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Ring expansion of cyclobutylmethylcarbenium ions to cyclopentane or cyclopentene derivatives and metal-promoted analogous rearrangements

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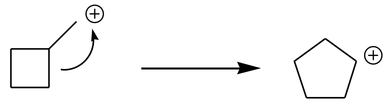
1 Introduction

The synthesis of five-membered carbocycles remains an important task within the design of functionalized target compounds bearing a cyclopentane unit.[1] Ring enlargement reactions are commonly used to access five-membered ring systems. Many of these methodologies utilize ring strain in consort with the generation of a positive charge on a carbon atom adjacent to a four-membered ring as a driving force for the ring expansion reaction.[2] In this way, the cyclobutylmethylcarbenium ion **1** can rearrange smoothly under mild conditions to provide the cyclopentylcarbenium ion **2** (Scheme 1).[3]



1 **2**

Scheme 1

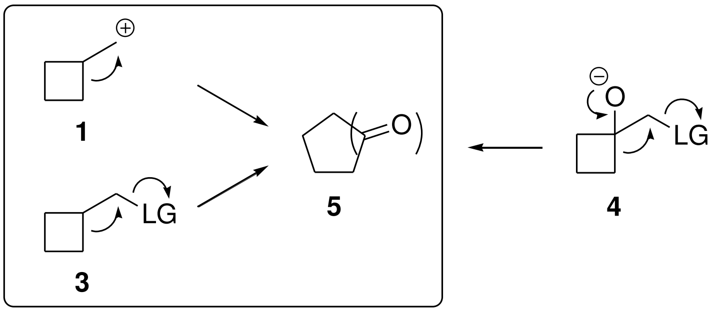
The ring enlargement of cyclobutanes to five-membered rings is associated with a release of 20 kcal/mol (ring strain energy). In contrast, the relief of strain associated with C_3 to C_4 and C_5 to C_6 enlargements is less pronounced,[4] but the activation barrier for 1,2-shifts is higher in cyclobutanes than in cyclopentanes or cyclohexanes.[5] In addition to experimental work, theoretical studies on cyclobutylmethyl and cyclopentylcarbenium ions have been performed in the past.[6]

Some of the classical methods applied to ring homologation by a one carbon atom are the Demjanov,[7] the Tiffeneau-Demjanov,[7] the Wagner-Meerwein[8] and the pinacol rearrangement.[9] Well-known ring homologation methods which incorporate a heteroatom into the ring are the Baeyer-Villiger reaction (oxygen)[10] and the Beckmann rearrangement (nitrogen).[11]

Cyclobutanones are readily available derivatives of cyclobutanes.[12] The chemical reactivity of cyclobutanones is considerably different from that of cyclic ketones with larger rings due to the ring strain of ca. 25 kcal/mol. Information regarding the influence of the ring strain on regio-, chemo- and stereoselective transformations of four-membered ring ketones is of particular importance.[13] Cyclobutanones can be constructed through a variety of methods[14] and may be further functionalized by means of Grignard reactions,[12] aldol reactions of cyclobutanone enolates with aldehydes,[15] and many other reactions to offer a convenient four-carbon ring substrate for further ring enlargement reactions. Enantioselective reactions involving deprotonations, alkylations, reductions, and other functionalization reactions of the carbonyl group of cyclobutanones represent practical approaches to optically enriched cyclobutanes starting from racemates.[16] The interest in cyclopentanes and cyclopentanones stems from their presence in a wide variety of natural products. Their structures characterize the core of different classes of substances like steroids and sesquiterpenes, but also jasmones,[17] pyrethroids and prostaglandins.[18] Substituted cyclopentenones are found in various naturally occurring, biologically active compounds, like pentenomycins.[19]

In 1988, Bellus and Ernst reviewed the ring enlargement of cyclobutanones and cyclobutenones to cyclopentanones very briefly.[13] Almost a decade later, in 1997, Wong published a review on the formation of five-membered rings through cyclobutylmethylcarbenium rearrangements.[20] Although Wong's review provided a useful introduction to the field of cyclobutylmethylcarbenium to cyclopentylcarbenium ion rearrangements, only a minor part of the existing literature was covered. The application of cyclobutane derivatives in organic synthesis in general was reviewed in 2003 by Namyslo and Kaufmann.[21] Transformations of cyclobutane rings through ring expansion reactions were described in a small paragraph in the latter review, where only a selected number of examples were given with a few in natural product synthesis. Furthermore, also other types of four- to five-membered ring expansion reactions, e.g. transformations of azetidines to pyrrolidines,[22] azetidinones to pyrrolidines[23] and oxetanes to tetrahydrofurans,[24] have been reported in the literature.

The purpose of the present review is to provide a comprehensive coverage on the ring rearrangement of four- to five-membered carbocyclic rings via cyclobutylmethylcarbenium ions and metal-promoted analogous rearrangements. The review is built up according to the creation of a positive centre for migration of a cyclobutane bond. Both the formation of localized carbenium ions and electrophilic π-complexes resulting from metal-activation of unsaturated C-C bonds will be dealt with. In addition to rearrangements through intermediate cyclobutylmethylcarbenium ions **1**, especially through semi-pinacol type rearrangements, ring expansion reactions of cyclobutylmethyl halides **3** (and analogous substrates) are of particular importance and will also be discussed in this overview. Although emphasis will be put on these two types of rearrangements, the relevance of anion-mediated ring enlargements through e.g. intermediates **4** will be highlighted as well.

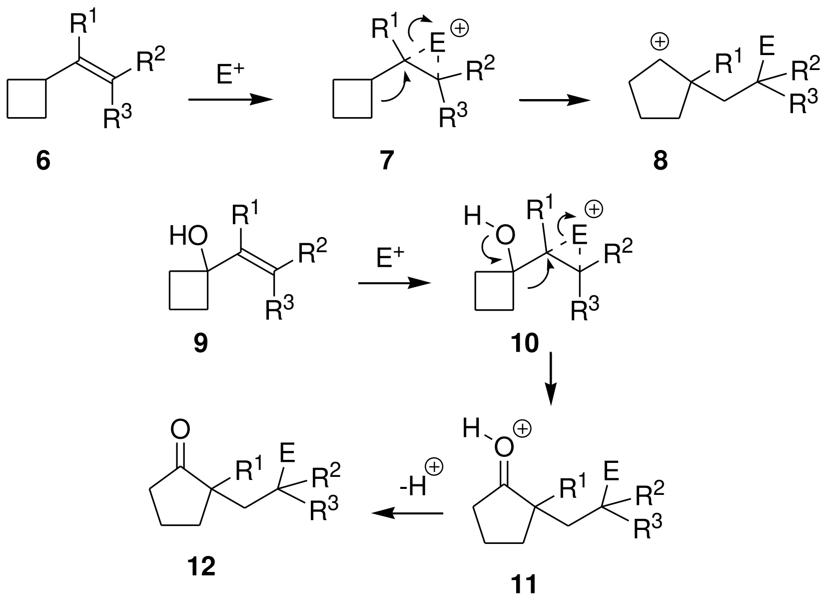


The activation of a double bond as a driving force for ring rearrangement is first described, followed by the activation of an allene substituent and a triple bond. In that part, the metal-promoted ring expansion of alkynylcyclobutanols towards cyclopentanones is covered for the first time. Subsequently, the activation of a carbonyl compound via several methods is described. In another part, different kinds of leaving groups, e.g. halogens, nitrogen gas, a nitro group, activated hydroxy and alkoxy groups, and activated sulfur and selenium species, are evaluated as precursors for the formation and ring expansion of cyclobutylmethyl carbenium ions. In a last paragraph, miscellaneous examples, which could not be subdivided into the previous classes, are described. The rearrangement of heterocycles fall out the scope of this review, as well as cyclobutene ring rearrangements and radical-mediated ring expansions.[25]

2 Ring expansion of cyclobutylmethylcarbenium ions through activation of a carbon-carbon double bond

Alkenylcyclobutanes **6** are interesting substrates for the synthesis of cyclopentanes and cylopentanones via rearrangement reactions. The π-system of the double bond is prone to a Markovnikov-controlled electrophilic attack, thereby creating electron-deficiency at the desired position to trigger a ring expansion (Scheme 2).[26] In particular, alkenylcyclobutanols **6** comprise suitable substrates for a cyclobutylmethyl to cyclopentyl rearrangement and are readily accessible through addition of an alkenyllithium reagent to cyclobutanones.

The cyclobutane ring possesses the capability of interacting with an adjacent alkenyl group or sp^2-hybridized centre. The direct conjugation of the Walsh orbitals in a cyclobutane ring with the π-orbitals of adjacent double bonds has been investigated by semiempirical[27] and *ab initio* calculations and photoelectron spectroscopy.[28] While the bonding of the cyclobutane ring attenuates its ability to delocalize charge, the approximately 20 kcal/mol of strain energy released by expansion of the four- to a five-membered ring may compensate for the electronic deficits.



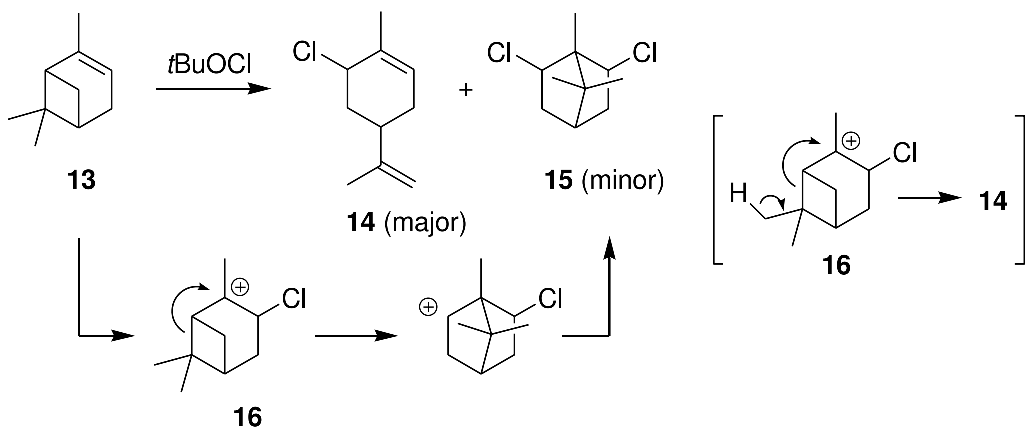
Scheme 2

Different activation types are described in this section, from acid-promoted and halogen/selenium cation-promoted activation to the use of metals for efficient ring rearrangement.

2.1 Acid-promoted activation of alkenylcyclobutanes

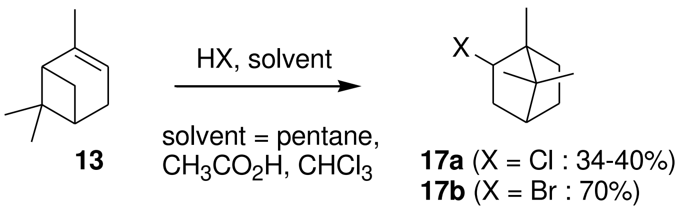
2.1.1 Pinene rearrangement

An important illustration of the acid-promoted ring expansion of vinylcyclobutanes to cyclopentanes or cyclopentenes comprised the conversion of *α*-pinene into camphane.[29] Addition of hydrogen chloride to *α*-pinene initially led to hydrogen chloride adduct, which isomerized to 2-chlorocamphane (= bornyl chloride) containing some fenchyl chloride.[29] In an analogous approach, chlorination of *α*-pinene **13** with undistilled *t*-butyl hypochlorite led to the formation of carvyl chloride **14** (see Schema 3 for a possible mechanism) and 2,6-dichlorocamphane **15** as a minor side product (Scheme 3).[30] The same reaction was also executed with bromine to synthesize 2,6-dibromocamphane as the sole product.[31] The corresponding yields were not mentioned in the original article.



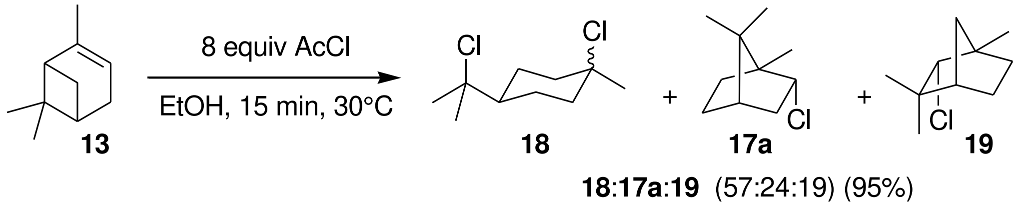
Scheme 3

Other authors have also reported the addition of hydrogen chloride to *α*-pinene **13**[32] with formation of 2-chlorocamphane **17a** in 34% yield in pentane[32a] or in 40% yield in acetic acid.[32b] In addition, hydrobromination was performed on *α*-pinene **13** in chloroform to yield 2-bromocamphane **17b** in 70% (Scheme 4).[33]



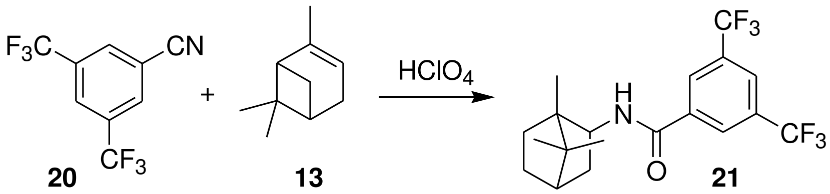
Scheme 4

2-Chlorocamphane **17a** was also obtained as a side product in 24% yield via hydrochlorination of *α*-pinene **13** through addition of eight equiv of acetyl chloride in ethanol at 30 °C for 15 minutes, affording 1-chloro-4-(1-chloro-1-methylethyl)-1-methylcyclohexane **18** in 57% yield and 2-chloro-1,3,3-trimethylbicyclo[2.2.1]heptane **19** in 19% yield (Scheme 5).[34]



Scheme 5

Other reagents were applied as well, such as sulfuric acid in chloroform[35] and thionylchloride in dichloromethane,[36] to synthesize 2-chlorocamphane in 54-63% yield. When oxalic acid was used, 2-hydroxycamphane was obtained in 41% yield.[37a] The same 2-hydroxycamphane was synthesized in 89% yield when benzoyl peroxide was added in combination with chloroacetic acid and sodium hydroxide in water (probably implying a sodium acetate-promoted reaction).[37b] When perchloric acid and 3,5-di(trifluoromethyl)benzonitrile **20** were added to (-)-α-pinene **13**, the corresponding racemic isobornylamide derivative **21** was isolated as the main product (Scheme 6). No yield was mentioned for this reaction.[38]

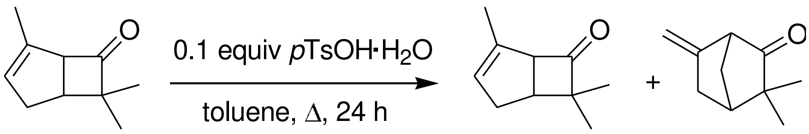


Scheme 6

2.1.2 Ring expansion of vinylcyclobutanes (different from pinene)

The same methodology as described above was applied to other types of vinylcyclobutanes. Acid- and Lewis acid-catalyzed rearrangements of α-vinylcyclobutanones via methanesulfonic acid or boron(III) fluoride etherate have been reported, leading to for example ring annelated cyclopentenones, bicyclo[3.1.0]hexanones, bicyclo[5.3.0]decenones, bicyclo[4.3.0]nonenones or spiro[4.5]decenones.

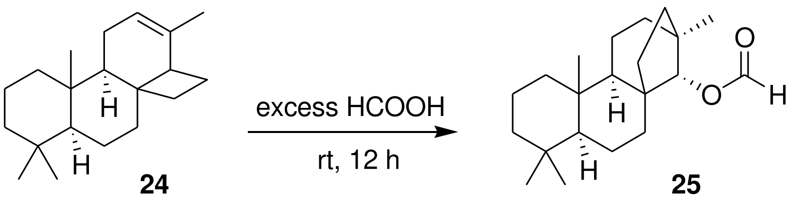
In a first example, Beereboom reported an acid-catalyzed rearrangement of 2,6,6-trimethylbicyclo[3.2.0]hept-2-en-7-one **22** with 0.1 equiv of *p*-toluenesulfonic acid monohydrate in toluene at reflux temperature for 24 hours to afford a mixture of three compounds in 89% crude yield.[39] The starting material was isolated, as well as the ring expanded 3,3-dimethyl-6-methylidenebicyclo[2.2.1]heptan-2-one **23** (no mechanism provided; Scheme 7). The author did neither mention the ratio of the compounds nor the identification of the third compound.



22 **22**:**23** (89% crude)

Scheme 7

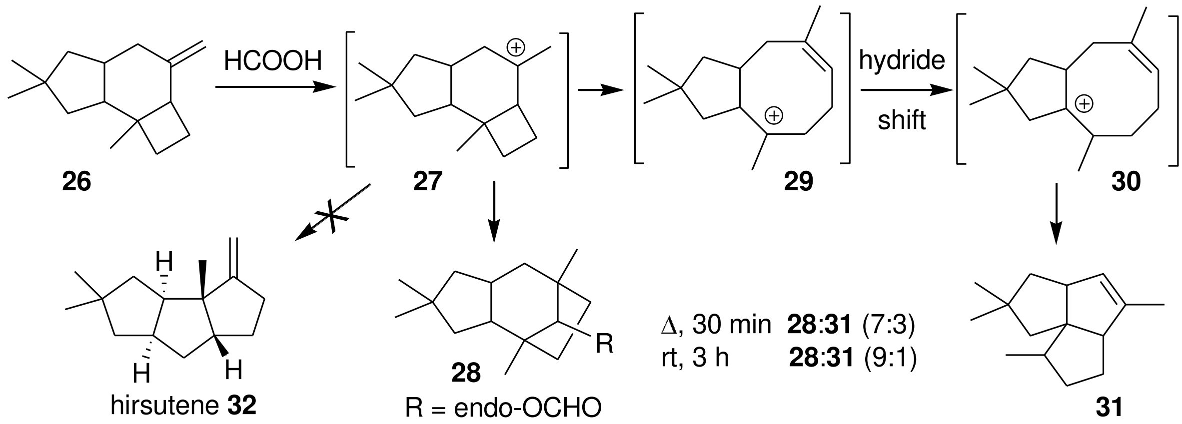
In a second example, the formate of hibaene **25**, a tetracyclic diterpene, was synthesized using formic acid as promoter for the ring expansion of compound **24**.[40] When tetracyclic olefin **24** was dissolved in an excess of formic acid and stirred at room temperature for 12 hours, the formate **25** was obtained in a quantitative yield (Scheme 8).



24 **25**

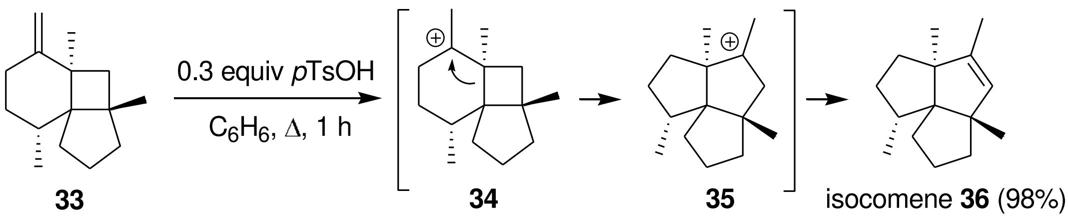
Scheme 8

In research on illudoid sesquiterpenes, a protoilludyl carbenium ion **27** was generated.[41] Stirring of alkene **26** in formic acid afforded a mixture of rearranged products **28** and **31** in a 7:3 ratio when the reaction took place at reflux for 30 minutes, and in a 9:1 ratio when the reaction was executed at room temperature for three hours (Scheme 9). The authors did not report the exact yields of the two products. No hirsutene skeleton **32** was found under these reaction conditions, which could be formed via a triple 1,2-shift from carbenium ion **27**.



Scheme 9

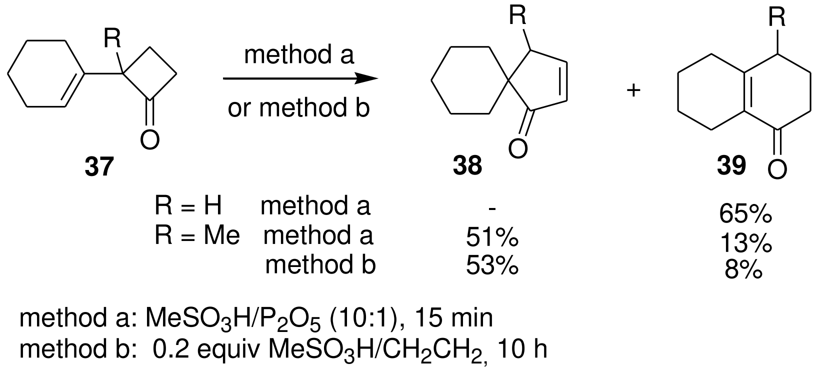
A racemic synthesis of the tricyclic sesquiterpene isocomene **36** was developed by Pirrung (Scheme 10).[42] The last step of this total synthesis involved an acid-catalyzed cyclobutylmethyl to cyclopentylcarbenium ion rearrangement. Upon treatment with 0.3 equiv of *p*-toluenesulfonic acid in benzene for one hour at reflux temperature, 2,6,8-trimethyl-5-methylenetricyclo[6.3.0.0^{1,6}]undecane **33** was transformed into racemic isocomene **36** in 98% yield.



Scheme 10

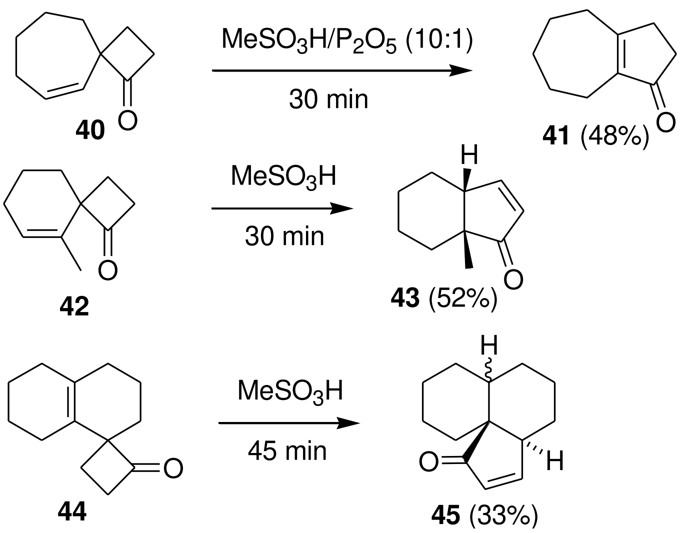
In the presence of a 10:1 mixture of methanesulfonic acid/P_2O_5 (Eaton's reagent), a 1,2-rearrangement of vinylic cyclobutanone **37** (R = Me) to 51% of spiro[4.5]dec-2-en-1-one **38** was observed, and accompanied by a minor but significant degree of 1,3-rearrangement (13%) toward bicycle **39** (Scheme 11). This reaction was improved to 53% of the 1,2-rearrangement product **38** and 8% of the 1,3-rearrangement product **39**, respectively, when no

P_2O_5 was added.[43] The *nor*-methyl analogue **37** (R = H) yielded only bicyclic compound **39** in 65% yield under the same reaction conditions.



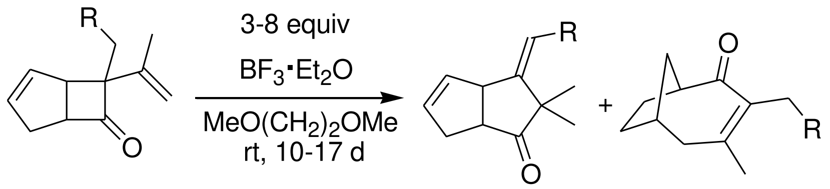
Scheme 11

The above described 1,3-rearrangement was completely suppressed in the ring enlargement of spirovinylcyclobutanones **40**, **42** and **44** (Scheme 12).[43a] Vinylcyclobutanones **40**, **42** and **44**, in the presence of 10:1 methanesulfonic acid/P_2O_5 or solely methanesulfonic acid, afforded only the corresponding 1,2-rearranged products **41**, **43** and **45**, in 33 to 52% yield, respectively. In this case, a 1,3-rearrangement would imply a violation of Bredt's rule. No reaction temperatures were mentioned in this article.



Scheme 12

Treatment of bicyclic dienones **46** with three to eight equiv of $BF_3 \cdot Et_2O$ in 1,2-dimethoxyethane gave rise to 4-alkylidenebicyclo[3.3.0]octenones **47** in moderate yield (35-36%), accompanied by a small amount of bicyclo[4.2.1]nonadienones **48** (7-10%) (Scheme 13).[44]

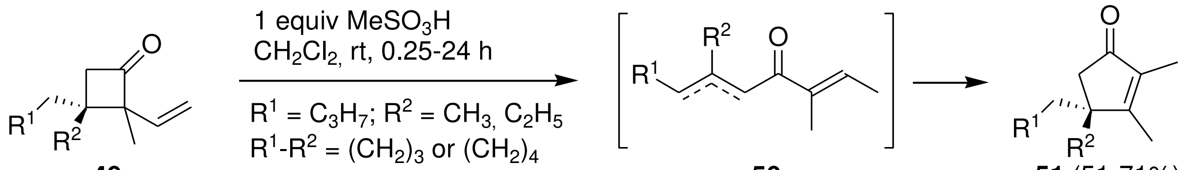


46 **47** (35-36%) **48** (7-10%)

47:**48** (80:20)

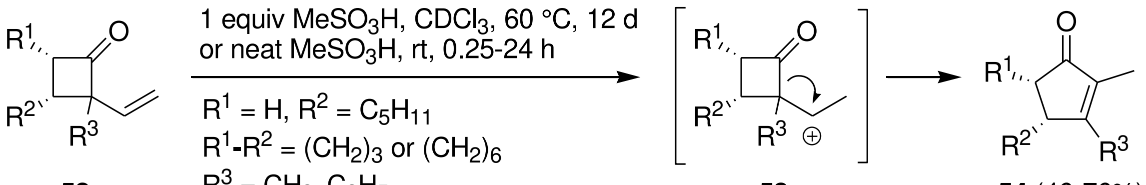
Scheme 13

Under Lewis acid or acid catalysis (0.2 equiv of $BF_3 \cdot Et_2O$ or 0.2 equiv of $MeSO_3H$), 3,3-dialkyl-2-methyl-2-vinylcyclobutanones **49** underwent ring opening to substituted allylvinyl ketones and divinylketones **50**. When higher acid concentrations were used, *i.e.* up to one equiv of methanesulfonic acid, cyclobutanones were transformed into cyclopentenones **49** in 51-71% yield (Scheme 14).[45] However, the authors stated that this transformation occurred by a Nazarov cyclisation of the intermediate dienones instead of through a cyclobutylmethylcarbenium to cyclopentylcarbenium ion rearrangement. The 3,3-dialkylcyclobutanones first underwent C(α),C(β)-bond cleavage under mild acid conditions, because in this way the original C(β) became a stable tertiary carbenium ion. Deprotonation produced the dienones **50**. The subsequent cyclization to cyclopentenones **49** required intermediate acid conditions via a Nazarov-type mechanism.



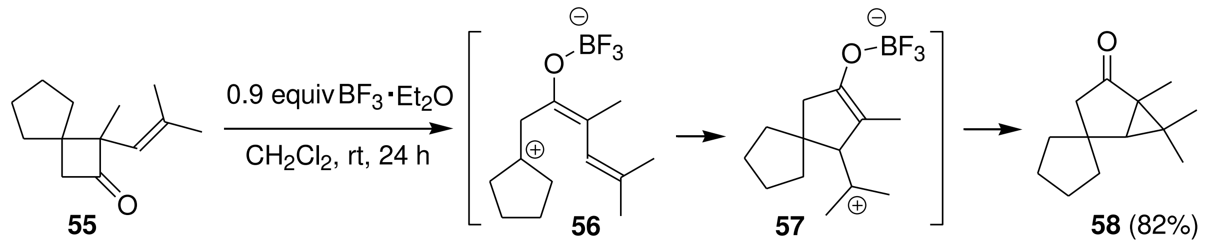
Scheme 14

On the other hand, 3-alkyl- and 3,4-dialkylcyclobutanones **52** did not yield the corresponding dienones **50** or cyclopentenones **51** using the above-described methods, but were converted into cyclopentenones **54** under more vigorous reaction conditions or under stronger acid catalysis, *i.e.* treatment with neat $MeSO_3H$. This transformation proceeded by a different mechanism. At first, a cyclobutylmethylcarbenium ion **53** is formed and ring expansion via a [1,2]-acyl shift to a cyclopentylcarbenium ion is followed by formation of a double bond to produce cyclopentenones **54** in 46 to 76% yield (Scheme 15).[45]



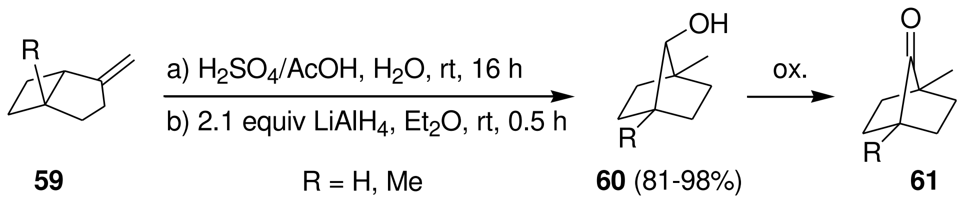
Scheme 15

When cyclobutanone **55**, which carried a 1-isobutenyl group at the *α*-position, was exposed to 0.9 equiv of boron(III) fluoride etherate in dichloromethane at room temperature for 24 hours, no cyclopentenone but the bicyclo[3.1.0]hexanone spiro derivative **58** was obtained in 82% (Scheme 16).[46] The proposed mechanism again involved a C(*α*),C(*β*)-bond cleavage to produce a tertiary carbenium ion **56** which cyclised to produce another tertiary carbenium ion **57**, which was finally trapped by the enolate to afford the highly substituted bicyclo[3.1.0]hexanone spiro derivative **58**. No cyclobutylmethylcarbenium ion was involved in this transformation.



Scheme 16

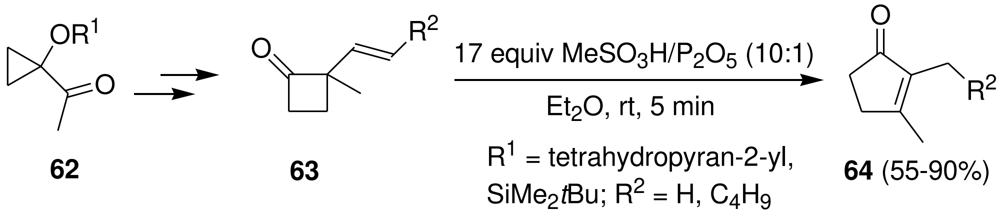
The synthesis of bicyclo[2.2.1]heptan-7-ols **60** was achieved in 81 to 98% yield by reaction of 4-methylenebicyclo[3.2.0]heptanes **59** with a 0.5 molar solution of sulfuric acid in acetic acid for 16 hours at room temperature, followed by reduction of the resulting acetate with lithium aluminium hydride in diethyl ether for 0.5 hours at room temperature (Scheme 17).[47] The exclusive formation of the norbornane derivative **60** under thermodynamic control was in accordance with the lower energy of the bicyclo[2.2.1]heptane skeleton (62.8 kJ mol^{-1}), as compared to that of bicyclo[3.2.0]heptane (138.2 kJ mol^{-1}). The obtained ring expanded products were used in the synthesis of 7-norbornanones **61**.



Scheme 17

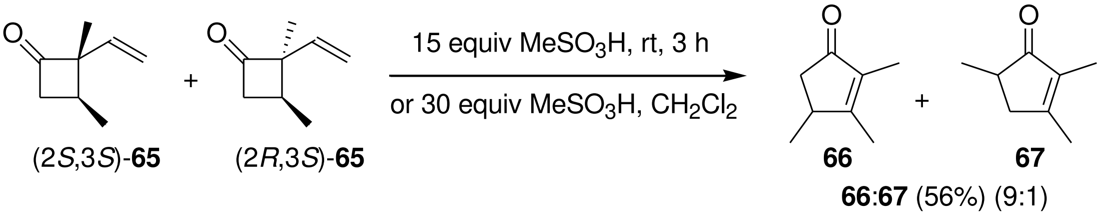
The synthesis of dihydrojasmone (R^2 = C_4H_9) and analogs **64** from cyclopropanol derivatives **62** was reported in 55-90% yield via the intermediacy of cyclobutanones **63** (Scheme 18).[48]

Precursors **63** were prepared from cyclopropanes **62** through a three-step synthesis involving (i) addition of the lithium salt of a terminal alkyne across the carbonyl group, (ii) $LiAlH_4$-promoted reduction of the triple bond to the corresponding alkene, and (iii) $BF_3{\cdot}Et_2O$- or $MeSO_3H/P_2O_5$-mediated cyclopropane to cyclobutane ring enlargement. The ring expansion of cyclobutanones **63** to cyclopentenones **64** was completed in five minutes using 17 equiv of methanesulfonic acid/phosphorus pentoxide (10:1) in diethyl ether at room temperature. The cyclopentenone **64** (R^2 = H) is a known synthetic precursor of methylenomycin B, a cyclopentanoid antibiotic produced by *Streptomyces coelicolor*.[49]



Scheme 18

Upon treatment with 15 equiv of methanesulfonic acid (neat) at room temperature for three hours, or 30 equiv of methanesulfonic acid in dichloromethane, enantiopure 2,3-dimethyl-2-vinylcyclobutanones (2*S*,3*S*)-**65** and (2*R*,3*S*)-**65** underwent acid-catalysed ring expansion into a 9:1 mixture of 2,3,4- and 2,3,5-trimethylcyclopentenones **66** and **67** in 56% yield (Scheme 19).[2b] This rearrangement led to a complete racemisation of the obtained cyclopentenones.

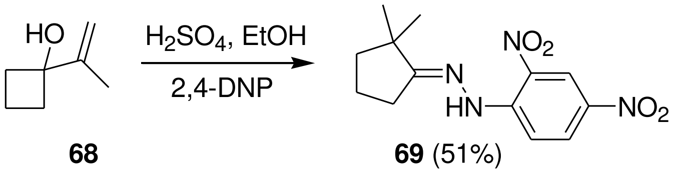


Scheme 19

2.1.3 Semipinacol rearrangement of 1-vinylcyclobutanols

As mentioned in the introduction, 1-(1-alkenyl)cyclobutanols **9** comprise suitable substrates for a semipinacol-type cyclobutylmethylcarbenium to cyclopentylcarbenium ion rearrangement.

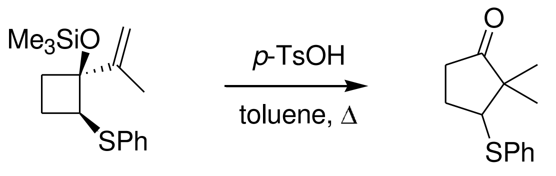
The acid-catalyzed ring expansion of 1-isopropenylcyclobutanol **68** was investigated using a variety of acids and solvents without success as no ketonic product could be detected, mostly delivering dark, tarry residues.[50] However, a solution of 1-isopropenylcyclobutanol **68** in sulfuric acid and ethanol in the presence of 2,4-dinitrophenylhydrazine (2,4-DNP) resulted in the hydrazone of 2,2-dimethylcyclopentanone **69** in 51% yield (Scheme 20).



Scheme 20

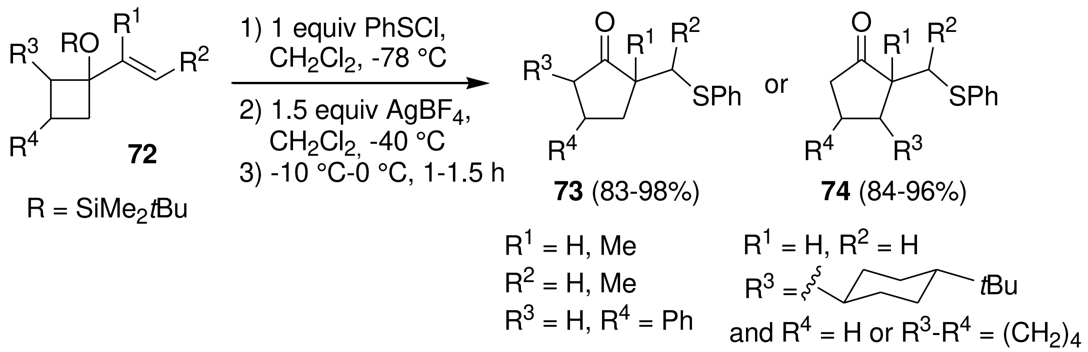
When a phenylsulfanyl group as carbanion-stabilizing sulfur substituent was introduced at the 2-position of 1-vinylcyclobutanol, different ring expansion products were obtained in the presence of acid.[51] *O*-Silylated 1-isopropenyl-2-phenylthiocyclobutanol **70** was treated with *para*-toluenesulfonic acid in toluene at reflux temperature, leading to 2,2-dimethyl-3-phenylthiocyclopentanone **71** in 62% yield (Scheme 21). The silyl ether protection of the hydroxy group was necessary because the unprotected cyclobutanol, upon treatment with potassium hydride to synthesize the corresponding potassium salts, gave 2-methyl-4-

phenylthiocyclohexanone as a mixture of *cis*- and *trans*-isomers (ratio 5:1) in 69% yield. The effect of sulfur was demonstrated by comparing 2-phenylthio-1-vinylcyclobutanol with 2-benzyl-1-vinylcyclobutanol. If both were subjected to reaction conditions which caused complete rearrangement of the first cyclobutanol, the reaction with the latter only resulted in unchanged starting material.



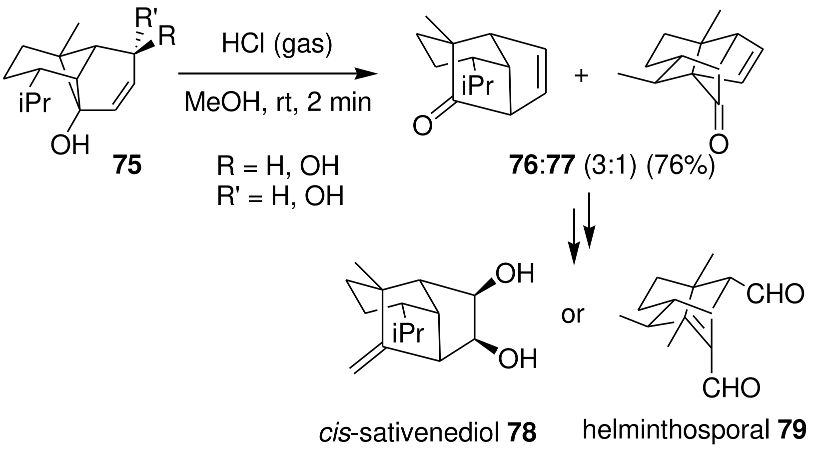
Scheme 21

In another approach, *tert*-butyldimethylsilyl ethers of 1-alkenylcyclobutanols **72** were rearranged to the corresponding ring expanded *α*-(1-phenylthioalkyl)cyclopentanones **73** or **74** in 83 to 98% or 84 to 96% yield, respectively, upon successive treatment with benzenesulfanyl chloride at -78 °C and silver tetrafluoroborate at -40 °C (Scheme 22).[52] The conversion was stated to occur via episulfonium ions. Depending on the different substituents (R^1, R^2, R^3 and R^4), 2,3,5- or 2,3,4-trisubstituted cyclopentanones were isolated as the sole reaction product. For unsymmetrical 1-alkenylcyclobutanols ($R^3 \neq$ H), the most substituted alkyl group migrated preferentially, following the expected migratory aptitudes.



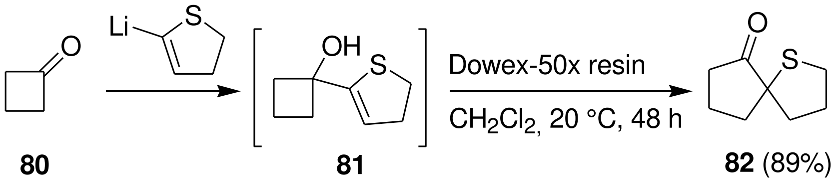
Scheme 22

In the total synthesis of (±)-*cis*-sativenediol **78** and (±)-helminthosporal **79**, one of the last steps comprised an acid-catalyzed semipinacol rearrangement of diols **75** (Scheme 23).[53] Treatment of each isomer (or the mixture) with methanolic hydrogen chloride for two minutes at room temperature afforded a 3:1 mixture of olefinic ketones **76** and **77** in 76% yield.



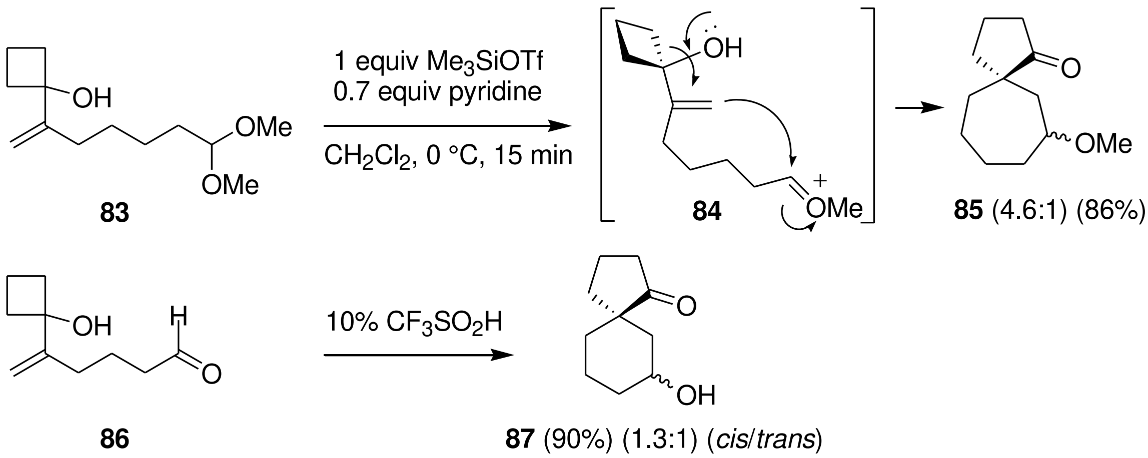
Scheme 23

A special case in the acid-catalyzed rearrangement of vinylcyclobutanols started with the reaction of cyclobutanone **80** with the 2-lithio derivative of 2,3-dihydrothiophene, reported by Paquette and co-workers.[54] The obtained product **81** was not isolated but immediately slurried with Dowex-50x resin in dichloromethane at 20 °C. After 48 hours the resin was filtered off and spiro compound **82** was obtained in 89% yield after purification by column chromatography (Scheme 24).



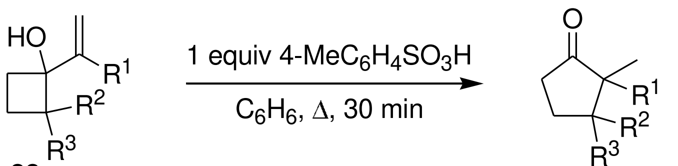
Scheme 24

The scope of the Bronsted and Lewis acid-promoted spirocyclization of 1-vinylcyclobutanols **83** with an acetal moiety acting as initiator in the cyclization reaction was demonstrated by Trost and Chen.[55] The spiroannelated products are cyclopentanones derived from ring expansion of the cyclobutanol unit from which the second ring was formed by attack of the terminator on the initiator moiety. Spirocyclization to [4.5]- and [4.6]-systems proceeded smoothly, whereas spirocyclization to a [4.7]-system failed. Examples of acids used were trimethylsilyl trifluoromethanesulfonate (TMSOTf), CF_3SO_3H, $SnCl_4$ and Ph_3CSbCl_6. When 0.7 equiv of pyridine and one equiv of trimethylsilyl triflate was added to a solution of 7,7-dimethoxy-2-(1-hydroxycyclobutyl)-1-heptene **83** in dichloromethane at 0 °C, 7-methoxyspiro[4.6]undecan-1-one **85** was isolated after 15 minutes in 86% yield (Scheme 25). Extension of this cyclization methodology to form eight-, nine- or 13-membered rings failed under the same reaction conditions. Subjecting aldehyde **86** to 10% triflic acid afforded a 1.3:1 *cis/trans* mixture of 7-hydroxyspiro[4.5]decan-1-one **87** in 90% yield.



Scheme 25

Another example of the acid-promoted ring expansion of propenylcyclobutanols comprised the synthesis of (±)-*α*-cuparenone[56] (R^1 = Me, R^2 = 4-MeC_6H_4) and cyclopentanone **89** (R^1 = Me, R^2 = 3-MeC_6H_4) as the direct precursor of (±)-herbertene.[57] Herbertanes belong to an expanding family of sesquiterpenes possessing a 3-methyl-(1,2,2-trimethylcyclopentyl)cyclohexane skeleton. In recent years, herbertanes have become popular synthetic targets as some members of this family exhibit a wide range of biological activities such as antifungal, neurotrophic and *anti*-lipid peroxidation.[58] Isopropenylcyclobutanols **88** were treated with one equiv of *p*-toluenesulfonic acid in benzene under reflux to synthesize the corresponding 2,2-dimethylcyclopentanones **89** in good to excellent yields (70-98%) (Scheme 26).[59] (±)-*α*-Cuparenone **89** was synthesized in 76% yield, and the precursor of (±)-herbertene in 70% yield. 3-(4-Methoxyphenoxymethyl)-2,2,3-trimethylcyclopentanone was synthesized in 70% yield and is a known precursor of capsorubin **90** (Figure 1), a ketocarotenoïd which, together with capsanthin, constitutes the red pigment of paprika.[60]

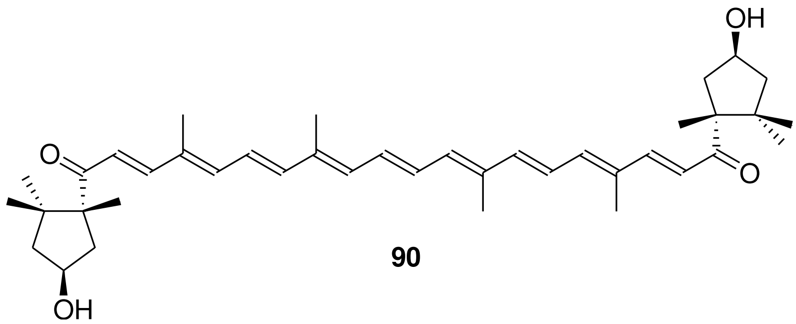


88

89 (70-98%)

R^1 = Me, $(CH_2)_4C_6H_5$; R^2 = H, Me
R^3 = $(CH_2)_2C_6H_5$, 4-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4OCH_2$, 3-$MeC_6H_4OCH_2$, $C_{10}H_{21}$

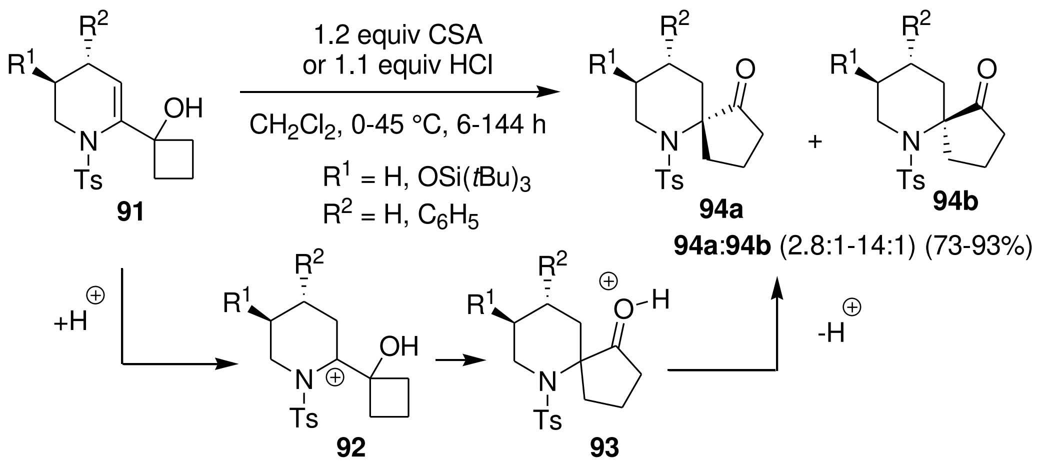
Scheme 26



90

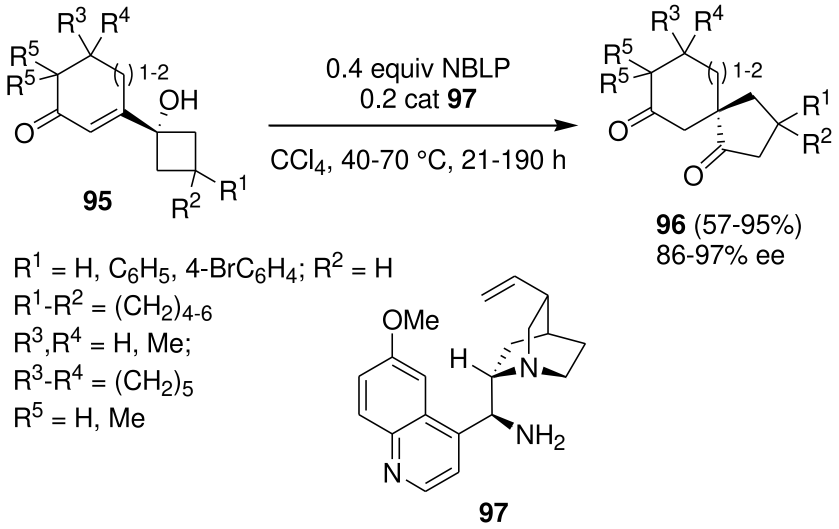
Figure 1

Recently, a semipinacol-based acid-promoted ring expansion of cyclobutanols toward functionalized 1-azaspirocyclic cyclopentanones has been reported.[61] Treatment of enamines **91** with camphor sulfonic acid (CSA) or hydrogen chloride produced the transient azacarbenium ion intermediates **92**. Migration of one of the adjacent cyclobutane carbon-carbon bonds with concomitant C=O π-bond formation furnished protonated azaspirocyclic ketones **93**, eventually giving rise to the desired azaspirocyclic ring systems **94a** and **94b** in 73-89% yield and in a diastereoselectivity of 2.8:1-14:1, which improved when the reaction was executed at lower temperatures (Scheme 27).



Scheme 27

In a final example, asymmetric spirocyclic diketones **96** have been synthesized via a semipinacol-type 1,2-carbon migration using a cinchona-based primary amine catalyst **97**.[62] Addition of a catalytic amount of *N*-Boc-*L*-phenylglycine (NBLP) and diamine **97** to cyclobutanols **95** afforded spirocyclic diketones **96** in 57-95% yield and in 86-97% enantiomeric excess (Scheme 28). The same group have also used chiral phosphoric acid catalysts in the asymmetric synthesis of spiroethers via semipinacol rearrangement through activation of a carbonyl group.[63]

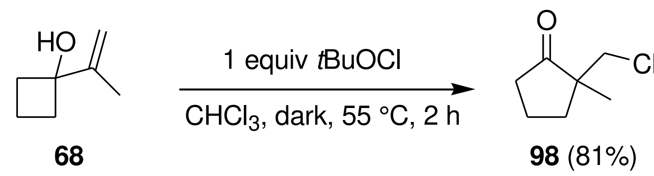


Scheme 28

2.2 *Halogen/selenium cation-promoted activation*

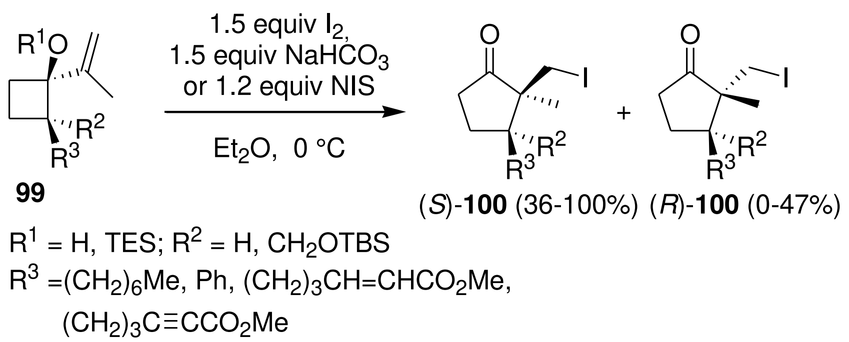
In addition to acid-catalyzed rearrangements of alkenylcyclobutanols, also halogen and selenium cation-promoted activation has been reported in the literature.

A chlorinative ring homologation of cyclobutanols with one equiv of the potentially explosive *t*-butyl hypochlorite in chloroform has been performed using isopropenylcyclobutanol **68** as starting material. This reaction provided 2-chloromethyl-2-methylcyclopentanone **98** in 81% yield (Scheme 29).[50] Another chlorinating agent, used for semipinacol type rearrangement reactions, comprised a bleach/acetic acid system which was utilized for the ring expansion of isopropenyl[2.2.1]heptanol.[64]



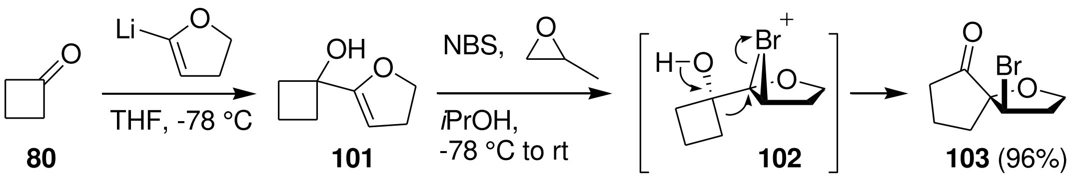
Scheme 29

The iodonium ion-mediated ring expansion of olefinic cyclobutanols **99** was examined using iodine in the presence of $NaHCO_3$ or by means of *N*-iodosuccinimide.[65] In all cases, the reaction proceeded in moderate to high yields, and the triethylsilyl ether (R^1 = TES) gave a slightly better result (59-100% yield of (*S*)-**100**, no (*R*)-**100**) than the corresponding alcohol (R^1 = H) (36-88% of (*S*)-**100** and 0-47% of (*R*)-**100**) (Scheme 30). Although no stereoselectivity was observed utilizing monosubstituted substrates (R^2 = H) giving a mixture of (*S*)-**100** and (*R*)-**100**, complete stereoselectivity was observed starting from geminally substituted substrates ($R^2 \neq$ H) to afford cyclopentanone (*S*)-**100** as the sole product.



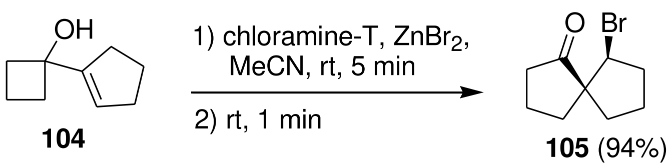
Scheme 30

In analogy with the acid-catalyzed rearrangement of vinylcyclobutanols **81** obtained via reaction of cyclobutanone **80** with the 2-litho derivative of 2,3-dihydrothiophene (Scheme 24),[54] a bromonium ion-promoted rearrangement of vinylcyclobutanol **101** has been reported.[66] Vinylcyclobutanol **101** was synthesized by addition of 5-lithio-2,3-dihydrofuran to cyclobutanone **80** in THF at -78 °C. Rearrangement of **101** was executed with *N*-bromosuccinimide (NBS) in the presence of an acid scavenger, propylene oxide, to give spirocyclic ketone **103**, exclusively, in 96 % yield through intermediate bromonium ion **102** (Scheme 31). This *N*-bromosuccinimide promoted ring expansion methodology has also been used in the formation of functionalized azaspirocyclic cyclopentanones such as compounds **94** (Scheme 27).[67]



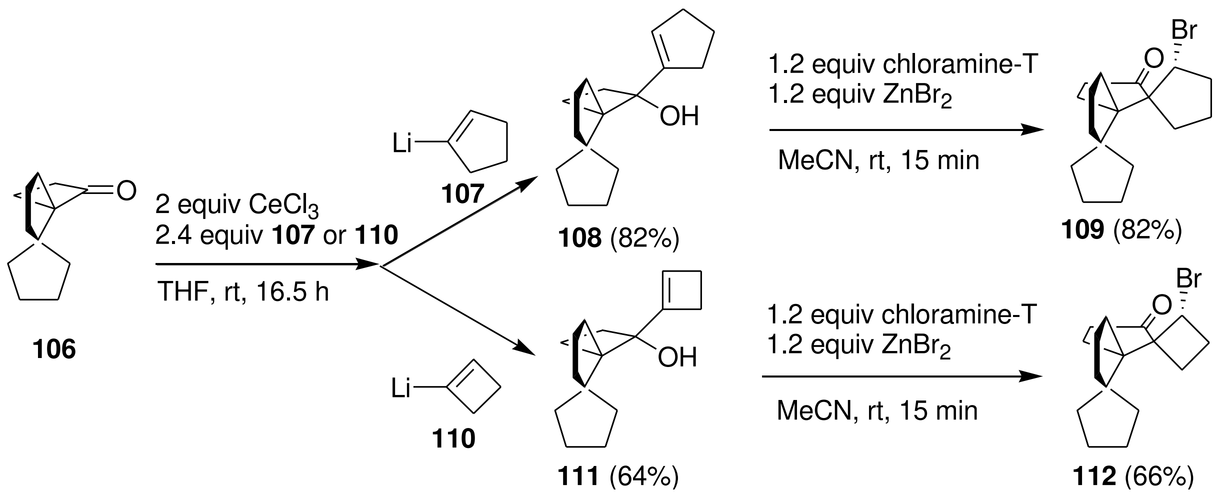
Scheme 31

Allylic alcohols were found to undergo a semipinacol type rearrangement induced by a halogen cation generated from the chloramine-T/ZnX_2 combination, which provided a highly efficient and stereoselective method for the preparation of *α*-quaternary *β*-bromoketones. It was presumed that the halogen anion in ZnX_2 was oxidized to a halogen cation by chloramine-T and existed in the form of XCl. An electrophilic addition of X^+, released from XCl, to the double bond occurred with concomitant 1,2-migration in a transition state geometry resembling that of an ordinary nucleophilic substitution proceeding with inversion of configuration. Using this methodology, 1-cyclopent-1-enylcyclobutanol **104** was converted into 6-bromospiro[4.4]nonan-1-one **105** in 94% yield in the presence of $ZnBr_2$ (Scheme 32).[68] $ZnCl_2$ and ZnI_2 were also used in the same reaction to prepare other *β*-haloketo compounds.



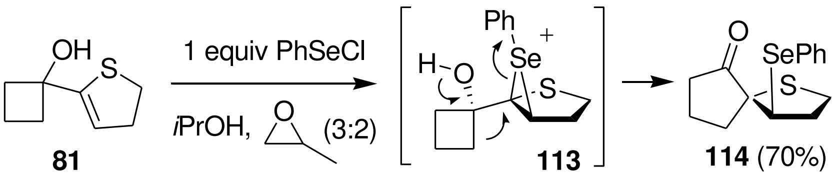
Scheme 32

Another application of this method involved the synthesis of pseudohelical hydrocarbons of four- and five-membered rings (Scheme 33).[69] Addition of 1-lithiocyclopentene **107** and 1-lithiocyclobutene **110**, respectively, to dispiroketone **106** led to allylic alcohols **108** and **111** in 82 and 64% yield, respectively, which were regio- and stereoselectively converted into cyclopentanones **109** and **112** by reaction with 1.2 equiv of chloramine-T and 1.2 equiv of $ZnBr_2$ in acetonitrile at room temperature in 82% and 66% yield, respectively.



Scheme 33

A last example of cation-promoted ring expansion of vinylcyclobutanols involved the rearrangement of selenonium ion **113**, in analogy with the bromonium ion rearrangement in Scheme 31.[54b] When vinylcyclobutanol **81** was treated with one equivalent of phenylselenenyl chloride in isopropylalcohol and propylene oxide (ratio 3:2), spirocyclic ketone **114** was synthesized in 70% yield (Scheme 34).



Scheme 34

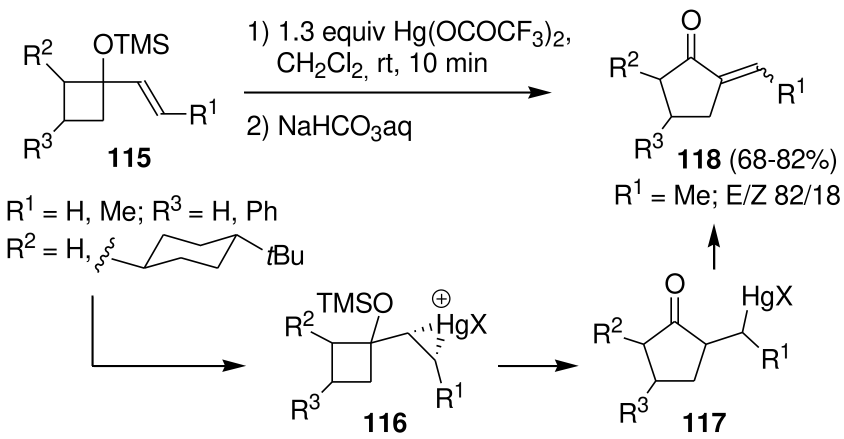
2.3 Metal-promoted activation

The electrophilic activation of an alkene by coordination to an electron-deficient metal ion toward nucleophilic attack is fundamental to organometallic chemistry, both conceptual as in synthetic applications.[70] Mercury- and palladium-promoted ring expansion reactions of alkenylcyclobutanols are well investigated reactions triggered by release of strain in four-membered ring systems.[71] These useful methodologies for the construction of five-membered ring systems have been successfully applied in the synthesis of natural products.[72] In the following section, distinction will be made between mercury-promoted, palladium-promoted ring expansion and thallium promoted reactions of cyclobutane derivatives toward five-membered ring systems.

It should be noted that the true nature of the electrophilic species resulting from metal-promoted activation of alkenes has not always been defined accurately in the papers described below. Nonetheless, the intermediacy of cyclobutylmethylcarbenium ion-type species can be assumed in order to explain the observed reactivity.

2.3.1 Mercury-promoted activation

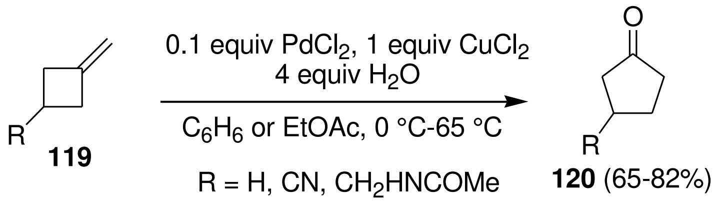
The mercury(II) ion-mediated ring expansion of 1-alkenyl-1-cyclobutanols **115** led to cyclopentanones **118** (Scheme 35),[73] which are of synthetic importance because *β*-mercurio cycloalkanones may undergo further ring expansion or carbon-carbon bond formation via free radical chain reactions[74] along with the conversion into *α*-methylene cycloalkanones or 1,4-dicarbonyl compounds.[75] Ring expansion reactions of trimethylsilyl ethers of 1-vinyl and 1-propenylcyclobutanols **115** with $Hg(OCOCF_3)_2$ in dichloromethane at room temperature gave the synthetically useful *α*-methylenecyclopentanones **118** in 68-82% yield via *π*-complex intermediates **116** after demercuration of **117** with aqueous sodium carbonate. For unsymmetrical substrates, and as expected, the most substituted alkyl group migrated preferentially.



Scheme 35

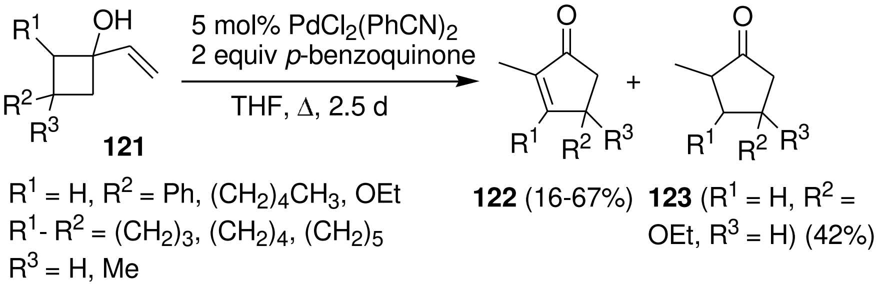
2.3.2 Palladium-promoted activation

The palladium(II)-catalysed conversion of terminal olefins into methyl ketones by $PdCl_2$-$CuCl_2$-O_2-H_2O has been known for some time and is analogous to the Wacker process.[76] A conversion of methylenecyclobutanes **119** into cyclopentanones **120** in 65 to 82% yield comprised a special case of rearrangement based on the reaction conditions of this Wacker oxidation (Scheme 36).[77]

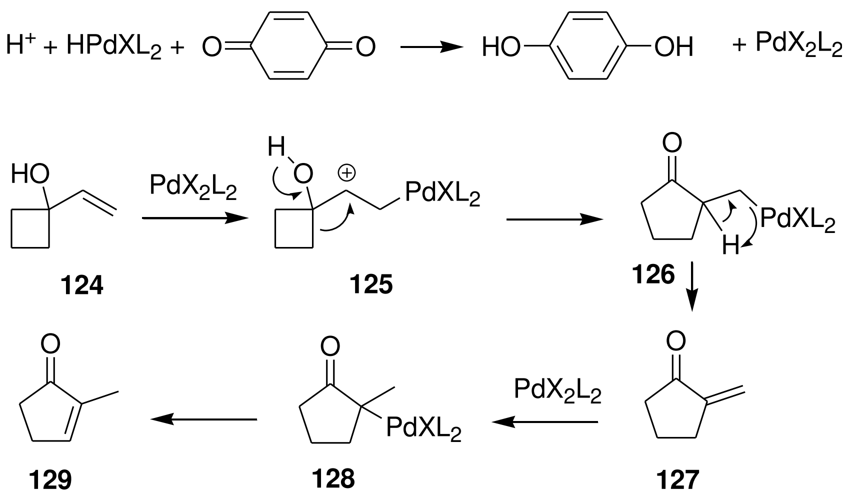


Scheme 36

The reaction of 1-vinyl-1-cyclobutanols **121** with one equivalent of bis(benzonitrile)palladium dichloride in THF quickly and smoothly gave cyclopentenones **122** in one hour at 25 °C (Scheme 37).[78] However, when two equivalents of benzoquinone were added, only a catalytic amount of palladium (5 mol%) was needed to obtain the desired cyclopentenone **122**, although reflux conditions were necessary for 2.5 days in THF. The two equivalents of added benzoquinone are responsible for the regeneration of the active catalyst. A plausible mechanistic pathway is given in Scheme 38 using intermediates **125** and **126** for the formation of cyclopentanone **127** and subsequently cyclopentenone **129** through intermediate **128**. Accordingly, several 1-vinyl-1-cyclobutanols **121** were rearranged into the corresponding 2-methyl-cyclopentenones **122** in 16-67% yield (Scheme 37) applying the optimized conditions (*vide supra*).[78] The reaction with substrate **121** (R^1 = H, R^2 = OEt, R^3 = H) produced a substantial amount of the diastereomeric 4-ethoxy-2-methylcyclopentanone **123** (42%) next to 21% of 4-ethoxy-2-methylcyclopentenone **122**, even in the presence of a ten-fold excess of benzoquinone. This reaction provided useful building blocks for prostaglandin synthesis.

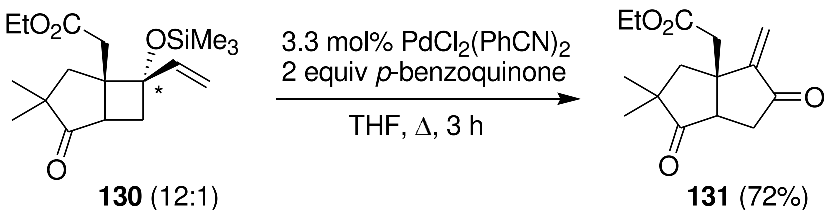


Scheme 37



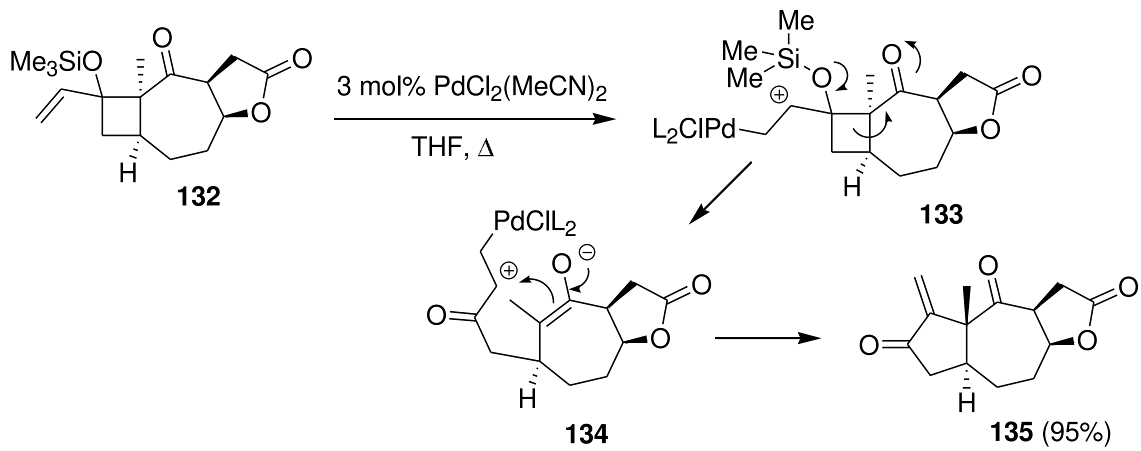
Scheme 38

The above-described method was used to synthesize the potential precursor **131** of pentalenolactone-G and -H antibiotics without the need to cleave the Me_3SiO group in **130** prior to the treatment with $PdCl_2(PhCN_2)$.[79] Treatment of ethyl 2-(3,3-dimethyl-4-oxo-7-trimethylsilyloxy-7-vinylbicyclo[3.2.0]hept-1-yl)acetate **130**, in a ratio of stereoisomers 12:1, with 3.3 mol% of bis(benzonitrile)palladium(II) chloride and two equiv of *p*-benzoquinone in THF for three hours under reflux afforded ethyl 2-(3,3-dimethyl-8-methylidene-4,7-dioxobicyclo[3.3.0]oct-1-yl)acetate **131** in 72% yield (Scheme 39).



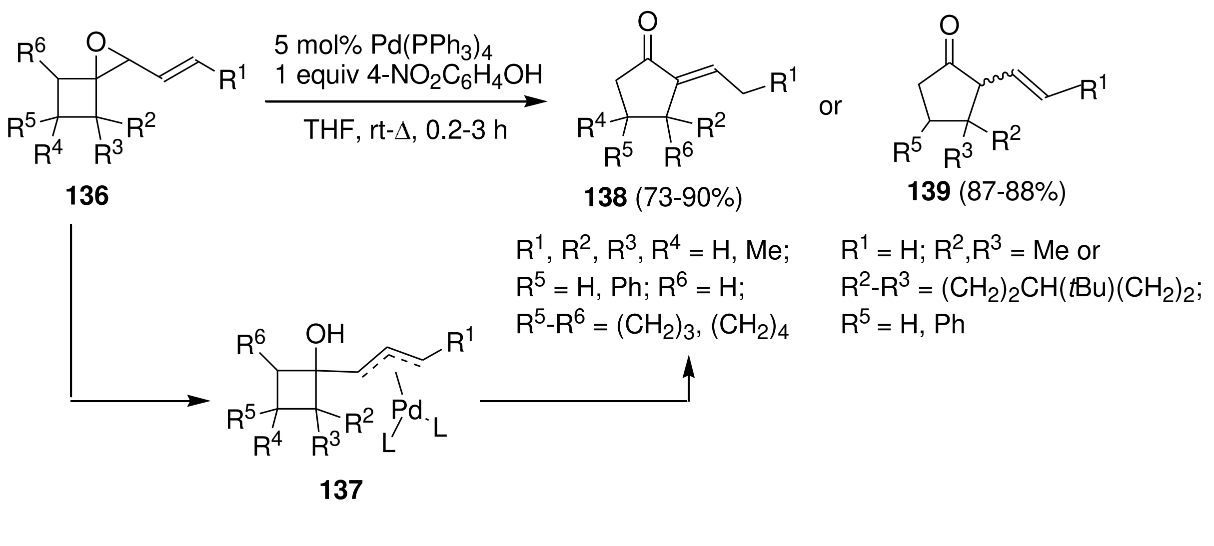
Scheme 39

A pseudoguaianolide-like structure was synthesized using a palladium-mediated ring expansion for the synthesis of the cyclopentanone ring (Scheme 40).[80] Reaction of tricyclic compound **132** with three mol% of bis(benzonitrile)palladium(II) chloride in tetrahydrofuran at reflux temperature resulted in a smooth rearrangement to provide the tricyclic *α*-methylenecyclopentanone **135** in 95% yield. The proposed mechanism involved the formation of an enolate **134** which preceded the construction of the cyclopentanone ring, although it is not clear how this process can be catalytic in palladium according to the suggested pathway. The obtained tricycle **135** was functionalized into analogues of helenalin, a typical pseudoguaianolide sesquiterpene.



Scheme 40

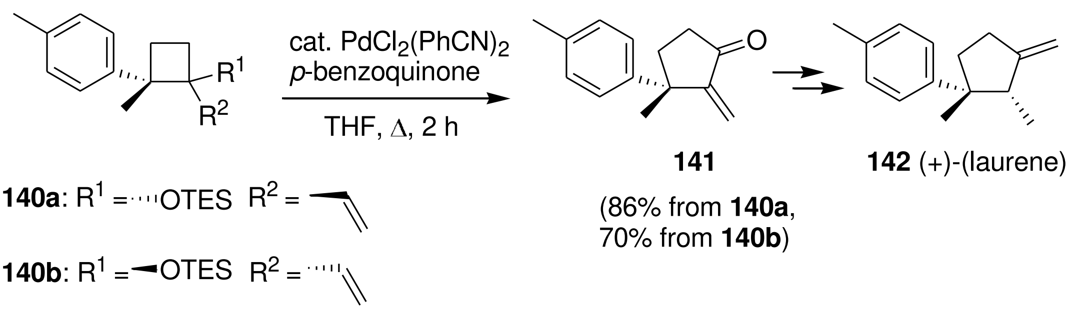
A special case involved the palladium-catalyzed ring expansion of vinyl oxaspirohexanes.[81] When vinyl oxaspirohexanes **136** were treated with five mol% of $Pd(PPh_3)_4$ in the presence of one equiv of 4-nitrophenol in tetrahydrofuran at room temperature or at reflux for one to three hours, the corresponding 2-alkylidenecyclopentanones **138** were obtained in 73-90% yield (Scheme 41). Pd(0) activated the double bond, forming a π-allyl palladium cationic complex **137**, which rearranged to the corresponding cyclopentanone. When the migrating group was a secondary alcohol, the reaction could be executed at room temperature. Furthermore, the presence of a methyl vinyl group (R^1 = Me) was expected to stabilize the π-allyl Pd-complex but, as a result, the reaction proceeded slowly and required heating for three hours. In the case of a tertiary migrating group (R^2, R^3 = Me or R^2-R^3 = -$(CH_2)_2CH(t\text{Bu})(CH_2)_2$-), the reaction was completed almost instantly (0.2 hours at room temperature) under the same reaction conditions, yielding only 2-vinylcyclopentanones **139** in 87-88% yield without migration of the double bond (Scheme 41).



Scheme 41

In the enantioselective total synthesis of (+)-laurene **142**, the five-membered ring was obtained via a palladium-mediated ring enlargement of a cyclobutane system (Scheme 42).[82]

The triethylsilyl (TES) ethers **140a** and **140b** were subjected to ring expansion in the presence of a catalytic amount of bis(acetonitrile)palladium(II) chloride and *p*-benzoquinone in tetrahydrofuran at reflux temperature for two hours to give the α-methylenecyclopentanone **141** in 86% or 70% yield, respectively, as the precursor for (+)-laurene **142**.



Scheme 42

A number of polycyclic compounds possessing a hydrindane (hexahydroindane) skeleton are found in nature[83a] and are important synthons for a variety of natural products.[83b] Several halogenated terpenes having such a ring system, for example oppositol **143**[84] and iriediol **144**,[85] have been isolated from marine sources (Figure 2).

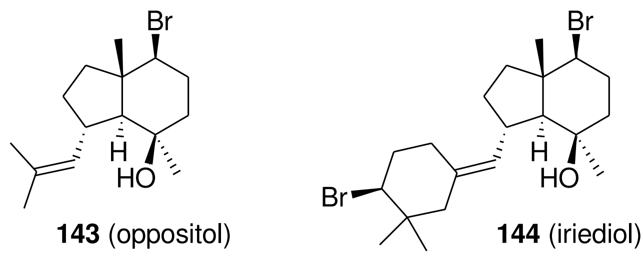
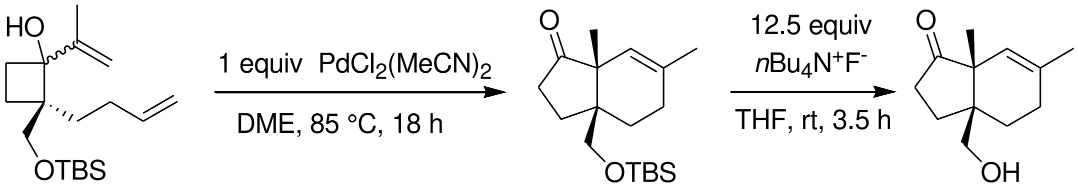


Figure 2

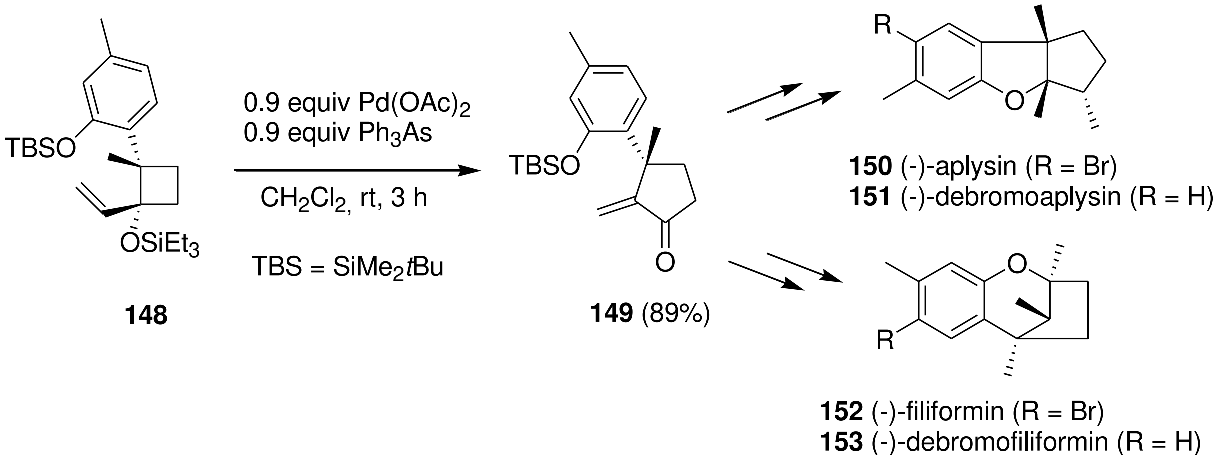
A new route to a hydrindane ring system was developed using a palladium-mediated ring expansion of alkenic cyclobutanols **145** in 1,2-dimethoxyethane (DME) to form a palladium-complex, followed by an insertion reaction and subsequent *β*-elimination to afford the hydrindan silyl ether **146** in 29% yield (Scheme 43).[71e,86] The palladium reagent, bis(acetonitrile)palladium(II) chloride, was added in one equivalent. Desilylation of the resulting silyl ether with tetra-*n*-butylammonium fluoride in THF furnished the hydrindane alcohol **147** in 72%.



145 **146** (29%) **147** (72%)

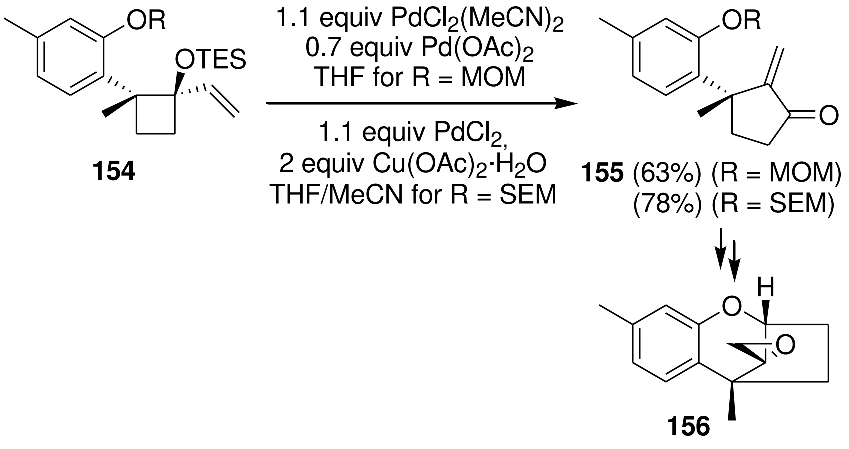
Scheme 43

The same authors described a palladium-mediated ring expansion of 1-vinylcyclobutanol **148** in the total synthesis of (-)-aplysin **150** and (-)-debromoaplysin **151**.[72a] The first natural product is a halogenated sesquiterpene, isolated from the sea hare, *Aplysia kurodai*. (-)-Aplysin displays antifeedant properties that helps to protect the mollusk from raptorial advances. The co-occurrence of (-)-debromoaplysin, the unhalogenated form, suggests that this might function as an antioxidant and scavenger of reactive halogens. The silyl ether **148** was subjected to 1.1 equivalents of bis(acetonitrile)palladium(II) chloride in THF at reflux temperature for two hours to give the unsaturated cyclopentanone **149** in 59% yield. However, the ring expansion reaction was more effective when 0.9 equivalents of palladium(II) acetate and 0.9 equivalents of triphenylarsine were used in dichloromethane at room temperature for three hours (Scheme 44), resulting in *α*-methylidenecyclopentanone **149** in 89% yield. This compound **149** was also used as a precursor for the synthesis[87] of (-)-filiformin **152** and its debromo analogue, (-)-debromofiliformin **153**, which are known marine sesquiterpenes.[88]



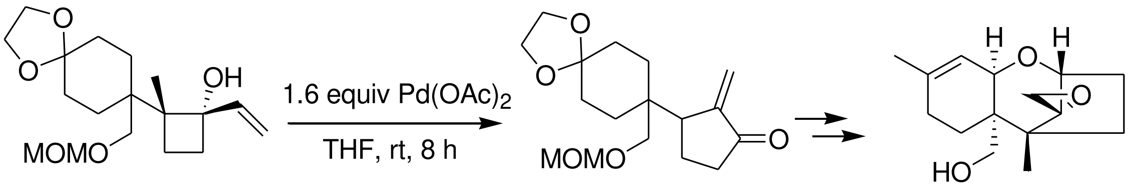
Scheme 44

The Nemoto group[89] developed an efficient synthesis of A-ring aromatic trichotecanes **156** since such compounds have been shown to possess significant *in vivo* antileukemic activity.[90] In this approach, triethylsilyl ethers of 1-vinylcyclobutanols **154** were subjected to a palladium-mediated ring expansion, and it was found that the reaction proceeded regioselectively to give 1-methylidenecyclopentanones **155** as the sole products in 63% for the methoxymethyl (MOM)-ether and 78% for the trimethylsilylethoxymethyl (SEM)-ether (Scheme 45). Cyclopentanones **155** were subsequently used as substrates for the synthesis of trichotecanes **156**.



Scheme 45

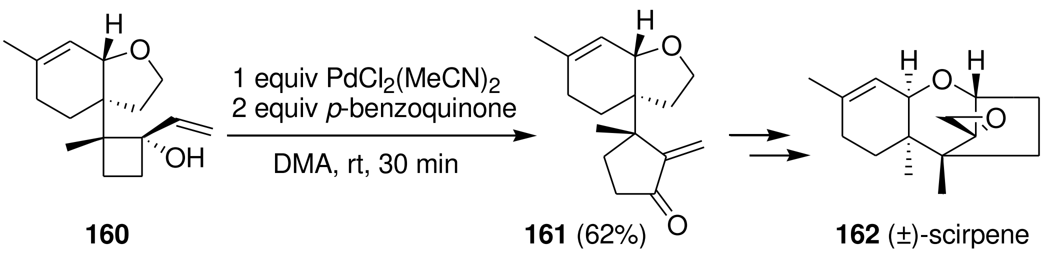
In addition, a new route to racemic 4-deoxyverrucarol **159** via a palladium-mediated ring expansion has been developed.[72d] This rearrangement of 1-vinylcyclobutanol **157** to the corresponding *α*-methylidenecyclopentanone **158** was executed in 90% yield by means of 1.6 equiv of $Pd(OAc)_2$ in tetrahydrofuran at room temperature for eight hours (Scheme 46). The asymmetric synthesis of 4-deoxyverrucarol **159** was carried out in 2000 by the same group.[91]



157 **158** (90%) **159**

Scheme 46

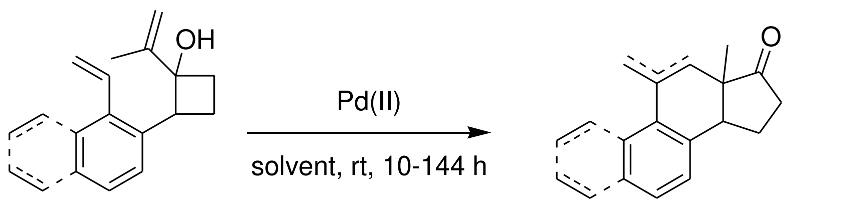
As an extension of the study of trichothecanes, Nemoto and Ihara reported the synthesis of racemic (±)-scirpene **162** through a palladium-mediated ring expansion of vinylcyclobutanols **160** as the key step to prepare the precursor **161** (Scheme 47).[92] The desired rearrangement was performed using one equivalent of $Pd(Cl_2)(MeCN)_2$ in the presence of *p*-benzoquinone as an oxidizing agent in *N*,*N*-dimethylacetamide (DMA) as solvent. The *α*-methylidenecyclopentanone **161** was obtained in 62% yield.



160 **161** (62%) **162** (±)-scirpene

Scheme 47

A cyclic cascade carbopalladation has been reported using previously described methods to synthesize benzo- and naphthohydrindans in a stereoselective manner.[71g] These hydrindans could be potential intermediates for the synthesis of A-*nor* steroids and C_{11}-β-substituted estradiols. Different palladium reagents such as $PdCl_2(MeCN)_2$, $Pd(OAc)_2(AsPh_3)_2$, $Pd(OAc)_2(PPh_3)_2$, $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ were tested in different solvents at room temperature for 10-144 hours, providing useful entries into A-*nor* steroids **164** or equilenin type steroids **165** through ring expansion of the cyclobutanol ring system in **163** (Scheme 48). This strategy was used in the synthesis of (+)-equilenin with 60% yield for the ring expansion of isopropenylcyclobutanol.[72c,93]

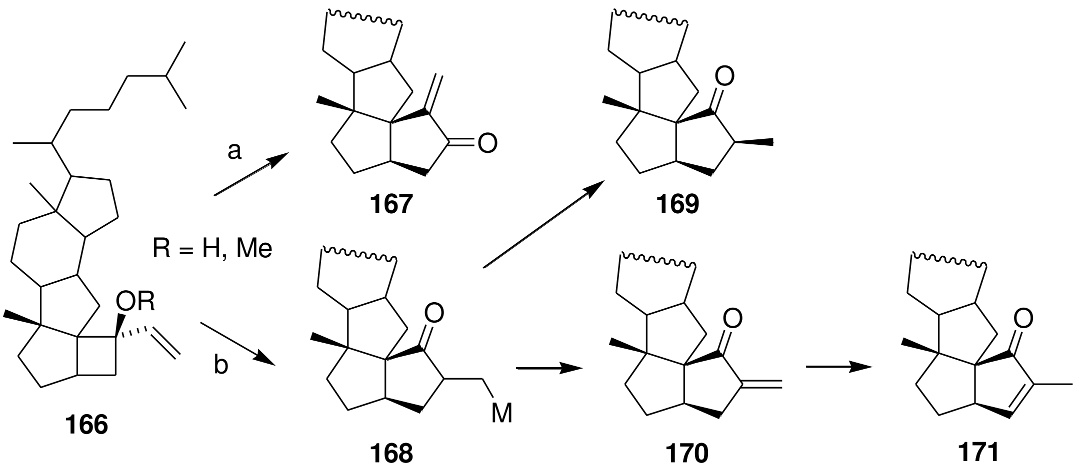


163

benzo-derivatives **164** (15-53%)
naphtho-derivatives **165** (46-81%)

Scheme 48

Nonlinear triquinane type building blocks were synthesized by means of metal-controlled skeletal rearrangements, type Wagner-Meerwein migration.[94] Several metal reagents have been evaluated for the rearrangement of pentacyclic vinylcyclobutane **166**. The thallium(III) and mercury(II) salts, being strong, soft electrophiles, favor migration of the more substituted carbon (path a), suggesting an electronically controlled process. By contrast, Pd(II), a transition metal, clearly favors path b (Scheme 49). When 1.03 equiv of thallium(III) nitrate trihydrate was used, α-methylidenecyclopentanone **167** was obtained in 76% yield next to **170** in 12% yield. Changing the reagent to 0.94 equiv of mercury(II) nitrate monohydrate afforded a lower yield of **167** (52%) besides 13% of **170** and 23% of **168**. When a stoichiometric reaction of vinylcyclobutanol **166** with palladium(II) nitrate was executed, 54% of cyclopentenone **171**, 36% of **167** and 2% of **170** and 2% of **169** were obtained. On the other hand, a catalytic reaction of **166** with five mol% of palladium(II) nitrate in the presence of three equiv of copper(II) nitrate afforded 60% of **171** and only 13% of **167**, next to 3% of **170** and **169**. The last reagent that was evaluated was bis(benzonitrile)palladium(II) chloride. If eight mol% of this reagent was added in the presence of two equiv of *p*-benzoquinone, 72% of *α*-methylidenecyclopentanone **169** was obtained, next to 12% of **167**, 11% of **171** and 2% of **170**.

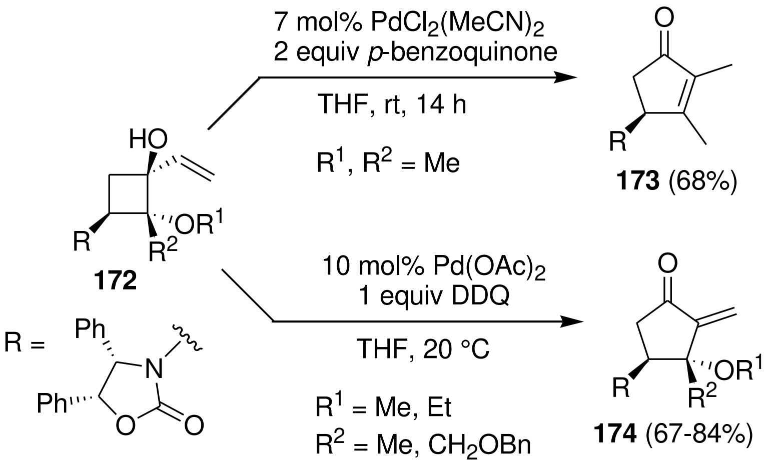


catalyst: $Tl(NO_3)_3{\cdot}3H_2O$, $Pd(NO_3)_2$, $Hg(NO_3)_2{\cdot}H_2O$, $PdCl_2(PhCN)_2$, $Cu(NO_3)_2$
M = metal complex

Scheme 49

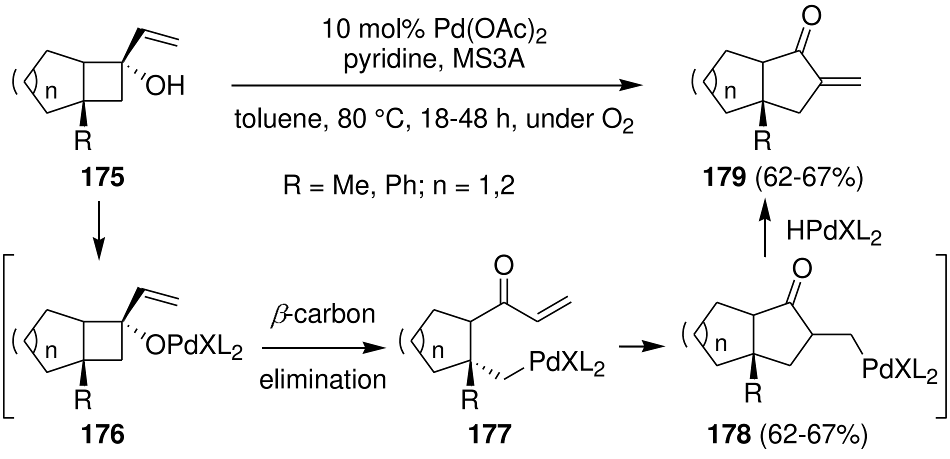
In addition to the previous studies, the first ring expansion of *α*-heteroatom-substituted 1-vinylcyclobutanols was examined.[95] When seven mol% of bis(acetonitrile)palladium(II) chloride and two equivalents of *p*-benzoquinone in tetrahydrofuran were added to *α*-alkoxy-1-vinyl-1-cyclobutanol **172**, 68% of cyclopentenone **173** was obtained and no *α*-methylidenecyclopentanone **174** was recovered (Scheme 50).[79] Changing the catalyst from palladium(II) chloride to palladium(II) acetate allowed the isolation of *α*-

methylidenecyclopentanones **174**. With one equiv of 2,3-dichloro-5,6-dicyanoquinone (DDQ) as a reoxidizing agent and tetrahydrofuran as the solvent only ten mol% of palladium(II) acetate was required to produce *α*-methylidenecyclopentanones **174** in 67 to 84% yield.



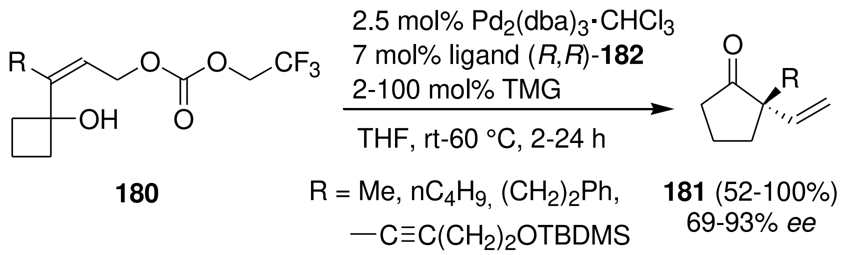
Scheme 50

A special case has been reported by Uemura *et al.*[96] The authors described the ring expansion of vinylcyclobutanols in which the less substituted carbon atom performed the ring rearrangement instead of the more substituted one. Bicyclic cyclobutanols **175** having an angular substituent, which blocks *β*-hydrogen elimination, were reacted with 10 mol% of $Pd(OAc)_2$ in the presence of pyridine and molecular sieves in toluene at 80 °C under O_2-atmosphere for 18-48 hours to afford the corresponding cyclopentanones **179** in 62-67% yield (Scheme 51). The results showed that an alkylpalladium intermediate **177**, which is formed by *β*-carbon elimination from a palladium alcoholate **176**, underwent cyclization in the 5-*exo* mode to an intermediate **178**, followed by *β*-hydrogen elimination to give an *α*-methylidenecyclopentanone **179**. In this case, no initial palladium-assisted activation of the olefinic moiety took place.

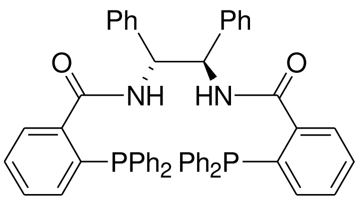


Scheme 51

A last ring expansion of vinylcyclobutanols using a palladium catalyst has been reported by the Trost group.[97] Exposing vinylcyclobutanols **180** to 2.5 mol% of a Pd(0) catalyst, i.e. $Pd_2(dba)_3{\cdot}CHCl_3$, in the presence of seven mol% of Trost ligand (*R*,*R*)-**182** (Figure 3) and two to 100 mol% of tetramethylguanidine (TMG) as a base led to smooth ring expansion affording α-vinylcyclopentanones **181** in 52% to quantitative yield and 69-93% *ee* (Scheme 52). When the amount of TMG was increased from two to 100 mol%, the *ee* increased from 77 to 89% but at the expense of conversion from quantitative yields down to 52% yield.



Scheme 52



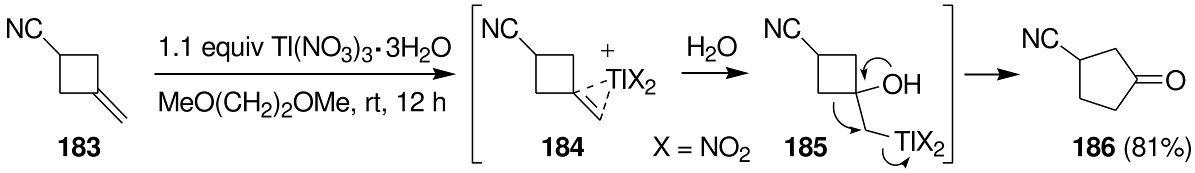
(*R*,*R*)-ligand **182**

Figure 3

2.3.3 Thallium-promoted activation

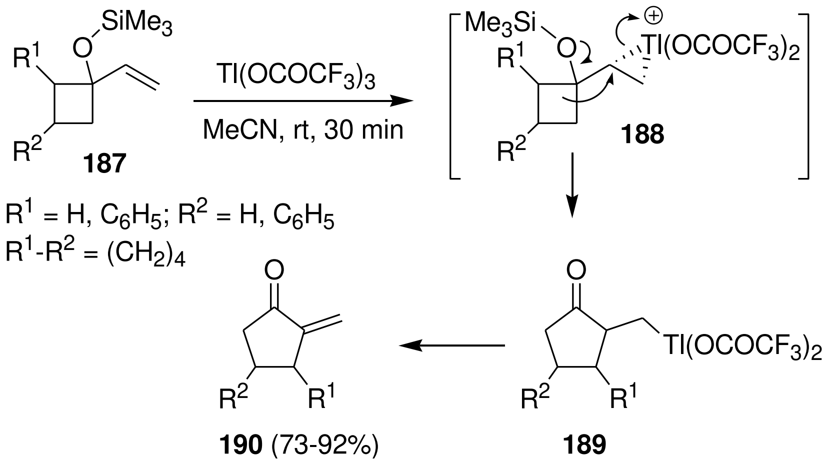
Oxythallation of alkenes with thallium(III) reagents, a reaction which closely resembles the well-known oxymercuration, is a unique method for the preparation of organothallium compounds which are produced in high regio- and stereoselectivity. Also, because the thallium moiety undergoes facile substitution by various functional groups, useful intermediates for further elaboration could be obtained.[98]

Ring expansion of 3-methylenecyclobutanecarbonitrile **183** has been executed via a thallic oxidation.[99] Treatment of methylenecyclobutane **183** with 1.1 equiv of thallium(III) nitrate trihydrate in 1,2-dimethoxyethane at room temperature for 12 hours afforded 3-cyanocyclopentanone **186** in 81% yield (Scheme 53). The mechanism involved initial formation of a cyclic thallonium ion **184**, followed by *trans* attack of water to give an intermediate **185** in which the thallium can function as a leaving group.[100]



Scheme 53

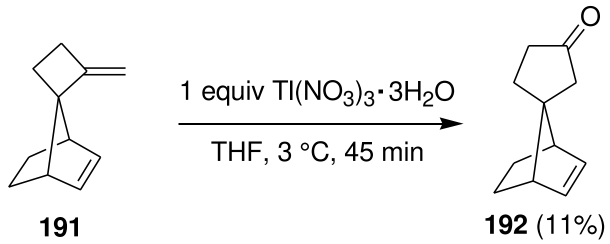
Alternatively, thallium ion-mediated ring expansions of 1-alkenyl-1-cyclobutanols **187** were envisioned using cationic species (*i.e.* $Tl(CF_3COO)_2^+$), generated from thallium(III) trifluoroacetate.[101] When trimethylsilylated cyclobutanols **187** were treated with $Tl(OCOCF_3)_3$ in acetonitrile at room temperature for 30 minutes, an electrophilic attack across the carbon-carbon double bond generated thallium intermediates **188**, which subsequently rearranged to the ring-expanded cyclic ketones **190** containing an α-methylene substituent. The hydroxy group of cyclobutanols **187** was trimethylsilylated because these ring expansions afforded better yields in comparison with the use of the corresponding alcohols.



Scheme 54

The thallic oxidation with $Tl(NO_3)_3$ has been used to rearrange diene **191** to the corresponding *syn*-3'-spirocyclopentanone **192**.[102] Treatment of 2'-*syn*-methylenespiro[bicyclo[2.2.1]heptene-7,1'-cyclobutanyl] **191** with one equiv of thallium(III) nitrate trihydrate in tetrahydrofuran at 3 °C for 45 min afforded *syn*-3'-spirocyclopentanone

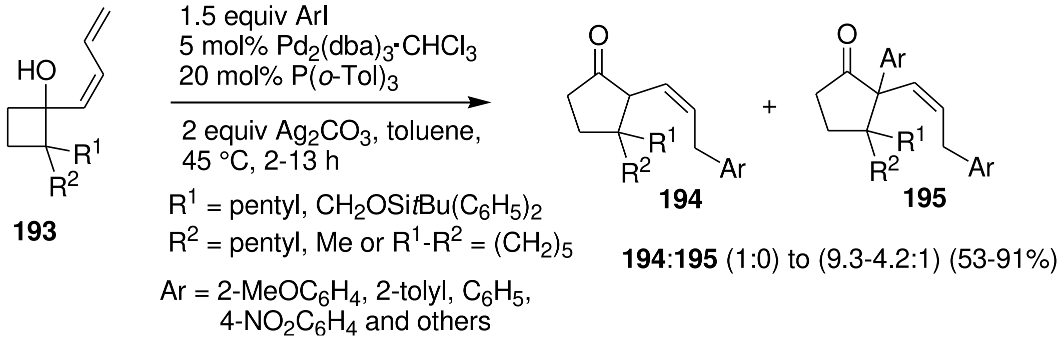
192 in a very low yield of 11% (Scheme 55). No explanation for this low yield was provided by the authors.



Scheme 55

2.4 Conjugated double bond (1,3-dienyl group) activation

Palladium-catalyzed ring expansion reactions of (*Z*)-1-(1,3-butadienyl)cyclobutanols with aryl iodides have been reported as a novel cascade ring rearrangement process.[103] The reaction proceeds in a stereospecific manner to produce (*Z*)-2-(3-aryl-1-propenyl)cyclopentanones. Treatment of 1,3-dienylcyclobutanols **193** with 1.5 equiv of an iodo arene in the presence of five mol% of $Pd_2(dba)_3$, 20 mol% of P(*o*-Tol)$_3$ and two equiv of Ag_2CO_3 in toluene for 2-13 hours at 45 °C afforded a mixture of cyclopentanones **194** and **195** in 53 to 91% yield and in a product ratio of 9.3-4.2:1, or **194** as the only formed product (Scheme 56).



Scheme 56

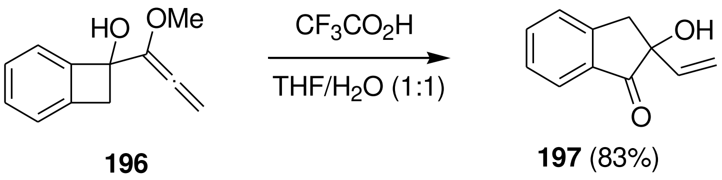
3 Ring expansion of cyclobutylmethylcarbenium ions through activation of an allene

Allenylcyclobutanols are versatile initiators for the synthesis of cyclopentanones. Two types of ring expansion reactions are described, one by means of acid activation and one by means of metal-promoted ring rearrangement. Palladium and ruthenium catalysts are used very frequently for the synthesis of a five-membered carbon skeleton.

3.1 Acid-promoted activation

In contrast to metal-promoted activation, very few examples are known regarding the acid-mediated activation of allenylcyclobutanols.

Allenylcyclobutanol **196**, synthesized by addition of 1-lithio-1-methoxyallene across benzocyclobutanone, on treatment with trifluoroacetic acid in a 1:1 tetrahydrofuran/water mixture underwent a hydrolysis-ring expansion providing 2-hydroxy-2-vinylindan-1-one **197** in 83% yield (Scheme 57).[104]



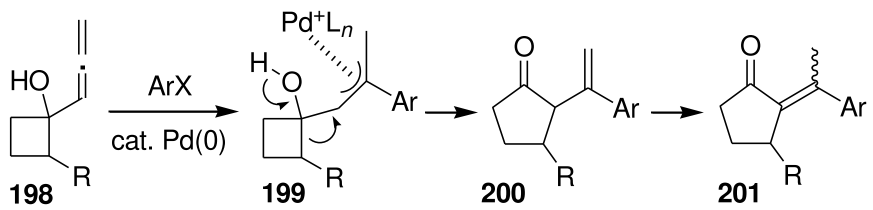
Scheme 57

3.2 Metal-promoted activation

3.2.1 Palladium-promoted activation

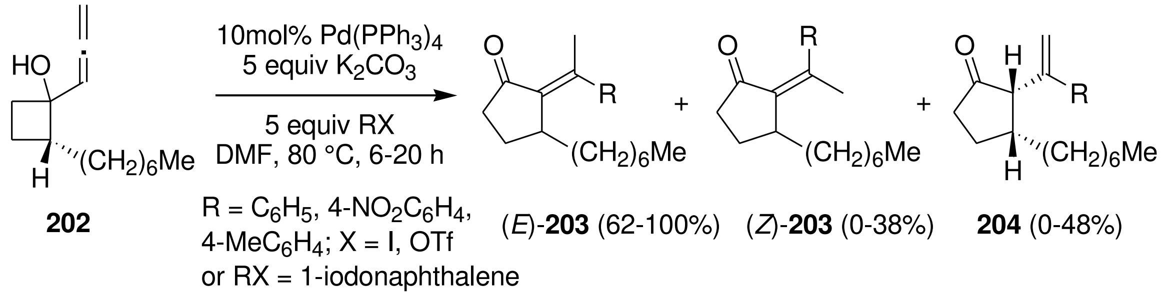
Carbopalladation has emerged as an important method for the preparation of a wide range of molecular frames. Both intermolecular[105] and intramolecular[106] carbopalladation of allenes comprise attractive approaches in that respect. Palladium-promoted ring expansion reactions of allenylcyclobutanols are well investigated reactions triggered by release of the strain of the four-membered ring systems.[107] A possible general mechanism is given in Scheme 58.[107c]

This reaction enables the formation of a carbon-carbon bond along with the expansion of the four-membered ring system via π-allylpalladium intermediates **199** in a one-pot process, and thereby constitutes a potentially useful synthetic method for the efficient preparation of natural products.



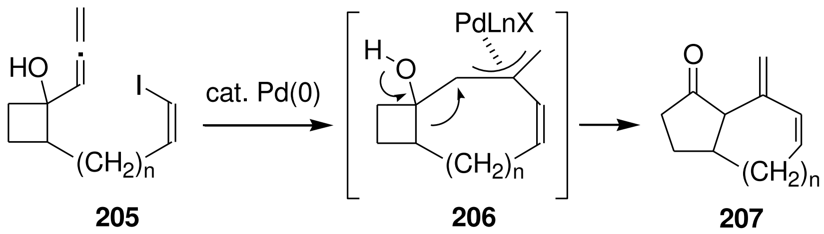
Scheme 58

Applying this methodology, Fukumoto *et al.* reported an intermolecular version of a carbopalladation reaction and subsequent ring expansion of allenylcyclobutanols **202** giving rise to the direct formation of substituted cyclopentanones, both the conjugated form **203** (62-100% *E*, 0-38% *Z*) and the less stable unconjugated form **204** (0-48%) depending on the *β*-substituent and the reaction conditions (Scheme 59).[107a]



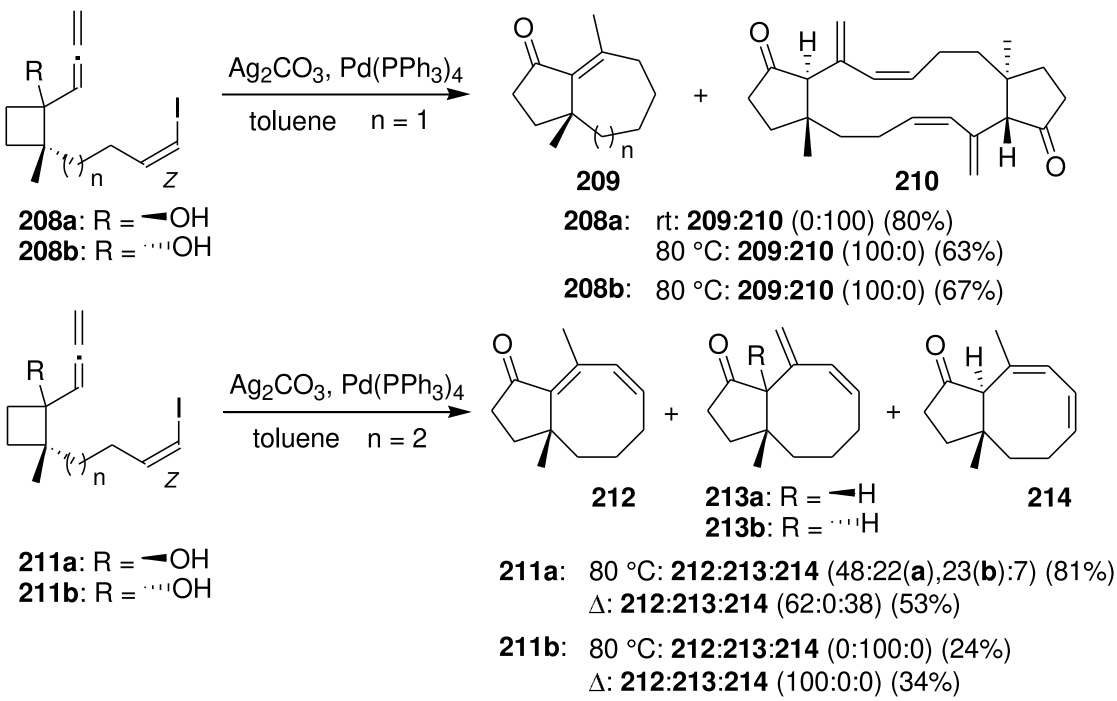
Scheme 59

The same authors also described a novel type of intramolecular palladium-catalyzed cascade reaction for the synthesis of bicyclo[5.3.0] and bicyclo[6.3.0] frameworks.[107a] The ring transformation of π-allylpalladium **206**, *in situ* generated by intramolecular carbopalladation of **205**, was accompanied by strain release of the cyclobutane ring to give directly the fused bicyclo[n + 3.3.0] ring system **207** (Scheme 60).



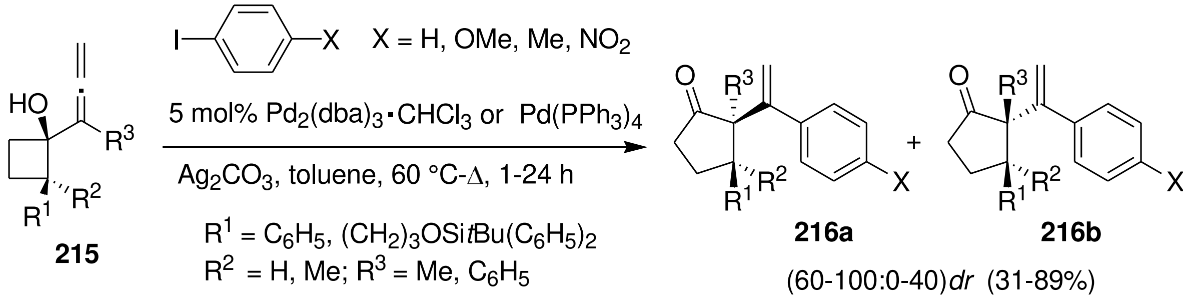
Scheme 60

This intramolecular carbopalladation reaction was executed on two substrates in which the allene and vinyl iodide units were tethered by four- and five-carbon chains (Scheme 61).[107a] The cascade reaction starting from **201** or **204** enabled the synthesis of bicyclo[5.3.0]decenone **202** in 67% yield, tricyclic compound **203** in 80% yield, 2,8-dimethylbicyclo[6.3.0]undeca-1,3-diene-11-one **205** in 34% yield or 2-methylidene-1,8-dimethylbicyclo[6.3.0]undeca-3-ene-11-one **206** in 24% yield, depending on the chosen starting isomer and the selected reaction temperature.



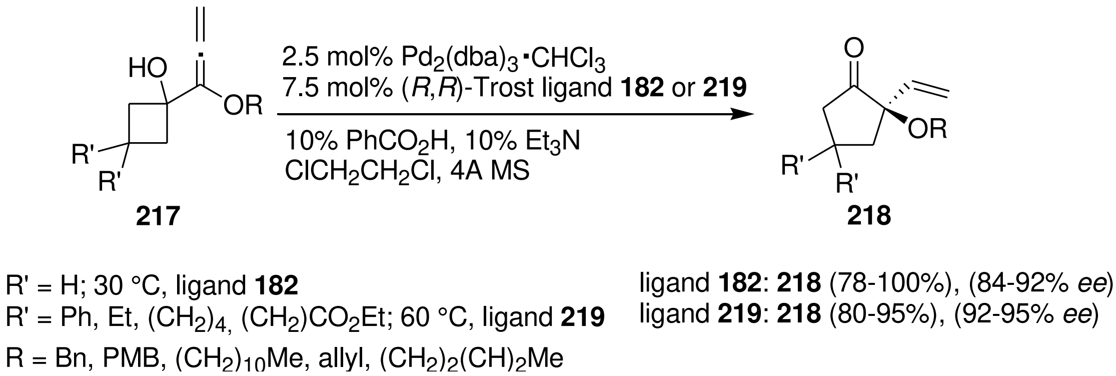
Scheme 61

A major restriction of the above-described method involved double bond isomerization to give more stable *α*,*β*-unsaturated cyclopentenones. A stereoselective synthesis of *α*-substituted cyclopentanones **216** with quaternary carbon stereocentres has been reported by Ihara and co-workers by introducing a substituent at the allenyl moiety to suppress the isomerization of the products.[107b,c] The stereochemistry of the reaction was controlled by the conformation of the *π*-allylpalladium complex during the ring expansion reaction. By choosing the reaction conditions, *e.g.* time and temperature, the rearrangement of cyclobutanol **215** proceeded in a stereospecific manner to give compounds **216** bearing a quaternary carbon stereocentre with high diastereoselectivity in 31 to 89% yield (Scheme 62).

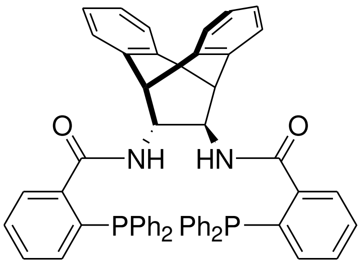


Scheme 62

The asymmetric Wagner-Meerwein shift of allenylcyclobutanols **217**, catalyzed by palladium, provided a general way to synthesize cyclopentanones **218** with an *α*-chiral *O*-tertiary centre using Trost ligands for the palladium catalyst.[108] The combination of benzoic acid and triethylamine gave the fastest reaction and was the key to good reactivity and selectivity. For unsubstituted cyclobutanols **217** (R' = H), the highest reactivity was obtained at 30 °C with ligand **182** (Figure 3) to obtain cyclopentanones **218** (78-100% yield, 84-92% *ee*), from which one derivative was used to determine the absolute configuration by transforming it into *trans*-kumausyne or bisabolangelone (Scheme 63).[109] 3,3-Disubstituted cyclobutanols **217** (R' ≠ H) were converted into cyclopentanones **218** in high yield (80-95%) at 60 °C with ligand **219** (Figure 4) in an enantiomeric excess of 92-95% (Scheme 63).



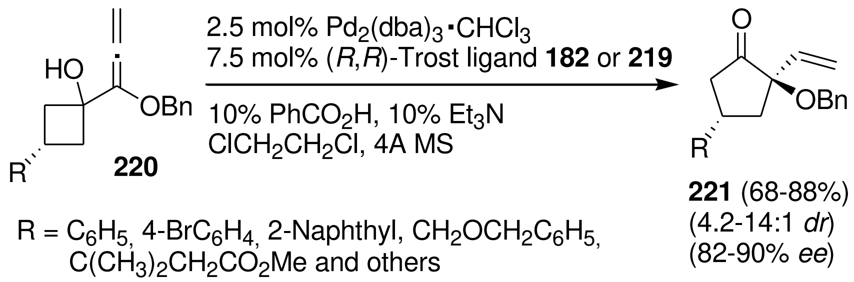
Scheme 63



(*R*,*R*)-ligand **219**

Figure 4

The above-described palladium-catalyzed method was applied to 3-monosubstituted allenylcyclobutanols **220** as substrates (Scheme 64).[110] Because the diastereomeric mixtures resulting from the allene additions to cyclobutanone were not completely separable, the ring expansion was conducted with the enriched diastereomeric mixture of allenylcyclobutanols, obtained after chromatography on silica gel. The corresponding cyclopentanones **221** were obtained in 68-88% yield with a *dr* of 4.2-14:1 and an enantiomeric excess of 82-90%.

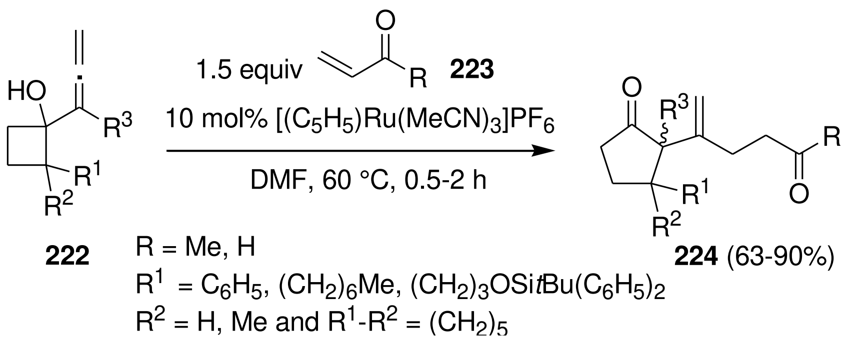


Scheme 64

3.2.2 Ruthenium- or gold-promoted activation

In contrast to palladium-promoted ring expansion reactions, only few examples are known concerning ring expansion reactions of cyclobutanols using other transition metals.

Ihara *et al.* reported a ruthenium-catalyzed ring expansion of 1-allenylcyclobutanols **222** with α,β-unsaturated carbonyl compounds **223** under conditions similar to those described by Trost *et al.* for cycloetherifications.[111] The reaction mechanism postulated the formation of a π-allylruthenium intermediate followed by nucleophilic attack of the internal hydroxy group. This reaction enabled the one-pot synthesis of α-substituted cyclopentanones **224** using $[CpRu(MeCN)_3]PF_6$ as a catalyst.[112] If cerium(III) chloride was added to the reaction mixture, according to the method of Trost and Pinkerton,[111b] bicyclic hemiacetals were formed as side products. Without the cerium additive, the allenylcyclobutanols **222** were exclusively transformed to cyclopentanones **224** in 63 to 90% yield with dimethylformamide as the best suitable solvent (Scheme 65).

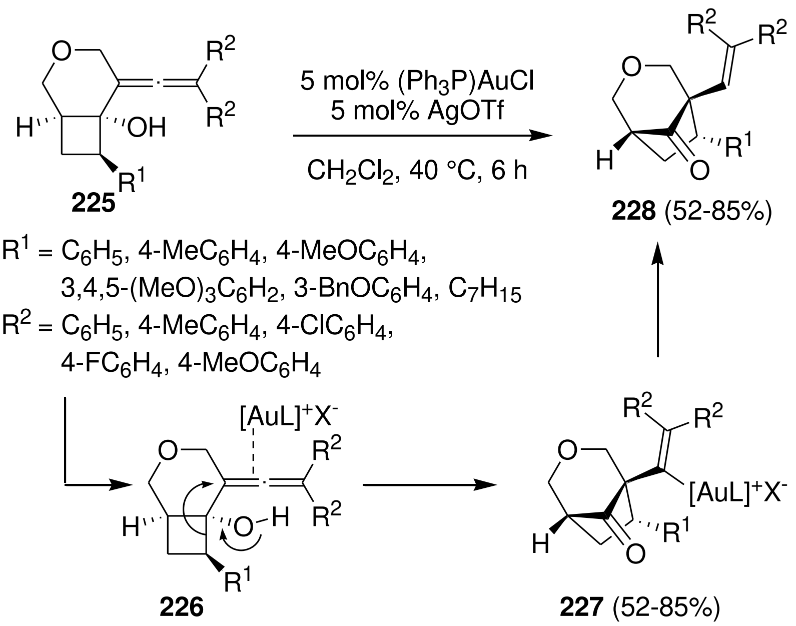


Scheme 65

It should be noted that a rhodium(I)-catalyzed rearrangement of allenylcyclobutanols has been reported by Cramer and co-workers as well.[113] In contrast to ruthenium- and palladium-catalyzed ring expansions of allenylcyclobutanols, the final products obtained were cyclohexenones instead of cyclopentanones.

Recently, a gold(I)-catalyzed intramolecular rearrangement of allenylcyclobutanols has been reported.[114] Treatment of allenylcyclobutanols **225** with 5 mol% of $(Ph_3P)AuCl$ and 5 mol%

of AgOTf in dichloromethane at 40 °C furnished 1-vinyl-3-oxabicyclo[3.2.1]octan-8-ones **228** in 52-85% yield as single stereoisomers (Scheme 66). Coordination of the cationic gold(I)catalyst to the internal double bond of the allene moiety in **226** triggered a ring expansion through a Wagner-Meerwein shift,[110] and produced vinyl gold intermediates **227**. A subsequent protodemetalation liberated the catalyst and released the bridged compounds **228**.



Scheme 66

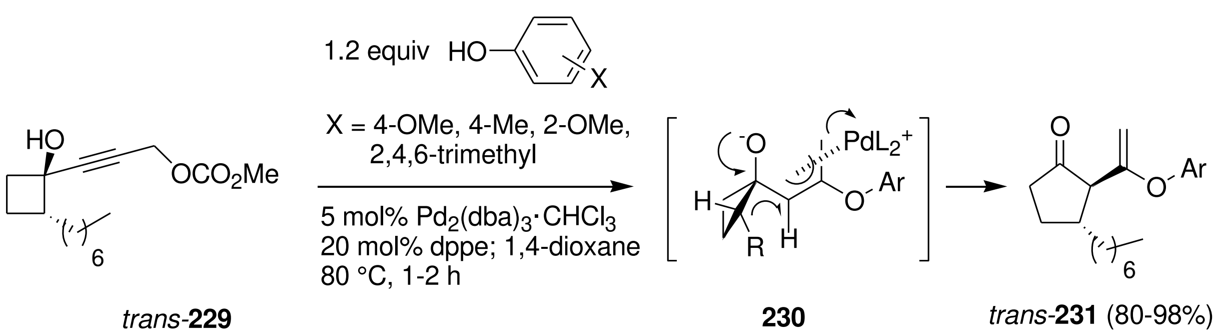
4 Ring expansion of cyclobutylmethylcarbenium ions through activation of an alkynyl substituent

Metal-promoted ring expansion reactions of alkynylcyclobutanols comprise well investigated reactions triggered by release of the strain of the four-membered ring systems.[115] Three different metals can be used for synthesis of the corresponding cyclopentanones by means of a semipinacol rearrangement, *i.e.* palladium, ruthenium or gold.

4.1 Palladium-promoted activation

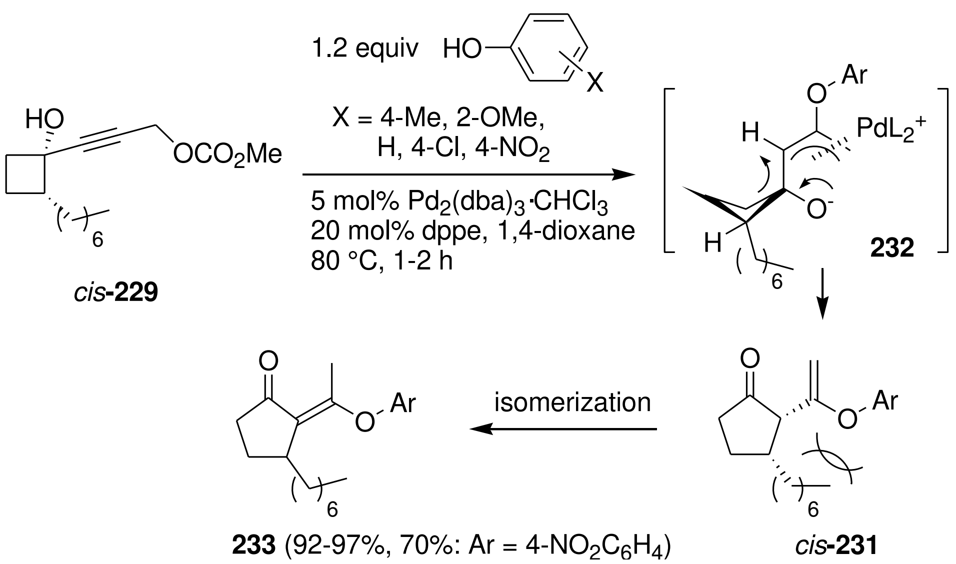
Propargylic compounds exhibit versatile reactivity in the presence of palladium complexes, affording a variety of applications in the field of palladium-catalysed reactions.[116] This approach has been used for the conversion of alkynylcyclobutanols to the corresponding cyclopentanones. The key step in these reactions is the formation of a π-propargyl/allenylpalladium complex by facile elimination of a leaving group, which furthermore reacts with other compounds such as soft nucleophiles to lead to a variety of substituted products.[117]

A novel type of palladium-catalyzed cascade ring expansion reaction of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols with phenols has been reported in that respect.[118] This reaction generated a carbon-oxygen bond to afford cyclopentanones in a one-pot process. When *trans*-cyclobutanols **229** were reacted with 1.2 equivalents of different substituted phenols, *trans*-cyclopentanones **231** were obtained in 80 to 98% yield (Scheme 67).[118a]



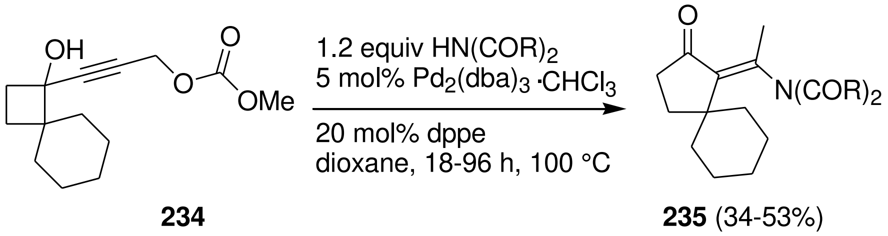
Scheme 67

In analogy with the rearrangement of *trans*-cyclobutanols **229**, *cis*-2-(1-aryloxyvinyl)cyclopentanones **231** were mainly obtained from the diastereomeric *cis*-cyclobutanols **229** when subjected to the same reaction conditions (Scheme 68).[118a] However, these compounds **231** were very unstable due to steric interaction and easily isomerized to 1-alkylidenecyclopentanones **233**. This reaction generally proceeded in high yields (92-97%), except in the case of 4-nitrophenol (70% yield).



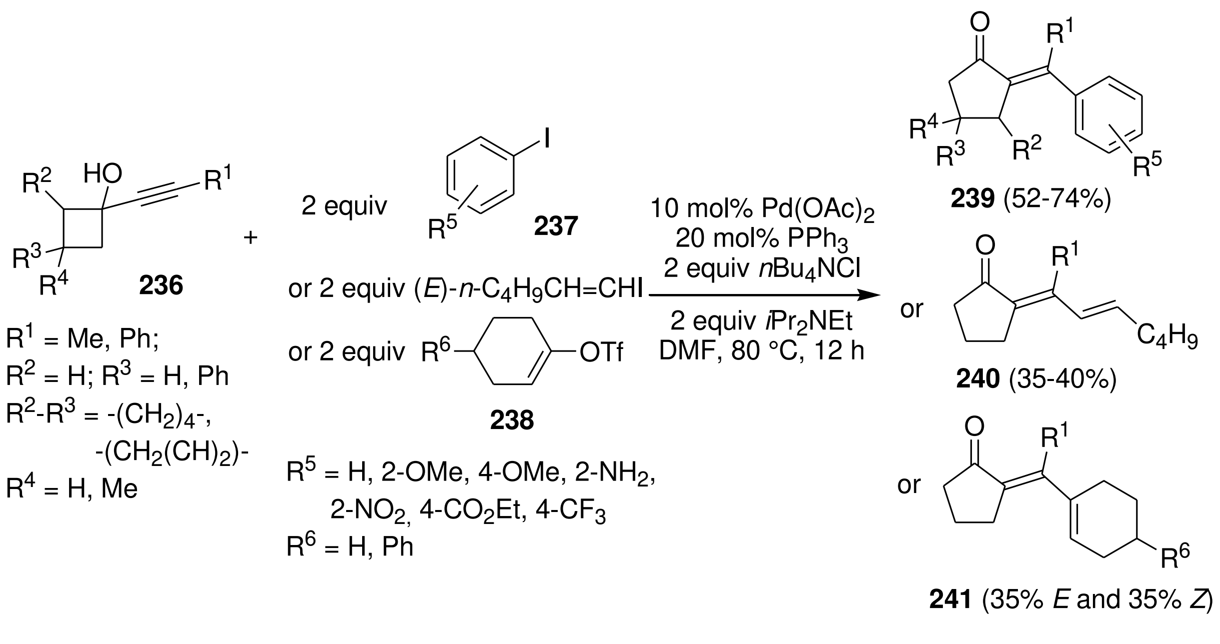
Scheme 68

Also other nucleophiles besides substituted phenols have been evaluated.[118c] For example, imides were found to be suitable reagents in the reaction with propargylic carbonates. When 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanol **234** was reacted with 1.2 equivalents of various imides in the presence of five mol% of $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol% of dppe in dioxane at 100 °C, the corresponding imidyl-substituted alkylidenecyclopentanones **235** were obtained in 34 to 53% yield (Scheme 69). The imides used were succinimide, phthalimide and benzo[*de*]isoquinoline-1,3-dione.



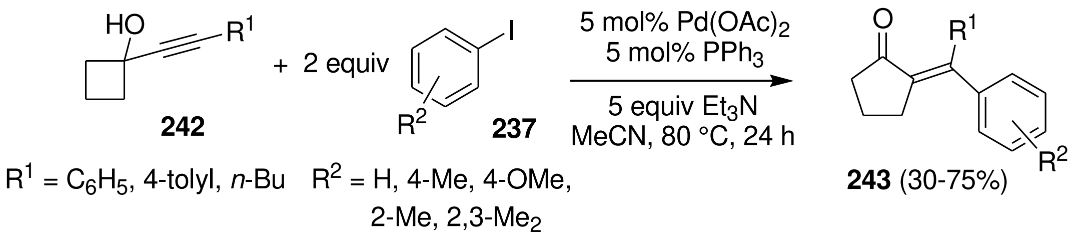
Scheme 69

2-Arylidene- and 2-alkenylidenecyclopentanones have been synthesized by a palladium-mediated cross-coupling of aryl and vinyl halides to 1-(1-alkynyl)cyclobutanols, respectively.[119] When 1-alkynylcyclobutanols **236** were treated with two equiv of an aryl or vinylic iodide, ten mol% of $Pd(OAc)_2$, 20 mol% of PPh_3, two equiv of diisopropylethylamine and two equiv of $n Bu_4NCl$ in DMF at 80 °C, a variety of highly substituted 2-alkylidenecyclopentanones **239**, **240** and **241** were synthesized regio- and stereoselectively in moderate to good yields (35-74%) (Scheme 70).



Scheme 70

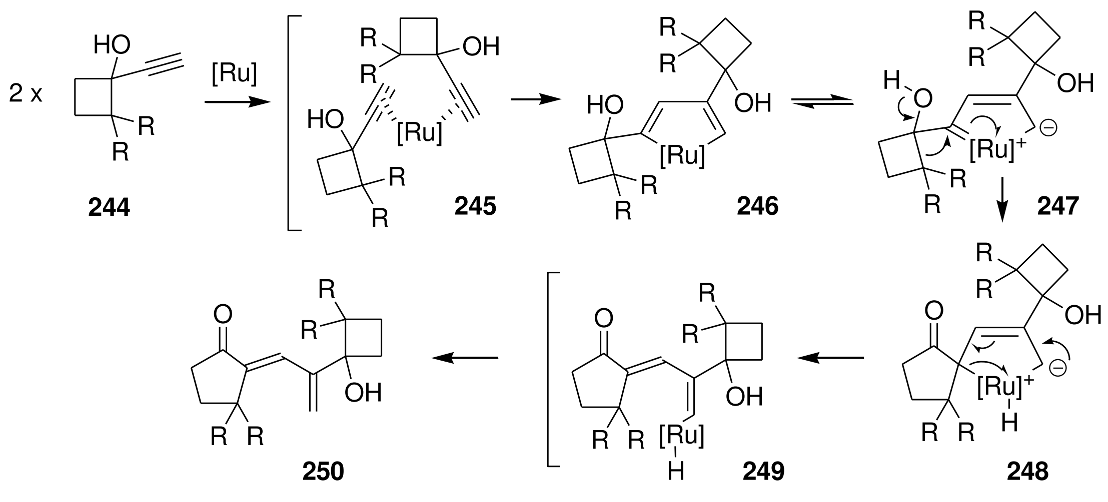
In accordance with the cascade insertion-ring expansion reaction of allenylcyclobutanols with aryl iodides,[107a,b] a tandem addition-ring expansion reaction of 1-alkynyl cyclobutanols under hydroarylation conditions has been reported.[120] Treatment of cyclobutanols **242** with two equiv of an aryl iodide **237**, five mol% of $Pd(OAc)_2$, five mol% of PPh_3 and five equiv of triethylamine in acetonitrile for 24 hours at 80 °C afforded 2-arylidenecyclopentanones **243** in 30-75% yield (Scheme 71).[120b]



Scheme 71

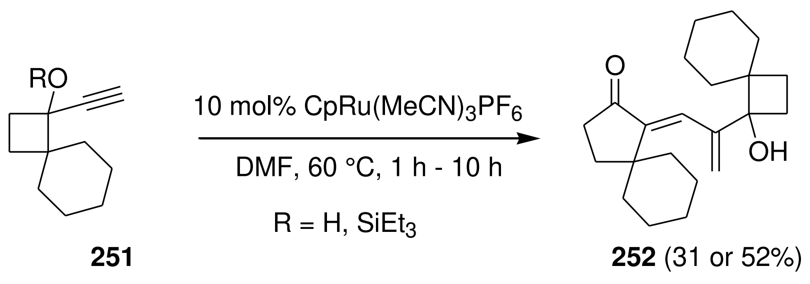
4.2 Ruthenium-promoted activation

The previously described ring rearrangements were triggered by palladium catalysts. On the other hand, a novel type of ring expansion reaction of alkynylcyclobutanols, triggered by a ruthenium catalyst, has been described by Ihara *et al.*[121] This reaction involved a dimerization process to obtain unsaturated cyclopentanones **250**. It was supposed that the key reaction intermediate was a ruthenacycle **246**, which was formed by coordination of a ruthenium catalyst with two molecules of alkynylcyclobutanol **244**. An equilibrium between complex **246** and zwitterionic intermediate **247** induced ring rearrangement, followed by ring opening of the ruthenacycle **248** to form an alkenyl ruthenium hydride **249**. Finally, reductive elimination of ruthenium from complex **249** produced a ring expanded dimeric compound **250** together with regenerated ruthenium catalyst (Scheme 72).



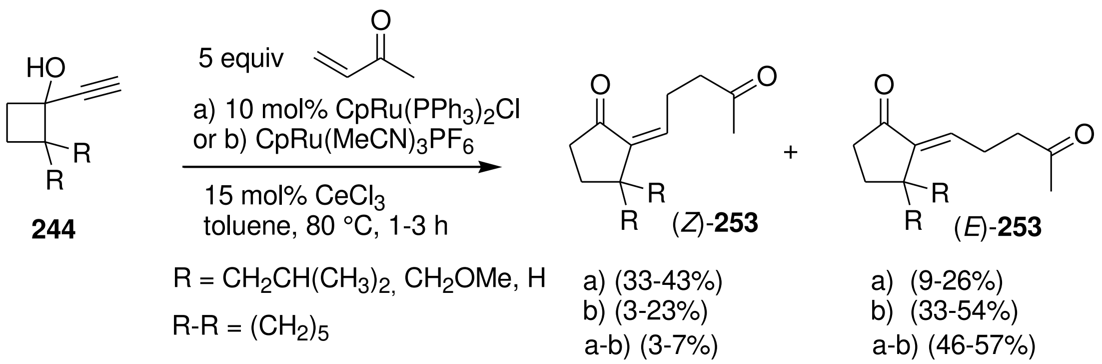
Scheme 72

As an example of this approach, alkynylcyclobutanol **251** was subjected to ten mol% of $CpRu(MeCN)_3PF_6$ in 0.5*M* of DMF at 60 °C for one hour to obtain the ring expanded dimer **252** in 52% yield (Scheme 73). The triethylsilylated (TES) product afforded the same dimeric compound **252** under similar reaction conditions but in lower yield (31%), even after a reaction time of ten hours.



Scheme 73

Additionally, a ruthenium-catalyzed cascade ring expansion reaction through 1,2-rearrangement of 1-ethynylcyclobutanols followed by carbon-carbon bond formation with 3-butene-2-one via a one-pot process has been developed to afford 2-alkylidenecyclopentanones in 45 to 71% total yield (Scheme 74).[122] The stereoselective synthesis of the *Z*- and *E*-isomers of the latter 2-alkylidene cyclopentanones **253** has been achieved using the appropriate ruthenium catalysts. When $CpRu(PPh_3)_2Cl$ was used, the major isomer obtained was (*Z*)-2-alkylidenecyclopentanone (*Z*)-**253** in 33-43% yield besides (*E*)-2-alkylidenecyclopentanone (*E*)-**253** as the minor isomer in 9-26% yield. On the other hand, when $CpRu(MeCn)_3PF_6$ was added to 1-ethynylcyclobutanols **244**, the major isomer isolated was (*E*)-**253** in 33-54% yield and the minor isomer (*Z*)-**253** in 3-23% yield. Only the reaction with a cyclobutanol derivative possessing coordinative 2,2-bis(methoxymethyl) substituents gave (*E*)-2-alkylidenecyclopentanone (*E*)-**253** as the major isomer for both above-mentioned ruthenium catalysts in 46 to 57% yield, next to 3-7% yield for the (*Z*)-isomer of cyclopentanone **253**.

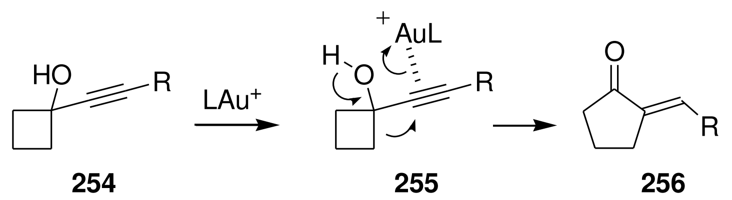


Scheme 74

4.3 Gold-promoted activation

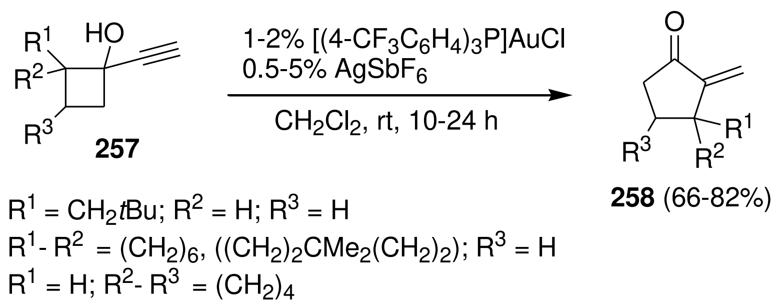
Cationic gold(I) complexes are capable of catalyzing ring expansion reactions by promoting migration of nucleophilic σ-bonds to alkynes.[123] 1-Alkynylcyclobutanols **254** were found to be viable substrates for gold(I)-catalyzed ring rearrangements to synthesize α-

alkylidenecyclopentanones **256**, in which coordination of a cationic gold(I) catalyst to the alkyne moiety (intermediate **255**) induced a 1,2-alkyl shift (Scheme 75).



Scheme 75

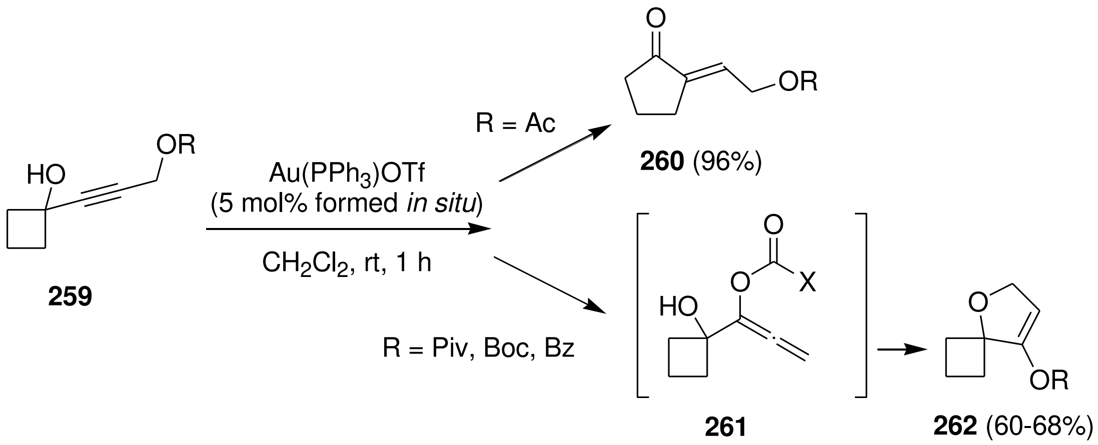
In a first example, alkynylcyclobutanols **257** were subjected to one or two mol% of a (4-trifluoromethylphenyl)phosphine gold(I) catalyst and $AgSbF_6$ in dichloromethane for 10 to 24 hours at room temperature. The subsequent rearrangement afforded *α*-methylidenecyclopentanones **258** in 66 to 82% yield (Scheme 76) with selective migration of the more substituted carbon atom of the cyclobutanol system.



Scheme 76

In a second approach, treatment of the acetate derivative of 1-(3-hydroxypropynyl)cycloalkanol **259** (R = Ac) with one mol% of $Au(PPh_3)OTf$ pre-catalyst in dichloromethane at room temperature for one hour furnished cyclopentanone **260** in an excellent yield of 96% (Scheme 77).[124] This direct ring expansion occurred without [3,3]-

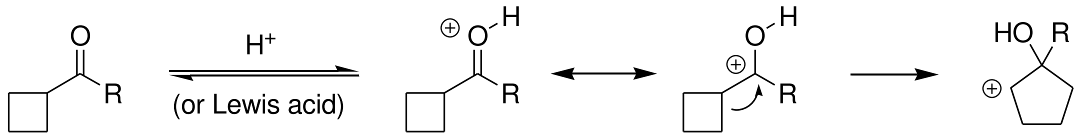
rearrangement. Changing the protecting group from acetate to *t*-butyloxycarbonyl (Boc), benzoyl (Bz) or pivaloyl (Piv), however, led to faster [3,3]-rearrangement and completely diverted the reaction into rearrangement followed by cycloisomerization, giving spirofurans **262** in 60-68% yield through an allenyl intermediate **261** without isolation of cyclopentanones.



Scheme 77

5 Ring expansion of cyclobutylmethylcarbenium ions through activation of a carbonyl group

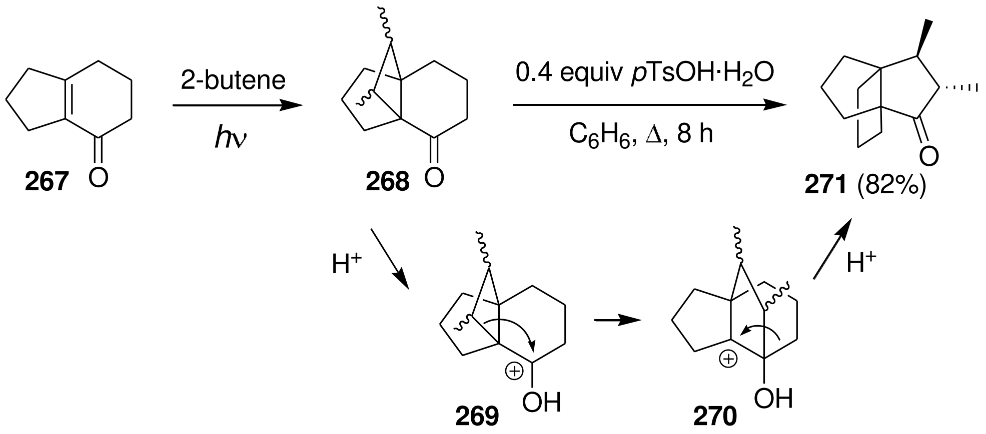
Another method by which a carbenium ion can be generated comprises protonation or activation by means of a Lewis acid of a carbonyl compound **263** (Scheme 78). The oxygen-stabilized cyclobutylmethylcarbenium ions **265**, thus formed, subsequently rearrange to give cyclopentylcarbenium ions **266**. Several examples, based on this principle, will be discussed in the following paragraphs using a broad scale of acids or Lewis acids, such as *p*-toluenesulfonic acid, hydrogen chloride, aluminium(III) chloride or bromide, silica, camphor sulfonic acid, and several others. Also two special cases are described, *i. e.* a $Co_2(CO)_8$ catalyzed ring expansion and activation of a conjugated carbonyl system.



Scheme 78

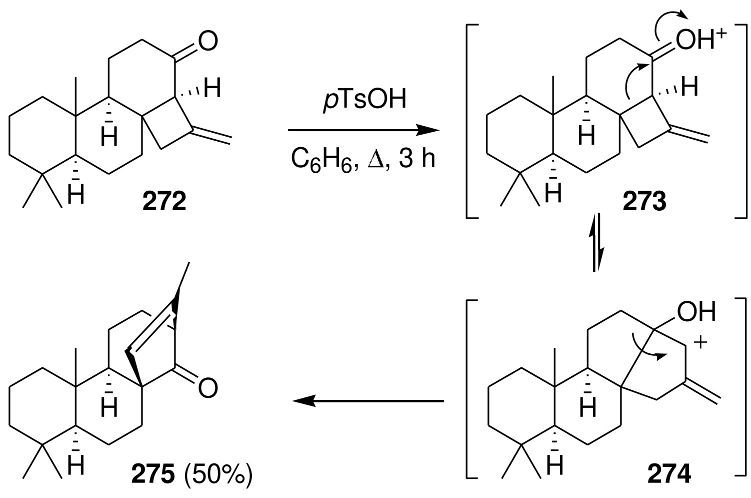
5.1 Direct activation

Propellanes containing one cyclobutane ring, *i. e.* [m.n.2]propellanes (m,n > 2), have been studied in terms of their reactivity toward acid treatment to give ring rearranged products.[125] An example of this pathway comprised the synthesis of 3,4-dimethyltricyclo[3.3.3.0]undecan-2-one **271**. A mixture of *trans*-isomers **268**, originating from cycloaddition of 2-butene across bicyclic enone **269**, when treated with 0.4 equiv of *p*-toluenesulfonic acid in benzene at reflux for eight hours, underwent two Wagner-Meerwein shifts to yield tricyclo[3.3.3.0]undecane-2-one **271** in 82% overall yield from enone **267** via carbenium intermediate **269** and **270** (Scheme 79).[125d] Only *trans*-isomer **271** was isolated after rearrangement, and the *trans*-relationship was ascertained by recovering *trans*-**271** unchanged after treatment with NaOMe in MeOH at reflux. Under the same ring expansion conditions, the synthesis of tricyclo[4.3.3.0]dodecane-7-one from bicyclo[4.4.0]dec-1-en-2-one and ethylene has been reported in 95% yield as well as another propellane-like skeleton.[125d] In general, the acid-catalyzed rearrangement of cyclobutyl ketones involved in polycyclic ring systems such as [m.n.2]propellanes is known as the Cargill reaction[125e] and has been used in the synthesis of natural products[2g] and several other compounds.[126]



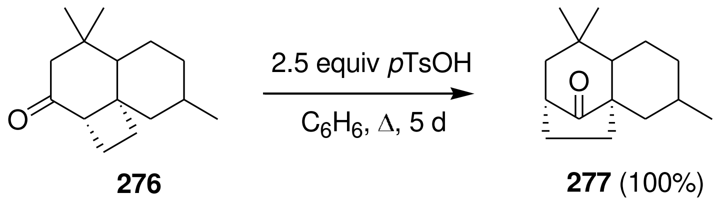
Scheme 79

In a short synthesis of (+)-isophyllocladenone **275**, the five-membered ring was obtained via ring rearrangement of an α-methylidenecyclobutane ring.[127] To this end, compound **272** rearranged to (+)-isophyllocladenone **275** in 50% yield when treated with a large amount of *p*-toluenesulfonic acid (1:1 by weight) in benzene at reflux temperature for three hours through skeletal reorganization via intermediates **273** and **274** (Scheme 80).



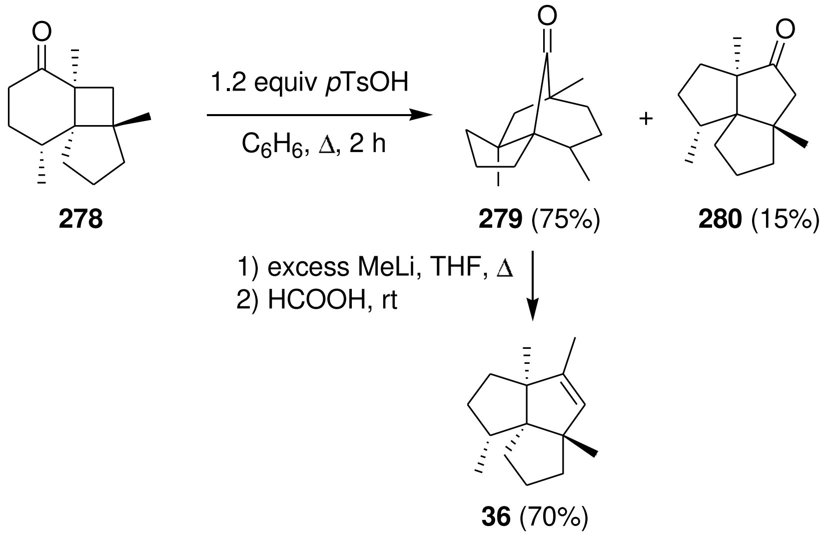
Scheme 80

In studies on the preparation of sesquiterpenes, a synthesis of tricyclic compound **277** has been reported by reaction of tricyclic ketone **276** with 2.5 equiv of *p*-toluenesulfonic acid in benzene at reflux for five days to afford the corresponding ring expanded ketone **277** in quantitative yield (Scheme 81).[128]

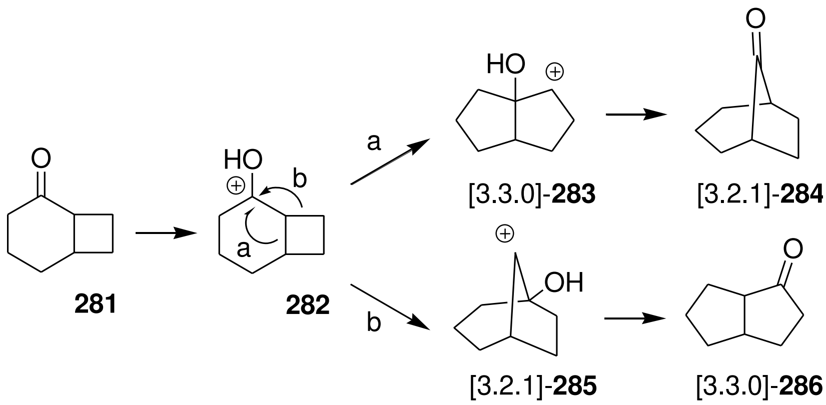


Scheme 81

As an alternative racemic route to the tricyclic sesquiterpene isocomene **36**, Pirrung reported a synthesis via a cyclobutyl carbinyl ketone rearrangement.[42b] The first synthesis by Pirrung was already described in this review in section 2.1.2.[42] Using the Cargill rearrangement,[125b] **278** was treated with 1.2 equiv of *p*TsOH in benzene under reflux to provide **279** and **280** in 75 and 15% yield, respectively, after column chromatography (Scheme 82). However, the more obvious precursor to isocomene **36** was the minor product. Yet, using the conversions of [3.3.0]- and [3.2.1]bicyclooctane carbenium ions **283** and **285** in the Cargill reaction (Scheme 83), compound **279** was treated with an excess of MeLi in tetrahydrofuran at reflux to give a mixture of tertiary alcohols in quantitative yield. Upon treatment with formic acid at room temperature, the crude mixture of alcohols was transformed into isocomene **36** in 70% yield (Scheme 82).

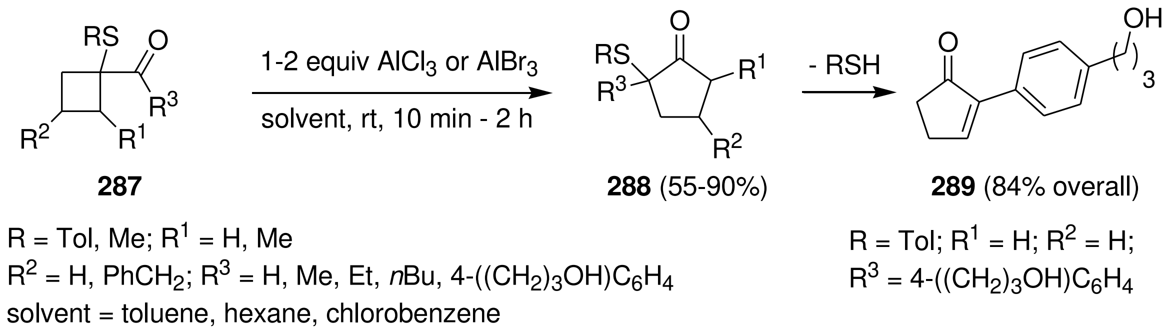


Scheme 82



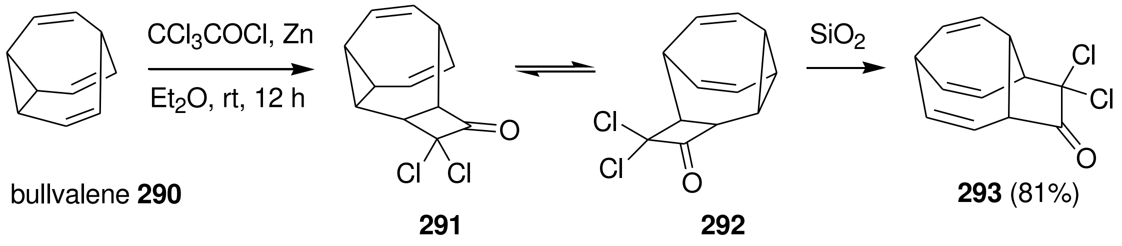
Scheme 83

When 1-alkanoyl-1-(*p*-tolylsulfanyl)cyclobutanes **287** were treated with one or two equiv of aluminium(III) chloride in toluene, hexane or chlorobenzene at room temperature, 2-alkyl-2-(*p*-tolylsulfanyl)cyclopentanones **288** were obtained in 55-90% yield (Scheme 84).[129] Other Lewis acids such as aluminium(III) bromide and iron(III) chloride were also effective for this reaction. Boron(III) fluoride etherate and protonic acids (sulfuric acid and perchloric acid) did not catalyse the rearrangement. The mechanism involved coordination of $AlCl_3$ to the carbonyl oxygen, followed by ring expansion to form a sulfur-stabilized carbenium ion, and migration of the alkyl group to the carbenium ion centre with concomitant regeneration of the carbonyl function to afford the corresponding cyclopentanones. This reaction was applied to the synthesis of 2-[4-(3-hydroxypropyl)phenyl]-2-cyclopentenone **289** in 84% yield from **287**, which is of interest since the corresponding carboxylic ester was proposed as a key intermediate for the synthesis of 4,5,6,7-tetra-*nor*-3-8-inter-*p*-phenylene-11-deoxyprostaglandin, a new prostaglandin analogue.[129,130]



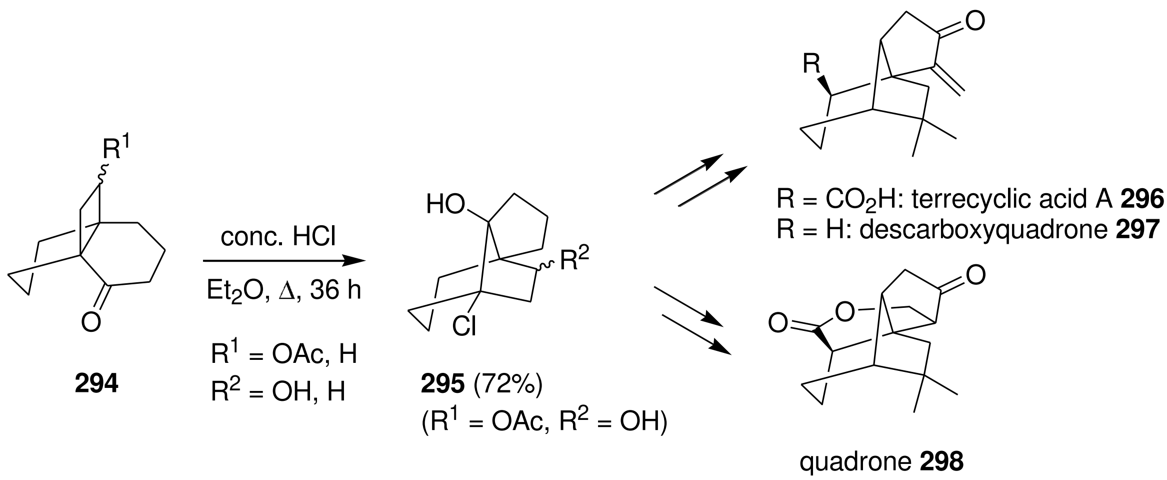
Scheme 84

In a curious example, slow addition of a slight excess of trichloroacetyl chloride in anhydrous ether to a slurry of activated zinc in an ether solution of bullvalene **290** at room temperature for 12 hours afforded α,α-dichlorocyclopentanone **293** in 81% yield (Scheme 85).[131] The proposed mechanism involved initial formation of an equilibrium mixture of 1,2-cycloadducts **291** and **292** (shown by detailed NMR analysis) via [2+2]-cycloaddition of the olefin with dichloroketene. However, these cycloadducts undergo Lewis acid-catalyzed ring opening and subsequent cyclization with skeletal rearrangement to form the 1,6-adduct **293**.



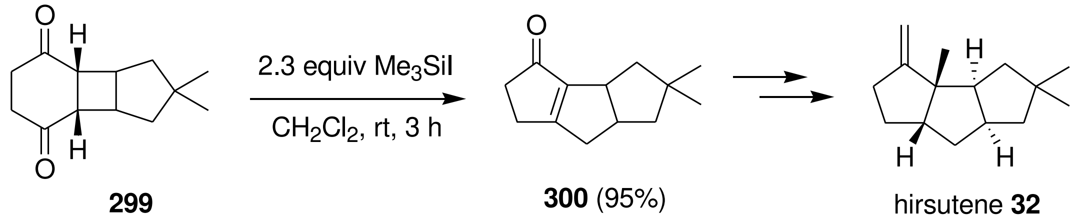
Scheme 85

The acid-catalyzed rearrangement of [4.3.2]propellanones **294** to tricyclo[4.3.2.0^{1,5}]undecanols **295** has been reported as a one-step construction of the carbocyclic skeleton of terrecyclic acid A **296**, descarboxyquadrone **297** and quadrone **298** (Scheme 86).[132] These compounds have been shown to display significant biological activities involving antitumor properties. When tricyclic ketone **294** was treated with conc. HCl in diethyl ether at reflux temperature for 36 hours, diol **295** was isolated in 72% yield (for R^1 = OAc, R^2 = OH) or, because of instability (R^1, R^2 = H), directly converted into the next product of the reaction sequence.



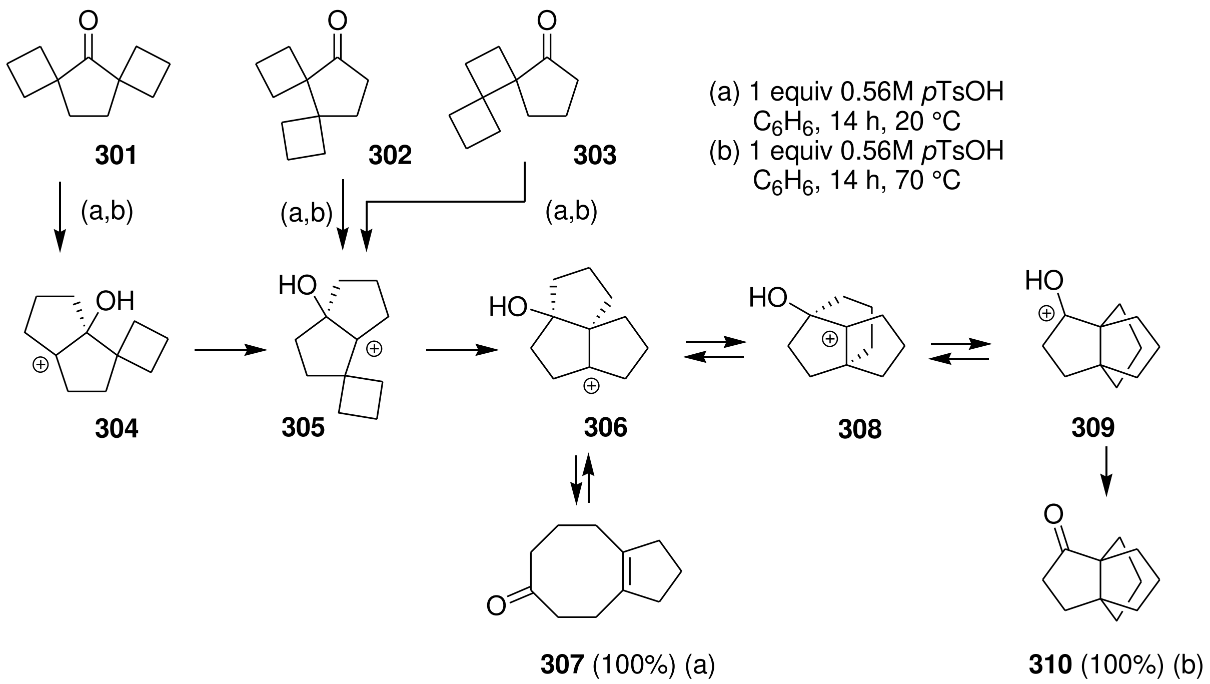
Scheme 86

In a short synthesis toward hirsutene **32**, the rearrangement of tricyclo[5.4.0.0^{2,6}]undecane-8,11-dione **299** represents the key step for the synthesis of the carbocyclic skeleton.[133] When **299** was treated with 2.3 equiv of iodotrimethylsilane in dichloromethane for three hours at room temperature, tricyclo[6.3.0.0^{2,6}]undec-2-ene-3-one **300** was isolated in 95% yield through rearrangement and a final dehydration step (Scheme 87).[133b]



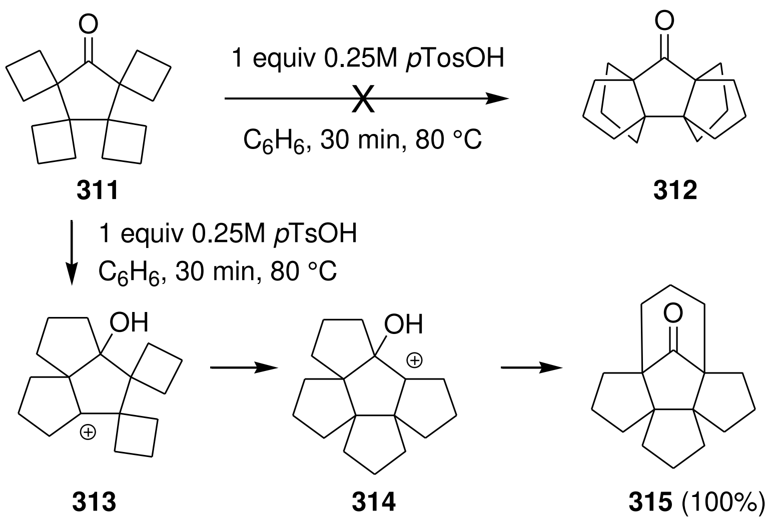
Scheme 87

When dispiroketones **301**, **302** and **303** were treated with equimolar amounts of a 0.56 molar solution of anhydrous *p*-toluenesulfonic acid in benzene for 14 hours at 20 °C, quantitative conversion into the bicyclic enone **307** was observed. The same conversion was complete within ten minutes at 70 °C, but after 14 hours at 70 °C the propellanone **310** was formed instead in a quantitative yield (Scheme 88).[134] These rearrangements proceeded via intermediate *β*-hydroxy carbenium ions. These ketones **301**, **302** and **303** were well suited for rearrangement because of the defined dihedral angle relationships favoring stereospecific rearrangements and the possibility of reactions through energetically favorable tertiary carbenium ions as depicted in Scheme 88,[135] besides the pronounced relief of strain associated with C_4-C_5 ring enlargements.



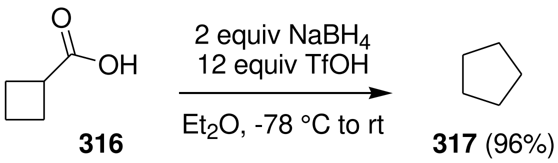
Scheme 88

According to the previous result, reaction of a tetraspiroketone **311** with equimolar amounts of anhydrous *p*-toluenesulfonic acid in benzene would lead to bispropellanone **312**. However, the bridged pentacyclic ketone **315** was isolated instead in 100% yield (Scheme 89).[134c] The observed reactivity was explained considering the carbenium ion intermediates **313** and **314** en route to ketone **315**.



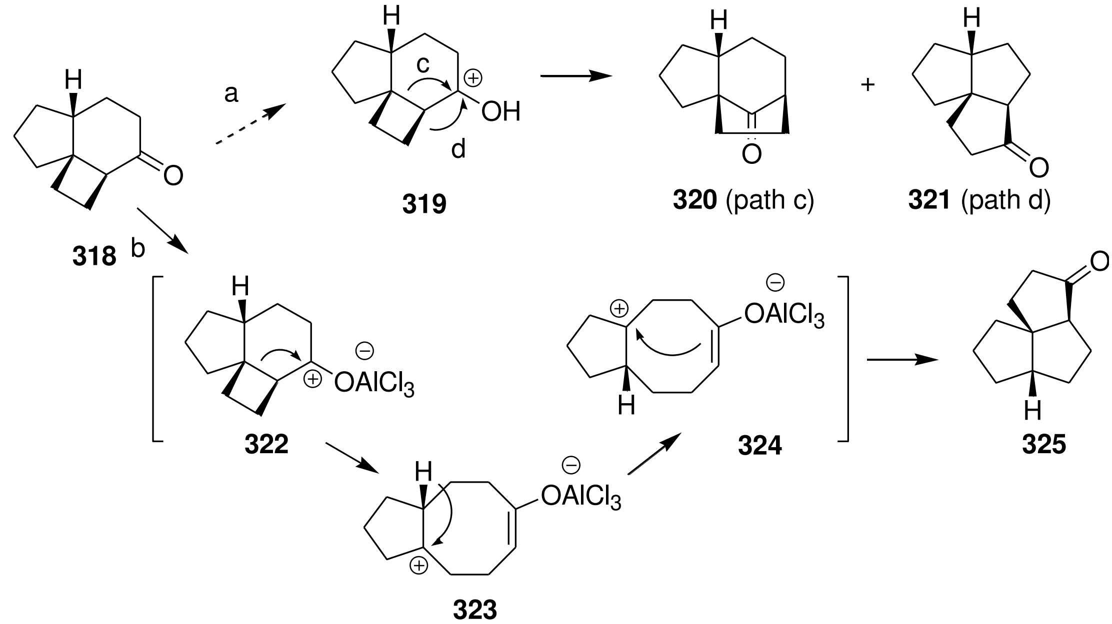
Scheme 89

In a formal reductive ring enlargement, cyclobutanecarboxylic acid **316** has been described to be converted to cyclopentane **317** in 96% yield through a primary carbenium ion utilizing a mixture of two equiv of sodium borohydride and 12 equiv of triflic acid in diethyl ether (Scheme 90).[136] In the original paper, the authors mainly focused on adamantine derivatives.



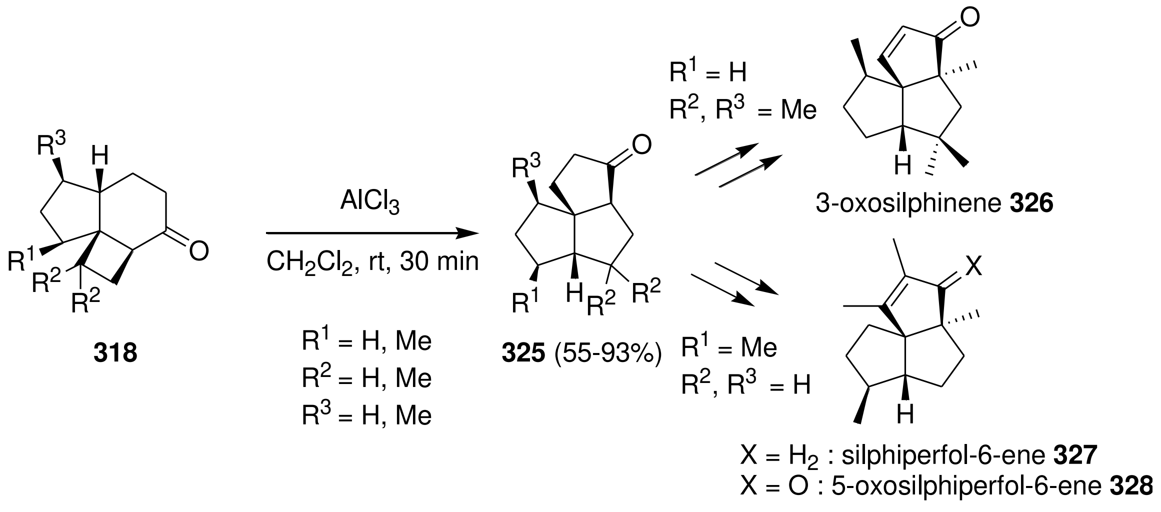
Scheme 90

Within the study of marine sesquiterpenes, a new pathway (path b) for the rearrangement of (1*S**,4*S**,8*R**)-tricyclo[6.3.0.0^{1,4}]undecan-5-one **318** has been reported under the action of a Lewis acid to give angularly fused triquinane **325** with high selectivity, which is entirely different from the Cargill pathway (path a) (Scheme 91).[137] Coordination of the carbonyl group to the Lewis acid generated intermediate **322**, followed by cleavage of the central cyclobutane bond to yield homoallylcarbinylcarbenium ion **323**. A 1,2-hydride shift afforded the carbenium ion **324**, which collapsed to give the desired product **325**.



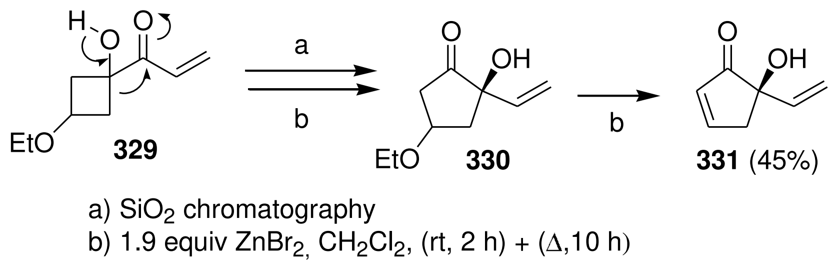
Scheme 91

The utility of this approach was further demonstrated by the total syntheses of (±)-3-oxosilphinene **326**, (±)-silphiperfol-6-ene **327** and (±)-5-oxosilphiperfol-6-ene **328** (Scheme 92).[137] The rearrangement of substrates **318** proceeded smoothly using aluminium(III) chloride in dichloromethane at room temperature for 30 minutes to obtain the angular ketones **325** in 55-93% yield, which could be converted into the desired products.



Scheme 92

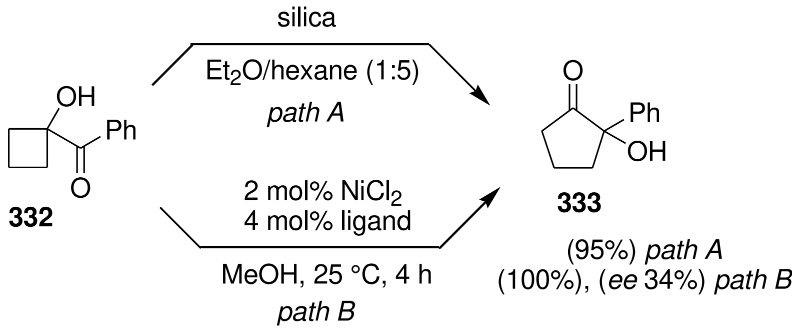
The reactivity of 1-alkanoylcyclobutanes toward ring enlargement can be further enhanced by the introduction of an electron-donating hydroxy group at the 1-position. Exposure of the relatively stable 1-(1-oxo-2-propenyl)cyclobutanol **329** (obtained via treatment of 3-ethoxycyclobutanone with 1-lithio-1-methoxyallene followed by acid hydrolysis) to the usual aqueous acid conditions (*i. e.* treatment with trifluoroacetic acid in a THF/H_2O (1:1) solvent mixture) did not rapidly induce ring expansion. However, exposure to SiO_2 provided the ring expanded cyclopentanone product **330** as one diastereomer.[104a] Treatment of the same cyclobutanol **329** with $ZnBr_2$ in dichloromethane for two hours at room temperature, followed by ten hours under reflux led to cyclopentenone **331** in 45% yield, presumably via cyclopentanone **330** (Scheme 93).



Scheme 93

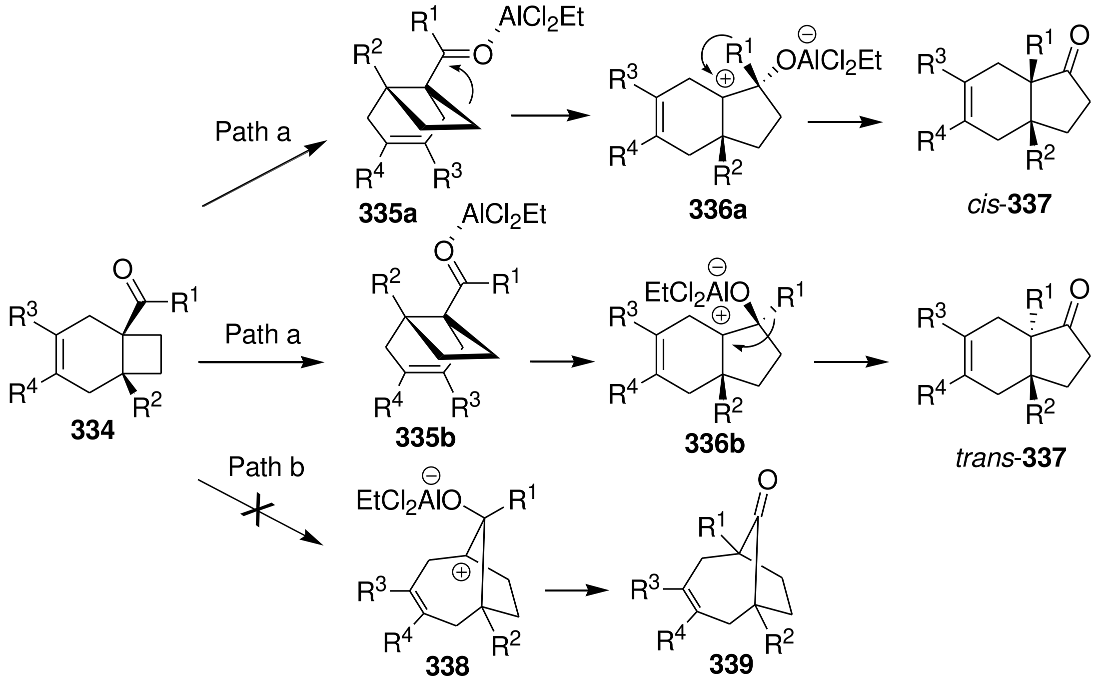
In analogy, the cyclobutyl system **332** rearranged completely to *α*-hydroxycyclopentanone **333** on silica gel chromatography using diethyl ether/hexane (1:5) in 95% yield (path A, Scheme 94).[138a] Furthermore, a nickel-catalyzed enantioselective *α*-ketol rearrangement of 1-benzoylcyclobutanol **332** was initiated with two mol% of $NiCl_2$ and four mol% of 2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine ($NiCl_2$/pybox) in methanol for four hours at 25 °C, to afford (-)-2-hydroxy-2-phenylcyclopentanone **333** in quantitative yield and in 34%

enantiomeric excess without knowing the exact absolute configuration (path B, Scheme 94).[138b]



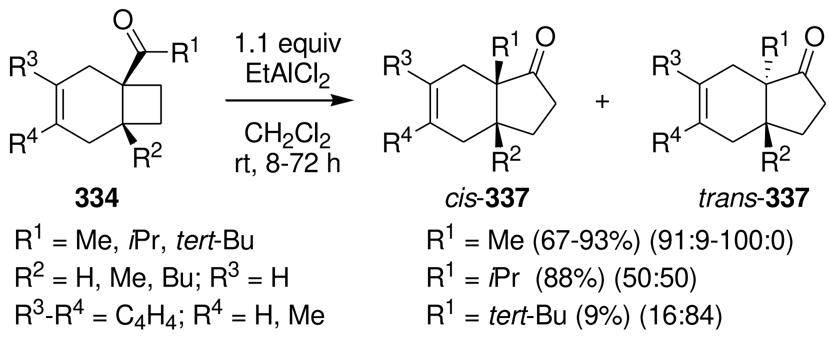
Scheme 94

Ring enlargement of cyclohexene-annelated acylcyclobutanes upon treatment with an appropriate Lewis acid has been reported to afford hydrindanone derivatives.[139] Ring enlargement of 1-acylbicyclo[4.2.0]oct-3-enes **334** could afford two isomeric ketones **337** and **339** depending on the direction of migration (pathways a and b) (Scheme 95). The formation of **339**, however, was unfavorable due to the lower stability of intermediate **338** as compared to carbenium ion **336**. The overlap of the *p*-orbital of the carbonyl group and the breaking *σ*-orbital of the cyclobutane ring must be maintained during the ring expansion of cyclobutane **334** to carbenium ion intermediate **336**. As a result, the acetyl group and the C-6 hydrogen or alkyl group (R^2) lay in the same plane in the transition state so that the ring enlargement proceeded through conformer **335a** or **335b**. Since the alkyl group migrated at the same face of the molecule, the main *cis*-isomer was produced via **335a** and hence the steric repulsion between R^2 and the carbonyl oxygen, coordinated to the Lewis acid, was larger than the repulsion between the R^2- and R^1-group.



Scheme 95

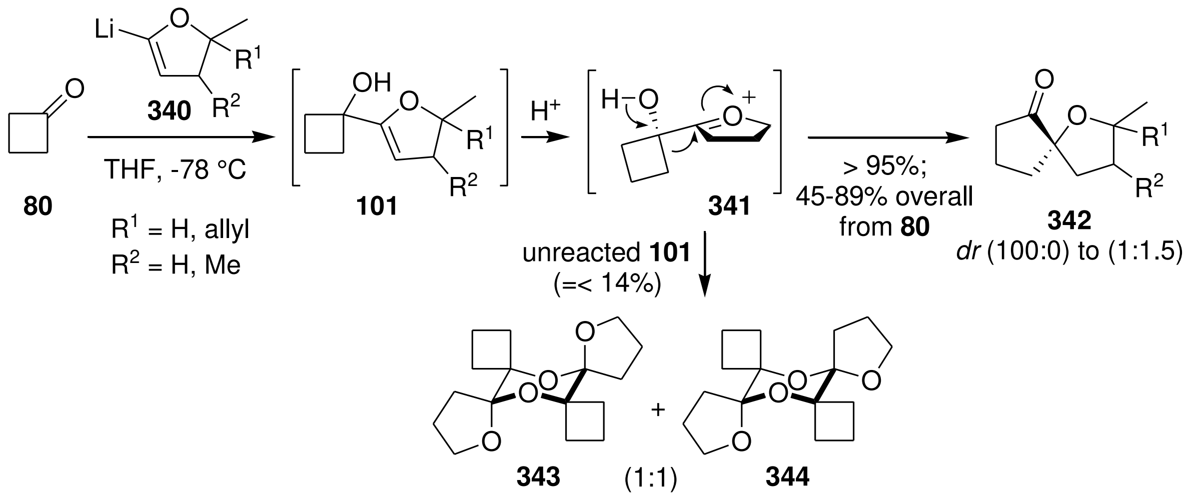
With 1.1 equiv of ethylaluminium dichloride, as the most efficient Lewis acid, the ring expansion of 1-acylbicyclo[4.2.0]oct-3-enes **334** in dichloromethane gave 6-alkylbicyclo[4.3.0]non-3-en-7-ones **337** in good yields (Scheme 96).[139] When substituted annelated cyclobutyl methylketones (R^1 = Me) were used, *cis*-hydrindanones were synthesized in good yield (67-93%) with high *cis*-stereoselectivity (82-100% *de*). With isopropyl and *tert*-butyl ketones (R^1 = *i*Pr, *tert*-Bu) instead of methyl ketones, a reduced stereoselectivity or even a reversal was observed, according to the steric demand of these substituents.



Scheme 96

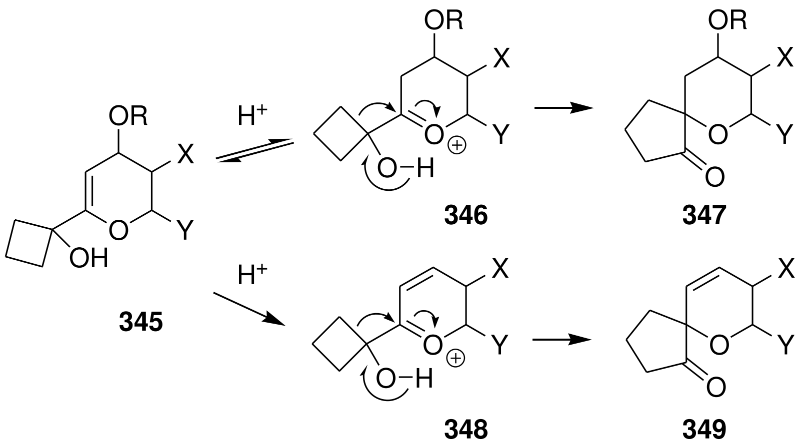
As part of the synthesis of enantiomerically pure spirocyclic *α,β*-butenolides, a bromonium ion- (*vide supra*, Scheme 31) or oxonium ion-induced rearrangement of carbinol **101** has been developed.[54a,66,140] This oxonium ion-promoted rearrangement was first executed by treatment of carbinol **101**, synthesized by the addition of 5-lithio-2,3-dihydrofuran **340** (R^1, R^2 = H) to cyclobutanone **80**, with different acids to produce the spirocyclic tetrahydrofuranyl ketone **342** (R^1, R^2 = H) in 45-87% yield with excellent selectivity (*dr* 100:0). Next to **342**, variable quantities (0-14%) of 1,4-dioxanes **343** and **344** (R^1, R^2 = H) in a 1:1 ratio were detected, depending on the used acidic ion exchange resin (Scheme 97). Only when Amberlyst-15[66] or methanol-free Dowex-50X resin[140b] was used in dichloromethane at room temperature, no dioxane side product was obtained.

When carbinols **101** (R^1 = H, allyl; R^2 = H, Me) were treated with camphor sulfonic acid (CSA) (0.2-1.7 mol%) in dichloromethane at room temperature for 30 minutes to two hours, spiro ketones **342** were obtained in 67 to 89% yield in a diastereomeric ratio ranging from 3.9:1 to 1:1.5.[141]



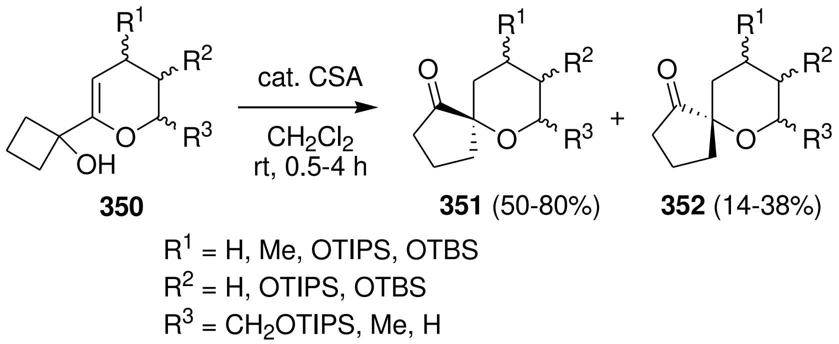
Scheme 97

In the field of carbohydrate chemistry, the acid-catalyzed rearrangement of dihydropyranylcarbinols such as **345** to spirocyclic bis-*C*,*C*-glycosides **347** and **349** has been examined and proved to be highly diastereoselective.[141,142] This efficient process resulted in the generation of a new stereogenic centre by means of controlled pinacol-like 1,2-migration to a cyclic oxonium ion. When glycols **345**, substituted with a leaving group in the allylic C(4) position, were subjected to acidic conditions, two intermediates **346** and **348** could be formed, resulting in spirocyclic compounds **347** and **349**, respectively. While the generation of intermediate **346** qualified as a potentially reversible process, the formation of **348** is essentially irreversible (Scheme 98).[142]



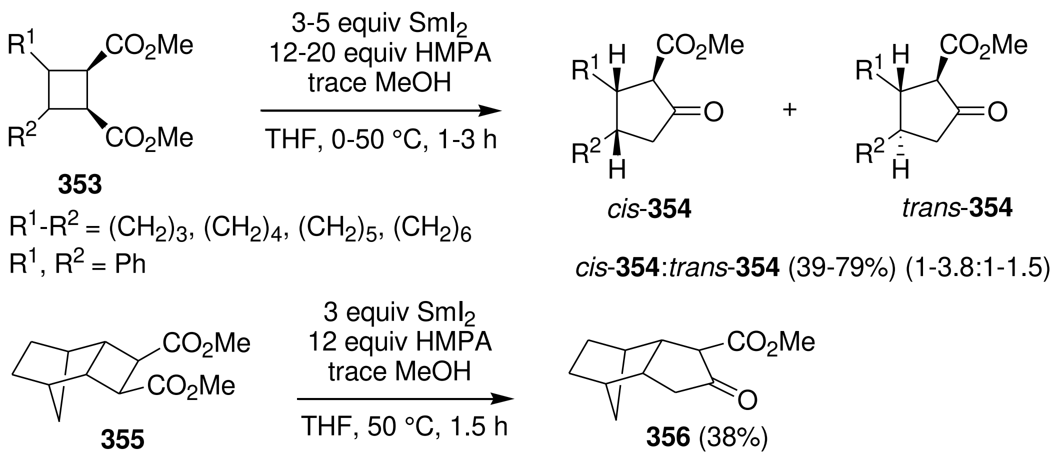
Scheme 98

In another example, simple substitution of the dihydropyran ring with one or two alkyl groups engendered sufficient inductive electron donation to reduce the potential for isomerization significantly,[141] although cyclobutanol derivatives still underwent ring expansion at a rate to be synthetically useful. In that respect, treatment of cyclobutanols **350** with a catalytic amount of camphorsulfonic acid (CSA) in dichloromethane at room temperature for 0.5 to four hours resulted in spirocyclic bis-*C*,*C*-glycosides **351** and **352** in 50-80% and 14-38% yield, respectively (Scheme 99).[142b]



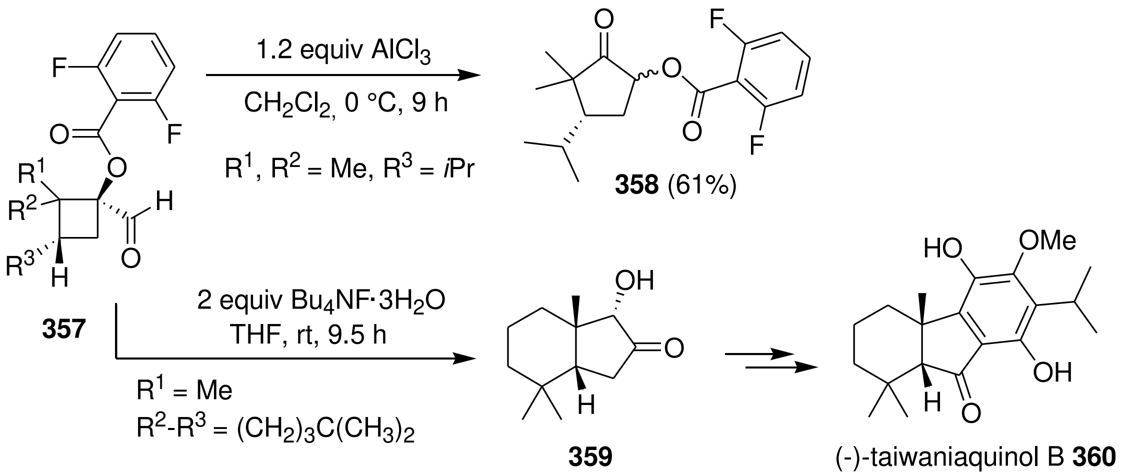
Scheme 99

Although based on a different reaction mechanism, the samarium(II)-induced ring expansion of 1,2-cyclobutanedicarboxylates **353** to cyclopentanones **354** is worth mentioning (Scheme 100).[143] Also, a single isomer **356** was obtained in the ring expansion of tricyclic compound **355** in 38% yield. It should be noted that the reaction of this rearrangement proceeded via a tandem reductive fragmentation-Dieckmann condensation.



Scheme 100

Ring expansion of cyclobutanecarboxaldehyde **357** (R^1, R^2 = Me, R^3 = *i*Pr) was executed upon treatment with 1.2 equiv of $AlCl_3$ in dichloromethane at 0 °C for nine hours through successive 1,2-shifts of a tertiary alkyl group and a hydride to synthesize 2-benzoyloxycyclopentanone **358** in 61% yield (Scheme 101).[144] The same authors reported the ring expansion of bicyclic compound **359** (R^1 = Me, R^2-R^3 = $(CH_2)_3C(CH_3)_2$) by treatment with two equiv of $Bu_4NF{\cdot}3H_2O$ through hydrolysis and subsequent 1,2-shift of a tertiary alkyl group to afford 2-hydroxycyclopentanone **359** as a chiral intermediate in the enantioselective total synthesis of 4a-methylhydrofluorene diterpenoids such as (-)-taiwaniaquinol B **360** (Scheme 101).[144a]

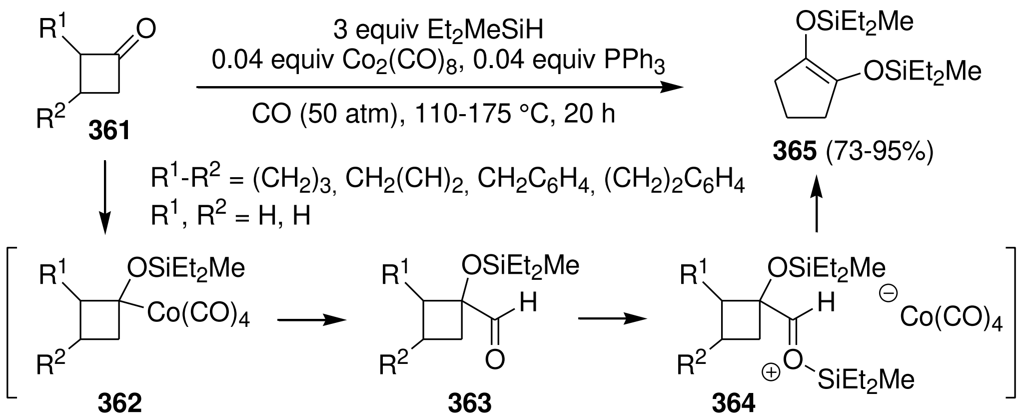


Scheme 101

5.2 Special cases

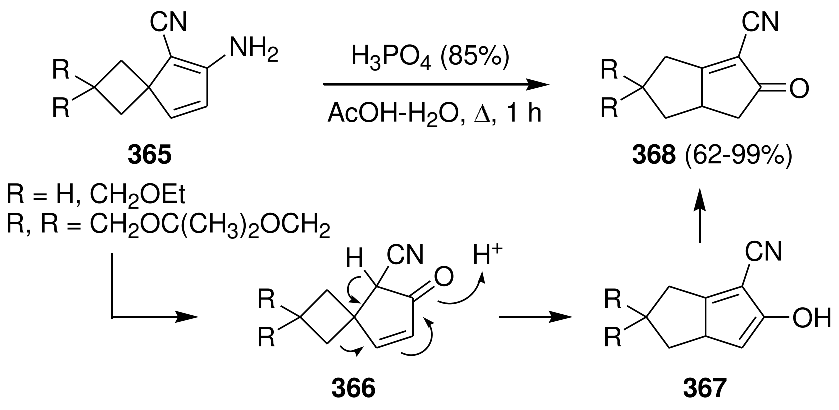
Although essentially based on a cyclobutane to cyclopentane ring enlargement through activation of a carbonyl moiety, the following examples deviate from a simple and direct carbonyl activation approach and are therefore discussed in a separate section.

The cobalt carbonyl-catalyzed ring expansion of cyclobutanone **361** to 1,2-bis(diethylmethylsiloxy)cyclopentene **365** with diethylmethylsilane and carbon monoxide (50 atm) comprised the first example of the catalytic incorporation of carbon monoxide into a simple ketonic C-C bond.[145] The ring-enlargement mechanism, as shown in Scheme 102, for the rearrangement of cyclobutanones **361** to cyclopentenes **365**, also involved a cyclobutylmethyl to cyclopentylcarbenium ion rearrangement. There was evidence that $MeEt_2SiCo(CO)_4$ was involved in the reaction, generated *in situ* in the trialkylsilane/carbon monoxide/dicobaltoctacarbonyl system. In addition to the ring strain of cyclobutanes, the high oxygenophilicity of silicon implied a strong driving force for this reaction. Addition of three equiv of diethylmethylsilane, 0.04 equiv of dicobaltoctacarbonyl, 0.04 equiv of triphenylphosphine and carbon monoxide (50 atm) to cyclobutanone **361** in benzene at 110-175 °C for 20 hours afforded the corresponding disiloxycyclopentenes **365** in 73-95% yield through formation of intermediates **362**, **363** and **364** (Scheme 102).



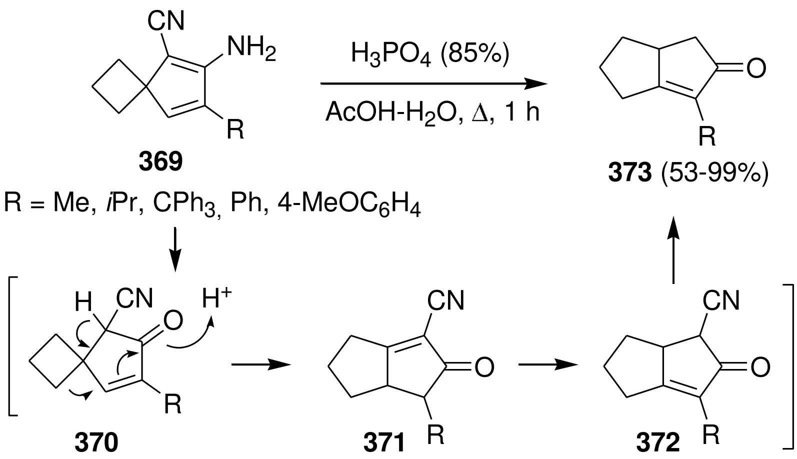
Scheme 102

Bicyclo[3.3.0]oct-1-en-3-ones **368**, obtained from spirocyclobutanes **365**, were applied in the synthesis of racemic 1-desoxyhypnophilin.[146] When enaminonitriles **365** were treated with phosphoric acid in aqueous acetic acid at reflux temperature for one hour, the corresponding cyclopentenones **368** were obtained in 62-99% yield. In a plausible mechanism, the acidic hydrolysis of the enamine function of **365** first gave enones **366**. Protonation of the carbonyl oxygen of enones **366**, followed by rearrangement of the cyclobutane ring furnished bicyclo[3.3.0]octenones **367** which, upon tautomerization, produced bicyclic enones **368**.



Scheme 103

When enaminonitriles **369** were subjected to the same reaction conditions as described before, not the expected 2-cyano-4-alkyl- or 4-arylbicyclo[3.3.0]oct-1-en-3-ones were obtained but instead 2-alkyl- or 2-arylbicyclo[3.3.0]oct-1-en-3-ones **373** were isolated in 53-99% yield.[146] A plausible mechanism for the formation of these compounds is provided in Scheme 104. First, acidic hydrolysis of the enamine moiety of **369** gave enones **370**. Subsequently the ring expansion of the cyclobutane ring took place as described above (Scheme 103) to give 2-cyano-4-alkyl- or 4-arylbicyclo[3.3.0]oct-1-en-3-ones **371**. Migration of the double bond in **371** occurred under the acidic conditions to afford enone **372**, in which the cyano group was hydrolyzed followed by decarboxylation to provide compounds **373**.



Scheme 104

6 Formation of cyclobutylmethylcarbenium ions through expulsion of a leaving group

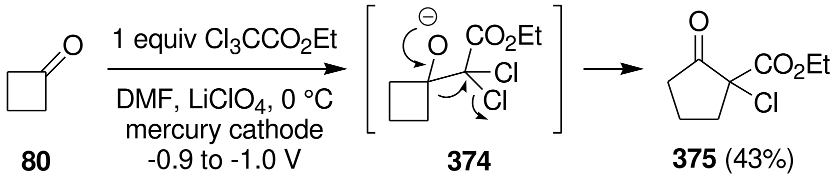
Different kinds of leaving groups, e.g. halogens, nitrogen gas, a nitro group, activated hydroxy and alkoxy groups, and sulfur and selenium groups, can be used to form and induce ring expansion of cyclobutylmethylcarbenium ions with ring strain as a driving force. Several examples of syntheses based on this approach are described in this section.

6.1 A halogen atom as leaving group

6.1.1 Cyclobutylmethyl chlorides

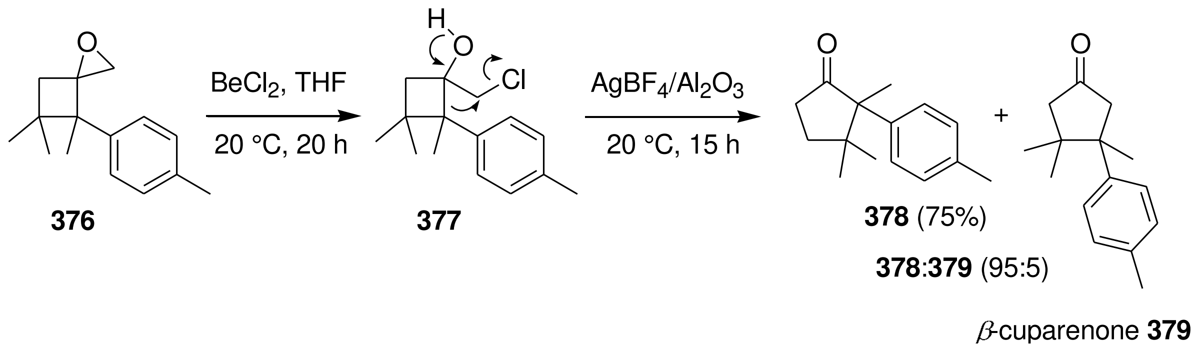
The ethyl dichloroacetate anion, cathodically generated from ethyl trichloroacetate, was added across cyclobutanone **80** in DMF at 0 °C to yield cyclopentanone **375** in 43% yield (Scheme

105).[147] The formation of this cyclopentanone was conceived by a ring expansion reaction of the adduct **374**, taking advantage of the electrophilicity of the dihalogenated carbon atom.



Scheme 105

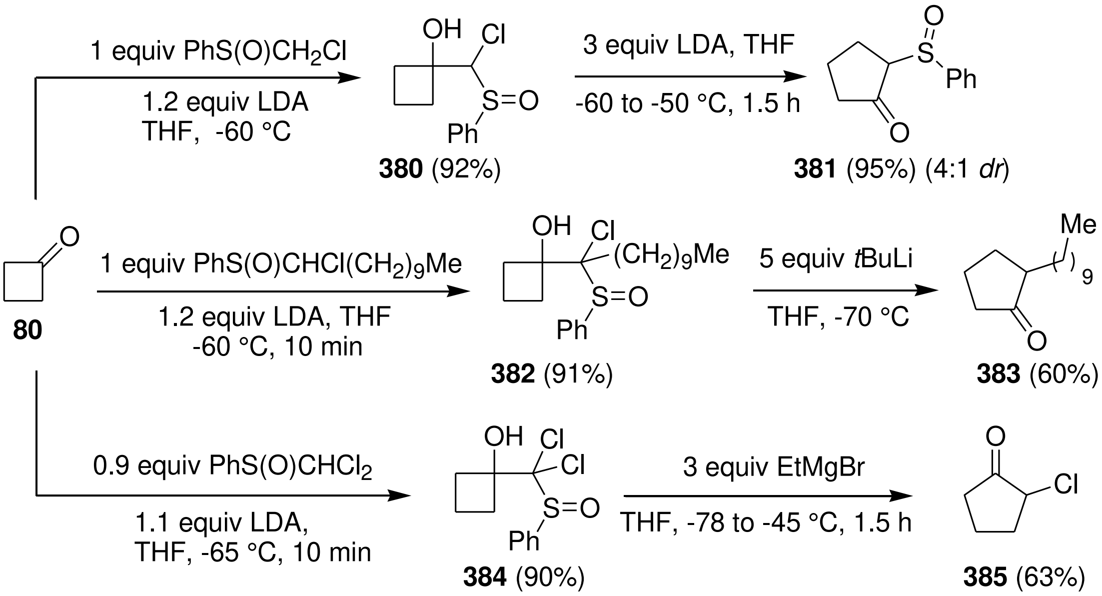
In the synthesis of the regioisomer of *β*-cuparenone **379**, Krief and co-workers reported a rearrangement of chlorohydrin **377**, synthesized from epoxide **376** with beryllium(II) chloride (Scheme 106).[148] Treatment of this chlorohydrin **377** with silver tetrafluoroborate in the presence of aluminium oxide at 20 °C for 15 hours afforded cyclopentanone **378** and a small fraction of *β*-cuparenone **379** in a ratio of 95:5. An overall yield of 75% was assigned to cyclopentanone **378** starting from epoxide **376**.



Scheme 106

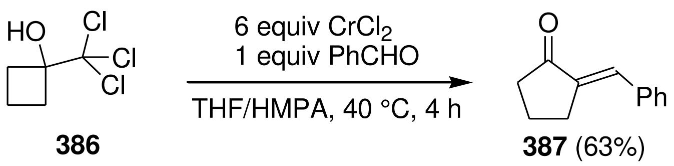
In another approach, a one-carbon homologation of ketones to α-sulfinyl ketones using (chloromethyl)phenylsulfoxide has been reported.[149] Treatment of (chloromethyl)phenylsulfoxide with 1.2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran at -60 °C formed a carbanion, which was reacted with cyclobutanone **80** to give adduct **380** as a single isomer in 92% yield (Scheme 107). This adduct **380** was treated with three equiv of LDA in tetrahydrofuran at -60 to -50 °C for 1.5 hours to afford *α*-sulfinyl cyclopentanone **381** in 95% yield as a mixture of two inseparable diastereomers in a 4:1 ratio. The previous method was applied to the one-carbon ring expansion of cyclic ketones to cyclic ketones bearing an alkyl substituent.[150] Addition of the carbanion of (1-chloroalkyl)-*p*-tolylsulfoxide to cyclobutanone **80** afforded chloro alcohol **382** in 91% yield (Scheme 107). When five equiv of *t*BuLi were added to the chloro alcohol **382** in tetrahydrofuran at -70 °C, the rearrangement afforded 1-decylcyclopentanone **383** in 60% yield.

The same authors used the previous ligand exchange reaction of sulfoxides for the synthesis of *α*-chloroketones from carbonyl compounds with one-carbon homologation.[151] When (dichloromethyl)phenylsulfoxide was treated with LDA in tetrahydrofuran at -60 °C followed by cyclobutanone addition, adduct **384** was synthesized in 90% yield (Scheme 107). The chloro alcohol **384** was treated with three equiv of EtMgBr in tetrahydrofuran at -78 to -45 °C for 1.5 h to synthesize *α*-chlorocyclopentanone **385** in 63% yield. In this case, a Grignard reagent (EtMgBr) was used for the ligand exchange reaction of the sulfoxides. Apparently, different approaches can be applied for the conversion of cyclobutanone **80** into cyclopentanones, in which either cationic or anionic intermediates intervene.



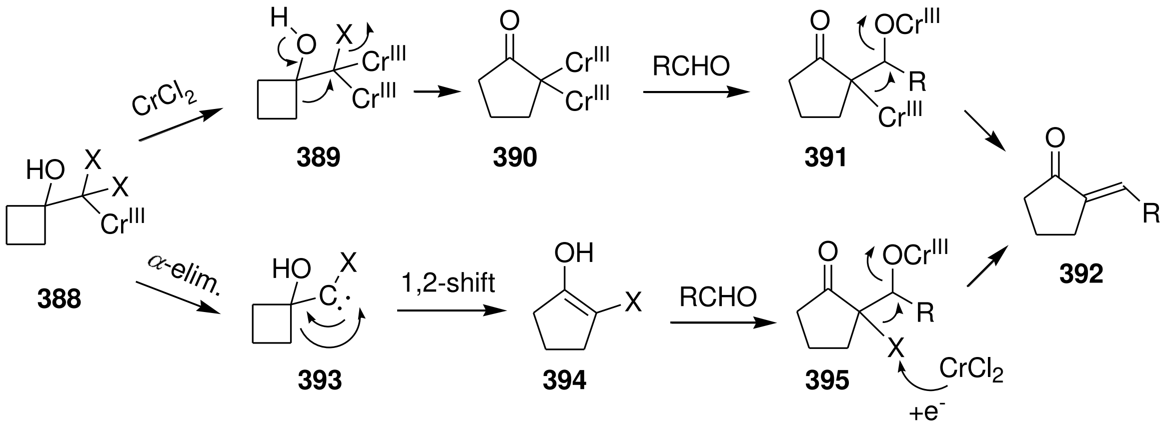
Scheme 107

Treatment of cyclic *tert*-trihalomethylcarbinols with $CrCl_2$ in THF/HMPA in the presence of aryl or aliphatic aldehydes initiated a cascade sequence of one-carbon ring expansion - olefination, affording conjugated exocyclic ketones.[152] As a specific example, exposure of cyclobutyl carbinol **386** to six equiv of $CrCl_2$ and one equiv of benzaldehyde in THF/HMPA for four hours at 40 °C afforded (*E*)-2-benzylidenecyclopentanone **387** in 63% yield (Scheme 108).



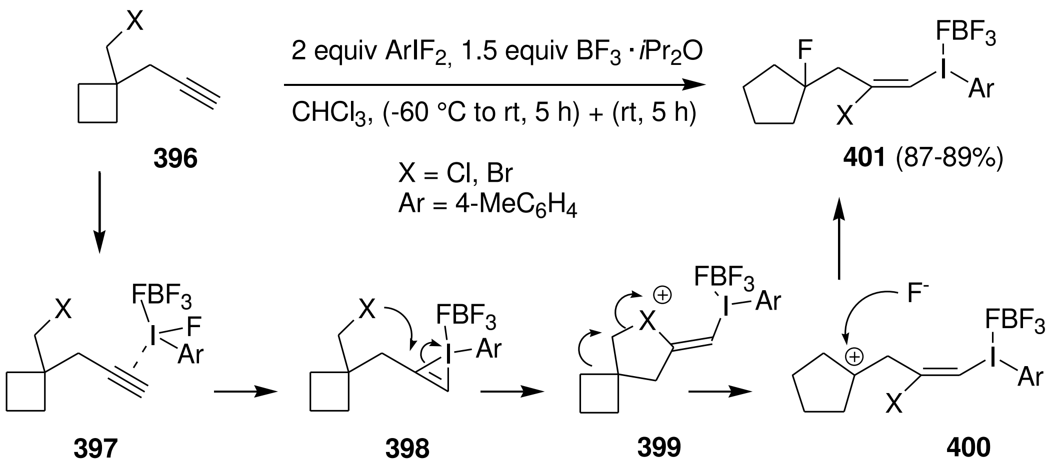
Scheme 108

Two plausible mechanistic pathways were disclosed (Scheme 109).[152] Initial metalation of the trihalomethyl moiety generated the key dihalochromium intermediate **388**. A second metalation led to **389**, which rearranged to dichromium ketone **390**. This ketone **390** was expected to add rapidly to the aldehyde and to collapse to the final product **392**. Alternatively, α-elimination of **388** formed carbene **393** and hence α-haloenol **394**, its rearrangement product. Addition of the aldehyde culminated in **392** via reduction of adduct **395**.



Scheme 109

A domino λ^3-iodination - 1,4-halogen shift - ring enlargement reaction of 5-chloro- or 5-bromopent-1-ynes **396** took place when the starting material was treated with two equiv of 4-(difluoroiodo)toluene in the presence of 1.5 equiv of $BF_3 \cdot iPr_2O$ in chloroform at -60 °C to room temperature for five hours with an additional five hours at room temperature (Scheme 110).[153] This domino reaction afforded (*E*)-3-cyclopentyl-2-halopropenyliodinanes **401** stereoselectively in 87-89% yield. A mechanistic rationale based on the formation and transformation of intermediates **397**, **398**, **399** and **400** was provided by the authors.

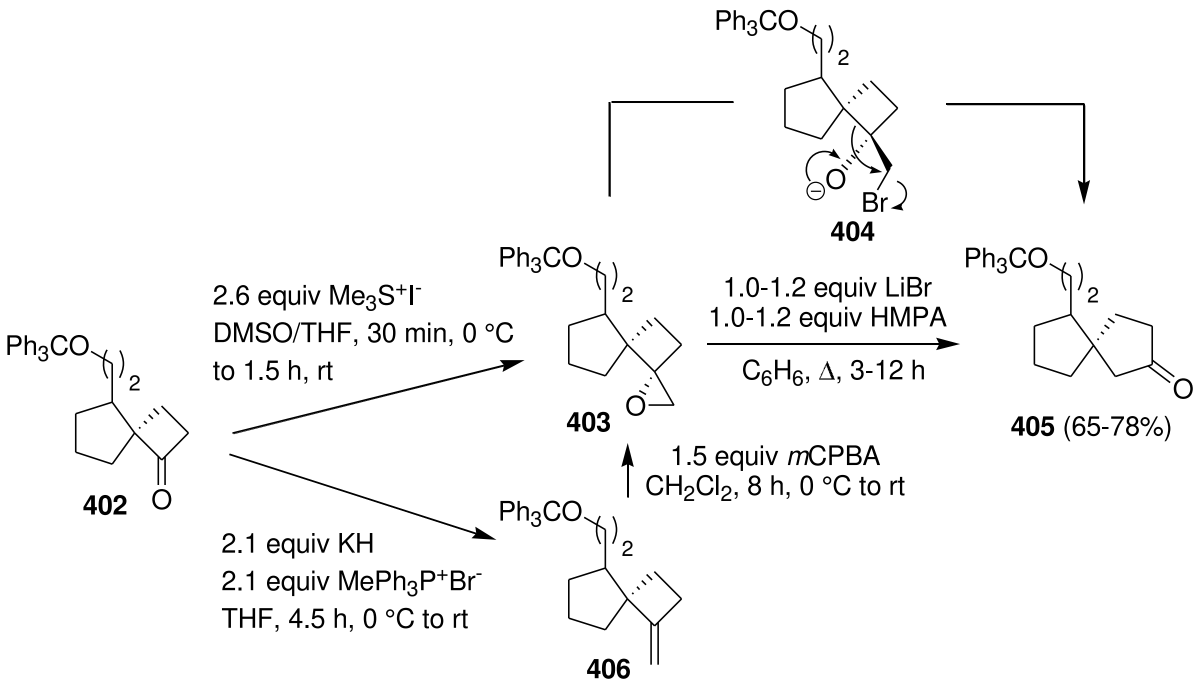


Scheme 110

6.1.2 Cyclobutylmethyl bromides

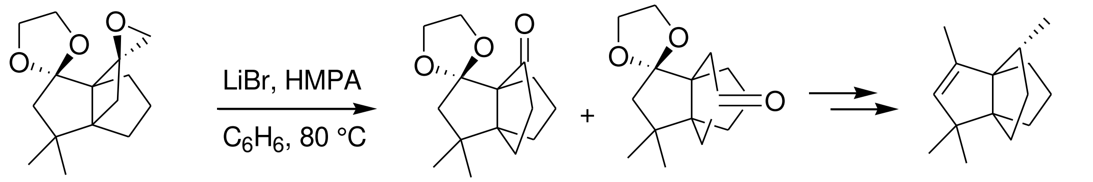
6.1.2.1 Rearrangement of oxaspiro[2.3]hexanes using LiBr

Ring enlargement of cyclobutanones by means of the rearrangement of spiroannelated oxiranes has been developed by Trost and Latimer as an important step in gibberellin synthesis (Scheme 111).[154] Treatment of cyclobutanone **402** with 2.6 equiv of dimethylsulfonium methylide gave **403**, and subsequent treatment with 1.2 equiv of lithium bromide in benzene containing 1.2 equiv of HMPA produced ketone **405** in 65% yield. The cyclobutane to cyclopentane ring expansion proceeded through initial ring opening of epoxide **403** by bromide toward the oxyanion of 1-(bromomethyl)cyclobutanol **404**, followed by skeletal rearrangement to furnish cyclopentanone **405**. Alternatively, conversion of substrates **402** to epoxide **403** via *m*CPBA epoxidation of the Wittig olefination product **406**, followed by rearrangement, gave spirocompound **405** in 78% overall yield. The latter procedure, although one step longer, proceeded in higher yield.



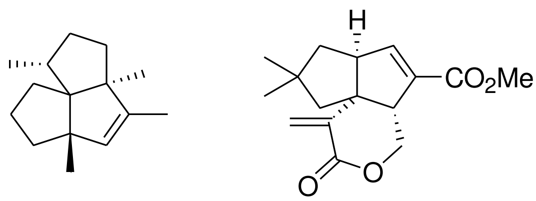
Scheme 111

The same type of epoxide-carbonyl rearrangement was executed in the synthesis of (±)-modhephene **410**.[155] The ring expansion of **407** was carried out in the same manner using lithium bromide and hexamethylphosphoramide in benzene at 80 °C, affording the desired ketone **408** in 86% yield, together with a small amount (9%) of the regioisomer **409** (Scheme 112).



Scheme 112

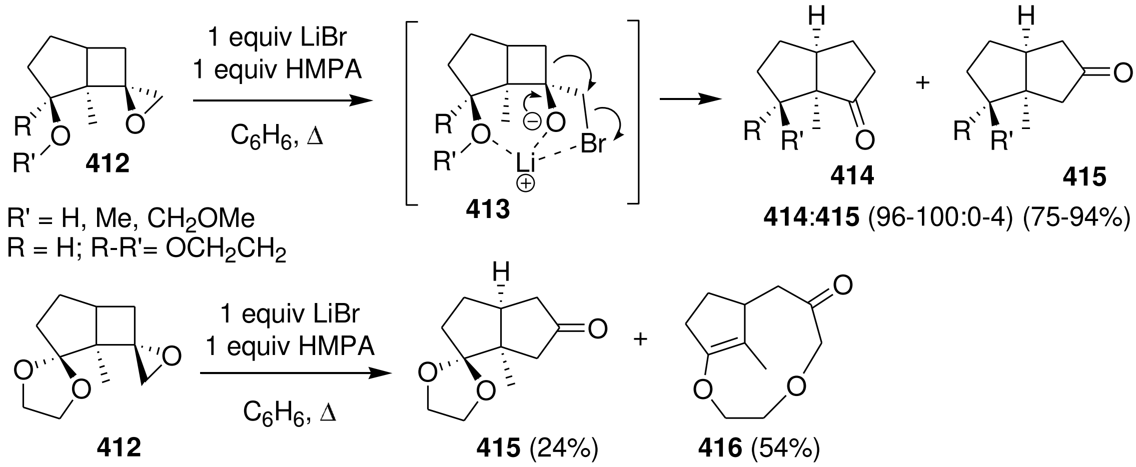
The same authors also published an alternative synthesis of (±)-isocomene **36** (Figure 5). The second five-membered ring was synthesized in 81% yield applying the same reaction conditions (LiBr, HMPA, benzene, 80 °C) from the corresponding epoxide.[156] On the other hand, Wenkert and Arrhenius used LiI in tetrahydrofuran at room temperature for 24 hours for the synthesis of the third five-membered ring of isocomene **36** in 91% yield, also starting from the corresponding epoxide.[157] Two other syntheses of isocomene have previously been described, one using the acid-promoted activation of a vinylcyclobutane (Scheme 10) and one via a cyclobutyl carbinyl ketone rearrangement (Scheme 82), both reported by Pirrung.[42] Pirrung has also described a ring expansion of an epoxide (LiBr, HMPA, benzene, 80 °C) in 85% yield in the synthesis of the precursor of the methyl ester of pentalenolactone G **411** (Figure 5).[158]



isocomene **36** **411**

Figure 5

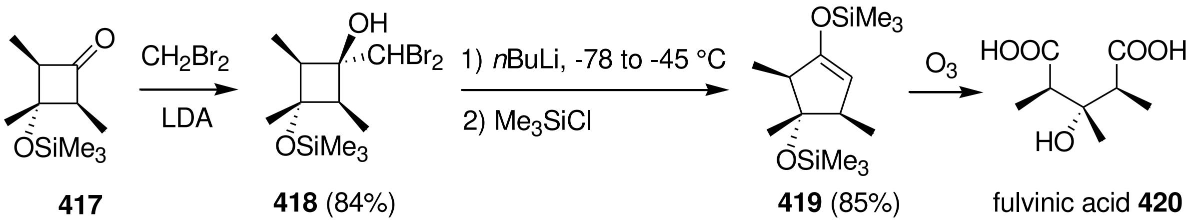
Research on the chelation-controlled regioselective epoxide-carbonyl rearrangement has been effected on 1-oxaspirohexane derivatives, giving difunctionalized bicyclo[3.3.0]octan-2-ones **414** (Scheme 113).[159] When epoxides **412** were subjected to one equiv of lithium bromide and one equiv of hexamethylphosphoramide in benzene at reflux temperature, migration of the less substituted carbon occurred, whose selectivity is controlled by chelation of oxygen to the lithium cation. This process afforded 2,8-disubstituted diquinanes **414** in high selectivity (96-100:0-4) in 75 to 94% yield. In contrast, the *anti*-epoxy acetal **412** did not afford **414** but gave **415** as the only ring expanded product in 24% yield, together with the macrocyclic enol ether **416** in 54% yield.[159]



Scheme 113

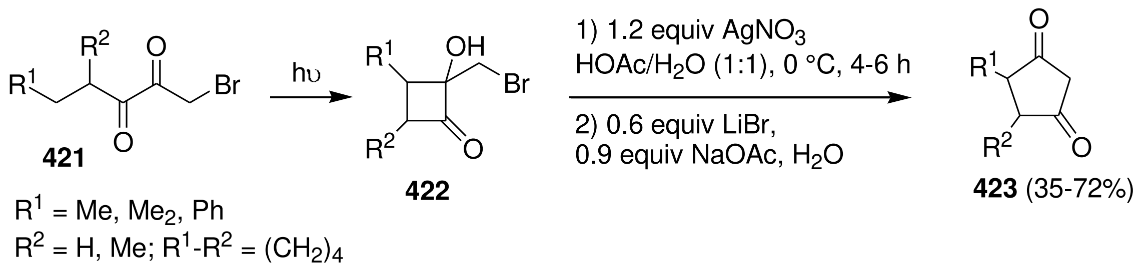
6.1.2.2 Other methods

A ring expansion of a 1-(dibromomethyl)cyclobutanol derivative has been reported by Vedejs and Larsen as part of a synthetic pathway to fulvinic acid **420**.[160] When cyclobutanone **417** was treated with CH_2Br_2 in the presence of LDA, cyclobutyl carbinol **418** was obtained in 84% yield (Scheme 114).[160b] Rearrangement by means of *n*BuLi and Me_3SiCl yielded the ring expanded product **419** in 85% yield which could be converted into fulvinic acid **420** through ozonolysis of the olefinic moiety.



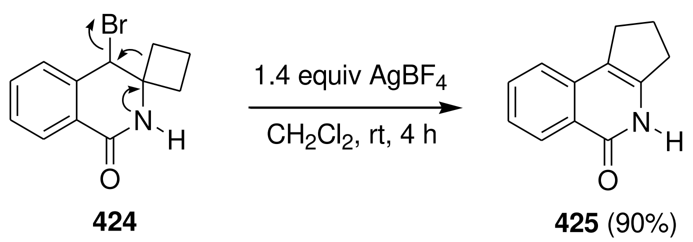
Scheme 114

A Ag^+-induced solvolysis of 2-bromomethyl-2-hydroxycyclobutanones **422**, obtained via photocyclisation of *α*-bromomethyl-1,2-diketones **421**, provided a route to 4-substituted and 4,5-disubstituted cyclopentane-1,3-diones **423**.[161] In that respect cyclobutanones **422** were treated with 1.2 equiv of silver nitrate in aqueous acetic acid (1:1) at 0 °C for four to six hours, after which a solution of 0.6 equiv of lithium bromide and 0.9 equiv of sodium acetate were added, giving rise to the corresponding cyclopentanones **423** in 35-72% yield (Scheme 115).



Scheme 115

In a final example, the formation of a cyclopentane annelated isoquinolone from a spirocyclobutane dihydroisoquinolone was executed by silver tetrafluoroborate addition.[162] The bromomethylcyclobutane derivative **424**, prepared photochemically by bromination using *N*-bromosuccinimide, underwent ring enlargement upon treatment with 1.4 equiv of silver tetrafluoroborate in dichloromethane at room temperature for four hours to provide tetrahydrophenanthridin-6(5H)-one **425** in 90% yield (Scheme 116).

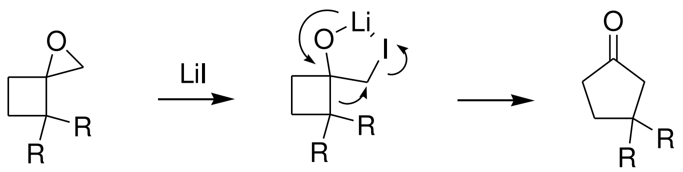


Scheme 116

6.1.3 Cyclobutylmethyl iodides

6.1.3.1 Rearrangement of oxaspiro[2.3]hexanes using LiI

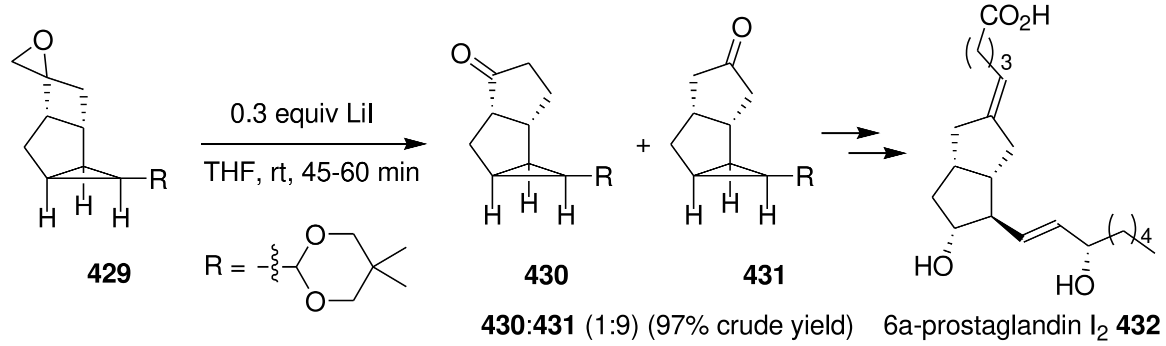
According to literature data, direct and regioselective transformation of oxaspirohexanes **426** into cyclopentanones **428** is best achieved using lithium iodide, although also lithium bromide has proven to give excellent results (*vide supra*).[163] Mechanistically, the isomerization occurres via initial ring opening of the epoxide by nucleophilic addition of iodide, followed by regioselective migration of the more substituted carbon atom of the cyclobutane ring (Scheme 117).



426 **427** **428**

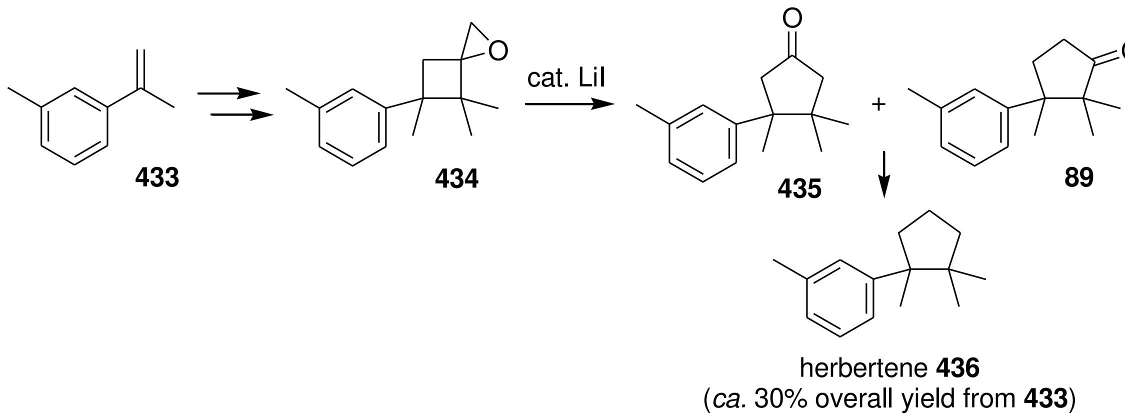
Scheme 117

For example, the synthetic sequence towards 6a-carbaprostaglandin I_2 **432** started with the optically active, tricyclic ketone **429** which was ring expanded to ketones **430** and **431** (Scheme 118).[164] This ring rearrangement was accomplished via the addition of 0.3 equiv of lithium iodide to isomeric spiro epoxides **429** in tetrahydrofuran at room temperature for 45 to 60 min, affording the isomeric cyclopentanones **430** and **431** in 97% crude yield in a 1:9 ratio.[163b]



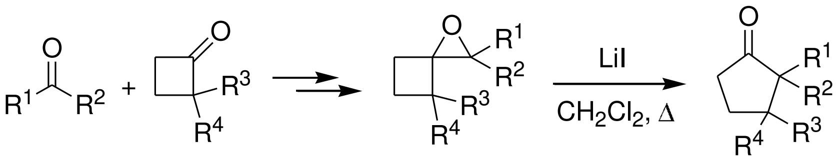
Scheme 118

In a short synthesis of (±)-herbertene **436**, starting from 1-isopropenyl-3-methylbenzene **433**, a carbenium ion promoted rearrangement afforded *β*-herbertenone **435** as the direct precursor (Scheme 119).[57] Spiroannelated oxirane **434**, in the presence of a catalytic amount of lithium iodide, rearranged mainly to *β*-herbertenone **435** next to a minor amount of the isomer **89**. The exact ratio of isomers **435** and **89** was not mentioned in the article. A Huang-Minlon reduction of both ketones using hydrazine in the presence of potassium hydroxide led to (±)-herbertene **436**, with an overall yield of *ca.* 30% from **433**. Synthesis of 2,2,3-trimethyl-(3-methylphenyl)cyclopentanone **89**, the minor isomer in this synthesis, was already described in the acid-promoted ring expansion of propenylcyclobutanols (Scheme 26).[59]



Scheme 119

The synthetic applicability of this approach was further demonstrated by the synthesis of polyalkylated cyclopentanones **440** in a regioselective way using cyclobutanones **439** and carbonyl compounds **437** as starting material (Scheme 120).[165] The final step in this approach comprised a ring expansion of epoxides **439**, which was achieved using lithium iodide in dichloromethane at reflux temperature to afford cyclopentanones **440** in 77 to 91% yield. This was the first example of a ring rearrangement of an epoxide ring bearing one or two alkyl groups. The ring rearrangement proved to be highly regioselective via migration of the more substituted carbon atom of the cyclobutane ring.



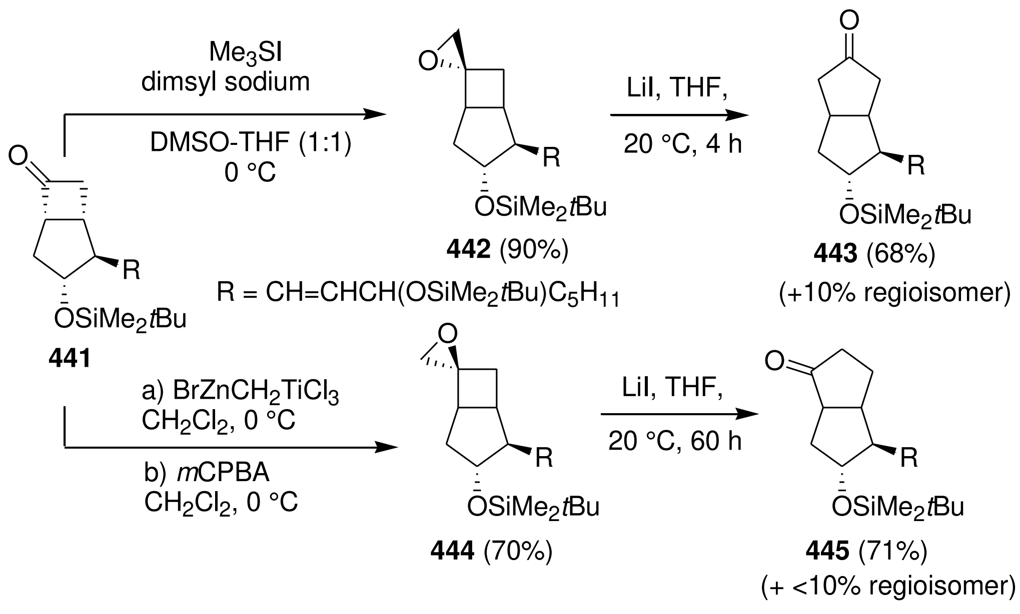
437 **438** **439** **440** (77-91%)

R^1, R^3 = H, Me
R^2 = H, C_9H_{19}, $C_{10}H_{21}$
R^4 = H, C_5H_{11}, C_9H_{19}

Scheme 120

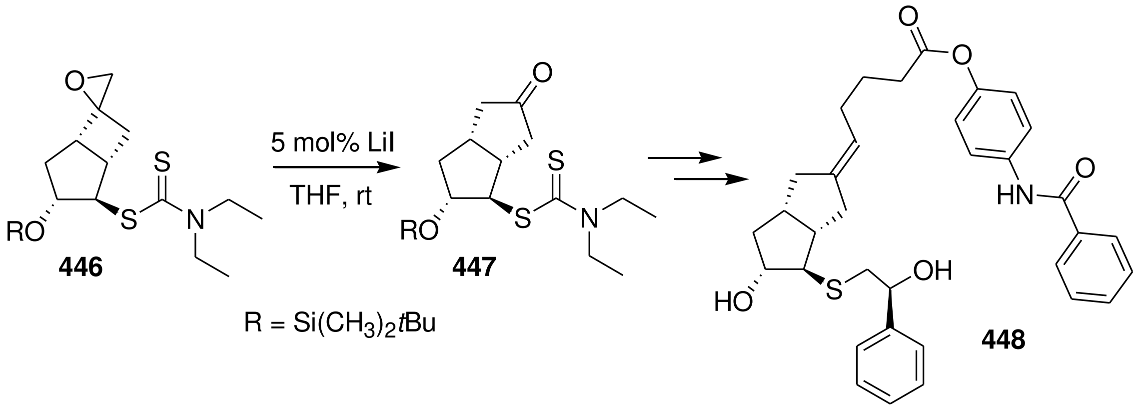
As mentioned before, Krief and co-workers have also used a spiro epoxide in the synthesis of *β*-cuparenone **379** (Scheme 106).[148] Treatment of the spiro epoxide **376** with lithium iodide in dioxane in the presence of one equiv of 12-crown-4, afforded *β*-cuparenone **379** and a small fraction of its regioisomer **378** in a selectivity of 94:6 in 95% yield. It should be noted that the opposite selectivity was obtained upon treatment of epoxide **376** with $BeCl_2$, as depicted in Scheme 106.

The regioselective synthesis of two bicyclo[3.3.0]octane systems **443** and **445** (carbaprostacyclin precursors) via spirooxiranes **442** and **444**, respectively, further demonstrated the feasibility of the spiroannelation methodology (Scheme 121).[166] α-Epoxide **442** was synthesized in 90% yield via the Corey-Chaykovsky method, and subsequent rearrangement of **442** afforded ketone **443** in 68% yield and its isomer **445** in 10% yield, after chromatography. The corresponding β-epoxide **444** was subsequently prepared in 70% overall yield, from the bicycloheptanone **441** after initial conversion into the analogous methylene derivative using the method of Lombardo, followed by epoxidation.[167] In direct contrast to the cleavage of the α-epoxide **442**, the β-epoxide **444** underwent a slow, regioselective rearrangement to yield ketone **445** in 71% accompanied by less than 10% of ketone **444**. The obtained bicyclo[3.3.0]octane framework is a structural unit shared by a variety of sesquiterpenes and many carbocyclic analogues of prostacyclin (PGI_2).



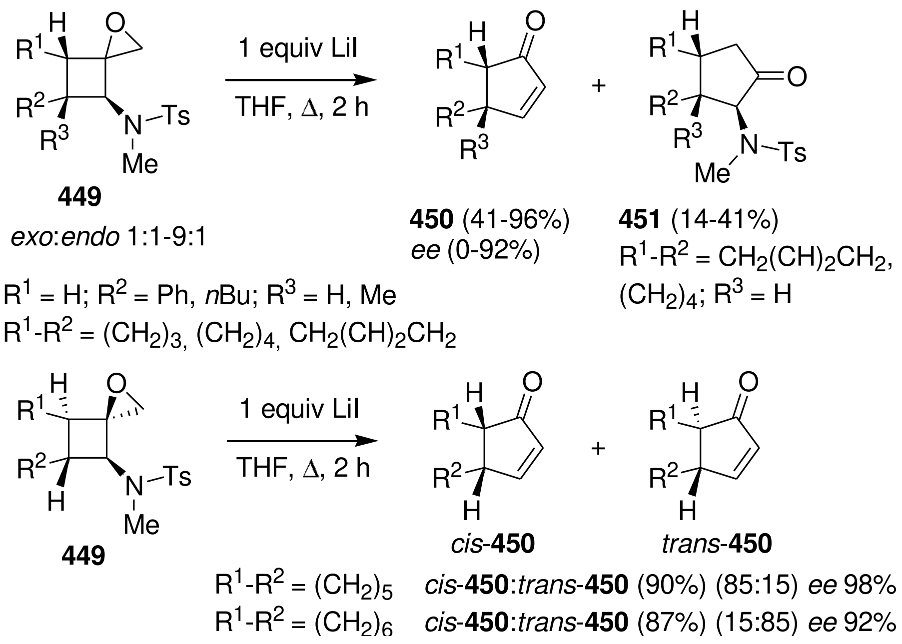
Scheme 121

As part of the synthesis of 13-thiacarbacyclines, used as medicines, lithium iodide was used in the formation of the bicyclo[3.3.0]octanone skeleton (Scheme 122).[168] When five mol% of lithium iodide was added to spirooxirane **446** in tetrahydrofuran at room temperature, bicyclo[3.3.0]octanone **447** was isolated. No yield was mentioned for the ring expansion step.



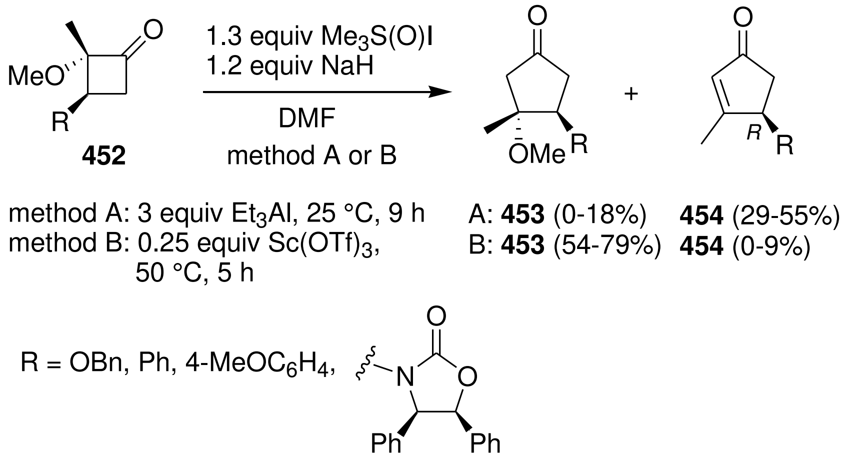
Scheme 122

The ring expansion of oxiranes **449**, prepared from 2-*N*-methyl-*N*-tosylcyclobutanones by reaction with dimethylsulfonium methylide,[169] with a stoichiometric amount of lithium iodide in tetrahydrofuran at reflux temperature for two hours afforded mono- or bicyclic cyclopentenones **450** in 41-96% yield with 0-92% *ee*, resulting from a *β*-elimination of *N*-methyl-*N*-tosylamide from a initially formed cyclopentanone. The ring expansion was completely selective with the exception of the bicyclo[4.2.0]octanone systems (R^1-R^2 = $CH_2(CH)_2CH_2$, $(CH_2)_4$), which afforded a side product **451** in 14-41% yield. The ring expansion of chiral *trans*-bicyclo[5.2.0]nonane **449** (R^1-R^2 = -$(CH_2)_5$-) or *trans*-bicyclo[6.2.0]decane **449** (R^1-R^2 = $(CH_2)_6$) afforded a mixture of *cis*- and *trans*-cyclopentenones **450** (85:15 *dr*, 98% *ee* and 15:85 *dr*, 92% *ee*, respectively) in 87 to 90% yield (Scheme 123).



Scheme 123

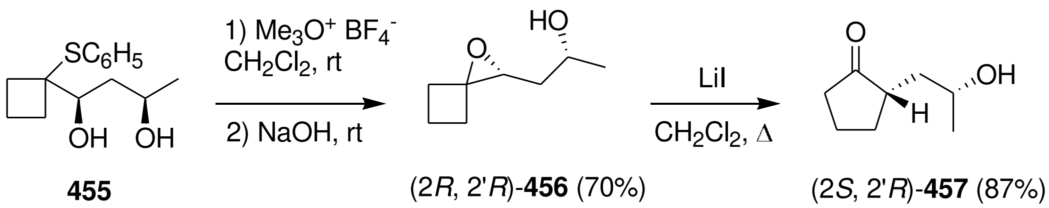
A Lewis acid-promoted one-pot ring expansion of trisubstituted cyclobutanones has been executed starting from 3-substituted 2-methoxy-2-methylcyclobutanones **452** (Scheme 124).[170] An ylide, generated from trimethyloxo-λ^4-sulfanium iodide ($Me_3S(O)I$) and sodium hydride, served as the C_1-equivalent. Addition of cyclobutanones **452** to a solution of $Me_3S(O)I$ and sodium hydride in dimethylformamide (DMF), followed by addition of three equiv of Et_3Al at 25 °C for nine hours, afforded the corresponding cyclopentanones **453** in 0-18% yield and cyclopentenones **454** in 29-55% yield. Replacing Et_3Al with 0.25 equiv of scandium(III) triflate at 50 °C for five hours improved the reaction, providing higher yields (54-79%) for cyclopentanones **453**, and little or no alkoxide elimination (0-9% cyclopentenones **454**).



Scheme 124

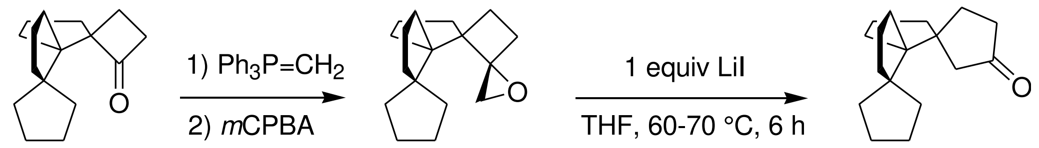
Another example concerning cyclopentanone synthesis through elaboration of spirooxiranes was recently reported.[171] Chiral diol (1*R*,3*R*)-*syn*-**455** was transformed into oxaspirohexane **456** which, by reaction with lithium iodide, gave cyclopentanone **457** in 87% yield (Scheme 125). This reaction was also the first to report the transformation of a chiral oxaspirohexane to obtain **457** diastereoisomerically pure with no loss of stereochemical integrity through inversion of configuration at the migrating terminus.

Analogous rearrangements have also been executed with lithium iodide in dichloromethane or with Et_2AlCl in toluene to afford 2-alkyl-2-arylcyclopentanones in 65-99% yield and in an enantiomeric excess of 70-90%.[172]



Scheme 125

A last example involves in the synthesis of pseudohelical hydrocarbons of four- and five-membered rings.[69] A sequential ring enlargement via a high temperature methylenation, an epoxidation, and a lithium iodide-induced rearrangement proved necessary to synthesize complex cyclopentanone **460** (Scheme 126). The ring expansion of spirooxirane **459** to cyclopentanone **460** proceeded in 88% yield by reaction with one equiv of lithium iodide in tetrahydrofuran at 60 to 70 °C for six hours. All attempts of a direct ring enlargement of **458** with diazomethane failed. The diazomethane type ring expansion will be discussed further in this review.



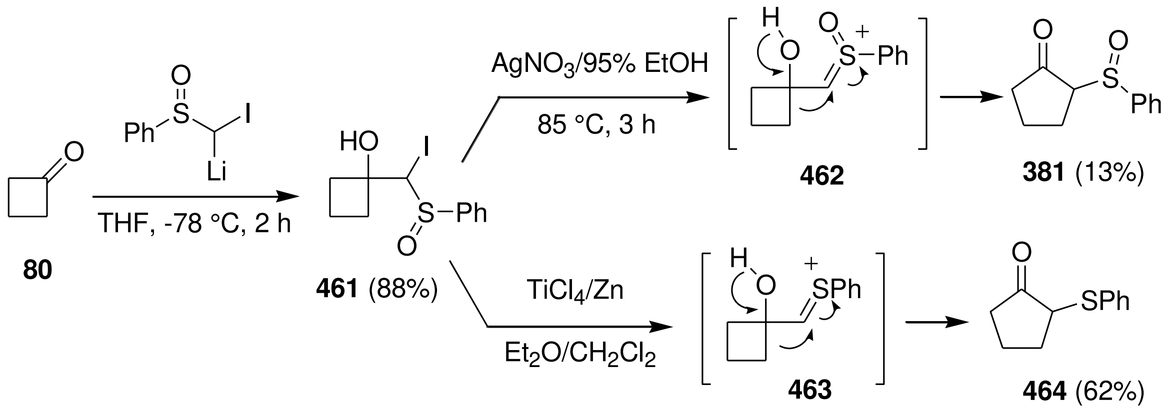
458 **459** **460**(88%)

Scheme 126

6.1.3.2 Other methods

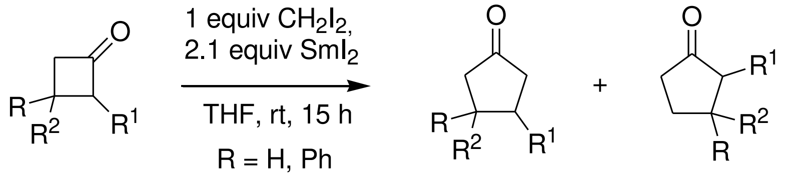
Whereas the majority of literature examples comprise rearrangements of oxaspiro[2.3]hexanes, a few other approaches via transformation of cyclobutylmethyl iodides are known.

In a first example, lithio(iodomethyl)phenylsulfoxide, generated by the reaction of (iodomethyl)phenylsulfoxide with LDA in tetrahydrofuran at -78 °C, reacted with cyclobutanone **80** to form adduct **461** in 88% yield (Scheme 127).[173] Reaction of the adduct **461** with silver nitrate in 95% ethanol at 85 °C for three hours gave compound **381** in 13% yield, involving the intermediacy of phenylsulfinyl ion **462**. Because of the low yield, compound **461** was treated with $TiCl_4$/Zn in an ether/dichloromethane mixture to synthesize *α*-phenylsulfenylcyclopentanone **464** in 62% yield, presumably via the intermediate thionium ion **463**.



Scheme 127

Alternatively, iodomethylation has been used in the transformation of cyclobutanones **465** to cyclopentanones **466** and **467**.[174] Samarium diiodide-induced iodomethylation of cyclobutanones with diiodomethane provided a simple way for the synthesis of iodohydrins, which underwent ring expansion when exposed to a base. When 3-monosubstituted and 3,3-disubstituted cyclobutanones **465** were treated with one equiv of CH_2I_2 and 2.1 equiv of SmI_2 in tetrahydrofuran at room temperature for 15 h, the corresponding cyclopentanones **466** and **467** were synthesized in 40-88% yield (Scheme 128). Only with bicyclic cyclobutanones, two regioisomers of cyclopentanone derivatives were produced as a 1:1 mixture (R^1-R^2 = $(CH_2)_4$ or $CH_2CH{=}CHCH_2$) or in a isomer ratio of 97:3 (R^1-R^2 = $(CH_2)_5$).



465 **466**:**467** (40-88%)

R^1 = H; R^2 = Ph, *n*Bu, *tert*-Bu, Me **466**:**467** (1:0)
R^1-R^2 = $(CH_2)_4$, $CH_2CH{=}CHCH_2$ **466**:**467** (1:1)
R^1-R^2 = $(CH_2)_5$ **466**:**467** (97:3)

Scheme 128

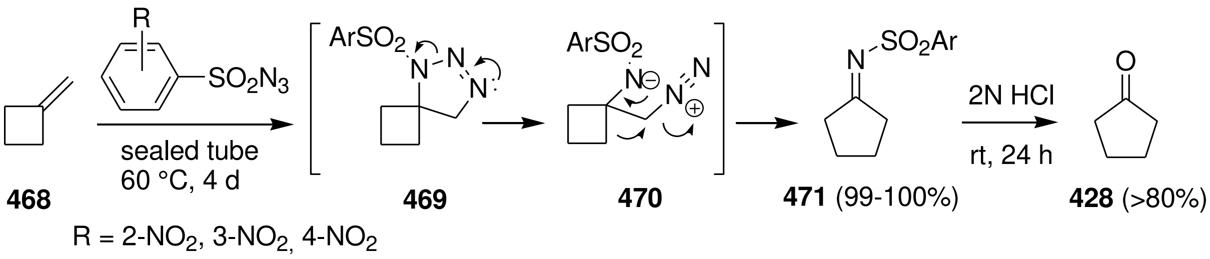
6.2 N_2 as leaving group

Numerous examples of cyclobutane to cyclopentane rearrangements are known based on the formation and ring expansion of intermediate cyclobutylmethylcarbenium ions through expulsion of nitrogen gas as a leaving group. Besides a few isolated examples as azide addition across methylenecyclobutanes, the vast majority of papers deal with semipinacol-type rearrangements via diazoalkanes.

6.2.1 Via azide addition across methylenecyclobutanes

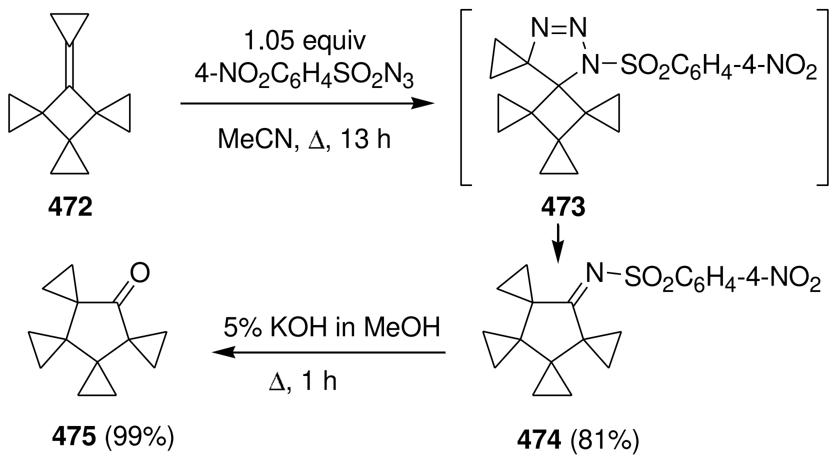
Methylenecyclobutane **468** has been reported to react with aromatic sulfonyl azides under high pressure at 60 °C for four days to give the corresponding ring enlarged *N*-sulfonylimines **471** in almost quantitative yield (Scheme 129).[175] This 1,3-dipolar addition of azides to electron-rich olefins was facilitated by strong electron-withdrawing substituents attached to the azide moiety. The resulting triazolines turned out to be relatively unstable, resulting in the evolution of nitrogen gas spontaneaously or upon gentle heating. This type of ring enlargement is closely related to the Demjanov-Tiffeneau reaction. In a last step, the *N*-

sulfonylimines **471** were hydrolysed to cyclopentanone **428** with aqueous hydrogen chloride in more than 80% yield.



Scheme 129

The same methodology has been used by Fitjer for the synthesis of tetraspiro[2.0.2.0.2.1]tridecan-13-one **475** (Scheme 130).[176] Treatment of 13-cyclopropylidenetetraspiro[2.0.2.0.2.0.2.1]tridecane **472** with 1.05 equiv 4-nitrobenzenesulfonyl azide in acetonitrile at reflux for 13 hours afforded tetraspiro[2.0.2.0.2.1]tridecan-13-one **474** in 81% yield. The corresponding ketone **475** was synthesized in 99% yield by reaction of **474** with a 5% potassium hydroxide solution in methanol at reflux temperature for one hour. The same ring enlargement sequence was applied in the synthesis of [3.3.0]propellanes.[134a,b]

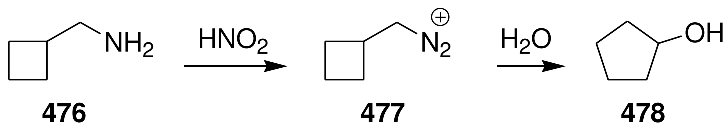


Scheme 130

6.2.2 Semipinacol rearrangement

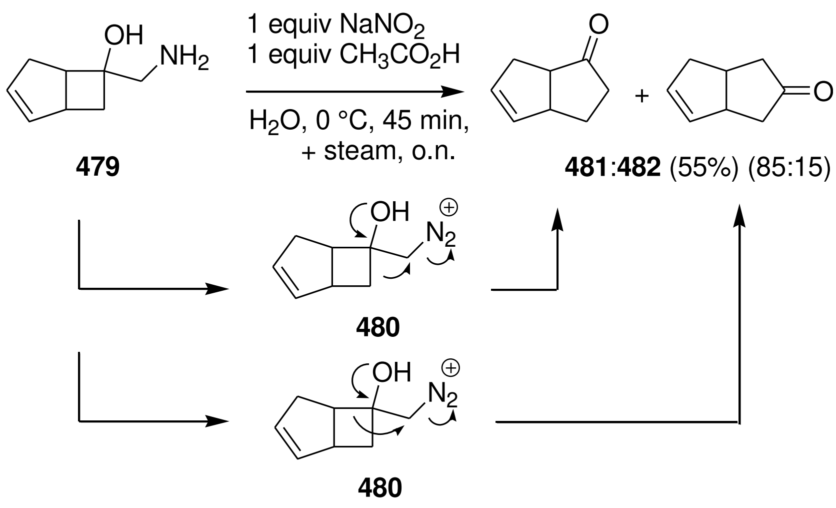
6.2.2.1 Semipinacol rearrangement of diazonium salts derived from 2-aminoalcohols (Tiffeneau-Demjanov rearrangement)

Cycloalkylmethylamines **476** can undergo ring expansion upon diazotation, affording cyclic alcohols **478**. This kind of reaction, the conversion of an amino to a diazonium group and subsequent ring expansion, is also known as the Demjanov rearrangement (Scheme 131).[177,178]



Scheme 131

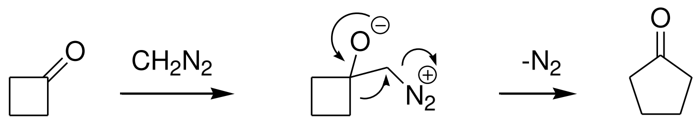
A semipinacol rearrangement of 6-(aminomethyl)bicyclo[3.2.0]-2-hepten-6-ol **479** has been executed using nitrous acid to afford a mixture of bicyclo[3.3.0]octenones **481** and **482** (85:15) in 55% yield (Scheme 132).[179] This type of reaction, the conversion of an amino to a diazonium group and subsequent carbonyl formation and ring expansion of intermediate **480**, is also known as the Tiffeneau-Demjanov rearrangement.



Scheme 132

6.2.2.2 Semipinacol rearrangement of diazoalkanes

Among the variety of carbocyclic ring expansions of cyclobutanones to cyclopentanones, the diazomethane methodology is the most extensively used (Scheme 133).[20,180] With a few exceptions, the rearrangement of the intermediate zwitter ion **483** is highly regioselective and only one product is generally isolated, particularly in cases were *α*-chloro- or *α*,*α*-dichlorocyclobutanones and substituted diazomethanes are used. With unsymmetrical cyclobutanones, diazomethane ring expansions tend to favor migration of the less substituted *α*-carbon and disfavor migration of *α*-positions bearing electronegative halogens. However, other factors including steric effects, ring strain, steric hindrance related to the approach of the diazomethane, and the conformation of the intermediate betaine can influence the regioselectivity of migration, making predictions difficult. Several examples will be described in this section.

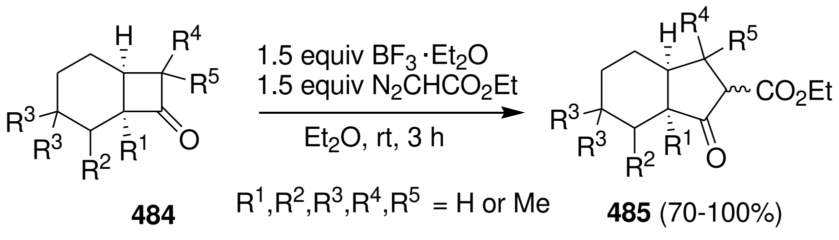


80 **483** **428**

Scheme 133

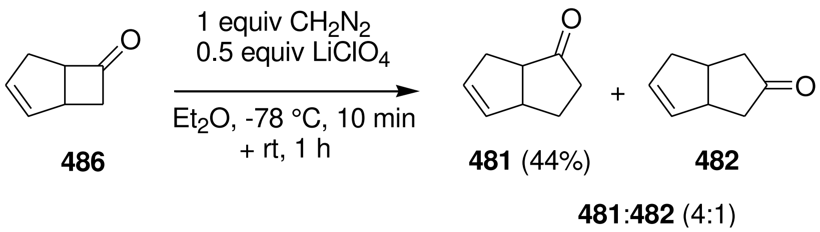
6.2.2.2.1 Non-halogenated cyclobutanone derivatives

In a first example, hydrindanonecarboxylates **485** have been synthesized using the diazoalkane ring expansion method in a highly selective manner (Scheme 134).[181] Bicyclo[4.2.0]octanones **484** reacted with 1.5 equiv of boron(III) fluoride etherate and ethyl diazoacetate in diethyl ether at room temperature for three hours to afford bicylo[4.3.0]nonanones **485** in 70 to 100% yield.



Scheme 134

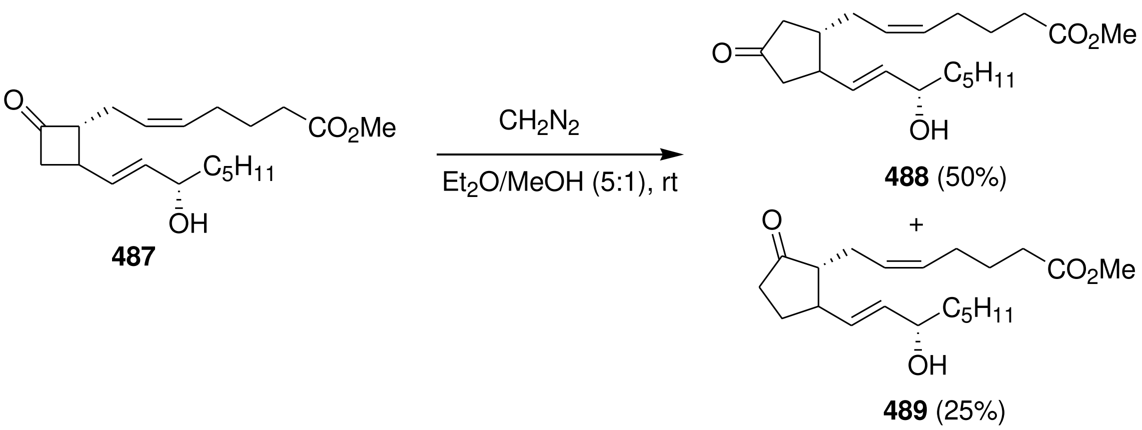
In research on bicyclooctanes, ring expansion of bicyclo[3.2.0]hept-2-en-6-one **486** using one equiv of diazomethane in the presence of 0.5 equiv of lithium perchlorate in diethyl ether at -78 °C for ten minutes and subsequently at room temperature for one hour provided a mixture of two regioisomers **481** and **482** in a 4:1 ratio (Scheme 135).[182] The desired bicyclo[3.3.0]oct-2-en-6-one **481** was isolated from the mixture in 44% yield. In the absence of a Lewis acid, the observed ratio was approximately 3:2.



Scheme 135

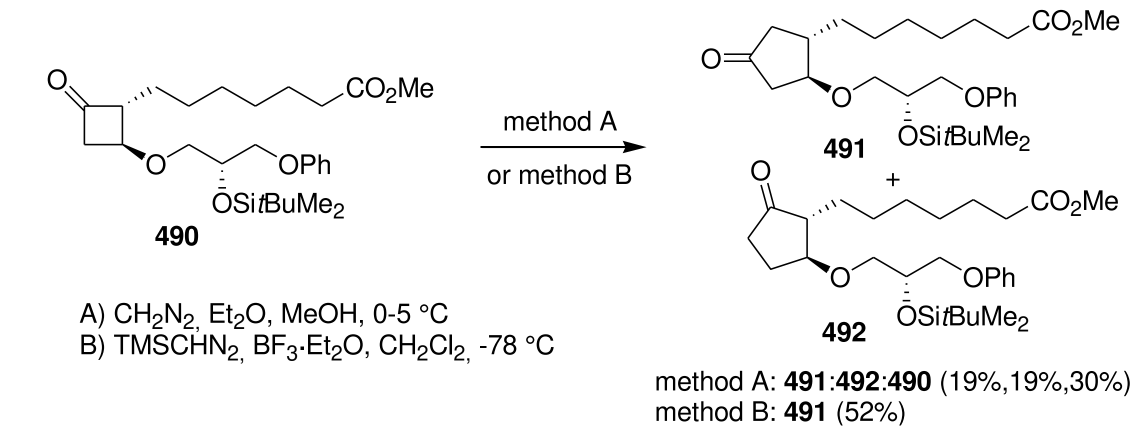
Ring expansion of 11-norprostaglandin **487** (11-nor PGE_2) toward methyl 15α-hydroxy-10-oxoprosta-5,13-dienoate **488** and 11-desoxy PGE_2 **489** was achieved by treatment with diazomethane in a 5:1 diethyl ether/methanol solution at room temperature (Scheme 136).[183,184] After chromatographic separation, methyl 15α-hydroxy-10-oxoprosta-5,13-

dienoate **488** was isolated in 50% yield, together with 11-desoxy PGE_2 **489** in 25% yield. However, this experiment clearly demonstrated that in the case of alkyl substituted cyclobutanones the ring enlargement with diazomethane occurred in good chemical yield but with poor regioselectivity.



Scheme 136

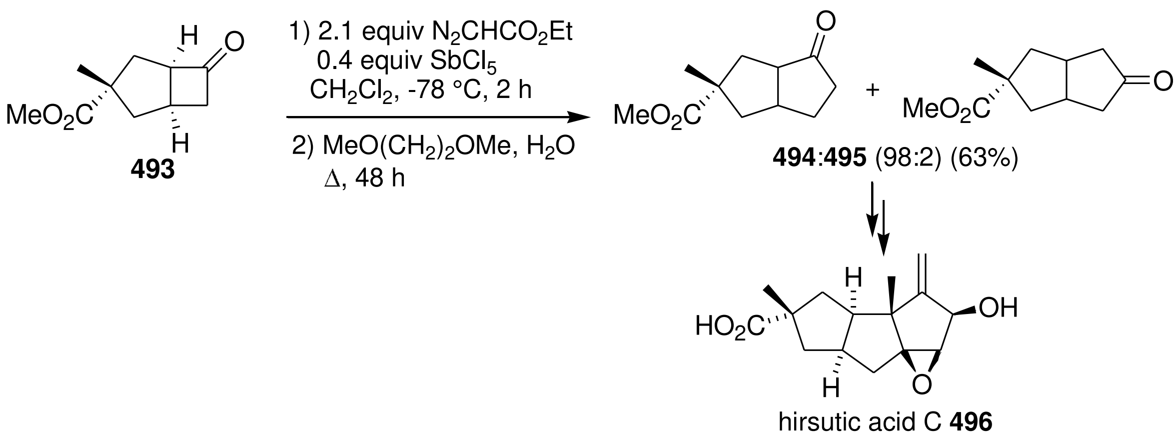
In another approach, an effort has been made to synthesize prostanoids containing an ether linkage in the lower side-chain as potent anti-ulcer compounds.[185] Again, the cyclopentanone ring was synthesized via a ring expansion of a suitable cyclobutane precursor. When cyclobutanone **490** was treated with diazomethane in ether and methanol at 0-5 °C, a mixture of regioisomers **491** and **492** was obtained in low yield (19% **491** and 19% **492**), next to 30% unreacted starting material **490** (Scheme 137). However, when trimethylsilyldiazomethane was used in the presence of $BF_3 \cdot Et_2O$ in dichloromethane at -78 °C, the reaction was regioselective, and only isomer **491** was isolated in 52% yield.



Scheme 137

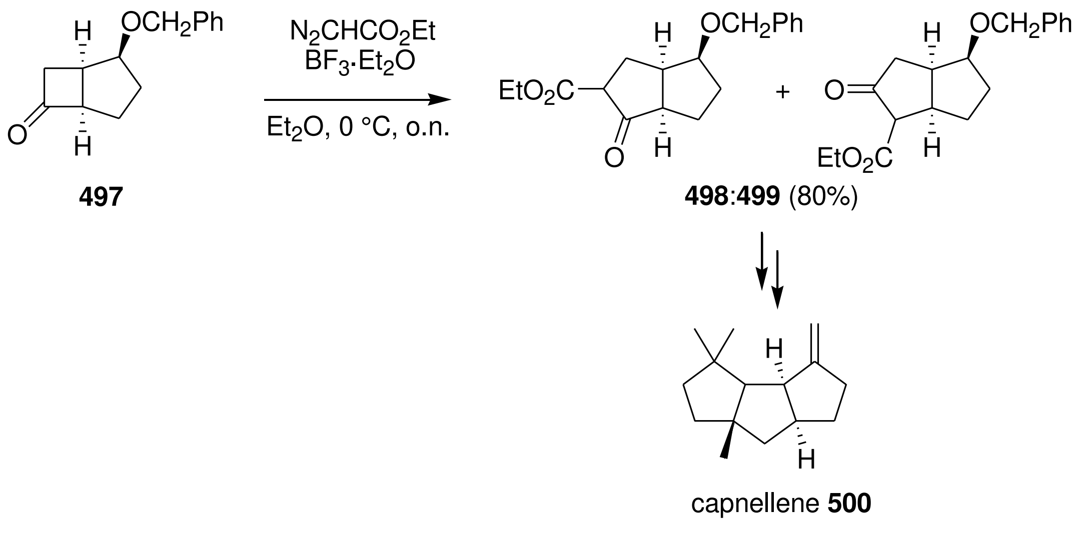
Plentiful synthetic routes have been developed toward the preparation of natural products and their derivatives employing the cyclobutanone to cyclopentanone ring expansion reactions with diazoalkanes.

In a first example, Greene *et al.* reported the total synthesis of natural hirsutic acid C **496** (Scheme 138) through adjustment of a known racemic synthesis (*vide infra*).[186] Cyclobutanone **493** was exposed to 2.1 equiv of ethyl diazoacetate and 0.4 equiv of antimony(V) chloride in dichloromethane at -78 °C for two hours to afford a regioselective ring expansion, which was followed by deethoxycarbonylation to provide a 98:2 mixture of ketones **494** and **495**, from which pure **494** was isolated by silica gel chromatography.



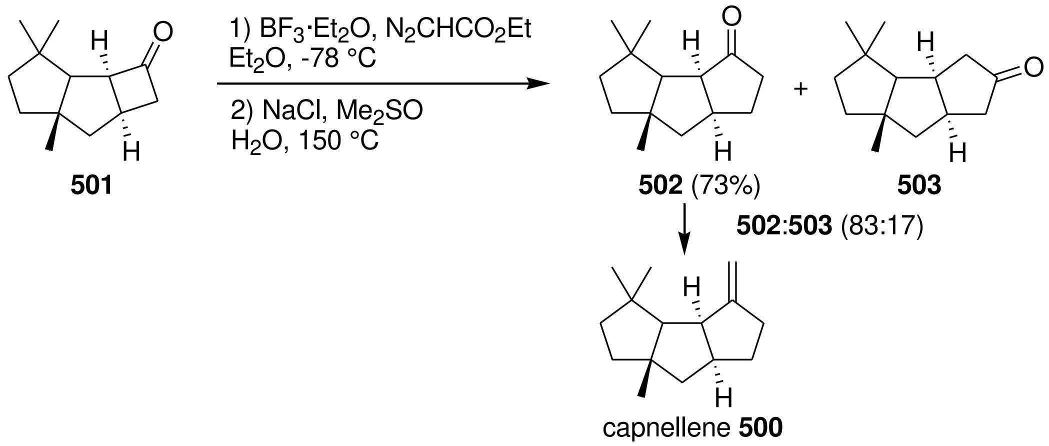
Scheme 138

Capnellene **500**, the presumed biosynthetic precursor of the capnellane family of nonisoprenoid sesquiterpenes, has received significant synthetic attention due to the *cis*-*anti*-*cis* tricyclo(6.3.0.0^{2,6})undecane skeletal framework. These compounds also display biological effects similar to those of their terrestrial counterparts, hirsutanes, which possess promising antibacterial and antitumor properties.[187] In a total synthesis of racemic capnellene **500**, the second five-membered ring was formed via a ring rearrangement of 2-benzyloxybicyclo[3.2.0]heptane-6-one **497**.[188] To induce the required ring expansion, compound **497** was treated with ethyl diazoacetate in diethyl ether in the presence of boron(III) fluoride etherate at 0 °C and stirred overnight (Scheme 139). The desired ketoester **498** was formed preferentially along with a small amount of its regioisomer **499** as an inseparable mixture in a total yield of 80%. The exact ratio of the two isomers was not reported in the article.



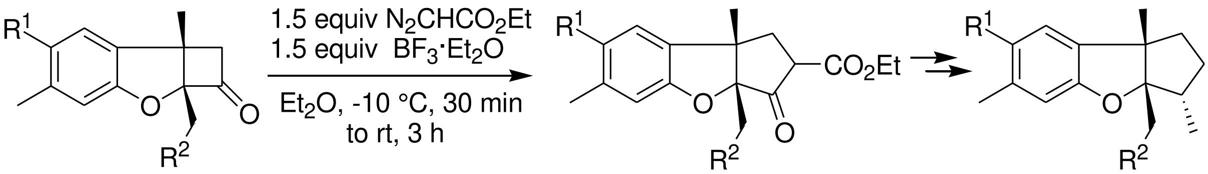
Scheme 139

An alternative synthesis of racemic capnellene was reported by Stille and Grubbs, who used the diazomethane ring expansion methodology to synthesize the third five-membered ring of the precursor of capnellene.[189] The ring expansion was executed via addition of boron(III) fluoride etherate and ethyl diazoacetate to cyclobutanone **501** in diethyl ether at -28 °C, followed by addition of sodium chloride and dimethylsulfoxide in water at 150 °C (Scheme 140). However, only a 83:17 ratio of **502** to its regioisomer **503** was obtained. Column chromatography afforded cyclopentanone **502** in 73% yield, which could be converted into (±)-$\Delta^{(9,12)}$-capnellene **500** in one step. A total and selective synthesis of (-)-$\Delta^{(9,12)}$-capnellene **500** and its antipode, based on a ring expansion for the synthesis of the second five-membered ring using ethyl diazoacetate in the presence of antimony(V) chloride, has been reported in 1991.[190] 2,2,5-Trimethylbicyclo[3.2.0]heptan-6-one rearranged via treatment with ethyl diazoacetate in the presence of antimony(IV) chloride to yield the corresponding 2,2,5-trimethylbicyclo[3.3.0]octan-6-one in 85% yield.



Scheme 140

A total synthesis of the marine sesquiterpenes (±)-aplysin **150** (R^1 = Br, R^2 = H), (±)-debromoaplysin **151** (R^1 = R^2 = H), (±)-aplysinol **506** (R^1 = Br, R^2 = OH), (±)-debromoaplysinol **507** (R^1 = H, R^2 = OH), and (±)-isoaplysin **508** (R^1 = H, R^2 = Br), has been reported using ethyl diazoacetate for the ring rearrangement.[191] A first synthesis of aplysin was already described previously (Scheme 44), involving a palladium-promoted ring expansion of alkenylcyclobutanols.[72] Treatment of compounds **504** with 1.5 equiv of ethyl diazoacetate in the presence of 1.5 equiv of boron(III) fluoride etherate in diethyl ether at -10 °C for 30 minutes and subsequently at room temperature for three hours furnished the *β*-ketoesters **505** regioselectively in 81-82% yield, which could be converted into the appropriate sesquiterpene **150**, **151** and **506-508** (Scheme 141).

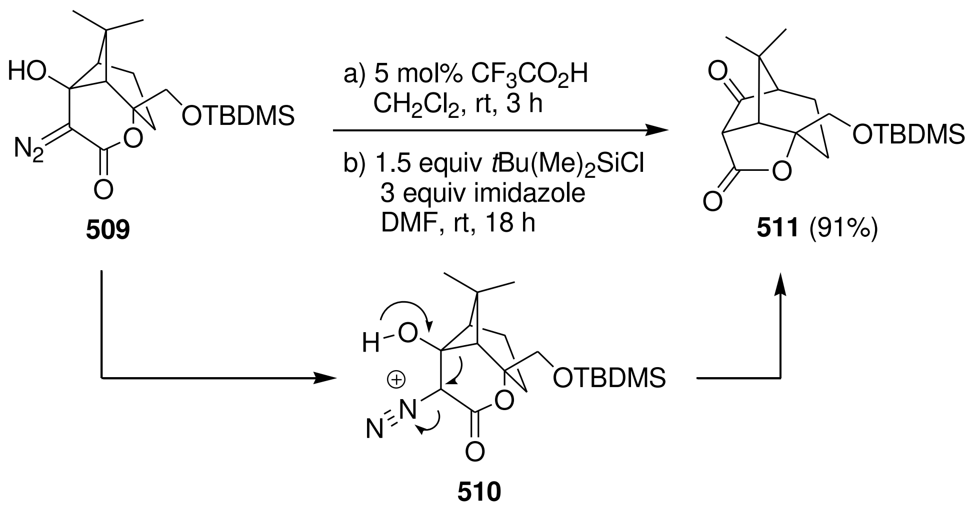


504 **505** (81-82%)

	R^1	R^2
aplysin **150**	Br	H
debromoaplysin**151**	H	H
aplysinol **506**	Br	OH
debromoaplysinol **507**	H	OH
isoaplysin **508**	H	Br

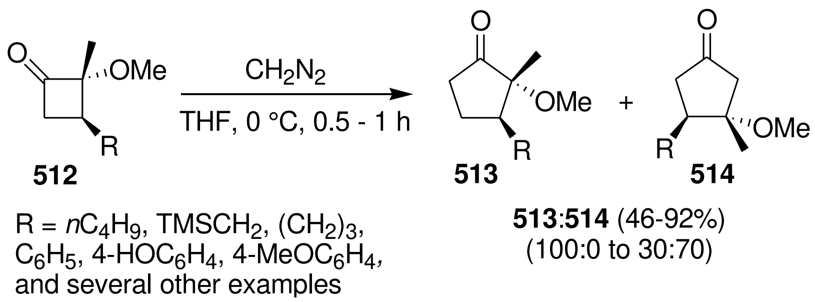
Scheme 141

In research on taxoids, a semipinacol rearrangement using nitrogen gas as a leaving group has been used for the synthesis of a 6-pinanone derivative.[192] Addition of 5 mol% of trifluoroacetic acid to diazolactone **509** in dichloromethane at room temperature, and treatment of the reaction mixture with 1.5 equiv of *tert*-butyldimethylsilyl chloride in the presence of three equiv of imidazole in dimethylformamide at room temperature afforded lactone **511** in 91% yield through rearrangement of intermediate **510** (Scheme 142).



Scheme 142

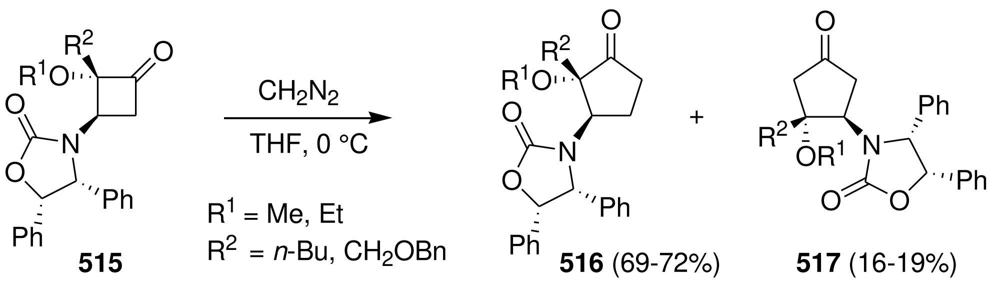
The ring expansion of β-substituted α-methyl-α-methoxycyclobutanones by diazomethane and the influence of the β-substituent on the regioselectivity has been studied by Reeder and Hegedus (Scheme 143).[193] β-Substituted 2-methoxy-2-methylcyclobutanones **512** with the α-methyl group in *syn*-position with regard to the β-substituent reacted with diazomethane in tetrahydrofuran at 0 °C to yield cyclopentanones **513** and **514** in 46 to 92% yield. Migration of the less-substituted α-position is favored and electronegative groups suppress migration, and thus ring expansion should strongly favor formation of regioisomer **513**. Although this was indeed the case, the observed ratios of **513** to **514** varied from 100:0 to 30:70 depending on the β-substituent. However, the root cause of this influence was unclear.



Scheme 143

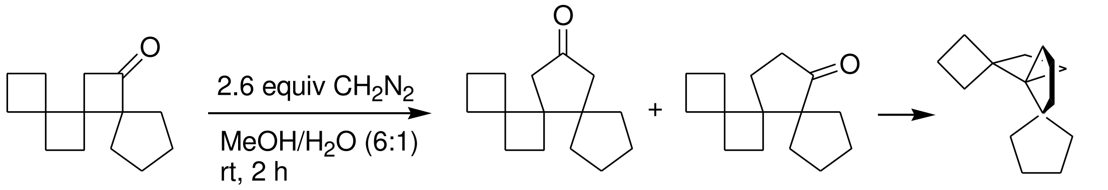
Aminocyclobutanones **515** rearranged to aminocyclopentanones **516** and **517** via a diazomethane ring expansion reaction (Scheme 144).[194a] When cyclobutanones **515** were treated with diazomethane, migration of the less substituted carbon predominated toward the formation of cyclopentanones **516** in 69 to 77% yield, next to the minor isomers **517** in 16 to 19% yield.

In the field of metal-catalyzed allylic substitution reactions, an analogous ring expansion (R^1, R^2 = Me) has been reported in 2002 where the corresponding cyclopentanone was synthesized in 72% yield.[194c]



Scheme 144

Structurally challenging pseudohelical hydrocarbons of four-and five-membered rings were synthesized by Widjaja *et al.*[69] Enantiopure ketone **518** was subjected to diazomethane to obtain a 55:45 mixture of ring expanded ketones **519** and **520** in 71% yield, which were reduced via a Wolff-Kishner approach to trispirane (*S*)-**521** (Scheme 145). In contrast to cyclobutanone **458** (Scheme 126), which could not be converted directly to the corresponding cyclopentanone using diazomethane, there were no problems detected for this conversion.

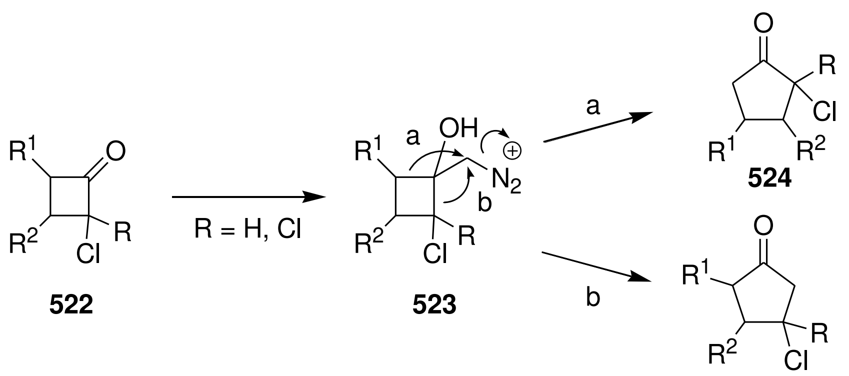


518 **519**:**520** (71%) (55:45) (*S*)-**521** (66%)

Scheme 145

6.2.2.2.2 α-Chloro- or α,α-dichlorocyclobutanone rearrangements

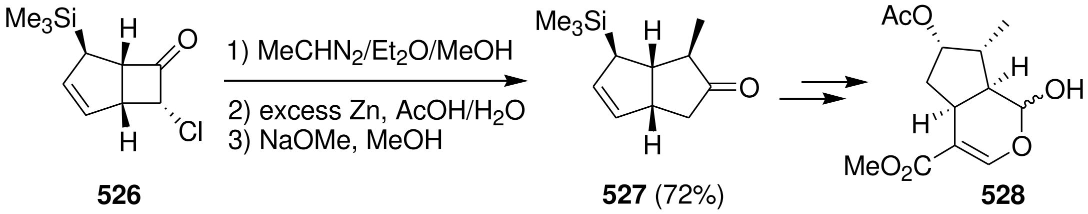
Although the above-mentioned ring expansions proceeded quite cleanly to afford the corresponding cyclopentanones, a low degree of regioselectivity in the migration was sometimes observed, especially in cases where unsubstituted diazomethane was used (see for example Scheme 136). However, the presence of *α*-chloro substituent(s) not only accelerates the rate of the reaction, but also favors path a over path b (Scheme 146).[195] *α*-Chloro and *α*,*α*-dichlorocyclobutanones **522** react faster and more regioselectively in the ring enlargement reaction using diazomethane. Epoxide formation is not significant, probably because of the strained nature of the four-membered ring,[196] in spite of the fact that epoxide formation generally increases with the introduction of electronegative substituents adjacent to the carbonyl.[180]



522 **523** **524** **525**

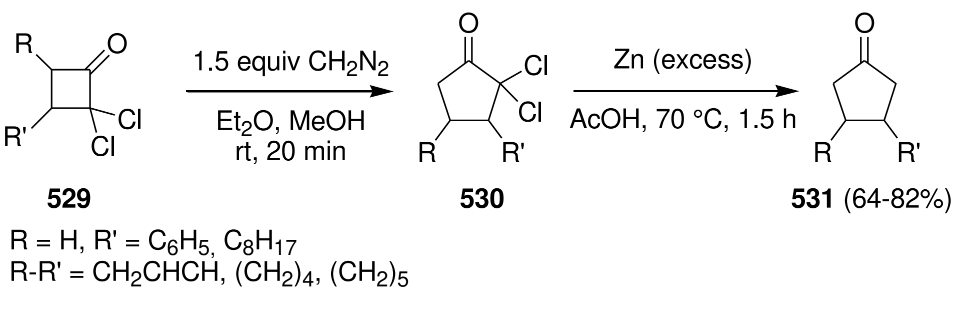
Scheme 146

In a first example, the racemic aglycon acetate **528** of loganine, a key compound in alkaloid biosynthesis, was readily prepared by the diazoethane-induced ring enlargement of *α*-chlorocyclobutanone **526**. Ring expansion followed by dechlorination afforded bicyclic ketone **527** in 72% yield as a synthetic precursor for oxaheterocyclic compound **528** (Scheme 147).[197]



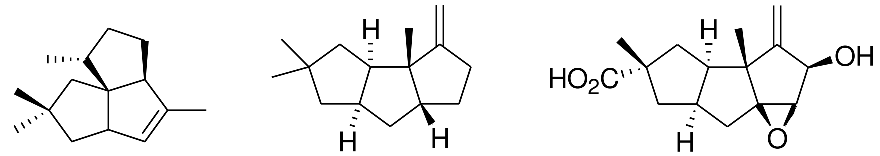
Scheme 147

In order to validate the synthetic applicability of *α*,*α*-dichlorocyclobutanones for the preparation of cyclopentanones, Greene and Deprés used *α*,*α*-dichlorocyclobutanones **529**, readily available cycloaddition adducts, for the highly regioselective, one-carbon ring expansion reaction with diazomethane to produce the corresponding *α*,*α*-dichlorocyclopentanones **530**. Dechlorination with an excess of Zn (one "pot") afforded cyclopentanones **531** in 64 to 82% yield (Scheme 148).[195] In addition, also the transformation of an *α*,*α*-dichlorocyclobutanone **529** into an *α*-methylsubstituted cyclopentanone in 74% yield has been reported utilizing diazoethane, followed by addition of an excess of Zn.[195,198]



Scheme 148

Numerous applications of this diazomethane ring enlargement protocol have been used in the synthesis of natural products. In the racemic synthesis of (±)-pentalenene **532**,[199] the least oxidized neutral precursor of pentalenic acid and of a variety of pentalenolactones, as well as the least oxidized neutral triquinane metabolite of *Streptomyces griseochromogenes*, the second five-membered ring was formed in 52% overall yield from a bicyclo[3.2.0]heptanone through ring expansion in the presence of diazomethane. Greene *et al.* reported the synthesis of racemic (±)-hirsutene **32** (Figure 6) with iterative three-carbon annelations, for which the third ring was introduced regioselectively via dichloroketene addition and subsequent ring expansion with diazomethane to form the precursor of (±)-hirsutene **32**.[200] The same authors accomplished the total synthesis of racemic (±)-hirsutic acid C **496** (Figure 6) and used diazomethane in two ring expansion steps.[201]



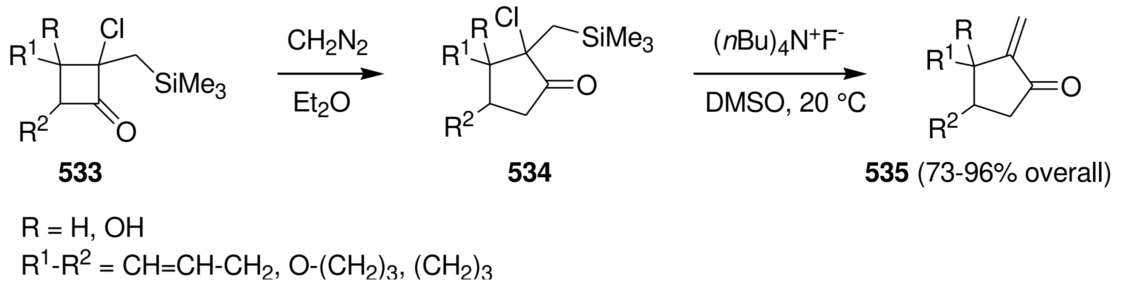
pentalenene **532** hirsutene **32** hirsutic acid **496**

Figure 6

Furthermore, also in a regioselective synthesis of racemic *α*-cuparenone **89** and *β*-cuparenone **379**, the diazomethane ring enlargement protocol has been used successfully.[202,203] Another synthetic approach to *α*-cuparenone **89** was already described in this review using an acid-promoted ring rearrangement of a vinylcyclobutanol (Scheme 26).[56]

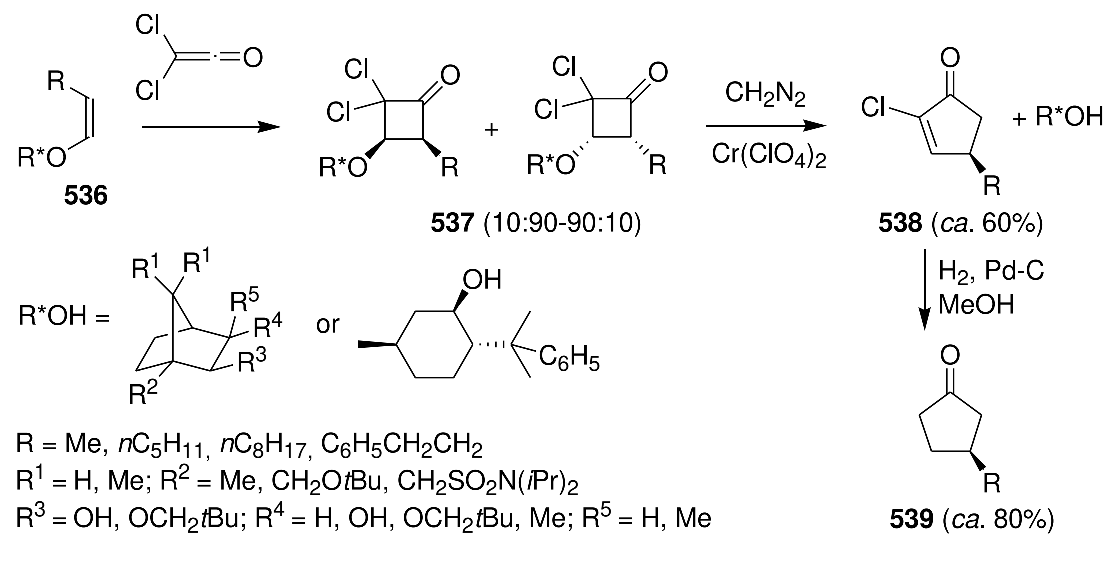
The regiocontrolled ring expansion of bicyclic cyclobutanones **533** to the corresponding bicyclic cyclopentanones **534** (Scheme 149) was achieved using diazomethane in ether. *α*-

Methylidene cyclopentanones **535** were obtained via treatment of bicyclic compounds **534** with tetrabutylammonium fluoride in DMSO in 73 to 96% overall yield.[204]



Scheme 149

Optically active *α*-chlorocyclopentenones **538** were synthesized in approximately 60% yield via asymmetric induction during a cycloaddition reaction of dichloroketene with chiral enol ethers **536**, followed by ring expansion of the obtained cyclobutanones **537** using diazomethane and $Cr(ClO_4)_2$ (Scheme 150).[205] Catalytic hydrogenation in methanol afforded (*S*)-(-)-cyclopentanones **539** in circa 80% yield.



Scheme 150

Other examples in which the diazomethane ring expansion has been used comprise the synthesis of the precursors of 4-oxo-1,2-cyclopentane dipropanoic acids **540**, angularly fused tricyclopentanoids **541**, bicyclic compounds **542** and the macrocycles exaltone **543** and the precursor of muscone **544** in quantitative yield, using an excess of diazomethane in diethyl ether in the presence of a catalytic amount of methanol (Figure 7).[206]

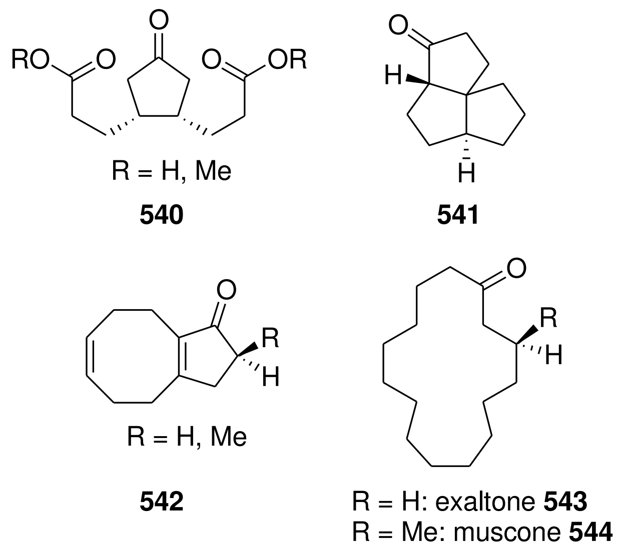
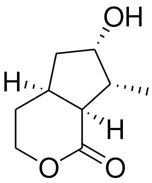
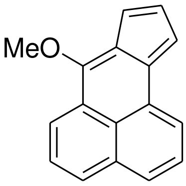


Figure 7

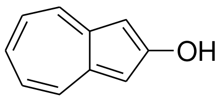
Additional illustrations on the use of the diazomethane ring expansion methodology involved the synthesis of the precursor of the monoterpene lactone (±)-boonein **545**,[207] of the precursor of 7-methoxycyclopenta[*a*]phenalene **546**,[208] and the precursor of 2-hydroxyazulene **547**,[209] but also in the synthesis of the cyclopentenone fragment of (-)-dihydrocryptosporiopsin **548**,[210] and in the key reaction step for an approach to brefeldin A **549** (Figure 8).[211]



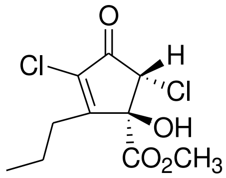
boonein **545**



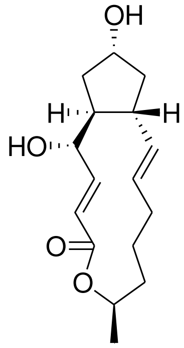
546



547



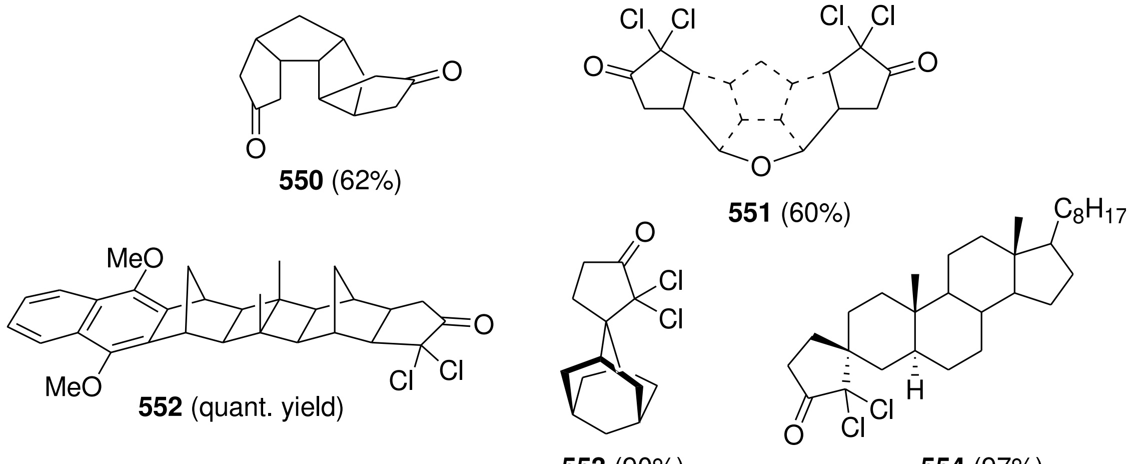
548



brefeldin A **549**

Figure 8

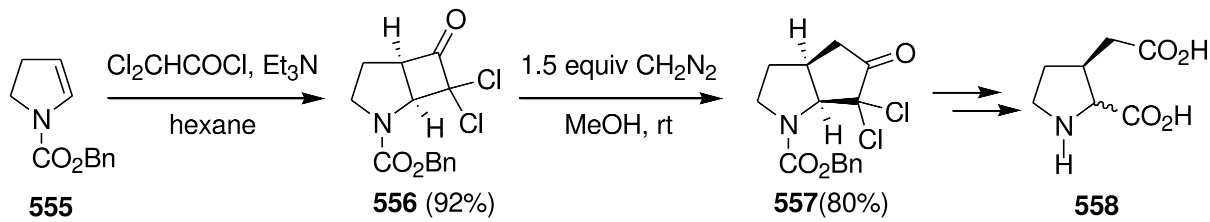
This efficient ring expansion has also been used for the synthesis of novel compounds, as illustrated in Figure 9. The diazomethane ring expansion approach was used in the synthesis of *cis*-*syn*-*cis*-*anti* tetraquinanedione **550** in 62% yield as part of experiments in pursuit of pentagonal dodecahedrane.[212] In similar research on polyquinanes, Mehta *et al.* reported the synthesis of a structurally interesting half-cage polyquinane **551** in 60% yield via diazomethane ring rearrangement of the appropriate cyclobutanone precursor.[213] In research on linked donor-acceptor systems designed to test the effect of bridge configuration on the dynamics of long-range intramolecular electron transfer processes, polycycle **552** was synthesized as single regioisomer in nearly quantitative yield from its precursor,[214] while adamantane derivative **553** was synthesized in 90% yield from the corresponding α,α-dichlorobutanone.[215] 5α-Cholestane-3-spirocyclopentanone **554** was synthesized in 97% yield from the precursor 5α-2',2'-dichlorospiro[cholestane-3,1'-cyclobutan]-3'-one via the described diazomethane ring enlargement.[216]



550 (62%) **551** (60%) **552** (quant. yield) **553** (90%) **554** (97%)

Figure 9

The preparation of conformationally restricted analogues of glutamic acid (both diastereomers), *e.g.* proline derivative **558**, from endocyclic enecarbamates proceeded through oxidative cleavage of bicyclic compound **557**, obtained via ring expansion of the corresponding 2-aza-7,7-dichlorobicyclo[3.2.0]heptan-6-one **556** (Scheme 151).[217] The starting cyclobutanone **556** was synthesized by [2+2]-cycloaddition of dichloroketene to a five-membered endocyclic enecarbamate. Ring expansion utilizing 1.5 equiv of diazomethane in the presence of methanol (3%) gave dichlorocyclopentanone **557** in 80% yield.

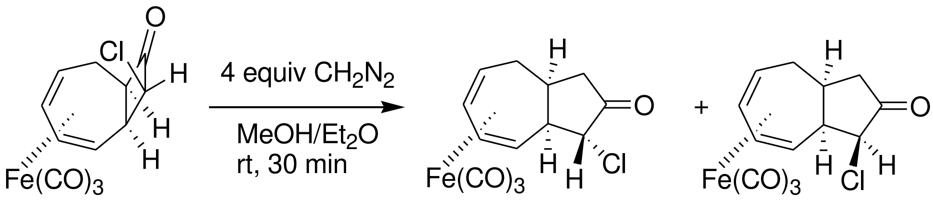


555 **556** (92%) **557**(80%) **558**

Scheme 151

In a final example, the cycloadduct **559**, when reacted with four equiv of diazomethane in methanol and diethyl ether, gave a mixture of two stereoisomers, *i.e.* tricarbonyl[(2,3,4,5-η)-

10-*exo*-chlorobicyclo[5.3.0]deca-2,4-dien-9-one]iron *exo*-**560** and 10-*endo*-chloro derivative *endo*-**560** in 30% and 19% yield, respectively (Scheme 152).[209b]

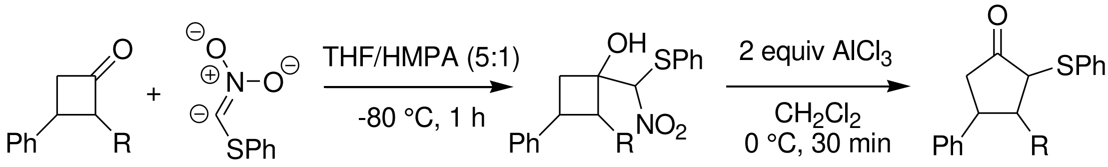


559 *exo*-**560** (30%) *endo*-**560** (19%)

Scheme 152

6.3 An activated nitro group as leaving group

The nitro group, when connected to a carbon atom bearing carbenium ion stabilizing substituents, has been reported to act as a leaving group in the presence of Lewis acids.[218] (Phenylthio)nitromethane was applied as a useful one carbon and α-heteroatom source in the ring expansion of cyclic ketones (Scheme 153).[219] Treatment of cyclobutanones **561** with the dianion of (phenylthio)nitromethane **562** at -80 °C afforded cyclobutanols **563** in 78 to 85% yield. The rearrangement proceeded upon treatment with two equiv of aluminium(III) chloride in dichloromethane at 0 °C for 30 minutes to produce ring expanded α-phenylthio ketones **564** in 66 to 74% yield.



561 **562** **563** (78-85%) **564** (66-74%)
R = H, Me

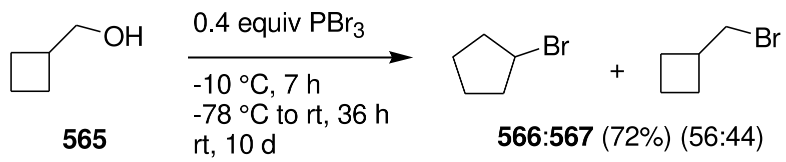
Scheme 153

6.4 An activated hydroxy group as leaving group

In this section, cyclopenta(e)ne and cyclopenta(e)none synthesis is described, starting from 1-(hydroxymethyl)cyclobutane or 1-(hydroxymethyl)cyclobutanol derivatives. Several methods are discussed in the next paragraphs.

6.4.1 Cyclopentane/Cyclopentene synthesis

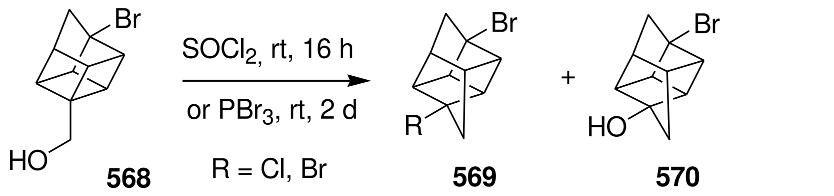
The first reaction described here comprises the classical and basic example of this type of ring expansions. In an attempt to prepare cyclobutylmethyl bromide, and not the rearranged product, cyclobutylcarbinol **565** was treated with 0.4 equiv of phosphorus(III) bromide without solvent.[220] The method of Bartleson, Burk and Lankelma[221] was chosen by the authors because it would be less likely to lead to rearrangement than for example by the use of hydrogen bromide.[222] However, a combined yield of 72% was obtained for a 56:44 mixture of cyclopentyl bromide **566** and cyclobutylmethyl bromide **567**, respectively (Scheme 154).



Scheme 154

Cationic rearrangement of homocubane carbinols **568** to bridgehead 1,3-bishomocubane alcohols **570** was executed via treatment with an excess of thionyl chloride or phosphorus(III) bromide.[223] Both reactions, performed at room temperature for 16 hours or two days, respectively, gave mixtures of the rearranged halocubane **569** and hydroxycubane **570**

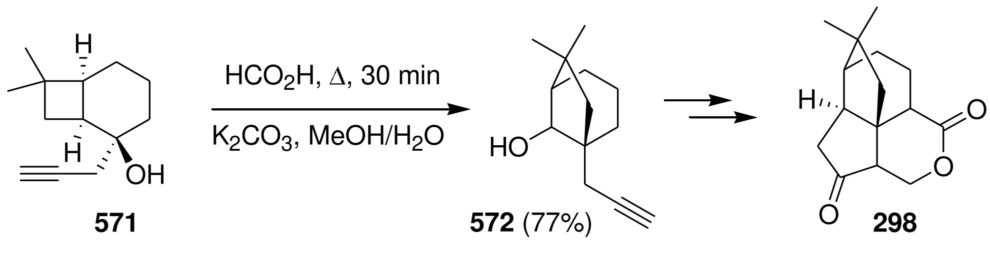
(Scheme 155). Again, the driving force in this ring expansion was the relief of strain leading to the 1,3-bishomocubane cage systems by selective bond migration in the homocubane skeleton. Isomeric 1,4-bishomocubane derivatives were not observed.



R = Cl **569**:**570** (30%:67%)
R = Br **569**:**570** (18%:yield not reported)

Scheme 155

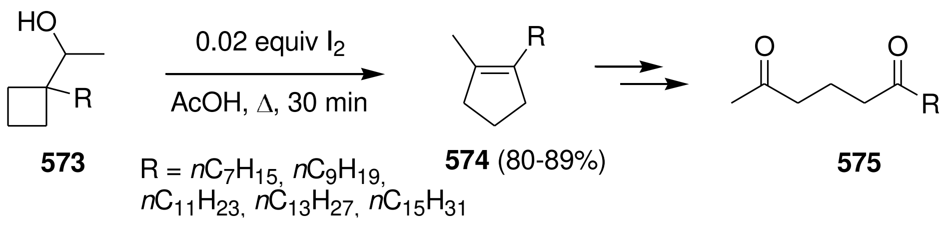
In a synthesis toward racemic (±)-quadrone **298**, the first bicyclic five-membered ring in the precursor 6,6-dimethyl-1-(2-propynyl)bicyclo[3.2.1]octan-8-ol **572** was synthesized in 77% yield using an acid-catalyzed ring expansion of 7,7-dimethyl-2-(2-propynyl)-*cis*-bicyclo[4.2.0]octan-2-ol **571** with 90% formic acid at reflux temperature for 30 minutes (Scheme 156).[224]



Scheme 156

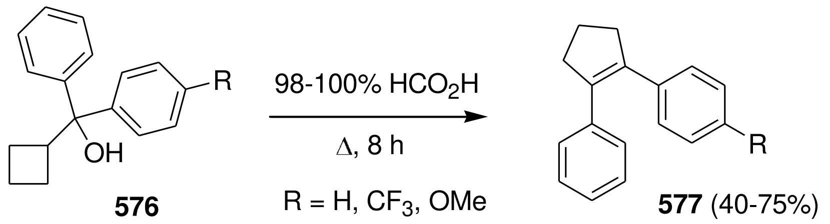
Next to formic acid, acetic acid has also been used as a promoter for the rearrangement of cyclobutylmethyl carbenium ions. When 1-(1-hydroxyethyl)-1-alkylcyclobutanes **573** were treated with 0.02 equiv of iodine in acetic acid at reflux for three hours, the corresponding 1-

alkyl-2-methylcyclopentenes **574** were obtained in 80 to 89% yield, as precursors for 1,5-diketones **575** (Scheme 157).[225]



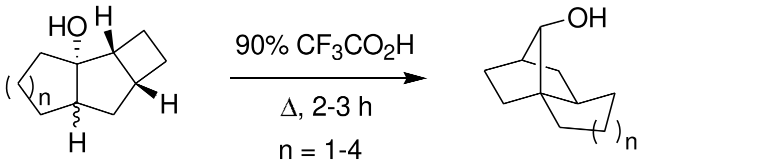
Scheme 157

In a study on base-induced proton tautomerism in the primary photocyclization product of stilbene, the starting compounds 1,2-diphenylcyclopentenes **577** were synthesized by means of ring enlargements of cyclobutyldiphenylcarbinols **576**.[226] Rearrangement was effective in 40-75% yield upon reaction of cyclobutyl carbinols **576** in 98-100% formic acid at reflux for eight hours (Scheme 158).[227]



Scheme 158

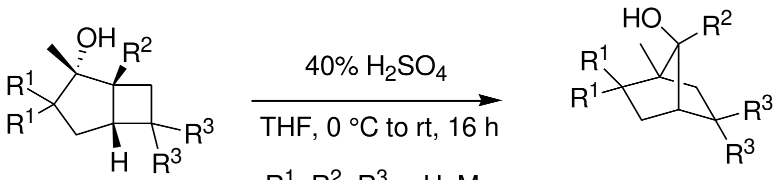
In another approach, solvolytic trifluoroacetic acid-catalyzed rearrangement of bicyclo[3.2.0]heptan-2-ols **578** has been reported to afford 7-hydroxynorbonane derivatives **579**.[228] The *exo*-isomer **579** was mainly formed by heating the starting products **578** in 90% trifluoroacetic acid at reflux temperature for two to three hours in 64 to 85% yield (maximum 17% of *endo*-isomer, ratio 83-98:2-17) (Scheme 159).



exo- or *endo*-**578** *exo*-**579** (64-85%) (83-98:2-17)

Scheme 159

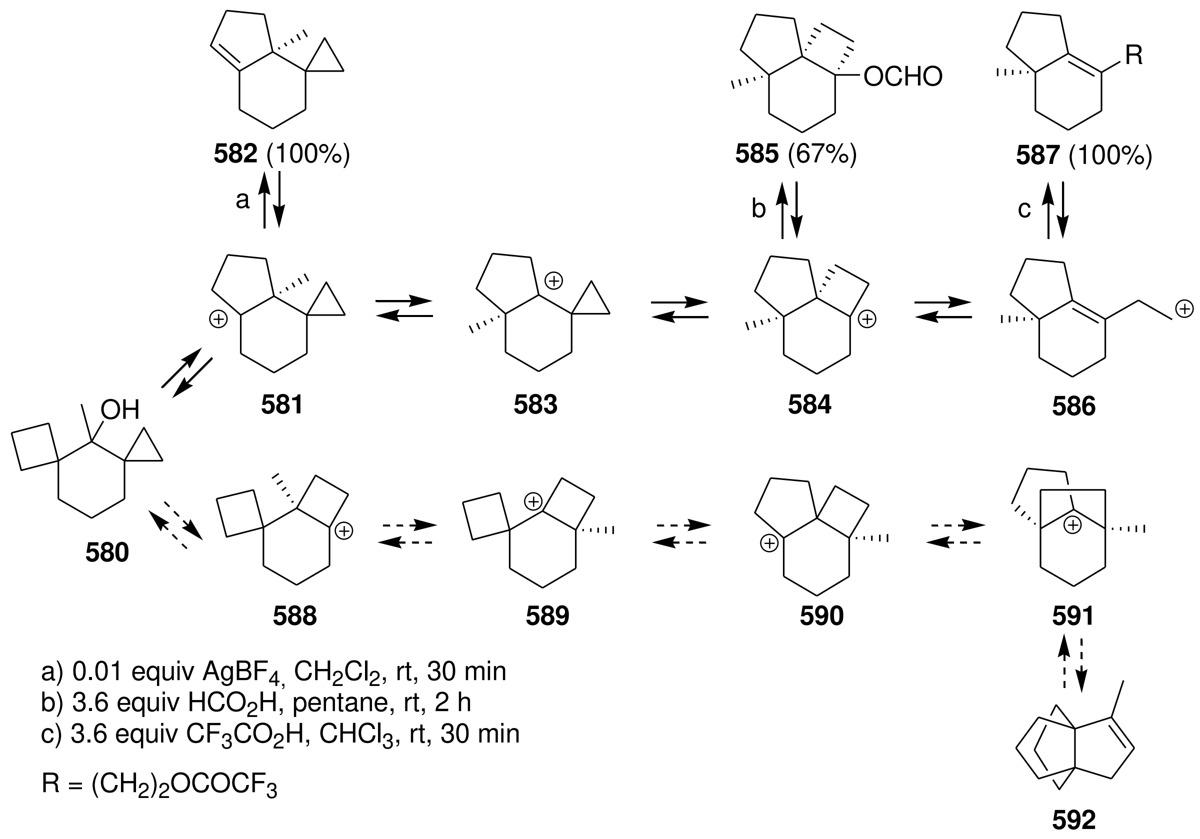
Other 7-hydroxynorbonane derivatives **579** have been synthesized by the same authors as single epimeric alcohols in 43 to 47% yield by reaction of bicyclo[3.2.0]heptan-2-ols **578** in a mixture of tetrahydrofuran and 40% sulfuric acid at 0 °C, followed by stirring for 16 hours at ambient temperature (Scheme 160).[228]



578 **579** (43-47%)

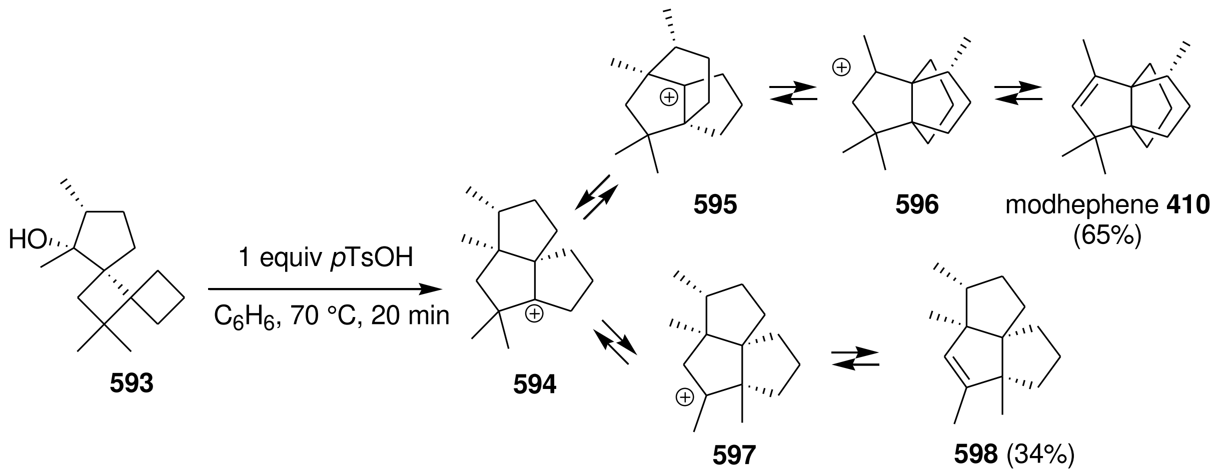
Scheme 160

Within the study on the synthesis of naturally occurring sesquiterpenes via rearrangement reactions, the conversion of dispiro[2.1.3.3]undecane **580** was achieved via three reaction pathways (Scheme 161),[229] *i.e.* (i) treatment of **580** with 0.01 equiv of silver tetrafluoroborate in dichloromethane for 30 minutes (path a), (ii) treatment with 3.6 equiv of formic acid in pentane for two hours (path b), and (iii) treatment with 3.6 equiv of trifluoroacetic acid for 30 minutes (path c). All reactions were executed at room temperature. Quantitative conversion into the bicyclic system **582** (path a) and **587** (path c), and preponderant conversion into the tricyclic compound **585** (path b) in 67% yield were observed. The formation of these three compounds was initiated by protonation and dehydration of carbinol **580**, followed by expansion of the four-membered ring. The carbenium ion **581** thus formed, rearranged further to carbenium ions **583**, **584** and **586** and thereby not only accounted for the formation of **582**, but also for **585** and **587**. An initial enlargement of the three-membered ring, which would have opened a way to synthesize **592**, was excluded since neither compound **592**, nor any product derived from carbenium ions **588**, **589**, **590** or **591** was detected. This was explained both by a more favorable alignment of the cyclobutane bond with respect to the neighbouring cationic centre[230] and by the greater thermodynamic advantage associated with C_4-C_5 as to C_3-C_4 ring enlargements.[231]



Scheme 161

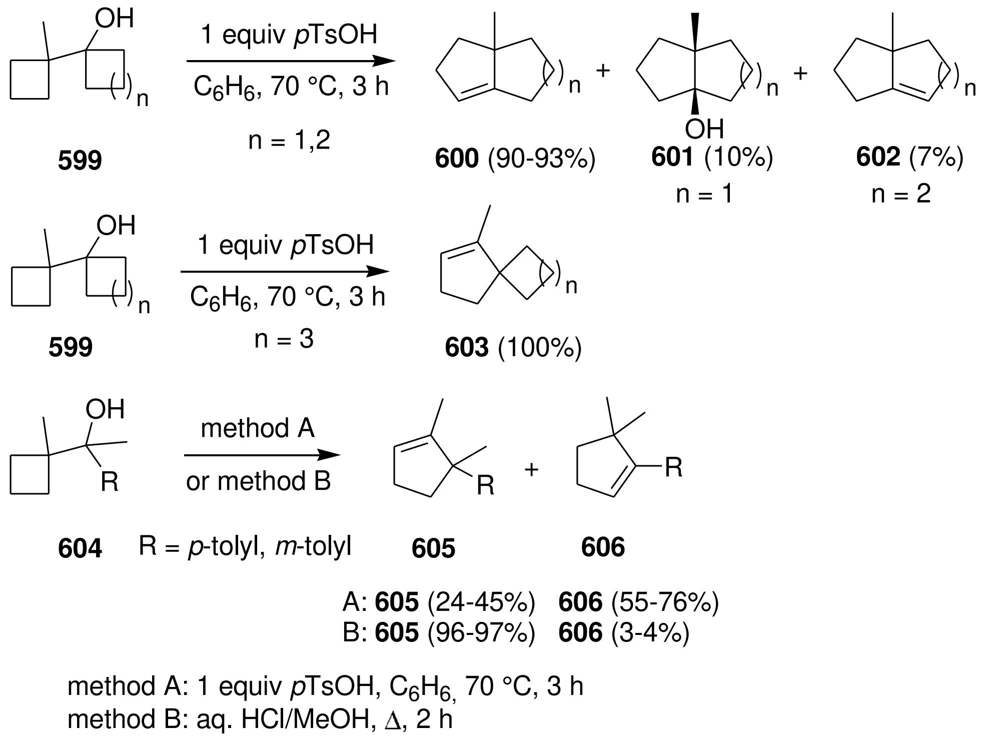
Among other cascade cationic reactions, also reported by Fitjer's group, a synthesis of (±)-modhephene **410** and its enantiomer (±)-epimodhephene was executed from the epimeric dispiroundecanols **593** (Scheme 162).[134d,232] The rearrangements were initiated by treatment with equimolar amounts of anhydrous *p*-toluenesulfonic acid in benzene at 70 °C. After 20 minutes, alcohol **593** was completely consumed and rearranged into 65% (±)-modhephene **410** and 34% triquinane **598**. The synthesis of (±)-epimodhephene was accomplished starting from the enantiomer of dispiroundecanol **593** to give 65% of (±)-epimodhephene and 35% of the corresponding triquinane.



Scheme 162

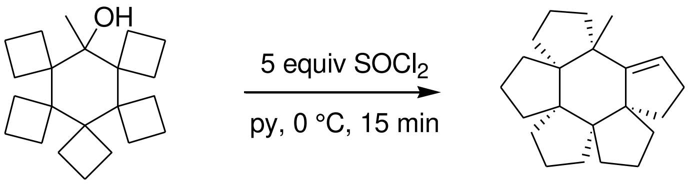
Another *p*-toluenesulfonic acid-catalyzed rearrangement, starting from 1-methylcyclobutylmethanols, has also been reported by Mandelt and Fitjer (Scheme 163).[233] Quantitative rearrangements were observed when compounds **599** were reacted with equimolar amounts of *p*-toluenesulfonic acid in benzene at 70 °C for three hours. With the exception of alcohol **601** (n = 1, 10% yield) and bicycle **602** (n = 2, 7% yield), only hydrocarbons **600** and **603** were formed in a high yield of 90-100%. In all cases, the product formation involved a cyclobutylmethyl to cyclopentyl rearrangement, eventually followed by a second cyclobutylmethyl to cyclopentyl rearrangement (**600** and **601**), a cyclopentylmethyl to cyclohexyl rearrangement (**602**), or a 1,2-methyl shift (**606**). Of the products formed, **605**

(R = *p*-tolyl) has been used in the synthesis of (±)-laurene **142**,[234a] **606** (R = *p*-tolyl) in the synthesis of (±)-cuparene[234b] and **605** (R = *m*-tolyl) for (±)-herbertene.[234c] These cyclopentenes **605** were produced in a much higher yield (96-97%) when 1-methylcyclobutylmethanols **604** were treated with hydrochloric acid in methanol at reflux temperature for two hours (method B).



Scheme 163

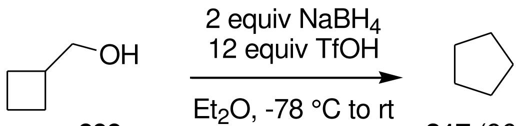
A final example of a cationic cascade reaction of this type of rearrangements included the five-fold cyclobutylmethyl to cyclopentyl rearrangement of pentaspirohenicosanol **607** to the all-*cis* annelated precursor **608** of [6.5]coronane (Scheme 164).[235] The reaction was speculated to proceed with conformational control, starting from an initially formed chlorosulfite. When pentaspirohenicosanol **607** was treated with five equiv of thionyl chloride in pyridine, the corresponding hexacyclohenicos-16-ene **608** was obtained in 83% yield.



607 **608** (83%)

Scheme 164

When an incipient primary carbenium ion centre is generated adjacent to an alicyclic ring, the latter is prone to undergo ring expansion. This principle has been used by Olah and co-workers.[136] A ring enlargement of cyclobutylmethyl alcohol **609** via treatment with a mixture of two equiv of sodium borohydride and 12 equiv of triflic acid in diethyl ether afforded cyclopentane **317** in 96% yield (Scheme 165). This approach comprised an alternative route for the synthesis of cyclopentane **317** starting from cyclobutanecarboxylic acid **316**, which was ring expanded applying the same reaction conditions (Scheme 90), also in 96% yield.

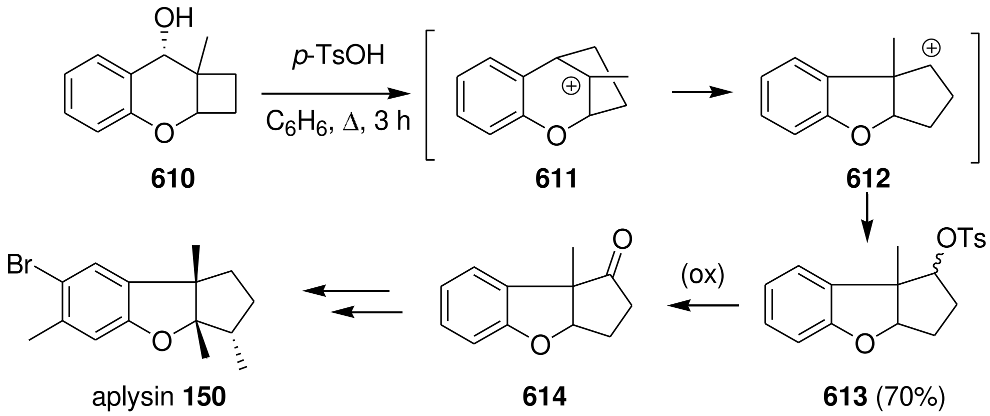


609 **317** (96%)

Scheme 165

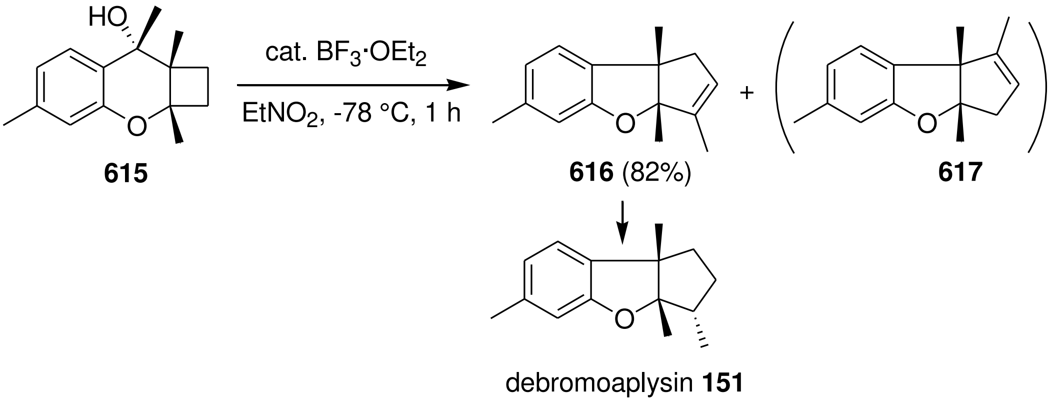
Venkateswaran *et al.* have developed an acid- or Lewis acid-catalyzed rearrangement of a methylcyclobutane unit attached to chromanol to three different types of five-membered ring systems, *i.e.* cyclopentanones, cyclopentenes or cyclopentanes. According to the substitution pattern, as well as the solvent and acid, the authors described the outcome of the reaction as predictable.[236] In the synthesis of the carbocyclic framework of the marine natural product aplysin,[72a] a rearrangement of tricyclic alcohol **610** via an incipient trichothecane-like cationic intermediate **611** has been reported.[236a] Treatment of cyclobutachromanol **610** with *p*-

toluenesulfonic acid in benzene at reflux temperature led to a mixture of *p*-toluenesulfonates **613** in 70% yield via migration of an external bond, followed by an aryl migration (Scheme 166). The oxidation of this mixture afforded the tricyclic compound **614** as the skeleton of aplysin **150**.



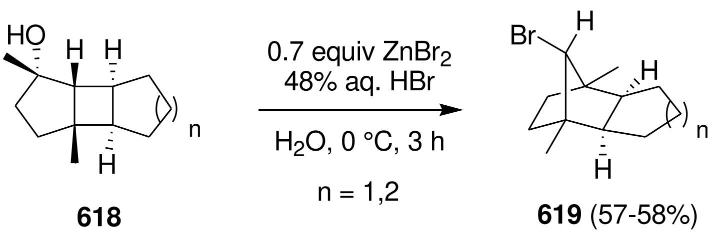
Scheme 166

In analogous research by the same group, rearrangement of cyclobutachromanol **615** proved to be predictable by choice of the catalyst and solvent.[236b] Treatment of this carbinol **615** with boron(III) fluoride etherate in benzene, petroleum ether or nitromethane gave mixtures of two different ring expanded products **616** and **617**. When a catalytic amount of boron(III) fluoride etherate in nitroethane at -78 °C was used, the desired precursor **616** of debromoaplysin **151** was obtained in 82% yield (Scheme 167).



Scheme 167

A last example of the acid-catalyzed rearrangement of (hydroxymethyl)cyclobutane derivatives involved the ring expansion of alcohols **618**.[237] When these carbinols **618** were treated with 0.7 equiv of $ZnBr_2$ in 48% aqueous hydrogen bromide at 0 °C for three hours, the corresponding norbornanes **619** were obtained in 57 to 58% yield (Scheme 168). Due to the retention of the stereocentres at C-1 and C-7, the rearrangement of **618** led to the C_S-symmetrical annelated norbornane derivatives **619**.

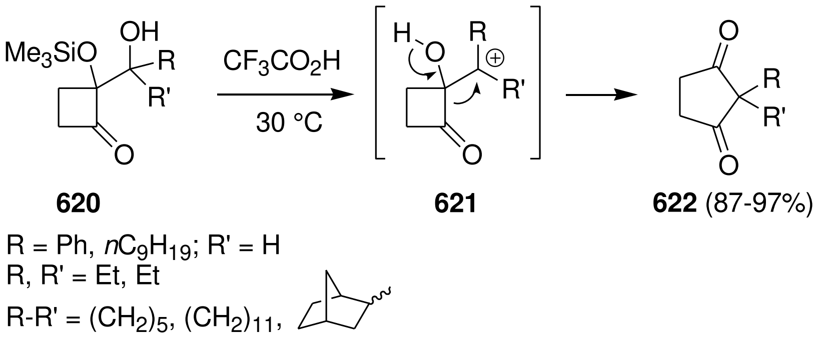


Scheme 168

6.4.2 Pinacol rearrangement (cyclopentanone synthesis)

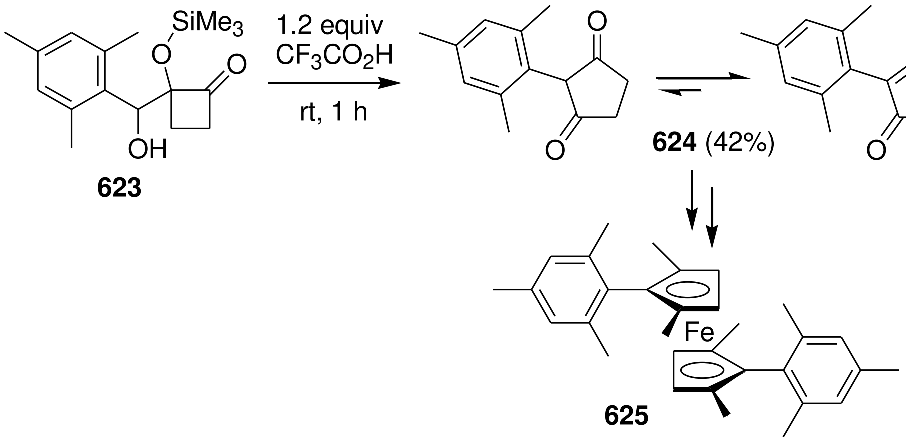
Since the pinacol rearrangement involves the formation of a carbenium ion, starting from a fully substituted 1,2-diol, followed by a 1,2-alkyl shift, this methodology has been applied for cyclobutylmethylcarbenium to cyclopentylcarbenium ion rearrangements as well.

For example, the rearrangement of monosilylated pinacols **620**, controlled by the presence of an acyl group adjacent to the diol moiety, has been reported to give 1,3-cyclopentanediones **622** in 87 to 97% yield upon treatment with trifluoroacetic acid (Scheme 169).[238] Exact reaction conditions were not given by the authors, except for a reaction temperature of 30 °C.



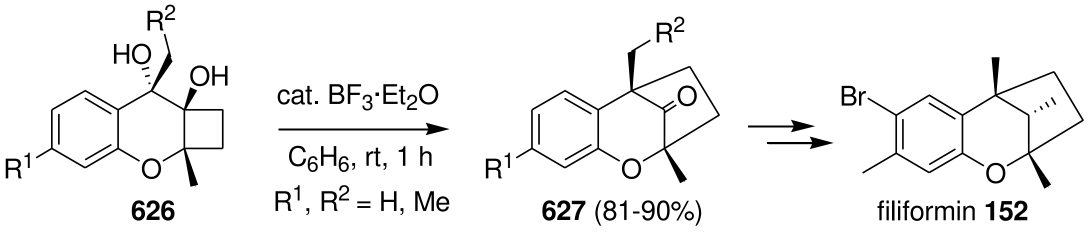
Scheme 169

In the study on the synthesis of ferrocenes, a pinacol rearrangement of (hydroxymesityl)cyclobutanone **623** was executed via treatment with 1.2 equiv of trifluoroacetic acid at room temperature for one hour, affording the corresponding ring expanded product **624** in 42% yield (Scheme 170).[239] The latter compounds served as substrates for the preparation of iron complex **625**.

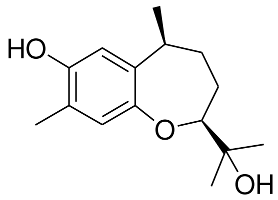


Scheme 170

In analogy with sesquiterpene syntheses described in the previous section, a synthesis toward filiformin **152** by means of a semipinacol rearrangement has been reported.[240] The rearrangement of diols **626** resulted in the bridged ketones **627** in 81-90% yield by treatment with a catalytic amount of $BF_3{\cdot}Et_2O$ in benzene at room temperature for one hour (Scheme 171). In all cases, only isomer **627** was formed, arising from the exclusive migration of the external bond.[240a] Also two other methods were described, *i.e.* addition of a catalytic amount of $BF_3{\cdot}Et_2O$ or H_2SO_4 in petroleum ether at -78 °C for one hour, or addition of a catalytic amount of $BF_3{\cdot}Et_2O$ or H_2SO_4 in nitroethane at -78 °C for 30 minutes, however without mentioning the yields of the obtained ketone.[240b] An analogous reaction has been reported in the synthesis of heliannuol D **628**, a phenolic sesquiterpene isolated from the sun flower *Helianthus annus* (Figure 10).[241]



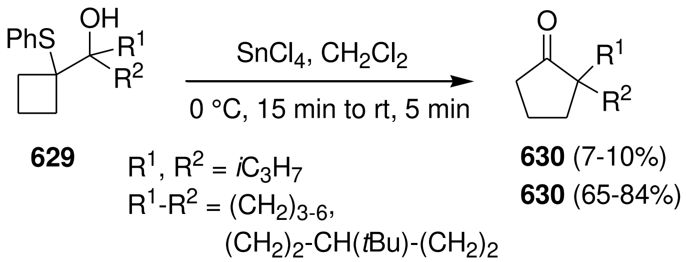
Scheme 171



heliannuol D **628**

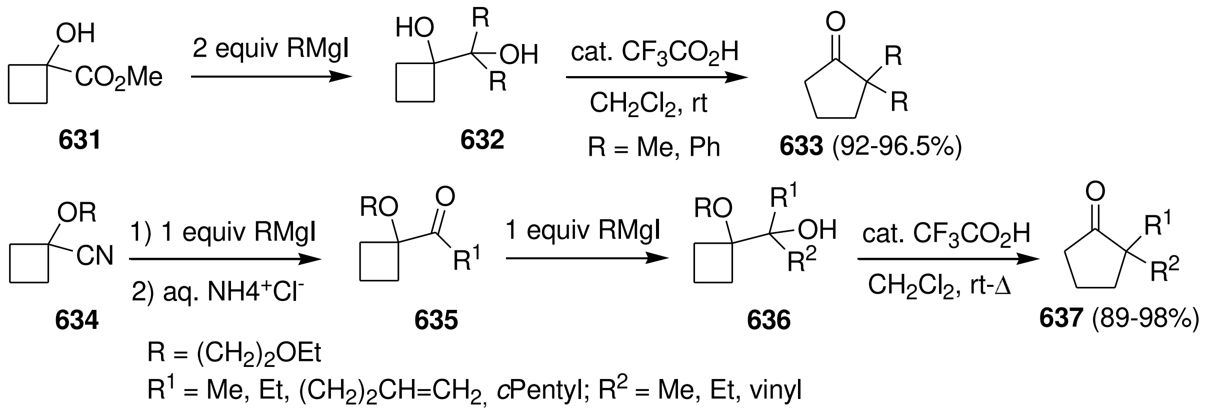
Figure 10

In an alternative approach, spiroannelated cyclopentanones have been synthesized using cyclobutyl phenyl sulfides.[242] Treatment of *β*-hydroxy sulfides **629** with tin(IV) chloride in dichloromethane for 15 minutes at 0 °C and five minutes at room temperature afforded the corresponding cyclopentanones **630** in 7 to 84% yield (Scheme 172). Cyclohexanones, cycloheptanones, cyclooctanones and acyclic ketones were shown to be well suited for the spiroannelation, but cyclobutanones (R^1-R^2 = $(CH_2)_3$) and cyclopentanones (R^1-R^2 = $(CH_2)_3$) were not.



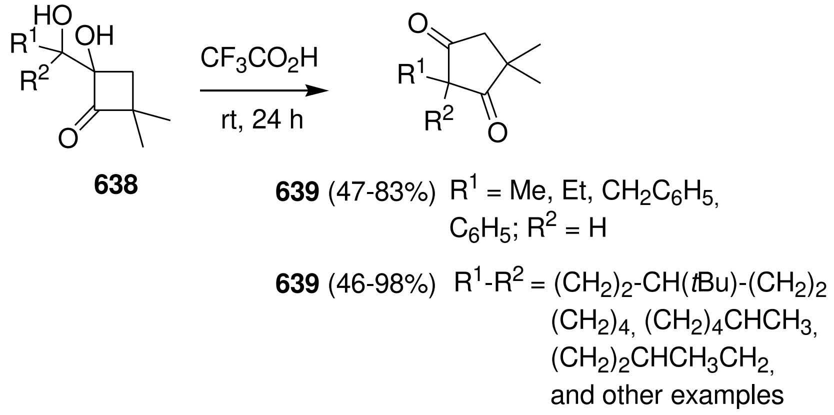
Scheme 172

Pinacol derivatives have also been prepared via Grignard addition across carbonyl compounds. For example, the synthesis of *α*,*α*-dialkylcyclopentanones was achieved via Brønsted and Lewis acid induced ring expansions of 1-hydroxycarbinols **632** and **636**.[243] The ring expansion step was executed via treatment of diols **632** and **636** with a catalytic amount of trifluoroacetic acid in dichloromethane at room temperature or reflux temperature to afford *α,α*-dialkylcyclopentanones **633** in 92 to 96.5% yield and *α,α*-dialkylcyclopentanones **637** in 89 to 98% yield, respectively (Scheme 173). The required 1,2-diols were prepared via Grignard addition across ester **631** or nitrile **634**.



Scheme 173

Finally, a pinacol-type rearrangement has been used in the synthesis of cyclopentanediones. Thus, 4,4-dimethyl-1,3-cyclopentanediones **639** were prepared from 2-alkyl-2-hydroxy-4,4-dimethylcyclobutanones **638**, which were generated from open-chain or cyclic ketones by boron halide-mediated aldol reactions.[244] The ring rearrangement was realized by means of trifluoroacetic acid at room temperature for 24 hours to afford 2-alkyl- or 2-aryl-2-methyl-1,3-cyclopentanediones **639** in 47 to 83% yield (Scheme 174) and spiro-1,3-cyclopentanediones **639** in 46 to 98% yield. In comparison with the method depicted in Scheme 169,[238] no silylation of the hydroxy group was used, but lower yields were obtained.

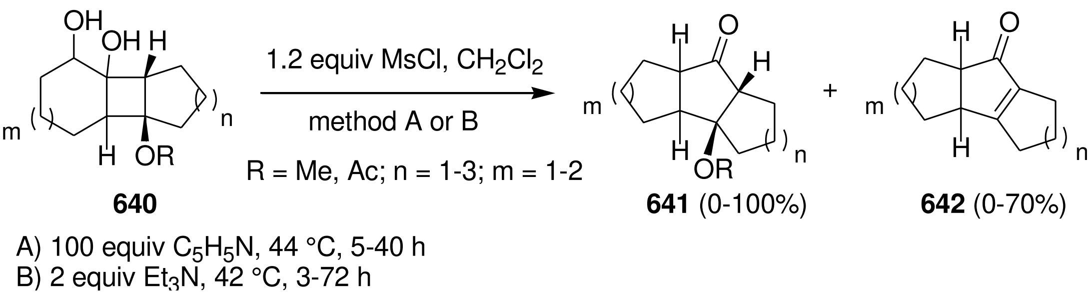


Scheme 174

6.4.3 A mesyloxy group as leaving group

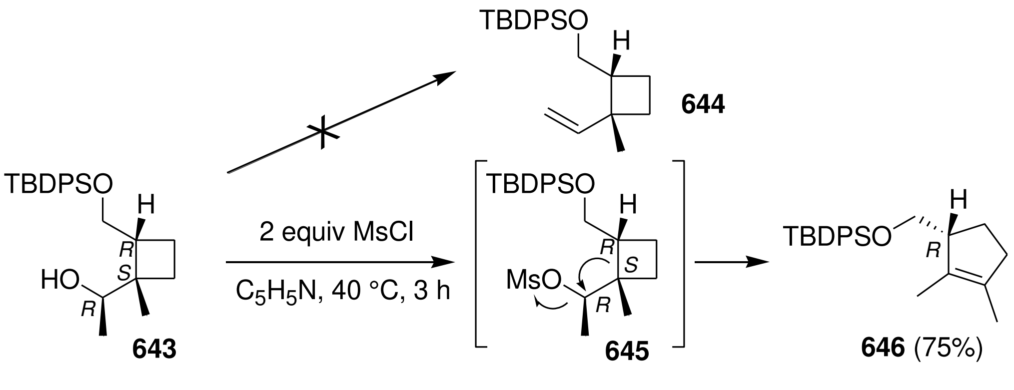
A convenient way to enhance the leaving group ability of a hydroxy moiety comprises its transformation into a sulfonyloxy group. The most frequently applied methods in that respect involve the use of a mesyloxy or a tosyloxy group (*vide infra*).

Tricyclic cyclobutanols **640** with a four-membered ring located in the middle of the framework have been shown to be useful precursors toward bisannelated cyclopenta- or cyclopentenones.[245] To this end, tricyclic compounds **640** were treated with 1.2 equiv of mesyl chloride in dichloromethane (Scheme 175). The monomesylated diol was then subjected to a ring enlargement reaction of the intermediate carbenium ion, generated by means of a base. Two different amines were evaluated as bases. The first method involved addition of 100 equiv of pyridine at 44 °C for five to 40 hours, while in a second method two equiv of triethylamine at 42 °C were applied for three to 72 hours. Both methods were used for the synthesis of the corresponding polycyclic cyclopentanones **641** in 0-100% yield and polycyclic cyclopentenones **642** in 0-70% yield.



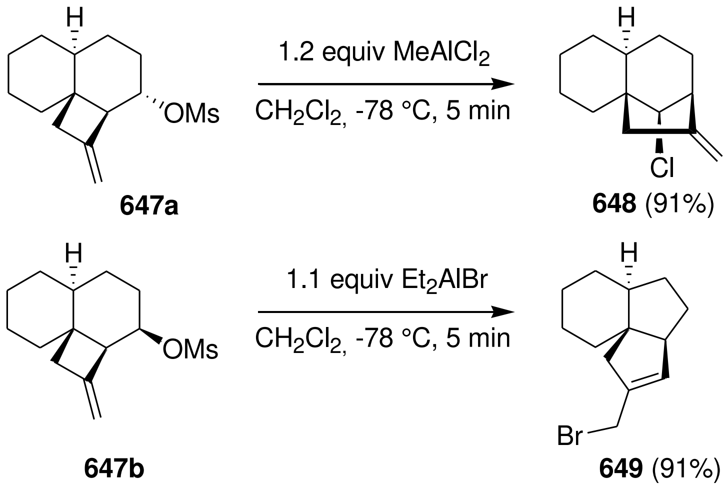
Scheme 175

In an attempt to transform the secondary alcohol **643** into a methanesulfonate to produce the elimination product **644** as a precursor of the pheromone grandisol or its *trans*-isomer fraganol, the rearranged cyclopentene **646** was obtained as the sole product (Scheme 176).[246] Treatment of cyclobutane **643** with two equiv of methanesulfonyl chloride in pyridine at 40 °C for three hours afforded cyclopentene **646** in 75% yield.



Scheme 176

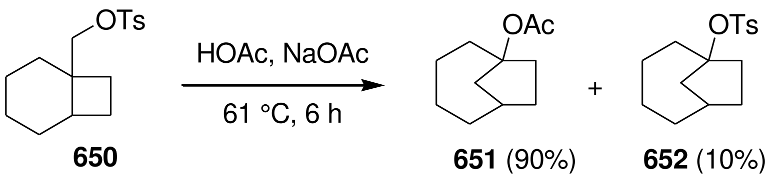
In another example, efforts have been made toward the construction of the bicyclo[3.2.1]octane skeleton, found in kaurenoids and gibberellins. In this work, the methylenecyclobutane annelated mesyloxydecalin **647a** was rearranged applying 1.2 equiv of methylaluminium dichloride in dichloromethane at -78 °C (Scheme 177).[247] The Lewis acid-catalyzed ring expansion reaction proceeded in 91% yield within five minutes, affording the annelated bicyclo[3.2.1]octane **648**. However, when epimer **647b** was treated with 1.1 equiv of diethylaluminium bromide in dichloromethane at -78 °C for five minutes, allylbromide **649** was isolated in 91% yield instead of the corresponding annelated bicyclo[3.2.1]octane.



Scheme 177

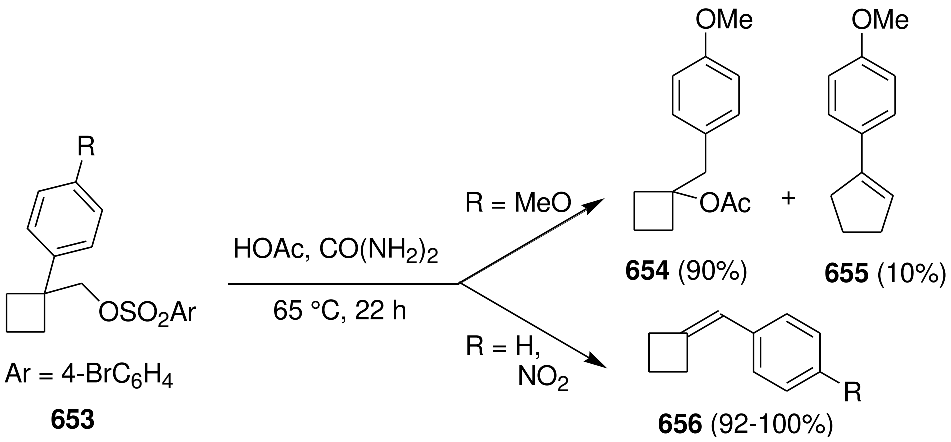
6.4.4 A tosyloxy group as leaving group

A first example involved the solvolysis of bicyclo[4.2.0]octane-1-methyl *p*-toluenesulfonate **650** (Scheme 178).[248] The rearrangement proceeded exclusively to the bicyclo[4.2.1]nonyl system by treatment with acetic acid and sodium acetate at 61 °C for six hours, giving 90% of 1-bicyclo[4.2.1]nonyl acetate **651** and 10% of 1-bicyclo[4.2.1]nonyl *p*-toluenesulfonate **652**.



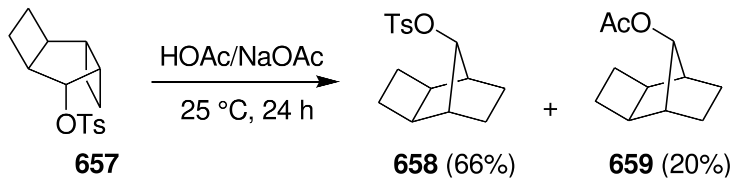
Scheme 178

A much less pronounced tendency toward ring expansion has been observed in the acetolysis of cyclobutylcarbinyl *p*-bromobenzenesulfonate **653** (R = MeO), affording the corresponding 1-(4-methoxyphenyl)cyclopentene **655** in only 10% as the minor component, next to 90% of 1-(4-methoxybenzyl)cyclobutyl acetate **654** (Scheme 179),[249] according to a Wagner-Meerwein rearrangement of the initially formed primary carbenium ion to a tertiary carbenium ion. Acetolysis of other derivatives (R = H, NO_2) did not yield any corresponding cyclopentene, and instead benzalcyclobutanes **656** were obtained in 92-100% yield.



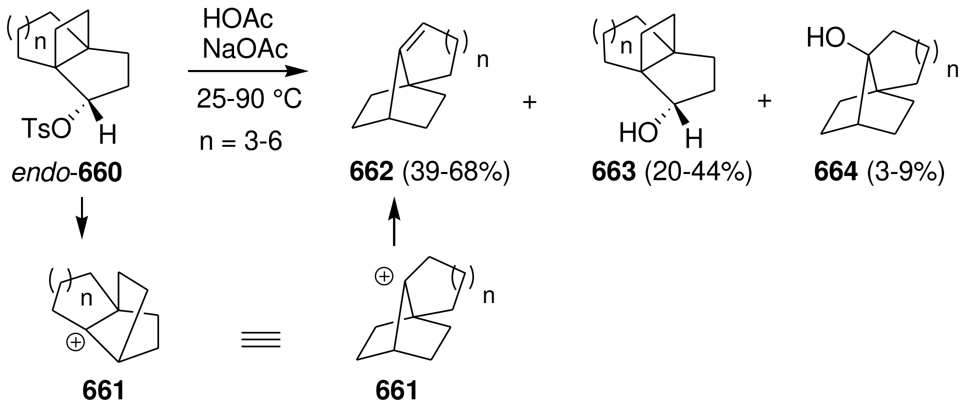
Scheme 179

On the other hand, acetolysis studies of bicyclo[3.2.0]hept-2-yls revealed stereospecific ring rearrangements.[250] For example, treatment of *anti*-tricyclo[5.2.0.0^{2,5}]non-6-yl tosylate **657** with an acetate buffer of HOAc and NaOAc in a sealed tube at 25 °C for 42 hours afforded ring expansion to a mixture of compounds **658** and **659** in 66% and 20% yield, respectively (Scheme 180).



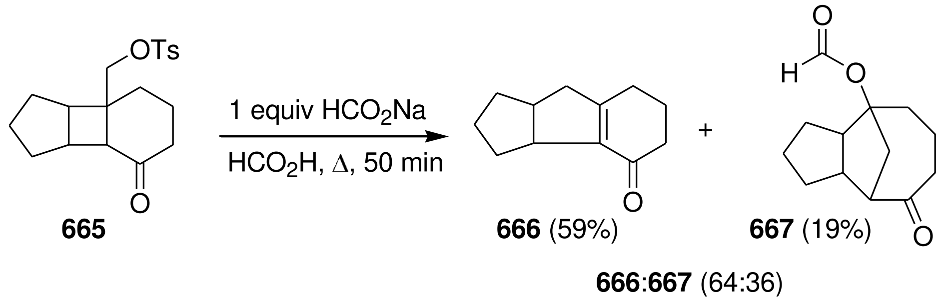
Scheme 180

Furthermore, ring rearrangements of [n.3.2]propellane tosylates have been achieved in the same manner.[251] When *endo*-[n.3.2]propellane tosylates **660** were subjected to acetolysis, the corresponding rearranged olefins **662** were obtained in 39-68% yield, next to the unrearranged alcohols **663** in 20-44% and a small amount of the rearranged alcohols **664** in 3-9% yield (Scheme 181). This transformation was believed to proceed through carbenium ion intermediate **661**.



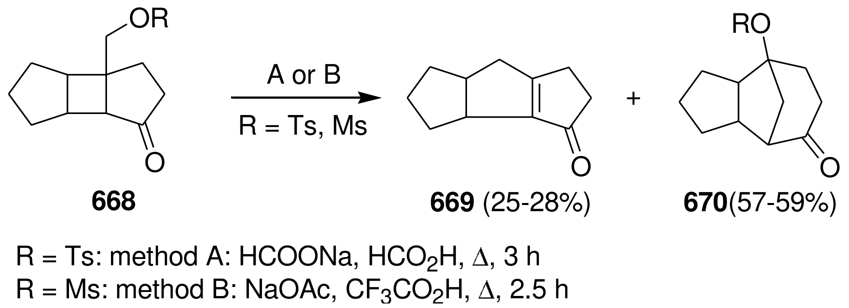
Scheme 181

As a key step in the synthesis of tricyclo[6.4.0.0^{2,6}]dodecane skeletons (6-5-5 ring systems), solvolysis of **665** sodium formate in formic acid afforded a mixture of enone **666** and the bridged formate **667** in a 64:36 ratio (Scheme 182). From this mixture, the desired tricyclic compound **666** was isolated in 59% yield and the bridged formate **667** in 19% yield.[252]



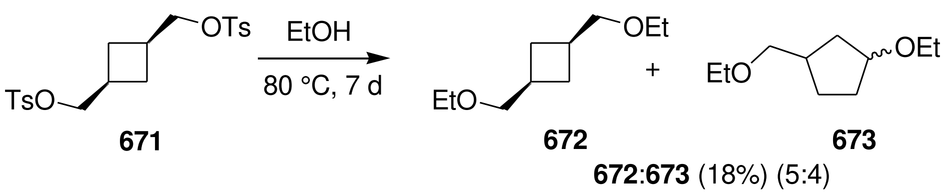
Scheme 182

The same authors prepared tricyclo[6.3.0.0^{2,6}]undecane skeletons as well, also called linear triquinane systems.[252] Upon solvolysis with sodium formate in formic acid or trifluoroacetic acid and sodium acetate, sulfonates **668** were converted into enones **669** and sulfonates **670** in a 1:2 ratio, and in 25-28% and 57-59% yield, respectively (Scheme 183).



Scheme 183

Finally, when *cis*-cyclobutane derivative **671** was heated in ethanol at 80 °C for seven days, a mixture of cyclobutane **672** (substitution product) and ring expanded cyclopentane **673** was obtained in a low yield of 18% and in a ratio of 5:4 (Scheme 184).[253]



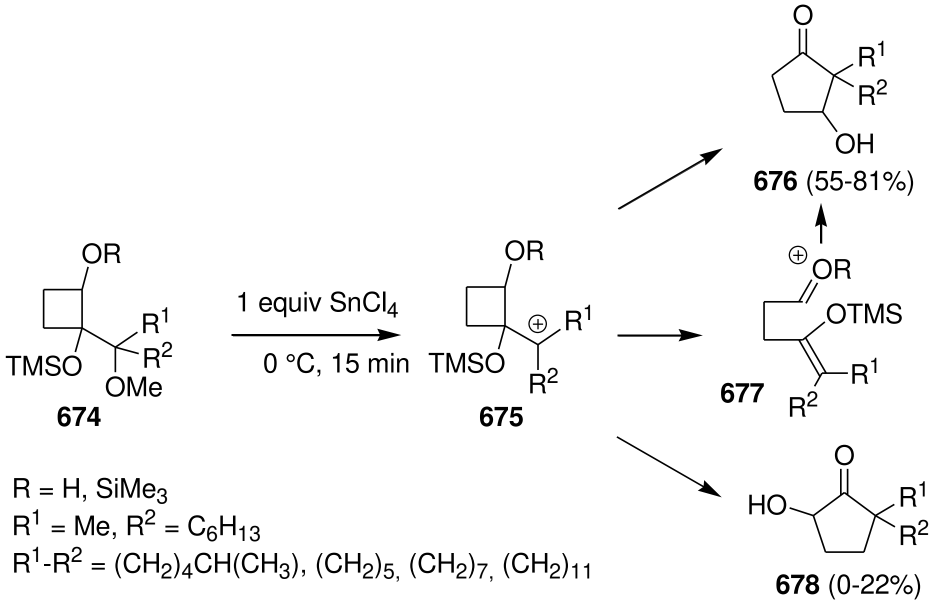
Scheme 184

6.5 An ether moiety as leaving group

6.5.1 An alkoxy or aryloxy group as leaving group

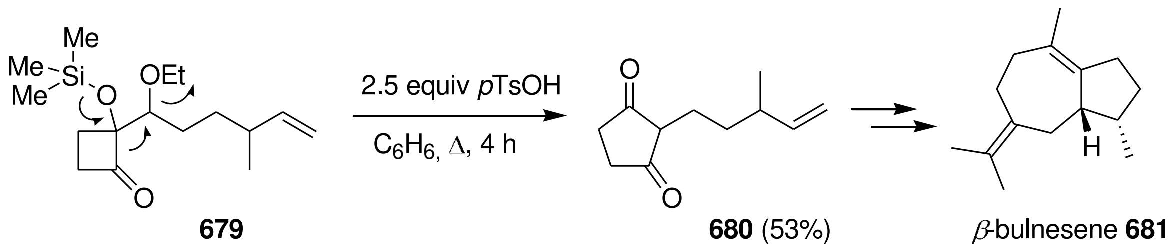
In principle, also an alkoxy or aryloxy group can be modified into a good leaving group upon treatment with a Lewis acid or a strong acid, enabling analogous ring transformations as compared to these starting from cyclobutylmethyl alcohols.

Treatment of monosilylated cyclobutane-1,2-diol derivatives **674** with one equiv of tin(IV) chloride at 0 °C for 15 minutes led to the formation of the corresponding *β*-hydroxycyclopentanones **676** as the major isomers in 55-81% yield and *α*-hydroxycyclopentanones **678** as the minor isomers in 0-22% yield (Scheme 185).[254] Only one derivative **674** (R = H, R^1-R^2 = $(CH_2)_5$) was ring expanded toward exclusively *β*-hydroxycyclopentanone **676** in 81% yield. The proposed mechanism involved initial formation of carbenium ion **675** under the influence of the Lewis acid. The ring opening reaction of the cyclobutane ring of **675** resulted in another oxygen-stabilized carbenium ion, *i.e.* oxonium ion **677**, which was trapped by the internally formed silyl enol ether moiety to yield **676** as the major isomer. The minor isomer **678** was formed through a pinacol type rearrangement.



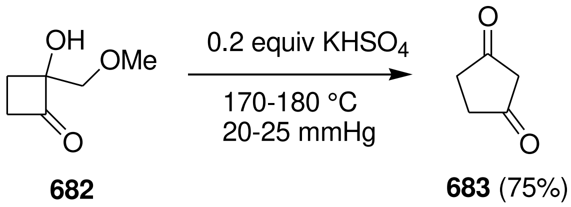
Scheme 185

In the total synthesis of the hydroazulenic sesquiterpene *β*-bulnesene **681**, precursor **680** was prepared via a pinacol-type rearrangement approach.[255] Addition of 2.5 equiv of *p*-toluenesulfonic acid monohydrate to cyclobutanone **679** in benzene at reflux for four hours afforded 2-(3-methyl-4-pentenyl)-1,3-cyclopentanedione **680** in 53% yield (Scheme 186). Again, the presence of an acyl group, adjacent to the diol moiety, controlled the rearrangement.



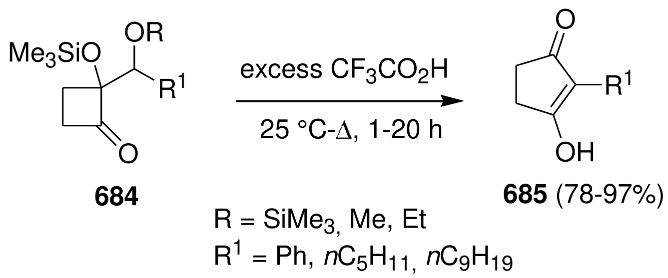
Scheme 186

Also other reagents have been used for the synthesis of 1,3-cycloalkadiones.[256] For example, treatment of 2-hydroxy-2-(methoxymethyl)cyclobutanone **682** with 0.2 equiv of potassium hydrogen sulfate at 170-180 °C under reduced pressure (20-25 mmHg) formed the ring expanded 1,3-cyclopentanedione **683** in 75% yield (Scheme 187).



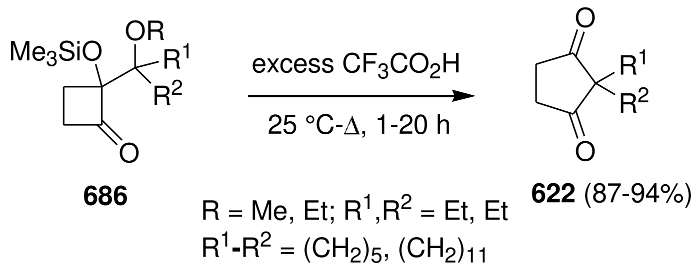
Scheme 187

As an extension of the synthesis of dicyclopentane-1,3-diones, different cyclobutanones have been treated with trifluoroacetic acid.[238a,257] Attached directly to the diol moiety, the cyclobutanone ring was expected to exert directive effects in the cationic rearrangements. When cyclobutanones **684** were treated with an excess of trifluoroacetic acid at 25 °C to reflux temperature for one to 20 hours, depending on the substrate, the corresponding 2-alkyl-3-hydroxy- or 2-aryl-3-hydroxy-2-cyclopentenones **685** were obtained in 78 to 97% yield (Scheme 188). *p*-Toluenesulfonic acid and boron(III) fluoride etherate were also found to be effective for this ring expansion.



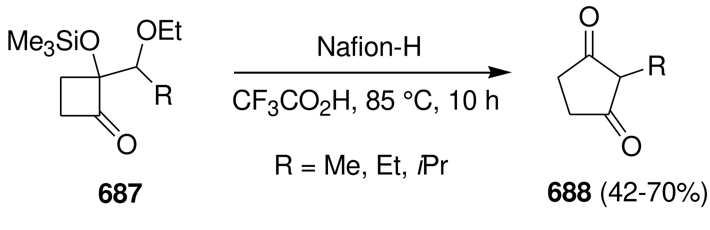
Scheme 188

However, when cyclobutanones **686**, having an extra substituent at the α-carbon of the ether, were treated with an excess of trifluoroacetic acid under the same conditions, 2,2-diethyl-1,3-cyclopentadione or spiro-1,3-cyclopentadiones **622** were isolated in 87 to 94% yield (Scheme 189). Again, different acids or Lewis acids could be used, but an excess of trifluoroacetic acid was chosen for the sake of easy workup (*vide supra*).



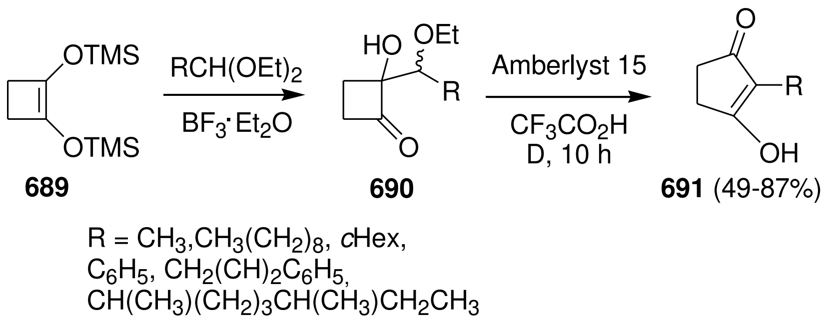
Scheme 189

In an effort to synthesize 2-methyl-, 2-ethyl- and 2-isopropyl-1,3-cyclopentadiones **688** the procedure of Nakamura and Kuwajima[238a] has been applied to silylated 2-hydroxycyclobutanones **687**.[258] Suprisingly, none of the expected products was obtained. Application of an additional acidic co-catalyst, *i.e.* Nafion-H, a sulfonated tetrafluoroethylene based polymer, which was reported to give high yields in pinacol rearrangements proved to be successful.[259] When Nafion-H was added to a solution of **687** in trifluoroacetic acid, followed by heating at 85 °C for ten hours, the corresponding 2-alkyl-1,3-cyclopentadiones **688** were obtained in 42-70% yield (Scheme 190).



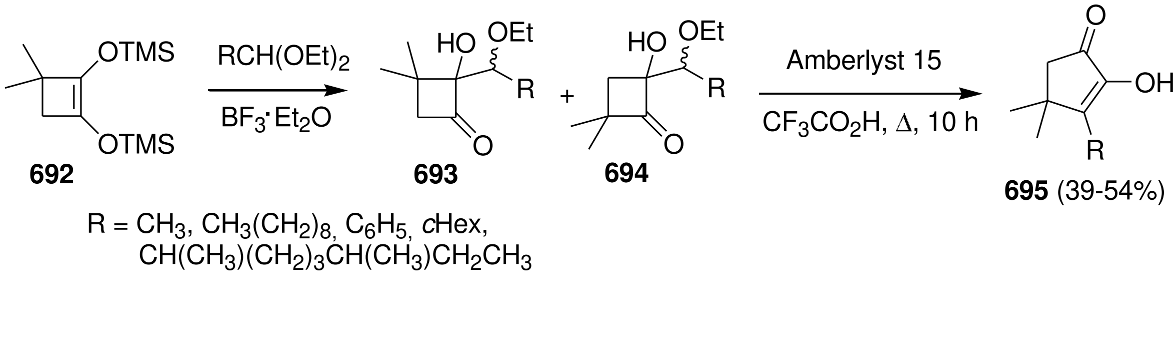
Scheme 190

Lewis acid-mediated reactions of 1,2-bis(trimethylsilyloxy)cyclobutene with acetals, followed by treatment with Amberlyst 15 resin in trifluoroacetic acid, have been reported to yield 1,3-cyclopentanediones.[260] This type of rearrangement had already been investigated before by Kuwajima *et al.* and Rao *et al.*[257,258] Now, the authors stated that addition of Amberlyst 15 resin to cyclobutanones **690** in trifluoroacetic acid afforded 1,3-cyclopentanediones, occurring mainly in the enolized form **691**, in 49-87% yield (Scheme 191).



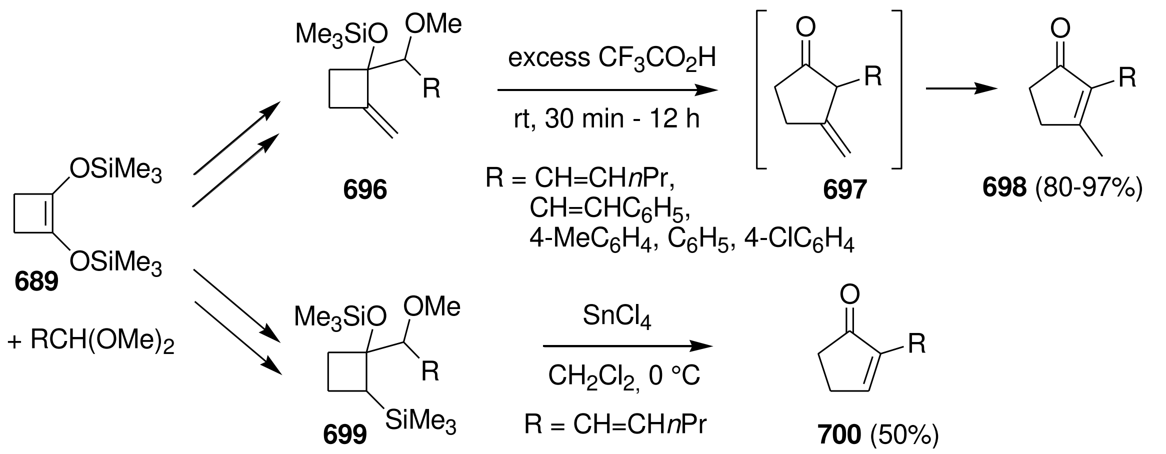
Scheme 191

In analogy, treatment of cyclobutene **692** with diethyl acetals afforded cyclobutanones **693** and a small fraction of **694** under the acidic conditions of the reaction.[260] However, when *gem*-dimethyl cyclobutanones **693** and **694** were treated with Amberlyst 15 resin, no 1,3-diketone was formed, but instead enols of 1,2-diketones **695** were obtained in 39-54% yield (Scheme 192).



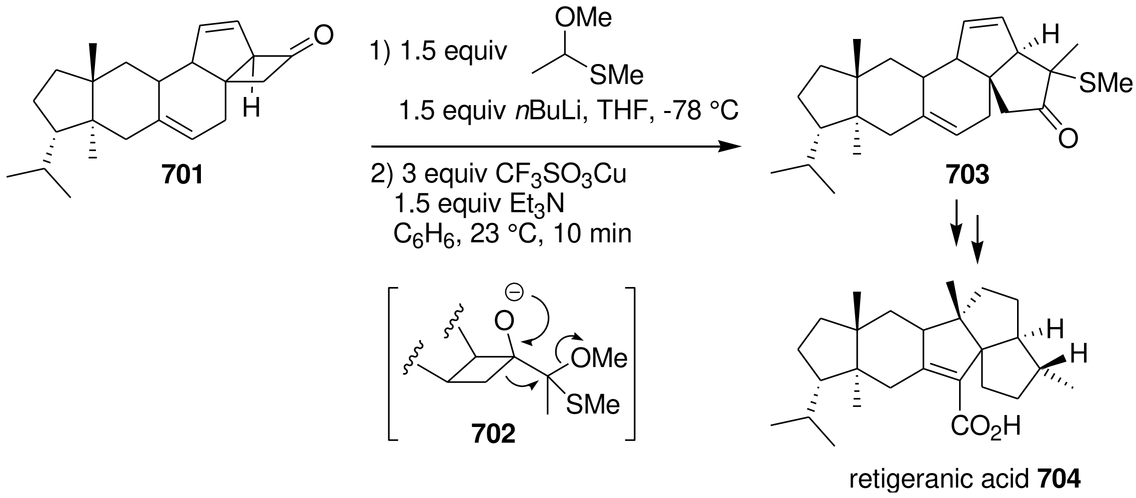
Scheme 192

The preparation of α-aryl- and α-vinylcyclopentenones has been achieved via two approaches. In a first method, silylated α-methylidenecyclobutanols **696** were treated with an excess of trifluoroacetic acid at room temperature for 30 min to 12 hours to afford the corresponding 3-methyl-2-cyclopentenones **698** in 80-97% yield (Scheme 193).[261] The second route involved tin(IV) chloride treatment of silylated 1,2-cyclobutanediol **699** for the preparation of enones **700** (Scheme 193). Substrates **696** and **699** were prepared from 1,2-bis(trimethylsilyloxy)cyclobutene **689**.



Scheme 193

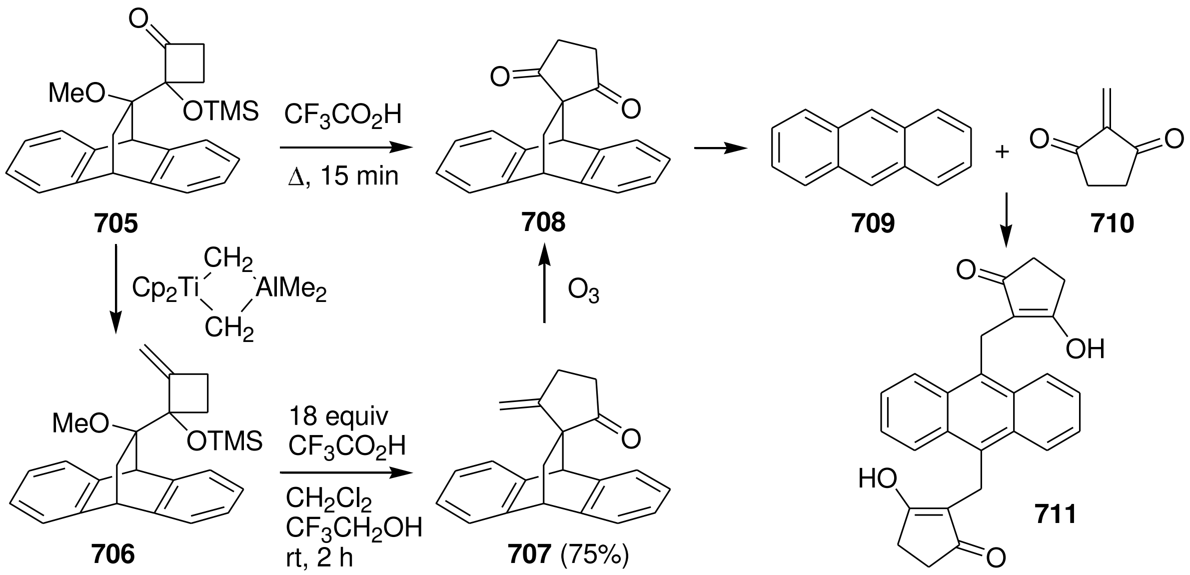
In the course of the total synthesis of (±)-retigeranic acid **704**, the last five-membered ring was constructed via ring enlargement of the corresponding cyclobutanone, using an activated methoxygroup as a promoter for this ring expansion.[262] Treatment of ketone **701** with 1.5 equiv of the lithio derivative of acetaldehyde dimethylmonothioacetal in tetrahydrofuran at -78 °C formed the corresponding carbonyl adduct in 73% via rearrangement of intermediate **702** utilizing three equiv of cuprous triflate in the presence of 1.5 equiv of triethylamine in benzene at 23 °C for ten minutes (Scheme 194). No yield was mentioned for this step, and the crude compound **703** was used in the next reactions toward retigeranic acid **704**.



Scheme 194

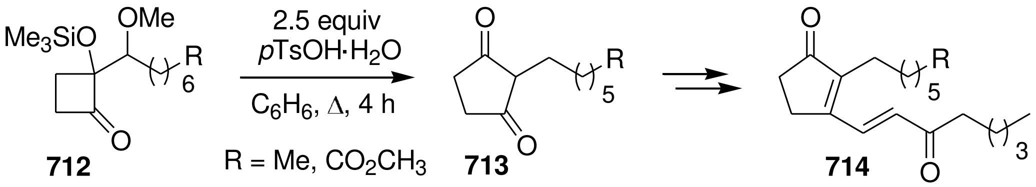
Within the field of polycyclic aromatic hydrocarbon chemistry, attempts to isolate anthracene adduct **708**, produced via an acid-catalyzed rearrangement, failed and instead, when heating cyclobutanone **705** in trifluoroacetic acid for 15 minutes, an equimolar mixture of anthracene **709** and 9,10-disubstituted anthracene **711** was isolated (Scheme 195).[263] At room temperature, consumption of substrate **705** took about two hours, but again only anthracene **709** and **711** were obtained. As expected, the pinacol rearrangement of **705** to **708** occurred, but the spirodiketone **708** was not stable under these conditions. Acid-catalyzed retro-Diels Alder fragmentation produced anthracene **709** and 2-methylene-1,3-cyclopentanedione **710**. Acceleration of the Diels Alder cycloaddition by acid-catalysis is well-known.[264] The two-fold electrophilic substitution of **710** on the cognate anthracene nucleus led to **711**, and the overall stoichiometry of the process provided for a molar equivalent of anthracene. No yields were mentioned for this reaction.

However, when the cyclobutanone ring of anthracene adduct **705** was converted into the corresponding methylenecyclobutane **706**, pinacolic ring expansion of **706** proceeded with clean migration of the vinyl group, providing the spiroannelated cyclopentanone **707** in 75% yield without tendency for retro-Diels Alder fragmentation. Conversion of alkene **707** to ketone **708** was accomplished by ozonolysis to synthesize the preferred adduct **708**.



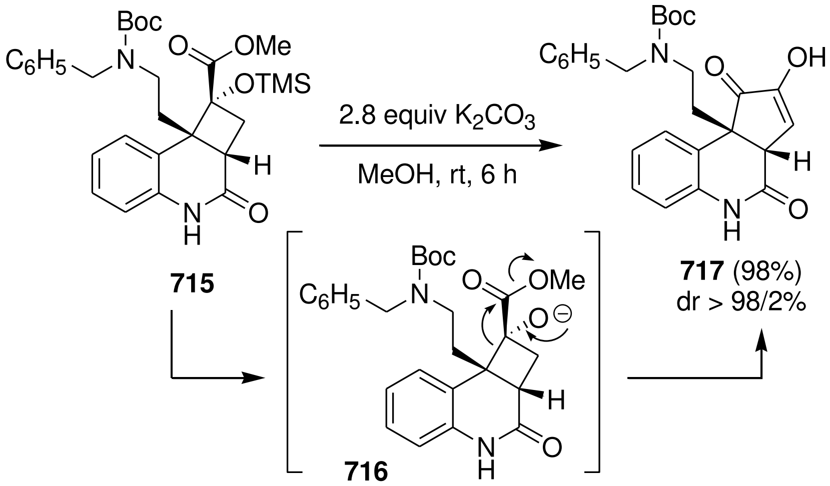
Scheme 195

With the intention to synthesize the five-membered ring of the methyl ester of 15-dehydroprostaglandin B1 **714** (R = CO_2CH_3),[265] a ring rearrangement of silylated 2-hydroxycyclobutanones has been performed according to Oppolzer's[255] and Kuwajima and Nakamura's method.[257] The silylated 2-hydroxycyclobutanones **712** were treated with 2.5 equiv of *p*-toluenesulfonic acid monohydrate in benzene at reflux for four hours to afford the corresponding 2-alkyl-1,3-cyclopentadiones **713**, which were immediately used as such in the next step (Scheme 196). Also pyridinium 4-toluenesulfonate has been used for a ring rearrangement toward the synthesis of 2-substituted cyclopentanones.[266]



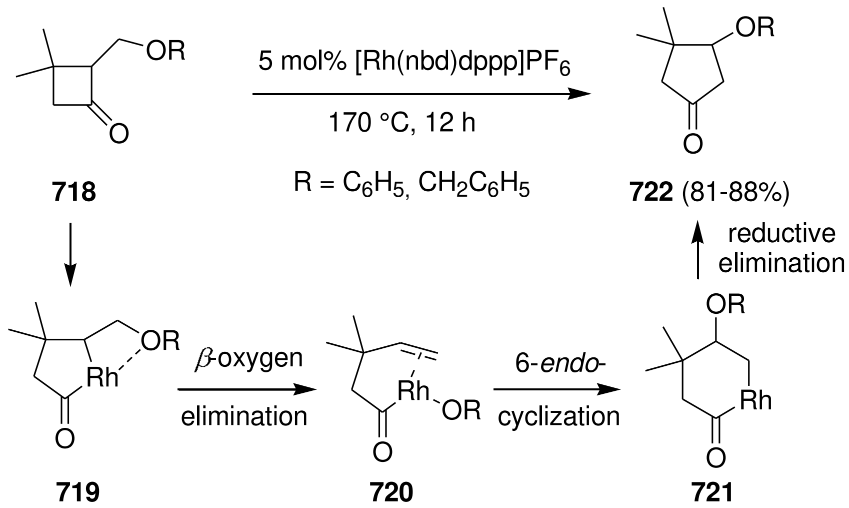
Scheme 196

Recently, in studies toward the synthesis of meloscine, a cyclobutane to cyclopentane rearrangement has been described using potassium carbonate.[267] When cyclobutane **715** was stirred in methanolic potassium carbonate at room temperature for six hours, a cyclopentane-1,2-diketone was formed in 98% yield, exclusively exisiting in the tautomeric enol form **717** (Scheme 197).



Scheme 197

A special case of cyclopentanone synthesis has been reported by Ito *et al.*[268] When cyclobutanones **718** were treated with five mol% of $[Rh(nbd)dppp]PF_6$ at 170 °C for 12 hours, cyclopentanones **722** were isolated in 81-88% yield (Scheme 198). First, a five-membered cyclic acylrhodium intermediate **719** underwent *β*-oxygen elimination to form the olefin-coordinated acylrhodium intermediate **720**, followed by recyclization to a sixmembered acylrhodium **721** by addition of the Rh-O linkage across the C-C double bond in a 6-*endo* mode. Finally, reductive elimination forming a C-C bond afforded cyclopentanones **722**. An important remark to this synthesis was the fact that the reaction lacked generality.



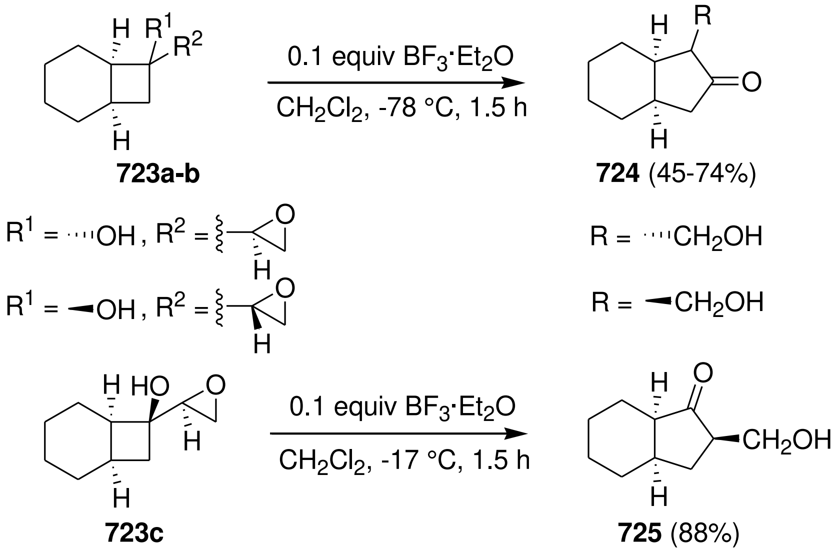
Scheme 198

6.5.2 Ring opening of an epoxide as driving force for the ring expansion reaction

Due to the high ring strain energy associated with epoxides, 2-cyclobutyl oxirane systems can be regarded as suitable substrates for a cyclobutane to cyclopentane rearrangement. Nevertheless, only few examples are known in the literature based on this approach.

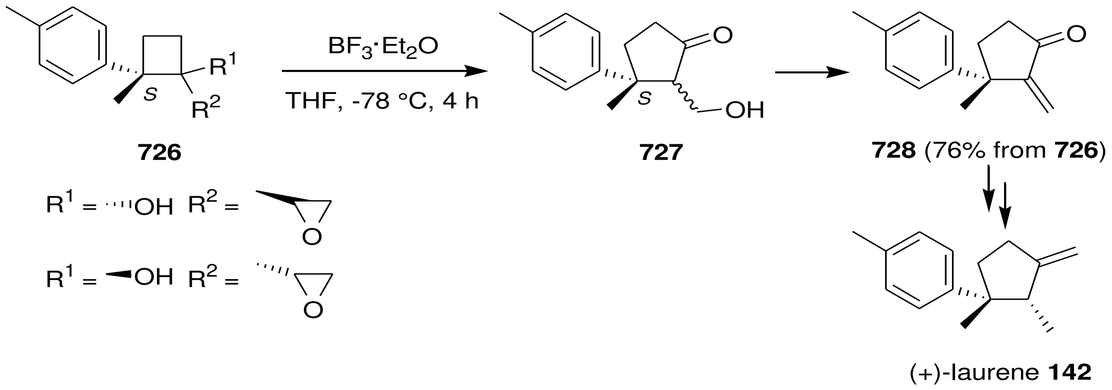
In a first example, the four racemic diastereoisomers of 7-oxiranylbicyclo[4.2.0]octan-7-ol **723** were treated with boron(III) fluoride etherate under mild conditions.[269] Three of the isomers underwent regio- and stereoselective rearrangements to the ring expanded hydroxymethyl substituted ketones **724** and **725**, the fourth diastereoisomer only gave unreacted starting material.

In particular, treatment of bicyclo[4.2.0]octan-7-ols **723a-b** with a catalytic amount of $BF_3{\cdot}Et_2O$ in dichloromethane at -78 °C afforded bicyclo[4.3.0]nonan-8-ones **724** with a shift of the bridgehead in a highly regioselective manner in 45% and 74% yield (Scheme 199). However, bicyclo[4.2.0]octan-7-ol **723c** rearranged to bicyclo[4.3.0]nonan-7-one **725** at -17 °C in 88% yield by a shift of the methylene group (Scheme 199).



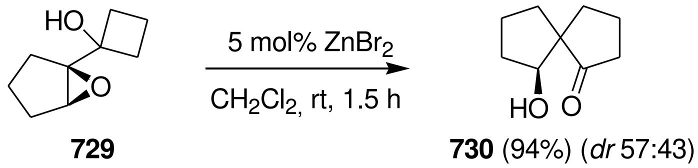
Scheme 199

In an alternative enantioselective total synthesis of (+)-laurene **142**, the five-membered ring was obtained via ring enlargement of the corresponding cyclobutane through activation of an adjacent epoxide (Scheme 200).[82] A first approach was already described in this review in the part on palladium-mediated ring enlargements of vinylcyclobutanols (Scheme 42). $BF_3{\cdot}Et_2O$ in tetrahydrofuran at -78 °C for four hours effected the ring expansion of the cyclobutane ring of epoxides **726** to cyclopentanone **727**, which underwent dehydration to furnish *α*-methylenecyclopentanone **728** in 76% overall yield from **726**. This compound **728** was used as a precursor for (+)-laurene **142**.



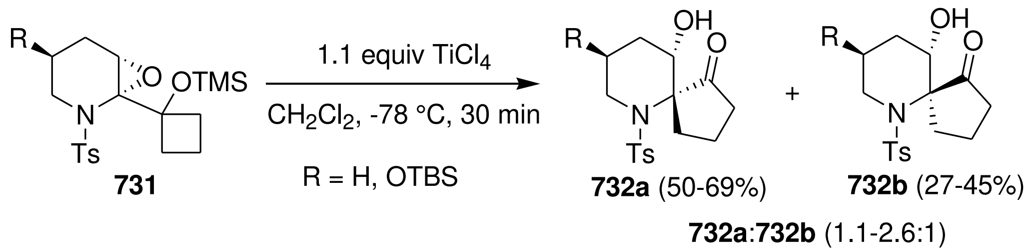
Scheme 200

Zinc(II) bromide has been used as a catalyst for the stereoselective construction of quaternary carbons in the synthesis of diastereomerically enriched spirocyclic diols.[270] When hydroxy epoxide **729** was treated with five mol% of zinc(II) bromide in dichloromethane at room temperature for 1.5 hours, the corresponding 1-hydroxyspiro[4.4]nonan-6-one **730** was isolated in 94% yield (Scheme 201). A bromo-substituted byproduct or a competitive rearrangement product (allylic alcohol) was not isolated.[271] The synthesized compound **730** could be used as substrate for the preparation of the corresponding spirocyclic diol.



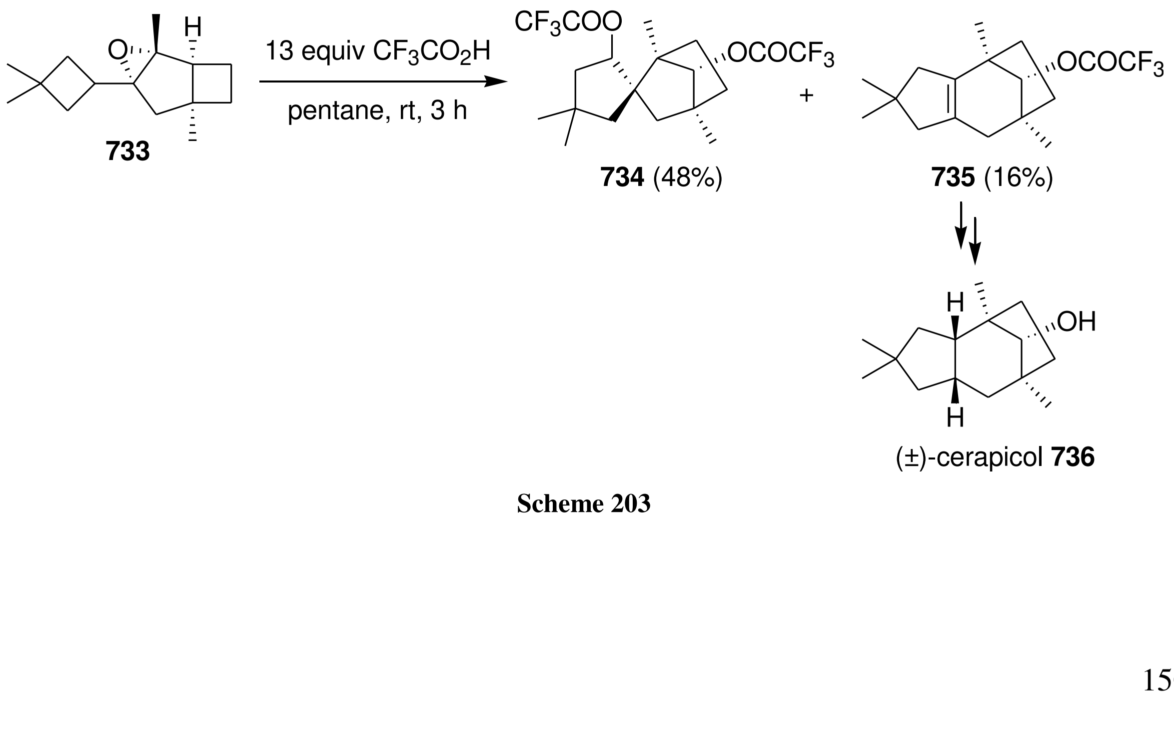
Scheme 201

In the next example, titanium(IV) chloride has been used for the formation of functionalized azaspirocyclic cyclopentanones **732** (Scheme 202).[272] Epoxides **731** underwent facile ring expansion toward cyclopentanones **732a** and **732b** in 95-96% yield as 1.1-2.6:1 mixtures of diastereoisomers via addition of 1.1 equiv titanium(IV) chloride in dichloromethane at -78 °C for 30 minutes, although with low stereoselectivity. Cyclopentanones **732a** are the apparent products of an antiperiplanar 1,2-alkyl migration toward the epoxide, while cyclopentanones **732b** seemingly result via a synperiplanar 1,2-alkyl migration process. Similar azaspirocyclic cyclopentanones have been made through an acid- and a halogen cation-promoted activation of a double bond (Scheme 27).[61,67]



Scheme 202

Recently, a rearrangement through ring opening of an epoxide has been reported in the synthesis of (±)-cerapicol **736**, a protoilludane sesquiterpene.[273] Upon treatment with 13 equiv of trifluoroacetic acid in pentane, bicycle **733** rearranged to yield a mixture of trifluoroacetates containing 48% of spiro compound **734** and 16% of tricyclic compound **735** (Scheme 203). The preferred formation of **734** indicated that the cyclopentyl cation formed by enlargement of the 3,3-dimethylcyclobutyl ring was effectively trapped.



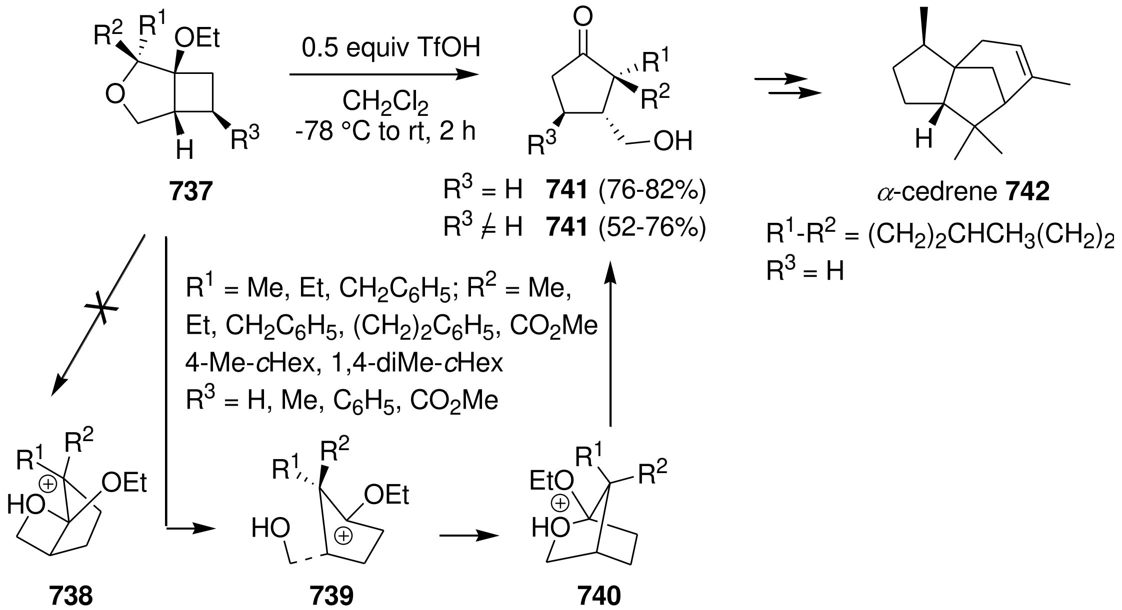
Scheme 203

6.5.3 Ring opening of an activated tetrahydrofuran ring as driving force for the ring expansion reaction

In a few isolated cases, an activated oxolane ring has been employed as a way to trigger a cyclobutane to cyclopentane ring expansion.

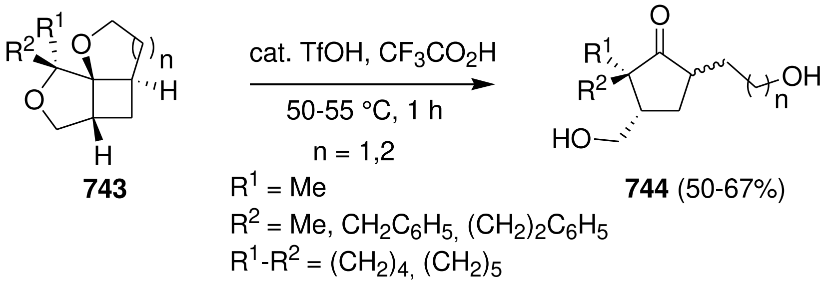
For example, when bicyclo[3.2.0]heptanes **737** were treated with 0.5 equiv of TfOH in dichloromethane at -78 °C to room temperature, a ring rearrangement was established toward 1,2-dialkylcyclopentanones **741** in 76-82% yield (R^3 = H)[274] and in 52-76% yield (R^3 ≠ H)[275] in a stereospecific manner via migration of the C_1-C_5 bond (Scheme 204). These cyclopentanones **741** can be used in the synthesis of many natural products.[276,277] For example, the same authors have reported the synthesis of spirocyclopentanone **741** (R^1-R^2 = $(CH_2)_2CHCH_3(CH_2)_2$) in 76% yield as a precursor in the total synthesis of the natural product (±)-*α*-cedrene **742**.[276] Also adduct **741** (R^1, R^2 = Me) is an advanced intermediate in the synthesis of planococcyl acetate, the pheromone of the citrus mealy bug.[278] The cyclopentanones **741** (R^1 = Me, R^2 = 4-methylcyclohexyl) and **741** (R^1 = Me, R^2 = 1,4-dimethylcyclohexyl) comprise the carbon skeletons of cuprenolide and trichodiene, respectively.

The selectivity observed in the pinacol rearrangement of cyclobutane derivatives **737**, involving exclusive migration of the C_1-C_5 bond in contrast to the stereoelectronically favoured C_1-C_7 bond, was explained based on the intermediates as depicted below. A concerted migration of the C_1-C_5 bond in the protonated species of **737** led to formation of carbenium ions **739**, which were stabilized by the OH group through formation of the cyclic intermediate **740**. Rapid collapse of **740** led to products **741**. In case of C_1-C_7 bond migration, the stabilization of the intermediate carbenium ions by the OH group required unfavorable formation of the strained oxetanes **738** and was thus inhibited.



Scheme 204

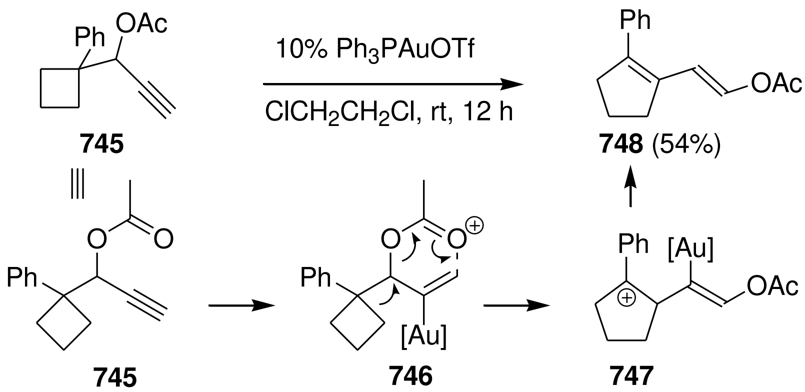
In an effort to synthesize hydroxyalkyl-substituted cyclopentanones, a mixture of strong acids was used to effect bond migration of the appropriate cyclobutanes.[279] Rearrangement of cyclobutanes **743** took place when treated with trifluoroacetic acid and a catalytic amount of trifluoromethane sulfonic acid at 50-55 °C for one hour to afford cyclopentanones **744** in 50-67% yield (Scheme 205). The cyclopentanones **744**, obtained in each case, were mixtures of diastereoisomers epimeric at C_5 in about 2.5:1 ratio. The stability of the carbenium ion formed after cyclobutane bond migration dictated the reaction course during rearrangement, providing a selectivity for 1,5-bond over 1,7-bond migration.



Scheme 205

6.5.4 A special case

A last and rather special example involved gold-catalyzed isomerization of a propargylic ester.[280] Treatment of cyclobutane **745** with 10% of gold(I) triflate in dichloroethane at room temperature for 12 hours led to the isolation of cyclopentene **748** in 54% yield (Scheme 206).



Scheme 206

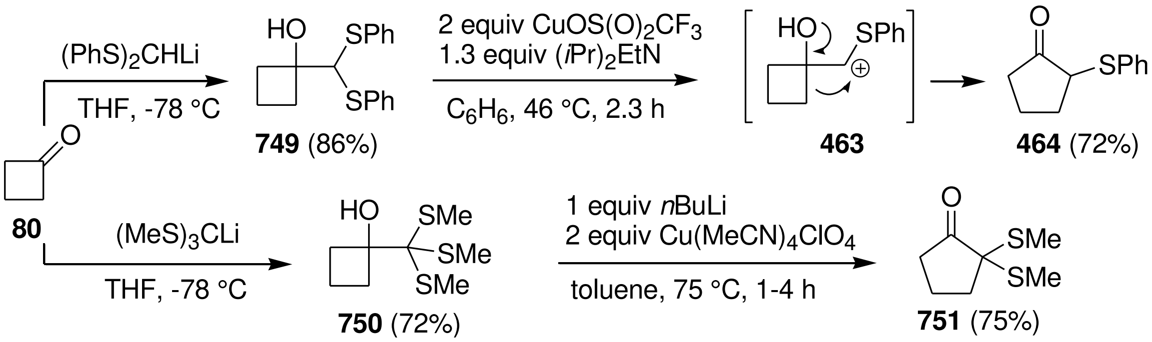
6.6 An alkyl- or arylthio group as leaving group

Changing the leaving group from an alkoxide to an alkyl- or arylthio group implies a weaker σ-bond, quantitatively reflected in the dissociation energy of the single bond which is 355-380 kJ/mol for the carbon-oxygen bond and 255 kJ/mol for the carbon-sulfur single bond.[281]

In pinacol-type ring expansions with removal of an alkyl- or arylthio group, thiophilic reagents such as copper(I) or mercury(II) salts are frequently used for generating cationic intermediates to direct the migrating group. Different examples of four-membered ring rearrangements using the acidity in α-position of a sulfide, are described in this section.

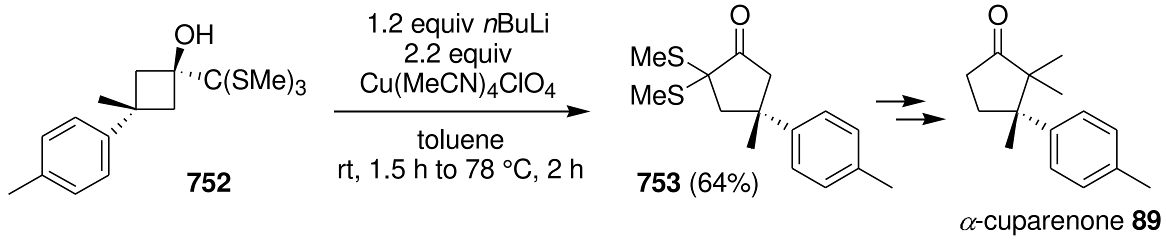
Sulfur-stabilized carbenium ions, generated in organic solvents under mild conditions by removal of a thiophenoxide ion from a thioacetal using soluble cuprous trifluoromethanesulfonate, have for example been used in the synthesis of 2-sulfanylated cycloalkanones.[282,283] Addition of the lithio derivative of bis(phenylthio)methane to cyclobutanone **80** afforded *α*-hydroxydiphenylthioacetal **749** in 86% yield (Scheme 207). Treatment of thioacetal **749** with two equiv of cuprous triflate and 1.3 equiv of diisopropylethylamine in benzene at 46 °C for 2.3 hours afforded *α*-thiophenoxy cyclopentanone **464** in 72% yield, presumably via the intermediate carbenium ion **463**.

This ring expansion was also evaluated alternatively using the lithio derivative of tris(phenylthio)methane and failed.[284] However, when the lithio derivative of tris(methylthio)methane was added to cyclobutanone **80**, the *α*-hydroxytrimethylthioacetal **750** was obtained in 72% yield (Scheme 207). One equiv of *n*-butyllithium converted the *α*-hydroxytrimethylthioacetal **750** to its lithium salt. Two equiv of tetrakis(acetonitrile)copper(I) perchlorate were added and the mixture was heated to 75 °C for one to four hours to afford *α,α*-dimethylthiocyclopentanone **751** in 75% yield.



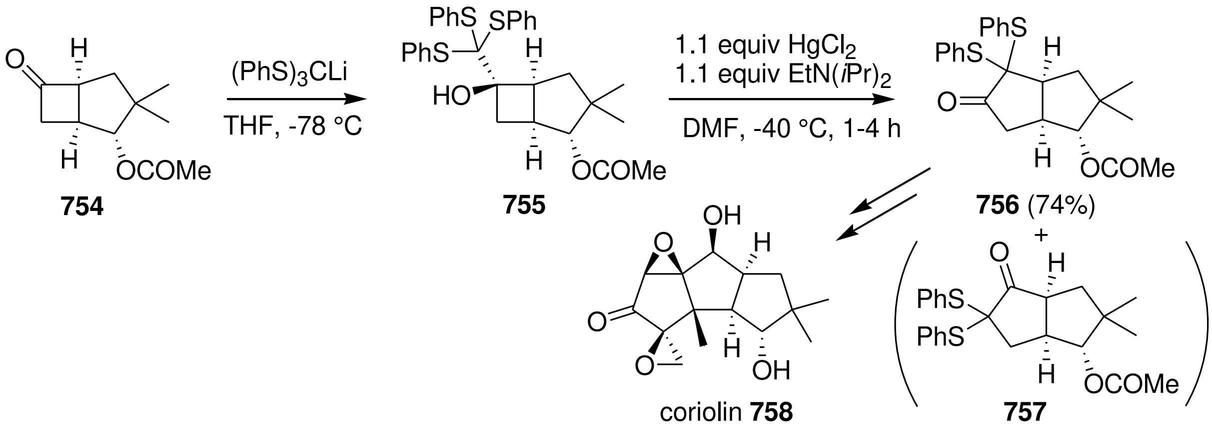
Scheme 207

The previous method has also been applied in an alternative synthesis of *α*-cuparenone **89**, reported by Ho and Chang.[285] Treatment of **752** with 1.2 equiv of *n*-butyllithium and 2.2 equiv of tetrakis(acetonitrile)copper(I) perchlorate in toluene afforded 2,2-di(methylthio)-3-methyl-3-(4-methylphenyl)cyclopentanone **753** in 64% yield (Scheme 208).



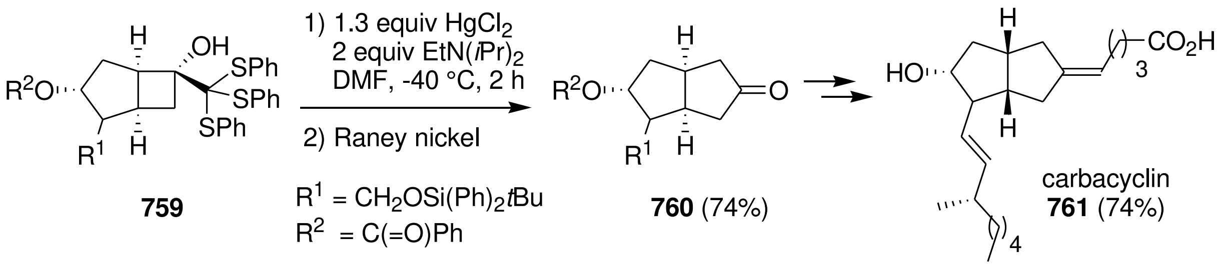
Scheme 208

Furthermore, the above-described method using the lithio derivative of tris(phenylthio)methane has been used in the synthesis of coriolin **758**, where the second five-membered ring was obtained via ring rearrangement of the four-membered ring precursor.[284] Treatment of bicyclo[3.2.0]heptanone **754** with the lithio derivative of tris(phenylthio)methane in tetrahydrofuran at -78 °C gave adduct **755** in one isomer (Scheme 209). Addition of 1.1 equiv of mercury(II) chloride and diisopropylethylamine in dimethylformamide at -40 °C resulted in the removal of one phenylthio group, and subsequent ring expansion resulted in cyclopentanone **756** in 74% yield with migration of the more substituted carbon atom. The authors stated that almost no regioisomer **757** was formed from ring expansion of the less substituted carbon atom, without mentioning the exact ratio.



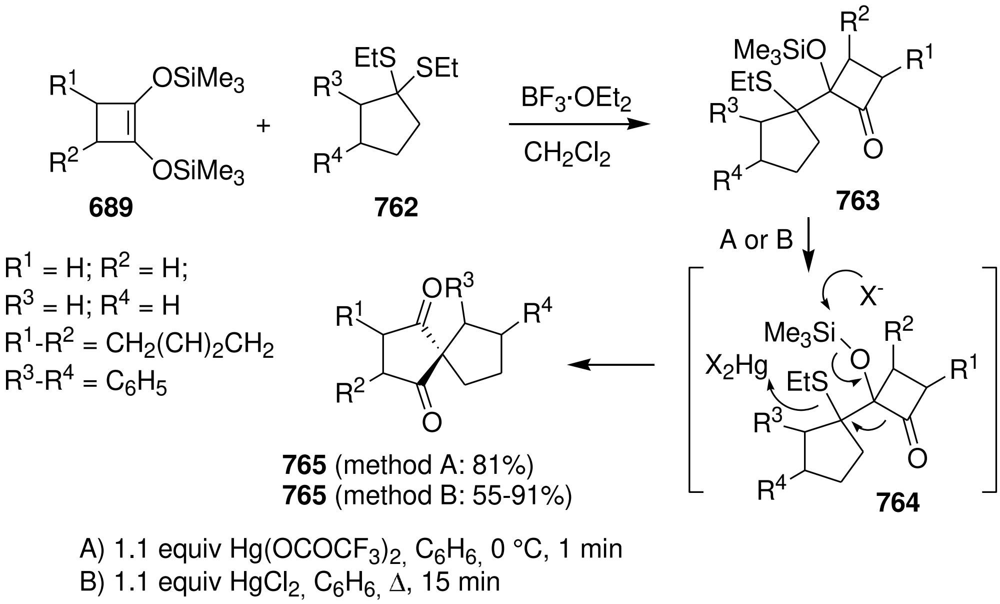
Scheme 209

Also 3-benzoyloxy-4-(*tert*-butyldiphenylsilyloxymethyl)bicyclo[3.3.0]octan-7-one **760**, as a precursor of carbacyclin **761**, has been synthesized in 74% yield via the same method as described above (*i.e.* 1.3 equiv $HgCl_2$, 1.1 equiv $(iPr)_2EtN$, DMF, -40 °C, 1-4 h, followed by reduction with Raney nickel) (Scheme 210).[286] Carbacyclin is a chemically stabilized modification of natural prostaglandin I_2 (prostacyclin), which has valuable biological activity.



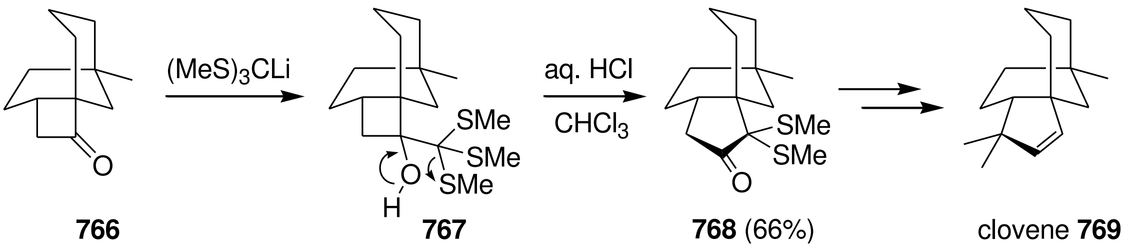
Scheme 210

In order to obtain the 1,4-diketospiro[4.4]nonane structure of fredericamycin A, which exhibits both antibiotic and antitumor activity, a mercury-mediated acyl migration in a modified version of the pinacol-type rearrangement has been reported.[287] Compounds **763**, generated from bissilylated cyclobutenediols **689** and dithioacetals **762**, were desulfurated/desilylated in a single step and rearranged via acyl migration to the mixture of spiro compounds *cis*-**765** in 81% yield (R^1-R^2 = $CH_2CH{=}CHCH_2$; R^3-R^4 = CH=CH-CH=CH) by treatment with 1.1 equiv of mercury bistrifluoroacetate in benzene at 0 °C or in 55-91% yield using 1.1 equiv of mercury(II) chloride in benzene at reflux temperature (Scheme 211). Method A has also been used in another total synthesis of fredericamycin A.[288]



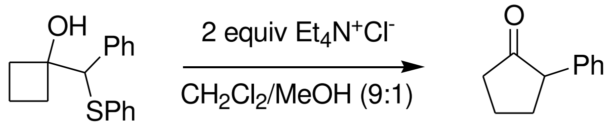
Scheme 211

In the total synthesis of (±)-clovene **769**, the crucial ring expansion step was effected by acid treatment of cyclobutanol **767**, obtained by adding the anion of tris(methylthio)methane to cyclobutanone **766**.[289] Treatment with a thiophilic Hg(II) salt was not required for rearrangement, as instead addition of aqueous HCl in chloroform promoted facile rearrangement to cyclopentanone **768** in 66% overall yield (Scheme 212).



Scheme 212

As a special case, an electrooxidative ring expansion of 1-(α-phenylthiobenzyl)cyclobutanol **770** was used to prepare 2-phenylcyclopentanone **771** (Scheme 213).[290] A solution of β-hydroxy sulfide **770** in dichloromethane/methanol (9:1), containing two equiv of tetraethylammonium chloride, was electrolyzed at 6.0 F/mol in an undivided cell equipped with carbon plate electrodes with a constant current of 100 mA, furnishing 2-phenylcyclopentanone **771** in 78% yield.



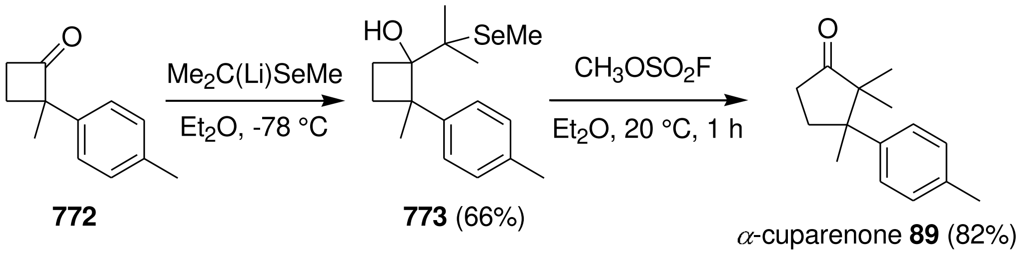
770 **771** (78%)

Scheme 213

6.7 An alkyl- or arylselenyl group as leaving group

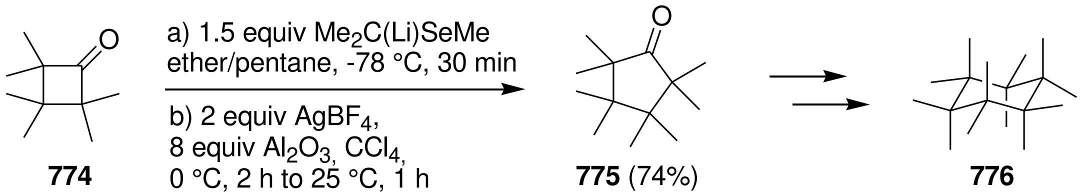
Krief and co-workers have described that *β*-hydroxyalkylselenides, bearing two alkyl groups on the carbon atom where the seleno moiety is attached, are prone to rearrange to carbonyl compounds upon reaction with silver(I) tetrafluoroborate. [148,291]

In the synthesis of *α*- and *β*-cuparenone, this rearrangement was used via *β*-hydroxyselenide **773** as a precursor for the five-membered ring (Scheme 214).[148] Addition of 2-lithio-2-methylselenopropane to cyclobutanone **772** in diethyl ether at -78 °C afforded *β*-hydroxyselenide **773** in 66% yield. Subsequently, three rearrangement conditions were investigated. The first method involved thallium ethoxide addition in chloroform to afford *α*-cuparenone **89** in 57% yield, though via generation of a carbene. A better yield of 69% was obtained when silver tetrafluoroborate on alumina in dichloromethane was added. Finally, *α*-cuparenone **89** was obtained in 82% yield upon reaction of *β*-hydroxyselenide **773** with methyl fluorosulfonate in diethyl ether at 20 °C for one hour.



Scheme 214

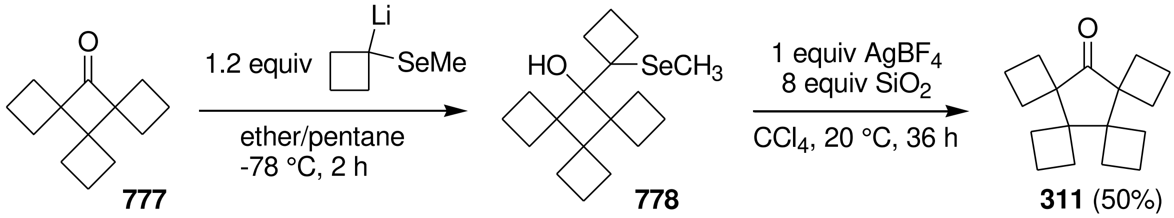
The first step in the synthesis of permethylcyclohexane **776** was a ring expansion of hexamethylcyclobutanone **774** to octamethylcyclopentanone **775** according to a general procedure developed by Krief.[292,293] Treatment of hexamethylcyclobutanone **774** with 1.5 equiv of 2-lithio-2-selenopropane in ether/pentane for 30 minutes at -78 °C afforded the corresponding *β*-hydroxyselenide, which was subsequently treated with two equiv of silver tetrafluoroborate and eight equiv of alumina in tetrachloromethane for two hours at 0 °C and one hour at 25 °C to obtain octamethylcyclopentanone **775** in 74% yield (Scheme 215).



Scheme 215

Next to other approaches (Scheme 89), the synthesis of tetraspiroketone **311** has been accomplished via ring expansion of trispiroketone **777** via *β*-hydroxyselenide **778** (Scheme 216).[134b] The trispiroketone **777** was reacted with 1-lithio-1-(methylseleno)cyclobutane in ether/pentane at -78 °C for two hours to afford the crude *β*-hydroxyselenide **778**, which was treated with one equiv of silver tetrafluoroborate and eight equiv of silicium oxide in tetrachloromethane at 20 °C for 36 hours to furnish the tetraspiroketone **311** in 50% yield.

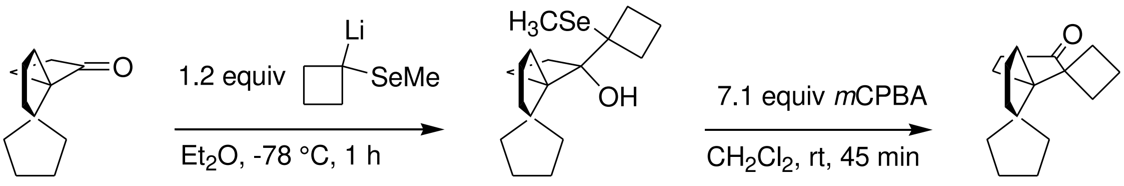
This ketone **311** proved to be unstable towards acids. The same ring expansion was applied in the synthesis of a [5.4]rotane, using silver tetrafluoroborate on aluminium oxide instead of silicium oxide.[294]



777 **778** **311** (50%)

Scheme 216

Because reductive debromination of compound **112** (Scheme 33) with zinc in acetic acid failed, an alternative approach to the synthesis of pseudohelical compound **780** was proposed.[69] This method used a rearrangement of *β*-hydroxyselenide **779**, synthesized in 37% yield by treatment of tricyclic cyclobutanone **106** with 1-lithio-1-(methylseleno)cyclobutane in diethyl ether at -78 °C for one hour. The ring expansion of *β*-hydroxyselenide **779** was executed via addition of 7.1 equiv of 3-chloroperoxybenzoic acid (*m*CPBA) in dichloromethane at room temperature for 45 minutes to afford trispiro[3.0.0.4.3.3]hexadecan-16-one in 70% yield (Scheme 217).



106 **779** (37%) **780** (70%)

Scheme 217

6.8 Sulfone, sulfoxide and selenoxide groups as leaving group

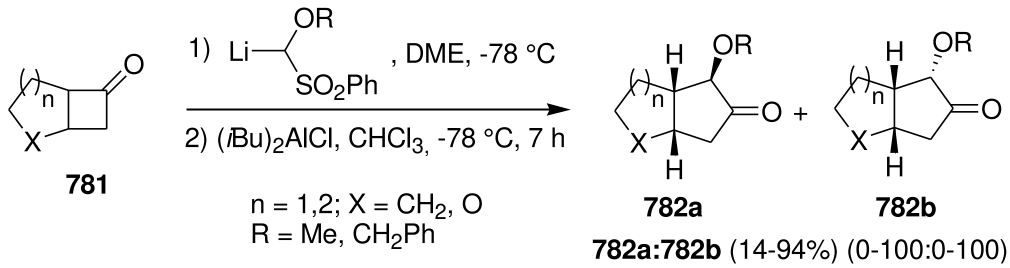
Using the synthetic versatility of sulfons, sulfoxides and selenoxides as leaving groups, different methods are in hand for the ring rearrangement of four- to five-membered carbocycles and will be discussed in the next paragraphs.

6.8.1 A sulfone group as leaving group

A one-pot procedure for the ring expansion of bicyclic ketone **781** (X = CH_2, n = 1) with concomitant introduction of an α-methoxy group has been reported by Trost and Mikhail.[295] In that approach, the sensitivity of sulfones as a leaving group in the presence of Lewis acids was used for the ring rearrangement. Addition of lithiated methoxymethylphenyl sulfone to bicyclo[3.2.0]ketone **781** (X = CH_2, n = 1), followed by cationic rearrangement initiated by an excess of diisobutylaluminium chloride in chloroform at -78 °C for seven hours, produced only bicyclo[3.3.0]ketone **782a** (R = Me, X = CH_2, n = 1) in an overall yield of 68% from the starting ketone (Scheme 218). The reaction proceeded in a regio- and stereoselective fashion toward the thermodynamically more stable diastereoisomer. The lithiation and addition reaction were carried out in dimethoxyethane using *tert*-butyllithium at -78 °C.

The potential of the previous approach has been employed in the synthesis of prostaglandin analogues, using different cyclobutanones as starting material.[296] The same reaction conditions, *i.e.* addition of lithiated methoxymethylphenyl sulfone, followed by rearrangement via diisobutylaluminiun chloride, were used to afford a mixture of bicyclic ketones **782a** and **782b** in 14-94% yield, in which for each example the one-pot reaction as well as the two-step reaction were investigated (Scheme 218). Only when cyclobutanone **781** was used (n = 1, X = CH_2) in a one-pot reaction, one isomer **782a** was isolated. These results showed that Trost-style ring expansions of cyclobutanone derivatives **781** rarely produced single stereoisomers.

Neither isolation of the intermediate alcohol, the nature of the sulfone, nor the presence of an oxygen atom in the larger ring of the bicyclic ketone did appear to significantly alter the stereochemical outcome of the ring expansion product, in contrast with the size of the larger ring in the starting bicyclic ketone. In general, the two-step process was higher yielding than the one-pot reaction.



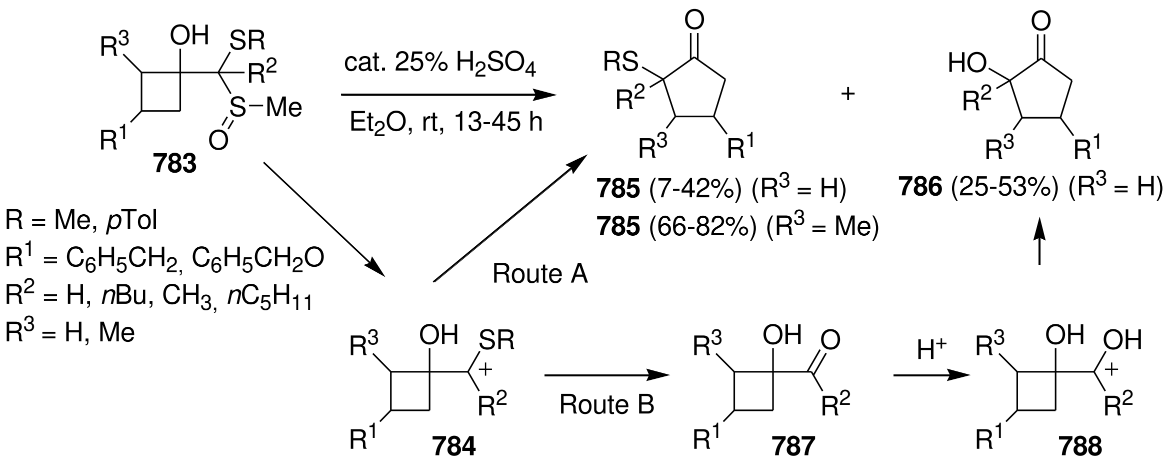
Scheme 218

6.8.2 A sulfoxide as leaving group

Ring expansion of 1-[1-methylsulfinyl-1-(methylthio)alkyl]cyclobutanol derivatives **783** has been achieved upon treatment with a catalytic amount of 25% sulfuric acid (Scheme 219).[297] Starting from **783** (R = Me; R^3 = H), two types of compounds were expected to be formed. If the ring expansion is fast, route A operated predominantly and a 2-(methylthio)cyclopentanone **785** was produced as the major product. In contrast, a 2-hydroxycyclopentanone **786** was preferably formed when the dithioacetal *S*-oxide group of **783** was first hydrolyzed to afford a 1-acylcyclobutanol **787** (route B). A solution of **783** in diethyl ether containing a few drops of 25% sulfuric acid was stirred at room temperature for 13-45 hours. The major product was alcohol **786** for R^2 = butyl, synthesized in 53% yield next to 7-21% of sulfide **785**, whereas **785** (42%) was predominantly formed when R^2 was a hydrogen atom besides 25% of **786**. This was explained by stabilization of the intermediate

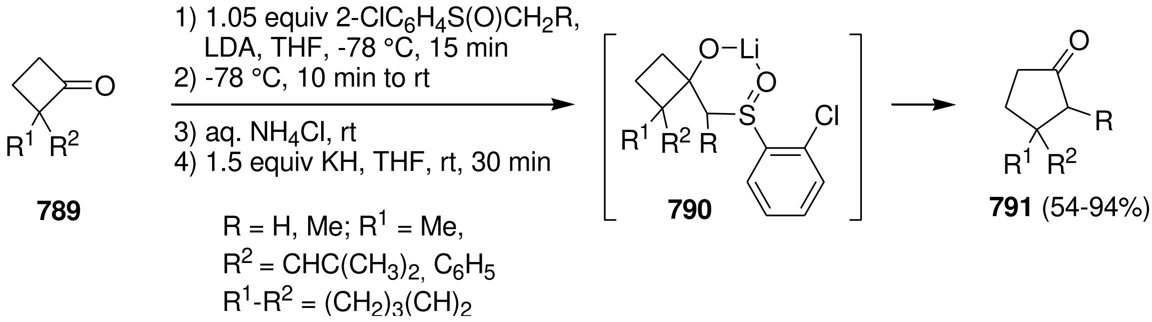
784 by the butyl group to make **784** longer-living, increasing the probability of the intermolecular reaction of **784** with water.

Next, the effect of introducing a 2-methyl group on the cyclobutane ring (R = Me, *p*Tol; R^3 = Me) was investigated (Scheme 219).[297] However, only one product was obtained in 66 to 82% yield when **783** was subjected to acidic conditions. No side products were observed, which could be attributed to the migration ability of the carbon atom enhanced by the presence of a methyl on the cyclobutanol ring of **783**, leading to the chemo- and regioselective formation of sulfide **785** (R^3 = Me).



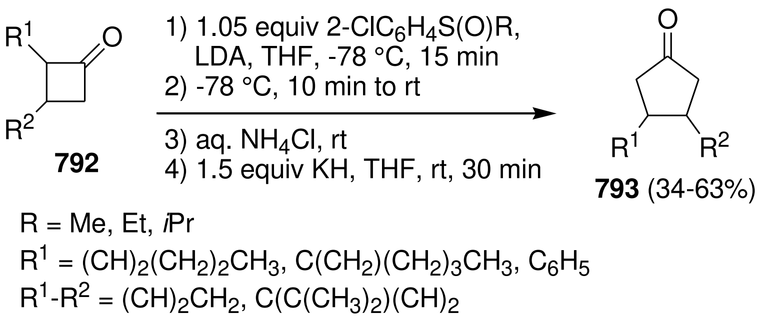
Scheme 219

Ring expansion of cyclobutanones **789**, which have both a 2-alkyl and a 2-aryl or 2-alkenyl substituent, produced cyclopentanones **791** in 54 to 94% yield on reaction with *α*-lithioalkyl 2-chlorophenyl sulfoxides, formed via deprotonation with LDA at -78 °C (Scheme 220).[298] The produced adducts underwent rapid ring expansion upon treatment with 1.5 equiv of potassium hydride at room temperature for 30 minutes. No evidence of the presence of *α*-phenylsulfenylcyclopentanones was provided, as was observed with the selenium reagents (*vide supra*). Only one regioisomer was isolated in each case with migration of the more substituted cyclobutanone α-carbon atom.



Scheme 220

Finally, also the ring expansion of cyclobutanones **792**, bearing a single 2-alkenyl or 2-phenyl substituent, has been reported.[298] The problem with this type of cyclobutanones upon treatment with any strongly basic carbanion was competitive proton transfer to afford the enolate. Still, reaction of cyclobutanones **792** with α-lithioalkyl 2-chlorophenyl sulfoxides provided the corresponding cyclopentanones **793** in 34 to 63% yield (Scheme 221). Again, the ring rearrangement proceeded regiospecifically with migration of the more substituted α-carbon atom.

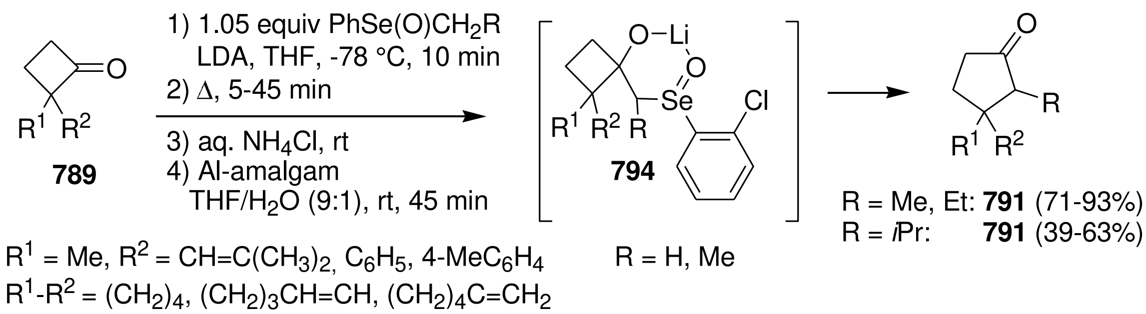


Scheme 221

6.8.3 A selenoxide as leaving group

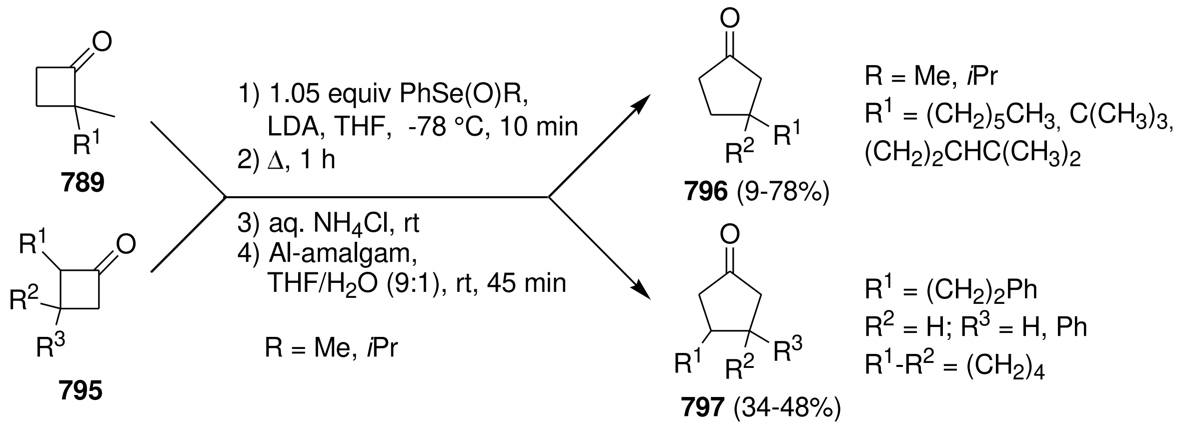
In a first example, ring expansion of 2,2-disubstituted cyclobutanones **789** using *α*-lithioalkyl phenyl selenoxides, prepared *in situ* from ethyl phenyl selenide, afforded an adduct **794**, which underwent ring expansion rather than the expected selenoxide elimination.[299] Presumably, chelation in the adduct **794** caused elimination to occur more slowly than ring expansion. The corresponding cyclopentanones **791** were obtained after quenching with saturated aqueous NH_4Cl and subsequent treatment with aluminium amalgam in 39 to 93% yield (Scheme 222). A lower yield was obtained somewhat in the reactions with the anion of isopropyl phenyl selenoxide (39-63%), in part due to competitive enolization of the cyclobutanone. One of these examples comprised a short synthesis of racemic (±)-*α*-cuparenone **89** (R = *i*Pr, R^1 = Me, R^2 = 4-MeC_6H_4) in the moderate yield of 39%.

This selenoxide procedure was regiospecific, with exclusive migration of the more highly substituted carbon. A drawback of this method involved reaction of the cyclopentanone product with electrophilic selenium species produced *in situ* to afford a mixture of the product and several isomeric *α*-phenylselenenylcyclopentanones. Reconversion of the *α*-phenylselenenyl derivatives back to the cyclopentanone could be accomplished by means of aluminium amalgam, but this treatment could interfere with other easily reducible functionalities and thus limited the generality of this methodology.



Scheme 222

Gadwood *et al.* generalized this research by dividing the cyclobutanones in two classes, in an analogous manner as described in the previous paragraph.[298] The first type included the cyclobutanones bearing two alkyl substituents at C_2, and the second type were those with only one alkyl substituent (Scheme 223). The first type, when reacted under the same conditions as previously described, led to the corresponding cyclopentanones **796** in 9 to 78% yield. Rearrangement of the second type of cyclobutanones, the least reactive ones toward ring expansion, still afforded cyclopentanones **797** in 34 to 78% yield. Again, for both types, phenylselenenyl containing impurities were obtained, thus requiring treatment of the crude reaction mixture with aluminium amalgam before purification. Exclusive migration of the more substituted cyclobutane carbon was observed during the ring expansion.

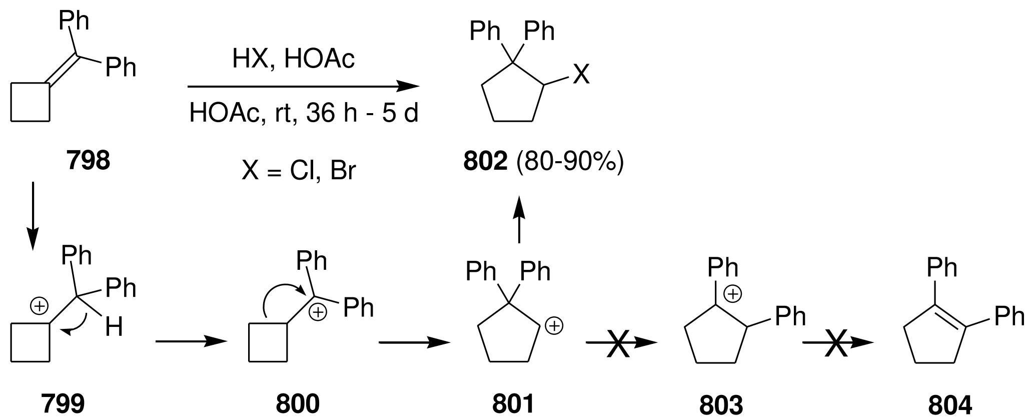


Scheme 223

7 Miscellanous

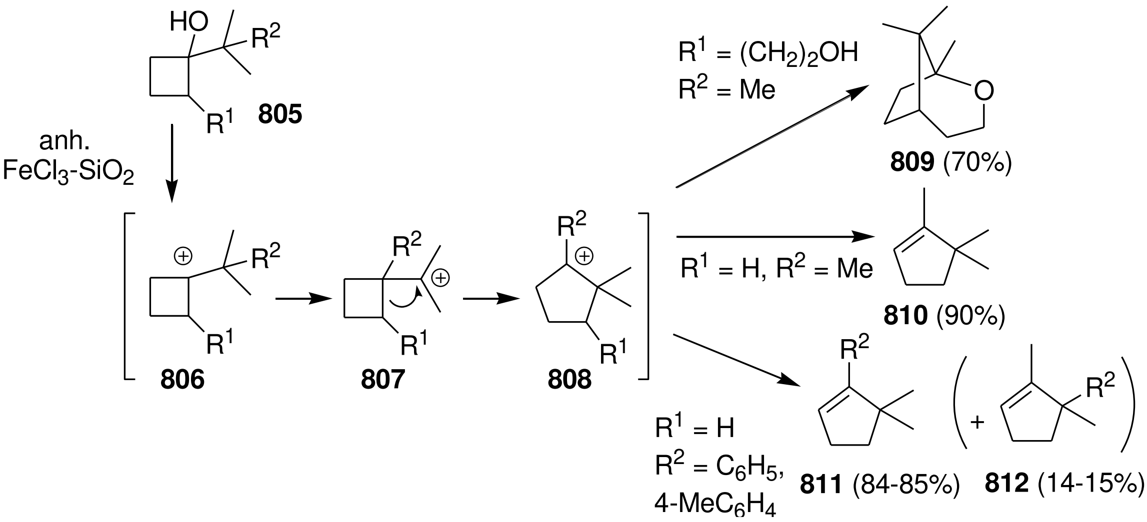
In this section, special or peculiar cases involving a cyclobutylmethyl to cyclopentyl rearrangement will be described which could not be divided into the previous subcategories. The first examples comprise ring expansions where a hydrogen or alkyl shift takes place before the actual rearrangement. Other examples involve rearrangement of iminium salts and palladium-catalyzed transformations of cyclobutanone *O*-benzoyloximes.

In a first example, addition of hydrogen bromide or hydrogen chloride to arylidenecyclobutane **798** produced 2,2-diphenylcyclopentyl halides **802** in 80-90% yield (Scheme 224).[300] The formation of these cyclopentanes **802** was expected to involve a 2,2-diphenylcyclopentyl carbenium ion **801**. Further rearrangement of this electron-deficient species to the 1,2-diphenylcyclopentyl ion **803** would be energetically favored, but the absence of 1,2-diphenylcyclopentene **804** showed that capture of **801** by a nucleophile was extremely selective.



Scheme 224

A specific ring enlargement of tertiary cyclobutanols **805** into cyclopentene derivatives has been reported through an initial 1,2-alkyl or –aryl shift prior to ring enlargement (Scheme 225).[301] Anhydrous iron(III) chloride, absorbed on silica gel, was reacted with tertiary cyclobutanol **805** (R^1 = H, R^2 = Me) to give 1,5,5-trimethylcyclopentene **810**, also know as isolaurolene, in 90% yield. The ring expansion involved Lewis acid induced formation of 1-*t*-butylcyclobutyl carbenium ion **806** and a Wagner-Meerwein-type methyl transfer giving the cyclobutylcarbinyl carbenium ion **807**, followed by a $C_4 \rightarrow C_5$ ring enlargement into cyclopentyl carbenium ion **808** and deprotonation to **810**. The same ring enlargement was executed starting from 1-*t*-butyl-2-(2-hydroxyethyl)cyclobutanol **805** (R^1 = $(CH_2)_2OH$, R^2 = Me), but the rearranged cyclopentyl carbenium ion was trapped into the campholenic ether (2-oxabicyclo[3.2.1]octane derivative) **809** in 70% yield. Ring enlargement of 1-(1-methyl-1-aryl)ethylcyclobutanols **805** gave the corresponding 2-aryl-3,3-dimethylcyclopentenes **811** as the major products in 84 to 85% yield and 3-aryl-2,3-dimethylcyclopentenes **812** as the minor products in 14 to 15% yield. 3,3-Dimethyl-2-*p*-tolylcyclopentene **811** was used as a precursor of (±)-cuparene, while the minor product, *i.e.* 3-*p*-tolyl-2,3-dimethylcyclopentene **812**, was used as precursor for (±)-laurene synthesis.



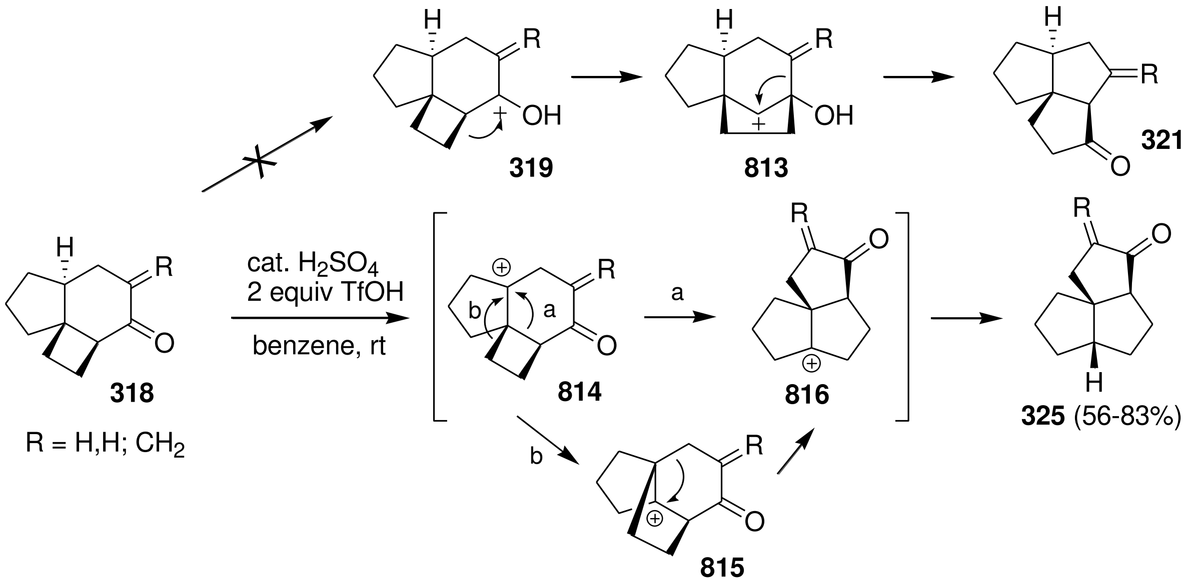
Scheme 225

Upon reaction with a catalytic amount of concentrated sulfuric acid and two equiv of trifluoromethanesulfonic acid in benzene at room temperature, *cis*,*trans*-tricyclo[6.3.0.0^{1,4}]undecan-5-ones **318** underwent an unusual and highly selective rearrangement to afford tricyclo[6.3.0.0^{1,5}]undecan-4-ones **325** in 56 to 83% yield (Scheme

226).[302] The use of Lewis acids was also investigated, *e. g.* $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$, $FeCl_3$ and $TiCl_4$, all giving rise to tricyclo[6.3.0.0^{1,5}]undecan-4-ones **325** in 63 to 99% yield.

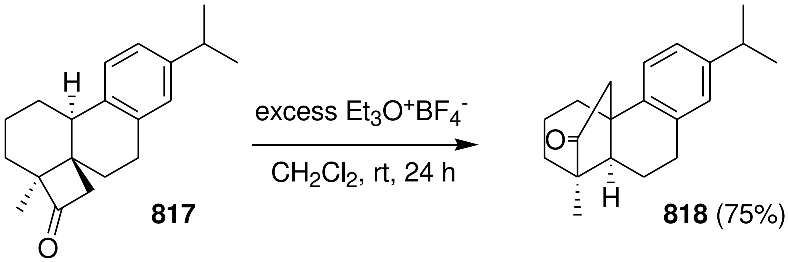
If the Cargill rearrangement of **318** would take place, tricyclo[6.3.0.0^{1,5}]undecan-4-ones **321** would be the rearranged products. In order to explain these observations, the authors proposed a 1,2-alkyl shift of the unexpected cyclobutylmethyl carbenium ions **814**, formed by hydrogen abstraction by the acid, followed by further rearrangement through carbenium ions **815** and/or **816** toward bicycles **325**. Nonetheless, the formation of carbenium ions **814** from **318** under the given reaction conditions should be regarded as highly unlikely, and alternative pathways, e.g. involving a hydride shift in intermediates **319** and further transformation, might provide a more plausible explanation for the observed reactivity.

Kakiuchi and co-workers also performed the rearrangement of an analogous product, as described previously in Scheme 91.[137]



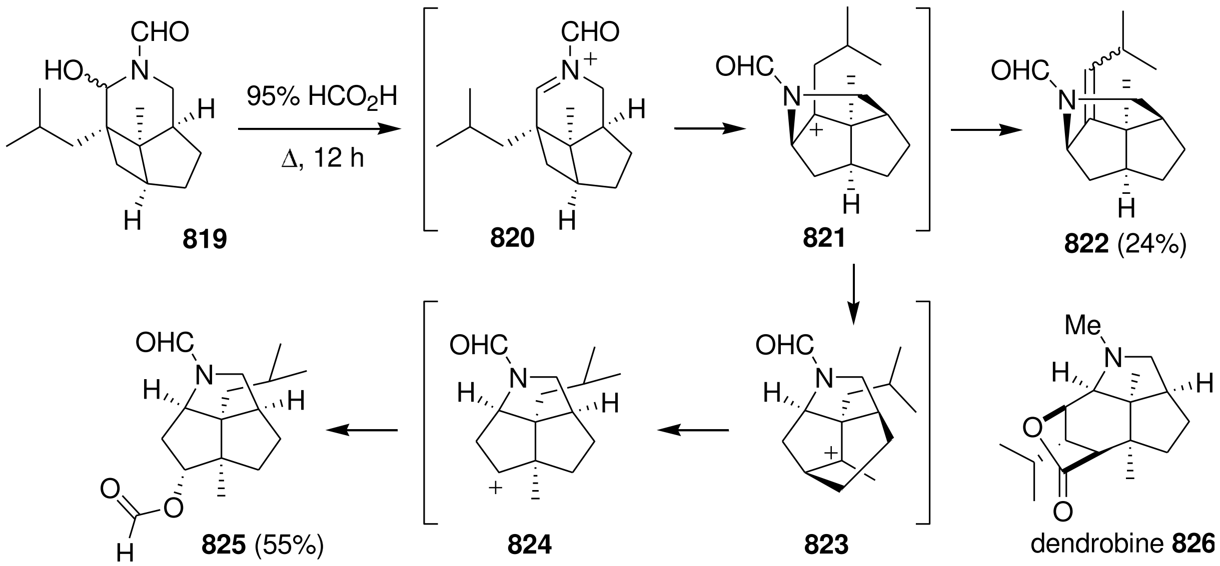
Scheme 226

Banik and Ghatak have published the synthesis of a cyclopentanone-bridged tricyclic system via a general route to functionalized abietane diterpenoids, involving a Meerwein salt-initiated cationic rearrangement of the ring-annelated cyclobutanone **817**.[303] The addition of an excess of triethyloxonium tetrafluoroborate in dichloromethane to cyclobutanone **817** for 24 hours at room temperature afforded the 19,20-cycloabieta-19-oxo-8,11,13-triene **818** in 75% yield (Scheme 227).



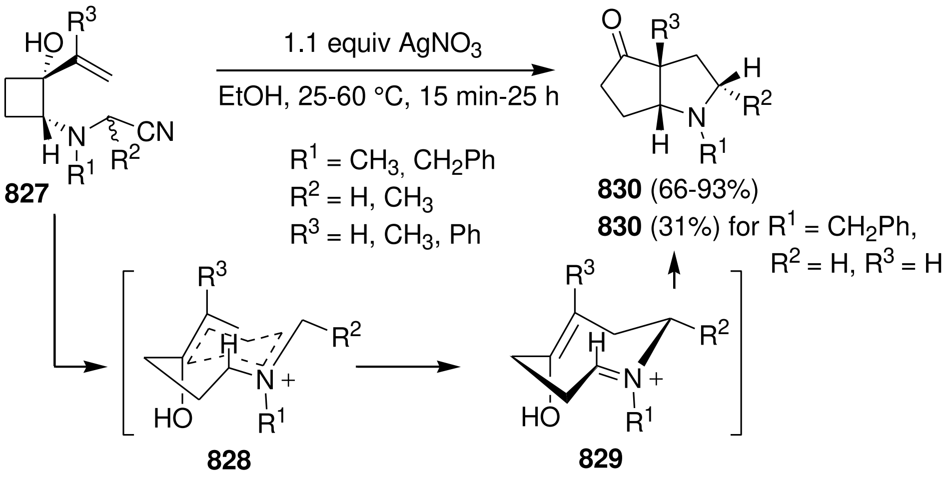
Scheme 227

In an approach to synthesize the precursor of dendrobine, a sesquiterpenoid alkaloid, a rearrangement of 5-azatricyclo[6.1.1.0^{5,9}]decane acyliminium ion **820** has been investigated.[304] Heating a mixture of 7-hydroxy-8-isobutyl-9-methyl-6-azatricyclo[6.1.1.0^{4,9}]decane-6-carbaldehyde **819** in 95% formic acid under reflux for 12 hours gave a 1:1 mixture of (*E*)- and (*Z*)-9-isobutylidene-8-methyl-2-azatricyclo[5.2.1.0^{4,10}]decane-2-carbaldehyde **822** and the secondary formate 10-isobutyl-8-formyloxy-7-methyl-2-azatricyclo[5.2.1.0^{4,10}]decane-2-carbaldehyde **825** in 24% and 55% yield, respectively (Scheme 228). Initial ionization of the starting product **819** formed the acyliminium species **820**, which was followed by exclusive migration of the *exo* cyclobutane bond to give the tertiary carbenium ion **821**. Once formed, **821** can lose a proton to form the isomeric mixture of olefins **822**. Alternatively, **821** can undergo a skeletally degenerate 1,2-alkyl shift to provide a secondary tricyclic tertiary carbenium ion **823**. A final 1,2-alkyl shift converted **823** into secondary carbenium ion **824**, which was quenched by the solvent to give formate **825**. Compound **825** is an analogue of the precursor of dendrobine **826**.



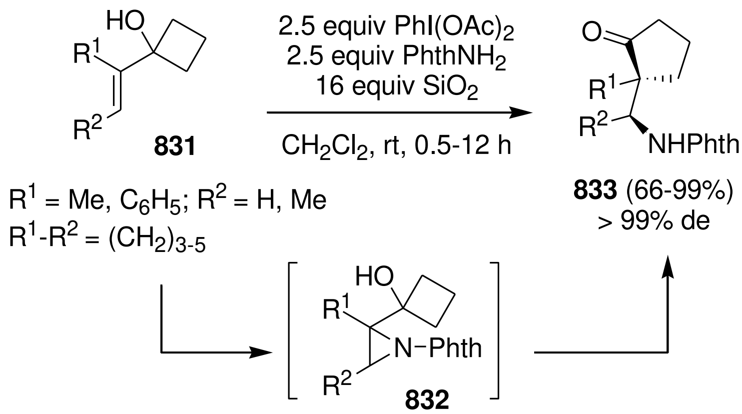
Scheme 228

In a totally different approach, *cis*-4-oxo-octahydrocyclopent[b]pyrroles **830** have been formed by a tandem cationic aza-Cope rearrangement – Mannich cyclization of 2-amino-1-vinylcyclobutanols **827** (Scheme 229).[305] Treatment of vinylcyclobutanols **827** with 1.1 equiv of $AgNO_3$ in ethanol at 25-60 °C for 15 minutes to 25 hours afforded the corresponding bicyclic compounds **830** in 66-93% yield (31% for derivative R^1 = CH_2Ph, R^2,R^3 = H). The stereoselectivity was explained via the intermediates formed. The iminium ions **828** underwent a [3,3]-sigmatropic rearrangement in a chair geometry to give the azacycloocta-1,5-diene intermediates **829**, and rapid intramolecular Mannich cyclization of the latter intermediates **829** led to bicycles **830**.



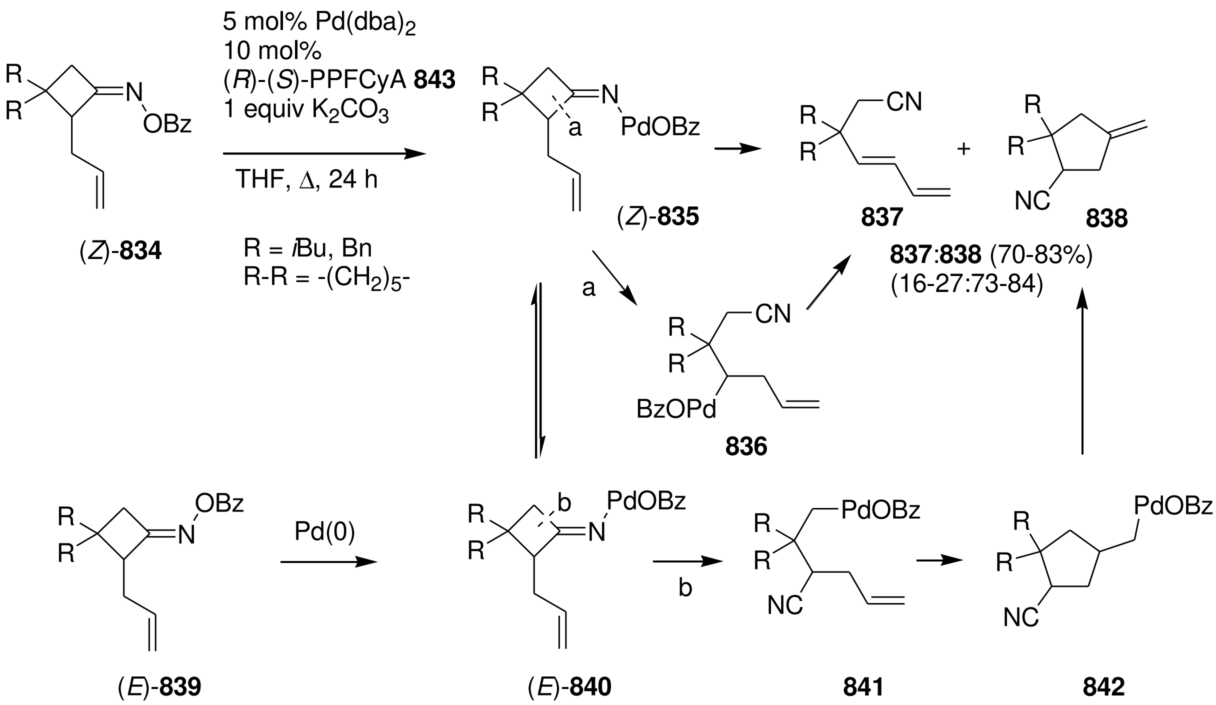
Scheme 229

Recently, a tandem aziridination/rearrangement protocol of alkenylcyclobutanols has been developed based on the combination of *N*-aminophthalimide and phenyliodine diacetate in the presence of silica gel.[306] When 2.5 equiv of $PhI(OAc)_2$, 2.5 equiv of $PhthNH_2$ and 20 equiv of SiO_2 were added to alkenylcyclobutanols **831** in dichloromethane, the corresponding cyclopentanones **833** were obtained in 66-99% yield and in more than 99% diastereomeric excess (Scheme 230). An analogous pinacol-type rearrangement has been reported by the same group using zinc(II) bromide, but the protocol suffered from low yields (20-30%) obtained for the aziridino alcohols.[307]

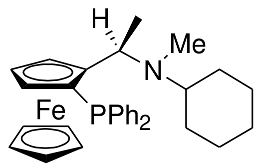


Scheme 230

In a final example, a palladium-catalyzed transformation of cyclobutanone *O*-benzoyloximes **834** to nitriles **837** and **838** was reported (Scheme 231).[308] When cyclobutanone *O*-benzoyloximes (*Z*)-**834** were treated with five mol% of Pd(dba)$_2$ and ten mol% of ligand (*R*)-(*S*)-PPFCyA **843** (Figure 11) in the presence of one equiv of K_2CO_3 in tetrahydrofuran at reflux temperature for 24 hours, oxidative addition of the *N-O* bond of the oxime to Pd(0) gave a (*Z*)-cyclobutylideneaminopalladium(II) species **835**. Then, the C-C bond (path a) was cleaved to afford a secondary alkylpalladium species **836**, from which the nitrile **837** was produced by successive *β*-hydrogen elimination. On the other hand, when the (*Z*)-cyclobutylideneaminopalladium(II) species **834** isomerized to **839** and was subsequently cleaved (path b), a sterically less hindered primary alkylpalladium species **840** was formed. The latter underwent intramolecular cyclization with the alkenic moiety, followed by *β*-hydrogen elimination to afford nitrile **838**. The ratio of the nitriles **837** and **838** was 16-27:73-84 in 70 to 83% yield.



Scheme 231



(*R*)-(*S*)-PPFCyA **843**

Figure 11

8 Concluding Remarks

Different methods have been described for the synthesis of cyclopentane and cyclopentene derivatives starting from cyclobuta(no)nes through ring expansion of intermediate cyclobutylmethylcarbenium ions. Acid activation of the double bond of vinylcyclobutanes or vinylcyclobutanols proved to be a suitable methodology for the preparation of cyclopenta(e)(no)nes in good to excellent yields, and in most of the cases only one regioisomer was formed. Also metal activation has been applied successfully, as exemplified in a variety of natural product syntheses. Furthermore, allene activation for the formation of cyclobuylmethylcarbenium ions has attracted considerable interest, based on several examples found in the more recent literature. Interesting approaches have also been reported concerning the ring expansion of cyclobutylmethylcarbenium ions obtained through activation of an alkynyl substituent, although moderate yields were obtained in most of the cases.

Alternatively, the activation of a carbonyl compound via several methods has been described, with yields varying from moderate to good. Nonetheless, the vast majority of ring expansions of cyclobutylmethylcarbenium ions are induced by the initial expulsion of a leaving group, present at the α-position with regard to the cyclobutane ring.

Although it is sometimes difficult to predict the outcome of the ring expansion reaction, in general, the more highly substituted carbon atom migrated preferentially. However, diazomethane induced ring expansions tend to favor migration of the less substituted *α*-carbon. In this case, *α*-chloro and *α*,*α*-dichlorocyclobutanones react faster and provide higher regioselectivities.

It is worth mentioning that recently the aza-analogue of the cyclobutylmethylcarbenium to cyclopentylcarbenium ion rearrangement has been described as well. In particular, a *β*-lactam to *γ*-lactam ring expansion has been developed starting from 4-(1-halo-1-methylethyl)azetidin-2-ones via *N*-acyliminium intermediates, providing access to a variety of functionalized mono- and bicyclic pyrrolidines-2-ones in good yields.[309] A similar approach has been described starting from 4-oxoazetidine-2-carbaldehydes to afford 5-cyano-3,4-dihydroxypyrrolidin-2-ones.[310] It seems that the onset is given to the development of many such ring expansions in the heterocyclic series.

Due to the high synthetic and biological relevance of cyclopentane derivatives, the search for novel methodologies for the construction of substituted five-membered carbocycles remains of primordial importance. Consequently, the development of new approaches based on the ring expansion of cyclobutylmethylcarbenium ions, especially those with a focus on regio- and stereoselectivity, will most certainly keep on attracting chemists in the future.

9 References

[1] (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

[2] Leading references: (a) Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Gutsche, G. D.; Redmore, D., Academic Press, New York, 1968, Chapter IV. (b) Salaün, J.; Karkour, B.; Ollivier, J. *Tetrahedron* **1989**, *45*, 3151. (c) Salaün, J. R. Y. *Top.

Curr. Chem. **1988**, *144*, 1. (d) Krief, A. *Top. Curr. Chem.* **1987**, *135*, 1. (e) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 1. (f) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. (g) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. *Top. Curr. Chem.* **1986**, *133*, 83.

[3] Breslow, R. in *Molecular Rearrangements*; de Mayo, P., Ed.; Wiley Interscience: New York, 1963, pp 276-280.

[4] The strain energies (kcal/mol) of cyclopropane (28.13), cyclobutane (26.90), cyclopentane (7.19) and cyclohexane (1.35), estimated based on single conformation increments; Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.

[5] Saunders, M.; Chandrasekhar, J.; Schleyer, P. v. R. Rearrangements of Carbocations. In *Rearrangements in Ground and Excited States*; de Mayo, P. Ed.; Academic Press: New York 1980, pp.41-43.

[6] (a) Richey, H. G. Jr. *Carbonium Ions* **1972**, *3*, 1201. (b) Gassman, P. G.; Armour, E. A. *J. Am. Chem. Soc.* **1973**, *95*, 6129. (c) Schindler, M. *J. Am. Chem. Soc.* **1987**, *109*, 1020. (d) Schleyer, P. V. R.; Carneiro, J. W. D. M.; Koch, W.; Raghavachari, K. *J. Am. Chem. Soc.* **1989**, *111*, 5475. (e) Prakash, G. K. S.; Reddy, V. P.; Rasul, G.; Casanova, J.; Olah, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 13362. (f) Reddy, V. P.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **2007**, *72*, 3076.

[7] Smith, P. A.; Baer, D. R. *Org. React.*, vol.11, Wiley, New York, N.Y., 1960, p157.

[8] For an overview of Wagner-Meerwein rearrangements and related reactions, see: Hanson, J. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Pattenden, G.; Eds.; ‘Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.1, pp 705-720; Rickborn, B., idem; Chapter 3.2, pp 721-732, and Chapter 3.3, pp 733-776; Coveney, D. J.; Chapter 3.4, pp 777-802.

[9] Pocker, Y. Molecular Rearrangements, Part 1, P. de Mayo, Ed., Wiley, New York, N.Y., 1964, p1.

[10] (a) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737. (b) Mihovilovic, M. D.; Rudroff, F.; Grotzl, B. *Curr. Org. Chem.* **2004**, *8*, 1057. (c) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.

[11] (a) Donaruma, L. G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 14.

[12] Lee-Ruff, E. New Synthetic Pathways from Cyclobutanones. In *Advanced Strain in Organic Chemistry*, Vol.1; Halton, B. Ed., JAI Press: Greenwich, CN., 1991.

[13] Bellus, D.; Ernst, B. *Angew. Chem. Int. Ed.* **1988**, *27*, 797.

[14] (a) Krepsi, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879. (b) Bak. D. A. *J. Org. Chem.* **1979**, *44*, 107. (c) Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003. (d) Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615. (e) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949.

[15] Clark, G. R.; Lin, J.; Nikaido, M. *Tetrahedron Lett.* **1984**, *25*, 2645.

[16] Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.

[17] For a review on jasmonoid synthesis, see: Ho, T.-L. *Synth. Commun.* **1974**, *4*, 265.

[18] Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286.

[19] (a) Umino, K.; Takeda, N.; Ito, Y.; Okuda, R. *Chem. Pharm. Bull.* **1974**, *22*, 1233. (b) Jernow, J.; Tautz, W.; Rosen, P.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 4210. (c) Nakayama, M.; Fukuoka, Y.; Nozaki, H.; Matsuo, A.; Hayashi, S. *Chem. Lett.* **1980**, 1243. (d) Marx, J. N.; Minaskanian, G. *J. Org. Chem.* **1982**, *47*, 3306. (e) Smith III, A. B.; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217; and references therein.

[20] Wong, H. C. N. *Houben-Weyl Methods of Organic Chemistry*; de Meijere, A., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1997; Vol. E17e, pp 495-515.

[21] Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

[22] (a) Couty, F.; Evano, G. *Synlett* **2009**, 3053. (b) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209.

[23] (a) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Salgado, N. R. *J. Org. Chem.* **1999**, *64*, 9596.

[24] Tran, J. A.; Chen, C. W.; Tucci, F. C.; Jiang, W.; Fleck, B. A.; Chen, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1124.

[25] Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

[26] Kočovský, P.; Tureček, F. *Tetrahedron Lett.* **1981**, *22*, 2699.

[27] (a) Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 5699. (b) Gleiter, R.; Kobayashi, R. *Helv. Chim. Acta* **1971**, *54*, 1081. (c) Jorgensen, W. L. *J. Am. Chem. Soc.* **1975**, *97*, 6649. (d) Gleiter, R.; Bischof, P.; Volz, W. E.; Paquette, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 8. (e) Bischof, P.; Gleiter, R.; Haider, R. *J. Am. Chem. Soc.* **1978**, *100*, 1036. (f) Borden, W. T.; Gold, A.; Jorgensen, W. L. *J. Org. Chem.* **1978**, *43*, 491.

[28] Hehre, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 6592.

[29] Simonsen, J. L. *The Terpenes*, 2nd ed.; Cambridge University Press: London, 1949; **II**, pp 156, 171.

[30] Ritter, J. J.; Ginsburg, D. *J. Am. Chem. Soc.* **1950**, *72*, 2381.

[31] Aschan, O. *Ber. Dtsch. Chem. Ges.* [Abteilung] B: Abhandlungen **1928**, *61B*, 38.

[32] (a) Erickson, G. W.; Fry, J L. *J. Org. Chem.* **1987**, *52*, 462. (b) Williams, C. M.; Whittaker, D. *J. Chem. Soc. [Section] D: Chem. Commun.* **1970**, *15*, 960. (c) Berthelot, M. *Annales de Chimie et de Physique* **1854**, *40*, 5. (d) Wagner, G.; Slawinski, K. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2064.

[33] Krishnamurti, R.; Kuivila, H. G. *J. Org. Chem.* **1986**, *51*, 4947.

[34] Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, 452.

[35] Wallace, R. H.; Lu, Y.; Liu, J.; Atwood, J. L. *Synlett* **1992**, 992.

[36] Kropp, P. J.; Daus, K. A.; Tubergen, M. W.; Kepler, K. D.; Wilson, V. P.; Craig, S. L.; Baillargeon, M. M.; Breton, G. W. *J. Am. Chem. Soc.* **1993**, *115*, 3071.

[37] (a) Yu, S.; Xiao, J.; Ping, Z. Faming Zhuanli Shenqing Gongkai Shuomingshu 1993, 5 pp. Patent written in Chinese. (b) Li, N.; Wang, Y. *Guilin Gongxueyuan Xuebao* **2001**, *21*, 280; *Chem. Abstr.* **2001**, *136*, 386264.

[38] Rodriguez, J. B.; Gros, E. G.; Caram, J. A.; Marschoff, C. M. *Tetrahedron Lett.* **1995**, *36*, 7825.

[39] Beereboom, J. J. *J. Org. Chem.* **1965**, *30*, 4230.

[40] Do Khac Manh, D.; Fetizon, M.; Flament, J. P. *Tetrahedron* **1975**, *31*, 1897.

[41] (a) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2869. (b) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1978**, 1301.

[42] (a) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82.

[43] (a) Matz, J. R.; Cohen, T. *Tetrahedron Lett.* **1981**, *22*, 2459. (b) Cohen, T.; Brockunier, L. *Tetrahedron* **1989**, *45*, 2917.

[44] Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 1563.

[45] Jackson, D. A.; Rey, M., Dreiding, A. S. *Tetrahedron Lett.* **1983**, *24*, 4817.

[46] Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 439.

[47] Kirmse, W.; Streu, J. *Synthesis* **1983**, 994.

[48] Barnier, J. P.; Karkour, B.; Salaün, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1270.

[49] Jernow, J.; Tantz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4212. Mikolajczyk, M. *Current Trends in Organic Synthesis*, ed. Nozaki, N., Pergamon Press, Oxford and New York, 1983, p347.

[50] Johnson, C. R.; Herr, W. *J. Org. Chem.* **1973**, *38*, 3153.

[51] Cohen, T.; Yu, L. C.; Daniewski, W. M. *J. Org. Chem.* **1985**, *50*, 4596.

[52] Kim, S.; Park, J. H. *Tetrahedron Lett.* **1989**, *30*, 6181.

[53] Wenkert, E.; Bookser, B. C.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1992**, *114*, 644.

[54] (a) Paquette, L. A.; Dullweber, U.; Branan, B. M. *Heterocycles* **1994**, *37*, 187. (b) Paquette, L. A.; Fabris, F.; Gallou, F.; Dong, S. *J. Org. Chem.* **2003**, *68*, 8625.

[55] Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541.

[56] Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281.

[57] Leriverend, M.-L.; Vazeux, M. *J. Chem. Soc. Chem. Commun.* **1982**, 866.

[58] Srikrishna, A.; Rao, M. S. *Tetrahedron Lett*. **2001**, *42*, 5781 and references cited therein.

[59] (a) Bernard, A. M.; Cadoni, E.; Frongia, A.; Piras, P. P.; Secci, F. *Tetrahedron* **2004**, *60*, 449. (b) Bernard, A. M.; Frongia, A.; Secci, F.; Piras, P. P. *Chem. Commun.* **2005**, 3853.

[60] Bowden, R. D.; Cooper, R. D. G.; Harris, C. J.; Moss, G. P.; Weedon, B. C. L.; Jackman, L. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1465.

[61] (a) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109. (b) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5668.

[62] Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626.

[63] Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8572.

[64] Ruggles, E. L.; Maleczka, R. E. Jr. *Org. Lett.* **2002**, *4*, 3899.

[65] (a) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 8799. (b) Nemoto, H.; Shiraki, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 1347.

[66] Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2828.

[67] (a) Hurley, P. B.; Dake, G. R. *Synlett* **2003**, 2131. (b) Hurley, P. B.; Dake, G. R. *J. Org. Chem.* **2008**, *73*, 4131.

[68] Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Chen, W. M. *Synlett* **2003**, 1497.

[69] (a) Widjaja, T.; Fitjer, L.; Pal, A.; Schmidt, H.-G.; Noltemeyer, M.; Diedrich, C.; Grimme, S. *J. Org. Chem.* **2007**, *72*, 9264. (b) Widjaja, T.; Fitjer, L.; Meindl, K.; Herbst-Irmer, R. *Tetrahedron* **2008**, *64*, 4304.

[70] Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042.

[71] (a) Boontanonda, P.; Grigg, R. *J. Chem. Soc. Chem. Commun.* **1977**, 583. (b) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503. (c) de Almeida Barbosa, L.-C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 177. (d) Kim, S.; Uh, K. H.; Lee, S.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 3395. (e) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Synlett* **1994**, 599. (f) Nemoto, H.; Miyata, J.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363. (g) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 7850.

[72] (a) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74. (b) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511. (c) Nemoto, H.; Yoshida, M.; Fukumoto, K.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 907. (d) Nemoto, H.; Miyata, J.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1933.

[73] Kim, S.; Uh, K. H. *Tetrahedron Lett.* **1992**, *33*, 4325.

[74] (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, New York, 1986 and references cited herein. (b) Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* **1982**, *23*, 931.

[75] Ryu, I.; Matsumoto, K.; Ando, M.; Murai, S.; Sononda, N. *Tetrahedron Lett.* **1980**, *21*, 4283.

[76] Smidt, J.; Hafner, W. R.; Jira, R.; Sieber, J.; Sedlemeier, J.; Sabel, A. *Angew. Chem. Int. Ed.* **1962**, 1, 80.

[77] Boontanonda, P.; Grigg, R. *J. Chem. Soc. Chem. Commun.* **1977**, 583.

[78] Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, *26*, 2503.

[79] Demuth, M.; Pandey, B.; Wietfeld, B.; Said, H.; Viader, J. *Helv. Chim. Acta* **1988**, *71*, 1392.

[80] de Almeida Barbosa, L.-C.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 177.

[81] Kim, S.; Uh, K. H.; Lee, S.; Park, J. H. *Tetrahedron Lett.* **1991**, *32*, 3395.

[82] Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2329.

[83] (a) Devon, T. K.; Scott, A. I. Handbook of Naturally Occurring Compounds, vol. II, Terpenes, Academic Press, New York, 1972. (b) Heathcock, C. H. Total Synthesis of Natural Products, ed. ApSimon, J. Wiley, New York, 1973, vol. 2, p.197.

[84] Hall, S. S.; Faulkner, D. J.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 7187.

[85] Fenical, W.; Howard, B.; Gifkins, K. B.; Clardy, J. *Tetrahedron Lett.* **1975**, 3983.

[86] Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 10391.

[87] (a) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511. (b) Nemoto, H.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Heterocycles* **1994**, *39*, 467.

[88] (a) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Aust. J. Chem.* **1976**, *29*, 2533. (b) Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1977**, *42*, 3343.

[89] Nemoto, H.; Miyata, J.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363.

[90] Anderson, W. K.; Lee, G. E. *J. Med. Chem.* **1980**, *23*, 96.

[91] Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 504.

[92] Nemoto, H.; Takahashi, E.; Ihara, M. *Org. Lett.* **1999**, *1*, 517.

[93] Yoshida, M.; Ismail, A.-H.; Nemoto, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2629.

[94] Kočovský, P.; Dunn, V.; Gogoll, A.; Langer, V. *J. Org. Chem.* **1999**, *64*, 101.

[95] Hegedus, L. S.; Ranslow, P. B. *Synthesis* **2000**, 953.

[96] (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455.

[97] Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162.

[98] McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W.; Eds.; Pergamon Press: New York, 1982, Vol. 7, p465-513.

[99] Fărcaşiu, D.; Schleyer, P. v. R.; Ledlie, D. B. *J. Org. Chem.* **1973**, *38*, 3455.

[100] (a) Byrd, J. E.; Halpern, J. *J. Am. Chem. Soc.* **1973**, *95*, 2586. (b) Abley, P.; Byrd, J. E.; Halpern, J. *J. Am. Chem. Soc.* **1973**, *95*, 2591.

[101] Kim, S.; Uh, K. H. *Tetrahedron Lett.* **1996**, *37*, 3865.

[102] Feiner, N. F.; Abrams, G. D.; Yates, P. *Can. J. Chem.* **1976**, *54*, 3955.

[103] Yoshida, M.; Sugimoto, K.; Ihara, M. *Org. Lett.* **2004**, *6*, 1979.

[104] (a) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem.* **1990**, *55*, 4614. (b) Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477.

[105] For studies on the intermolecular carbopalladation of allenes, see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482. (c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (d) Desarbre, E.; Mérour, J.-Y. *Tetrahedron Lett.* **1996**, *37*, 43. (e) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *J. Chem. Soc., Chem. Commun.* **1996**, 381.

[106] For studies on the intramolecular carbopalladation of allenes, see: (a) Ma, S.; Negishi, E. *J. Org. Chem.* **1994**, *59*, 4730. (b) Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345. (c) Doi, T.; Yanagisawa, A.; Nakanishi, S.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 2602.

[107] (a) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450. (b) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 5089. (c) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron* **2002**, *58*, 7839.

[108] Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

[109] (a) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Overman, L. E., Mishra, P. *J. Am. Chem. Soc.* **1991**, *113*, 5365. (b) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *113*, 5378.

[110] Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

[111] (a) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 3877. (b) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842.

[112] Gill, T. B.; Mann, K. R. *Organometallics* **1982**, *1*, 485.

[113] Seiser, T.; Cramer, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 9294.

[114] Yao, L.-F.; Wei, Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 9466.

[115] (a) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908. (b) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291.

[116] Tsuji, J. *Palladium Reagents and Catalysts*, John Wiley & Sons Ltd., England, 2004, p.543.

[117] For reviews on palladium-catalysed reactions of propargylic compounds, see: (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225. (c) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2589.

[118] (a) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583. (b) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874. (c) Yoshida, M.; Komatsuzaki, Y.; Nemoto, H.; Ihara, M. *Org. Biomol. Chem.* **2004**, *2*, 3099.

[119] (a) Larock, R. C.; Reddy, C. K. *Org. Lett.* **2000**, *2*, 3325. (b) Larock, R. C.; Reddy, C. K. *J. Org. Chem.* **2002**, *67*, 2027.

[120] (a) Wu, M.-J.; Wei, L.-M.; Lin, C.-F.; Leou, S.-P.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7839. (b) Wei, L.-M.; Wei, L.-L.; Pan, W.-B.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 595.

[121] Yoshida, M.; Sugimoto, K.; Ihara, M. *ARKIVOC* **2003**, *VIII*, 35.

[122] Sugimoto, K.; Yoshida, M.; Ihara, M. *Synlett* **2006**, 1923.

[123] Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708.

[124] Yeom, H.-S.; Yoon, S.-J.; Shin, S. *Tetrahedron Lett.* **2007**, *48*, 4817.

[125] (a) Cargill, R. L.; Beckham, M. E.; Siebert, A. E.; Dorn, J. *J. Org. Chem.* **1965**, *30*, 3647. (b) Cargill, R. L.; Damewood, J. R.; Cooper, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 1330. (c) Cargill, R. L.; Crawford, J. W. *Tetrahedron Lett.* **1967**, 169. (d) Peet, N. P.; Cargill, R. L.; Bushey, D. F. *J. Org. Chem.* **1973**, *38*, 1218. (e) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond. D. M. *Acc. Chem. Res.* **1974**, *7*, 106.

[126] (a) Tobe, Y.; Kimura, K.; Odaira, Y. *J. Org. Chem.* **1979**, *44*, 639. (b) Tobe, Y.; Hayauchi, Y. Sakai, Y.; Odaira, Y. *J. Org. Chem.* **1980**, *45*, 637. (c) Eaton, P. E.; Jobe, P. G.; Nyi, K. *J. Am. Chem. Soc.* **1980**, *102*, 6636.

[127] (a) Do Khac Manh, D.; Fetizon, M.; Lazare, S. *J. Chem. Soc. Chem. Commun.* **1975**, 282. (b) Do Khac Manh, D.; Fetizon, M.; Lazare, S. *J. Chem. Soc. Chem. Commun.* **1980**, 1209.

[128] Do Khac Manh, D.; Fetizon, M.; Flament, J. P. *Tetrahedron* **1978**, *34*, 3513.

[129] Yamashita, M.; Onozuka, J.; Tushihashi, G.-I.; Ogura, K. *Tetrahedron Lett.* **1983**, *24*, 79.

[130] Birch, A. J.; Dahler, P.; Narula, A. S.; Stephenson, C. R. *Tetrahedron Lett.* **1980**, *21*, 3817.

[131] Erden, I. *Tetrahedron Lett.* **1985**, *26*, 5635.

[132] (a) Kakiuchi, K.; Nakao, T.; Takeda, M.; Tobe, Y.; Odaira, Y. *Tetrahedron Lett.* **1984**, *25*, 557. (b) Kakiuchi, K.; Itoga, K.; Tsugaru, T.; Hato, Y.; Tobe, Y.; Odaira, Y. *J. Org. Chem.* **1984**, *49*, 659. (c) Kakiuchi, K.; Tsugaru, T.; Takeda, M.; Wakaki, I.; Tobe, Y.; Odaira, Y. *J. Org. Chem.* **1985**, *50*, 488. (d) Kakiuchi, K.; Ue, M.; Takaki, T.; Tobe, Y.; Odaira, Y. *Chem. Lett.* **1986**, 507.

[133] (a) Sasaki, K.; Kushida, T.; Iyoda, M.; Oda, M. *Tetrahedron Lett.* **1982**, *23*, 2117. (b) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc. Chem. Commun.* **1986**, 1049.

[134] (a) Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron Lett.* **1985**, *26*, 5277. (b) Fitjer, L.; Quabeck, U. *Angew. Chem. Int. Ed.* **1987**, *26*, 1023. (c) Fitjer, L.; Quabeck, U. *Angew. Chem.* **1987**, *26*, 1054. (d) Fitjer, L.; Majewski, M.; Kanschik, A. *Tetrahedron Lett.* **1988**, *29*, 1263. (e) Fitjer, L.; Quabeck, U. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 94. (f) Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron* **1994**, *50*, 10867.

[135] Compare the heats of formation (kcal/mol) of the primary (201), secondary (183) and tertiary butylcarbenium ion (166): Lossing, F. P.; Holmes, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 6917, and references therein.

[136] Olah, G. A.; Wu, A. H.; Farooq, O. *J. Org. Chem.* **1989**, *54*, 1452.

[137] (a) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Shimizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707. (b) Kakiuchi, K.; Ohnishi, Y.; Kobiro, K.; Tobe, Y.; Odaira, Y. *J. Org. Chem.* **1991**, *56*, 463. (c) Ue, M.; Ohnishi, Y.; Kobiro, K.; Kakiuchi, K.; Tobe, Y.; Odaira, Y. *Chem. Lett.* **1990**, 149.

[138] (a) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932. (b) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2001**, *12*, 497.

[139] (a) Fujiwara, T.; Tomaru, J.; Suda, A.; Takeda, T. *Tetrahedron Lett.* **1992**, *33*, 2583. (b) Takeda, T.; Fujiwara, T. *Synlett* **1996**, 481.

[140] (a) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765. (b) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (c) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

[141] Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702.

[142] (a) Paquette, L. A.; Dullweber, U.; Cowgill, L. D. *Tetrahedron Lett.* **1993**, *34*, 8019. (b) Paquette, L. A.; Kinney, M. J.; Dullweber, U. J. *J. Org. Chem.* **1997**, *62*, 1713.

[143] Shinohara, I.; Nagaoka, H. *Tetrahedron Lett.* **2004**, *45*, 1495.

[144] (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930. (b) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692. (c) Dai, X.; Davies, H. M. L. *Adv. Synth. Catal.* **2006**, *348*, 2449.

[145] Chatani, N.; Furukawa, H.; Kato, T.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1984**, *106*, 430.

[146] Kashima, H.; Kawashima, T.; Wakasugi, D.; Satoh, T. *Tetrahedron* **2007**, *63*, 3953.

[147] Karrenbrock, F.; Schäfer, H. J. *Tetrahedron Lett.* **1978**, 1521.

[148] Halazy, S.; Zutterman, F.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 4385.

[149] (a) Satoh, T.; Hayashi, Y.; Mizu, Y.; Yamakawa, K. *Tetrahedron Lett.* **1992**, *33*, 7181. (b) Satoh, T.; Hayashi, Y.; Mizu, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1412.

[150] (a) Satoh, T.; Itoh, N.; Gengyo, K.; Yamakawa, K. *Tetrahedron Lett.* **1992**, *33*, 7543. (b) Satoh, T.; Itoh, N.; Gengyo, K.; Takada, S.; Asakawa, N.; Yamani, Y.; Yamakawa, K. *Tetrahedron* **1994**, *50*, 11839.

[151] (a) Satoh, T.; Mizu, Y.; Kawashima, T.; Yamakawa, K. *Tetrahedron* **1995**, *51*, 703. (b) Satoh, T.; Awata, Y.; Ogata, S.; Sugiyama, S.; Tanaka, M.; Tori, M. *Tetrahedron Lett.* **2009**, *50*, 1961.

[152] Falck, J. R.; He, A.; Reddy, L. M.; Kundu, A.; Barma, D. K.; Bandyopadhyay, A.; Kamila, S.; Akella, R.; Bejot, R.; Mioskowski, C. *Org. Lett.* **2006**, *8*, 4645.

[153] Ochiai, M.; Hirobe, M.; Yoshimura, A.; Nishi, Y.; Miyamoto, K.; Shiro, M. *Org. Lett.* **2007**, *9*, 3335.

[154] Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1978**, *43*, 1031.

[155] Tobe, Y.; Yamashita, S.; Yamashita, T.; Kakiuchi, K.; Odaira. Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1259.

[156] Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 898.

[157] Wenkert, E.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 2030.

[158] Pirrung, M. C.; Thomson, S. A. *J. Org. Chem.* **1988**, *53*, 227.

[159] (a) Tobe, Y.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1985**, 898. (b) Tobe, Y.; Kishida, T.; Yamashita, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1985**, 1437.

[160] (a) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1592. (b) Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030.

[161] Hamer, N. K. *Tetrahedron Lett.* **1986**, *27*, 2167.

[162] Jahangir; Fisher, L. E.; Clark, R. D.; Muchowski, J. M. *J. Org. Chem.* **1989**, *54*, 2992.

[163] (a) Leriverend, M. L.; Leriverend, P. *C. R. Acad. Sci. Ser. C.* **1975**, *280*, 791. (b) Leriverend, M.-L.; Leriverend, P. *Chem. Ber.* **1976**, *109*, 3492.

[164] Morton, D. R., Jr.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880.

[165] Halazy, S.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1200.

[166] Hart, T. W.; Comte, M.-T. *Tetrahedron Lett.* **1985**, *26*, 2713.

[167] Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.

[168] Riefling, B. F. *Tetrahedron Lett.* **1985**, *26*, 2063.

[169] (a) Mahuteau-Betzer, F.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 5183. (b) Mahuteau-Betzer, F.; Ghosez, L. *Tetrahedron* **2002**, *58*, 6991.

[170] Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865.

[171] Bernard, A. M.; Frongia, A.; Guillot, R.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2007**, *9*, 541.

[172] (a) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 1429. (b) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455.

[173] Reutrakul, V.; Panyachotipun, C.; Hahnvajanawong, V.; Sotheeswaran, S. *Tetrahedron Lett.* **1984**, *25*, 1825.

[174] Fukuzawa, S.; Tsuchimoto, T. *Tetrahedron Lett.* **1995**, *36*, 5937.

[175] (a) Wohl, R. A. *J. Org. Chem.* **1973**, *38*, 3862. (b) McManus, S. P.; Ortiz, M.; Abramovitch, R. A. *J. Org. Chem.* **1981**, *46*, 336.

[176] Fitjer, L. *Chem. Ber.* **1982**, *115*, 1047.

[177] (a) Demjanov, N. J.; Lushnikov, M. *Russ. Phys. Chem. Soc.* **1903**, *35*, 26. (b) Demjanov, N. J.; Lushnikov, M. *Chem. Zentralbl.* **1903**, *1*, 828. (c) Smith, P. A. S.; Baer, D. R. *Org. React.* **1960**, *11*, 157. (d) Sietter, H.; Goebel, P. *Chem. Ber. Recl.* **1963**, *96*, 550. (d) Kotani, R. *J. Org. Chem.* **1965**, *30*, 350. (e) Dave, V.; Stothers, J. B.; Warnhoff, E. W. *Can. J. Chem.* **1979**, *52*, 1557. (f) Murray, R. K.; Ford, T. M. *J. Org. Chem.* **1979**, *44*, 3504. (g) Fattori, D.; Henry, S.; Vogel, P. *Tetrahedron* **1993**, *49*, 1649.

[178] (a) Smith, P. A. S.; Baer, D. R. *Org. React.* **1960**, *11*, 157. (b) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991; pp9-16.

[179] (a) Roberts, J. D.; Gorham, W. F. *J. Am. Chem. Soc.* **1952**, *74*, 2278. (b) Nee, M.; Roberts, J. D. *J. Org. Chem.* **1981**, *46*, 67.

[180] For reviews on the diazomethane ring expansion reaction, see: (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364. (b) *Carbocyclic Ring Expansion Reactions*; Gutsche, G. D.; Redmore, D., Academic Press, New York, 1968, Chapter IV. (c) Cowell, G. W.; Ledwith, A. *Q. Rev. Chem. Soc.* **1970**, *24*, 119. (d) *Synthetic Reagents 2*; Pizey, J. S.; Wiley: New York 1974.

[181] (a) Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, 4937. (b) Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5*, 125.

[182] Whitesell, J. K.; Minton, M. A.; Flanagan, W. G. *Tetrahedron* **1981**, *37*, 4451.

[183] (a) Greene, A. E.; Deprés, J. P.; Nagano, H.; Crabbé, P. *Tetrahedron Lett.* **1977**, 2365. (b) Deprés, J. P.; Greene, A. E.; Crabbé, P. *Tetrahedron* **1981**, *37*, 621.

[184] Greene, A. E.; Deprés, J. P.; Meana, M. C.; Crabbé, P. *Tetrahedron Lett.* **1976**, 3755.

[185] Collington, E. W.; Finch, H.; Montana, J. G.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1839.

[186] Greene, A. E.; Luche, M. J.; Serra, A. A. *J. Org. Chem.* **1985**, *50*, 3957.

[187] (a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (b) Takeuchi, T.; Takahashi, S.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1971**, *24*, 631.

[188] Liu, H. J.; Kulkarni, M. G. *Tetrahedron Lett.* **1985**, *26*, 4847.

[189] Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855.

[190] Sonawane, H. R.; Nanjundiah, B. S.; Shah, V. G.; Kulkarni, D. G.; Ahuja, J. R. *Tetrahedron Lett.* **1991**, *32*, 1107.

[191] (a) Ghosh, A.; Biswas, S.; Venkateswaran, R. V. *J. Chem. Soc, Chem. Commun.* **1988**, 1421. (b) Biswas, S.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1990**, *55*, 3498.

[192] Hébrault, D.; Uguen, D.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 6703.

[193] Reeder, L. M.; Hegedus, L. S. *J. Org. Chem.* **1999**, *64*, 3306.

[194] (a) Wen, X.; Norling, H.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 2096. (b) For a review, see: Bereubar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779. (c) Sebahar, H. L.; Yoshida, K.; Hegedus, L. S. *J. Org. Chem.* **2002**, *67*, 3788.

[195] Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003.

[196] (a) Jaz, J.; Davreux, J. P. *Bull. Soc. Chim. Belg.* **1965**, *74*, 370. (b) Fachinetti, G.; Pietra, F.; Marsili, A. *Tetrahedron Lett.* **1971**, 393.

[197] Au-Yeung, B.-W.; Fleming, I. *J. Chem. Soc. Chem. Commun.* **1977**, 81.

[198] Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036.

[199] (a) Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92. (b) Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504. (c) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358.

[200] Greene, A. E. *Tetrahedron Lett.* **1980**, *21*, 3059.

[201] Greene, A. E.; Luche, M.-J.; Deprés, J.-P. *J. Am. Chem. Soc.* **1983**, *105*, 2435.

[202] Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1983**, *48*, 4763.

[203] Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931.

[204] Paquette, L. A.; Valpey, R. S.; Annis, G. D. *J. Org. Chem.* **1984**, *49*, 1317.

[205] Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525.

[206] (a) Mehta, G.; Padma, S.; Rao, K. S. *Synth. Commun.* **1985**, *15*, 1137. (b) Mehta, G.; Rao, K. S. *Tetrahedron Lett.* **1984**, *25*, 1839. (c) Mehta, G.; Rao, K. S. *Tetrahedron Lett.* **1984**, *25*, 3481.

[207] Lee, T. V.; Toczek, J.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1985**, 371.

[208] Sugihara, Y.; Fujita, H.; Murata, I. *J. Chem. Soc., Chem. Commun.* **1986**, 1130.

[209] (a) Yokoyama, R.; Ito, S.; Watanabe, M.; Harada, N.; Kabuto, C.; Morita, N. *J. Chem. Soc., Perkin Trans.* 1 **2001**, *18*, 2257. (b) Ito, S.; Yokoyama, R.; Asao, T.; Watanabe, M.; Harada, N.; Morita, N. *J. Organomet. Chem.* **2002**, *648*, 164.

[210] MaGee, D. I.; Mallais, T.; Strunz, G. M. *Can. J. Chem.* **2004**, *82*, 1686.

[211] Cousin, D.; Mann, J. *Tetrahedron* **2008**, *64*, 3534.

[212] Mehta, G.; Rao, K. S. *J. Org. Chem.* **1985**, *50*, 5537.

[213] Mehta, G.; Nair, M. S. *J. Am. Chem. Soc.* **1985**, *107*, 7519.

[214] Craig, D. C.; Lawson, J. M.; Oliver, A. M.; Paddon-Row, M. N. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3305.

[215] (a) Farcasiu, D.; Seppo, E.; Kizirian, M.; Ledlie, D. B.; Sevin, A. *J. Am. Chem. Soc.* **1989**, *111*, 8466. (b) Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. P.; Le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.

[216] Paryzek, Z.; Blaszczyk, K. *Liebigs Ann. Chem.* **1993**, 615.

[217] Carpes, M. J. S.; Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1997**, *38*, 1869.

[218] (a) Ono, N.; Yanai, T.; Kaji, A. *J. Chem. Soc. Chem. Commun.* **1986**, 1040. (b) Ono, N.; Yanai, Y.; Kamimura, A.; Kaji, A. *J. Chem. Soc. Chem. Commun.* **1986**, 1285. (c) Miyake,

H.; Yamamura, K. *Tetrahedron Lett.* **1986**, *27*, 3025. (d) Ono, N.; Hashimoto, T.; Jun, T. X.; Kaji, A. *Tetrahedron Lett.* **1987**, *28*, 2277.

[219] Kim, S.; Park, J. H. *Chem. Lett.* **1988**, *8*, 1323.

[220] Kuivila, H. G.; Masterton, W. L. *J. Am. Chem. Soc.* **1952**, *74*, 4953.

[221] Bartleson, J. D.; Burk, R. E.; Lankelma, H. P. *J. Am. Chem. Soc.* **1946**, *68*, 2513.

[222] Noller, C. R.; Adams, R. *J. Am. Chem. Soc.* **1926**, *48*, 1080.

[223] Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1973**, *29*, 161.

[224] Takeda, K.; Shimono, Y.; Yoshii, E. *J. Am. Chem. Soc.* **1983**, *105*, 563.

[225] Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 603.

[226] Somers, J. B. M.; Couture, A.; Lablache-combier, A.; Laarhoven, W. H. *J. Am. Chem. Soc* **1985**, *107*, 1387.

[227] Rio, G.; Bricout, D. *Bull. Soc. Chim. Fr.* **1971**, 3557.

[228] Avasthi, K.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 2556.

[229] Fitjer, L.; Majewski, M.; Kanschik, A.; Egert, E.; Sheldrick, G. M. *Tetrahedron Lett.* **1986**, *27*, 3603.

[230] If alternative 1,2-shifts can occur, the bond which forms the smaller dihedral angle with the vacant p-orbital, will be broken: Saunders, M.; Chandrasekhar, J.; Schleyer P. v. R. in Rearrangements in Ground and Excited States (P. de Mayo Ed.), Vol. 1, Academic Press, New York 1980.

[231] (a) Compare the heats of formation of ethylcyclopropane[b] ($\Delta H_f°$ = 1.1 kcal/mol), methylcyclobutane[c] ($\Delta H_f°$ = -0,6 kcal/mol) and cyclopentane[c] ($\Delta H_f°$ = -18.5 kcal/mol). (b) Turner, R. B.; Goebel, P.; Mallon, B. J.; von E. Doering, W.; Coburn, J. F. Jr.; Pomerantz, M. *J. Am. Chem. Soc.* **1968**, *90*, 4315. (c) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279.

[232] (a) Fitjer, L.; Kanschik, A.; Majewski, M. *Tetrahedron Lett.* **1988**, *29*, 5525. (b) Fitjer, L.; Majewski, M.; Monzó-Oltra, H. *Tetrahedron* **1995**, *51*, 8835.

[233] (a) Mandelt, K.; Fitjer, L. *Synthesis* **1998**, 1523. (b) Mandelt, K.; Meyer-Wilmes, I.; Fitjer, L. *Tetrahedron* **2004**, *60*, 11587.

[234] (a) McMurry, J. E.; von Beroldingen, L. A. *Tetrahedron* **1974**, *30*, 2027. (b) de Mayo, P.; Suau, R. *J. Chem. Soc., Perkin Trans 1* **1974**, 2559. (c) Chandrasekaran, S.; Turner, J. V. *Tetrahedron Lett.* **1982**, *23*, 3799.

[235] Giersig, M.; Wehle, D.; Fitjer, L.; Schormann, N.; Clegg, W. *Chem. Ber.* **1988**, *121*, 525.

[236] (a) Sengupta, D.; Venkateswaran, R. V. *J. Chem. Soc, Chem. Commun.* **1986**, 1638. (b) Nath, A.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1992**, *57*, 1467. (c) Mal, J.; Nath, A.; Venkateswaran, R. V. *J. Org. Chem.* **1996**, *61*, 9164.

[237] Grota, J.; Domke, I.; Stoll, I.; Schroeder, T.; Mattay, J.; Schmidtmann, M.; Boegge, H.; Mueller, A. *Synthesis* **2005**, 2321.

[238] (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961. (b) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *J. Org. Chem.* **1977**, *42*, 4166.

[239] Eberhardt, U.; Deppisch, B.; Musso, H. *Chem. Ber.* **1983**, *116*, 119.

[240] (a) Nath, A.; Venkateswaran, R. V. *J. Chem. Soc, Chem. Commun.* **1993**, 281. (b) Nath, A.; Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1996**, *61*, 4391. (c) Mal, J.; Nath, A.; Venkateswaran, R. V. *J. Org. Chem.* **1998**, *63*, 3855.

[241] Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 983.

[242] Fitjer, L.; Schlotmann, W.; Noltemeyer, M. *Tetrahedron Lett.* **1995**, *36*, 4985.

[243] Estieu, K.; Ollivier, J.; Salaün, J. *Tetrahedron* **1998**, *54*, 8075.

[244] Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 5708.

[245] Jamart-Gregoire, B.; Brosse, N.; Ianelli, S.; Nardelli, M.; Caubere, P. *J. Org. Chem.* **1993**, *58*, 4572.

[246] Martín, T.; Rodríguez, C. M.; Martín, V. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1151.

[247] Corey, E. J.; Liu, K. *Tetrahedron Lett.* **1997**, *38*, 7491.

[248] Dauben, W. G.; Chitwood, J. L. *J. Am. Chem. Soc.* **1970**, *92*, 1624.

[249] Roberts, D. D. *J. Org. Chem.* **1976**, *41*, 486.

[250] Yano, K.; Isobe, M.; Yoshida, K. J. *J. Am. Chem. Soc.* **1978**, *100*, 6166.

[251] Tobe, Y.; Hayauchi, Y. Sakai, Y.; Odaira, Y. *J. Org. Chem.* **1980**, *45*, 637.

[252] Lange, G. L.; Decicco, C. P.; Wilson, J.; Strickland, L. A. *J. Org. Chem.* **1989**, *54*, 1805.

[253] Bentley, T. W.; Llewellyn, G.; Kottke, T.; Stalke, D.; Cohrs, C.; Herberth, E.; Kunz, U. Christl, M. *Eur. J. Org. Chem.* **2001**, *7*, 1279.

[254] Kuwajima, I.; Azegami, I. *Tetrahedron Lett.* **1979**, *25*, 2369.

[255] Oppolzer, W.; Wylie, R. D. *Helv. Chim. Acta* **1980**, *63*, 1198.

[256] Nishiguchi, I.; Hirashima, T.; Shono, T.; Sasaki, M. *Chem. Lett.* **1981**, *4*, 551.

[257] Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

[258] Martinez, R.; Rao, P.; Kim, H. *Synth. Commun.* **1989**, *19*, 373.

[259] Olah, G. A.; Meidar, D. *Synthesis* **1978**, *5*, 358.

[260] Gao, F. Y.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356.

[261] Nakamura, E.; Shimada, J.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 498.

[262] Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.

[263] Bunnelle, W. H.; Shangraw, W. R. *Tetrahedron* **1987**, *43*, 2005.

[264] (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436. (b) Fray, G. I.; Robinson, R. *J. Am. Chem. Soc.* **1961**, *83*, 249.

[265] Hyuga, S.; Hara, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2303.

[266] Lange, A.; Heydenreuter, W.; Menz, H.; Kirsch, S. F. *Synlett* **2009**, 2987.

[267] Selig, P.; Herdtweck, E.; Bach, T. *Chem. Eur. J.* **2009**, *15*, 3509.

[268] Murakami, M.; Itahashi, T.; Amii, H.; Takahashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9949.

[269] (a) Hwang, C.-S.; Reusch, W. *Heterocycles* **1987**, *25*, 589. (b) Hwang, C.-S.; Ward, D. L.; Reusch, W. *J. Org. Chem.* **1989**, *55*, 4318.

[270] Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791.

[271] (a) Eschinasi, E. *J. Org. Chem.* **1970**, *35*, 1598. (b) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629.

[272] Dake, G. R.; Fenster, M. D. B.; Fleury, M.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5676.

[273] El-Hachach, N.; Gerke, R.; Noltemeyer, M.; Fitjer, L. *Tetrahedron* **2009**, *65*, 1040.

[274] Ghosh, S.; Patra, D. *Pure Appl. Chem.* **1996**, *68*, 597.

[275] Samajdar, S.; Patra, D.; Ghosh, S. *Tetrahedron* **1998**, *43*, 1789.

[276] Patra, D.; Ghosh, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2635.

[277] (a) Patra, D.; Ghosh, S. *J. Org. Chem.* **1995**, *60*, 2526. (b) Nayek, A.; Ghosh, S. *Tetrahedron Lett.* **2002**, *43*, 1313.

[278] Ghosh, A.; Banerjee, U. K.; Venkateswaran, R. V. *Tetrahedron* **1990**, *46*, 3077.

[279] Haque, A.; Ghatak, A.; Ghosh, S.; Ghoshal, N. *J. Org. Chem.* **1997**, *62*, 5211.

[280] Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 1465.

[281] Schaumann, E. *Top. Curr. Chem.* **2007**, *274*, 1.

[282] Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 4749.

[283] Abraham, W. D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1987**, *28*, 2203.

[284] Knapp, S.; Trope, A. F.; Ornaf, R. M. *Tetrahedron Lett.* **1980**, *21*, 4301.

[285] Ho, T.-L.; Chang, M.-H. *Can. J. Chem.* **1997**, *75*, 621.

[286] Ferrier, R. J.; Tyler, P. C.; Gainsford, G. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, *2*, 295.

[287] (a) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1986**, *51*, 749. (b) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1986**, *27*, 1983. (c) Evans, J. C.; Klix, R. C.; Bach, R.D. *J. Org. Chem.* **1988**, *53*, 5519.

[288] Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921.

[289] Funk, R. L.; Novak, P. M.; Abelman, M. M. *Tetrahedron Lett.* **1988**, *29*, 1493.

[290] Kimura, M.; Kobayashi, K.; Yamamoto, Y.; Sawaki, Y. *Tetrahedron* **1996**, *52*, 4303.

[291] (a) Laboureur, J. L.; Krief, A. *Tetrahedron Lett.* **1984**, *25*, 2713. (b) Krief, A.; Laboureur, J. L. *Tetrahedron Lett.* **1987**, *28*, 1545. (c) Krief, A.; Laboureur, J. L. *J. Chem. Soc. Chem. Commun.* **1986**, 702. (d) Krief, A.; Laboureur, J. L.; Dumont, W. *Tetrahedron Lett.* **1987**, *28*, 1549.

[292] (a) Labar, D.; Krief, A. *J. Chem. Soc. Chem. Commun.* **1982**, 564. (b) Labar, D.; Laboureur, J. L.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 983. (c) Fitjer, L.; Scheuermann, H.-J.; Wehle, D. *Tetrahedron Lett.* **1984**, *25*, 2329.

[293] Fitjer, L.; Wehle, D.; Scheuermann, H.-J. *Chem. Ber.* **1986**, *119*, 1162.

[294] Fitjer, L.; Steeneck, C.; Gaini-Rahimi, S.; Schroeder, U.; Justus, K.; Puder, P.; Dittmer, M.; Hassler, C.; Weiser, J.; Noltemeyer, M.; Teichert, M. *J. Am. Chem. Soc.* **1998**, *120*, 317.

[295] Trost, B. M.; Mikhail, G. K. *J. Am. Chem. Soc.* **1987**, *109*, 4124.

[296] Finch, H.; Mjalli, A. M. M.; Montana, J. G.; Roberts, S. M.; Taylor, R. J. K. *Tetrahedron* **1990**, *46*, 4925.

[297] Ogura, K.; Yamashita, M.; Suzuki, M.; Tsuchihashi, G.-I. *Chem. Lett.* **1982**, 93.

[298] Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 774.

[299] Gadwood, R. C. *J. Org. Chem.* **1983**, *48*, 2098.

[300] Graham, S. H.; Williams, A. J. S. *J. Chem. Soc. C* **1969**, 390.

[301] Fadel, A.; Salaün, J. *Tetrahedron* **1985**, *41*, 413.

[302] Ue, M.; Tsukahara, H.; Kobiro, K.; Kakiuchi, K.; Tobe, Y.; Odaira, Y. *Tetrahedron Lett.* **1987**, *28*, 3979.

[303] Banik, B. K.; Ghatak, U. R. *Tetrahedron* **1989**, *45*, 3547.

[304] Connolly, P. J.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 4135.

[305] Overman, L. E.; Okazaki, M. E.; Jon Jacobsen, E. *J. Org. Chem.* **1985**, *50*, 2403.

[306] Zhang, E.; Tu, Y.-Q.; Fan, C.-A.; Zhao, X.; Jiang, Y.-J.; Zhang, Z.-Y. *Org. Lett.* **2008**, *10*, 4943.

[307] Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Shi, Y. *Org. Lett.* **2002**, *4*, 363.

[308] Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 5342.

[309] (a) Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 3369. (b) Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 8717.

[310] (a) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Synthesis* **2008**, 2835. (b) Alcaide, B.; Almendros, P.; Cabrero, G.; Callejo, R.; Pilar Ruiz, M.; Arnó, M.; Domingo, L. R. *Adv. Synth. Catal.* **2010**, *352*, 1688.