The Cargill Rearrangement

The normal Cargill rearrangement creates bridged ketones from fused systems.

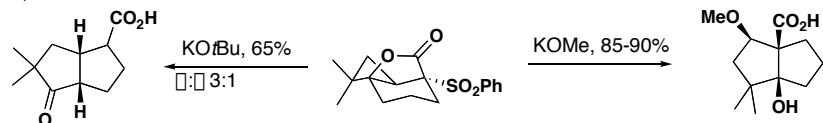


White reported an interrupted Cargill rearrangement that [4.2.0] system to a [3.3.0] one in his synthesis of Verrucarol. *Synthesis*, **1998**, 619-626.

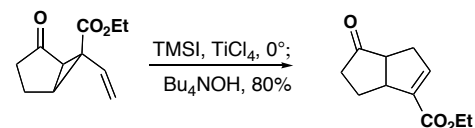
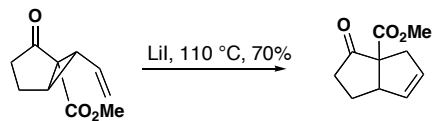


Miscellaneous Ring Expansions

Kende reported an interesting Grob fragmentation-recombination creating a [3.3.0] system. *Tet. Lett.* **1989**, 30, 7329-7332.

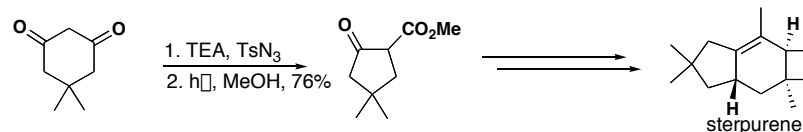


Ikegami reported that the opening of cyclopropanes with Lil can form cyclopentenones. *Tet. Lett.* **1986**, 37, 2885.



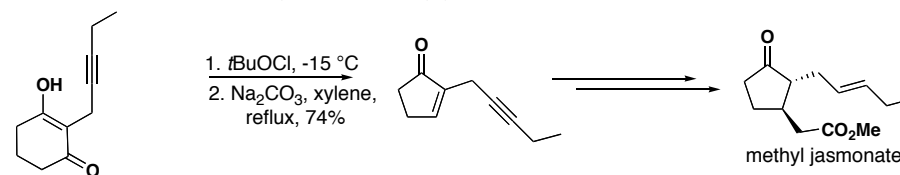
Wolff Rearrangement

The Wolff rearrangement (rearrangement of α -diazoketones to ketenes) is normally used for one carbon homologation of esters (the Arndt-Eistert homologation), but can also be used as a ring contraction method. Harmata and Bohnert used this technique in their synthesis of sterpuren. *Org. Lett.*, **2003**, 5, 59-61.

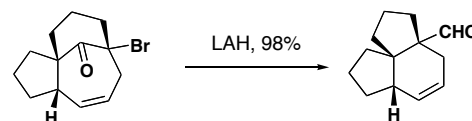


Favorskii and Quasi-Favorskii Rearrangements

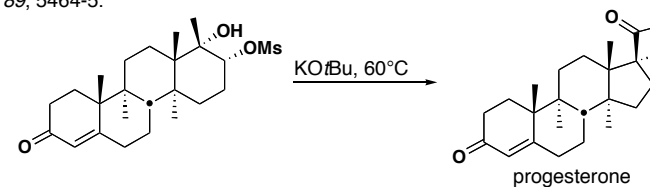
The Favorskii rearrangement is the ring contraction of α -halo cycloalkanones via a cyclopropanone. Büchi used this reaction in his synthesis of methyl jasmonate. *JOC*, **1971**, 36, 2021-2.



Nonenolizable ketones can undergo a similar reaction called the quasi-Favorskii reaction. Harmata *et. al.* *Tet. Lett.* **2002**, 43, 2347-9.

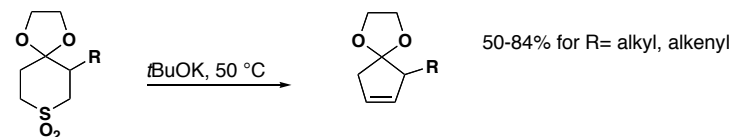


A similar reaction can be initiated by the mono-mesylation of pinacols. Stork and McMurry, *JACS*, **1967**, 89, 5464-5.



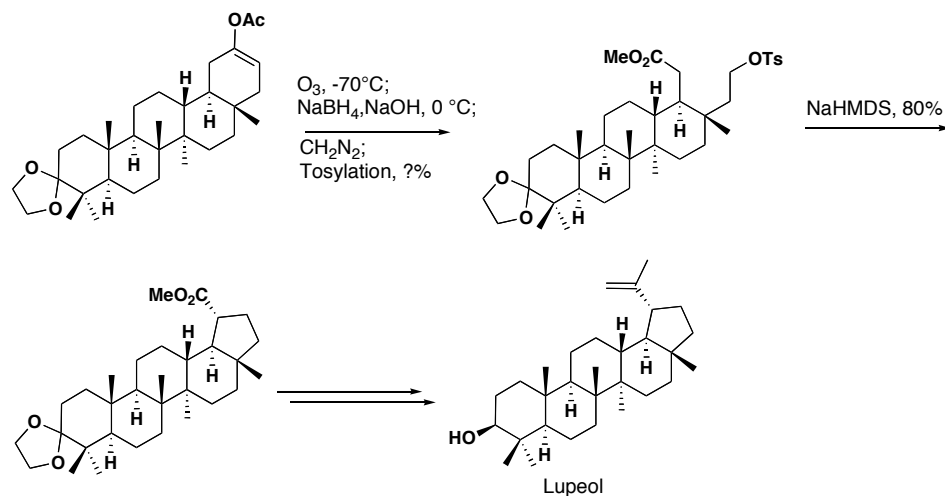
Ramburg-Bäcklund Rearrangement

The Ramburg-Bäcklund Rearrangement is the thermal extrusion of SO₂ from a sulphone to generate an olefin. This can be used to generate cyclopentenones. Matsuyama *et. al.*, *JOC*, **1987**, 52, 1703-1710.

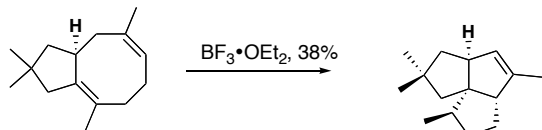


Miscellaneous Ring Contractions

Stork used a fragmentation/recombination of a cyclohexene to complete the final ring in his synthesis of lupeol. *JACS*, **1971**, *93*, 4945-7.



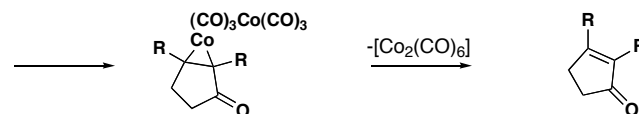
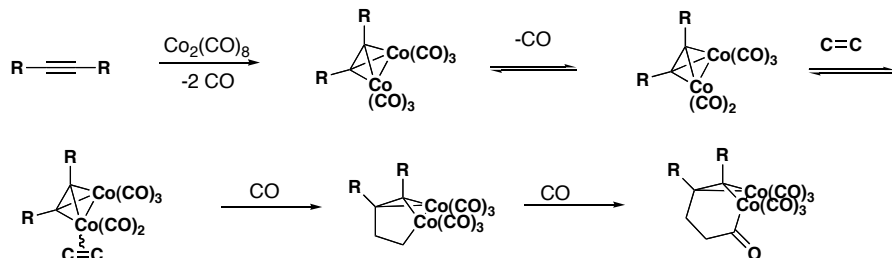
Pattenden used a carbo-Prins reaction to contract a cyclooctadiene to a [3.3.0] system in his synthesis of pentalene. *Tetrahedron*, **1987**, *43*, 5637-5652.



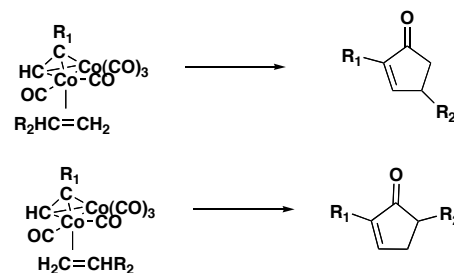
VII. Notes Added in Proof

The Pauson Khand Reaction

The Pauson Khand reaction is the cobalt-mediated synthesis of cyclopentanones from alkynes and alkenes. Recently, other metals such as Rhodium have been found to mediate this reaction. Much work has been done on the Pauson-Khand Reaction lately, including development of catalytic and enantioselective versions. For a collection of material on the Pauson-Kand reaction, see the Baran group meeting "Organometallic Oddities". This reaction has also been reviewed. *Org. React.*, **1991**, *40*, 1.



Regioselectivity:



preferred on steric grounds, but only for very large R_1 and R_2

Dodecahedrane

Composed of twelve fused cyclopentanes, the Platonic dodecahedrane represents perhaps the ultimate goal in cyclopentane synthesis. After a number of convergent approaches failed, Paquette and co-workers finally succeeded in surmounting this seemingly impossible task. *JACS*, **1982**, *104*, 4502-3; 4503-4; 5441-6; 5446-5450., *JOC*, **1979**, *44*, 3616-3630. Prinzbach later achieved a shorter in which pagodane was isomerized to dodecahedrane. *Angewandte*, **1987**, *26*, 451-3. These syntheses are reviewed in Hopf's *Classics in Hydrocarbon Synthesis*, Wiley, **2000**, 63-80.