Synthesis of β-, γ-, δ-, ..., ω-Halogenated Ketones and Aldehydes

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1. Introduction

Successful organic synthesis most often departs from a good and high yielding preparation of multifunctionalized starting materials. Although many of these compounds look structurally straightforward, the synthesis of reagents with a high density of functional groups remains a challenge in many ways. Especially industrial applications are rather based on sound straightforward procedures than on trendy, sophisticated, and expensive reagents.

Bart Roman was born in Kortrijk, Belgium, in 1984. He obtained his chemical engineering degree from the University College of West-Flanders, Department PIH, Kortrijk, in 2006. For his master thesis, he worked on the synthesis of tricyclic phosphonopyrrolidines via IMDAF under the guidance of Prof. Stevens at Ghent University. Currently, he is working as a Fellow Researcher of the Fund for Scientific Research (FWO Flanders) in the Ph.D. program at Ghent University, in the research group SynBioC of Prof. Stevens. His research interests are focused on the synthesis of anti-invasive flavonoids and related heterocyclic compounds, QSAR-methodology, and microreactor technology.

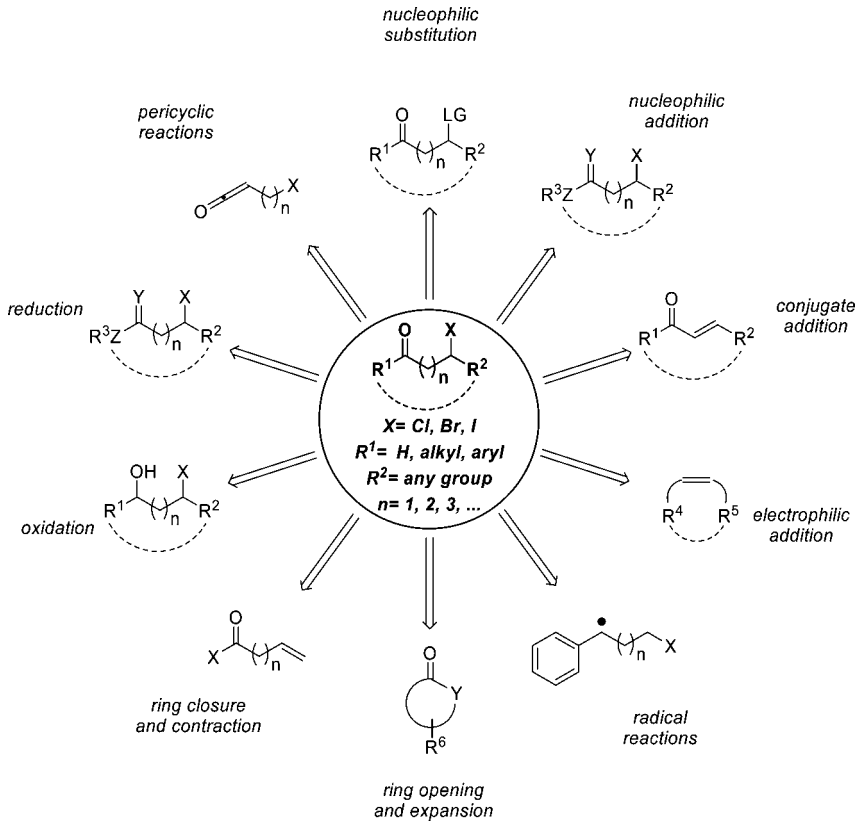
Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, a Ph.D. degree in 1975, and a habilitation degree in 1985, all from Ghent University, Ghent (Belgium). He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He continued his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at Ghent University, where he took up teaching positions since 1987. He is now full professor in organic chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda, Central Africa) and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina), and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998 and from the University of Szeged (Szeged, Hungary) in 2007. He obtained the Medal of Honour of Sofia University (Bulgaria) in 2006. He is a Member of the Royal Flemish Academy of Belgium, Section Natural Sciences and the Academia Scientiarum et Artium Europea (European Academy of Sciences and Arts), Salzburg (Austria). He is a Fellow of the Royal Society of Chemistry (U.K.). He is the author of 504 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with a focus on agrochemicals, pharmaceuticals, and natural products, (2) flavor chemistry, and (3) the bioassay-guided isolation of bioactive natural products from medicinal plants.

Christian V. Stevens (born 1965) is currently full professor at the Department of Organic Chemistry at the Faculty of Bioscience Engineering (Ghent University). He graduated at the same department as a chemical agricultural engineer in 1988 and obtained his Ph.D. in 1992, working with Prof. Norbert De Kimpe. After his Ph.D., he did postdoctoral work at the University of Florida, U.S.A., under the direction of Prof. Alan Katritzky as a NATO Research Fellow. In 1994, he performed a short postdoctoral stay at the University of Alicante (Spain) under the direction of Prof. Miguel Yus and became research leader of the FWO−Flanders in 1995. In 2000, he became associate professor at the Faculty of Bioscience Engineering, and he became full professor in 2008. Stevens published over 130 international peer reviewed scientific papers and reviews and presented his scientific work at more than 50 international conferences. He holds several patents on the synthesis and applications of renewable resources. He is scientific editor of the European Journal of Organic Chemistry, Arkivoc, Biofpr, and is a member of the editorial board of *Advances in Heterocyclic Chemistry*. His research interest is focused on synthetic heterocyclic chemistry related to agrochemical and medicinal applications, the chemical modification of renewable resources, and microreactor technology. He is an active member of the Flemish Royal Society of Chemistry, a member of the Royal Society of Chemistry Britain, and a member of the American Chemical Society.

A class of compounds that is very often used as versatile starting materials to produce more complicated organic architectures is that of the halogenated ketones and aldehydes. In this context, the chemistry of α-halogenated ketones has been described in detail numerous times before.[1] Strikingly, up to now, no overview has been prepared of the immense data set published over the years on the synthesis of their *β*-, *γ*-, *δ*-, ..., *ω*-halogenated counterparts, although the synthetic methodology as well as the reactivity of these aldehydes and ketones is quite different from that of the α-halogenated analogues. Hence, this literature review concentrates on the synthesis of *β*-, *γ*-, *δ*-, ..., *ω*-halogenated ketones and aldehydes (Scheme 1). Because of their distinctive features and differing synthesis, fluoro-substituted compounds have been omitted from this overview.

The present overview has been organized into four sections, discussing the synthesis of *β*-, *γ*-, *δ*-, or *ω*-halogenated ketones and aldehydes, respectively. Each of these parts was subsequently arranged according to the mechanism of the reaction that ultimately furnishes the halo ketone or aldehyde, or its protected form, if the latter was then easily converted to the title compounds using standard procedures. For each strategy, a number of representative examples and a set of references is offered. The experimental procedures depicted in the schemes are as detailed as possible, while the yields of the purified compounds are indicated whenever reported. Although the time frame of the covered literature encompasses a larger period, this overview mainly focuses on work from the last five decades.

Scheme 1. Overview of Synthetic Methods To Produce *β*-, *γ*-, *δ*-, ..., *ω*-Halogenated Ketones and Aldehydes, with Examples of Possible Precursors



2. Synthesis of β-Halo Ketones and Aldehydes

β-Halo ketones are useful substrates in organic synthesis, for example in annelation reactions as well as for the generation of a multitude of heterocyclic compounds.

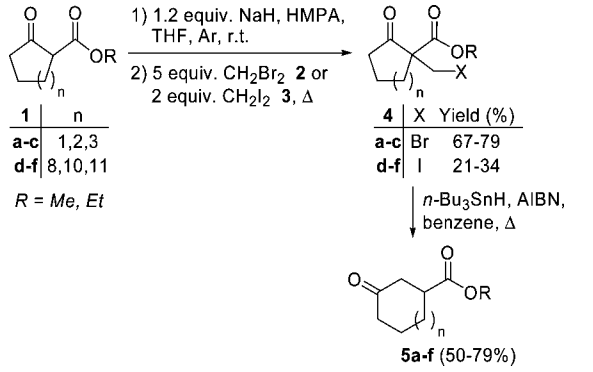
2.1. Nucleophilic Substitution

2.1.1. Enolate Alkylation

A straightforward and commonly applied strategy for the preparation of β-halogenated aldehydes and ketones is the alkylation of the enolate of the parent carbonyl compound with a dihalomethane as the electrophile.

The "Dowd−Beckwith" radical ring expansion/chain extension methodology serves as a good example to illustrate the scope of enolate halomethylation. Dowd, Choi, and Beckwith developed a general pathway for the one-carbon homologation of medium-[2,3] and large-sized[4,5] rings by treatment of the corresponding methyl or ethyl cycloalkanonecarboxylates **1a−f** with NaH and a methylene dihalide, followed by a free radical promoted ring expansion (Scheme 2).[6] For both steps, the exact reaction conditions were strongly substrate dependent. Nevertheless, significantly higher yields were obtained for the alkylation of medium-sized rings, compared to their larger counterparts. The depicted alkylation conditions, employing NaH as a base and HMPA as a cosolvent, are typical for this type of transformation.

Scheme 2

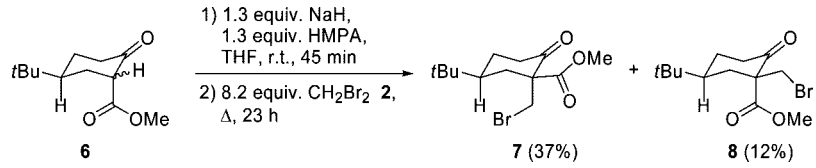


This homologation strategy was also employed by Curran and co-workers in the synthesis of fused bicyclic compounds, *via* a tandem ring expansion/cyclization (Scheme 3).[7] The formation of brominated ketoester **7** as the major product of the alkylation step can be rationalized through the stereoelectronic control of the reaction.

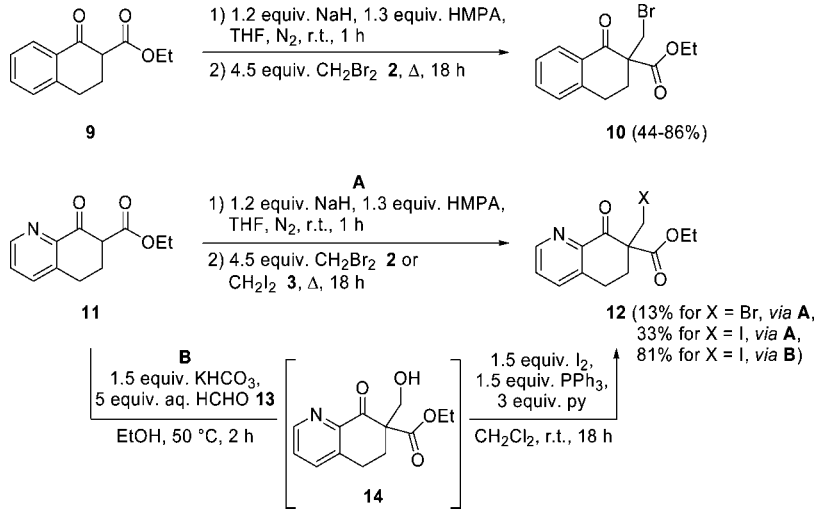
Bowman[8] and Dowd[9] proved the applicability of the methodology for benzoannulated ketones and 1,3-diketones. Interestingly, while Bowman reported a yield of 44% for the conversion of compound **9** to its bromomethylated analogue **10**, the same reaction was reported to proceed in 86% yield by Yoshizumi and co-workers (Scheme 4).[10] In their synthesis of tetrahydrocycloheptapyridines, the latter researchers showed that direct alkylation is more difficult for the heterocyclic analogues **11** of the corresponding ketones. Therefore, a hydroxymethylation strategy, followed by a nucleophilic displacement to afford the iodide using I_2/PPh_3, proved to be far more fruitful (pathway **B**, Scheme 4).

The alkylation-rearrangement strategy was also useful to convert acyclic β-ketoesters into their γ-analogues.[2] In an analoguous investigation on the free radical chain extension of 1,3-diketones by Zou and co-workers, the outcome of the iodomethylation of 2-methyl-1,3-diphenylpropane-1,3-diones **15** proved to be highly substrate dependent (Scheme 5).[11] In this study, K_2CO_3 was used to generate the enolate of the 1,3-diketone. Besides, other bases can be used in enolate haloalkylation reactions. In one example, Mayer and Alder alkylated a β-ketoester with CH_2Br_2 using KOH.[12]

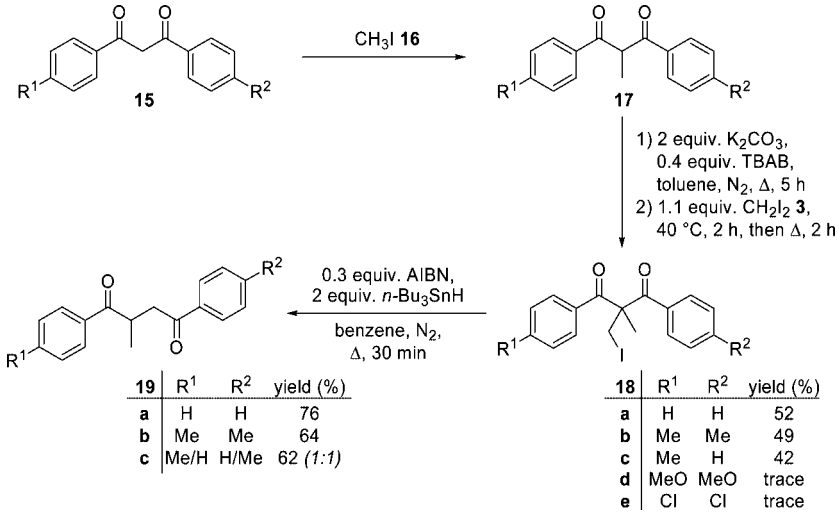
Scheme 3



Scheme 4



Scheme 5



19	R^1	R^2	yield (%)
a	H	H	76
b	Me	Me	64
c	Me/H	H/Me	62 *(1:1)*

18	R^1	R^2	yield (%)
a	H	H	52
b	Me	Me	49
c	Me	H	42
d	MeO	MeO	trace
e	Cl	Cl	trace

2.1.2. Conversion of an Alcohol or Ether into an Alkyl Halide

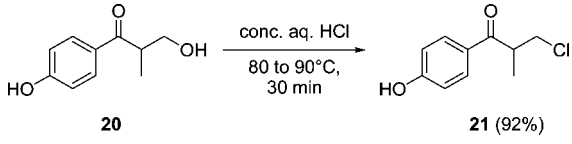
Because of the poor leaving group capacity of the hydroxyl moiety, alcohols do not react directly with nucleophiles. Any nucleophile, strong enough to produce the hydroxide ion, would instead create an alkoxide. Other methods, however, have been developed to convert these versatile substrates into halocarbons.

2.1.2. 1. Substitution in Acidic Medium. When treated with a suitable acid, alcohols are converted into alkylhydroxonium ions. A subsequent attack of a nucleophile will cause H_2O to be expelled. As such, the treatment of hydroxyketones **20** with concentrated HCl to form the corresponding β-chloro ketones **21** has repeatedly been reported (Scheme 6).[13]

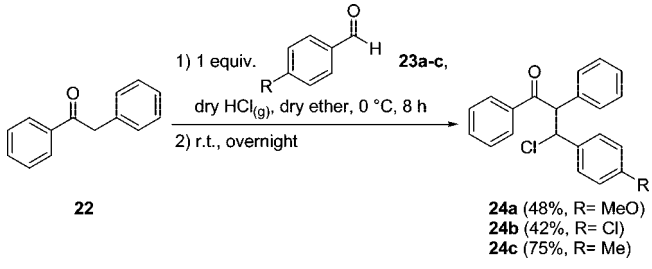
Moreover, when aldol reactions are performed using HCl as a catalyst, the aldol product can undergo *in situ* conversion to a β-halo ketone. This was illustrated by Armesto and coworkers in the reaction of deoxybenzoin **22** with various benzaldehydes **23a**−**c** (Scheme 7), affording β-chloro ketones **24a**−**c**.[14]

Similarly, HBr induces the condensation of ketones **25a**−**b** and **27a** with benzaldehyde **23a**, furnishing β-halo ketones **26a**−**b** and **28a** (Scheme 8).[15] Diketone **27b** unexpectedly furnished the rather labile indanone **28b**, presumably *via* a Nazarov-type cyclization of an intermediate α,β-unsaturated ketone **29**.

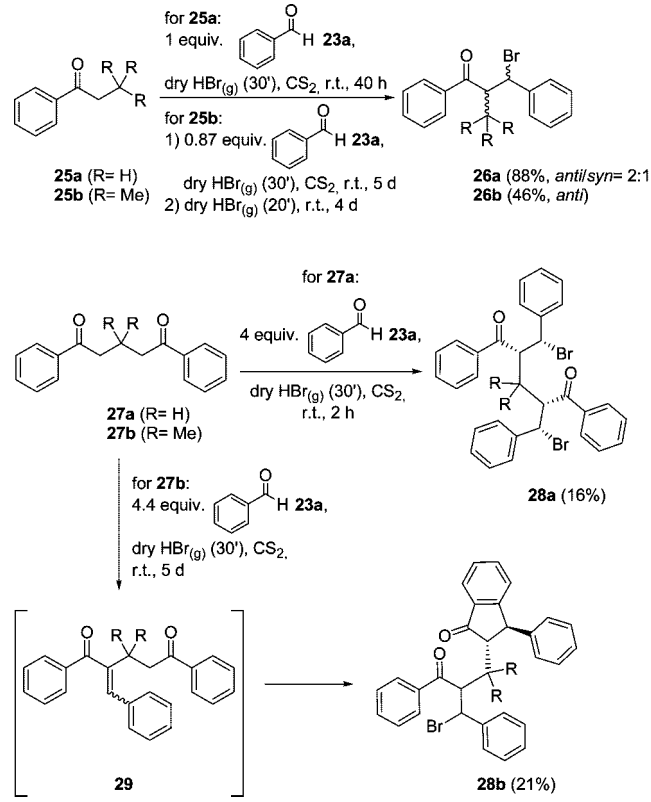
Scheme 6



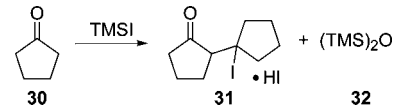
Scheme 7



Scheme 8



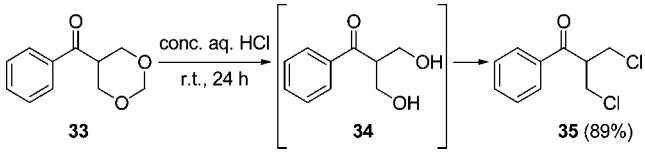
Scheme 9



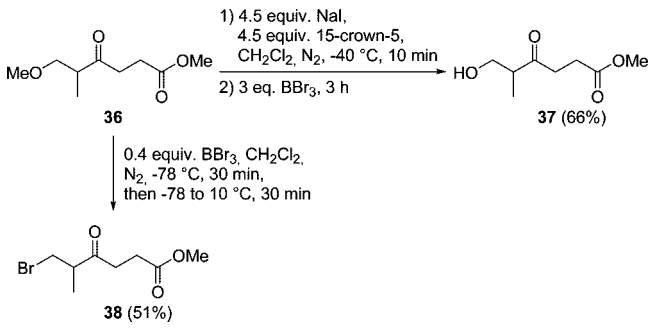
Russ and co-workers reported the self-condensation of cyclopentanone **30** upon treatment with TMSI. Taking into account that ketones are able to form labile adducts with anhydrous HI, structural elucidation pointed toward β-iodo ketone **31** as the reaction product (Scheme 9).[16]

As illustrated by Fuson and co-workers, an acetal protected diol **33** can be converted into the corresponding dichloride **35** in one step upon treatment with concentrated HCl (Scheme 10).[17]

Scheme 10



Scheme 11



Mixtures of a Brönsted and a Lewis acid (such as $AlCl_3$ in concentrated HCl) can also be used to substitute a hydroxyl group for a halide.[18] Furthermore, BBr_3 is a widely used reagent for the cleavage of methyl ethers. In a noteworthy example illustrating the reactivity of this reagent, Kuehne and co-workers were able to convert methyl ether **36** into either alcohol **37** or bromide **38**, depending on the applied conditions (Scheme 11).[19]

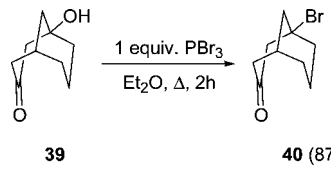
2.1.2.2. Substitution of Phosphoryl Activated Alcohols. Activation of the hydroxyl function with an element that forms a very strong bond to oxygen, such as phosphorus or sulfur, is a general method to create a better leaving group. A widely used reagent to accomplish this goal is PBr_3. Subsequent to the attack of PBr_3 by the OH group, an oxyanion bound to phosphorus is displaced. As such, several reports[20−22] have been published on the ease of substitution of a bridgehead hydroxyl group by bromine in bicyclo[3.3.1]nonan-3-ones **39** upon treatment with PBr_3 (Scheme 12).[23]

When organoiodides need to be prepared, an Appel-type reaction with PPh_3 and I_2 can be adopted.[24] In their synthesis of tetrahydrocycloheptapyridines, Yoshizumi and co-workers compared a hydroxymethylation/Appel reaction sequence and a direct iodomethylation for the preparation of heterocyclic β-ketoester **11** (Scheme 4, pathway **B**).[10] The former strategy proved to be the superior alternative.

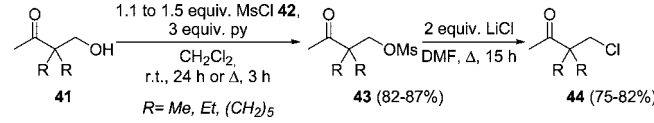
2.1.2.3. Substitution of Sulfuryl Activated Alcohols. As stated above, creating a strong oxygen−sulfur bond significantly improves the leaving capacity and thus the reactivity of alcohols in substitution reactions. As a result, alcohols are often transformed into sulfonic esters as a means of activation. One possibility is the creation of mesylates **43** (Scheme 13).[25,26]

In a typical procedure, the alcohol is treated with mesyl chloride (MsCl) in a dry solvent (such as CH_2Cl_2) in the presence of a base, e.g. pyridine, at room temperature or below. Subsequent reaction of the mesylate with LiCl or LiBr

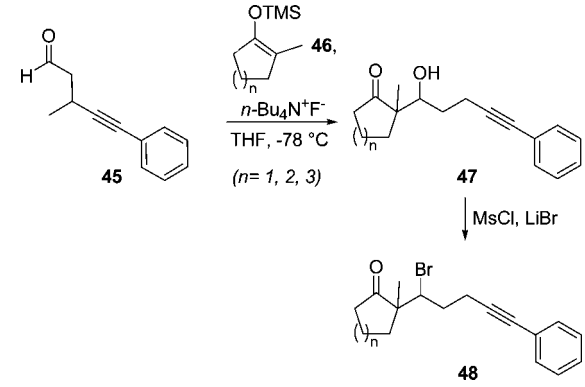
Scheme 12



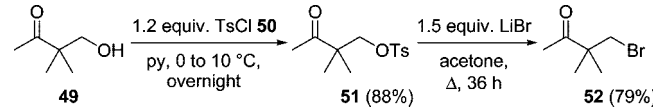
Scheme 13



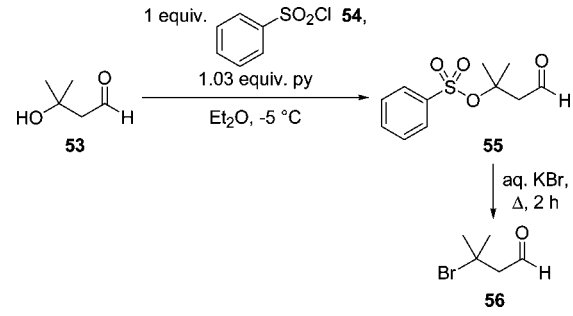
Scheme 14



Scheme 15



Scheme 16



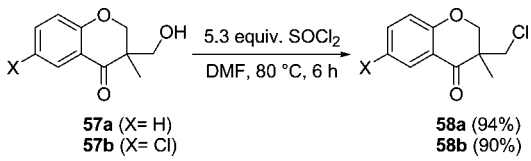
in an aprotic solvent such as dimethyl formamide (DMF) or 2-butanone yields the target alkyl halides.[27] Similarly, β-bromo ketones **48** are accessible from β-hydroxy ketones **47** in this way (Scheme 14).[28]

The alcohol can also be activated by formation of a *p*-toluenesulfonate. In one case, a mesylate was preferred over its *p*-toluenesulfonate alternative, because of facile distillation purification of the former.[29] Nevertheless, tosylate activation is a common procedure.

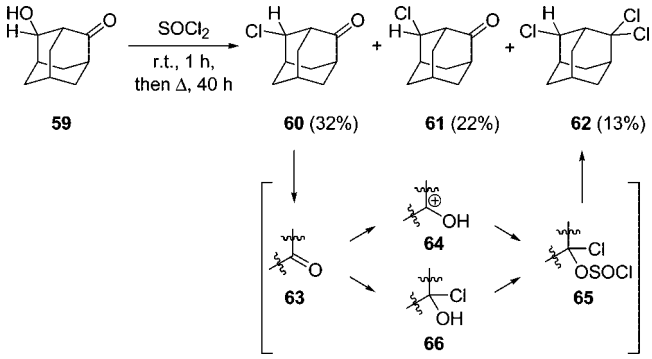
Similar to the earlier described preparation of mesylates, the alcohol **49** is reacted with tosyl chloride **50** in the presence of a suitable base, followed by displacement of the halide upon treatment with lithium[30,31] or potassium[32] halides in a polar aprotic solvent (methyl ethyl ketone,[30] DMF,[31] DMSO,[32] HMPA,[33] acetone) upon heating. Substitution proceeds rather sluggishly for sterically hindered substrates,[30] such as neopentylic tosylate **51** (Scheme 15).[34]

Alcohols have also been activated toward substitution by conversion into benzenesulfonates **55**, as illustrated by Temnikova and co-workers (Scheme 16).[35] Treatment of the sulfonate with aqueous KBr under reflux thus furnished 3-bromo-2,2-dimethylpropanal (**56**). This β-bromo aldehyde proved to be unstable, as it deposited a solid, devoid of the carbonyl group, upon standing.

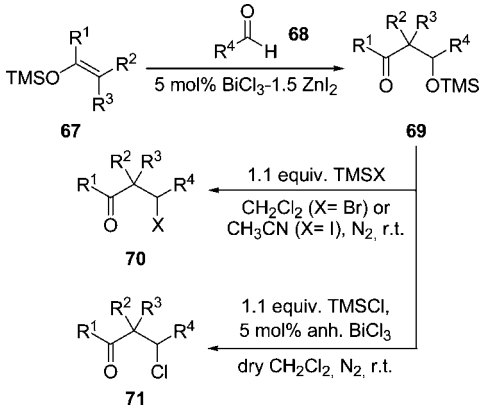
Scheme 17



Scheme 18



Scheme 19



$SOCl_2$ effectuates both the activation and the displacement of a hydroxyl moiety. Employing this reagent, Gignarella and co-workers prepared 3-chloromethyl-3-methyl-4-chromanones **58a**−**b** from the corresponding alcohols **57a**−**b** in high yield (Scheme 17).[36]

Moreover, the reaction of hydroxylated and chlorinated adamantanones **59** and diamantanones with $SOCl_2$ was investigated by Janků and co-workers (Scheme 18).[37] Substrates containing a secondary hydroxyl moiety undergo substitution by the chloride *via* an S_N1 mechanism. The reaction of the carbonyl group of the chlorinated ketones **60** with $SOCl_2$ was found to be catalyzed by the HCl present in the reaction mixture and probably proceeds *via* intermediate **65**. Steric hindrance in functionalized adamantanones only arose with substituents in the α-, β-, and, in some cases, γ-axial position to the carbonyl group. Of greater influence on the rate of the reaction was the inductive effect of the substituents. Moreover, the presence of a second carbonyl group in the diones lowered the reaction rate by about 2 orders of magnitude.

2.1.3. Miscellaneous

A rather mild synthesis of β-halo ketones was presented by Dubac and co-workers.[38] β-Silyloxyketones **69**, resulting from the $BiCl_3 \cdot 1.5ZnI_2$ catalyzed aldol reaction of enoxysilanes **67** with aldehydes **68**, can readily be brominated or iodinated upon treatment with TMSBr or TMSI (Scheme 19). Anchimeric assistance of the carbonyl oxygen, by coordination with silicon, weakens the carbon−oxygen bond β to silicon and causes the reaction to proceed faster than the corresponding halogenation of simple alkoxysilanes. Introduction of chloride by TMSCl, however, only proceeded after activation of the silicon−chlorine bond by $BiCl_3$ and did not exhibit stereoselectivity. Although the tandem aldol-halogenation reaction can be carried out in a one-pot procedure, the yield and purity of the β-halocarbonyl compounds were always higher after isolation of the intermediate aldol product **69**.

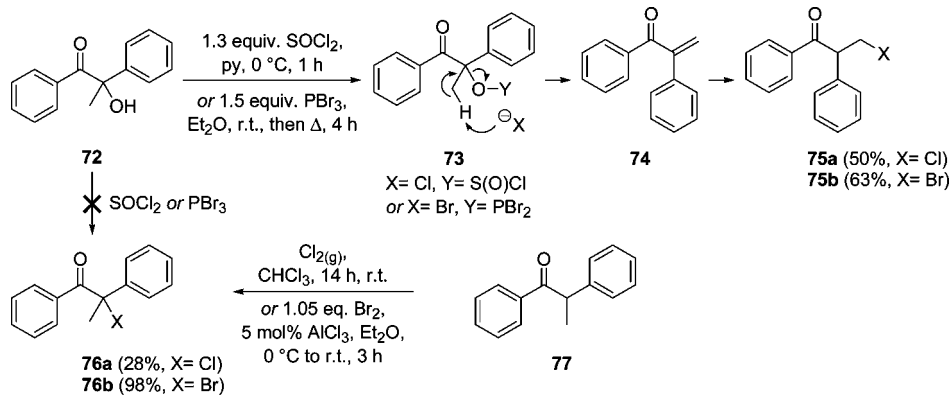
Recently, Aitken and co-workers attempted to reinvestigate the reaction of α-hydroxyketone **72** with $SOCl_2$ or PBr_3, since considerable confusion exists in the literature about the outcome of these transformations (Scheme 20).[39] Contrary to earlier reports, not α-halo ketone **76** but the rearranged compound **75** was indentified as the reaction product. A mechanism was proposed, in which an intermediate enone **74** undergoes a Michael-type addition of the *in situ* liberated HX. Further, an appropriate synthesis for the α-halo ketone **76** was discussed.

2.2. Nucleophilic Addition

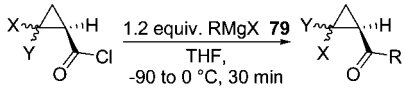
2.2.1. Addition of Grignard Reagents

A straightforward entry toward β-halo ketones is the nucleophilic addition of an organomagnesium halide to a β-halogenated carboxylic acid derivative. Kulinkovich and co-workers, for example, successfully persued this strategy in the synthesis of numerous (2-chlorocyclopropyl)- and (2,2-dichlorocyclopropyl) alkyl ketones **80a**−**h** (Scheme 21).[40,41] In like manner, Tanabe, Nishii, and co-workers prepared (1-

Scheme 20



Scheme 21

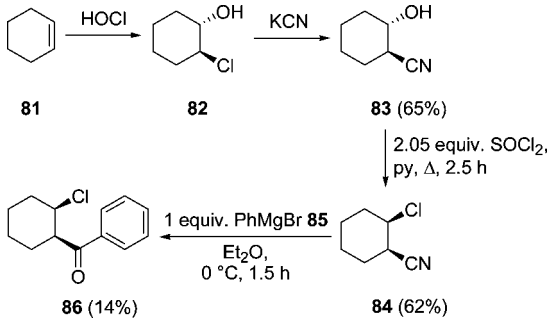


78a (X= Cl, Y= H)
78b (X,Y= Cl)

80	from	R	Yield (%)
a	95a	Me	68[a]
b	95a	*n*-Pr	71[b]
c	95a	*n*-C_5H_{11}	75[b]
d	95a	*n*-C_8H_{17}	83[b]
e	95b	Me	40
f	95b	*n*-Pr	74
g	95b	*i*-C4H9	85
h	95b	*n*-C_5H_{11}	78

cis/*trans*: [a]15:85, [b]10:90

Scheme 22



methyl-2,2-dihalocyclopropyl) aryl ketones[42] and a range of enantiopure (2,2-dichloro-3-arylcyclopropyl)[43] and (2,2-dichloro-3-alkylcyclopropyl) aryl ketones.[44]

The *cis*-isomer **86** of 2-chlorocyclohexyl phenyl ketone was stereospecifically prepared from cyclohexene **81** by Kosak and co-workers (Scheme 22).[45] Reaction of phenylmagnesium bromide **86** with *cis*-2-chlorocyclohexyl cyanide **84** proceeded without isomerization or dehydrochlorination of the chloronitrile. However, given the poor yield of the latter step, the stereospecific addition of HCl to 1-cyclohexenyl phenyl ketone, reported by the same researchers, proved a superior strategy (see Scheme 27).

2.2.2. Enolate Additions

2.2.2.1. Aldol-Type Reactions. The nucleophilic acylation of α-chlorocarbonyl compounds **89** with benzaldehyde **87a** or 2-furaldehyde **87b** upon *umpolung* of the latter compounds with TMSCN was reported by Hünig and co-workers. This approach provided a new entry to β-chlorinated O-silylacyloins **90a**−**f**, and further on to α,β-epoxyketones (Scheme 23).[46] Application of this *umpolung* methodology to α,β-unsaturated aldehydes proved unsuccesful when using THF as a solvent, since formation of 2:1 adducts of the nucleophile and electrophile prevailed. In diethyl ether, however, the desired β-chloro-α-silyloxyketones **94a**−**d** were obtained in reasonable yields.

2.3. Conjugate Addition

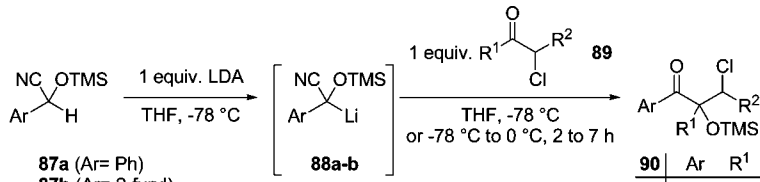
It is common knowledge that C=C double bonds conjugated with a carbonyl group react profoundly differently than their isolated counterparts. The conjugated C=C bond is of electrophilic nature, and therefore, nucleophilic additions to it proceed normally well.

2.3.1. Michael Addition of Hydrogen Halides to α,β-Unsaturated Aldehydes and Ketones

1,4-Addition of HCl or HBr to an α,β-unsaturated ketone readily leads to the corresponding β-chloro or β-bromo ketone. However, this process is easily reversible, and therefore, many authors mention the sensitivity of these species toward elimination and polymerization. Only at low temperatures and protected from direct light are β-halo ketones sufficiently stable to be stored for several days.

In practice, the addition is very often conducted by cooling a solution of the enone using an ice(-salt)-bath, after which gaseous HCl or HBr is bubbled through the mixture. Several reports on the addition of hydrogen halide to (2-alkylated) acroleins are available.[47,48] However, isolated yields for the adducts were not reported, since they were immediately processed further, presumably because of their instability.

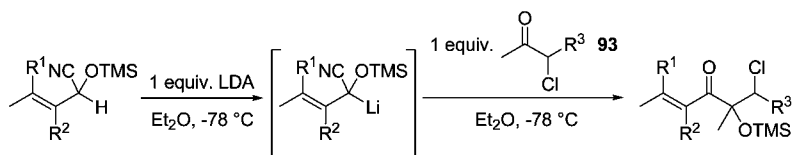
Scheme 23



87a (Ar= Ph)
87b (Ar= 2-furyl)
88a-b

90	Ar	R1	R2	Yield (%)	*anti/syn*
a	Ph	Ph	H	87	
b	Ph	Me	H	69	
c	Ph	H	Me	93[a]	b
d	Ph	Me	Me	82	87:13
e	2-furyl	Me	H	62	
f	2-furyl	Me	Me	100[a]	100:0

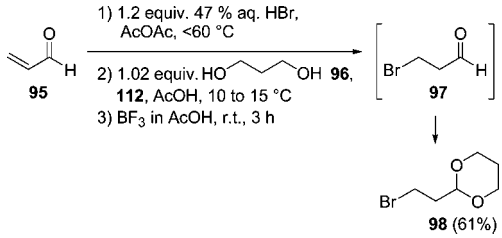
[a]crude; [b]not reported



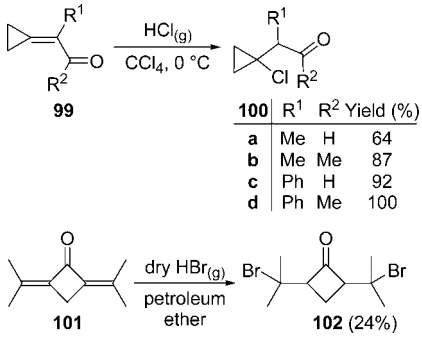
91a (R^1, R^2= H)
91b (R^1= Me, R^2= H)
91c (R^1= H, R^2= Me)
92a-c

94	R^1	R^2	R^3	Yield (%)	*anti/syn*
a	H	H	H	71	
b	H	H	Me	64	*79:21*
c	Me	H	H	43	
d	H	Me	Me	50	*85:15*

Scheme 24



Scheme 25



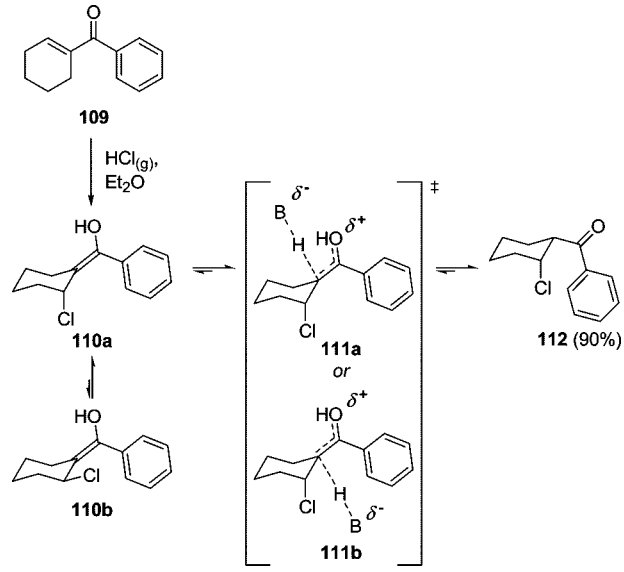
In another example, Christensen and co-workers reported a one-pot hydrobromination−acetalization sequence of acrolein, yielding the useful three-carbon synthon 2-(2-bromoethyl)-1,3-dioxane **98** (Scheme 24).[49]

Furthermore, hindered β,β-disubstituted enones such as pulegone[50] and 2-methyl-6-phenylhept-2-en-4-one[51] were also proven to be suitable substrates in HX conjugate addition reactions. In like manner, Conia and co-workers prepared β-halogenated cyclopropyl ketones **100a−d** and cyclobutanone **102** (Scheme 25).[52,53]

Two syntheses of *N*-containing heterocycles in which a conjugated addition of HX to an α,β-unsaturated ketone is performed are depicted in Scheme 26. Addition of HBr to the D-mannose derivative **103** gave partial deprotection of the 5,6-*O*-isopropylidene group due to traces of moisture in the mixture.[54] Since this concomitant hydrolysis was desired, 2 equiv of H_2O was added in subsequent runs. The resulting bromide **104** was not isolated, but treated with Na_2CO_3 in H_2O to affect cyclization toward 2-alkylated 3-pyrrolidinone **105**. In the case of 4-piperidinone **108**, HCl-mediated deprotection of the *tert*-butyloxycarbonyl group of enone **106** proceeded much slower than addition of the same acid across the unsaturation, which was evidenced by the isolation of β-chloro ketone **107** after 24 h.[55]

A thorough investigation on the stereochemistry of the addition of HCl to endocyclic α,β-unsaturated ketones was

Scheme 27

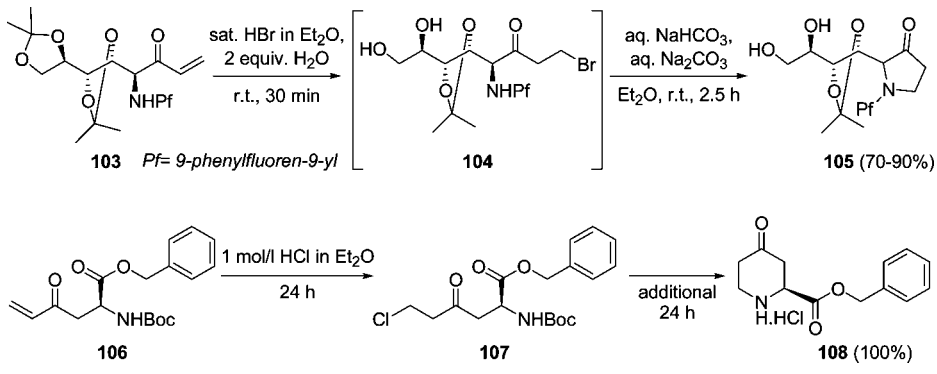


reported by Blair and co-workers (Scheme 27).[56] For 1-benzoylcyclohexene **109**, *cis*-1-benzoyl-2-chlorocyclohexane **112** was selectively obtained in excellent yield. A probable explanation involves the preferred formation of the most stable enol adduct **110a**, since geometrical isomer **110b** would suffer from a destabilizing $A_{1,3}$-allylic interaction between the chlorine and the phenyl substituents. Subsequent tautomerization of enol **110a** toward ketone **112** occurs *via* a preferential attack of the acid species BH along the path depicted in transition state **111a**, since the presence of the chlorine atom will cause severe steric compression when following the alternative route shown in **111b**.

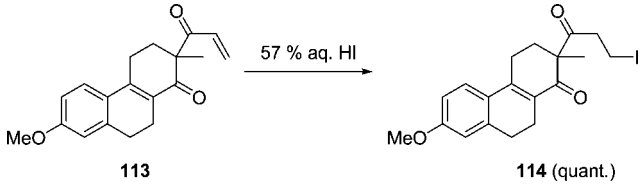
Since alkyl iodides are often synthetically more useful compared to chlorides and bromides, for example in nucleophilic substitution and carbon−carbon bond formation reactions, research has been performed to develop mild entries toward β-iodo aldehydes and ketones. One of the most straightforward manners to accomplish this goal, although rather drastic in character, involves the treatment of an α,β-unsaturated ketone with concentrated HI. This approach was followed by Narasimhan and co-workers during the conversion of enone **113** into β-iodinated ketone **114**, which was part of a synthesis of estrone *via* a novel cyclopentane annulation reaction (Scheme 28).[57] Nevertheless, since a solution of HI tends to liberate iodine, on its turn giving rise to side reactions, alternative methods have been developed.

In an alternative route, TMSI, a powerful electrophile, was employed to generate the intermediate iodotrimethylsilyl enol

Scheme 26

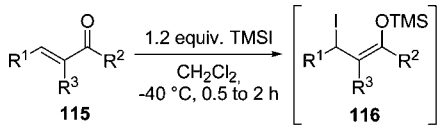


Scheme 28



113 **114** (quant.)

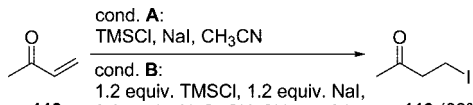
Scheme 29



115 **116**

117	R^1	R^2	R^3	Yield (%)
a	H	Et	H	85
b	$(CH_2)_4$		H	81
c	H	$(CH_2)_4$		85
d	H	$(CH_2)_5$		75
e	H	Ph	Me	93
f	H	2-$R^3C_6H_4$	$(CH_2)_2R^3$	80

Scheme 30



118 **119** (66% *via* **B**)

ethers **116**, which hydrolyzed to the corresponding β-iodocarbonyl compounds **117a**−**f** in high yield upon aqueous workup (Scheme 29).[58] When the intermediate iodotrimethylsilyl enol ethers **116**, instead of undergoing an aqueous workup, were treated with an alcohol, β-halogenated acetals are obtained.[59,60]

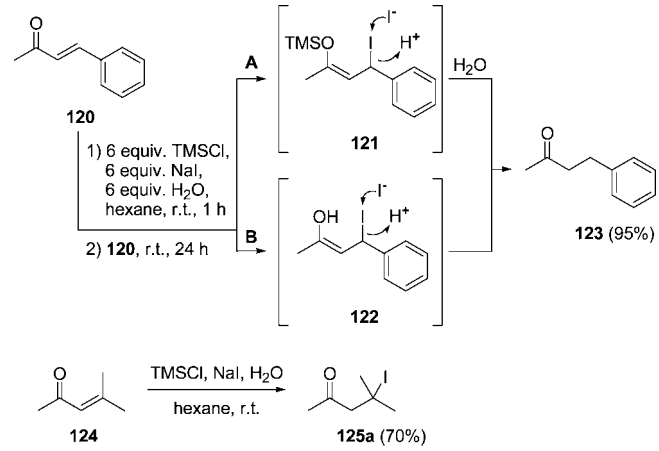
Often, instead of TMSI, which is difficult to handle, TMSCl is used together with NaI in acetonitrile (conditions **A**, Scheme 30).[61] Addition of H_2O to the reaction mixture has been reported to broaden the range of substrate opportunities, since this approach represents a convenient entry to the *in situ* generation of HI (conditions **B**).[62]

Intriguingly, benzalacetone **120** undergoes a reduction toward their saturated counterparts **123** using the TMSCl/NaI reagent in protic solvents (Scheme 31).[63] Two possible mechanistic pathways were proposed for this transformation. Still, β-methyl analogue **124** again yields the corresponding β-methyl β-iodo ketone **125a**.

In another example on the synthesis of β-iodinated ketones, Kulinkovich and co-workers prepared a series of secondary iodides **127a**−**d** *via* a Michael addition of HI or TMSI to the corresponding enones **126a**−**d** (Scheme 32).[64] Both approaches gave excellent yields.

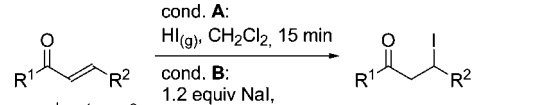
A simple and convenient synthesis of β-chloro, β-bromo, as well as β-iodo ketones **142a**−**c** was described by Marx, who reacted tetraethylammonium halides with enones **141** in CF_3COOH at room temperature (Scheme 33).[65] The rate of trapping of the protonated enone **145** shows a dramatic effect on the halide used ($I^- \gg Br^- > Cl^-$; fluorides failed to react in all cases). This is also valid for β-halo ketones **147a**−**c**, **148a**−**c**, and **149a**−**c**. Furthermore, the reaction is

Scheme 31



120 **121** **122** **123** (95%) **124** **125a** (70%)

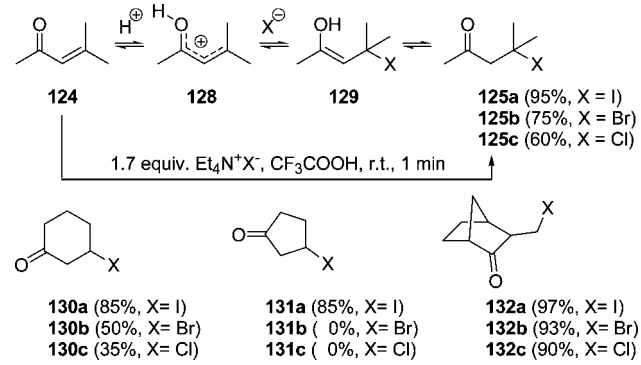
Scheme 32



126	R^1	R^2
a	Me	*n*-Pr
b	*n*-Pr	Me
c	*i*-Pr	Me
d	*t*-Bu	Me

127a-d (95-100%, *via* **A**, 90-95%, *via* **B**)

Scheme 33



124 **128** **129** **125a** (95%, X = I) **125b** (75%, X = Br) **125c** (60%, X = Cl)

130a (85%, X= I) **130b** (50%, X= Br) **130c** (35%, X= Cl)
131a (85%, X= I) **131b** (0%, X= Br) **131c** (0%, X= Cl)
132a (97%, X= I) **132b** (93%, X= Br) **132c** (90%, X= Cl)

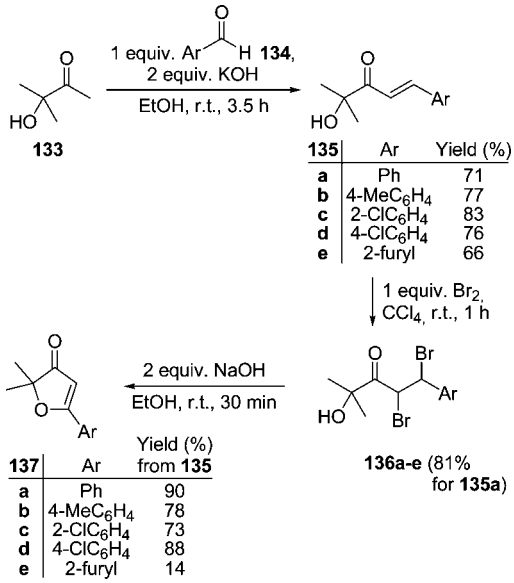
adversely affected by the presence of H_2O, presumably because of the strong hydrogen bonding between X^- and H_2O. As several simple α,β-unsaturated esters, amides, and nitriles, as well as unactivated alkenes, were shown to be inert to the depicted conditions, the protocol appears to be selective for the formation of simple β-halo ketones.

2.3.2. Dihalogenation of α,β-Unsaturated Aldehydes and Ketones

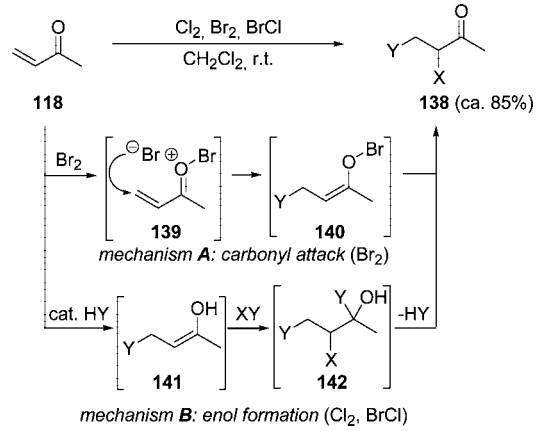
Dihalogens add across the C=C bond of α,β-unsturated aldehydes and ketones with the same net result as for isolated double bonds. The resulting α,β-dihalo ketones are frequently used in ring closing reactions. Takeda and co-workers, for example, applied this transformation in a novel synthetic method of 3-(2*H*)-furanone derivatives **137a**−**e** (Scheme 34).[66] Earlier, Marx[67] dibrominated pulegone upon treatment with Br_2 at −10 °C in ether, whereas Griesbaum[68] prepared 3,4-dibromo-3-methylbutan-2-one out of the corresponding enone in 79% yield, employing CCl_4 as a solvent.

A mechanistic investigation of the reaction of halogens with some common α,β-unsaturated aldehydes and ketones (phenyl vinyl ketone, acrolein, methyl vinyl ketone, *cis*- and *trans*-3-penten-2-one) was reported by Heasley and co-

Scheme 34



Scheme 35

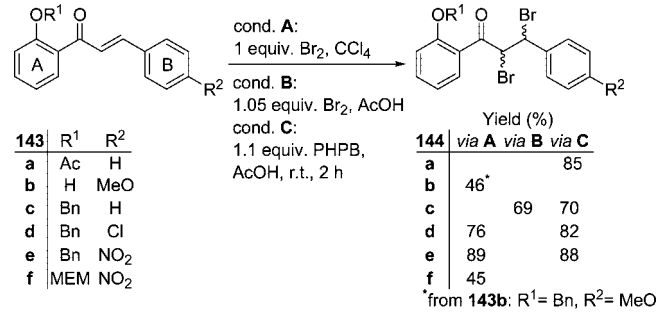


workers.[69] Unlike the very slow addition of Br_2 or BrCl to α,β-unsaturated esters, enones react extremely rapidly—almost violently. Moreover, with BrCl, α-bromo-β-chloro compounds are obtained exclusively, whereas the corresponding reaction with esters provides both regioisomers. Still, comparative rate studies for the bromination evidenced the great reactivity of enones compared to 1-heptene. These observations render an electrophilic attack of the halogen on the unsaturation unlikely. Therefore, two other mechanisms were proposed (Scheme 35). Detailed investigations suggested that Cl_2 and BrCl add by pathway **B**, whereas Br_2 reacts *via* route A.

When functionalized chalcones **143a**−**f** are dibrominated, attention needs to be paid to the substitution pattern.[70] The group in the *para* position of ring B significantly influences the stability of the protective group in the *ortho* position of ring A. When the B-ring is substituted with a nitro group or a chlorine atom, even the methoxymethyl (MEM) protective group, which is otherwise unstable, is not split off during the bromination step (Scheme 36). Furthermore, this transformation illustrates the use of pyridinium hydrobromide perbromide (PHPB, py.HBr_3) as an alternative brominating reagent.

In a preparation of α,α-dichloropropanal *via* HCl-catalyzed chlorination of propanal in DMF, De Buyck and co-workers observed an appreciable amount of self-condensation of the

Scheme 36



starting aldehyde due to the strong acidity of the medium. Subsequent rapid addition of Cl_2 across the unsaturation of the thus formed 2-methylpent-2-enal led to the isolation of 2,3-dichloro-2-methylpentanal as a major side product in 20% yield.[71]

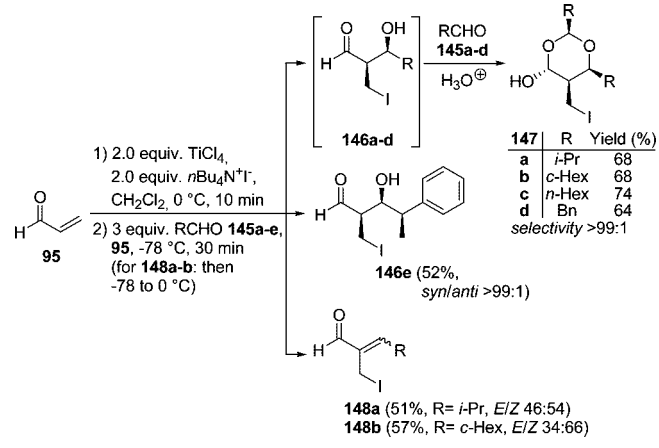
2.3.3. $TiCl_4$-Assisted Tandem Michael Addition−Aldol Reaction

It is well-known that $TiCl_4$ can mediate highly stereoselective coupling reactions between α,β-unsaturated ketones and aldehydes. Upon conjugate addition of a nucleophile, in the context of this review a halide, the thus created enolate is prone to react with electrophiles and will undergo carbonyl coupling with a second aldehyde or ketone moiety.

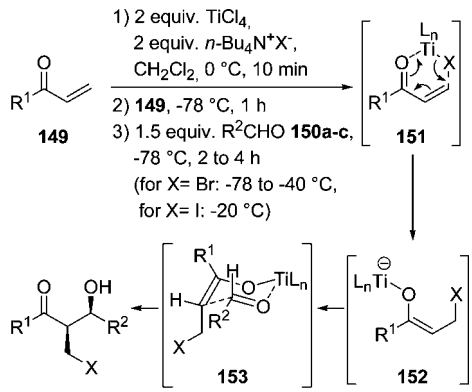
As a consequence, Oshima and co-workers observed a high level of diastereofacial selectivity in the formation of *syn*-3-hydroxyaldehydes **146** when treating acrolein **95** with an array of aldehydes **145a**−**e** in the presence of a $TiCl_4$/n-$Bu_4N^+I^-$ system (Scheme 37).[72] Only in the case of 2-phenylpropanal **145e**, however, was the steric bulk sufficient to prevent the addition of an extra molecule of the aldehyde. In all other cases, the initial aldol adduct **146a**−**d** was converted into the corresponding cyclic hemiacetal **147a**−**d**. Warming the reaction mixture to 0 °C prior to quenching provided the corresponding dehydration product **148a**−**b**.

Likewise, treatment of vinyl ketones **149** with stoichiometric amounts of $TiCl_4$/n-$Bu_4N^+X^-$ (X = Cl, Br, I) in the presence of an aldehyde **150a**−**c** provides *syn*-α-halomethyl-β-hydroxy ketones with high stereoselectivity (Scheme 38).[73] Competitive rate experiments for this halide induced aldol reaction showed a logical order of relative nucleophilicity of the combined reagents (I > Br > Cl). Both aromatic and aliphatic aldehydes were equally reactive. Methyltriph-

Scheme 37



Scheme 38



154	R^1	R^2	Yield[a] (%) X= I	X= Br	X= Cl
a	Ph	Ph	89		
b	Ph	*i*-Pr	70[b]	60	
c	Me	Ph	84[c]	90	61
d	Ph	Me	96		

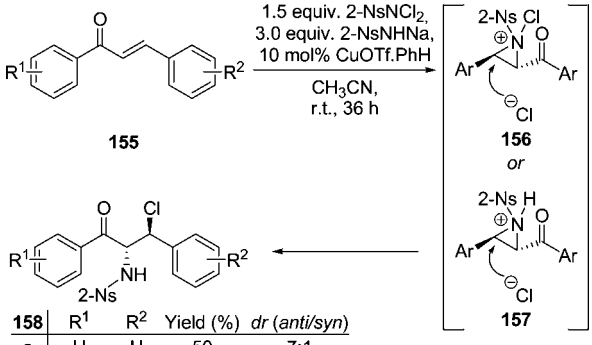
selectivity (*syn*/*anti*): [a]>99:1, [b]89:11, [c]96:4

enylphosphonium iodide also acts as an efficient halide source, contrary to the case of $Me_4N^+I^-$, which is not soluble enough in CH_2Cl_2. Selective generation of the *syn* isomer was explained through formation of a (*Z*)-titanium enolate **152** upon conjugate addition of a Ti−X species to the vinyl ketone **149** in an *s-cis* conformation. Subsequent reaction with the aldehyde proceeds through a rigid six-membered transition state corresponding with the Felkin−Ahn model **153**. Furthermore, a mechanism was also provided for an earlier reported similar reaction, in which $TiCl_4$ was combined with a catalytic amount of n-$Bu_4N^+X^-$ (X = Br, I) and the aldehyde was added prior to the enone.[74] Following this approach, contrary to what can be expected from the comparative rate experiment, only chlorinated aldol-type products are obtained.

2.3.4. Miscellaneous

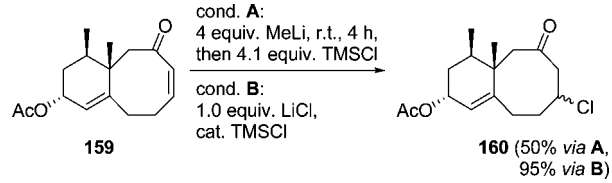
Although vicinal haloamines are interesting structural motifs in organic chemistry, a successful aminohalogenation protocol for α,β-unsaturated ketones was only developed fairly recently, by Li and co-workers (Scheme 39).[75] Using a combination of 2-$NsNCl_2$/2-NsNHNa (2-Ns = 2-nosyl = 2-nitrophenylsulfonyl) as a source of nitrogen and chlorine and CuOTf as a catalyst, vicinal *anti*-haloamines **158a**−**f** were obtained with high regio- and stereoselectivity. The

Scheme 39

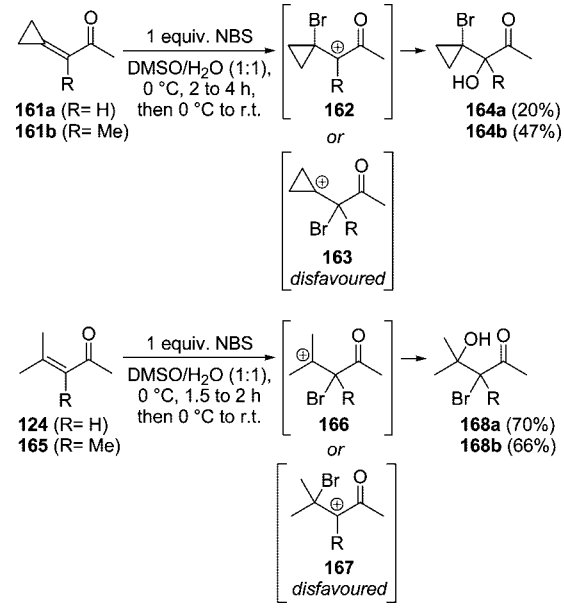


158	R^1	R^2	Yield (%)	*dr* (*anti*/*syn*)
a	H	H	50	7:1
b	4-NO_2	H	72	10:1
c	4-Cl	H	52	9:1
d	H	4-F	58	15:1
e	H	4-Cl	44	7:1
f	H	4-MeO	41	15:1

Scheme 40



Scheme 41



reaction was suggested to proceed through the formation of an aziridinium salt, resulting from the attack of the electrophilic amination species 2-$NsNCl_2$ (leading to intermediate **156**) or *in situ* formed 2-NsNHCl (yielding **157**). Subsequent attack of chlorine at the more electrophilic β-position in an S_N2 manner accounts for the observed regio- and stereoselectivity.

An unexpected case in which a halide acts as a nucleophile in a conjugate addition was reported by Majetich and co-workers (Scheme 40).[76] Upon treatment of enone **159** with an excess of MeLi and a subsequent quench with TMSCl (conditions **A**), the isolated product was not the expected silyl enol ether but ketone **160**. Reaction of TMSCl with MeLi produced the chloride anion, while the excess of TMSCl promoted the Michael reaction. This was confirmed by treating the enone with 1 equiv of LiCl and a catalytic amount of TMSCl (conditions **B**).

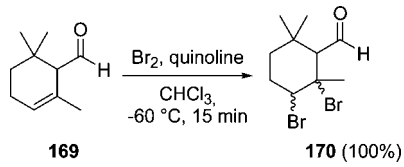
As demonstrated by Conia and co-workers, α,β-unsaturated ketones can be bromohydroxylated by treatment with NBS under aqueous conditions (Scheme 41).[52] The regiochemical outcome of this reaction is determined by the relative stability of the two possible transient carbenium ions **162** and **163**, formed upon the attack of Br^+ across the olefinic double bond. This stability is strongly substrate dependent and explains the inverse regiochemistry observed for α-cyclopropylidene ketones **161a**−**b** and α-isopropylidene ketones **124** and **165**.

2.4. Electrophilic Addition

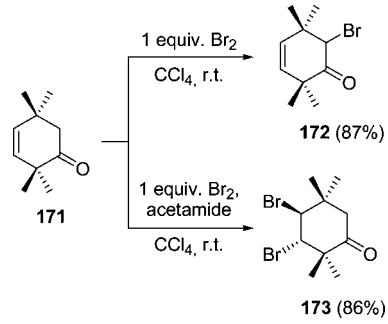
2.4.1. Dihalide Additions to Olefins

Dihalogenated ketones and aldehydes can be obtained *via* electrophilic addition of a dihalogen to an unsaturated parent

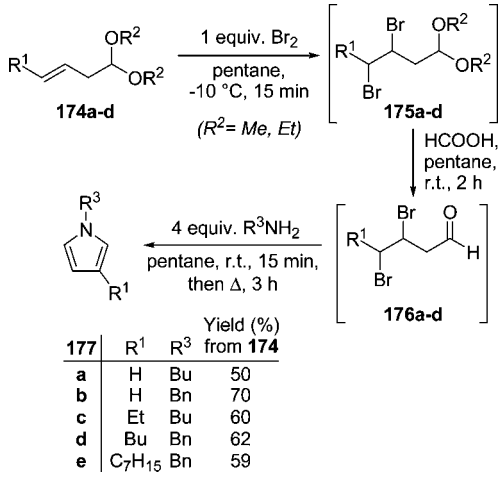
Scheme 42



Scheme 43



Scheme 44



177	R^1	R^3	Yield (%) from **174**
a	H	Bu	50
b	H	Bn	70
c	Et	Bu	60
d	Bu	Bn	62
e	C_7H_{15}	Bn	59

carbonyl compound. Hence, α-cyclocitral **169** has been brominated quantitatively, resulting in a mixture of two diastereoisomers of dibromo aldehyde **170** (Scheme 42).[77]

As encountered by Schaltegger and co-workers, α-bromination can predominate when this position is unsubstituted (Scheme 43).[78] To overcome the issue of α-bromination, a proton acceptor such as acetamide can be added. In this way, *trans*-3,4-dibromo-2,2,5,5-tetramethylcyclohexanone **173** was obtained in good yield.

Olefin dibromination with Br_2 is compatible with the use of acetal protective groups, as was demonstrated by Kulinkovich and co-workers for acetals **174a−d** (Scheme 44).[79] Upon deprotection under acidic conditions, β,γ-dibromoalkanals **176a−d** were formed. Since the dibromides **175a−d** and **176a−d** were unstable, no attempts were made to isolate these species. They were immediately reacted further toward 1,3-disubstituted pyrroles **177a−e**.

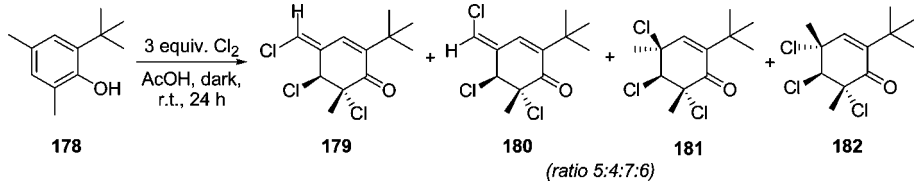
The chlorination of 2-*tert*-butyl-4,6-dimethylphenol **178** and 2,6-di-*tert*-butyl-4-methylphenol in AcOH was investigated by Hartshorn and co-workers (Scheme 45).[80] Though both transformations gave mixtures of polychlorinated compounds, a notable feature was the modification of the 4-methyl group of the phenols. The mode of formation of the reaction products and their structure determination were discussed.

2.4.2. Pinacol-Type Rearrangements

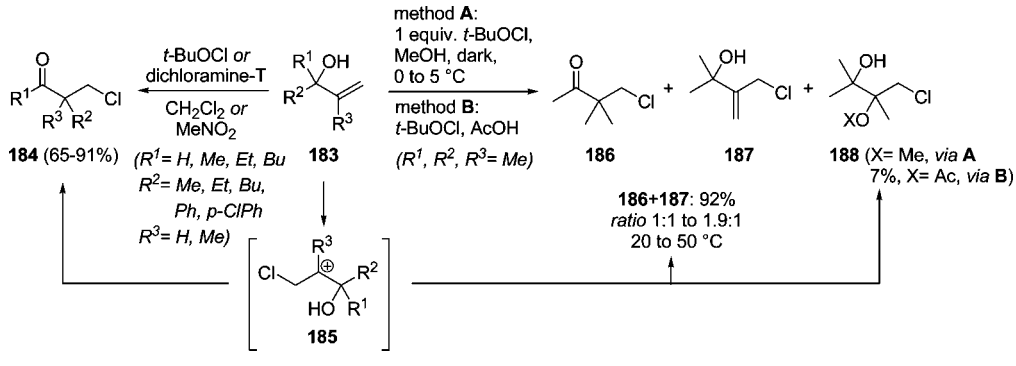
Another commonly used source of positive chlorine is *tert*-BuOCl. When allylic tertiary alcohol **183** is treated with this reagent, the intermediary chlorinated cation **185** is prone to a pinacol-type rearrangement (Scheme 46). Hence, in non-nucleophilic solvents such as CH_2Cl_2 or CH_3NO_2, a good yield of chlorinated ketones **184** can be obtained.[81,82] These transformations also proceed using dichloramine-T as the halide source.[81] However, when the reaction is performed in MeOH[83] or AcOH,[84] the expected ketone **186** is accompanied by products of proton abstraction or from solvent addition to cationic intermediate **185**.

This kind of electrophile-induced rearrangement of allylic alcohols was also observed by Rousseau and co-workers in the reaction of α- and β-substituted cinnamyl alcohols **189** with bis(collidine)bromine(I) hexafluorophosphate [$Br^+(coll)_2PF_6^-$, Scheme 47].[85] Again, migration of a hydrogen or a methyl group led to the isolation of β-chlorinated ketones **190**. Interestingly, cinnamyl alcohols lacking a substituent on the double bond yield oxetanes (e.g., **191**) under identical conditions.

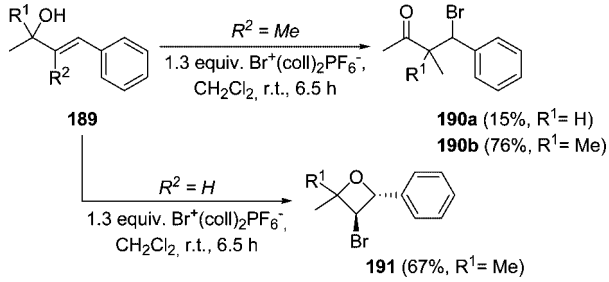
Scheme 45



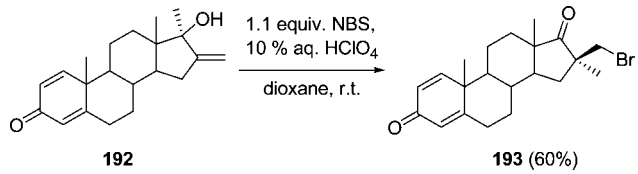
Scheme 46



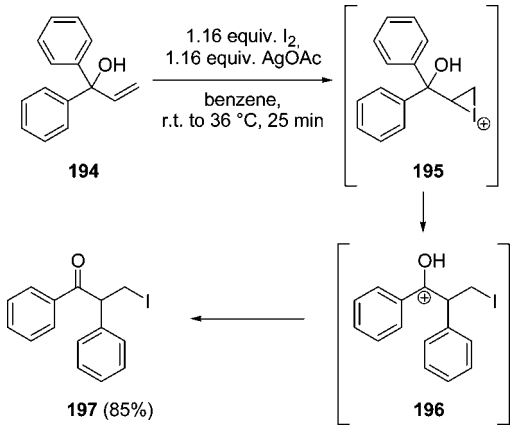
Scheme 47



Scheme 48



Scheme 49



Yet another interesting application of this type of transformation was presented by Brückner and co-workers in the synthesis of 17-ketosteroids. Upon treatment with NBS in acidic medium, 1-dehydro-16-methylene-17α-methyltestosterone **192** was converted into 16β-bromomethyl-17-ketosteroid **193** (Scheme 48).[86]

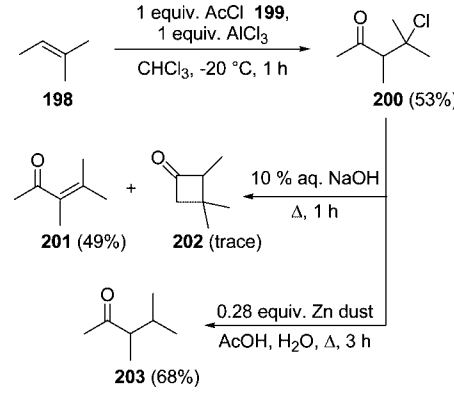
Similarly, β-iodo ketones can be obtained, as exemplified by the treatment of 1,1-diphenylprop-2-en-1-ol **194** with I_2 in the presence of AgOAc, furnishing the targeted ketone **197** through a rearrangement of the initially formed iodonium ion **195** (Scheme 49).[87]

2.4.3. Friedel−Crafts Acylation of Alkenes

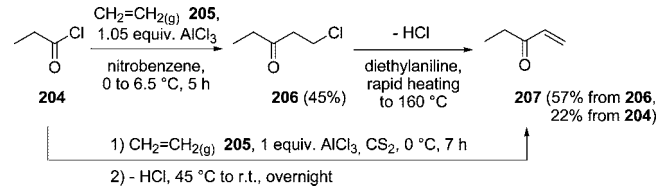
The Friedel−Crafts ketone synthesis in the aliphatic series is a well-known transformation, wherein an acylating agent reacts with an olefin in the presence of a Lewis acid such as $AlCl_3$. The thus obtained intermediary cation, formed according to Markovnikov's rule, is subsequently trapped by a nucleophile, usually chloride (Scheme 50).[88] Treatment of the resulting β-chloro ketones with a base usually provides a good yield of the corresponding α,β-unsaturated ketones. Another frequently effected subsequent transformation is a reductive dehalogenation.

For this type of acylation reactions, anhydrous CH_2Cl_2 or $CHCl_3$ is generally the solvent of choice, as introduced by Baddeley and co-workers.[89] However, solvent free additions have also been reported.[90,91] The strong Lewis acid $AlCl_3$ is the most common acylation promoter, with $FeBr_3$[92] or

Scheme 50



Scheme 51



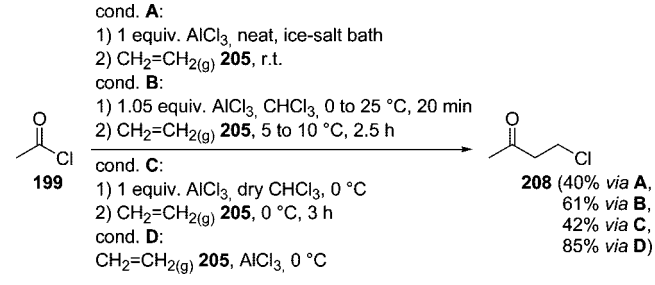
$EtAlCl_2$[93] sometimes being used as an alternative. Moreover, the use of $SnCl_4$,[94] $ZnCl_2$, BF_3, $TiCl_4$, and H_3PO_4 has also been reported.[95]

Additions to Ethylene. A very commonly used Friedel−Crafts acceptor is ethylene, which converts acid chlorides into β-chloro ketones. McMahon and co-workers, for example, synthesized ethyl vinyl ketone **207** by reaction of propanoyl chloride **204** with ethylene **205** and a subsequent elimination of HCl.[96] The intermediately formed ethyl β-chloroethyl ketone **206** was reasonably heat stable up to 50−60 °C (Scheme 51).

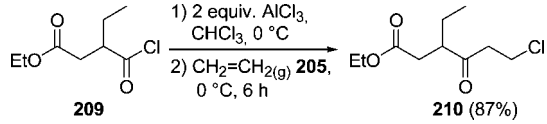
The $AlCl_3$ catalyzed reaction of AcCl with ethylene has been reported to yield 4-chloro-2-butanone with varying success (Scheme 52). Catch, for example, recommended the use of excess AcCl and the absence of solvent, but achieved a mere yield of 40% (**A**).[90] Sondheimer, on the contrary, recorded an improved outcome when utilizing a slight excess of acid chloride and $CHCl_3$ as the solvent (**B**),[97] while Brown obtained only 42% of the desired β-chloro ketone under similar conditions (**C**).[98] A far more successful result was finally reported by Babler (**D**).[99]

Analogously, more complex β-chloro ketones have been prepared by Friedel−Crafts acylation of ethylene with long chain fatty acid chlorides,[100] phenylacetyl chlorides,[101] methylated benzoyl chlorides,[102] and succinic acid derivatives **209** (Scheme 53).[103] Similar conditions have been applied in the synthesis of bis(β-chloroethyl) ketone from 3-chloropropanoyl chloride.[104]

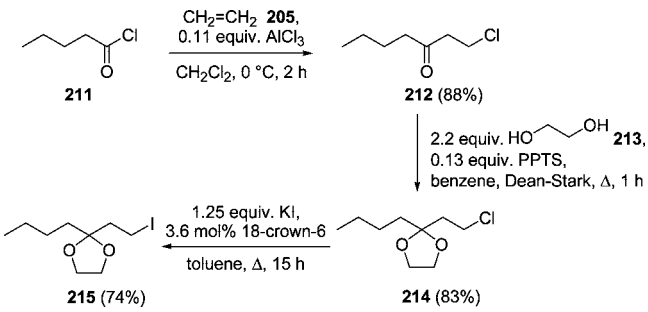
Scheme 52



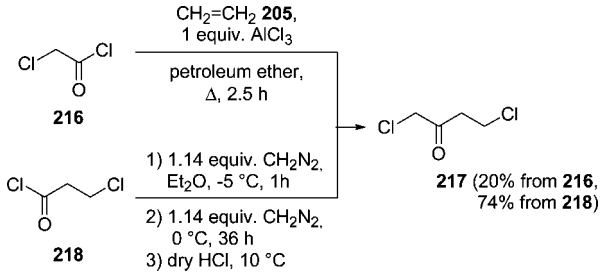
Scheme 53



Scheme 54



Scheme 55



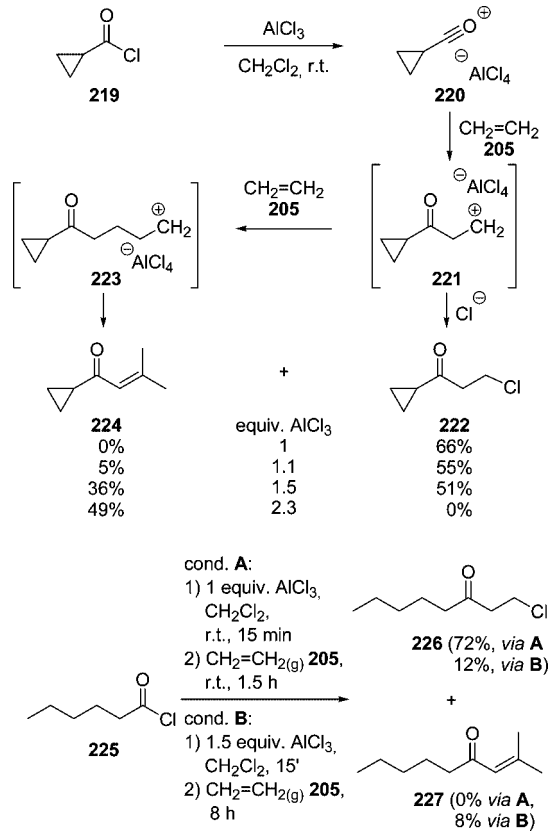
β-Iodinated acetals **215** have been prepared by reaction of acid chlorides **211** with ethylene and a subsequent halogen exchange step (Scheme 54).[105] The intermediate protection of the carbonyl moiety was necessary in the light of a further alkylation step.

An interesting formal comparison can be made between the addition of acid chlorides across ethylene, for which the net result is the insertion of two methylene groups in between the carbonyl and the chlorine moiety, and the Nierenstein reaction, where one methylene group is inserted by the action of CH_2N_2. In the synthesis of 1,4-dichlorobutan-2-one **217**, both strategies were pursued, starting from acid chlorides **216** and **218**, respectively (Scheme 55).[106] The latter approach clearly proved to be superior.

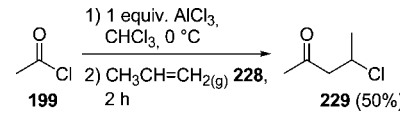
A possible side reaction when performing the Friedel−Crafts ketone synthesis was reported by Donnelly and co-workers. Besides the expected β-chloro ketones **222** and **226**, reaction of acid chlorides **219** and **225** with ethylene in the presence of excess $AlCl_3$ also furnishes rearranged diaddition products **224** (in up to 49%) and **227** (in only 8%), carrying a dimethylvinyl moiety (Scheme 56).[107] This observation could be accounted for by the ambiguous reactivity of carbenium ion **221**, which, in the absence of excess $AlCl_3$, can react with a chloride ion, forming the expected β-chloro ketone **222**. However, when excess $AlCl_3$ is present, the cation is unable to compete with it for chloride ions and instead reacts with a second molecule of ethylene to form a new cation, formally of the type **223**, which rearranges to the nonhalogenated product **224**. Weaker Lewis acids failed to bring about both the Friedel−Crafts acylation of ethylene and the subsequent reaction of a second molecule of ethylene with carbocation **221**. Furthermore, the analogous acylation of propylene did not lead to the diaddition product.

Additions to Substituted Double Bounds. The simplest unsaturated hydrocarbon beyond ethylene is propylene.

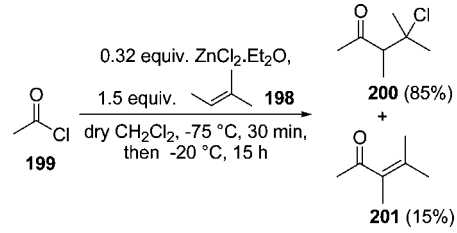
Scheme 56



Scheme 57



Scheme 58

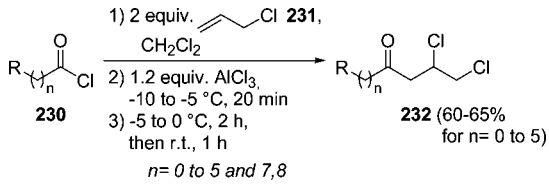


β-Chloro-β-methylketones are usually obtained in a straightforward manner upon reaction of this olefin with acid chlorides in the presense of an acylation promoter. The addition of AcCl to propylene, for example, has been reported by Brown (Scheme 57),[98] Pinder,[108] and Jones.[109]

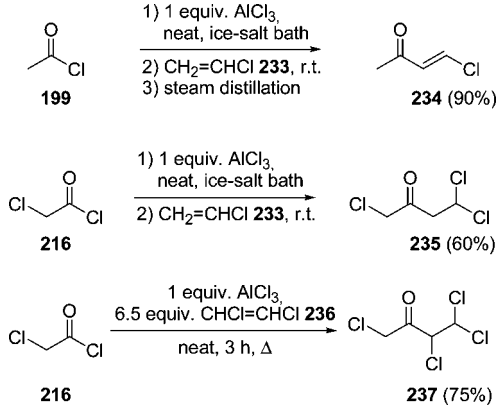
The sterically more encumbered 2-methyl-2-butene **198** proved to be a suitable Friedel−Crafts acceptor in the reaction with AcCl **199**, both under $AlCl_3$[88] (Scheme 50) and $ZnCl_2$ catalysis (Scheme 58).[110] *Via* the latter protocol, however, an appreciable amount of dehydrochlorinated product **201** was formed. Besides, the addition of several acid chlorides to cyclohexene has been reported (see also Stereochemical Considerations).[89]

A straightforward entry toward β,γ-dichlorinated ketones **251** involves the use of allyl chloride **250** as the ene-partner in a Friedel−Crafts reaction. This approach was repeatedly employed by Kulinkovich and co-workers in the synthesis of γ-ketoaldehydes and related compounds (Scheme 59).[111−113]

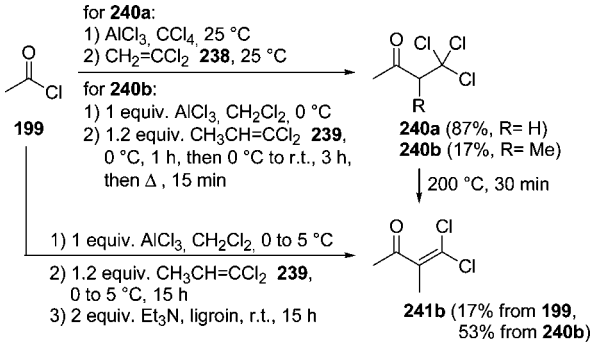
Scheme 59



Scheme 60



Scheme 61



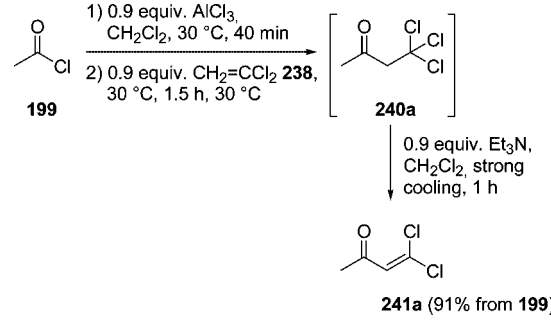
A closely related report was published by Mamedov and co-workers, regarding the synthesis of β,γ-dichloro ketones and their heterocyclization toward furans.[114]

When vinyl chloride is used as the Friedel−Crafts acceptor, preferential formation of β,β-dichloro ketones over their α,β-dichloro isomers has been reported (Scheme 60).[90] Isolation of these 2,2-dichloroethyl ketones, however, proved fairly difficult given their tendency to lose HCl spontaneously, yielding β-chlorovinylketones **253**. Nevertheless, utilizing chloroacetyl chloride **235**, the comparatively stable chloromethyl 2,2-dichloroethyl ketone **254** could be isolated. Furthermore, reaction of **235** with 1,2-dichloroethylene **255** under more drastic conditions provided tetrachloro ketone **256** in reasonably good yield.

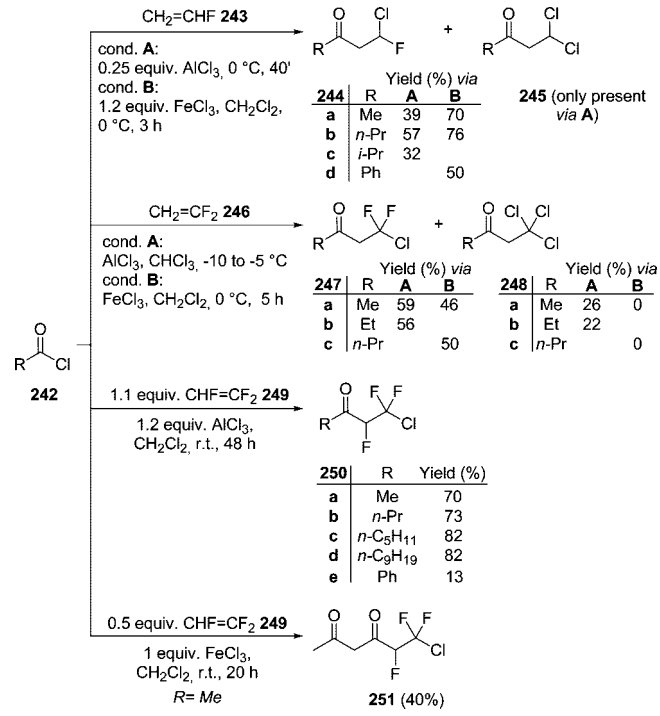
The same regioselectivity in the addition process was obtained by employing vinylidene chloride **238** and 1,1-dichloropropene **239** (Scheme 61).[115] Dehydrochlorination of the thus formed trichloroketones **240a−b** proved to be unexpectedly difficult, requiring heating at 200 °C or prolonged treatment with a base. With Et_3N in ligroin, however, the dehydrohalogenation toward dichloro ketone **241b** proceeded well.

Later, Wilson and co-workers were able to optimize the reaction after discovering that all the $AlCl_3$ has to be complexed with the acyl chloride **199** before adding the vinylidene chloride **238**. In this way, the dichloro ketones

Scheme 62



Scheme 63

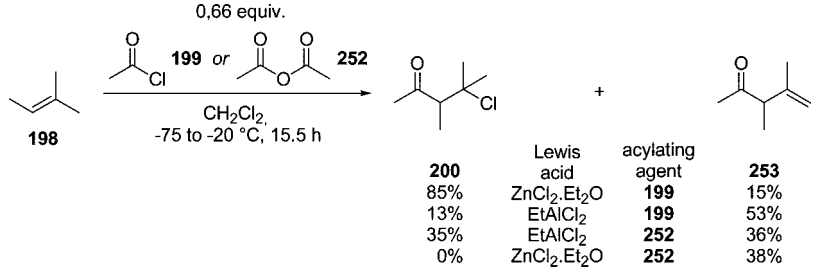


241a could be obtained in high yields upon dehydrochlorination, however, without isolation of the intermediate trichloro ketone **240a** (Scheme 62).[116]

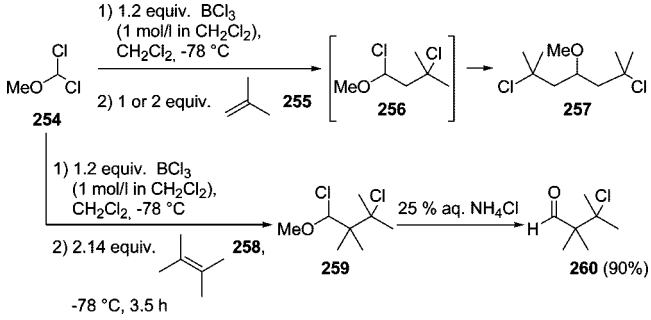
Vinyl fluoride **243** readily reacts with various carboxylic acid chlorides **242** in the presence of $AlCl_3$ to form β-chloro-β-fluoro ketones **244a−d** (Scheme 63).[92] The concomitant formation of the β,β-dichloro side product **245** via a halogen exchange reaction was avoided by the use of $FeCl_3$, moreover delivering higher yields of the desired products **244** (conditions **B**). When vinylidene fluoride **246** was used, $FeCl_3$ again avoided transhalogenation. Using this Lewis acid, however, the yield of the desired ketone was lower than with $AlCl_3$, and acylated condensation products were included in the mixture. Furthermore, vinylidene fluoride failed to react with aroyl chlorides, which are weaker electrophiles than their aliphatic counterparts, in the presence of both $FeCl_3$ and $AlCl_3$. β-Chloro-α,β,β-trifluoro ketones **250a−e** were obtained in rather good yields when reacting trifluoroethene **249** with various acyl chlorides for a prolonged time in a pressure vessel at room temperature, employing $AlCl_3$ as a Lewis acid. When $FeCl_3$ was used instead, reaction of AcCl with trifluoroethene **249** furnished β-diketone **251** as the main product.

Finally, it has to be noted that Lewis acid complexes of acid anhydrides, when treated with olefins, are also able to

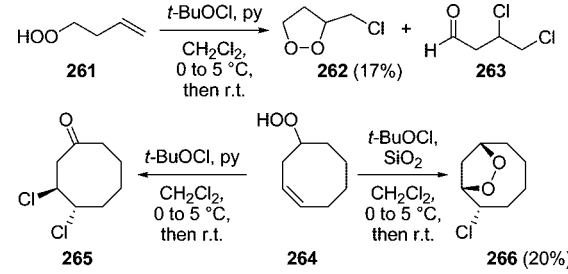
Scheme 64



Scheme 65



Scheme 66



yield β-chloro ketones. According to a direct comparison made by Mayr and co-workers, however, the acylation of the sterically hindered 2-methyl-2-butene **198** proceeded in significantly lower yield with Ac_2O **252** than when using AcCl **199** (Scheme 64).[110] Still, Dubois and co-workers reported that treatment of cyclohexene with Ac_2O in the presence of $ZnCl_2$ does not yield 1-acetyl-2-chlorocyclohexane in a straightforward manner, but rather as one of five products formed during the reaction.[91]

Stereochemical Considerations. The electrophilic addition of AcCl to cyclohexene in the presence of $SnCl_4$ or $AlCl_3$ stereoselectively leads to *trans*-1-acetyl-2-chlorocyclohexane (*trans*:*cis* 3:1), which for stereoelectronic reasons requires an intermolecular chlorine delivery.[94] An identical ratio was reported by Snider and co-workers when the reaction was carried out with $EtAlCl_2$ as the Lewis acid. In this case, however, the dehydrochlorinated β,γ-unsaturated ketone was the major product.[93]

Miscellaneous. Mayr and co-workers introduced dichloromethyl methyl ether **254** as a formylating agent for sterically hindered olefins. When 2-methylpropene **255** is treated with this reagent, the transient chloro ether **256** is more reactive than starting ether **254** and therefore readily adds to another 2-methylpropene molecule (Scheme 65).[117] Under similar conditions, however, tetramethylethylene **258** selectively gives the 1:1 addition product **260** upon hydrolysis, since steric strain obviously inhibits the addition of **259** to a second alkene molecule.

2.4.4. Miscellaneous

In their research on the synthesis of 1,2-dioxolanes **262** *via* treatment of unsaturated hydroperoxides **261** with *t*-BuOCl, Bloodworth and co-workers reported the formation of the corresponding dichlorinated ketones or aldehydes **263** as an important byproduct for most of the investigated substrates (Scheme 66).[118] Moreover, in the case of cyclooct-3-en-1-yl hydroperoxide **264**, *trans*-3,4-dichlorocyclooctanone **265** was the major product, whereas no peroxide formation could be detected. No explanation was provided on the origin of these β,γ-dichlorinated products. When SiO_2 was used instead of pyridine, however, formation of these unexpected dichlorinated compounds could be suppressed and the desired peroxide **266** was obtained (see also Scheme 156).

2.5. Electrophilic Aromatic Substitution

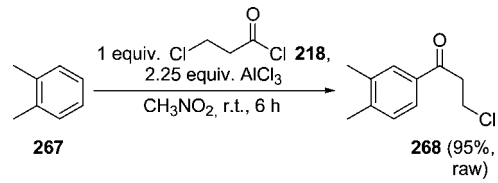
2.5.1. Friedel−Crafts Acylation

In fairly all organic chemistry textbooks, the Friedel−Crafts acylation of benzene is presented as a classic example of an electrophilic aromatic substitution. When an ω-halogenated acid chloride is used as the electrophile, the corresponding ω-halogenated phenones are formed. In this way, Rüger and co-workers prepared β-chlorinated propiophenone **268** starting from *o*-xylene **267** and ω-chloropropionyl chloride **218** (Scheme 67).[102] Much earlier, Conant[119] and Arnold,[120] respectively, synthesized β-chloropropiophenone and 5-β-chloropropionylhydrindene in like manner.

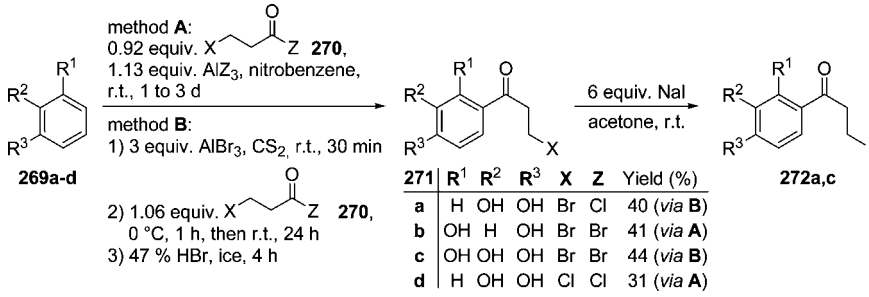
In the Friedel−Crafts reaction, it is common to select a Lewis acid and an acid halide bearing the same halide to prevent halogen exchange. In some cases, however, the combination of an acid chloride and $AlBr_3$ proved to be successful as well (Scheme 68, entry **a**).[121] The combination of an acid chloride and BF_3 has also been reported, albeit with moderate success (Scheme 69).[122] As was the case for the methods discussed in the previous sections, when employing an $S_{E,Ar}$ strategy, β-iodo ketones are often prepared *via* a Finkelstein transhalogenation of the corresponding β-chloro or bromo ketones, obtained through a Friedel−Crafts reaction (Scheme 68).[121]

Regioselective Friedel−Crafts acylations can be conducted by using the directing effect of silyl substituents. In this way, *ipso* substitution takes place (Scheme 70).[123]

Scheme 67

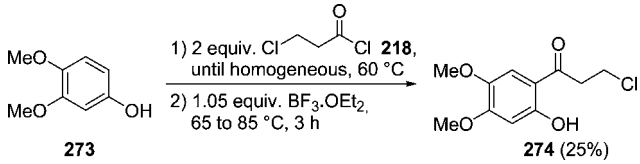


Scheme 68

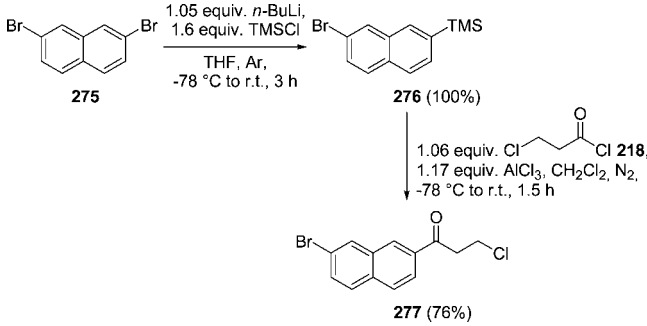


271	R^1	R^2	R^3	X	Z	Yield (%)
a	H	OH	OH	Br	Cl	40 (*via* **B**)
b	OH	H	OH	Br	Br	41 (*via* **A**)
c	OH	OH	OH	Br	Br	44 (*via* **B**)
d	H	OH	OH	Cl	Cl	31 (*via* **A**)

Scheme 69



Scheme 70



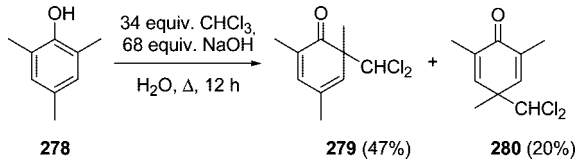
2.5.2. Reimer−Tiemann Reaction

A classical method for the formylation of phenols is the treatment with $CHCl_3$ in alkaline medium. In this so-called Reimer−Tiemann reaction, the initially generated dichlorocarbene, a one carbon electrophile, reacts with the electron-rich phenolic ring to form a dichloromethyl substituted phenol. Under basic conditions, the latter species is readily hydrolyzed into a phenolic aldehyde.

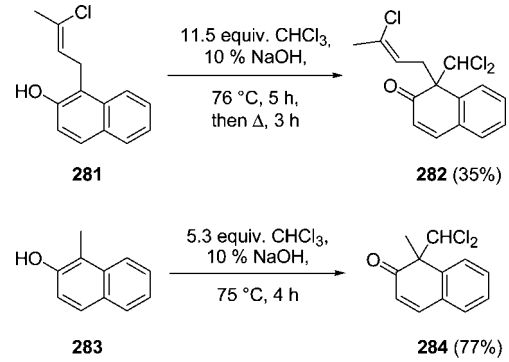
With *ortho*- and *para*-substituted phenols, however, rearomatization *via* proton-loss cannot occur, and β- or δ-dihalogenated cyclohexadienones are formed. The first case where both possible dienones were isolated from the reaction mixture was recorded by Wynberg and co-workers.[124] Treatment of mesitol **278** under typical Reimer−Tiemann conditions provided, after workup, an oily fraction which contained the 2- and 4-(dichloromethyl) ketones **279** and **280** in a ratio of 7:3 (Scheme 71). It is noteworthy that the reduction of the reaction time from 12 to 1 h caused a decrease in the yield from 68 to 48%, whereas the ratio of the isomers changed from 7:3 to 40:1.

Dodson and co-workers used this reaction in the synthesis of polycyclic compounds starting from 1-alkyl-2-naphthols.[125]

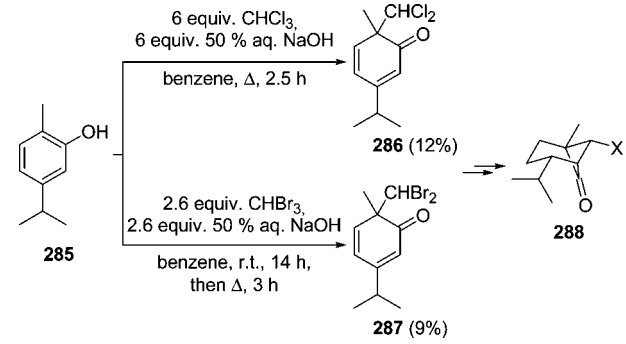
Scheme 71



Scheme 72



Scheme 73



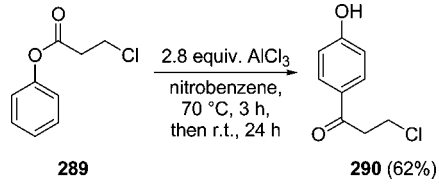
In this way, 1,1-disubstituted 2-keto-1,2-dihydronaphthalenes were obtained in various yields (Scheme 72). Interestingly, compound **284** proved to be relatively stable to H_2SO_4, whereas similar treatment of **282** resulted in polymeric materials.

En route to bicyclic ketones **288**, an often pursued strategy is the formation of β-dihalogenated cyclohexadienones **286** and **287** through Reimer−Tiemann reactions of substrates such as carvacrol **285** (Scheme 73). Drawbacks of this methodology are the low yield, the constraint to six membered dienones, and the fact that the introduced halomethyl substituent is necessarily a dichloromethyl or dibromomethyl group.[126]

2.5.3. Fries Rearrangement

This particular intramolecular Friedel−Crafts acylation enables the preparation of hydroxyphenones from phenolic esters. In one example, 3-chloro-4′-hydroxypropiophenone **290** was obtained from the corresponding ester **289** (Scheme 74).[127]

Scheme 74



289 **290** (62%)

2.6. Radical Reactions

2.6.1. Radical Halogenation

One of the most apparent radical reactions is the free radical halogenation of alkanes. The regiochemistry of this type of transformation is controlled by the preferential formation of the most stable radical intermediate and can often satisfactorily be controlled when suitable functionalities are present. Therefore, allylic positions are of the most common halogenation sites (Scheme 75).[128] A widespread protocol to accomplish this transformation involves the use of NBS in a nonpolar solvent, a procedure known as the Wohl−Ziegler bromination.[129,130] Again, thus obtained bromides can be converted into their fluorinated analogues *via* transhalogenation.[131]

Oxidative halodecarboxylations of the Hunsdiecker type also proceed *via* radical substitution. Classically, the carboxylic acid is treated with Br_2 and HgO in CCl_4, delivering the corresponding bromide after loss of CO_2. Numerous alternative conditions for this transformation have been proposed, such as the use of lead tetraacetate and NCS. In this way, Huang and co-workers prepared bicyclic β-chloro ketone **294** from the corresponding acid **293**, a transformation which proved to be a key step in the synthesis of a new bridgehead enone (Scheme 76).[132] Since many free-radical reactions have been observed at bridgehead carbons, it is clear that the free radical can possess a nonplanar geometry.

Russel and co-workers investigated the free radical chain substitution reactions (S_H2') of tin(IV) enolates **295** and **298** with tetrahalocarbons under photoactivation (Scheme 77).[133] Transformations with CCl_4 and $BrCCl_3$ proceeded in good yield and gave the expected bimolecular homolytic substitution products **296a**,**b** and **299a**,**b**, whereas CBr_4 and PhSSPh failed to react. Unstable 2-(dibromomethyl)cyclohexanone **296c**, the primary reaction product of stannane **295** and $CHBr_3$, could be detected spectroscopically but underwent dehydrobromination upon distillation, to furnish the unsaturated ketone **297c** in rather low yield. Reaction of stannane **298** with $CHBr_3$ provided not only dibromomethyl aldehyde **299c**, the expected S_H2' product, but also epoxide **300c**. Formation of the latter product was suggested to occur *via* an initial α-addition of the $Br_2CH^{\bullet}$ radical, followed by internal displacement (S_Hi) of the $Bu_3Sn^{\bullet}$ radical.

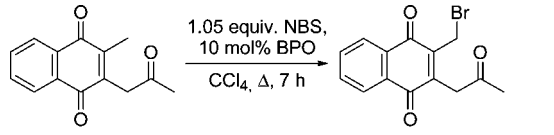
2.6.2. Ring-Opening and Expansion

Ring-opening and expansion methods provide interesting tools for the synthesis of medium and large carbocyclic natural products. Very often, this strategy involves the vicinal annulation of a new carbocyclic ring onto the existing molecular framework, followed by a regioselective cleavage of the ring-fusion bond.

Cerium(IV) ammonium nitrate (CAN) has found wide application in carbon−heteroatom bond-forming reactions, usually involving the generation of heteroatom-centered radicals from the parent anions. As such, Flowers and coworkers were able to obtain β-halogenated ketones **302a**−**f** from cyclopropanols **301a**−**c** by reaction with a halide salt (NaI, KBr) and CAN (Scheme 78).[134] The yields for iodides **302a**,**c**,**e** were excellent (86−96%). The corresponding bromides **302b**,**d**,**f** were obtained in good yield after switching to a two-phase solvent system, because the significantly harder to oxidize bromide anion made the oxidation of the alcohol a competing reaction. Furthermore, unsymmetrical cyclopropanols **304** regioselectively opened *via* attack at the least hindered side. Still, the bridgehead bicyclic alcohol **307a** underwent a more clean ring expansion to the β-iodinated cycloalkanone **308** after conversion into its trimethylsilyl ether **307b**.

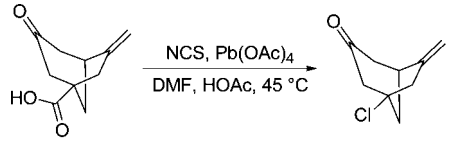
A one-carbon ring homologation of cyclic ketones with formation of β-chlorocycloalkanones **310a**−**g** was presented by Saegusa and co-workers (Scheme 79).[135,136] 1-Silyloxybicyclo[*n*.1.0]alkanes **309a**−**g**, readily prepared

Scheme 75



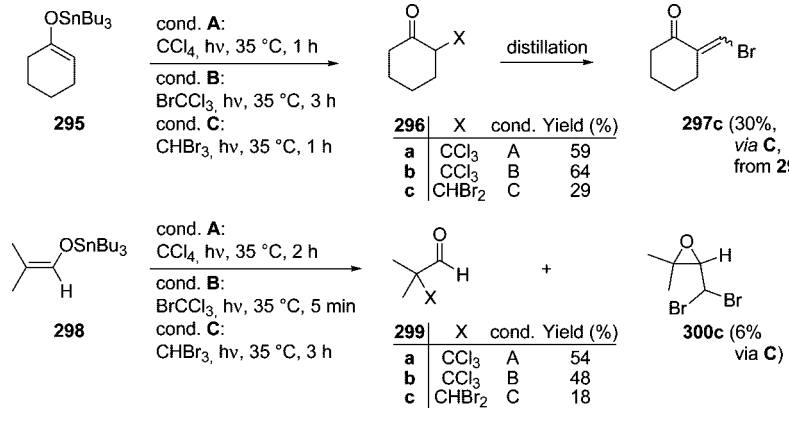
291 **292** (100%, purity >95%)

Scheme 76



293 **294** (82%)

Scheme 77



295

296	X	cond.	Yield (%)
a	CCl_3	A	59
b	CCl_3	B	64
c	$CHBr_2$	C	29

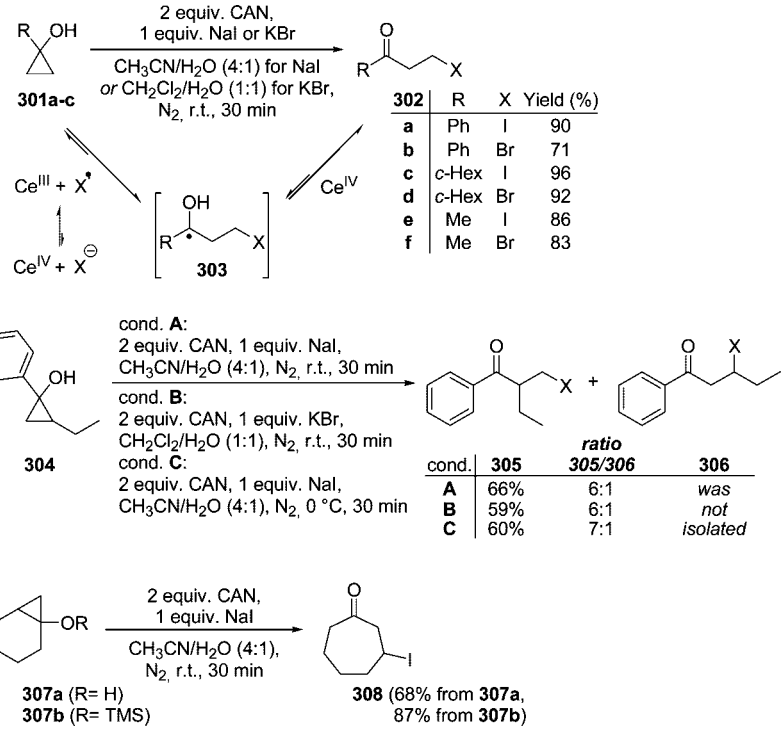
297c (30%, *via* **C**, from **295**)

298

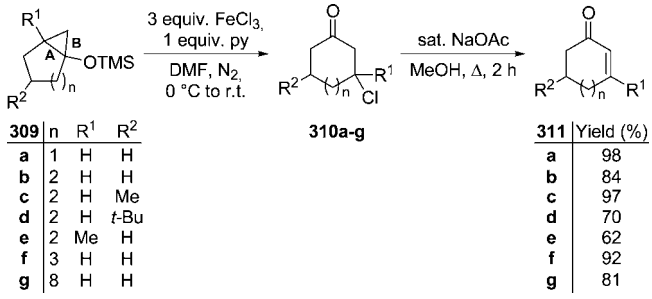
299	X	cond.	Yield (%)
a	CCl_3	A	54
b	CCl_3	B	48
c	$CHBr_2$	C	18

300c (6% via **C**)

Scheme 78



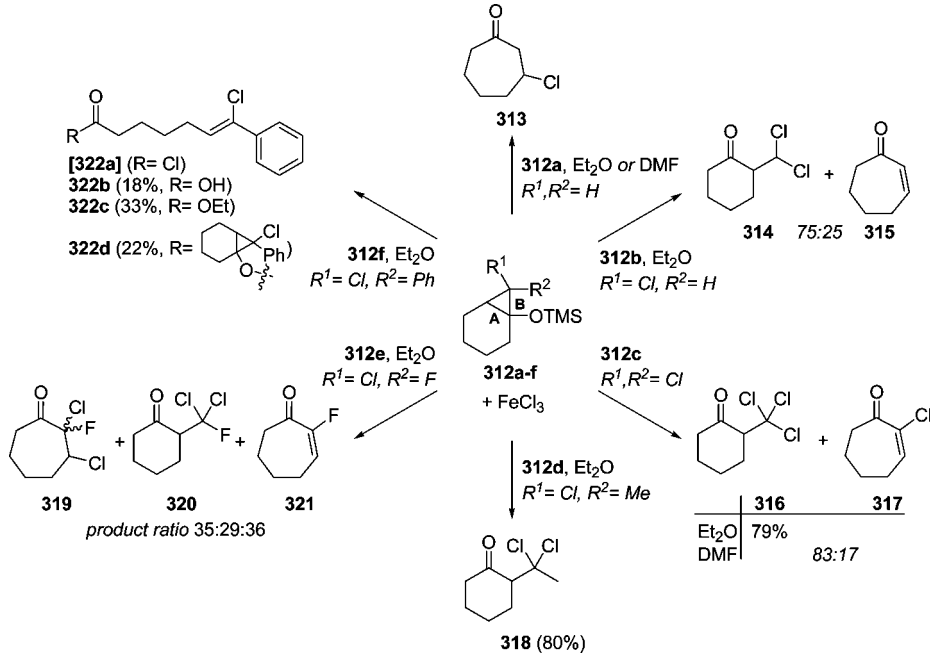
Scheme 79



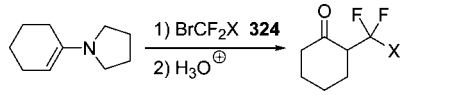
by the Simmons−Smith reaction of silyl enol ethers of cycloalkanones, were oxidized with $FeCl_3$, leading to the corresponding β-chlorocycloalkanones **310a**−**g** in good yields. An alkoxy radical mechanism was suggested for the ring expansion step. Upon dehydrohalogenation with a saturated solution of NaOAc in MeOH, the corresponding cyclic enones were obtained.

In the case of substituted cyclopropanols, the reaction occurs by cleavage of the more substituted cyclopropane bond (bond **A** in Scheme 79). The influence of vicinal heteroatoms (R^3, R^4) on the regioselectivity of the cleavage was investigated in more detail by Blanco and co-workers (Scheme 80).[137] Comparison of the results for nonchlorinated, monochlorinated, and dichlorinated silyloxybicycloheptanes **312a**,**b**,**c** clearly points out the increasing tendency to cleave

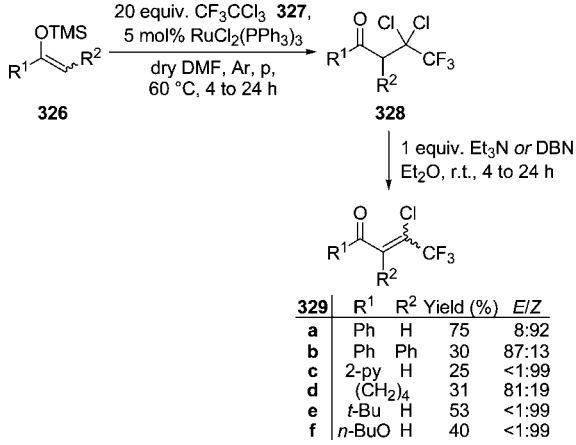
Scheme 80



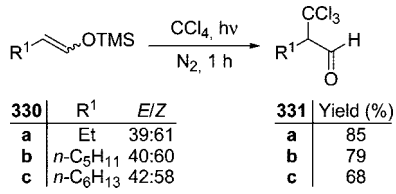
Scheme 81



Scheme 82



Scheme 83



bond **B** when heteroatoms are present. Furthermore, the selective formation of cyclohexanone **318** reveals a similar directing behavior of the methyl group. A poor regioselectivity was obtained with fluorine and chlorine substituents on the cyclopropane moiety (**312e**), because the presence of the fluorine atom makes the cleavage of bond **A** easier. Chlorophenylsilyloxycyclopropane **312f** behaved totally differently, resulting in products from cleavage of both the **A** and **B** bonds. Presumably, acid chloride **322a** is the initial reaction product, which subsequently hydrolyzes to **322b** or reacts with diethyl ether or a starting bicycloalkane, providing **322c** and **322d**, respectively.

2.6.3. Miscellaneous

When enamines are treated with $BrCF_2X$ (X = Br, Cl, CF_2Br) and the reaction mixture is subjected to hydrolysis, α-perhaloalkyl ketones **325a**−**c** are formed (Scheme 81).[138] Wakselman and co-workers proposed a radical chain mechanism for this transformation, which is supported by the fact that nitrobenzene inhibits the reaction.

Eguchi and co-workers presented $RuCl_2(PPh_3)_3$ as a useful catalyst for the synthesis of β,β-dichloro-β-(trifluoromethyl) carbonyl compounds **328** from trimethylsilyl enol ethers **326** and CCl_3CF_3 **327** (Scheme 82).[139] The Ru(II)−Ru(III) catalytic cycle was found to be superior to its Cu(I)−Cu(II) counterpart. The intermediate β,β-dichloro ketone underwent a ready dehydrochlorination upon treatment with base, furnishing β-chloro-β-(trifluoromethyl) enones **329a**−**f**.

Reaction of silyl enol ethers **330** with CCl_4 under photoirradiating conditions gives rise to trichlorinated aldehydes **331**, derived from the addition of the trichloromethyl group to the ene moiety of the silyl substrates (Scheme 83).[140] Since these transformations are enhanced in a nonpolar solvent and suppressed by the addition of $LiClO_4$, they may occur *via* homolytic scission of the C−Cl bond.

Much earlier, the reaction of CCl_4 with enamine **332** had been investigated by Elkik and co-workers (Scheme 84).[31,141] In the presence of light, formation of an unstable iminium salt **333** was observed, which could easily be hydrolyzed to its free, crystalline aldehyde **334**. Normal chain enamines **335a**−**b**, on the contrary, only reacted with CCl_4 upon heating and addition of a base, thus providing α-alkylated dichloroacroleins **338a**−**b**.

2.7. Ring-Opening and Ring Expansion

2.7.1. Cyclic Acetals

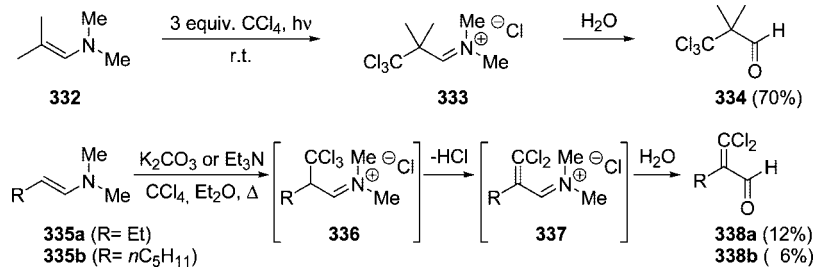
When suitable conditions are chosen for the cleavage of cyclic acetals, the deprotected hydroxyl groups will undergo immediate substitution for a halide. Brooks and co-workers envisaged this transformation when treating bis-1,3-dioxane **339** with PPh_3 and Br_2 in refluxing benzonitrile (Scheme 85, route **A**).[142] The desired tetrabromide **343**, however, was only obtained in a disappointing yield due to extensive decomposition. Switching to chlorobenzene as the solvent (route **B**), bis(bromomethyl ether) **340** was formed, a stable product, except toward hydrolysis. In two extra steps, *via* the diether **342**, tetrabromide **343** was obtained in reasonable yield.

2.7.2. Epoxides

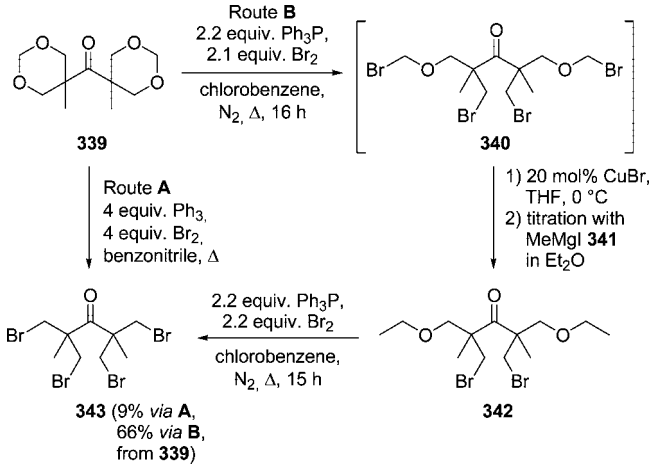
Epoxides are very useful intermediates in numerous synthetic pathways and are readily opened by nucleophilic attack under basic as well as acidic conditions. In their search for selective reactions of substrate **344** and its analogues with Lewis acids, Zwanenburg and co-workers observed the interesting behavior of $SnCl_4$ (Scheme 86).[143]

Treatment of epoxy diazomethyl ketone **344** with a slight excess of Lewis acid produces chlorohydrin **345**, with retention of the stereochemistry at both carbon atoms of the

Scheme 84



Scheme 85



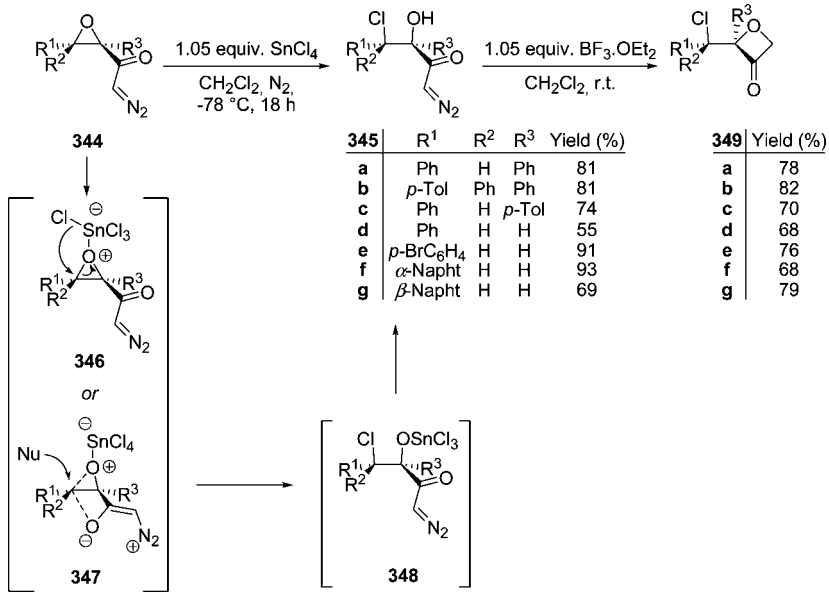
epoxide. This implies an attack of the halide in a selective *syn* fashion, which was attributed to the halide releasing nature of the Lewis acid in intermediate **346**. An alternative mechanism, supported by earlier suggestions for similar reactions, involves the anchimeric assistance of the diazoketone moiety, facilitating a *syn* attack of a chloride on species **347**. Furthermore, intramolecular alcoholysis of the thus obtained chlorohydrins **348** upon treatment with BF_3, produced oxetanones **349**. In some cases, the reaction of the epoxides with $SnCl_4$ was very sluggish at −78 °C, whereas, at higher temperature, the oxetanones **349** were directly obtained without the possibility to isolate the intermediate chlorohydrins.

Analogously, treatment of epoxide **350** with excess $TiCl_4$ by Majetich and co-workers led to the formation of chlorohydrin **351** as a single diastereoisomer, with allylic alcohol **352** as a minor side product (Scheme 87).[76] In this case, the retention of the stereochemistry was explained by assuming an S_N1 mechanism, involving an attack on cation **353** from the sterically more accessible front face of the molecule, or *via* an S_Ni displacement by the chloride ligand of the coordinated Lewis acid in intermediate **354**.

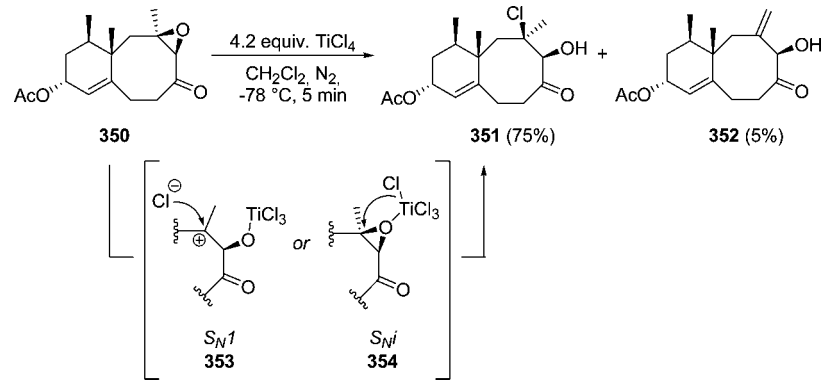
2.7.3. Cycloalkanes

2.7.3.1. Cyclopropanes. *Cyclopropanols and Cyclopropyl Ethers.* The ready electrophile-induced opening of cyclopropanols was extensively described by De Puy and co-workers (Scheme 88).[144] In an initial experiment, these researchers demonstrated that 1,2,2-trimethylcyclopropanol **355** undergoes a fast and exclusive C(1)−C(3) bond cleavage upon treatment with various halogen electrophiles under mild conditions. To investigate whether the direction of the ring-opening is a function of the steric requirements of the incoming halogen or is determined by the relative stability of the incipient carbanion, if involved, the opening of *trans*-

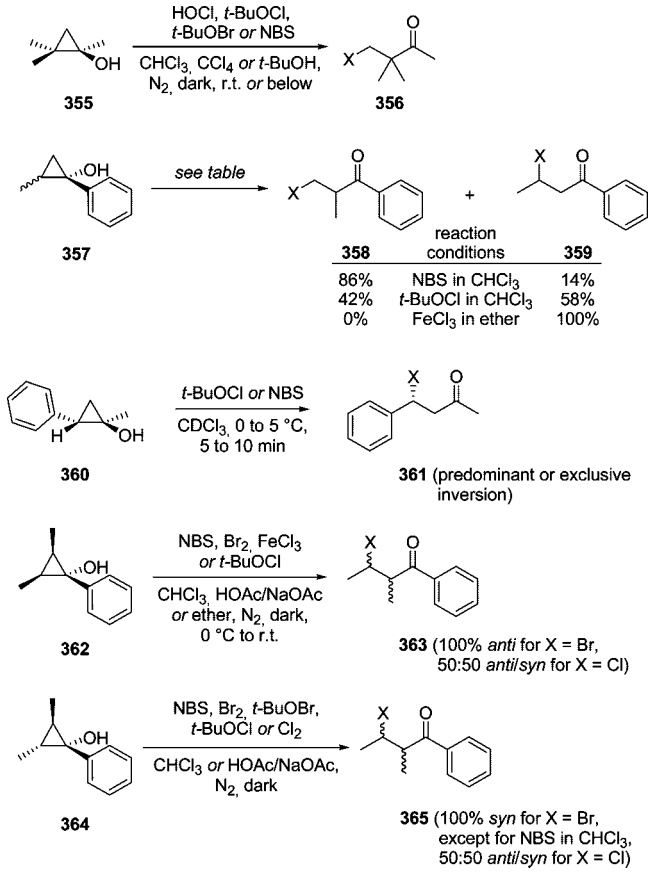
Scheme 86



Scheme 87



Scheme 88

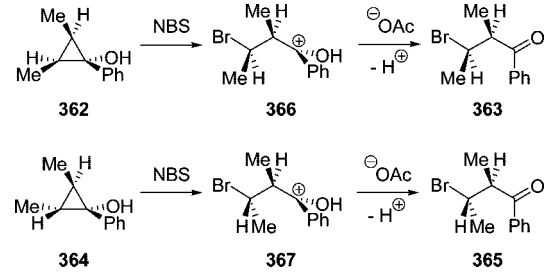


2-phenyl-1-methylcyclopropanol **360** was examined. Indeed, it was anticipated that the steric and electronic factors would be in opposition for this substrate. In this case, selective C(1)−C(2) bond cleavage was reported. An analogous investigation for 1-phenylcyclopropanol **357** gave the expected results for NBS and $FeCl_3$, with the reactions proceeding respectively *via* an attack of the electrophile on the least substituted carbon and *via* the generation of the most stable radical.[145] Although the results using *t*-BuOCl were difficult to account for, the addition of radical inhibitors did not alter the product distribution.

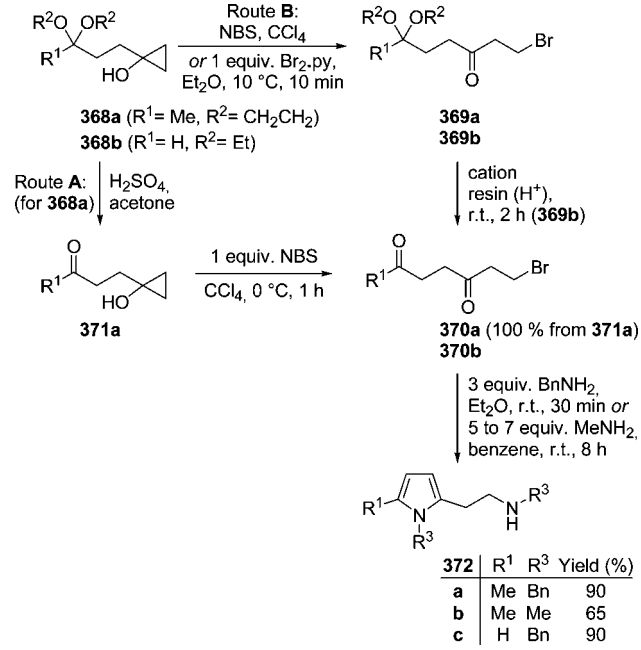
Next, the stereochemistry of the ring cleavage was investigated on *cis*,*trans*- and *trans*,*trans*-2,3-dimethyl-1-pheynylcyclopropanols **362** and **364**.[144] Interestingly, the bromination reactions (except for the treatment of **364** with NBS in $CHCl_3$) proceed in a stereospecific manner, while all chlorinating agents give identical mixtures of diastereomeric chloro ketones. Since $FeCl_3$, a reagent known to induce free-radical ring-openings in cyclopropanols, gave the same product mixture as the chlorinating agents, it was suggested that the latter reagents might not act through ionic paths. In contrast, cleavage by protons occurs with retention of configuration. Furthermore, cleavage of 2-phenyl substituted cyclopropanol **360** gives predominant or exclusive inversion at the benzylic carbon, with both electropositive bromine and chlorine.[145] Thus, it is clear that the stereochemistry of electrophilic reactions of cyclopropanols depends in some way on the nature of both the electrophile and the substrate.[146]

A theoretical study on electrophilic additions to cyclopropanes was performed by Yamabe and co-workers.[147] These researchers observed an inversion of the stereochemical configuration of the reaction center attacked by the electrophile in the treatment of cyclopropanols **362** and **364**

Scheme 89



Scheme 90



372	R^1	R^3	Yield (%)
a	Me	Bn	90
b	Me	Me	65
c	H	Bn	90

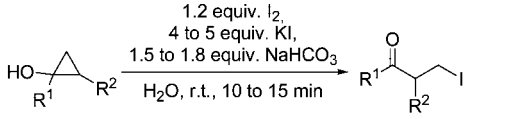
with brominating reagents (Scheme 89), in accordance with the report of De Puy and co-workers.

This type of halogenative ring-opening of cyclopropanols has successfully been applied to several syntheses, with both brominating[148−150] and iodinating[64] reagents. In a new approach toward 2-(2-aminoethyl)pyrroles **372**, cyclopropanol **368a** underwent a successful deprotection−bromination sequence affording β-bromo diketone **370a** (Scheme 90, Route **A**).[150] However, when analogue **368b** was subjected to the deprotection conditions of route **A**, formation of a cyclic acetal was observed. Reversing the order of the two steps (Route **B**) provided an outcome toward 6-bromo-4-oxo hexanal **370b**. Both β-bromo ketones proved unstable and readily lost HBr upon mere contact with an adsorbent for chromatography. Hence, they were immediately converted into the targeted 2-(2-aminoethyl)pyrroles **372a**−**c**.

In another example, β-iodo ketones **374a**−**d** were conveniently prepared from 1,2-disubstituted cyclopropanols **373a**−**d** by reaction with I_2 in an aqueous solution of KI and $NaHCO_3$ (Scheme 91).[64] The yields of this transformation were excellent, and no isomeric products with the iodine atom bound to a secondary carbon atom could be detected.

However, in other cases, the procedure cannot be applied, since cyclopropanols are fairly unstable and not readily obtainable. Moreover, the hydrogen halide formed during the course of the reaction can decompose the starting material, and the addition of a base, to circumvent this problem, can cause dehydrohalogenation of the product. Therefore, Murai and co-workers proposed the readily

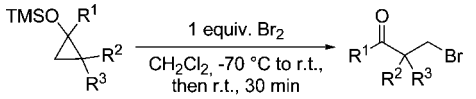
Scheme 91



373	R^1	R^2
a	Me	*n*-Pr
b	*n*-Pr	Me
c	*i*-Pr	Me
d	*t*-Bu	Me

374a-d (95-100%)

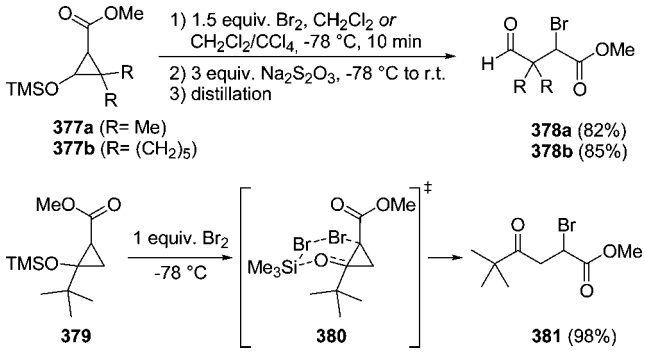
Scheme 92



375	R^1	R^2	R^3
a	Ph	H	H
b	*t*-Bu	H	H
c	Ph	Me	H
d	$(CH_2)_4$		Me

376a-d (quant.)

Scheme 93



377a (R= Me)
377b (R= $(CH_2)_5$)

378a (82%)
378b (85%)

379 **380** **381** (98%)

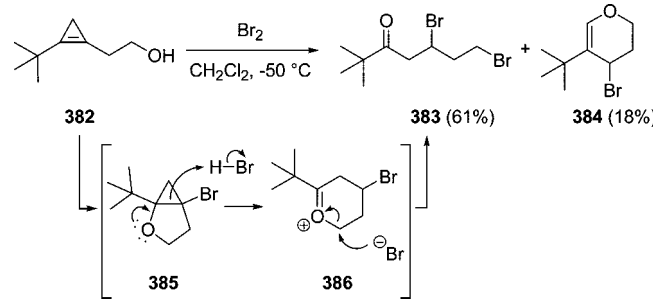
obtainable trimethylsilyl cyclopropyl ethers **375** as a synthetic equivalent of cyclopropanols (Scheme 92).[151] The only byproduct of the bromination reaction of these substrates is the neutral and easily removable TMSBr.

Likewise, Wenkert and co-workers reported thoroughly on the halogenative and protolytic cleavage of bicyclic cyclopropyl silyl ethers, two new procedures for the formation of α-(halomethyl)cycloalkanones.[126] Furthermore, fluoride ion-mediated ring-opening gave not only halide solvolysis products but also protolysis products.

Donor−Acceptor Substituted Cyclopropanes. The easily available methyl 2-silyloxycyclopropanecarboxylates, as well as other vicinally donor−acceptor-substituted cyclopropanes, are very valuable building blocks in organic synthesis. These substrates possess a special versatility to give, upon ring-opening, a range of 1,4-difunctionalized compounds, which can hardly be obtained by other methods with the same simplicity and flexibility in view of the substitution pattern.

α,β-Unsaturated-γ-ketoesters are incorporated in many macrolide antibiotics and can serve as dienophiles in the Diels−Alder reaction. These compounds are accessible from silyloxy substituted methyl cyclopropanecarboxylates by cleavage with Br_2 and subsequent dehydrobromination. However, when 3,3-disubstituted cyclopropanes **377** are used, the elimination cannot take place, and the polyfunctional β-bromo aldehydes **378** are obtained (Scheme 93).[152] In all of the investigated reactions, that cyclopropane bond is cleaved which is activated by the vicinal location of both the donor and acceptor substituent. This regiochemistry may best be rationalized by assuming a transition state similar to

Scheme 94



382 **383** (61%) **384** (18%)

385 **386**

380. However, neither the possibility of a stepwise process nor an autocatalytic effect of TMSBr was excluded.

Miscellaneous. Bromination of cyclopropene **382** gives β,δ-dibromo ketone **383** as the major, and dihydropyran **384** as the minor, product (Scheme 94).[153] Formation of the former compound was proposed to involve an addition of Br^+ to the less hindered end of the π-bond, followed by intramolecular trapping by the alcohol moiety. Protonation of the 1,5-bond of the thus formed tetrahydrofuran **385** by the acid generated in the previous step and cleavage of the oxonium ion **386** by bromide could then lead to the dibrominated ketone **383**.

2.7.3.2. Cyclobutanones. The synthetic accessibility and high reactivity of cyclobutanones have marked these compounds as valuable synthetic reagents. Next to useful transformations initiated by nucleophilic addition to the carbonyl moiety and resulting in ring expansion, contraction, or opening, also electrophilically initiated rearrangements have been reported.

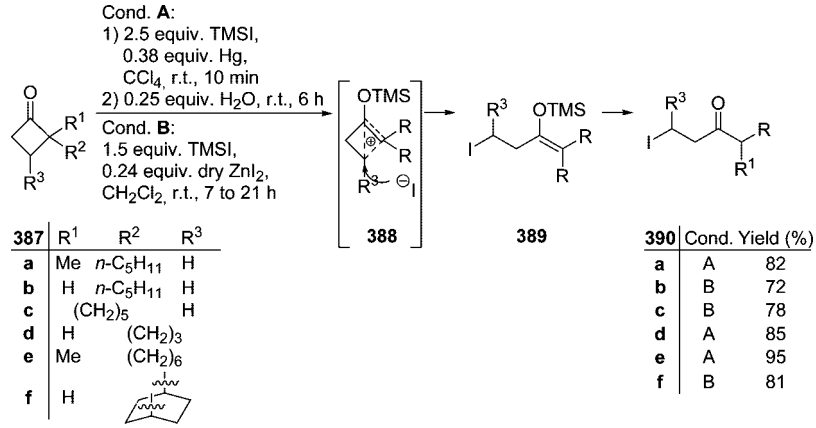
In this context, Miller and co-workers introduced TMSI as a potent reagent for the regioselective ring cleavage of a wide variety of cyclobutanones **387a−f**, giving rise to the corresponding β-iodo ketones **390a−f** (Scheme 95).[154] The presence of ZnI_2 or $Hg-H_2O$ as a catalyst significantly increases both reaction rate and yield. α,α-Disubstitution is not essential for a successful rearrangement, since monosubstituted derivative **387b** as well as fused ring compounds **387d−f** also open regioselectively. The latter observation is particularly interesting, since it represents a simple two carbon cyclohomologation of a cyclic olefin to β-functionalized cycloketones *via* an intermediate olefin−ketene cycloadduct. A mechanistic hypothesis was proposed to account for the regioselectivity of the rearrangement, involving the preferential formation of the more substituted enol or trimethylsilyl enol ether **389**.

2.7.3.3. Miscellaneous. Reaction of nopinone **391** with HCl gas affords trichloride **394**, for which the relative stereochemistry was determined by X-ray crystallography (Scheme 96).[155] The racemic nature of this trichloro ketone, obtained from optically active (+)-nopinone **391**, is consistent with a reaction involving the intermediacy of achiral cyclohexanone **392**, which subsequently undergoes an intermolecular aldol condensation and stereoselective addition of HCl. Support for the proposed mechanism came from the isolation of intermediate **393** from the reaction mixture and its successful conversion with HCl into trichloro ketone **394**.

2.7.4. Ozonides

Mono-ozonolysis of dienes such as isoprene **395** can furnish the two possible unsaturated secondary ozonides **396** and **397** (Scheme 97).[156] As shown by Griesbaum and co-

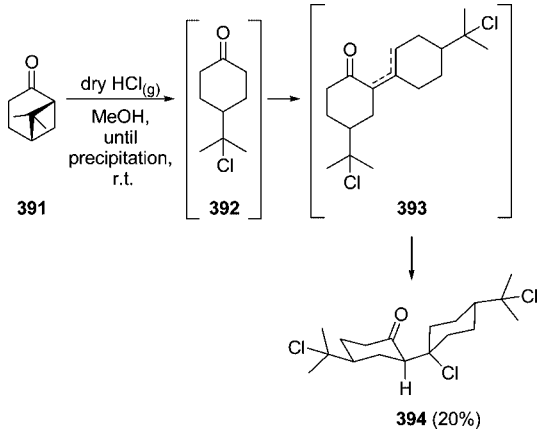
Scheme 95



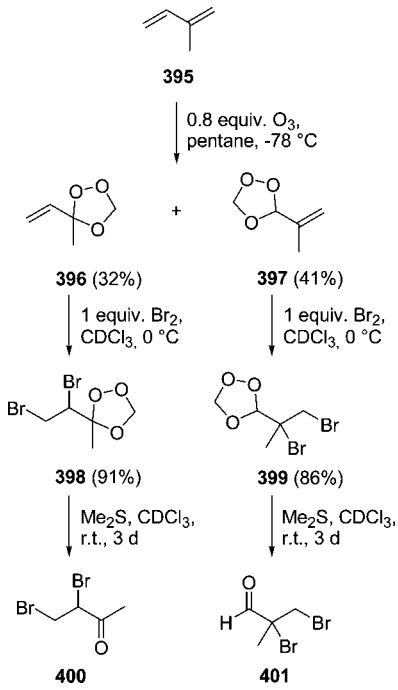
387	R^1	R^2	R^3
a	Me	*n*-C_5H_{11}	H
b	H	*n*-C_5H_{11}	H
c		$(CH_2)_5$	H
d	H	$(CH_2)_3$	
e	Me	$(CH_2)_6$	
f	H		

390	Cond.	Yield (%)
a	A	82
b	B	72
c	B	78
d	A	85
e	A	95
f	B	81

Scheme 96



Scheme 97



workers, the latter species can easily be brominated, resulting in the formation of dibromoozonides **398** and **399**. Subsequent treatment with Me_2S induces the well-known reductive ring-opening reaction and gives rise to dibrominated ketone **400** and its aldehyde isomer **401**.

2.7.5. Ring Expansion

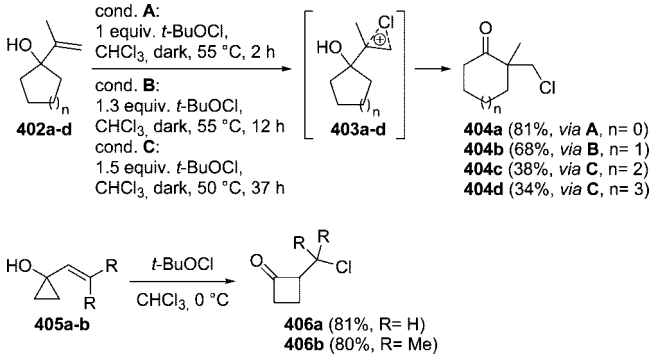
The homologation of alicyclic systems is often effected by cationic methods, with the Demjanov reaction and pinacol rearrangement being notable examples. These transformations proceed *via* the generation of a carbenium ion character on a carbon atom attached directly to the ring, whereupon the ring enlargement produces a new carbenium ion with lower energy.

On the basis of these observations, Johnson and co-workers introduced a new ring expansion protocol, involving the addition of electrophiles, *in casu* electropositive halides, to 1-vinylcycloalkanols **402a−d** (Scheme 98).[157,158] The reaction products are 2-chloromethyl cycloalkanones **404a−d**. In the search for the most suitable halide source, *t*-BuOCl gave clean conversions, in contrast to Br_2 or Cl_2. Furthermore, it was reported that Cl_2 promotes ring enlargement to a greater extent than Br_2, probably due to the increased stability of the intermediate carbenium ion **403**. A decreasing yield is observed with an increasing ring size. Related ring-expansion reactions on lower members of the 1-alkenylcycloalkanol series **405a−b** were later reported by Wasserman and co-workers.[159]

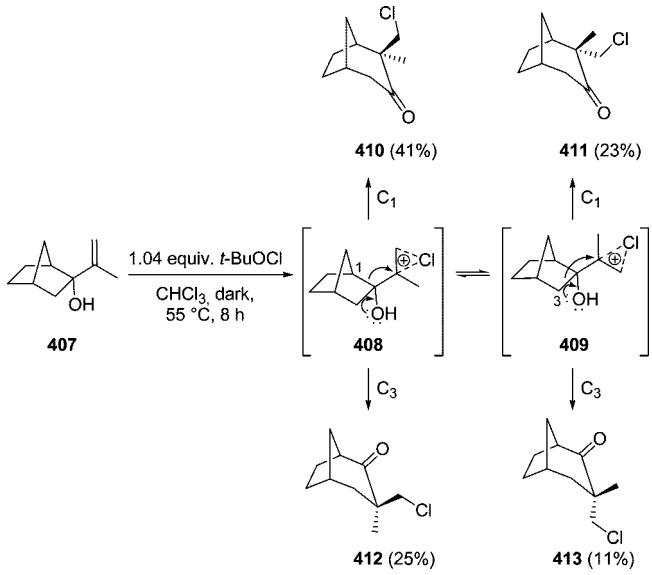
More demanding substrates that successfully undergo ring expansion upon treatment with *t*-BuOCl are 1-isopropenyl-1-indanol and *exo*-2-isopropenyl norbornan-2-ol.[158] Analogously, 1-ethynylcyclopropanol could be transformed into 2-chloromethylenecyclobutanone in moderate yield.

A mechanistic study of this transformation was undertaken by Johnson and co-workers (Scheme 99).[158,160] When subjected to the hypochlorite-induced ring expansion, *exo*-2-isopropenylnorbornan-2-ol **407** gave a mixture of four isomeric ketones. Preferential bridgehead migration (C(1) migration) was rationalized by assuming a nonconcerted mechanism involving intermediate carbenium ions **408** and **409**. Indeed, electronic considerations might favor migration of the more electron-rich bridgehead carbon to a carbon center with a poor leaving group, as found in chloronium ions. This is supported by the observations of Wasserman and co-workers, who also reported the preferential migration of the more substituted carbon atom.[161] As expected, selectivity was higher in solvents with a lower dielectric constant, since there is less carbenium ion stabilization in more apolar media. Further arguments in favor of a nonconcerted mechanism with some carbenium ion character in the transition state were again given by Johnson and co-workers.[158]

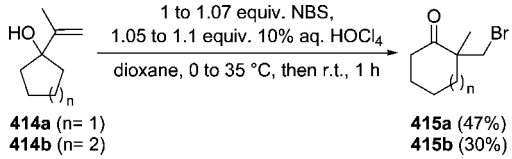
Scheme 98



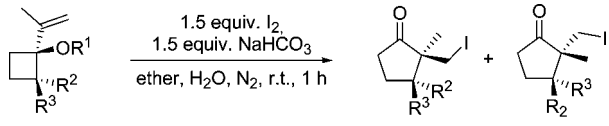
Scheme 99



Scheme 100



Scheme 101

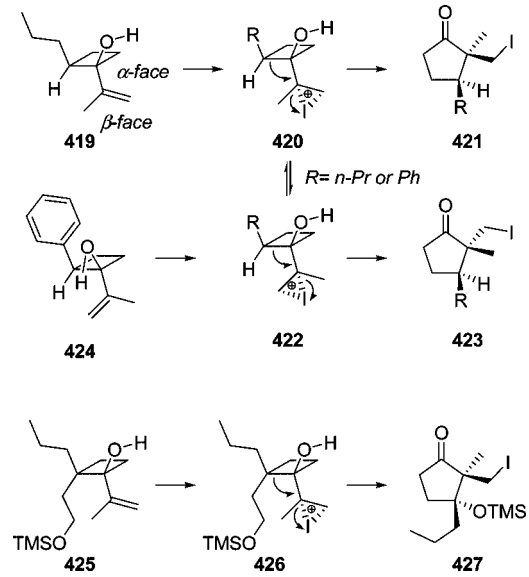


416	R^1	R^2	R^3	417	418
a	H	H	n-C_7H_{15}	40	39
b	H	H	Ph	39	55
c	H	H	$(CH_2)_3CH{=}CHCO_2Me$	37	36
d	H	CH_2OTBS	$(CH_2)_3CH{=}CHCO_2Me$	88	0
e	TES	CH_2OTBS	$(CH_2)_3CH{=}CHCO_2Me$	96	0
f	H	CH_2OTBS	$(CH_2)_3C{\equiv}CCO_2Me$	59	0
g[a]	TES	CH_2OTBS	$(CH_2)_3C{\equiv}CCO_2Me$	100	0

[a] 1.2 equiv. I_2, CCl_4, r.t., 1 h

The *endo*/*exo* ratios of compounds **411**/**410** and **413**/**412** were suggested to be related to the conformational preference of the isopropenyl group of **407**. Following the formation of **408**, alkyl migration was presumed to occur prior to rotational equilibration of the cation.[158,160]

Scheme 102



Furthermore, an analogous approach employing NBS as the positive halide source was used by Julia and co-workers to conduct a ring-expansion from cycloalkanols **414a**−**b** into cycloalkanones **415a**−**b** (Scheme 100).[162,163] β-Brominated cyclohexanone **415a** was reported to decompose at 60 °C.

Likewise, Fukumoto and co-workers developed an iodonium ion-mediated ring-expansion of olefinic cyclobutanols **416** with I_2/$NaHCO_3$ or NIS (Scheme 101).[164] All investigated reactions furnished neopentyl-type β-iodinated cyclopentanones **417** and **418** in moderate to high yields.

Comparing entries **d** and **e**, the silyl ether gives a slightly better result than the corresponding alcohol. Interestingly, monosubstituted substrates (entries **a**−**c**) give a mixture of diastereoisomers, while complete stereoselectivity is observed in the cases of geminally substituted substrates (entries **d**−**g**).

This remarkable phenomenon could be rationalized by analyzing the GMMX (global MMX force field)-calculated, most stable conformers of substrates **419**, **424**, and **425** (Scheme 102).[165] In these conformers, the β-face of the olefins is shielded by the alcoholic hydrogen, suggesting α-face approach of the iodonium ion. Intermediates **420** and **421** are readily interconvertible, thus furnishing both diastereomers **421** and **423**. In contrast, iodonium intermediate **426** cannot undergo rotational equilibration because of steric congestion, due to the presence of the silyloxymethylene moiety at the vicinal position. Hence, β-iodo ketone **427** was formed as a single diastereoisomer.

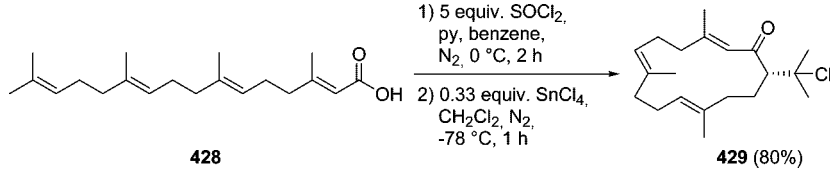
2.8. Ring Closure and Contraction

2.8.1. Ring Closure

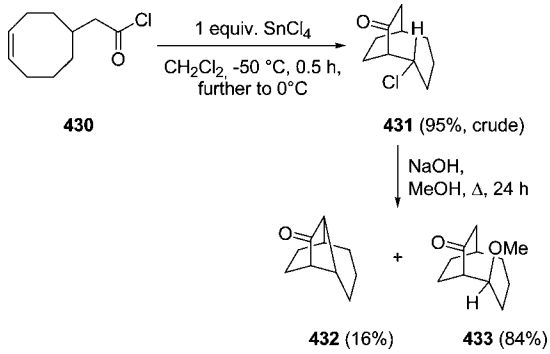
2.8.1.1. Electrophilic Addition. *Intramolecular Aliphatic Friedel*−*Crafts Acylation.* When unsaturated acid chlorides are treated with a suitable Lewis acid, an intramolecular acylation reaction will give rise to β-halocycloalkanone addition products. This methodology is applicable in the synthesis of products of varying ring size, including macrocyclic halogenated ketones, as shown by Bevan and coworkers (Scheme 103).[166]

An interesting study on the stereochemical outcome of the $SnCl_4$-catalyzed intramolecular Friedel−Crafts acylation of cyclooct-4-enyl acetyl chloride **430** was made by Moon and

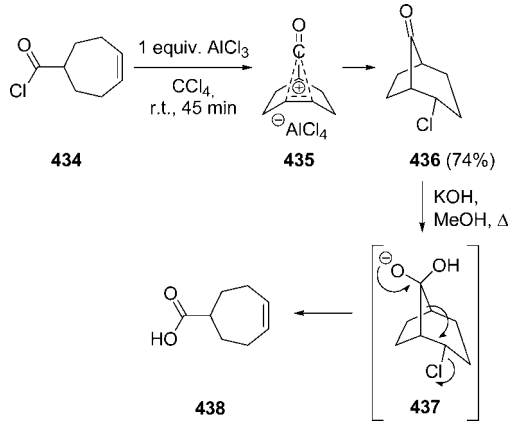
Scheme 103



Scheme 104



Scheme 105



co-workers (Scheme 104).[167] Besides the evidence from the spectral data, the stereochemistry of the main reaction product, *endo*-2-chlorobicyclo[4.2.2]decan-8-one **431**, was assigned by stereoelectronic reasons, on the basis of the fact that the tricyclodecanone **432** must arise from an S_N2 displacement of the chloro group by the enolate of the ketone. This transformation cannot take place if the chloro atom has an *exo* orientation. The stereochemical outcome of the intramolecular acylation was attributed to the generation of a fairly large complex between $SnCl_4$ and the carbonyl group in the intermediately generated cation. This prevents chloride attack in a *cis* fashion, thus averting the formation of the *exo* product.

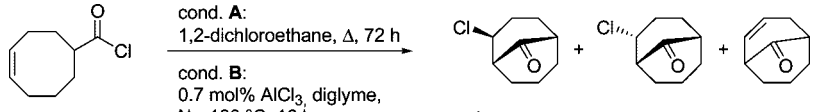
In a similar study performed by Kemp and co-workers, cyclohept-4-enecarbonyl chloride **434** was transformed stereoselectively into the *endo*-2-chlorobicyclo[3.2.1]octan-8-one **436** (Scheme 105).[168] Here, the stereochemistry of the addition was ascribed to the formation of an intermediate nonclassical type carbocation **435**. The structure of the bicyclic product was assigned by means of chemical and spectral data. Ring fragmentation rather than elimination by KOH pointed out that the C−Cl bond is *trans* coplanar with the C(1)−C(8) bond. These observations were later confirmed by Nelsen and co-workers in the synthesis of *syn*- and *anti*-8,8′-bibicyclo[3.2.1]octylidene.[169]

Since intramolecular addition of the acid chloride functionality of cyclooctene **439** to its olefin moiety would produce a bicyclic ketone, unable to undergo enolization, Erman and co-workers chose this system to investigate the stereochemistry of acyl halide additions to olefins (Scheme 106).[170] As depicted in the scheme, a moderate control of the reaction outcome could be achieved by altering the catalyst. Two possible, preliminary explanations for the observed selectivity were given: on the one hand, the rate of collapse of an initially formed *exo*-chloro ion pair to **440**, relative to the rearrangement to an *endo*-chloro ion pair, could be affected by the presence of a catalyst. Also consonant with the observations, on the other hand, is the addition of a chloride ion from the least-hindered side of a completely dissociated intermediary cation.

As described by Kuwajima and co-workers, the intramolecular reaction of acyl chlorides with homoallylsilanes features an excellent regiocontrol on cyclization to five-, six-, and seven-membered ring systems **444**, substituted with a cyclopropyl moiety (Scheme 107).[171] However, since cyclobutanone formation is greatly disfavored, β-chloro cyclopentanone **446** was formed exclusively against the directing effect of the silyl group. In this case, the intermediary cation did not give rise to the formation of a cyclopropyl moiety but was rather attacked by a chloride. Further, reaction at a homoallylsilane site predominates over that on a methallyl moiety, as can be seen in the ratio of products **449** and **450**. Still, the greater stability of the intermediary formed tertiary carbenium ion overrides the directing effect of the silyl group in the synthesis of **452**. To conclude, the transformation of substrate **453** indicates the restriction of the stabilizing effect of the silyl group to the three-membered ring systems.

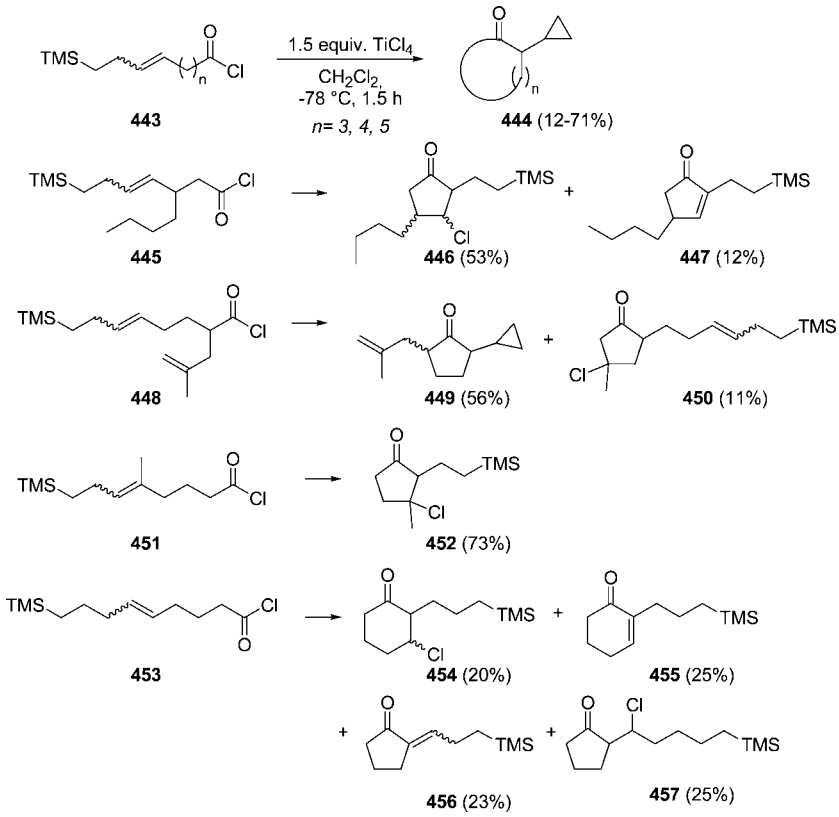
Intramolecular Aromatic Friedel−Crafts Acylation. A remarkable intramolecular Friedel−Crafts-type acylation was observed by Tanabe and co-workers during their investigations on the synthesis of 1-napthol derivatives from 2,2-dichlorocyclopropanecarbonyl chlorides **458** (Scheme 108).[43]

Scheme 106

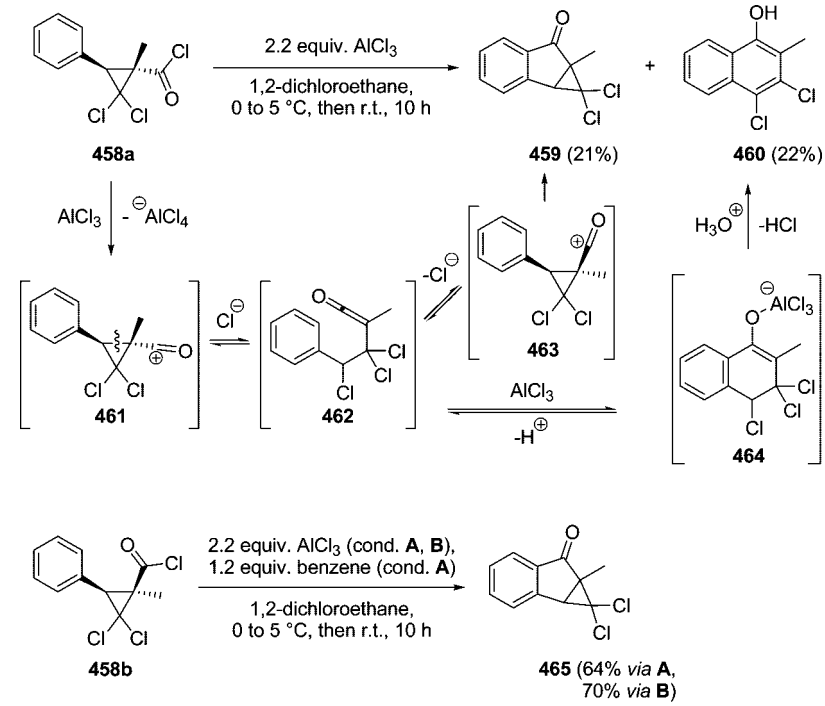


cond.	440	441	442
A	41%	16%	5%
B	8%	20%	18%
C	5%	3%	53%

Scheme 107



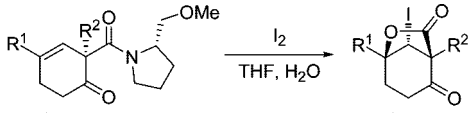
Scheme 108



Treatment of (*E*)-2,2-dichloro-1-methyl-3-phenylcyclopropanecarbonyl chloride **458a** with $AlCl_3$ afforded tricyclic β-chloro ketone **459** as a major product, together with 3,4-dichloro-1-naphtol **460**. In the presence of benzene, however, 3-chloro-2-methyl-4-phenyl-1-naphtol was obtained due to intermolecular trapping of intermediate **464**. Furthermore, reaction of (*Z*)-isomer **458b** with or without benzene furnished tricyclic ketone **465** as the major product in good yield. The latter result clearly demonstrates that an (*E*)-configuration in the starting acyl chloride is critical for successful benzannulation. These results were rationalized by assuming a reaction mechanism involving key ketene intermediate **462**, formed upon a highly regioselective cleavage of the cyclopropyl ring of acylium ion **461**.

Iodolactonization. Reaction of I_2 with carboxylic acids bearing an unsaturation in a suitable position gives rise to the formation of iodolactones. This iodolactonization is initiated by the attack of the powerful electrophile across

Scheme 109



466	R^1	R^2	467	Yield (%)
a	H	Me	a	90
b	H	$(CH_2)_3Cl$	b	75
c	H	2-$BrC_6H_4(CH_2)_2$	c	82
d	Me	Et	d	80
e	2-$MeOC_6H_4$	Me	e	98

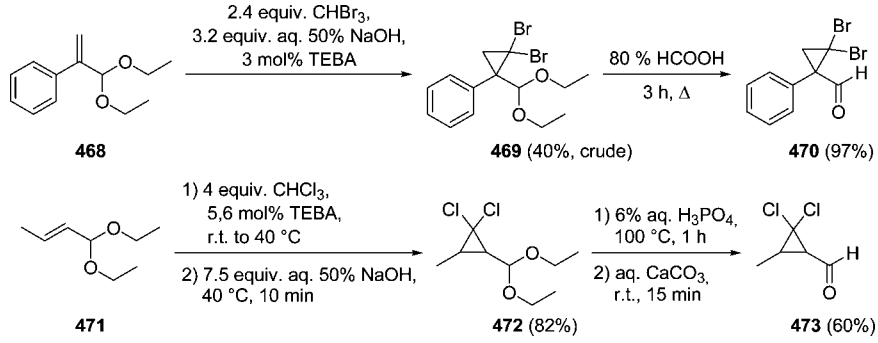
the unsaturation, whereupon the carboxyl group acts as a nucleophile and attacks the thus formed iodonium ion in a controlled *anti*-fashion. Moreover, the use of a chiral amide can promote enantioselective cyclizations. This was exemplified by Schultz and co-workers in their iodolactonization of β,γ-enones **466a**−**e**, affording enantiomerically pure 2-alkyl-3-iodo-1-oxocyclohexan-2,4-carbolactones **467a**−**e** in excellent yields (Scheme 109).[172]

2.8.1.2. Carbene Addition to Double Bonds. One option to create cyclopropanes is the addition of a dihalocarbene to a double bond. For atropaldehyde diethyl acetal **468**, however, this transformation proceeded in rather poor yield (Scheme 110).[173] A comparable dichlorocyclopropanation of cinnamaldehyde diethyl acetal was only moderately successful (45% yield), while the analogous dimethyl acetal underwent the same transformation in a significantly higher yield (72%).[174] Yanovskaya and co-workers, on the other hand, obtained acceptable yields for the dichlorocyclopropanation of 2-butenal diethyl acetal **471** and similar substrates, provided a 4-fold excess of $CHCl_3$ was used.[175]

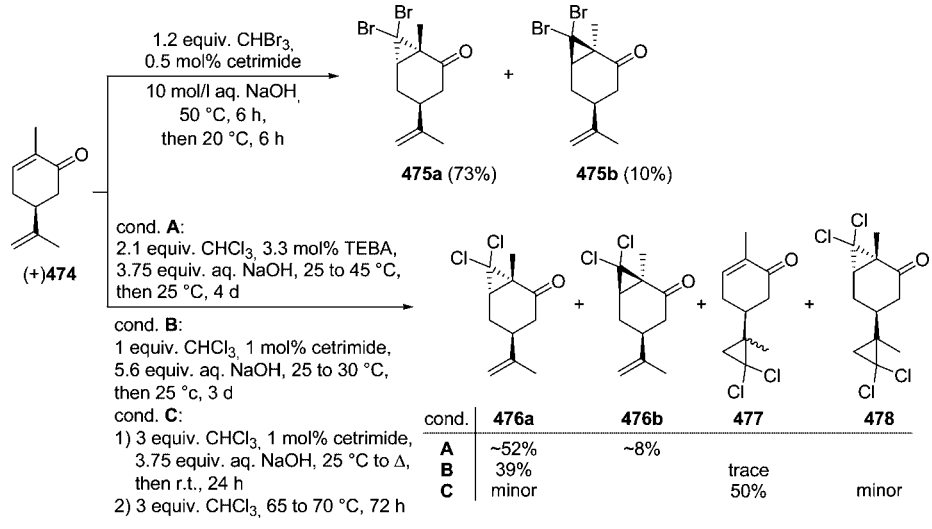
2.8.1.3. Conjugate Addition. Carvone was reported to form adducts **475** and **476** upon reaction with $CHCl_3$ or $CHBr_3$ respectively, in alkaline medium under phase-transfer conditions (Scheme 111).[176] The presumed reaction mechanism involves initial Michael-addition of a trihalomethyl anion to the enone system, followed by cyclization with loss of a halide ion. When employing $CHBr_3$, the major product formed is the *trans*-isomer **475a**. Analogously, with 1 or 2 equiv of $CHCl_3$, *trans*-selectivity was observed (conditions **A** and **B**). Nevertheless, a larger excess of $CHCl_3$ favored the formation of the carbene adduct at the isopropenyl group (conditions **C**). Although phase-transfer reactions are known to be somewhat dependent on the exact reaction conditions and the formation of products apparently derived from a trichloromethyl anion (compounds **476a**−**b**) or a dichlorocarbene (product **477**) can be controlled by varying the catalyst, the dramatic change in mechanism was rather unexpected in the present example.

As discussed in the part on conjugate addition earlier in this chapter (see p 38), α,β-unsaturated ketones undergo a highly stereoselective coupling reaction with aldehydes *via* a halide-initiated sequential Michael addition−aldol reaction. An intramolecular variant of this remarkable reaction was reported by Shinokubo and co-workers (Scheme 112).[177] Hence, upon treatment with $TiCl_4$ and an ammonium halide (n-$Bu_4N^+I^-$ or BTEAC), ε-formyl α,β-enone **479** furnished 2-benzoyl-3-halocycloalkanols **480a**−**b** with three highly controlled consecutive stereogenic centers. In like manner, the $TiCl_4$/n-$Bu_4N^+I^-$ combination affects the cyclization of bis-α,β-enones **481a**−**d**. As could be expected, the unsym-

Scheme 110

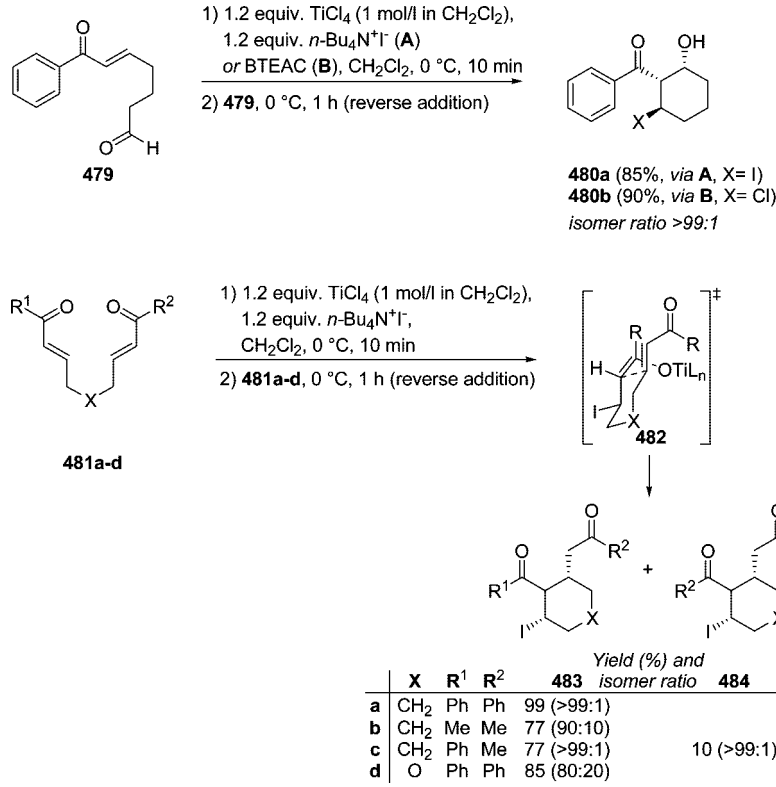


Scheme 111

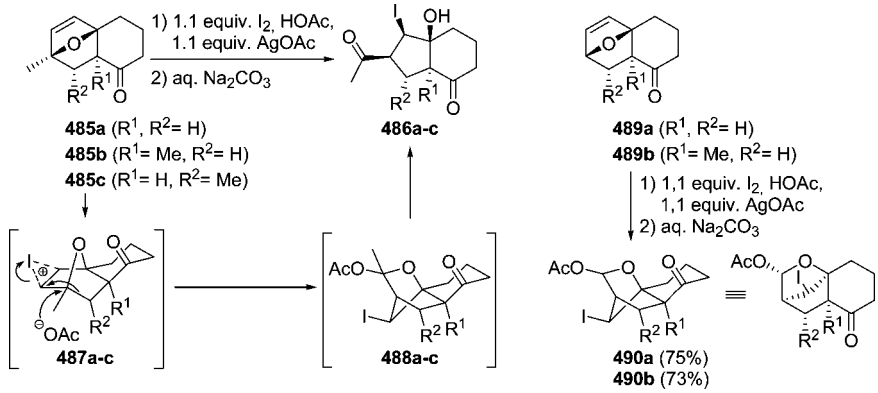


cond.	476a	476b	477	478
A	~52%	~8%		
B	39%		trace	
C	minor		50%	minor

Scheme 112



Scheme 113



metrical substrate **481c** predominantly underwent enolate formation at the phenyl-substituted α,β-enone.

2.8.2. Ring Contraction

In the final stages of a synthetic pathway, it is not uncommon to conduct a ring contraction step to attain the targeted molecular structure. For example, Keay and co-workers synthesized bicyclic β-iodo ketones **486a−c** *via* a Wagner−Meerwein rearrangement of decalone derivatives **485a−c** (Scheme 113).[178] The oxatricyclo intermediates **488a−c** could be neither detected nor isolated. In contrast, substrates lacking the methyl group at the oxygen bridge (**489a−b**) yielded these rearranged oxatricyclo compounds **490a−b** in good yield.

2.8.3. Ring Rearrangements

For reasons of clarity, the synthesis of 8,10- and 9,10-dibromocamphor is discussed in the paragraph on γ-bromocamphor derivatives (see Scheme 199).

2.9. Oxidation

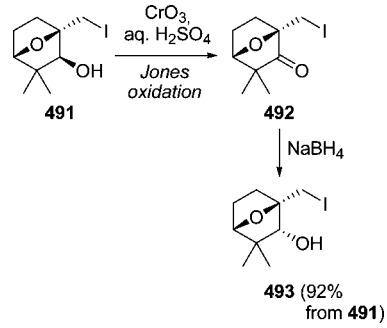
2.9.1. Oxidation of Halogenated Alcohols

The classical oxidants for converting an alcohol into an aldehyde or a ketone are Cr(VI) reagents. In the past decades, however, several procedures have been developed that obviate the toxicity associated with the use of chromium reagents and eliminate the risk of overoxidation of primary alcohols.

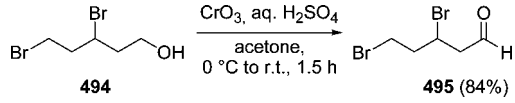
2.9.1.1. Chromium-Based Oxidants. *Jones Oxidation.* The use of the Jones reagent, an aqueous solution of CrO_3 in H_2SO_4, is a standard practice for the oxidation of secondary alcohols. Successful application of this procedure has, for example, been reported in the epimerization sequence of an iodomethylated oxanorbornane **491** (Scheme 114).[179]

Treatment of primary alcohols, however, is generally discouraged because of the likely conversion of the initially formed aldehydes into the corresponding carboxylic acids. Nevertheless, as illustrated by Weyerstahl and co-workers,

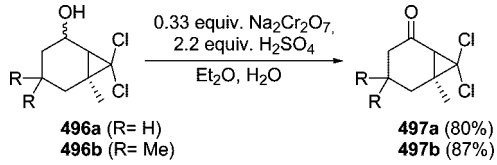
Scheme 114



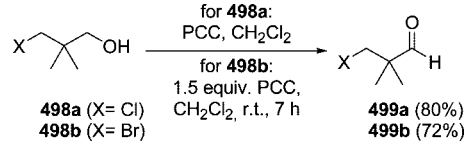
Scheme 115



Scheme 116



Scheme 117



in some cases, the outcome of the oxidation can be satisfying for these substrates as well (Scheme 115).[180]

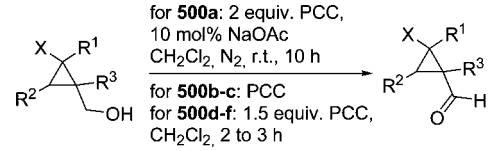
Analogously, treatment of an alcohol with $Na_2Cr_2O_7$ or $K_2Cr_2O_7$ in the presence of H_2SO_4 has been reported in the synthesis of halogenated cyclopropyl ketones[181] and chlorinated bicyclo[4.1.0]heptan-2-ones (Scheme 116).[182] This procedure is compatible with water-immiscible solvents such as Et_2O and benzene.[183]

Pyridinium Chlorochromate (PCC). Both pyridinium chlorochromate (PCC) and pyridinium dichromate (Collins−Ratcliff reagent, PDC) are superior alternatives to the Jones reagent for the oxidation of primary and secondary alcohols in the presence of acid-sensitive functionalities. Oxidations with PCC, however, proceed more readily than with the PDC. As a result, a smaller excess of oxidant is needed to allow the reaction to proceed satisfactorily. Using PCC, Wilt[31,184] and Reinhoudt,[185] respectively, oxidized the chlorinated and brominated neopentylic alcohols **498a**−**b** to the corresponding pentanals in reasonable yields (Scheme 117; see also Scheme 121). An analoguous synthesis of 2-chloromethyl-2-methyl-3-phenylpropanal was presented by Quéguiner and co-workers.[186]

Furthermore, PCC can be employed to generate brominated and chlorinated formylcyclopropanes from the parent hydroxymethyl analogues. This conversion usually proceeds with excellent yields, as was illustrated by Porter,[187] Brinker,[188] and Al Mohana[189] for the respective mono- and dibrominated cyclopropanes **501a** and **501b**−**c** and for chloro- formylcyclopropanes **501d**−**f** (Scheme 118).

In the same manner, Banwell and co-workers prepared several β,β-dichlorocyclopropyl ketones and aldehydes.[190]

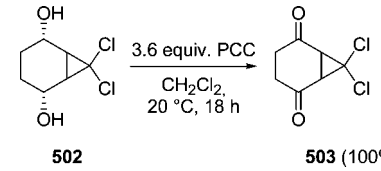
Scheme 118



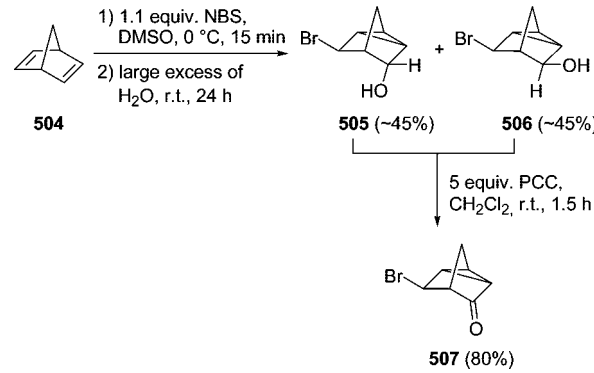
500	R^1	R^2	R^3	X
a	H	*n*-C_5H_{11}	H	Br
b	Br	Me	Me	Br
c	Br	Me	H	Br
d	H	H	H	Cl
e	H	Me	H	Cl
f	H	Ph	H	Cl

501	Yield (%)
a	95
b	88
c	84
d	76
e	65
f	65

Scheme 119



Scheme 120



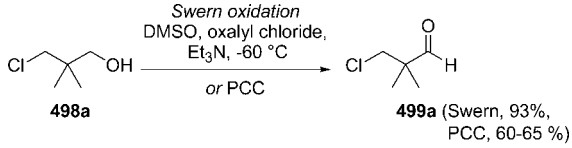
Another interesting example, provided by the same researchers, illustrates the applicability of PCC to β-chloro dione synthesis. Oxidation of chlorinated 7,7-dichlorobicyclo[4.1.0]-heptane-3,6-diol **502** into dione **503** was reported to proceed quantitatively under the depicted conditions (Scheme 119).[191]

In the first detailed investigation of the hydroxybromination of norbornadiene **504**, Laurent and co-workers obtained two bromohydrins **505** and **506**.[192] Oxidation of these species by PCC yielded a single brominated nortricyclanone **507** (Scheme 120). This clearly proved the identical orientation of the C−Br bond in bromohydrins **505** and **506**, excluding the possibility of a simultaneous *exo* and *endo* attack during the hydroxybromination step.

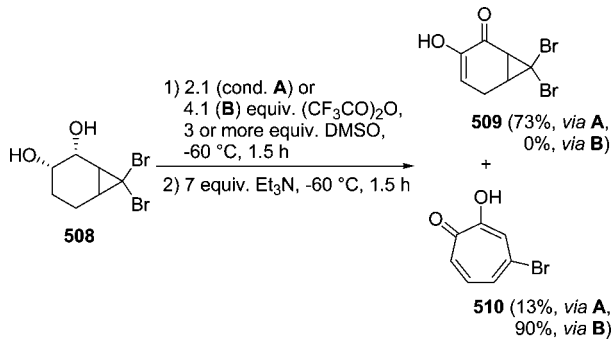
2.9.1.2. Non-Chromium Based Oxidants. *Swern Oxidation.* The Swern protocol, a rapid low-temperature oxidation procedure under rather tolerant conditions, has repeatedly been applied in the synthesis of β-halogenated aldehydes and ketones. In a direct comparison reported by De Kimpe and co-workers, the oxidation of β-chloroalcohol **498a** to β-chloro aldehyde **499a** proceeded with significantly higher yield when using Swern conditions than by means of PCC (Scheme 121).[193] The use of $K_2Cr_2O_7$ proved even inferior.[183] Interestingly, Wilt and co-workers reported the PCC-mediated reaction to proceed in somewhat higher yield (Scheme 117).

Moreover, alternatives to oxalyl chloride can be used. Banwell and co-workers successfully transformed 7,7-

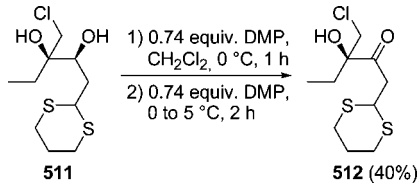
Scheme 121



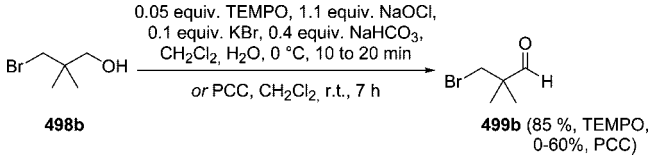
Scheme 122



Scheme 123



Scheme 124

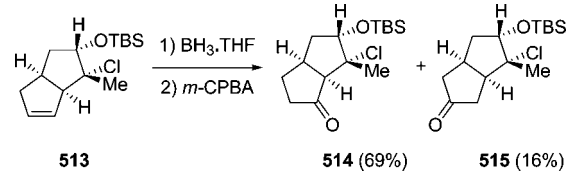


dibromobicyclo[4.1.0.]heptane-2,3-diol **508** into the corresponding bicyclic β,β-dibromo ketone **509** by means of a Swern-type oxidation with $(CF_3CO)_2O$ (conditions **A**, Scheme 122).[191] To some extent, this monoenolic ketone underwent *in situ* ring-expansion and loss of hydrogen halide to afford halogenated tropolone **510**. The latter species was obtained selectively by increasing the amount of oxidant used (conditions **B**).

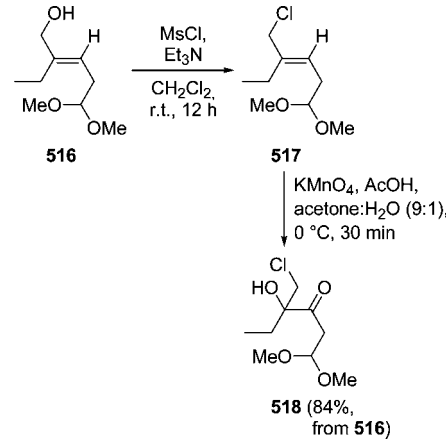
Dess−Martin Periodinane. A very mild reagent for the conversion of primary and secondary alcohols into aldehydes and ketones is Dess−Martin periodinane (DMP). This oxidant is particularly suitable for multifunctional substrates and therefore often preferred over Cr(VI)- and DMSO-based approaches. In an example provided by Chavan and co-workers, no other oxidizing agents than DMP were useful for the selective transformation of the secondary hydroxyl group of diol **512** (Scheme 123).[194] Although removal of a dithiane moiety by the action of DMP has been reported, the depicted reaction proceeded with complete chemoselectivity.

2,2,6,6-Tetramethyl-1-piperidinyloxy Radical (TEMPO). TEMPO, in conjunction with NaOCl as a co-oxidant, proved to be a reliable and environmentally benign alternative to PCC (see also Scheme 117) in the preparation of 3-bromo-2,2-dimethylpropanal **499b**, starting from the corresponding alcohol **498b** (Scheme 124).[195]

Scheme 125



Scheme 126



2.9.2. Oxidation of Olefins

β-Chlorinated carbonyl compounds **514** can be prepared from the corresponding homoallylic chlorides **513** *via* a hydroboration−oxidation sequence. In this context, *m*-chloroperbenzoic acid (*m*-CPBA) has been reported as a suitable oxidant (Scheme 125).[196] The γ-regioisomer **515** was formed as a minor reaction product.

Another way of functionalizing a double bond was exemplified by Chavan and co-workers in the oxidation of the functionalized allyl chloride **517** (Scheme 126).[194] Treatment with $KMnO_4$ under acidic conditions furnished β-chloro-α-hydroxyketone **518**. It is furthermore remarkable that allyl chloride **517** was obtained from the corresponding alcohol **516** upon mere treatment with mesyl chloride and Et_3N at room temperature.

2.10. Pericyclic Reactions

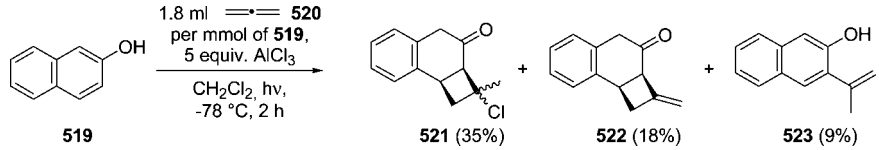
2.10.1. Cycloadditions

In their investigation on new photochemical reactions of 1- and 2-naphthols, Kakiuchi and co-workers observed that, upon irradiation of 2-naphthol **519** in the presence of $AlCl_3$ and a large excess of allene **520**, chlorinated cycloadduct **521** was formed as the major product (Scheme 127). This observation can be explained through a cycloaddition to the benzocyclohexadienone canonical form of **519**, with the latter being formed due to the presence of the Lewis acid.[197]

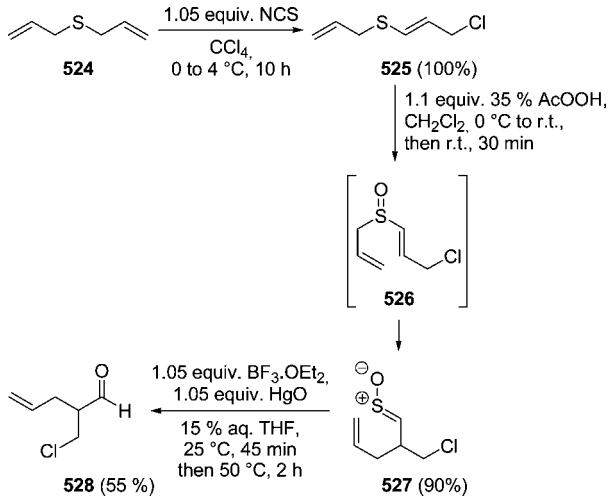
2.10.2. Sigmatropic Rearrangements

2.10.2.1. Thio-Claisen Rearrangement. During a study on antithrombotic organosulfur compounds present in garlic (*Allium sativum*), Block and co-workers attempted to oxidize 3-chloro-1-propenyl sulphide **525** to the corresponding sulfoxide **526** (Scheme 128).[198] To their surprise, (*Z*)-2-chloromethyl-4-pentenethial *S*-oxide **527** was formed *via* a sulfoxide-accelerated thio-Claisen reaction. This β-chlorinated sulfine was subsequently desulfurized using $BF_3 \cdot Et_2O$ and HgO, affording β-chloro aldehyde **528** in good yield.

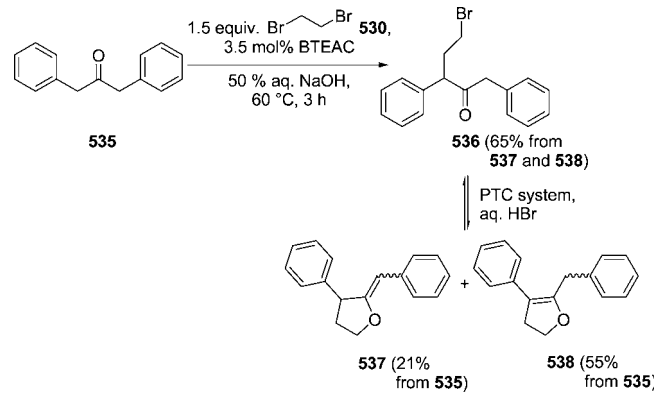
Scheme 127



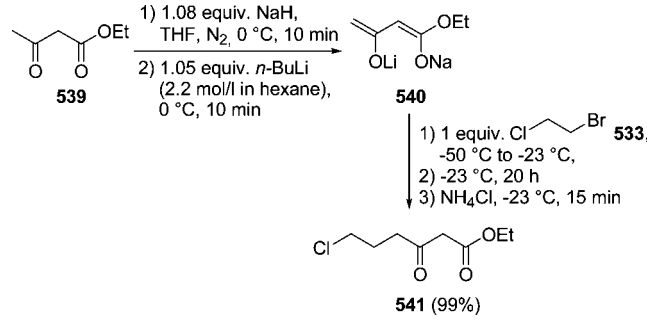
Scheme 128



Scheme 130



Scheme 131



3. Synthesis of γ-Halo Ketones and Aldehydes

3.1. Nucleophilic Substitution

3.1.1. Enolate Alkylation

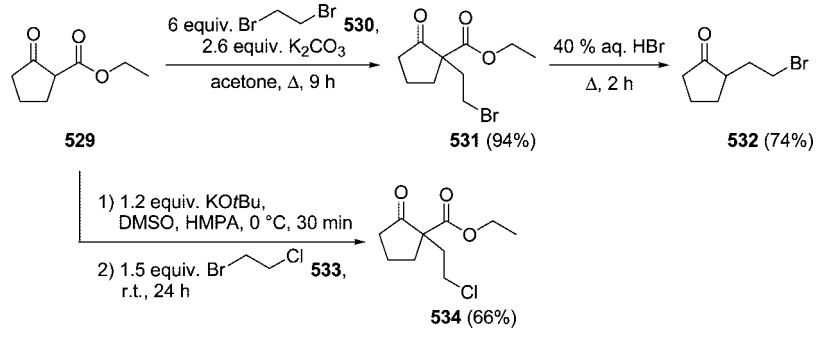
As for their β-analogues, γ-halogenated aldehydes and ketones can be prepared through an alkylation of a parent enolate. Very often, the enolate is formed from an activated substrate, such as a β-ketoester. Subsequently, when the desired product should not contain the ester moiety, it can evidently be removed *via* a decarboxylation.

In an illustrative example, Jaworski and co-workers converted 2-ethoxycarbonylcyclopentanone **529** into γ-brominated ketoester **531** by treatment with 1,2-dibromoethane **530** in the presence of K_2CO_3 (Scheme 129).[199] The corresponding γ-bromo ketone **532** was obtained after decarboxylation. This reaction sequence had been reported earlier by Mayer and Alder, though in far lower yields (23% for the alkylation step, using KOH and 66% for the decarboxylation step employing 40% aqueous HBr).[12] Interestingly, Sakai and co-workers were only able to obtain the chloro analogue **534** of β-ketoester **529** in 66% yield (Scheme 129).[200] These researchers used KO*t*Bu as a base, while employing a solvent mixture of DMSO and HMPA.

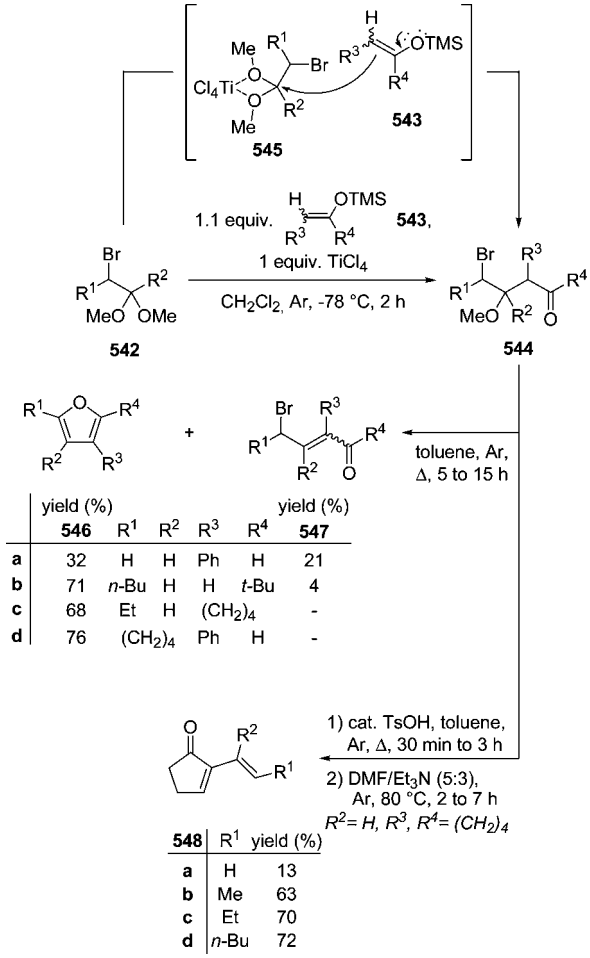
Jończyk and co-workers used a phase transfer catalyst system with BTEAC and aqueous NaOH to alkylate dibenzylketone **535** (Scheme 130).[201] Under these conditions, the intermediate bromo ketone **536** could not be isolated, owing to its rapid cyclization. However, heating of the mixture of **537** and **538** with an excess of HBr afforded crystals of the parent ketone **536** in reasonable yield.

By carefully choosing reaction conditions and quench temperatures, γ-halogenated-β-dicarbonyl compounds **541** can be obtained as the mono-γ-alkylation products of the dianions **540** of the parent dicarbonyl compounds **539**. Although the γ-alkylation of dianions of β-dicarbonyl compounds had been achieved with a variety of electrophiles,[202,203] Carrié and co-workers were the first to thoroughly explore the reaction of these nucleophilic species with α,ω-dihaloalkanes (Scheme 131).[204] They obtained the desired γ-halo-β-dicarbonyl products **541** in good yields by maintaining low reaction and quench temperatures. More examples of this

Scheme 129



Scheme 132



	yield (%) 546	R1	R2	R3	R4	yield (%) 547
a	32	H	H	Ph	H	21
b	71	*n*-Bu	H	H	*t*-Bu	4
c	68	Et	H	$(CH_2)_4$		-
d	76	$(CH_2)_4$		Ph	H	-

548	R^1	yield (%)
a	H	13
b	Me	63
c	Et	70
d	*n*-Bu	72

interesting and useful transformation are provided in the sections on δ- and ω-halogenated ketones and aldehydes.

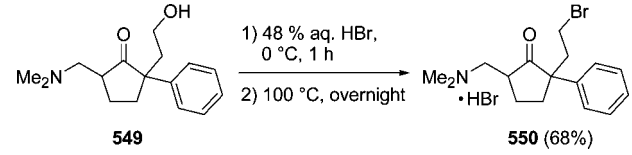
In all previously presented examples, the alkylating reagent underwent substitution at a less hindered primary center, thus *via* an S_N2 mechanism. However, with many secondary alkyl halides, a competing base-induced elimination reaction can be observed, the extent of which depends on the pK_a value of the ketone. Furthermore, tertiary alkyl halides will inevitably undergo elimination in the presence of enolates.

Silyl enol ethers, electron-rich yet nonbasic nucleophiles, can be applied as an alternative to enolates in these cases. In this context, a variation of the widely used Mukaiyama aldol reaction can be employed for the synthesis of β-alkoxylated γ-halogenated carbonyl compounds **544**, as originally presented by Mukaiyama and co-workers (Scheme 132).[205,206] The actual alkylation step proceeds *via* a Lewis acid-mediated activation of the α-bromoacetal alkylating reagent **542** to form complex **545**. The thus obtained polyfunctional ketones **544** proved to be a convenient entry to furans **546**[205] and 2-(1-alkenyl)-2-cyclopentenones **548**.[206]

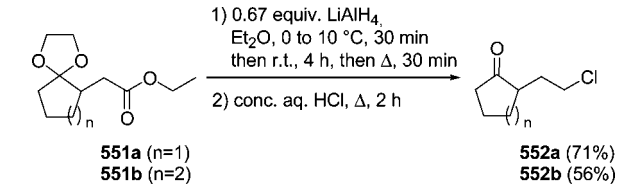
3.1.2. Conversion of an Alcohol or Ether into an Alkyl Halide

3.1.2.1. Substitution in Acidic Medium. As discussed for the β-analogues, γ-halogenated ketones can also be prepared from the corresponding alcohols upon treatment with a suitable acid. In this manner, Mazzocchi and co-workers displaced the hydroxyl group of Mannich base **549** for bromide *via* reaction with concentrated HBr (Scheme 133).[207]

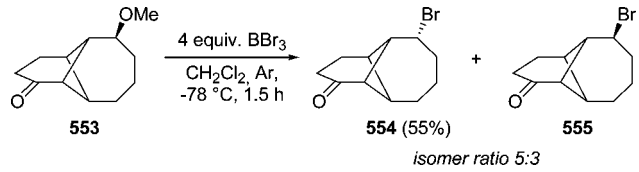
Scheme 133



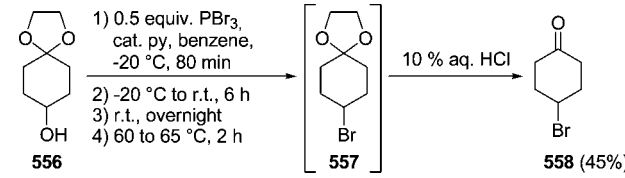
Scheme 134



Scheme 135



Scheme 136



Shatzmiller and co-workers employed this transformation for the development of a new, convenient one-pot synthesis of γ-chloro ketones **552a**−**b** from the corresponding γ-acetal esters **551a**−**b** (Scheme 134).[208]

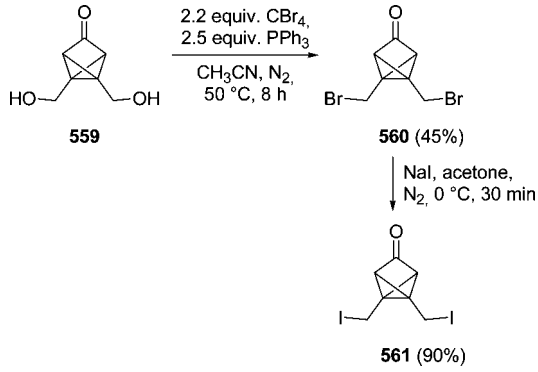
Lewis acids are capable of cleaving ethers, concurrently creating an alkyl halide. Substitution of the methoxy moiety of ether **553** for bromide, for example, was achieved by Gleiter and co-workers using BBr_3, a reagent commonly used for methyl ether cleavage (Scheme 135).[209] Two isomeric bromides were obtained in a ratio of 5:3, product **554** as the major one.

3.1.2.2. Substitution of Phosphoryl Activated Alcohols. As explained for β-halo ketones, PBr_3 can be used to produce halides from the corresponding alcohols. Vig and co-workers used this reagent to obtain 4-bromocyclohexanone **558**, an intermediate in their synthesis of isopropenylic terpenes (Scheme 136).[210] Deprotection of the acetal moiety, present because of a foregoing reduction step, was performed *via* a mild acid-catalyzed hydrolysis. PBr_3-mediated transformations have also been applied for the primary neopentylic hydroxyl group of 8-hydroxycamphor **573** (Scheme 139).[211] Here as well, prolonged reaction times were compulsory to achieve a good conversion.

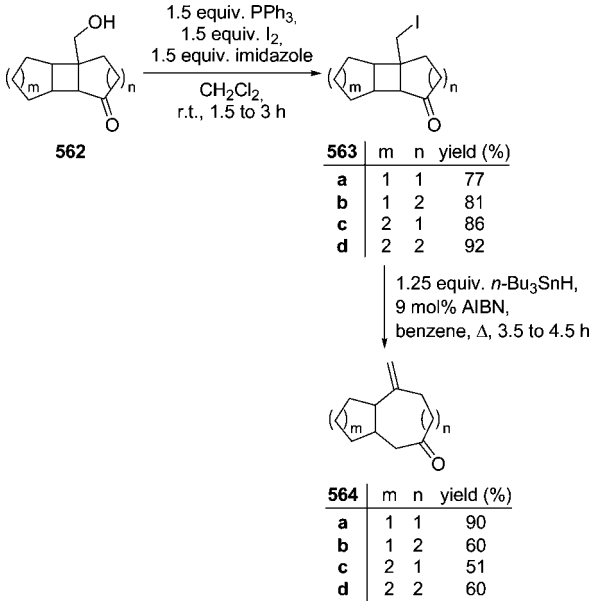
Besides, the Appel reaction has been adopted to transform a γ,γ'-dihydroxyketone **559** into the corresponding dibromide **560** (Scheme 137).[130] In one more step, *via* a Finkelstein reaction, the corresponding diiodide **561** was obtained. This transhalogenation is driven to completion, owing to the insolubility of NaBr in acetone.

In another example of an Appel-type transformation, Lange and co-workers were able to convert the neopentyl alcohols **562** into the corresponding iodides **563a**−**d** (Scheme

Scheme 137



Scheme 138



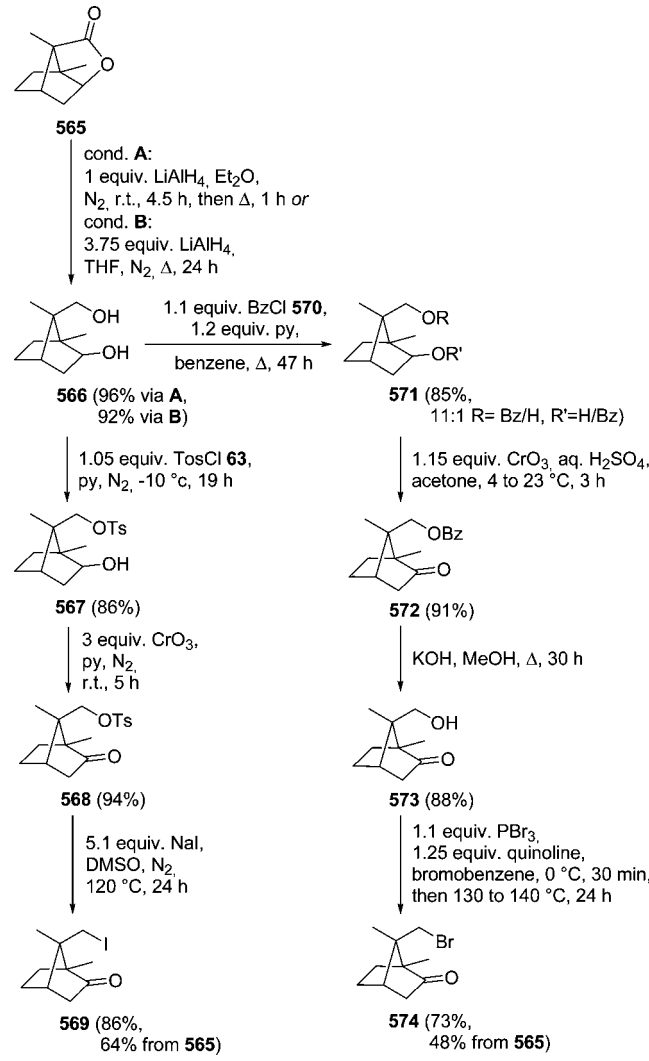
138).[212] These products were utilized in a free radical fragmentation study, affording bicyclo[5.3.0]decane systems **564a−d**.

3.1.2.3. Substitution of Sulfuryl Activated Alcohols. Starting from the corresponding alcohols, tosylate activation also provides an entry to γ-halogenated ketones. A noteworthy comparison between this strategy and the use of PBr_3 can be made by contrasting the syntheses of 8-iodo- and 8-bromocamphor by Rodig[213] (Scheme 139, **A**) and Meyer[211] (**B**), respectively. Both approaches involve a $LiAlH_4$-mediated reduction of lactone **565** and require a selective substitution and oxidation of the 8- and 2-hydroxyl moieties, respectively. Moreover, in both strategies a selective functionalization of the primary hydroxyl group in the presence of a secondary counterpart was achieved. However, since the tosylation strategy requires one step less, its overall yield was significantly higher.

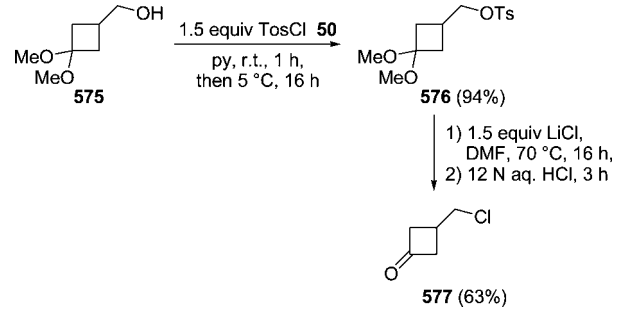
In another example, De Kimpe and co-workers obtained 3-(chloromethyl)cyclobutanone **577** in reasonable yield *via* a straightforward tosylation of alcohol **575**, followed by a treatment with LiCl in DMF and subsequent hydrolysis of the acetal (Scheme 140).[214]

1-Chloro-4-adamantanone was prepared from the corresponding alcohol upon treatment with $SOCl_2$.[37] This synthesis, reported by Janků and co-workers, is described in more detail in the section on β-halogenated compounds (see Scheme 18).

Scheme 139

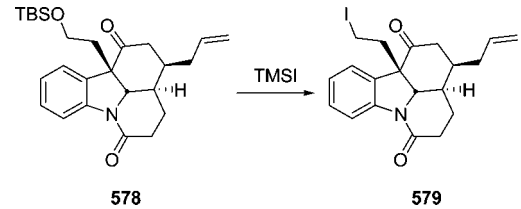


Scheme 140



3.1.2.4. Miscellaneous. In their preparation of a hexacyclic intermediate for the synthesis of strychnos alkaloids, Kraus and co-workers successfully converted a TBS-protected primary alcohol **578** into the corresponding iodide **579** upon treatment with TMSI (Scheme 141).[215]

Scheme 141



3.2. Nucleophilic Addition

3.2.1. Additions of Organometallic Compounds

3.2.1.1. Grignard Reagents. The fact that the nitrile of a halogenated acid yields a halogenated ketone upon treatment with a Grignard reagent was first reported by Conant and co-workers in the preparation of γ-chloropropyl phenyl ketone **581a** (Scheme 142).[216]

This approach was also followed by Hanack and co-workers in the synthesis of several arylcyclopropyl ketones, *via* the intermediary γ-chloro ketones.[217] Takeuchi and co-workers applied the reaction to three arylmagnesium bromides **621a**−**c** with moderate success (Scheme 143).[218]

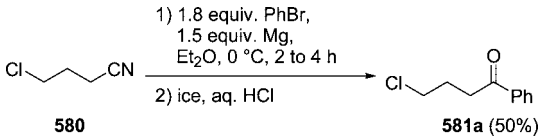
3.2.1.2. Organozinc Reagents. In a similar fashion as for a Grignard reaction, Barbier conditions can be employed in the synthesis of γ-halogenated carbonyl compounds. When a Barbier-type reaction is conducted with a halogenated electrophile **584** and an alkyl halide **583**, itself bearing a carbonyl moiety, halogenated adducts **585** are formed (Scheme 144).[219]

In their total synthesis of the paralytic shellfish poisons saxitoxin and gonyautoxins II and III, Kishi and co-workers developed an improved procedure for the Blaise reaction, the addition of a zinc ester enolate to a nitrile.[220] As such, treatment of an ω-chloronitrile **587** with excess of α-bromo ester **586** in the presence of activated zinc dust provided, upon acid hydrolysis, a reasonable yield of γ-chloroketo ester **589** *via* enaminone **588** (Scheme 145).

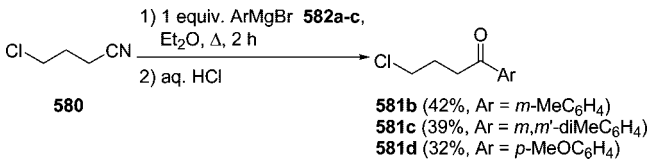
Allylic zinc reagents can be generated from sterically hindered homoallylic alcohols **590** *via* a fragmentation reaction of the corresponding zinc alkoxides **592**. The latter species, masked allylic organozinc reagents, were introduced by Knochel and co-workers in order to circumvent the formation of the Wurtz homocoupling product, a commonly encountered problem when reacting an allylic halide with a metal. In one example, unsaturated γ-chloro ketone **591** was prepared in reasonable yield employing this novel methodology (Scheme 146).[221]

3.2.1.3. Organomanganese Reagents. Organomanganese(II) reagents are of particular interest for synthetic organic chemistry, since they react with high chemoselectivity and can be used under mild conditions. Friour and co-workers reacted these nucleophiles **593a**−**c** with ω-chloro acyl chloride **595**, thus obtaining the corresponding ketones **596a**−**c** (Scheme 147).[222] The yields of these transformations were comparable or even superior to those obtained using organo species of cadmium, magnesium, lithium, zinc, or copper.

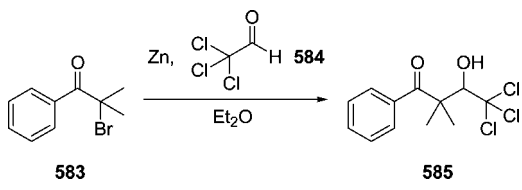
Scheme 142



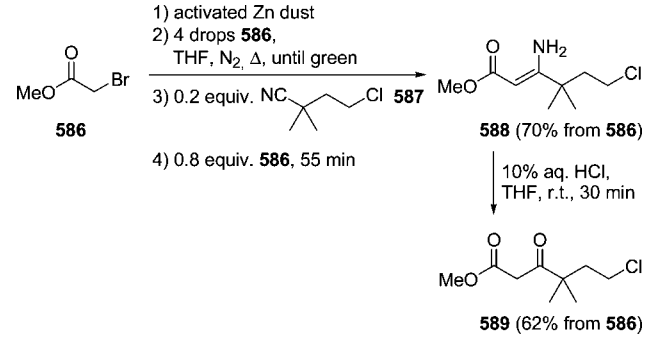
Scheme 143



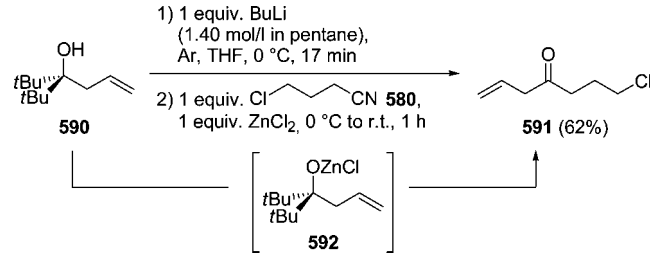
Scheme 144



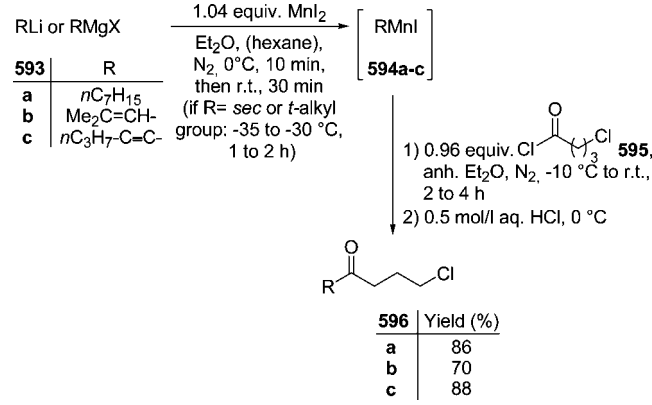
Scheme 145



Scheme 146



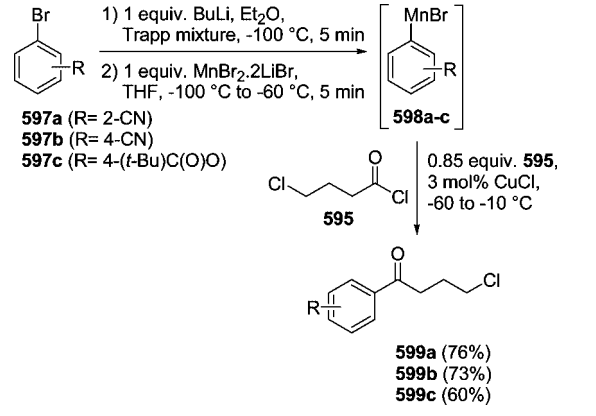
Scheme 147



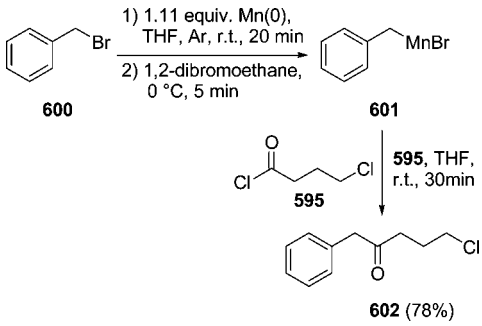
593	R
a	nC_7H_{15}
b	Me_2C=CH-
c	nC_3H_7-C≡C-

596	Yield (%)
a	86
b	70
c	88

Scheme 148



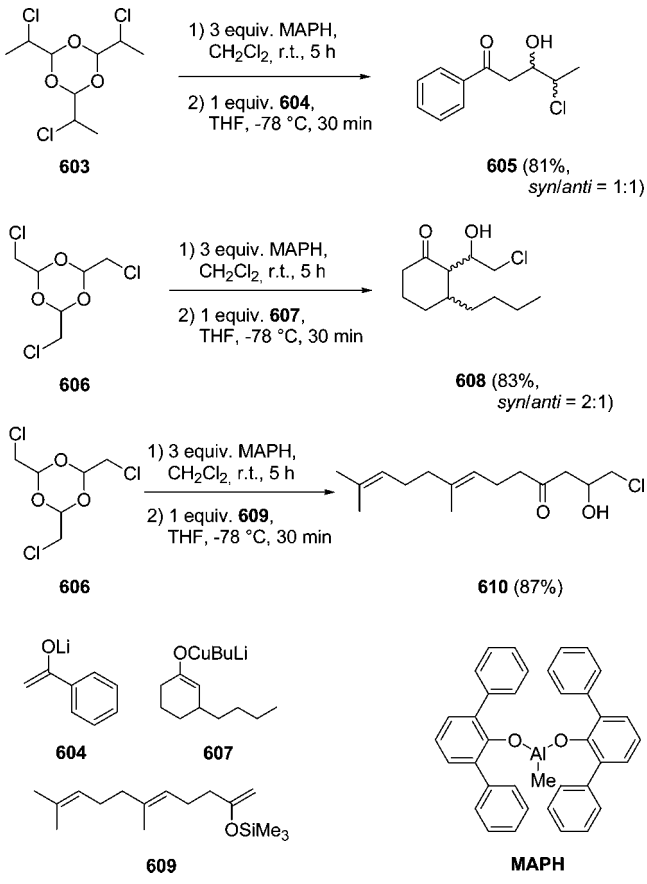
Scheme 149



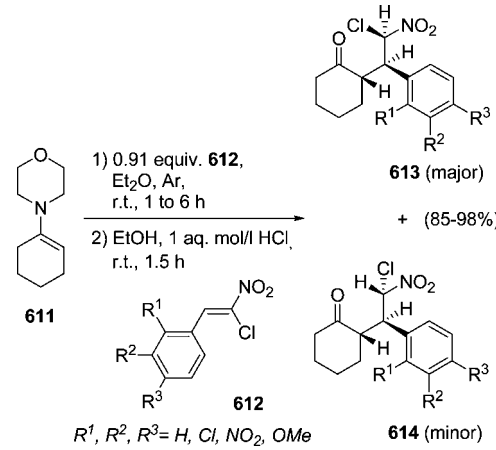
Knochel and co-workers also published on the straightforward and selective manner in which organomanganese(II) compounds react.[223] In an attempt to broaden the scope of application of these nucleophiles, these researchers prepared several chlorinated aryl and alkenylmanganese halides (see the section on ω-halogenated compounds). Aryl or alkenyl manganese reagents **598a−c** bearing more reactive functional groups, such as a nitrile or a hindered ester moiety, were obtained at low temperature using the Trapp mixture (THF/ether/pentane 4:4:1, a mixture which is a liquid down to −110 °C) as a solvent and the well-soluble $MnBr_2 \cdot 2LiBr$ as the manganese source (Scheme 148). These functionalized nucleophiles reacted with γ-chlorinated acid chlorides to form various γ-chloro ketones **599a−c**.

In their investigation on the use of benzylic manganese halides, sulfonates, and phosphates in organic synthesis, Rieke and co-workers prepared γ-chloro ketone **602** from benzyl bromide and 4-chlorobutyryl chloride (Scheme 149).[224] Remarkably, both the oxidative addition and the coupling step took place in a short time and under mild conditions.

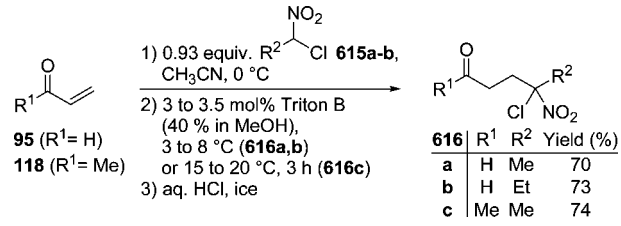
Scheme 150



Scheme 151



Scheme 152



3.2.2. Enolate and Enamine Additions

Yamamoto and co-workers presented methylaluminium bis(2,6-diphenyloxide) (MAPH) as a means of generating reactive aldehydes from readily available trimers **603** and **606** (Scheme 150).[225] As such, stabilized 1:1 coordination complexes of α-chloro aldehydes with MAPH can be trapped with various enolates (**604**, **607**, **609**) to furnish the respective chlorinated aldol adducts **605**, **608**, and **610** in good yields.

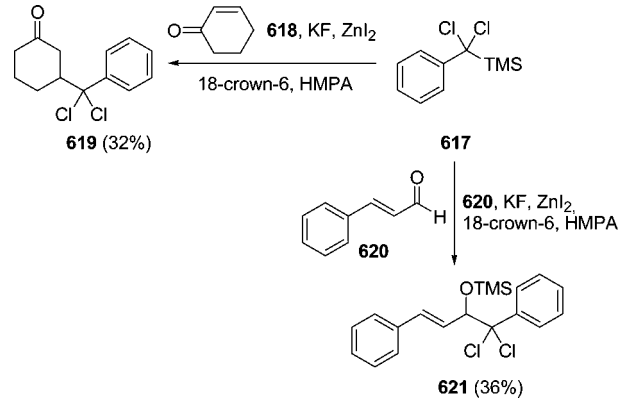
Nucleophilic attack of 1-morpholino-1-cyclohexene **611** across (2-chloro-2-nitroethenyl)benzenes **612**, followed by alcoholic hydrolysis of the intermediate enamine adduct, gives rise to the rather complex γ-chloro ketones **613** and **614** as a mixture of two diastereoisomers (Scheme 151).[226]

3.3. Conjugate Addition

Next to the halides discussed in the section on β-halogenated ketones and aldehydes, also carbon nucleophiles can initiate conjugate addition reactions. When treated with Triton B (benzyltrimethylammonium hydroxide), 1-chloro-1-nitroalkanes **615a−b** add as Michael donors to α,β-unsaturated ketones and aldehydes, affording γ-halo-γ-nitro analogues **616a−c** (Scheme 152).[227] Besides, Et_3N has been employed as a base in a like preparation of ketone **616c**.[228]

Larson and co-workers reported the formation of the chlorinated conjugate addition product **619** in the reaction of α,α-dichlorobenzyltrimethylsilane **617** with 2-cyclohexenone **618** (Scheme 153).[229] Interestingly, similar treatment of (*E*)-cinnamaldehyde **620** with **617** gave the 1,2-addition product **621**. In the absence of ZnI_2 and HMPA, disappointing yields of adducts were obtained.

Scheme 153



3.4. Electrophilic Addition

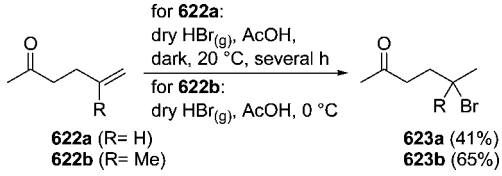
3.4.1. Hydrobromination of Olefins

The electrophilic addition of HBr to a double bond is a straightforward and common reaction in organic synthesis. When γ,δ-unsaturated ketones or aldehydes are employed as the olefin partner in the reaction, the corresponding γ-brominated carbonyl compounds can be formed. Commonly, gaseous HBr is led through an AcOH solution of the alkene, resulting in a fast addition of the electrophile according to Markovnikov's rule. In this way, Mihailović[230] and Cossy,[231] respectively, synthesized γ-bromo ketones **623a**,**b** in moderate to good yields (Scheme 154).

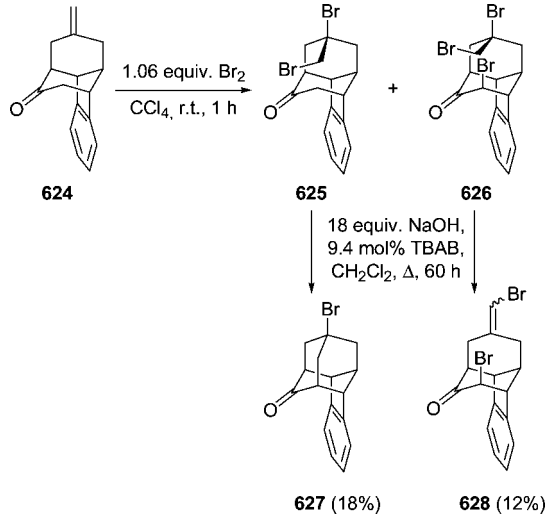
3.4.2. Reactions of Olefins with Br_2

Klein and co-workers investigated the bromination of tricyclic olefin **624** with the correct stereochemistry at C(14), allowing a subsequent ring closure to adamantanone **627** (Scheme 155).[232] This selectivity was accounted for by assuming a less hindered exocyclic approach of Br_2 toward

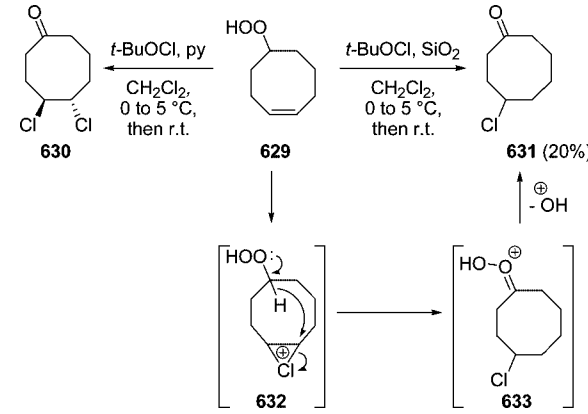
Scheme 154



Scheme 155



Scheme 156



the unsaturation. Nevertheless, partial overbromination led to the formation of olefin **628**.

3.4.3. Miscellaneous

As reported in the section on β-halogenated compounds (see Scheme 66), Bloodworth and co-workers observed the formation of dichlorinated ketones or aldehydes as a major byproduct during the preparation of 1,2-dioxolanes from unsaturated hydroperoxydes and *t*-BuOCl. This was also the case for cyclooct-4-en-1-yl hydroperoxide **629** (Scheme 156).[118] Moreover, in contrast to the case of cyclooct-3-en-1-yl hydroperoxide, the use of silica instead of pyridine did not provide an entry toward the desired peroxide for this substrate, as γ-chlorocyclooctenone **631** proved to be the major product in this case. This observation was rationalized by assuming a mechanism that involves a well-established transannular 1,5-hydride transfer.

3.5. Radical Reactions

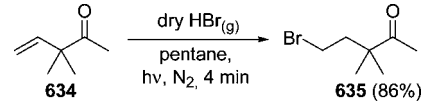
3.5.1. Additions

A textbook procedure for the synthesis of ω-halogenated carbonyl compounds is the anti-Markovnikov, radical addition of a hydrogen halide to the unsaturated parent structure. However, conditions have to be chosen that minimize the tendency for the keto-function to tautomerize to its enol form. Radical chain hydrohalogenations of olefins are often light-initiated, typically realized through irradiation with a medium or high pressure mercury lamp. In this way, 3,3-dimethyl-pent-4-en-2-one (**634**) was readily converted into 5-bromo-3,3-dimethyl-2-pentanone (**635**), the expected anti-Markovnikov adduct (Scheme 157).[27]

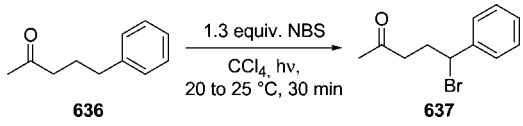
3.5.2. Radical Halogenation

The free radical halogenation of alkanes can selectively furnish one product over other regioisomers when stabilization of the intermediate radical is possible at a certain position. Hence, 5-phenyl-2-pentanone undergoes a controlled conversion into 5-bromo-5-phenyl-2-pentanone when subjected to UV-irradiation in the presence of NBS (Scheme 158).[233] Analogously, 2-methylbenzophenone can selectively

Scheme 157

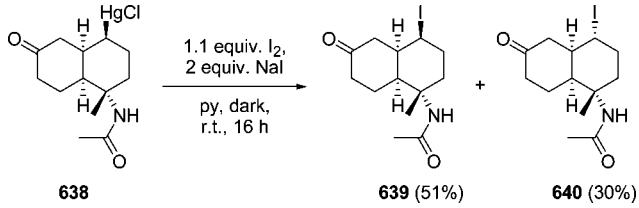


Scheme 158



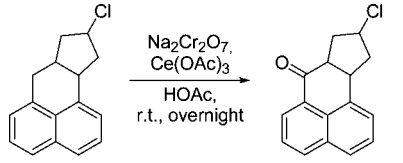
636 **637**

Scheme 159



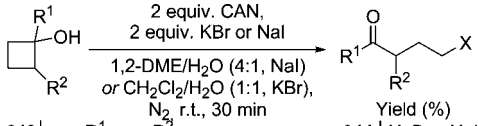
638 **639** (51%) **640** (30%)

Scheme 160



641 **642** (38%)

Scheme 161



643	R^1	R^2	Yield (%) 644 X=Br	X=I
a	Ph	H	87	79
b	*p*-$MeOC_6H_4$	H	70	67
c	*p*-FC_6H_4	H	95	79
d	c-Hex	H	mix[a]	64
e	*n*-Hex	H	mix[a]	80
f	*p*-FC_6H_4	Et	37[b]	80

[a]mixture; [b]crude

undergo a radical bromination at the benzylic position (Scheme 158).[234]

Organomercuric halides are also susceptible to radical halogenation. Substitution of the mercury halide group of ketone **638** with I_2 afforded epimeric iodides **639** and **640** under both "dark" and "light" conditions. These results strongly point toward a free-radical mechanism for this transformation (Scheme 159).[235]

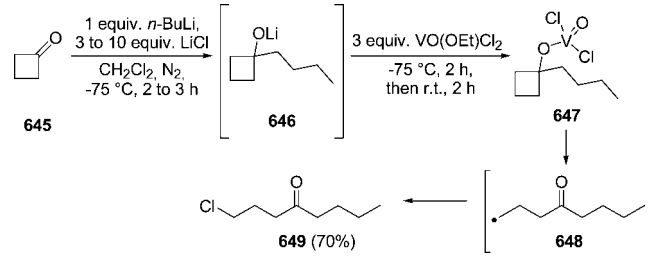
3.5.3. Oxidation

For similar reasons as with radical halogenations, benzylic positions are prone to radical oxidation. This was exemplified by Sugihara and co-workers by the conversion of 9-chlorohexahydrocyclopenta[*a*]phenalene **641** into the corresponding ketone **642**, albeit in low yield (Scheme 160).[236]

3.5.4. Ring-Opening

γ-Halogenated ketones can be obtained through a Ce(IV)-mediated oxidative coupling of 1-substituted cyclobutanols and inorganic halides. When NaI is oxidized with CAN in a H_2O/dimethoxyethane solvent mixture, the resulting iodine radical will selectively add to the least hindered carbon of the cyclobutanol (Scheme 161).[237] In this way, a range of aromatic and aliphatic γ-iodo ketones **644a**−**f** were prepared. The CAN-mediated oxidation of bromide is relatively slow compared to that of iodide. Thus, in order to avoid the direct oxidation of the cyclobutanols, reactions with KBr were

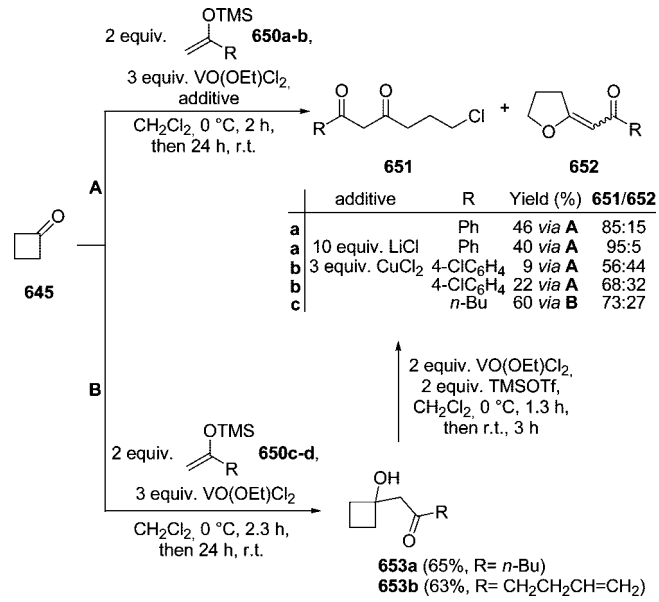
Scheme 162



645 **646** **647**

649 (70%) **648**

Scheme 163



	additive	R	Yield (%)	651/652
a		Ph	46 *via* **A**	85:15
a	10 equiv. LiCl	Ph	40 *via* **A**	95:5
b	3 equiv. $CuCl_2$	4-ClC_6H_4	9 *via* **A**	56:44
b		4-ClC_6H_4	22 *via* **A**	68:32
c		*n*-Bu	60 *via* **B**	73:27

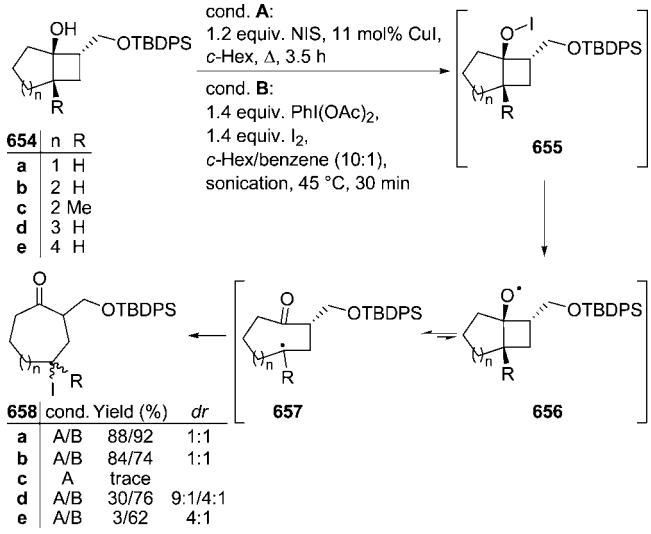
653a (65%, R= *n*-Bu)
653b (63%, R= $CH_2CH_2CH{=}CH_2$)

carried out in a two-phase solvent system. These brominations, however, proved only successful in the case of 1-aryl substituted cyclobutanols, even when other oxidants were evaluated [copper(I) perchlorate hexahydrate, ferrocenium hexafluorophosphate]. The presence of α-brominated products for 1-alkyl substituted cyclobutanols evidenced the formation of Br_2 during the course of the reaction. Hence, these substrates must be less reactive than their 1-aryl substituted counterparts, allowing homocoupling of bromo atoms to become a competitive pathway.

$VO(OEt)Cl_2$ is a useful reagent for the oxidative ring-opening of cyclic carbonyl compounds. In contrast with other vanadium(V) reagents, which are to be used in aqueous acidic media, this one-electron oxidizing Lewis acid can be employed in organic solvents. As shown by Hirao and co-workers, $VO(OEt)Cl_2$ can be employed to convert cyclobutanone into 1-chlorooctan-4-one in two steps (Scheme 162).[238] Upon transmetalation of lithium cyclobutoxide **646** toward its oxovanadium equivalent **647**, homolytic ring-opening takes place to generate radical **648**. Subsequent reaction of this intermediate with a halogen source yields γ-halogenated ketone **649**. It should be noted that this reaction is characteristic of $VO(OEt)Cl_2$, since $VO(OEt)_3$ did not act as an oxidant in this system. Moreover, the absence of LiCl resulted in a lower yield.

To extend the scope of these $VO(OEt)Cl_2$-mediated transformations, the same researchers investigated the tandem nucleophilic addition−oxidative ring-opening of cyclobutanones in the presence of silyl enol ethers **650a**−**b**, furnishing chlorinated β-diketones **651a**−**b** (Scheme 163).[239] The silyl species **650** behave as nucleophiles and are not

Scheme 164



oxidized under the conditions employed, an observation which contrasts with reports on their radical precursor and acceptor properties. Furthermore, the formation of a tetrahydrofurylidene ketone side product was suppressed by the addition of LiCl. For alkyl-substituted silyl enol ethers **650c−d**, however, oxidative transformation was not observed, as only aldols **653a**,**b** were isolated. Yet, upon subsequent treatment with a $VO(OEt)Cl_2$/TMSOTf system, possessing a higher oxidation capability, oxidative ring-opening occurred. A plausible mechanistic pathway was presented.

Medium-sized cyclic γ-halo ketones can be synthesized by means of a radical-mediated ring-opening reaction of *cis*-bicyclo[*n*.2.0]alkan-1-ols **654a−e** (Scheme 164).[240] The two most satisfying reagent combinations to accomplish this transformation are NIS-CuI (**A**) and $PhI(OAc)_2$-I_2 (**B**). The diastereomeric ratio of the obtained ketones **658a−e** depends upon the ring size. This type of reaction is dealt with in more detail in the section on δ-halogenated compounds.

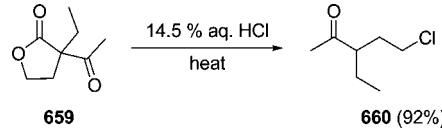
3.6. Ring-Opening and Expansion

3.6.1. Lactones

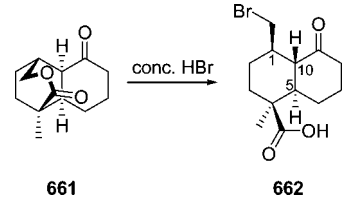
The hydrogen halide-mediated decarboxylation of α-acyl lactones is a widely used, straightforward procedure for the synthesis of γ-halogenated ketones. Numerous examples of this transformation, mostly conducted in warm aqueous solutions of HBr[241−244] or HCl[245−247] have been reported (Scheme 165).[248] Workup usually consists of a purification by distillation after the reaction.[248,249] However, it is also common practice to continuously distill off the end product into an ice-cooled flask.[250,251]

In the total synthesis of (±)-myrocin C, Danishefsky and co-workers opened bridged lactone **661** by treatment with concentrated HBr (Scheme 166).[252] Interestingly, the ring junction hydrogen at C(10) underwent epimerization during this transformation.

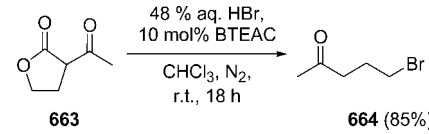
Scheme 165



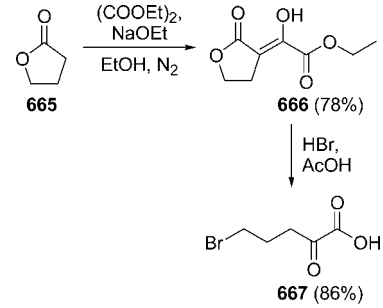
Scheme 166



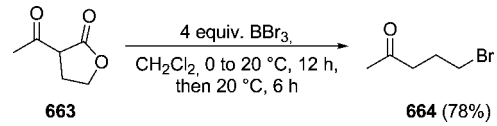
Scheme 167



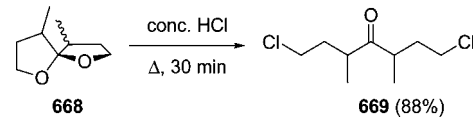
Scheme 168



Scheme 169



Scheme 170



However, according to ApSimon and co-workers, the above-described approaches are often nonreproducible, and prolonged exposure to acidic conditions frequently leads to polymerization. Hence, these researchers presented a more elegant phase transfer catalyzed variant of the decarboxylation reaction (Scheme 167).[253] Next to $CHCl_3$, toluene has also been employed as the organic solvent.[254]

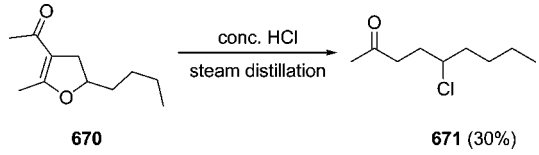
Burke[255] and Yates[256] reported the successful use of HBr in AcOH for the preparation of δ-halogenated-α-ketoacid **667** (Scheme 168). Starting from γ-butyrolactone **665**, the intermediate α-ethyloxalyl-γ-butyrolactone **666** was obtained upon treatment with diethyl oxalate.

Furthermore, as illustrated by Langer and co-workers, simple γ-bromo ketones such as 1-bromo-4-pentanone **664** can be synthesized in good yield by a BBr_3-mediated ring-opening of the corresponding lactones (Scheme 169).[257]

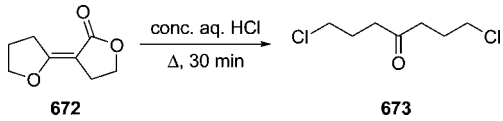
3.6.2. Cyclic Acetals

Cleavage of spiroacetal **668** with a 10-fold excess (by volume) of concentrated HCl causes substitution of the hydroxyl groups for chloride, giving rise to dichlorinated ketone **669** in very good yield (Scheme 170).[258]

Scheme 171



Scheme 172

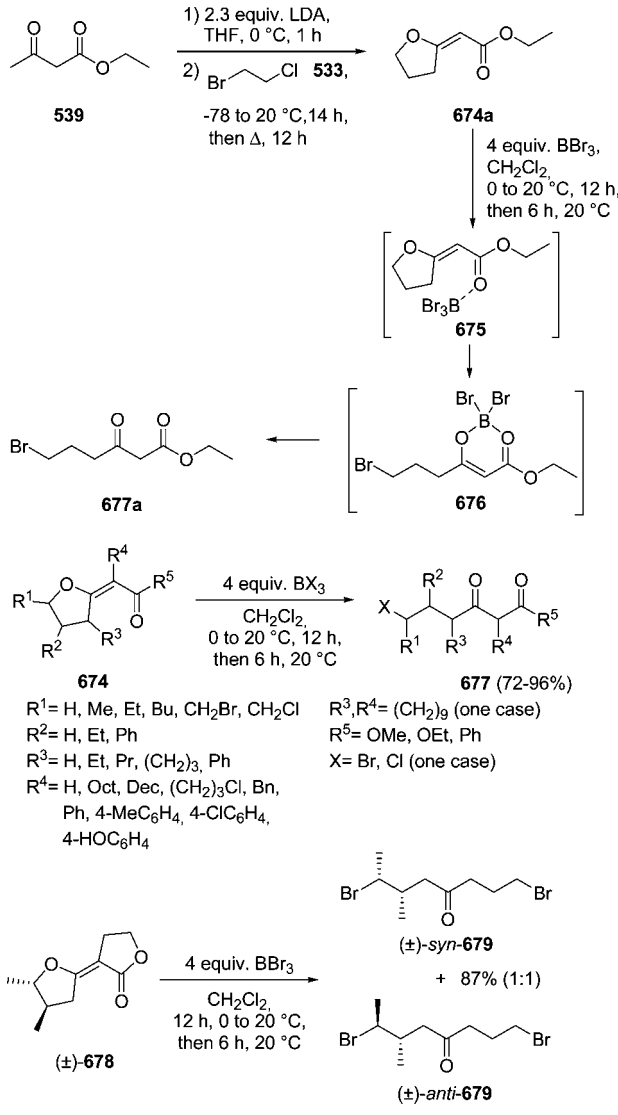


3.6.3. Cyclic Ethers

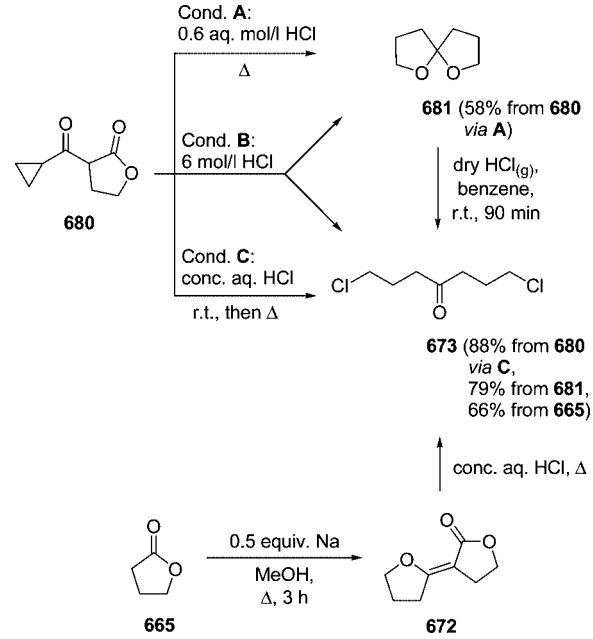
3.6.3.1. Enol Ethers. The cleavage of enol ethers under acidic conditions is a well-known transformation. As such, upon heating with concentrated HCl, dihydrofuran **670** underwent ring-opening and further conversion to furnish 5-chloro-2-nonanone **671** (Scheme 171).[259]

In a standard procedure for the preparation of dicyclopropyl ketone, Curtis and co-workers studied the ring-opening of both the enol and lactone moieties of compound **672** by treatment with concentrated HCl under reflux, affording 1,7-dichloroheptan-4-one **673** (Scheme 172).[260]

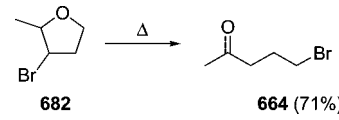
Scheme 173



Scheme 174



Scheme 175



Whereas the BBr_3-mediated cleavage of methyl aryl ethers is well-known and frequently used, reactions with other ethers are more scarce. Langer and co-workers, however, reported a "ring-closure/ring-cleavage" methodology involving the regio- and chemoselective reaction of 2-alkylidenetetrahydrofurans **674** with BX_3 to afford ε-halo-β-ketoesters **677** and γ,γ'-dibromoalkanones **679** (Scheme 173).[257] The latter compounds were obtained from tetrahydro[2,3′]bifuranyliden-2′-ones **678**, *via* a BBr_3-mediated cleavage of both the cyclic enol and the lactone moiety, a reaction identical to the above one reported by Curtis and co-workers. In contrast to the cleavage of methylaryl ethers, ring-opening of the furan moiety proceeds *via* an S_N1 rather than an S_N2 mechanism, resulting in epimerization at C(5) and thus affording a 1:1 mixture of the *syn*- and *anti*-diastereoisomers.

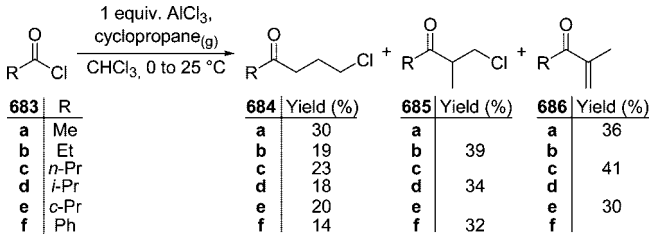
A closely related report was published by Hart and co-workers, concerning the synthesis of 1,7-dichloro-4-heptanone **673** (Scheme 174).[261] This symmetrical ketone was obtained *via* HCl -mediated ring-opening of different cyclic substrates such as cyclopropanes (to be discussed further on), lactones, spiro-acetals, and cyclic enol ethers.

3.6.3.2. Miscellaneous. Polivin and co-workers reported on the thermal isomerization of 2-methyl-3-bromotetrahydrofuran **682** to terminally brominated methylketone **664** (Scheme 175).[262] Besides, De Buyck and co-workers described a one-pot route from tetrahydrofuran to 2,2,4-trichlorobutanal involving the isomerization of 2,3,3-trichlorotetrahydrofuran by $AlCl_3$.[263,264]

3.6.4. Cycloalkanes

3.6.4.1. Cyclopropanes. *Cyclopropanes as Friedel−Crafts Acceptors.* A well-known parallel exists between cyclopropane and olefin chemistry, given the similarity in physical properties and chemical behavior of the olefinic double bond

Scheme 176



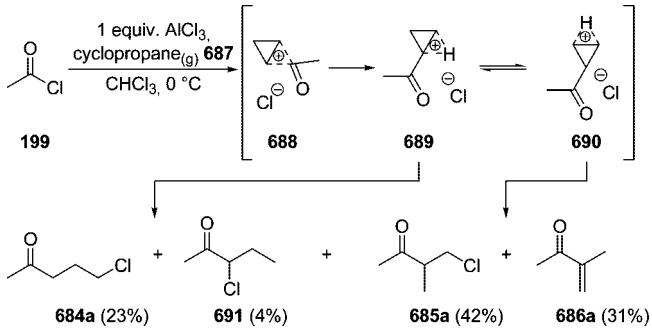
683	R
a	Me
b	Et
c	*n*-Pr
d	*i*-Pr
e	*c*-Pr
f	Ph

684	Yield (%)
a	30
b	19
c	23
d	18
e	20
f	14

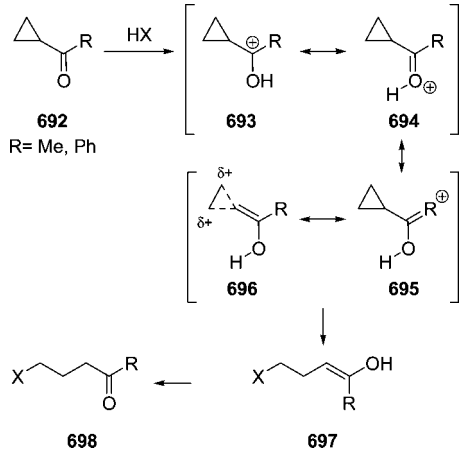
685	Yield (%)
a	
b	39
c	
d	34
e	
f	32

686	Yield (%)
a	36
b	
c	41
d	
e	30
f	

Scheme 177



Scheme 178



and the cyclopropane ring. Hence, a cyclopropane can act as an acceptor in Friedel−Crafts acylation reactions. Treatment of an acid chloride with cyclopropane in the presence of $AlCl_3$ will thus provide a γ-chloro ketone. The net result of the reaction is the insertion of three methylene groups between the carbonyl and chlorine moieties, which draws a direct parallel to the two-carbon counterpart when utilizing olefins. Hart and co-workers noted, however, that the γ-chloro ketones are only the minor reaction products. In all cases, the major products unexpectedly were β-chloro-α-methyl ketones (Scheme 176).[265] Analogous observations were made for several other substituted cyclopropanes and additional acylating reagents.[88]

A thourough explanation for this curious addition process was only provided several years later, again by Hart and co-workers, involving the intermediacy of protonated cyclopropanes **688**−**690** (Scheme 177).[266] A notable exception, however, was 1,1-dimethylcyclopropane, which undergoes a rapid isomerization to isoprene, catalyzed by the acid present in the reaction medium. This olefin is then subsequently acylated.

Cyclopropyl Ketones. Functionally activated cyclopropanes are versatile synthetic intermediates in organic chemistry, because they undergo facile and predictable ring-opening reactions. Due to the softness of the β-carbon in a cyclopropyl carbonyl compound, analogous reactions to the Michael addition across α,β-unsaturated aldehydes and ketones can be performed. As a consequence, the addition of hydrogen halides to cyclopropanes bearing an electron-withdrawing group is a well-known and widely used reaction, furnishing γ-halo ketones in the case of acylated cyclopropanes.

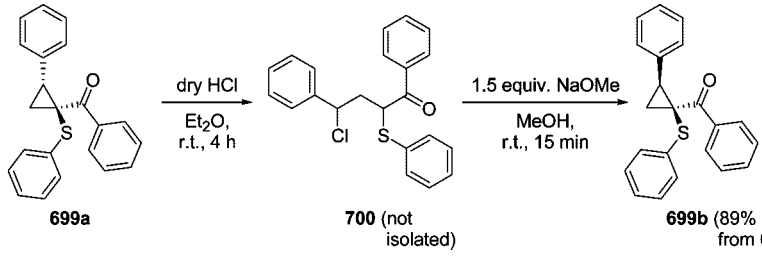
Scope and Mechanism. A survey of the mechanistic effects of the electron-withdrawing group was reported by Lambert and co-workers (Scheme 178).[267] When the side chain has a basic site for protonation and when the positive charge thus formed at the α-carbon can be delocalized to the unsubstituted cyclopropane carbons (**696**), the addition of the hydrogen halide was found to proceed *via* a 1,5-homoconjugate addition, by analogy with the 1,4-conjugate addition to α,β-unsaturated ketones. This fashion of addition is aided by stronger acids and better nucleophiles, whereas highly acidic solvents with low nucleophilicity, such as concentrated H_2SO_4, may cause direct cyclopropane protonation to become important. While delocalization of the positive charge into the three-membered ring enhances its susceptibility to, and thus the rate of, nucleophilic attack, the presence of a phenyl group (R = Ph) will cause some degree of delocalization toward the aromatic system as well and hence reduce the overall reaction rate compared to when R is methyl.

Numerous reports on the addition of HCl[268] or HBr[269,270] to cyclopropyl ketones have been published. In one example, as part of the isomerization sequence of *trans*-1-benzyl-2-phenyl-1-phenylthiocyclopropane **699a** to the *cis*-analogue **699b**, Kulinkovich and co-workers successfully ring opened the cyclopropyl moiety of substrate **699a** upon treatment with dry HCl (Scheme 179).[271]

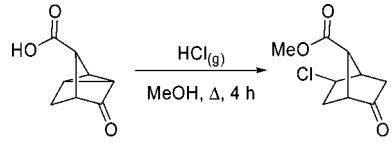
Furthermore, nortricyclene systems, e.g. **701**, are suitable substrates, delivering chlorinated norbornone **702** upon treatment with HCl (Scheme 180).[272,273] Brominated analogues are similarly accessible through reaction with HBr.[274]

In contrast, treatment of tricycloalkane **703** with excess HCl led to the formation of bicyclic ketone **704** (Scheme 181).[275] With *p*-toluenesulfonic acid, or a smaller amount of HCl, the only transformation observed was the hydrolysis of the acetal moiety, thus delivering the corresponding tricyclic ketone.

Scheme 179

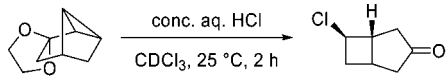


Scheme 180



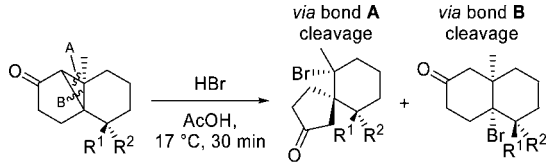
701 **702** (80%)

Scheme 181



703 **704** (79%)

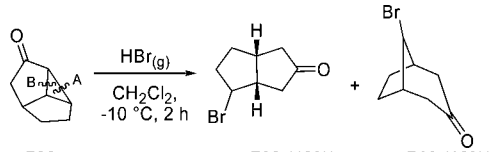
Scheme 182



705

	706	R^1	R^2	707
a	17%	H	Me	83%
b	~99%	Me	H	~1%
c	~65%	H	H	~35%

Scheme 183



708 **709** (49%) *via* bond **A** cleavage **710** (12%) *via* bond **B** cleavage

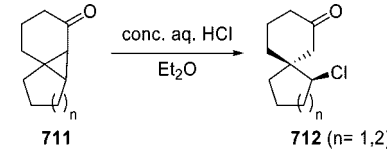
Regioselectivity. 4,5-Cyclopropanocholestan-3-ones[276] and 3α,5α-cyclo-6-oxosteroids[277] undergo cyclopropane ring cleavage upon treatment with HBr. Besides, the opening of the cyclopropane ring in tricyclo[4.4.0.0^{2,6}]decan-2-one moiety **705**, fused to the C-ring of steroid systems, with HCl[278] or HBr[279] has been reported.

This cleavage, studied by Caine and co-workers, can yield both spiro and fused-ring bromo ketones **706** and **707** (Scheme 182).[280] The outcome of the reaction is determined by the kinetically controlled attack of the halide in the 1,5-homoconjugate addition mechanism, which proceeds in a diaxial manner with respect to the most stable conformation of the six-membered ring. Thus, the location and stereochemistry of the substituents have a profound influence upon the course of the reaction.

Analogously, Monti and co-workers investigated the cleavage of tricyclic ketone **708** under acidic conditions (Scheme 183).[281] Selective cleavage of the cyclopropane σ-bond best oriented for overlap with the adjacent p-orbital led to the formation of ketone **709** as the predominant reaction product. However, since the ring-opening is essentially reversible, the selectivity was lower than that observed for a dissolving metal opening.

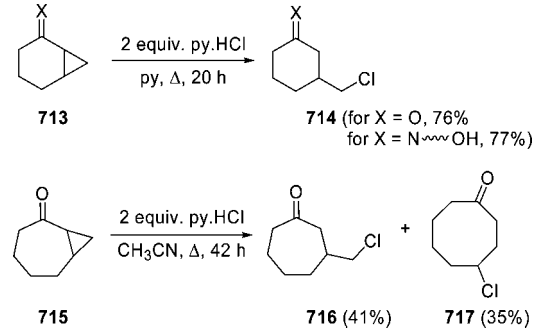
Similar ring-opening reactions of tricyclic ketones have been reported by White and co-workers. Their findings are in accordance with the observations of Monti and co-workers, since the sole product obtained upon treatment with HCl was spiro compound **712** (Scheme 184).[282] The fast regeneration of ketone **711** from the end product **712** allowed for the assignment of the configuration of the chlorinated ketone, since the easy displacement of chloride results from a stereoelectronically favorable relationship between the leaving group and the internally formed enolate anion.

Scheme 184



711 **712** (n= 1,2)

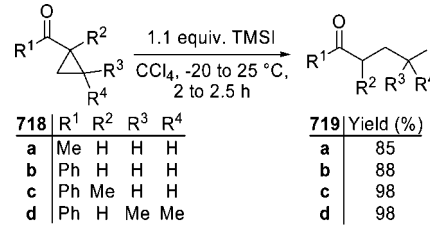
Scheme 185



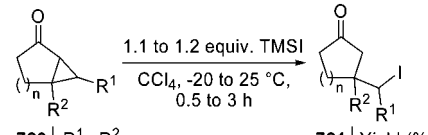
Tardella and co-workers presented pyridine hydrochloride (py·HCl) in dry pyridine as a mild, anhydrous alternative reagent for the cleavage of the conjugated and fused cyclopropyl ring of bicyclo[4.1.0]heptan-2-one **713** and its oximes (Scheme 185).[283] In these substrates, the C(1)−C(7) bond is selectively opened because of its large orbital overlap with the adjacent π-system. Conjugation of the cyclopropyl ring with a π-system and the strain caused by the fusion with another ring seemed determinant for the swiftness of the reaction. Preservation of the oxime function makes this protocol useful in the synthesis of azabicycloalkanes. Pyridine hydrochloride is also frequently employed in combination with the more polar solvent acetonitrile,[284] which renders the reaction applicable to other cyclopropyl ketones, such as the nonfused, exocyclic carbonyl bearing cyclopropyl methyl ketone.[285]

In contrast to heptanone **713**, bicyclo[5.1.0]octan-2-one **715** did not open selectively in the hands of Tardella and co-workers, as two isomeric chloro ketones **716** and **717** were obtained.[286] While investigating the selectivity of the ring fission for various other substrates, these researchers furthermore noted that the less reactive pyridine hydroiodide

Scheme 186

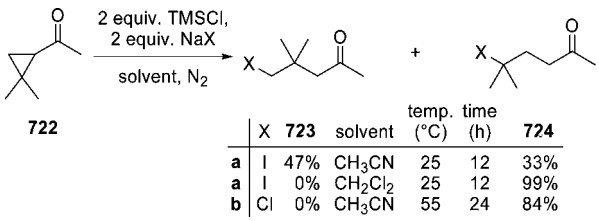


718	R^1	R^2	R^3	R^4	719	Yield (%)
a	Me	H	H	H	a	85
b	Ph	H	H	H	b	88
c	Ph	Me	H	H	c	98
d	Ph	H	Me	Me	d	98

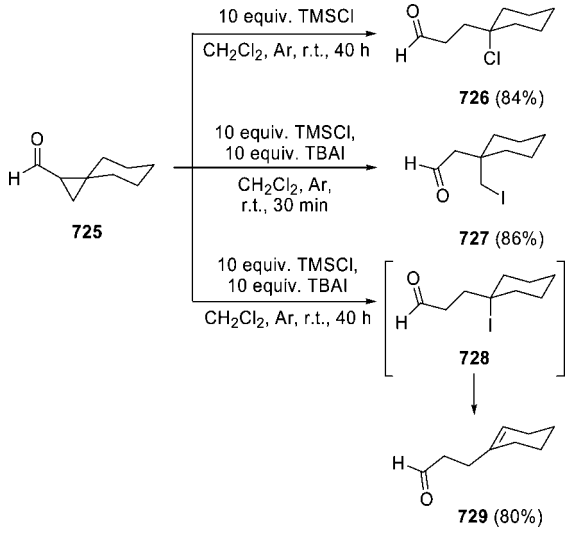


720	R^1	R^2	n	721	Yield (%)
a	H	H	1	a	95
b	H	H	2	b	90
c	$(CH_2)_4$		2	c	89

Scheme 187



Scheme 188



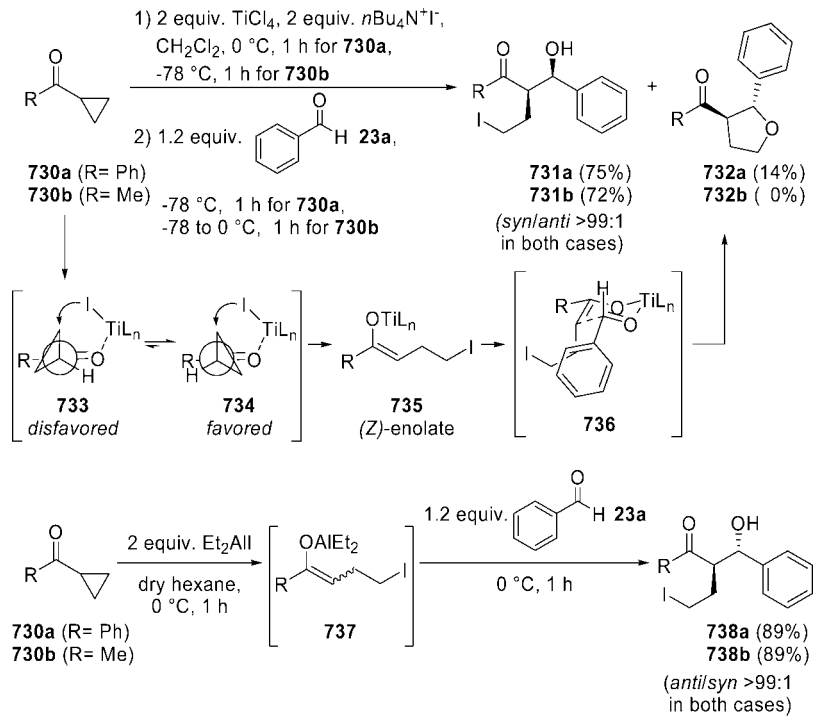
allowed for a better selectivity. Besides, it was suggested that the outcome of the reaction is not completely kinetic of origin, but also to a certain extent thermodynamically controlled.[287]

Given the incompatibility of acidic reagents with numerous sensitive functionalities, and the possible unpredictable regioselectivity of the ring cleavage, Miller and co-workers introduced TMSI as a new reagent for the opening of cyclopropyl ketones (Scheme 186).[288] This kind of combination of a rather soft nucleophile and a hard electrophile is a well-established, mild technique of considerable synthetic importance. Employing TMSI, ring-opening of rigid systems proceeds rapidly and with a high degree of regioselectivity, predictable by bond overlap considerations.

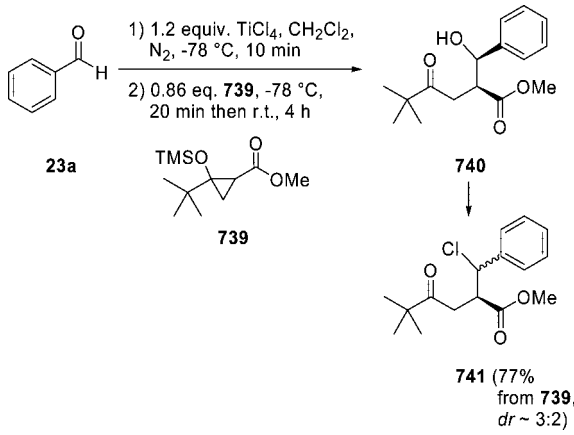
In this context, Dieter and co-workers investigated the influence of the electrophile−nucleophile combination on the regioselectivity of the ring-opening for cyclopropanes with freely rotatable carbonyl moieties, such as 2,2-dimethylcyclopropyl methyl ketone **722** (Scheme 187).[289] For this substrate, a concerted S_N2 reaction process would explain the formation of **723**, while **724** would be expected to arise from an S_N1 type mechanism, thus with a considerable carbenium ion character in the transition state. Whereas the stronger nucleophilic iodide afforded a nearly equimolecular mixture of the two isomers, the weaker nucleophilic chloride led to regioselective ring-opening *via* the S_N1-pathway. The same selectivity can be accomplished by switching to less polar solvents, that disfavor solvent-separated ion pairs, such as CH_2Cl_2. Besides, $AlCl_3$, in the presence of NaI, gave a clean and efficient cleavage of cyclopropyl methyl ketone.

Interestingly, while investigating the regioselective cyclopropyl ring-opening of 6-formyl-spirobicyclo[5.2]octane with trialkylsilyl halides, Forsyth and co-workers also pointed toward the influence of the β-substitution, conformational rigidity, nucleophilicity, and solvent polarity on the regiochemical outcome of the cyclopropyl fragmentation (Scheme 188).[290] These authors were able to develop a reliable approach for the opening of formyl substituted spiro-fused cyclopropane **725** in high yields with absolute regiochemical control. When TMSCl was used in the presence of a large excess of the highly dissociative tetra-*n*-butylammonium iodide (TBAI), an exclusive rapid S_N2 type ring-opening of the silylated intermediate was observed, whereas the weakly nucleophilic chloride anion, under prolonged reaction conditions, gave a clean conversion into tertiary chloride **726**. As can be expected, prolonged treatment of spiro-fused cyclo-

Scheme 189



Scheme 190



propane **725** under the reaction conditions for the formation of aldehyde **727** gave rise to the thermodynamic product **728**, whereupon elimination of HI yielded cyclohexene derivative **729**.

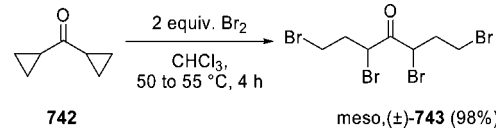
Several other examples of this mild type of cyclopropane cleavage, employing TMSI[291,292] or TMSBr[293] and affording γ-halo ketones, have been reported.

Oshima and co-workers investigated the ring-opening of cyclopropyl ketones **730a**−**b** with *n*-$Bu_4N^+I^-$ or Et_2AlI for the preparation of enolates, and the influence of these Lewis acids on the stereochemical outcome of a subsequent reaction with various aldehydes (Scheme 189).[294] $TiCl_4$/*n*-$Bu_4N^+I^-$-induced ring-opening furnished (*Z*)-enolates **735** and thus, according to the Zimmerman and Traxler model **736**, preferably *syn*-aldol adducts **731a**−**b**. The corresponding *trans*-acyltetrahydrofurans **732a**−**b** were isolated as the minor products. Et_2AlI, on the contrary, afforded mixtures of the *anti*- and *syn*-isomers at low temperature and the thermodynamically more stable *anti*-adduct **738a**−**b** as a single product at 0 °C. At this temperature, only acetaldehyde provided a mixture of the two isomers. Thus, $TiCl_4$/*n*-$Bu_4N^+I^-$ and Et_2AlI possess a complementary behavior from a diastereoselective point of view.

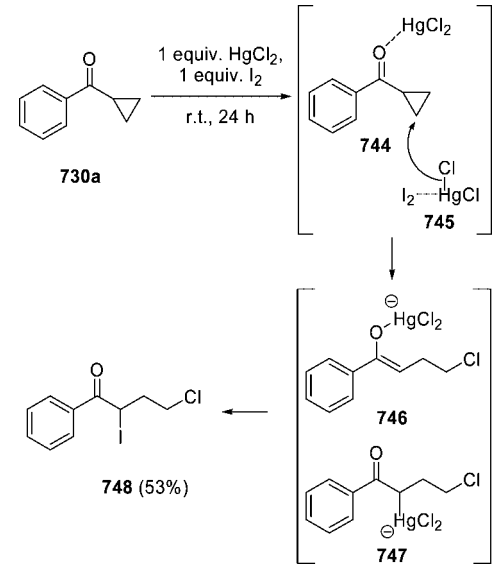
Mukaiyama conditions, using TMSI as the Lewis acid, gave no significant diastereoselectivity in most cases. Besides, the regioselectivity of the ring-opening was examined for 2-methylcyclopropyl phenyl ketone. $TiCl_4$/*n*-$Bu_4N^+I^-$ regioselectively attacked at the less hindered site, whereas Et_2AlI showed a slightly lower preference for the same mode of attack. TMSI, on the other hand, showed opposite regioselectivity. An explanation for this behavior was given *via* a conformational analysis. Furthermore, Li and co-workers successfully applied the Et_2AlI-mediated reaction on a cyclopropyl imide bearing a chiral oxazolidinone.[295]

Donor−*Acceptor Substituted Cyclopropanes.* Reissig and co-workers reported a mode of cyclopropane ring cleavage comprising the simultaneous formation of a new carbon−carbon bond, affording γ-oxocarboxylates (Scheme 190).[296] As such, cyclopropane **739** underwent a highly stereoselective reaction with benzaldehyde, leading to the formation of homoaldol product **740**. This highly interesting transformation, both from a synthetic and a mechanistic point of view, was demonstrated to proceed *via* a titanoxycyclopropane intermediate, which accounts for the observed stereoselectivity. However, when the reaction mixture was allowed to warm up to ambient temperature, the Lewis-acidic conditions allowed for an S_N1-substitution to take place, thus forming chlorinated oxocarboxylate **741** as a mixture of two diastereoisomers.

Scheme 191



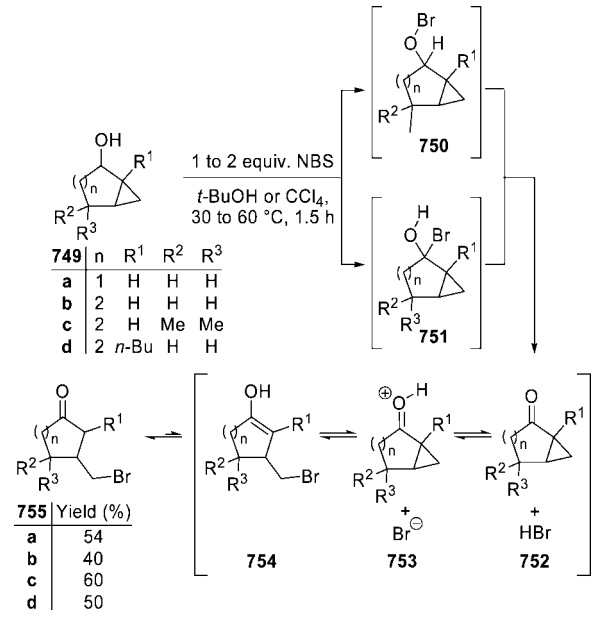
Scheme 192



Miscellaneous. As exemplified by Fitjer, cyclopropyl ketones can be converted into α,γ-dibromo ketones upon treatment with Br_2 (Scheme 191).[297] Traces of HBr, present in the reaction mixture, will initiate ring cleavage, while the subsequent bromination will release additional HBr, necessary to keep the reaction going.

In their research on mercury(II) halides as a source of electrophilic iodine for the iodofunctionalization of cyclopropanes, Barluenga and co-workers were able to convert cyclopropyl phenyl ketone **730a** into (3-chloro-1-iodopropyl)phenyl ketone **748** upon treatment with $HgCl_2$ and I_2 (Scheme 192).[298] The proposed mechanism for this bifunctionalization involves an activated iodine molecule **745**.

Scheme 193



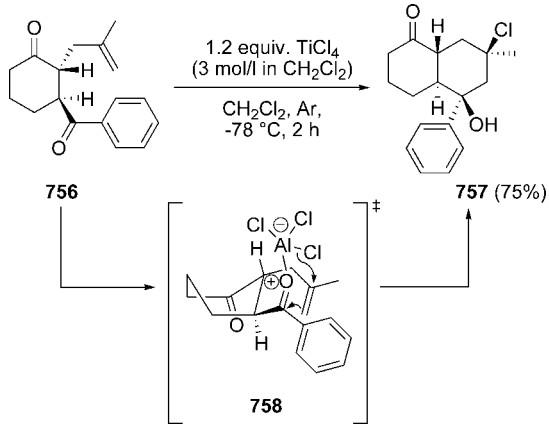
Miscellaneous. Cossy and co-workers reported on the NBS-mediated oxidation of cyclopropylcarbinols **749** to 3-(bromomethyl)cycloalkanones **755** (Scheme 193).[299] Investigation of this oxidative ring-opening pointed toward an ionic mechanism, in which a bromonium ion produces hypobromite **750** or bromohydrine **751**. Either of these intermediates is prone to lose HBr, that subsequently can activate the carbonyl group of intermediate **752** and induce ring-opening by nucleophilic attack of the bromide on species **753**. Nevertheless, it has to be noted that ester substituted derivatives of bicyclic alcohols **749** underwent Reichstein's oxidation without ring-opening, furnishing cyclopropyl ketones.

3.7. Ring Closure, Contraction, and Rearrangement

3.7.1. Ring Closure

Intramolecular, Lewis-acid-mediated carbonyl-ene reactions have been studied widely for the construction of highly functionalized bicyclic compounds. As such, Wartski and co-workers investigated the intramolecular ring closure of cyclohexanone **756**, bearing aroyl and allylic moieties in a *trans* vicinal manner, upon treatment with $TiCl_4$ (Scheme 194).[300] Interestingly, a highly regio- and stereoselective attack at the aryl ketone group took place, leading to highly functionalized *trans*-fused bicyclic ketone **757**. Detailed structural assignments were made based on NMR and single crystal X-ray analyses. These observations lead to the suggestion of a six-center transition state **758**, involving the carbonyl−Lewis acid complex in the preaxial position and the phenyl group in the pre-equatorial position. Transfer of a chloride ion is favored by the development of a positive charge at the C(7)-position.

Scheme 194



3.7.2. Ring Contraction

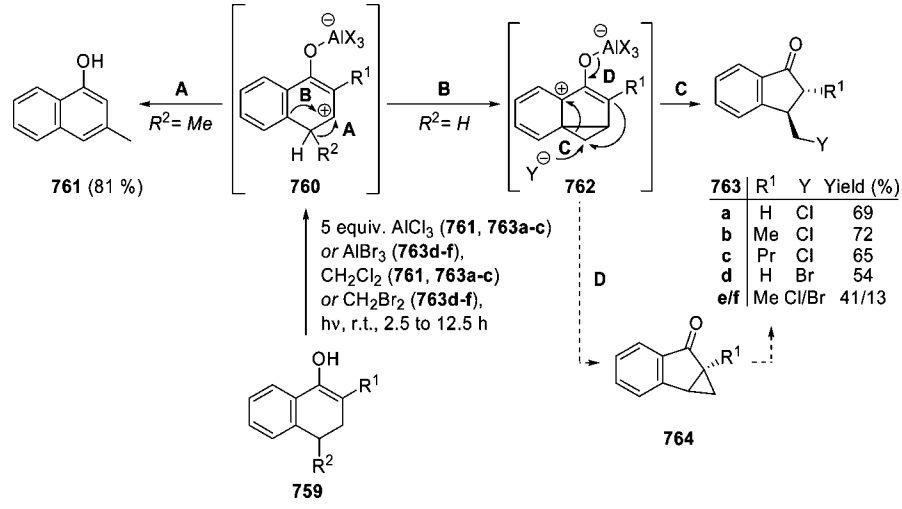
Irradiation of CH_2Cl_2 or CH_2Br_2 solutions of 1-naphthols **759** in the presence of AlX_3 yields (halomethyl)indanones **763a**−**f** (Scheme 195).[301] The source of halogen in this remarkable ring contraction is the solvent, *via* a well-known halogen exchange between AlX_3 and haloalkanes. A mechanism for this reaction was proposed, involving the direct formation of the indanones from the naphthols (path **B**,**C**), rather than *via* benzobicyclo[3.1.0]hexenones **764** (path **B**,**D**). Under the same conditions, however, 4-methyl-1-naphthol undergoes isomerization to **761**, which is apparently unreactive toward ring contraction (path **A**).

3.7.3. Ring Rearrangement

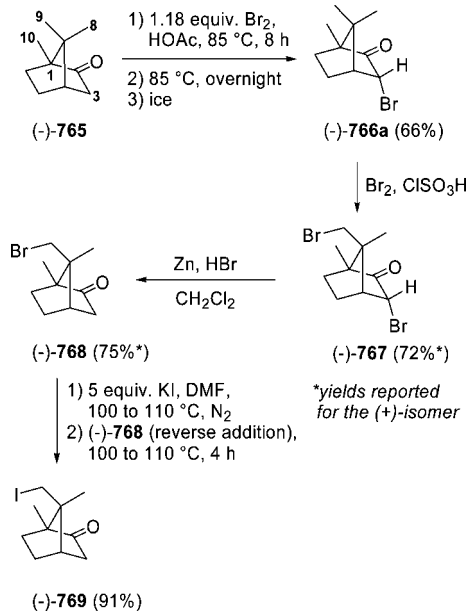
From the end of the 19th century until the appearance of a series of papers by Money and co-workers, the direct bromination of camphor and 3-bromocamphor at the C(8)-, C(9)-, and C(10)-methyl groups had been the subject of considerable investigation.[302] The first isomer for which a practical synthetic procedure and thorough mechanistic explanation was provided was 9-bromocamphor (Scheme 196). Meanwhile, each step in this stereospecific sequence has been optimized. Starting from (−)-camphor **765**, bromination provides (−)-3-bromocamphor **766a**.[303] Subsequent treatment of the latter with bromine in chlorosulfonic acid furnishes (−)-3,9-dibromocamphor **767**.[304] A regiospecific debromination employing zinc in AcOH ultimately yields (−)-9-bromocamphor **768**.[305] Furthermore, a convenient protocol for its conversion into the corresponding iodide **769** was reported by Stevens and co-workers.[303]

The key step of this interesting reaction sequence, the regioselective bromination of 3-bromocamphor **766a** at C(9), involves a highly remarkable set of rearrangements which proceeds with complete retention of chirality (Scheme 197). Initially, (+)-3-bromocamphor **766a** is transformed into key intermediate **773a** *via* Wagner−Meerwein rearrangement (WM), Nametkin shift (2,3-Me), and subsequent bromination. Next, a 2,3-*exo* methyl shift (pathway **a**) provides intermediate **774**, which rearranges to (+)-3,9-dibromocamphor **767**.

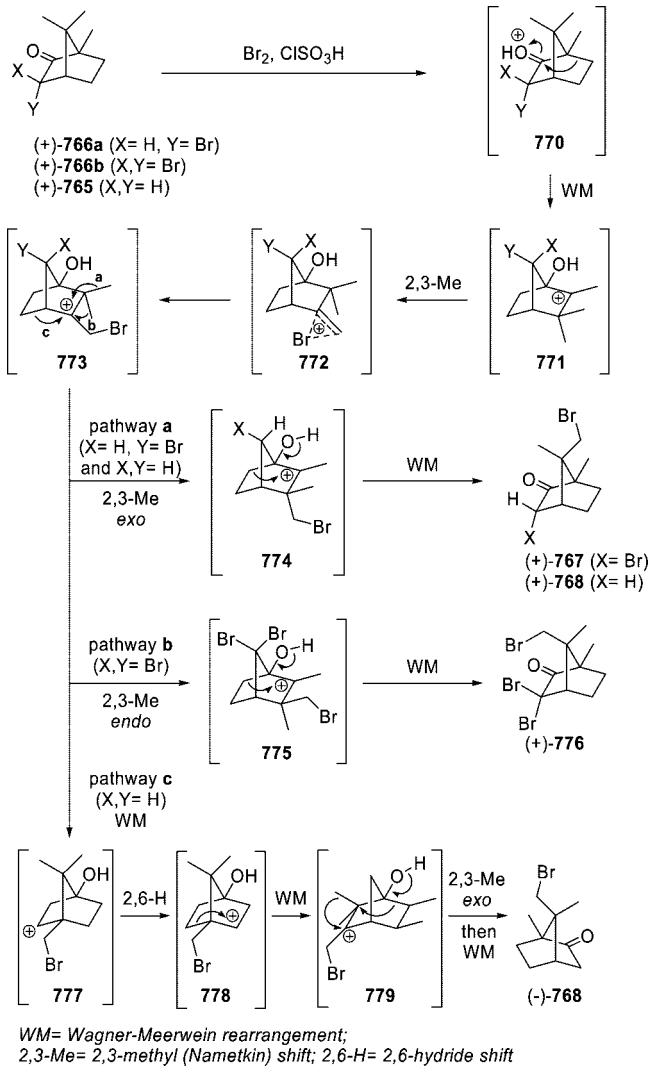
Scheme 195



Scheme 196

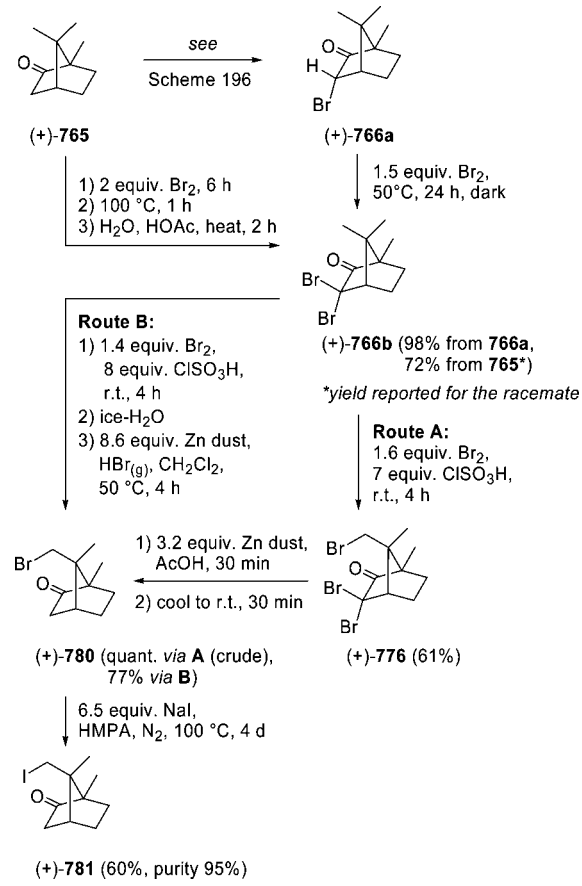


Scheme 197



Strikingly, when (+)-camphor **765** is treated under identical conditions, partially racemic 9-bromocamphor **768** is obtained. This observation can be explained by an alternative series of rearrangements, which convert key intermediate **773** into (−)-**768** (pathway **c**).

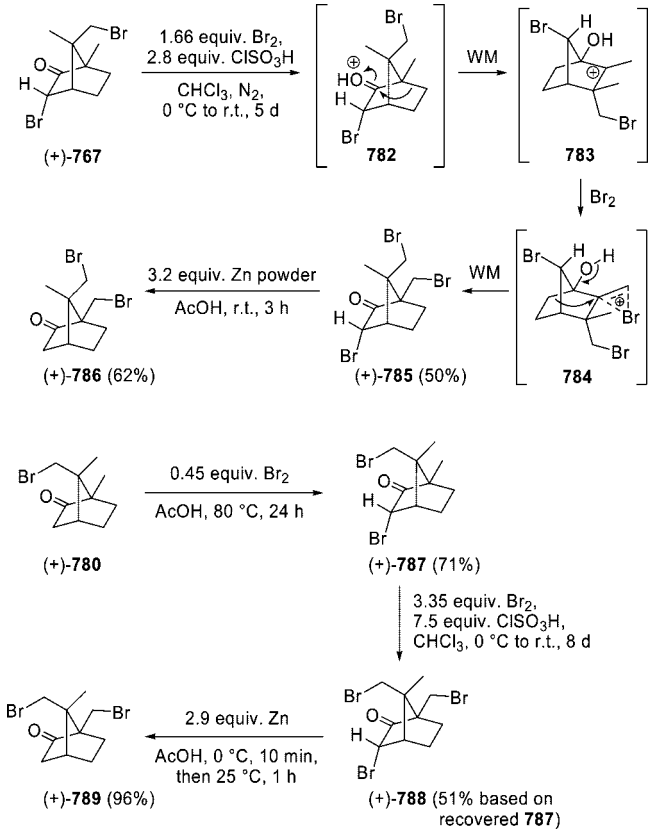
Scheme 198



A comparable regio- and stereospecific direct bromination of camphor at C(8) was developed by Money and co-workers (Scheme 198), obviating an earlier cumbersome 12-step sequence employing 9-bromocamphor (see Scheme 139).[306−308] The protocol of Money proceeds *via* an almost identical mechanism as that of the 9-bromination reaction but involves a rare *endo*-methyl migration furnishing intermediate **775** (Scheme 197, pathway **b**). Reversal of the preference for *exo*- over *endo*-migration was accomplished by introducing a large group in the 7-*syn* position of key intermediate **773**, which implicated the use of 3-*exo*-substituted camphor as a starting material. Elegantly, 3,3-dibromocamphor **766b** was chosen as the starting product, enabling a straightforward removal of both bromo substituents at C(3) in the end product under standard conditions (Zn/HBr, Scheme 202). Money and co-workers later provided evidence for the suggested 2,3-*endo* methyl shift, employing 8- and 9-deuterated camphor as starting materials.[309] Furthermore, (+)-8-iodocamphor **781** was obtained in moderate yield by simple nucleophilic displacement.[310]

In an effort to increase the versatility of chiral camphor derivatives as starting materials for terpenoid and steroid synthesis, Money and co-workers expanded their aforementioned work with a synthetic route toward (+)-8,10- and (+)-9,10-dibromocamphor **789** and **786** (Scheme 199).[311] The latter products can be obtained optically pure upon treatment of (+)-3,8- and (+)-3,9-dibromocamphor (**787**, **767**) under conditions similar to those normally employed for the preparation of 8- and 9-bromocamphor (Br_2/$ClSO_3H$ followed by Zn/AcOH). The authors assumed a reaction

Scheme 199



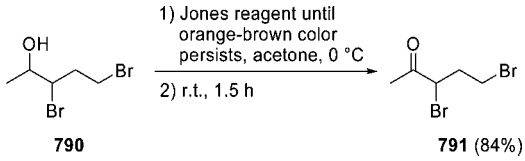
mechanism which involves an initial Wagner−Meerwein rearrangement, followed by bromination of an intermediate camphene derivative (**784**) and a subsequent reversion to the camphor framework.

3.8. Oxidation

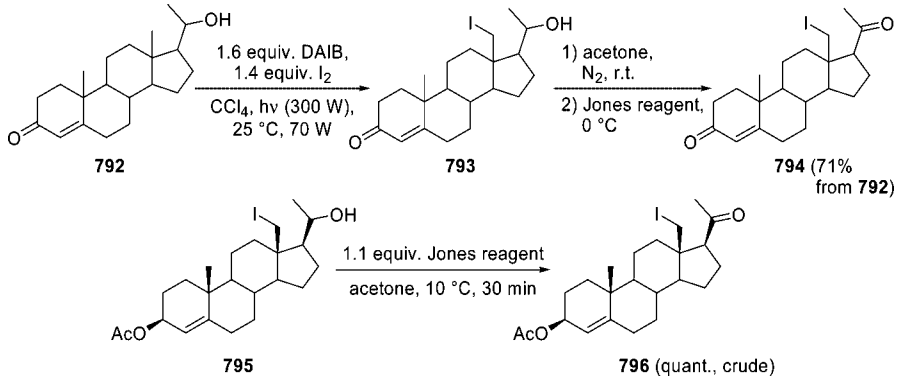
3.8.1. Oxidation of Halogenated Alcohols

3.8.1.1. Chromium-Based Oxidants. *Jones Oxidation.* An aqueous solution of CrO_3 in H_2SO_4 is a standard means for the oxidation of secondary alcohols and is commonly referred

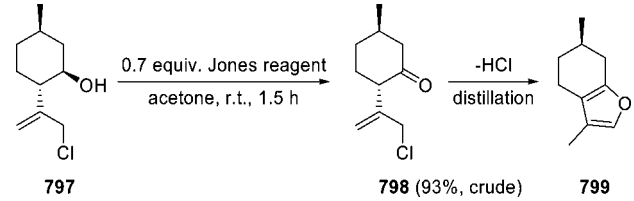
Scheme 200



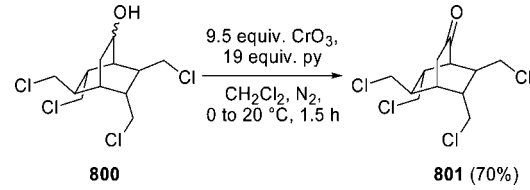
Scheme 201



Scheme 202



Scheme 203



to as the Jones reagent. However, application on primary alcohols is generally disfavored because of the likely overoxidation to the corresponding carboxylic acids. In a first, rather straightforward example, Weyerstahl and co-workers were able to oxidize 3,5-dibromopentan-2-ol **790** using the Jones procedure, furnishing the corresponding ketone **791** in good yield (Scheme 200).[180]

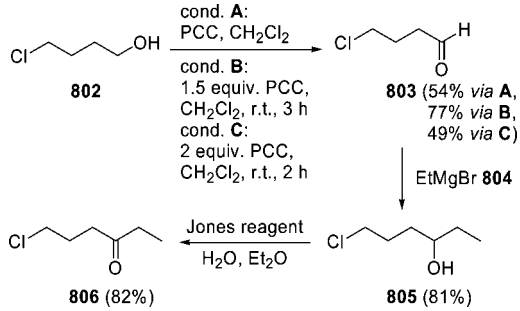
Successful employment of this protocol has also been reported in several syntheses of iodinated steroid derivatives, such as iododiketone **794** (Scheme 201).[312] In the case of 3-acetoxy-18-iodo-20-hydroxysteroid **795**, Choay and co-workers reported a quantitative conversion to the corresponding ketone.[313] In a similar way, Meystre and co-workers reported on the synthesis of 3β,11α-diacetoxy-18-iodo-20-oxo-5α-pregnan.[314]

10-Chloroisopulegol **797** could be oxidized to the corresponding pulegone **798** using the Jones procedure (Scheme 202).[315] Attempted distillation purification of the ketone, however, led to the formation of menthofuran **799** with the liberation of HCl gas.

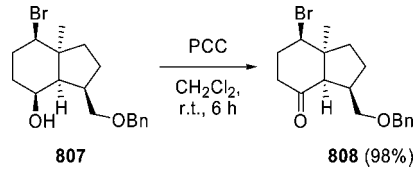
Collins−Ratcliff Reagent. A chromium-based oxidant for primary or secondary alcohols, tolerant toward acid-sensitive functionalities, is the Collins−Ratcliff reagent ($CrO_3 \cdot 2py$ in CH_2Cl_2). This complex was used by Vogel and co-workers to convert chlorinated bicyclo[2.2.2]octan-2-ol derivative **800** into the corresponding octanone **801** (Scheme 203).[316]

Pyridinium Chlorochromate. Closely related to the Collins−Ratcliff reagent, pyridinium chlorochromate (PCC) is a slightly more acidic and reactive oxidant. It is often used in the controlled conversion of primary alcohols into aldehydes, avoiding overoxidation toward the carboxylic acids. Khusid and co-workers, for example, used PCC to transform

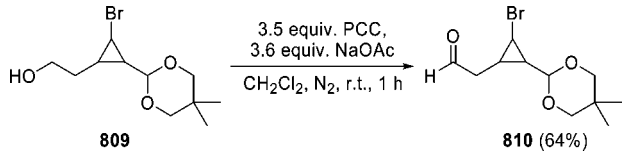
Scheme 204



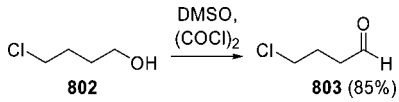
Scheme 205



Scheme 206



Scheme 207



4-chlorobutanol **802** into 4-chlorobutanal **803**, albeit in modest yield (Scheme 204, conditions **A**).[1,317] (It should be noted that this reaction is wrongly described in CASREACT as yielding 4-chloro-2-butanone.) Subsequently, the aldehyde was treated with EtMgBr **804**. The thus formed secondary alcohol **805** is not susceptible to overoxidation and could hence be treated with the Jones reagent to obtain 6-chlorohexan-3-one **806**. Remarkably, in the hands of Marek and co-workers, the PCC-mediated oxidation of 4-chlorobutanol **802** furnished aldehyde **803** in a significantly higher yield (condition **B**, see also Scheme 207).[318] Still, Alexakis and co-workers reported a very poor yield for this transformation (condition **C**).[319]

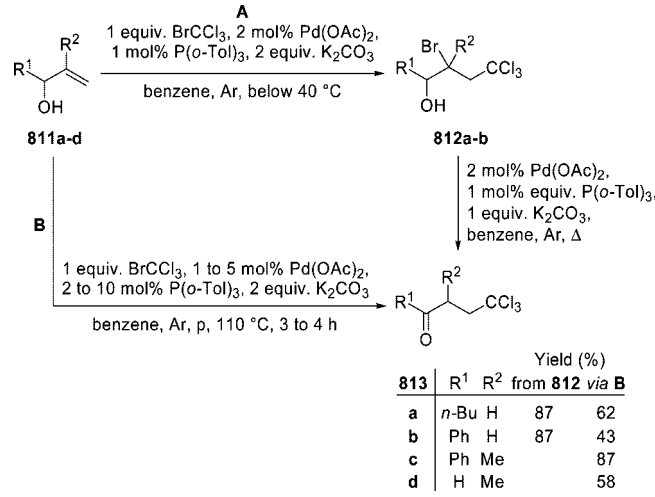
In addition, more demanding ketones such as octahydroinden-4-ones **808** have been prepared *via* a PCC-mediated oxidation (Scheme 205).[320]

Given the slight acidity of PCC, powdered NaOAc is added to the reaction medium when acid-labile groups are present in the substrate. This precaution, for example, was taken by Porter and co-workers while oxidizing the acetal containing alcohol **809**, due to the presence of the labile acetal moiety (Scheme 206).[187]

3.8.1.2. Non-Chromium-Based Oxidants. *Swern Oxidation.* The Swern oxidation is generally regarded as a mild low-temperature transformation, applicable to a wide range of primary and secondary alcohols. Crombie and co-workers used this method to convert 4-chlorobutanol **802** into its aldehyde equivalent **803** (Scheme 207).[321] Interestingly, their approach proved far more successful than the strategy of Khusid and co-workers, employing PCC (Scheme 204).

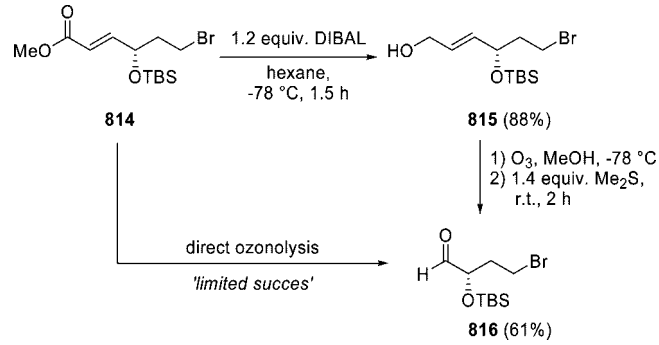
Miscellaneous. Polyhaloalkanes undergo ready addition to olefins in the presence of Pd catalysts. Besides, Tsuji and co-workers presented a palladium-catalyzed oxidation of alcohols **812a**,**b**, with CCl_4 as a novel Pd(0) oxidant.[322] Therefore, reaction of allylic alcohols **811a**−**d** with CCl_4 or $BrCCl_3$ at high temperatures smoothly provided γ,γ,γ-trichloro ketones **813a**−**d** in one step (Scheme 208, pathway **B**). Compounds with internal olefinic bonds, however, reacted slowly because of steric hindrance; hence, simple oxidation of the hydroxyl group predominated. Reactions with primary alcohols were ambiguous.

Scheme 208



813	R^1	R^2	Yield (%) from **812** *via* **A**	Yield (%) from **812** *via* **B**
a	*n*-Bu	H	87	62
b	Ph	H	87	43
c	Ph	Me		87
d	H	Me		58

Scheme 209

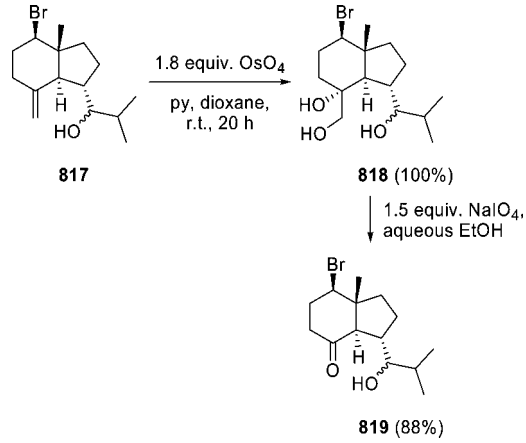


Allylic alcohols possessing a methyl group at the 2-position (**811c**,**d**) underwent smooth conversion into trihalo ketones, even at 40 °C. Substrates **811a**,**b**, on the contrary, selectively yielded halohydrin adducts **812a**,**b** below 40 °C (Scheme 208, pathway **A**). However, the latter species readily smoothly converted into γ,γ,γ-trichloro ketones **813a**−**b** in one extra step under palladium catalysis. In this case, for halohydrins bearing a terminal halide, concomitant epoxide formation significantly reduced the yield of the desired ketones.

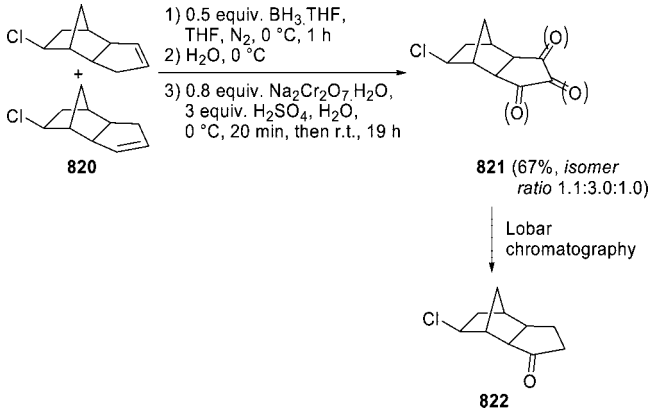
3.8.2. Oxidation of Olefins

Ozonolysis of chiral brominated ester **814** affords aldehyde **816** with only limited success, probably due to the poor reactivity of the conjugated, electron poor double bond toward ozone (Scheme 209).[323] Upon DIBAL reduction, however, the thus obtained alcohol **815**, with a more electron-rich double bond, afforded γ-bromo aldehyde **816** in better yield. Both transformations proceeded with retention of configuration. Reductive workup of the ozonide is traditionally conducted with Me_2S under mild conditions.

Scheme 210



Scheme 211



A useful alternative to ozonolysis, with the same net result, is offered by the Lemieux−Johnson oxidation. Subsequent to the OsO_4-mediated dihydroxylation of the olefin **817**, the intermediate glycol **818** is cleaved by $NaIO_4$, thus yielding the aldehyde or ketone **819** (Scheme 210).[324] $NaIO_4$ is also frequently used during the dihydroxylation step to regenerate the toxic and expensive OsO_4, which is often only present in a catalytic amount.

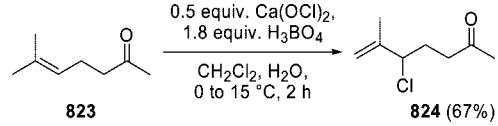
γ-Chlorinated carbonyl compounds can also be prepared from the corresponding olefins *via* a hydroboration−oxidation sequence. In this manner, Jordan and co-workers obtained *exo*-9-chloro-*exo*-tricyclo[5.2.1.$0^{2,6}$]decan-3-one **822** (Scheme 211).[325] The successful transformation of olefin **820** was accomplished using $Na_2Cr_2O_7$ as an oxidant and employing Lobar chromatography (commercially available preparative low-pressure LC system) for the separation of the regioisomers contained in the reaction mixture.

As reported in the section on β-halogenated analogues, one of the two possible regioisomers formed when applying this strategy to homoallylic chloride **513** is γ-chlorinated ketone **515** (Scheme 125).[196] Here, *m*-CPBA was used as an oxidant.

3.8.3. Miscellaneous

Upon electrophilic addition of chlorine to an olefin, concomitant reintroduction of the double bond can be mediated employing an oxidant such as H_3BO_4. This was illustrated by Miyakoshi and co-workers in the preparation of 5-chloro-6-methyl-6-hepten-2-one **824** (Scheme 212).[326]

Scheme 212



3.9. Reduction

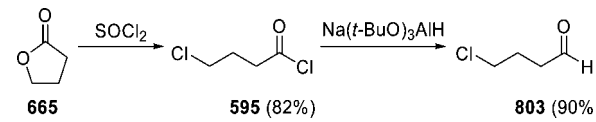
A straightforward entry toward aldehydes consists of the reduction of the parent carboxylic acid derivatives, most commonly esters or acid chlorides. The latter species undergo a facile and controlled reduction to aldehydes when treated with Na(*t*-BuO)$_3$AlH, a valuable alternative to the Rosenmund reduction. Hence, 4-chlorobutyryl chloride **595**, obtained *via* a $SOCl_2$-mediated ring-opening of γ-butyrolactone **665**, was converted into 4-chlorobutanal **803** in very good yield (Scheme 213).[327]

Nevertheless, the Rosenmund reduction remains a valuable way of reducing compounds at the carboxylic acid chloride oxidation level to the corresponding aldehydes. In order to neutralize the HCl liberated during this C−Cl hydrogenolysis process, a tertiary amine such as lutidine is commonly added to the mixture. Moreover, this additive also moderates the activity of the catalyst, thus preventing overreduction. This way, Chen and co-workers reduced 4-chlorobutyryl chloride **595** to the corresponding aldehyde **803**, which was immediately protected as its dimethyl acetal **825** (Scheme 214).[328]

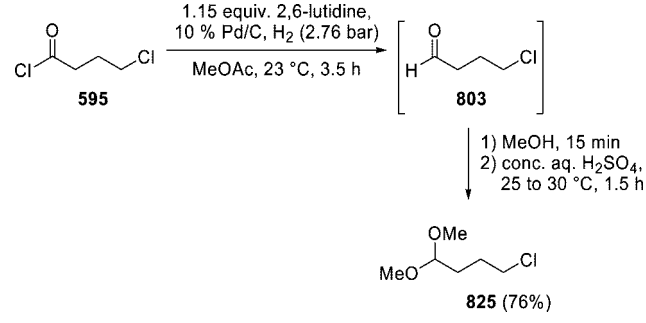
The reduction of carboxylic acid derivatives to aldehydes is very often conducted in two steps, consisting of a $LiAlH_4$-mediated reduction to the alcohol followed by a reoxidation to the aldehyde. With suitable substrates, however, this transformation can be conducted in one single step, employing *i*-Bu_2AlH (DIBAL, DIBAL-H). As such, when utilizing a stoichiometric amount of this reagent, nitriles can undergo a controlled reduction toward the corresponding aldehydes upon hydrolysis of the intermediately formed imine (Scheme 215).[329] This has proved a valuable method due to the high substrate generality.

Tschesche and co-workers converted γ-butyrolactone **665** into 4-chloro-2,2-dimethylbutanal **832** (Scheme 216).[330] α,α-Dialkylation and $ZnCl_2/SOCl_2$-mediated ring-opening furnished the intermediate acid chloride **829**, which was converted into its imidazolide prior to the reduction toward the desired butanal derivative **832**. The alternative approach,

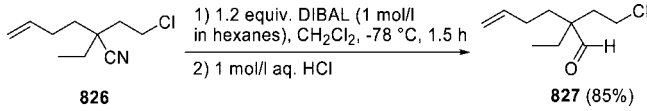
Scheme 213



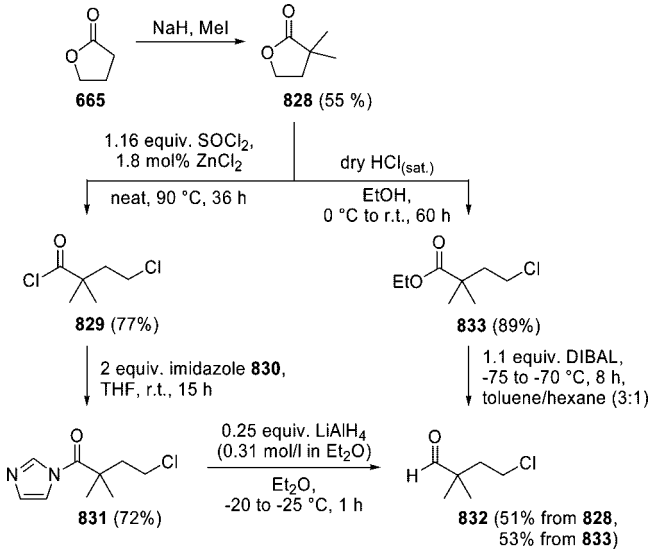
Scheme 214



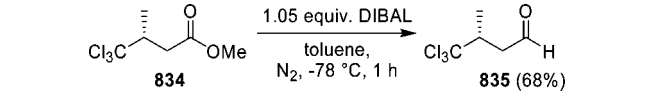
Scheme 215



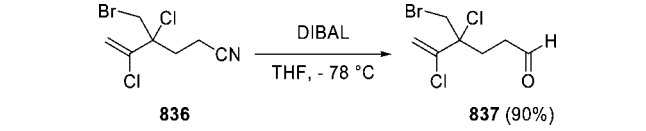
Scheme 216



Scheme 217



Scheme 218



consisting of a ring-opening in HCl/EtOH and subsequent reduction of ethyl ester **833** with DIBAL, comprises one step less and is to be preferred despite the more critical reaction conditions.

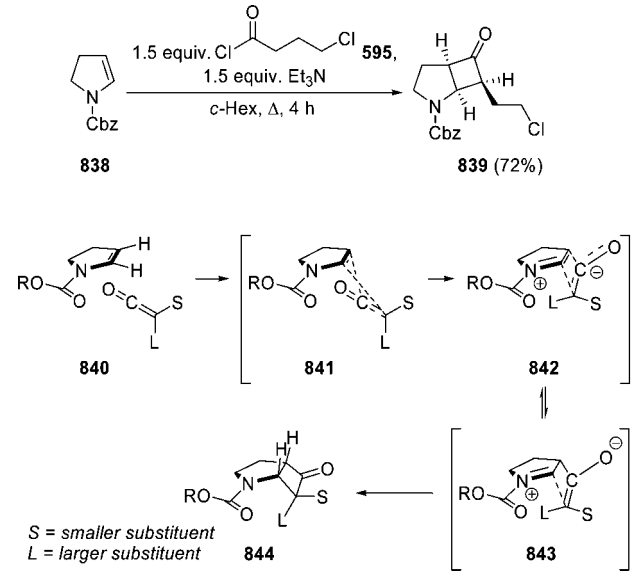
DIBAL is *de facto* the standard reagent for the reduction of esters to aldehydes, given its intermediate reactivity when compared to $LiAlH_4$ and $NaBH_4$. The former reagent will overreduce esters to the corresponding alcohols with high selectivity, while the latter alternative is too mild to give the corresponding aldehydes. In a second example of the use of DIBAL, Williard and co-workers prepared γ,γ,γ-trichloro aldehyde **835** from the parent methyl ester **834** in moderate yield (Scheme 217).[331]

In another application of DIBAL, nitrile **836** underwent a controlled low-temperature reduction to the corresoponding aldehyde **837** in excellent yield (Scheme 218).[332]

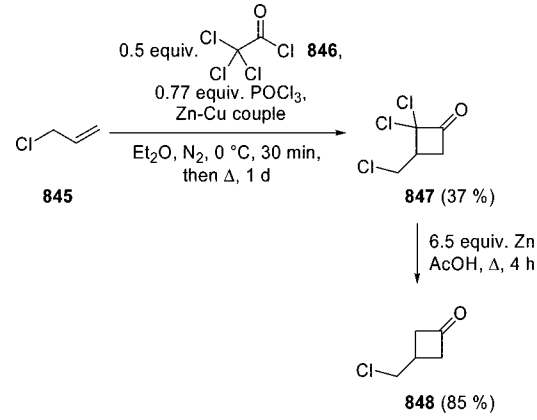
3.10. Pericyclic Reactions

When ω-halogenated alkyl ketenes react with olefins *via* a [2 + 2]cycloaddition mechanism, halogenated cyclobutanones are formed *ipso facto*. Furthermore, these transformations frequently proceed in a stereocontrolled manner. In one example employing this strategy, 2-azabicyclic cyclobutanone **839** was prepared from enecarbamate **838** and the *in situ* formed 2-chloroethyl ketene by Correia and co-workers

Scheme 219



Scheme 220



(Scheme 219).[333] Employing cyclohexane as a solvent, the adduct could be obtained with almost absolute *endo*-selectivity, controlled by secondary orbital interactions. The stereochemistry of product **848** was confirmed by X-ray structure determination.

Much interest and controversy exists concerning the mechanism of [2 + 2]-cycloadditions of ketenes to olefins. For electron-rich (nucleophilic) alkenes, the most probable pathway proposed involves the participation of ionic intermediates in a stepwise mechanism or of a polar transition structure in a "quasi-pericyclic" mechanism. In the report of Correia and co-workers, the excellent degree of *endo*-stereoselectivity observed for the [2 + 2]-cycloadditions was accounted for by assuming a stepwise mechanism involving the participation of a zwitterionic enolate-*N*-acyliminium intermediate **843**. Internal electrostatic interaction could stabilize the transition state **842** and the proposed intermediate **843**, allowing an orthogonal approach of the ketene on the *N*-acylenamine double bond from its least congested side, being that of the smaller (S) substituent.

Furthermore, also the ene-partner in the cycloaddition reaction can bear a halogen atom, as was illustrated by Stevens and co-workers in their new short synthesis of 3-(chloromethyl)cyclobutanone **848** (Scheme 220).[334] The first and key step of this sequence consisted of a [2 + 2]-cycloaddtion of dichloroketene and allyl chloride, furnish-

ing 2,2-dichloro-3-(chloromethyl)cyclobutanone **847**. This transformation proved to be rather hard to accomplish, as the optimized yield after evaluating many different conditions was still a rather disappointing 37%. Nevertheless, reductive removal of the geminal α-chlorine atoms upon treatment with zinc in AcOH furnished the desired 3-(chloromethyl)cyclobutanone **848** in a much higher yield than the only previously reported synthesis (eight steps, 6% overall yield), enabling the preparation on a multigram scale.

4. Synthesis of δ-Halo Ketones and Aldehydes

4.1. Nucleophilic Substitution

4.1.1. Enolate Alkylation

One of the most straightforward methods for the generation of δ-halogenated ketones is enolate haloalkylation. Next to their saturated analogues, α,β-unsaturated ketones are also suitable substrates for this approach.[335] As expected, the reaction of the enolate of cyclic vinylogous ester **849** with 1-bromo-3-chloropropane **850** chemoselectively provided the corresponding δ-chloro ketone **851**, given the better leaving capacity of bromide compared to chloride (Scheme 221).[336]

Occasionally, reactive enolates are obtained from the parent carbonyl compounds *via* the intermediacy of a more stable silyl enolate. Suginome and co-workers, for example, followed this approach in their synthesis of 2-(3-chloropropyl)cycloalkanones **856a**−**b** (Scheme 222).[337]

Not unlike their β- and γ-analogues, δ-halogenated ketones are often generated from an activated substrate. Hence, β-ketoesters **857** are common starting materials. Very often, these substrates are converted into their enolates by the appropriate alkoxides, such as NaOMe[338] and NaOEt[339] for methyl acetoacetate and ethyl acetoacetate, respectively. The ester moiety can be removed by a widely employed decarboxylation reaction (Scheme 223).[340] Other bases used in the alkylation of β-ketoesters with 1,3-dihalopropanes are NaH,[8,341,342] KO*t*Bu,[200] and finely divided potassium.[343]

As pointed out in the section on γ-halogenated ketones and aldehydes, regioselective mono-γ-alkylations of β-dicarbonyl compounds are possible when ensuring meticulously controlled reaction conditions. Carrié and co-workers proved the applicability of this transformation on a β-ketoester as well as a β-diketone (Scheme 224).[204] Furthermore, also α-(acetyl)butyrolactone **723** underwent a successful conversion.

Later, Langer and co-workers employed this reaction sequence in their synthesis of 3-substituted 2-hydroxybenzoates (Scheme 225).[344] Surprisingly, they obtained ethyl 7-chloro-3-oxoheptanoate **864a** in a significantly lower yield than that found by Carrié and co-workers.

Phenylthioalkyl chlorides were described as excellent means for the regioselective haloalkylation of ketones and enones by Lee and co-workers.[345] These authors investigated more thoroughly the only previously reported example of this reaction, published by Overman and co-workers (Scheme 226).[346] The latter researchers employed the phenylthioalkylation in the total synthesis of pentacyclic *Aspidosperma* alkaloids. The procedure tolerates the presence of a variety of substituents on the proposed alkylating reagent, among others a (halogenated) alkyl group, a cyano function, a methoxycarbonyl group, a ketone function, and an alkenyl function.

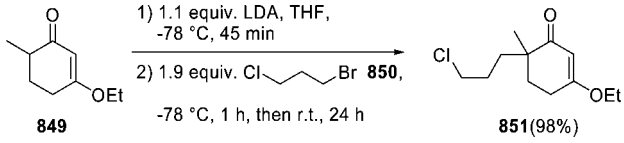
An example of a diastereoselective alkylation was published by Curran and co-workers (Scheme 227).[7] These researchers obtained ω-iodo ketone **873** with a good *trans*-selectivity. Chromatographic separation of the reaction mixture furnished the pure *trans*-isomer **873**.

δ-Bromo ketones have been prepared using the Corey−Enders hydrazone alkylation, followed by a cupric ion-catalyzed hydrolysis step (Scheme 228).[347] An analogous approach was chosen by Aubé and co-workers for the alkylation of 4-*tert*-butylcyclohexanone using LDA as a base.[16]

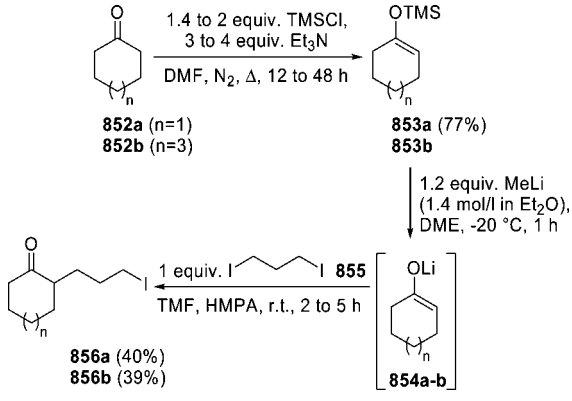
Furthermore, Kuehne and co-workers successfully prepared δ-chloro aldehyde **877** from the *N*-cyclohexyl imine of butanal and 1-bromo-3-chloropropane (Scheme 229).[348] That 1-azaenolate formation not necessarily requires such stringent cooling was exemplified by De Kimpe and co-workers in the synthesis of δ-halo imine **879**, en route to the alkaloid stenusine.[349] In like manner, these researchers also obtained 5-chloro-2-methylpentanal.[350]

An analogous reaction with ketimines was reported by De Kimpe and co-workers in the synthesis of the natural bread flavor component 6-acetyl-1,2,3,4-tetrahydropyridine. Deprotonation of imines **881a**−**b** with LDA at low temperature gave the corresponding 1-azaenolate, whereupon alkylation with 1-bromo-3-chloropropane **850** smoothly provided alkoxylated δ-haloimines **882a**−**b** (Scheme 230).[351] This reaction sequence illustrates the influence of the acid on the chemoselectivity of imine and

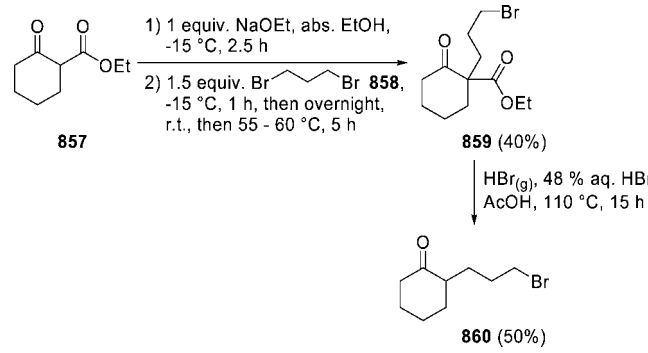
Scheme 221



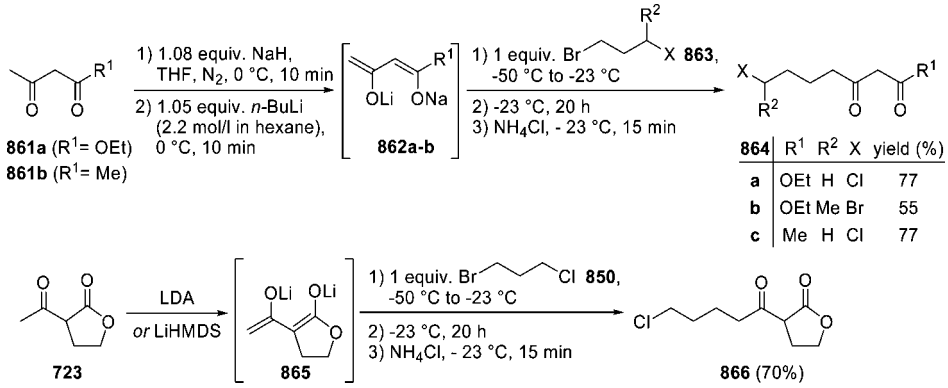
Scheme 222



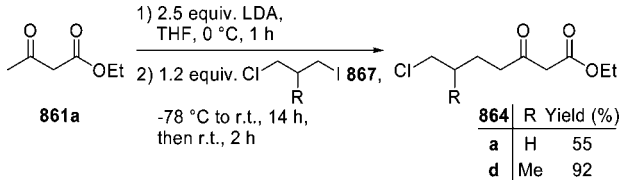
Scheme 223



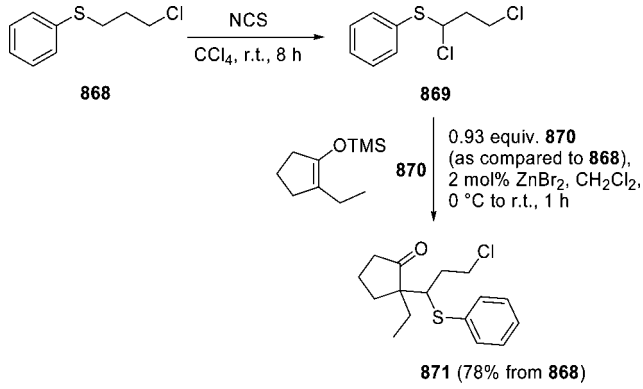
Scheme 224



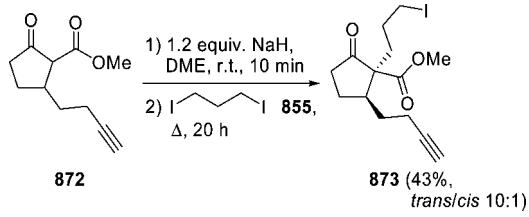
Scheme 225



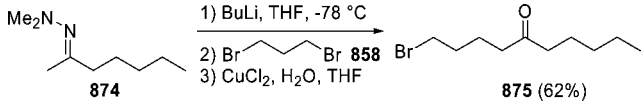
Scheme 226



Scheme 227



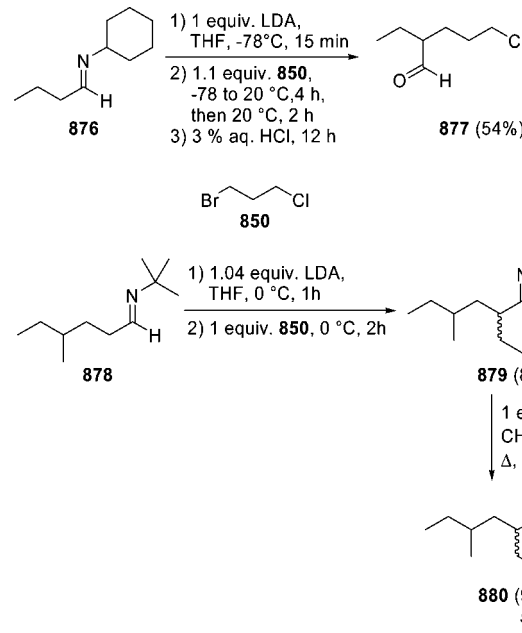
Scheme 228



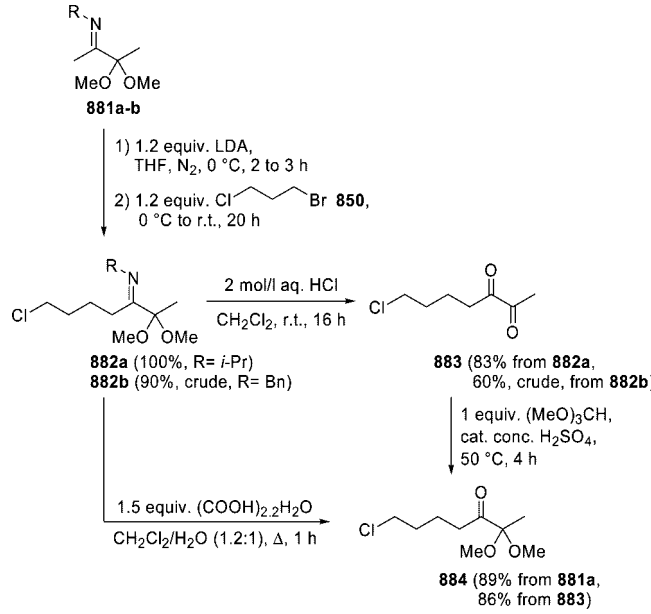
acetal hydrolysis: whereas aqueous HCl provided 7-chloroheptane-2,3-dione **883**, selective hydrolysis of the imino function of compound **882a** was accomplished using aqueous $(COOH)_2$. In this way, α-ketoacetal **884** was obtained in much better yield than *via* the more conventional two-step sequence through dione **883**.

In an alternative approach, Duhamel and co-workers readily prepared *β*-lithioenamines **887** from the parent enamines **885** by a bromination/halogen−metal exchange sequence (Scheme 231). Reaction of these nucleophiles with

Scheme 229

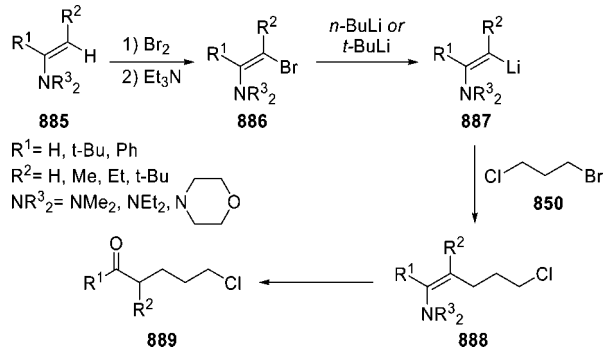


Scheme 230

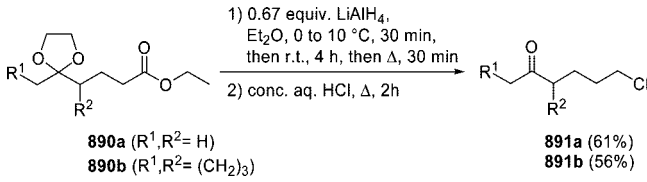


1-bromo-3-chloropropane exclusively lead to *δ*-chloro ketones **889**.[352]

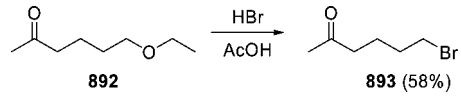
Scheme 231



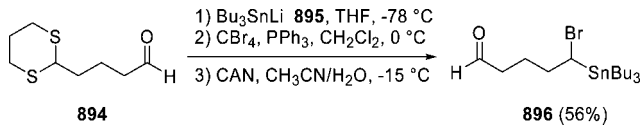
Scheme 232



Scheme 233



Scheme 234



4.1.2. Conversion of an Alcohol or Ether into an Alkyl Halide

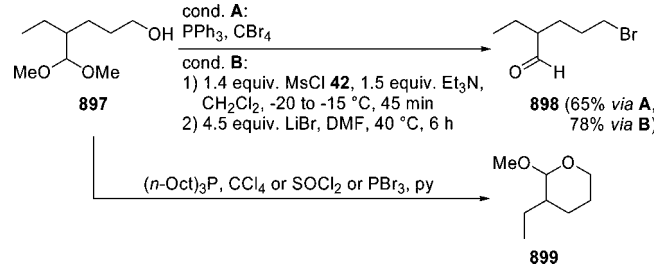
4.1.2.1. Substitution in Acidic Medium. As discussed for β- and γ-analogues, δ-halo ketones can be prepared from δ-hydroxy ketones upon treatment with concentrated hydrohalic acid. In this context, Shatzmiller and co-workers presented a one-pot synthesis of δ-halo ketones starting from the corresponding acetal esters (Scheme 232).[208]

Besides, it has long been known that ethers, such as 6-ethoxyhexan-2-one **892**, can be cleaved upon treatment with HBr, affording the corresponding alkyl bromides **893** (Scheme 233).[244]

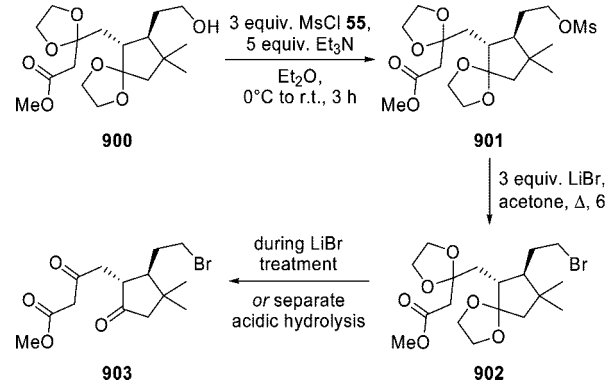
4.1.2.2. Substitution of Phosphoryl Activated Alcohols. In the previous sections, the usefulness of the Appel reaction in the synthesis of β- and γ-halo ketones and aldehydes was demonstrated. Fraser-Reid and co-workers applied this approach to the synthesis of the δ-iodo aldehyde 3-(2′-iodoethyl)-5-hexenal.[353] Also noteworthy is the compatibility of this transformation with Bu_3Sn groups, as demonstrated by Tsai and co-workers (Scheme 234).[354] Attack of the organotin nucleophile **895** on monoprotected dialdehyde **894** gave an intermediate α-stannyl alcohol, which was converted into the corresponding bromide under Appel-type conditions. Oxidative deprotection of the dithiane moiety thus gave δ-bromo-δ-tributylstannyl aldehyde **896** in a reasonable overall yield. The latter compound was employed in a study on the reactivity of the corresponding α-stannyl radicals.

4.1.2.3. Substitution of Sulfuryl Activated Alcohols. Mesylate activation has already been thoroughly discussed in the previous sections. In the same manner, δ-halo ketones

Scheme 235



Scheme 236



and -aldehydes can be obtained by treatment of the corresponding δ-hydroxy analogues with mesyl chloride in a dry solvent (e.g., pyridine[16,355] or ether[356]) in the presence of a base such as Et_3N,[356] at room temperature or below. Subsequently, the mesylate is treated with LiCl[16] or LiBr,[355,356] mostly in dipolar aprotic solvents (acetone,[355,356] DMF[16]), to yield the target alkyl halides.

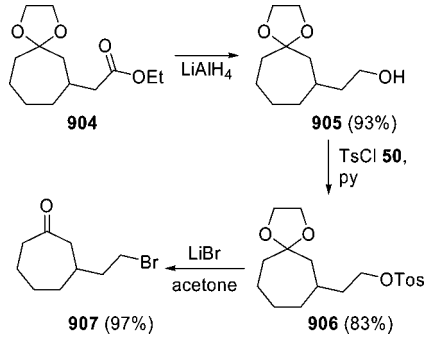
In their synthesis of vincadifformine, Kuehne and co-workers attempted several techniques described earlier in this section in order to convert alcohol **897** to its corresponding bromide **898** (Scheme 235).[357] However, most of these trials yielded primarily tetrahydropyran **899** as a result of intramolecular methoxy *O*-alkylation. Although Appel-type conditions provided the desired bromide (route **A**), the most satisfactory synthesis involved mesylate activation and subsequent displacement of the methanesulfonate moiety upon treatment with LiBr (route **B**). An alternative synthesis of bromo aldehyde **898**, though somewhat less successful, was proposed by Oppolzer and co-workers (Scheme 239).

It should be noted that the conditions used to displace a mesylate for a halide can cause the hydrolysis of acetal moieties present in the substrate, as was the case in the synthesis of cyclopentanone **903**, reported by Danishefsky and co-workers (Scheme 236).[358] This coincident transformation was also observed by Kakiuchi and co-workers in their synthesis of *cis*-3-(ω-halopropyl)bicyclo[3.3.0]octan-2-ones.[356]

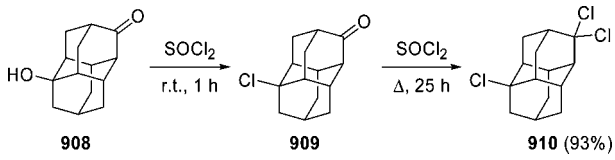
Again, tosylate activation provides an alternative to mesylation. This way, Casanova and co-workers prepared δ-brominated cycloheptanone **907** (Scheme 237).[359] Similarly, Suginome and co-workers converted 2-(3′-hydroxypropyl)cyclododecanone into its corresponding iodide in reasonable yield.[360]

Furthermore, $SOCl_2$ can be used to substitute a hydroxyl moiety for a chloride. This approach enabled Janků and co-workers to synthesize δ-chlorinated adamantanone **909** (Scheme 238), which was more comprehensively discussed in the section on β-halogenated compounds (Scheme 18).[37]

Scheme 237



Scheme 238



4.1.2.4. Miscellaneous. A method to convert γ,δ-unsaturated aldehyde **911** into its δ-brominated counterpart **914** was proposed by Oppolzer and co-workers (Scheme 239).[361] The first two steps of this procedure comprised the protection of the carbonyl group and a hydroboration of the double bond. Subsequently, the thus formed organoborane was brominated. Hydrolysis of the acetal ultimately yielded bromo aldehyde **914** in 55% overall yield.

In their synthesis of (+)-grandisol starting from (+)-citronellol, Monteiro and co-workers were able to successfully cleave methyl ether **915** upon treatment with NaI and TMSCl, producing iodide **916** in good yield (Scheme 240).[362] The mixture of these two reagents in acetonitrile was shown to be superior to TMSI itself for the cleavage of ethers and the subsequent formation of iodides from the intermediate alcohols.[363]

4.2. Nucleophilic Addition

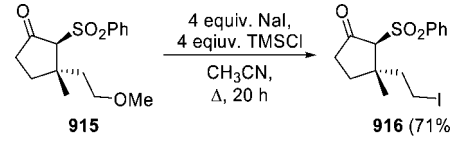
4.2.1. Grignard Addition

During the establishment of a short enantioselective total synthesis of piperidine alkaloids, Buchwald and co-workers utilized δ-chloro ketones **919a**−**b** as convenient entries to otherwise difficultly obtainable endocyclic imines (Scheme 241).[364] The depicted Grignard additions to ω-chloronitriles proceeded only in moderate yields.

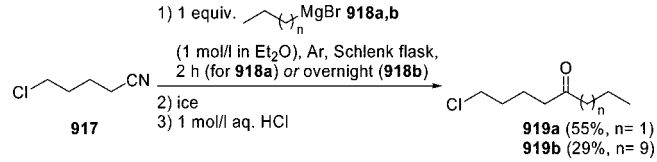
4.2.2. Addition of Organozinc Reagents

As was discussed more thoroughly for the γ-halogenated analogue, Kishi and co-workers were able to synthesize several δ-chloro ketones **922a**−**c** in good yield by utilizing a modified Blaise reaction, *via* enaminones **921a**−**c** (Scheme 242).[220]

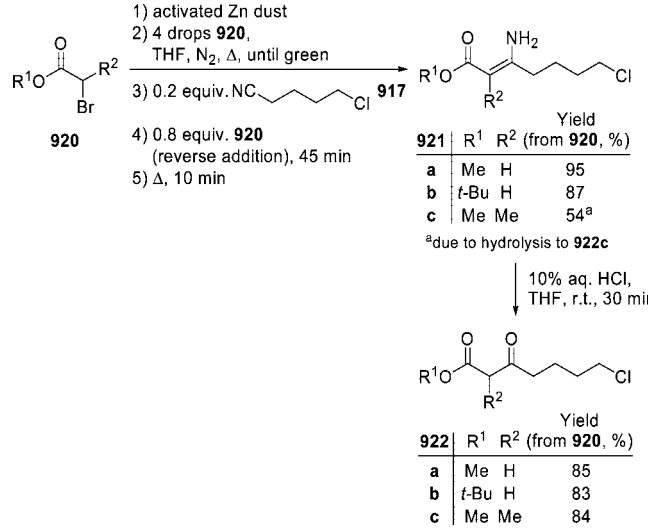
Scheme 240



Scheme 241



Scheme 242

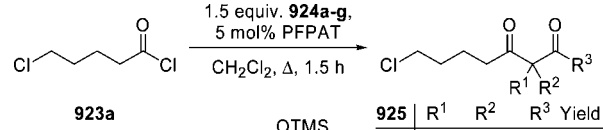


921	R^1	R^2	Yield (from 920, %)
a	Me	H	95
b	*t*-Bu	H	87
c	Me	Me	54[a]

[a]due to hydrolysis to **922c**

922	R^1	R^2	Yield (from 920, %)
a	Me	H	85
b	*t*-Bu	H	83
c	Me	Me	84

Scheme 243



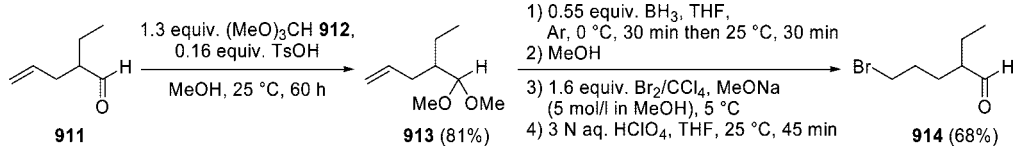
925	R^1	R^2	R^3	Yield (%)
a	Me	Me	*i*-Pr	90
b	Me	Me	Ph	85
c	Me	Me	OMe	76
d	Me	Et	OMe	85
e	Et	Ph	OMe	77
f	Me	OTBS	OMe	75
g	Me	Me	SOct	71[a]

[a]2.0 equiv. of **924d** were used

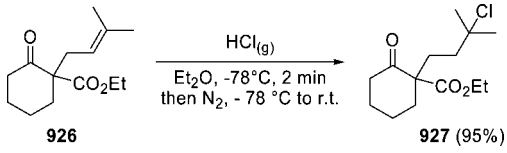
4.2.3. Addition of Silyl Enol Nucleophiles

Due to the value of 1,3-dicarbonyl compounds in organic synthesis, C-acylation of the α-position of carbonyl compounds is a C−C bond forming reaction of paramount importance. In this context, Tanabe and co-workers presented a mild and efficient pentafluorophenylammonium triflate (PFPAT)-catalyzed C-acylation of enol silyl ethers **924a**,**b**, ketene silyl acetals **924c**−**f**, and ketene silyl thioacetals **924g** (Scheme 243).[365] In contrast to metal catalysts, the stable

Scheme 239



Scheme 244



and easy to handle PFPAT was able to completely suppress competing O-acylation of the nucleophile. Employing this methodology, several terminally chlorinated α,α-disubstituted ketoesters and thioesters (**925a**−**g**) were obtained.

4.3. Electrophilic Addition

4.3.1. Reaction of Olefins with Electrophilic Reagents Containing a Nucleophilic Halogen

The addition of a hydrogen halide across a double bond is a classical textbook reaction. Its usefulness has been widely proven, as in the conversion of prenylated ketoester **926** into its chlorinated counterpart **927** (Scheme 244).[366]

4.3.2. Reaction of Olefins with Electrophilic Halogens

N-Bromosuccinimide (NBS) is a convenient source of bromine in both radical and electrophilic addition reactions. This reagent was utilized by Gleiter and co-workers to perform a highly regio- and stereoselective fuctionalization of the double bond in bicyclic ketone **928** (Scheme 245).[209] To rationalize this, conformation **928a** was identified as a local minimum with the help of molecular models and force-field calculations. Here, the approach of an electrophile occurs with clear preference from the *exo*-side. Subsequently, bromonium intermediate **929** must be attacked in an *endo*-fashion, yet for steric reasons at the α-position of the methylene group.

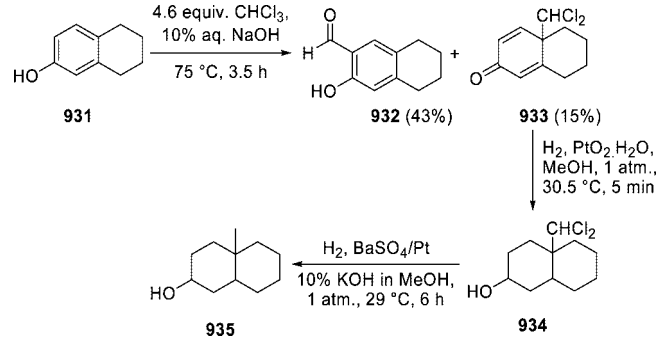
4.4. Electrophilic Aromatic Substitution

4.4.1. Reimer−Tiemann Reaction

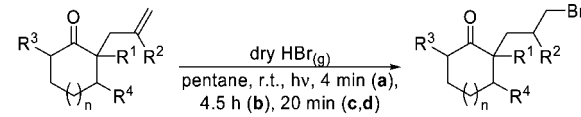
As mentioned in the section on *β*-halogenated compounds, properly substituted phenols yield *δ*,*δ*-dihalogenated cyclohexadienones when subjected to Reimer−Tiemann conditions. Hence, Wynberg and co-workers obtained *δ*,*δ*-dichlorinated cyclohexadienone **301**, albeit as a minor compound, upon treatment of mesitol **299** with $CHCl_3$ and alkali (Scheme 71).[124] Interestingly, reduction of the reaction time from 12 to 1 h significantly lowered the amount of the *δ*,*δ*-dichloro isomer.

As a model for the conversion of estrone into androgenic hormones, Woodward described the direct introduction of an angular methyl group to 6-hydroxy-1,2,3,4-tetrahydronaphthalene **931** (Scheme 246).[367] Treatment of the latter compound with $CHCl_3$ and aqueous NaOH resulted in two products: the expected aldehyde **932** and 4a-dichloromethyl-5,6,7,8-tetrahydro-4a*H*-naphthalen-2-one **933**. Upon hydrogenation in MeOH with Adams' catalyst ($PtO_2 \cdot H_2O$), the dienone smoothly added 3 mol of hydrogen, with the formation of dichloro alcohol **934**. Under more drastic conditions, 10-methyldecalol **935**, which bears clear resemblance to the androgenic hormones, was obtained.

Scheme 246



Scheme 247



936	n	R^1	R^2	R^3	R^4
a	1	H	H	H	Me
b	1	Me	H	Me	H
c	7	H	H	H	H
d	7	H	Me	H	H

937	Yield (%)
a	93
b	95[a]
c	75
d	54

[a]crude

4.5. Radical Reactions

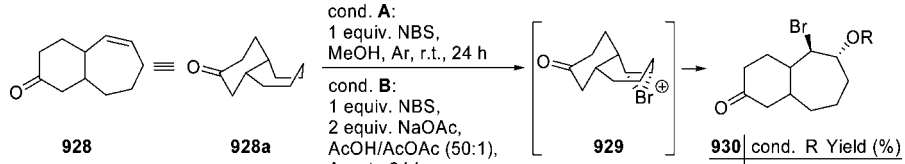
4.5.1. Hydrogen Halide Additions

The anti-Markovnikov radical chain addition of HBr to *γ*,*δ*-unsaturated ketones regioselectively provides the corresponging *δ*-halo ketones. Typical reaction conditions include the use of dry pentane as a solvent and irradiation with a medium or high pressure mercury lamp for light-initiation. This way, House,[27] Gambacorta,[368] and Fehr,[369] respectively, obtained *δ*-bromo cycloalkanones **937a**, **937b**, and **937c**,**d** in moderate to excellent yields (Scheme 247). Besides, analogous hydrobrominations of 1-acetyl-2-allylcyclopentane[370] and substituted acyclic hex-5-en-2-ones[27] were reported to be successful. These bromides can again be converted into the analogous *δ*-iodo ketones *via* a Finkelstein transhalogenation.[371]

Similarly, Dowd and co-workers prepared iodoalkyl cyclododecanones **940a**−**b** *via* a hydrobromination−transhalogenation sequence (Scheme 248).[4,5]

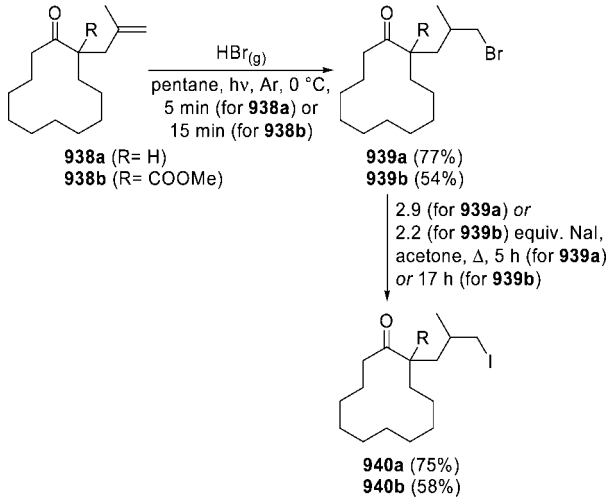
Next to light irradiation, radical hydrohalogenations are very often initiated by dibenzoyl peroxide (BPO), as illustrated in the preparations of *δ*-bromo ketones **942**[372,373] and **946**[374] (Scheme 249). It is noteworthy that no epimerization of diketone **941**, which was used as a four-to-one

Scheme 245

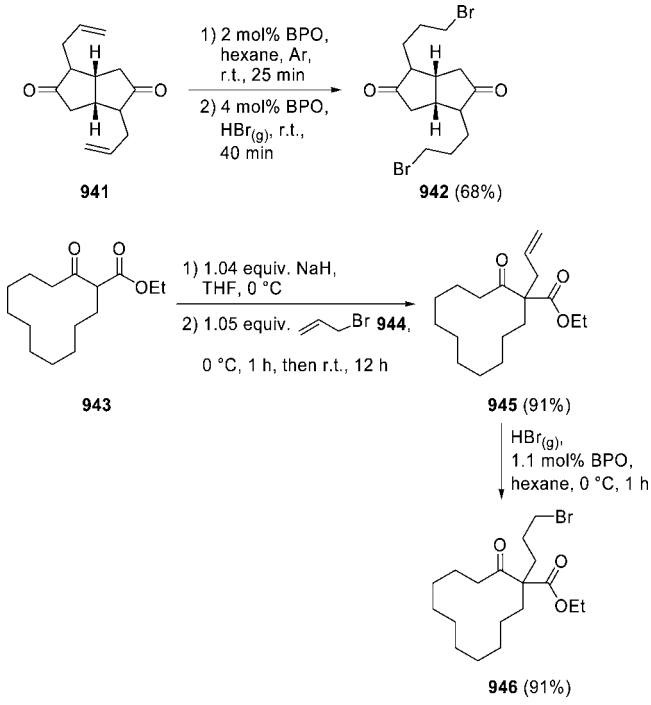


930	cond.	R	Yield (%)
a	A	Me	81
b	B	Ac	92

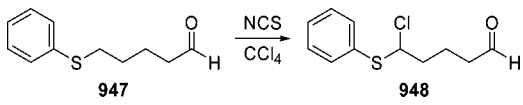
Scheme 248



Scheme 249



Scheme 250



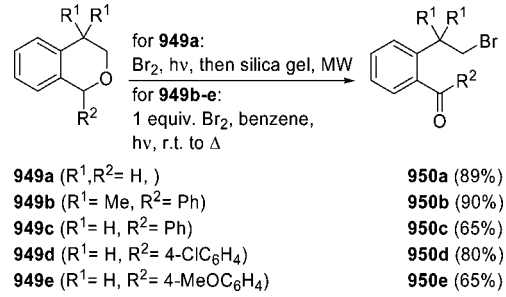
mixture of the *exo*, *exo*- and *endo*-, and *endo*-diastereomers, occurred under the depicted conditions.

4.5.2. Radical Halogenations

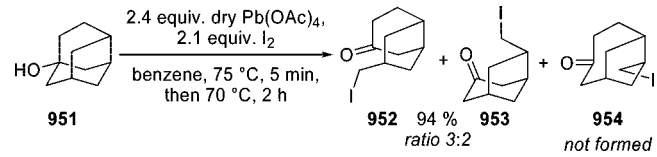
As already discussed in the previous sections, radical halogenations proceed through formation of the most stable radicals, which offers a means of regiochemical control. As a result, (phenylthio)alkanals have been clorinated selectively at the α-position of the sulfur atom (Scheme 250).[375]

When treated with Br_2 under light-irradiation, isochromenones are regioselectively halogenated adjacent to oxygen (Scheme 251).[376] The resulting species are prone to ring-opening, which can be performed by adsorption on silica gel and subjection to microwave irradiation, affording 2-(2-bromoethyl)benzaldehyde **950a** in good yield. Analogously, brominated benzophenones **950b**−**e** were synthesized in reasonable to excellent yields from 1-phenylisochromanes **949b**−**e**.[234]

Scheme 251



Scheme 252



4.5.3. Ring-Opening

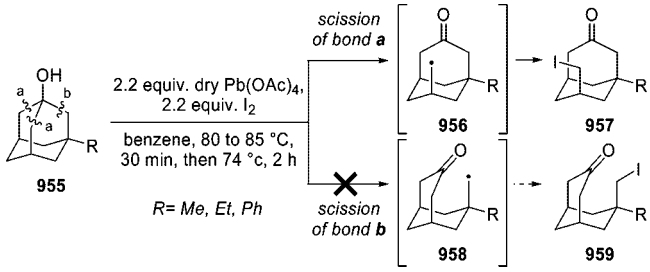
A myriad of research articles has been devoted to ring-opening reactions involving the β-scission of alkoxy free radicals. These species are readily produced *via* thermolysis of *in situ* generated hypoiodites, which in turn can be obtained from the corresponding cycloalkanols. The following paragraphs provide an overview of the most important communications regarding this transformation, which provides an interesting entry to a rather wide range of halo ketones. For reasons of clarity and fluency, no division between δ- and ω-halogenated analogues was made here.

In an early report, Majerski and co-workers investigated the thermolysis of tertiary polycyclic hypohalites, easily obtained from the corresponding alcohols by the action of $Pb(OAc)_4$ and I_2. Employing substrates of the adamantine series, the direction of β-scission appears to be controlled by the relative thermodynamic stabilities of the intermediate carbonylalkyl free radicals (Scheme 252).[377,378] In most cases, this may be approximated by combining the relative strain energies of the corresponding hydrocarbons and the relative stabilities of the free-radical centers. For example, the calculated strain energy of the hydrocarbon corresponding to **954** (20.95 kcal/mol) is twice as high as that of the hydrocarbons related to **952** (9.86 kcal/mol) and **953** (12.06 kcal/mol). Since all three possible products are derived from a primary free radical, the relative strain energies are the distinctive and, indeed, determining factor for the observed product distribution.

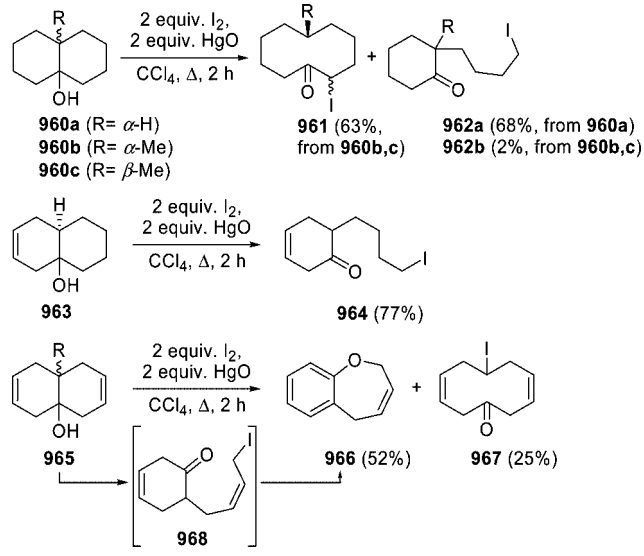
In the case of substrate **955**, however, the difference in strain energy of both possible δ-iodo ketones is negligible, which makes the selectivity of the cleavage statistically and sterically determined (Scheme 253).[379] Hence, ω-iodo ketone **957** was selectively formed, since the precursing radical **956** can result from two of three possible bond scissions and is less hindered than competing species **958**.

Macdonald and co-workers focused their attention on hypoiodites derived from decalin-9-ol substrates (Scheme 254).[380] The direction of β-scission proved to be extremely sensitive to changes in the molecular geometry of the bicyclic

Scheme 253



Scheme 254



system, due to its influence on radical stability and cycloalkanone ring strain. Interestingly, both alcohols **960b** and **960c** yielded an identical mixture of ketones **961** and **962b**, which suggests preequilibrum decalinoxyl radical epimerization prior to iodine trapping.

Further insight into this matter was given by Beckwith and co-workers, who observed two different ring-opening pathways for these 9-decalinoxyl radicals, depending on the applied conditions: photolysis at 0 °C of the mixture formed by interaction of *trans*-9-decalinol **969** with Br_2 and AgOAc in benzene afforded cyclodecanone **972** as the sole ring-opened product, whereas treatment of the same alcohol with HgO and Br_2 in boiling benzene gave cyclohexanone **976** as the major product (Scheme 255).[381] While stereoelectronic effects in the radical precursor and the nature of the metal salt or the halogen were immaterial, the influence of the temperature on the reaction outcome seemed determinative. As such, 1,9-fission, leading to the formation of 2-(4-bromomethyl)cyclohexanone **976**, begins to predominate above 50 °C. The higher activation energy for the 1,9-fission compared to the 9,10-fission is consistent with the respective formation of a primary versus a secondary alkyl radical. Furthermore, and enabling the complete explanation of the observed thermal selectivity, 1,9-bond fission is essentially irreversible under the depicted conditions, while the 9,10-fission is reversible.

Later, Macdonald and co-workers concluded that a similar interplay of kinetic and thermodynamic factors also determines the alkoxy radical β-scission of several structurally related hydrindan-8-ol (**977a**,**b** and **981**) and hydrinden-8-ol systems (**983**, **986**; Scheme 256).[382] However, *a priori* considerations concerning the mode of β-scission in these cyclic systems remained tenuous.

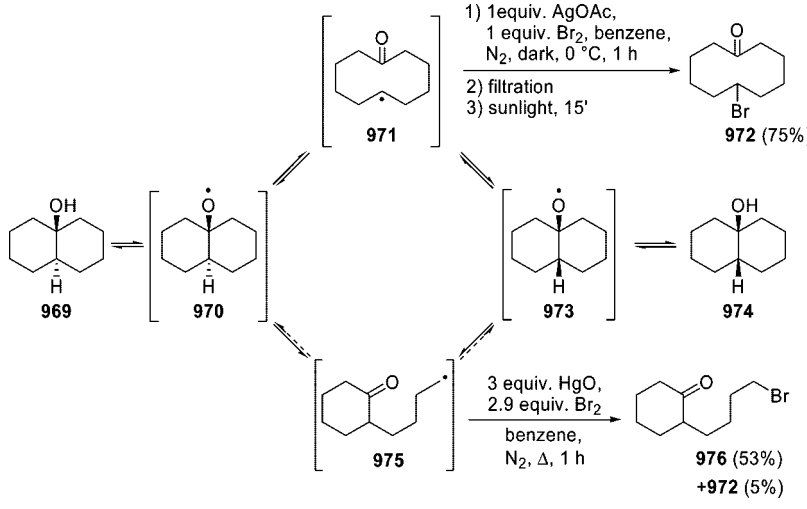
An analogous rationale, as provided by Beckwith, was followed by Murray and co-workers to account for the selective transformation of tertiary alcohol **989** into iodo ketone **993** (Scheme 257).[383] Cleavage to the more stable tertiary radical **992** may be rapid but reversible, whereas the formation of the alternative, primary radical **991** is relatively slow but essentially irreversible.

The photolysis of the hypoiodites of conformationally flexible five- to eight-membered monocyclic alcohols in the presence of HgO and I_2 was investigated by Suginome and co-workers. These transformations gave rise to rather complex product mixtures, consisting of iodinated acyclic formates and aldehydes as the major products (Scheme 258).[384]

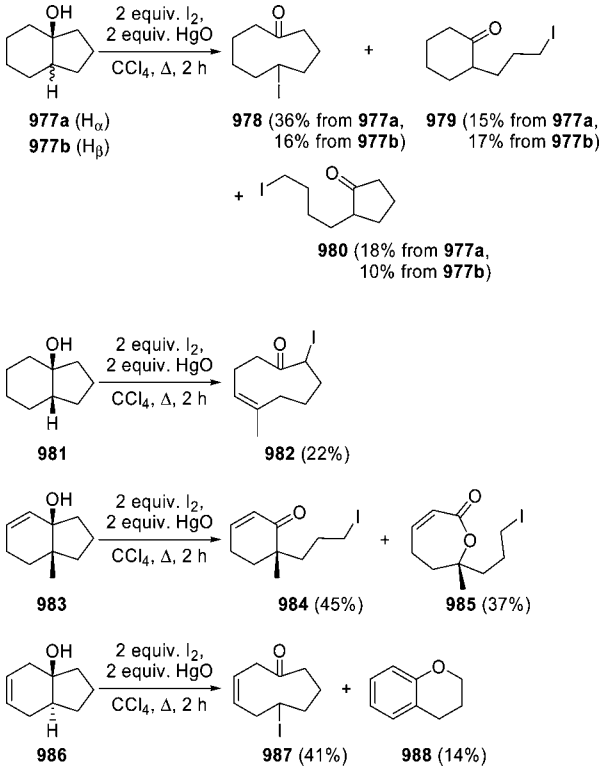
In a later report, it was observed that the alkoxyl radical, generated from 1-(ethoxycarbonylmethyl)cyclopentanol **1005**, preferentially undergoes an endoxyclic cleavage to form δ-iodo ketone **1006**. This selectivity is remarkable, since exocyclic cleavage would involve the generation of stabilized radicals (Scheme 259).[385]

In their study on the scope of the decomposition of tertiary alkyl hypochlorites, Greene and co-workers observed the formation of several ω-chlorinated carbonyl compounds (Scheme 260).[386] All of the decomposition products were derived from thermal or photoinitiated free radical chain reactions. The principle reaction path starts with the genera-

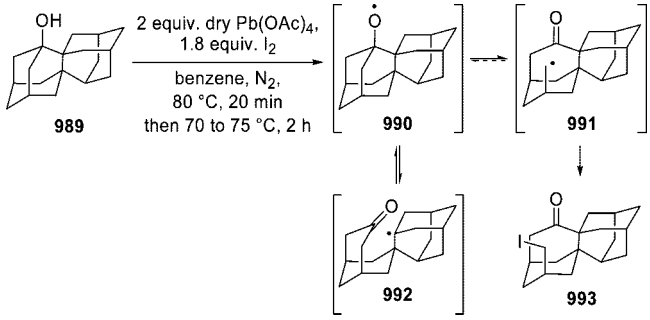
Scheme 255



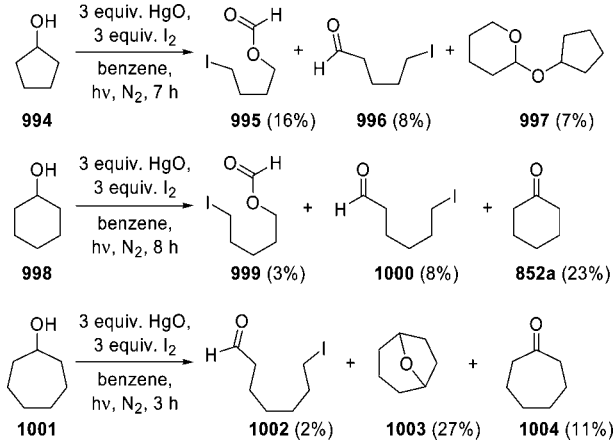
Scheme 256



Scheme 257

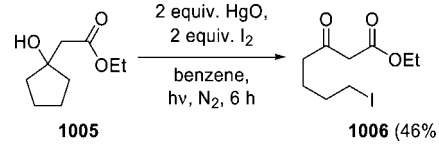


Scheme 258

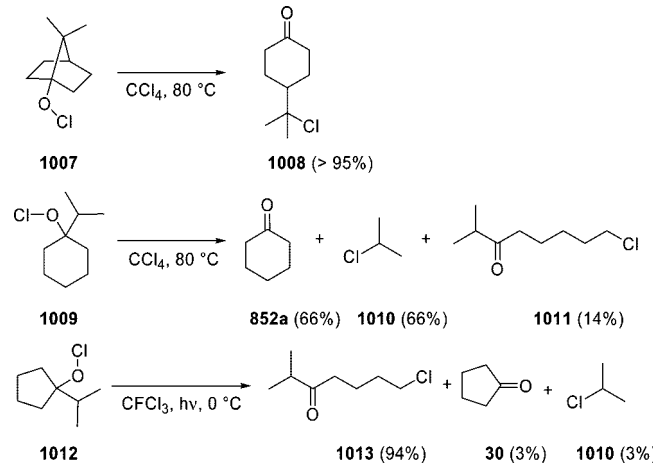


tion of an alkoxy radical, followed either by fragmentation into a ketone and an alkyl radical or by an intramolecular 1,5-hydrogen abstraction, leading to α,δ-chlorohydrins. Scheme 260 also depicts the influence of ring strain on the direction of the cleavage: the opening of five-membered ring

Scheme 259



Scheme 260



1012 proceeds much smoother than for a six-membered analogue **1009**.

4.5.4. Ring-Closure

The $FeCl_3$-mediated ring-opening of cyclopropyl silyl ethers described in the section on β-halogenated compounds (see section 2.6.2) can be used to prepare bicyclic ketones *via* a radical ring-opening−ring-closure sequence. During this process, carbocyclic radical **1018** is trapped intramolecularly by the alkene via a 5-*exo* radical cyclization, whereupon chlorine abstraction from the Lewis acid furnishes the δ-chloro ketone (Scheme 261).[387] This transformation seemed to verify the radical nature of the reaction, upon which two mechanisms were proposed.[388] Furthermore, the relative stereochemistry of the resulting bicyclic δ-chloro ketone **1019**, obtained as a single diastereoisomer, was elucidated using X-ray analysis and explained through conformational analysis of the intermediate carbocyclic radical **1018**.

4.6. Ring-Opening

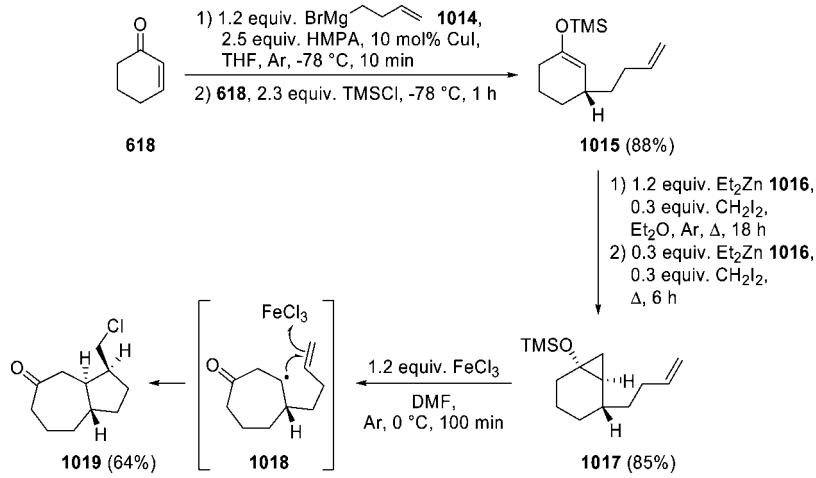
4.6.1. Cyclic Acetals

Ring-opening of hemiacetal **1020** under Appel-type conditions, a mild and effective procedure for the cleavage of acetals, leads to the displacement of the hydroxyl group, thus affording δ-iodo ketone **1021** (Scheme 262).[389]

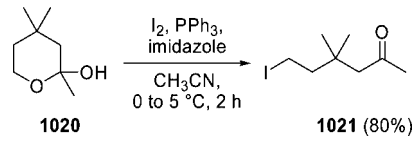
4.6.2. Cyclic Ethers

4.6.2.1. Epoxides. As an alternative to $Co_2(CO)_8$ or noble metal catalysis for the highly selective rearrangement of aliphatic terminal epoxides to methyl ketones, Kauffman and co-workers presented the use of Me_4FeLi_2, Me_3FeLi, or catalytic systems consisting of alkyllithium reagents and $FeCl_3$. Mechanistic considerations for the different catalysts were described, and applying Me_4FeLi_2, brominated epoxide **1022** could be converted to the corresponding δ-bromo ketone **893** in good yield (Scheme 263).[390]

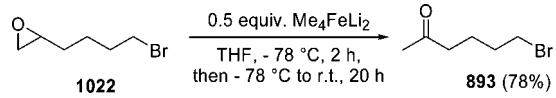
Scheme 261



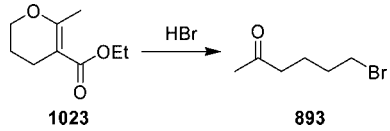
Scheme 262



Scheme 263



Scheme 264



4.6.2.2. Enol Ethers. Dihydropyran derivatives undergo cleavage upon treatment with hydrogen halides to give the corresponding halogenated carbonyl compounds, as exemplified for δ-bromo ketone **893** (Scheme 264).[391]

Another strategy for the ring-opening of cyclic enol ethers was employed by Mioskowski and co-workers (Scheme 265).[392] In the synthesis of the long chain, alkanone sex pheromone of the Douglas-fir tussock moth, enol ether **1024** was converted into δ-iodo ketone **1025** by treatment with TMSCl and NaI.

4.6.2.3. Miscellaneous. Thermally induced ring-opening of halogenated cyclic ethers also provides an entry toward halo ketones. In one example, Polivin and co-workers reported on the thermal isomerization of 2-methyl-3-bromotetrahydropyran **1026** to terminally brominated methylketone **893** (Scheme 266).[262]

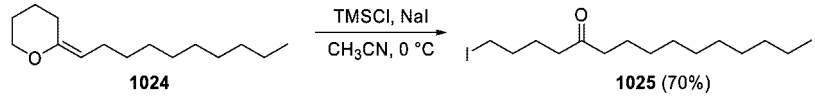
4.6.3. Cycloalkanes

As can be expected, lactones undergo ring-opening upon treatment with TMSI. Nevertheless, treatment of tricyclic ketolactone **1027** with TMSI to a certain extent also causes ring-opening of the activated cyclobutane moiety, leading to a mixture of δ-iodo ketone **1028** and isomeric iodocarboxylic acid **1029** (Scheme 267).[393]

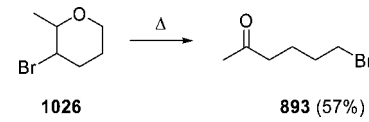
tert-Cyclopentyl hypochlorites undergo a thermal rearrangement to δ-chloro ketones (Scheme 268).[394] This reaction is discussed more thouroughly in the section on ω-halo ketones.

Besides, tertiary cyclopentyl alcohols are succeptible to a retro-Barbier fragmentation reaction upon treatment with Br_2 and K_2CO_3 in $CHCl_3$, furnishing the corresponding δ-bromo ketones in excellent yields (Scheme 269).[395] Again, this reaction is discussed more profoundly in the section on the synthesis of ω-halo ketones and aldehydes.

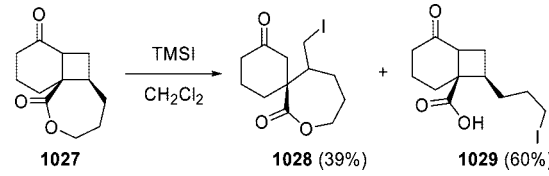
Scheme 265



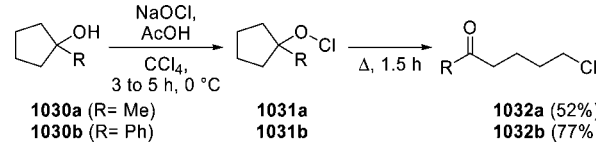
Scheme 266



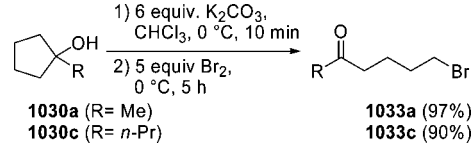
Scheme 267



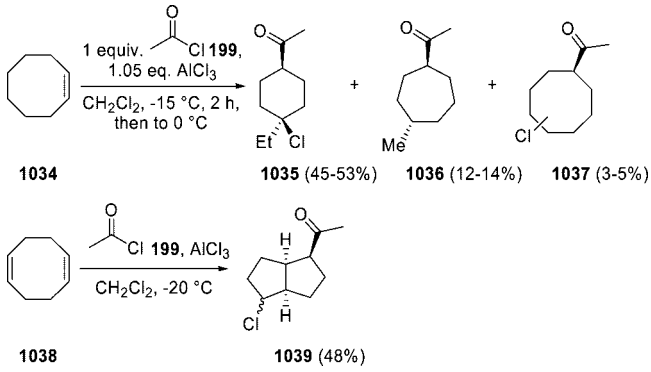
Scheme 268



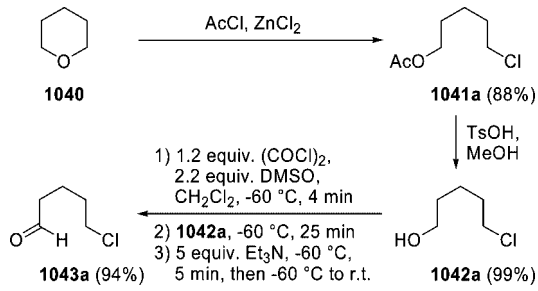
Scheme 269



Scheme 270



Scheme 271



4.7. Ring Closure and Contraction

4.7.1. Ring Closure

As described in the section on β-halogenated carbonyl compounds, carvone was reported to form bicyclic δ,δ-dichloro ketones **477** and **478** upon addition of dichlorocarbene across its isopropenyl group (see Scheme 111).[176]

4.7.2. Ring Contraction

Reaction of cyclooctene **1034** with AcCl under Friedel−Crafts conditions results in a mixture of three ketones of different ring size, of which 1-chloro-1-ethyl-4-acetylcyclohexane **1035** was the major product (Scheme 270).[396] In contrast, the use of $SnCl_4$ as the Lewis acid catalyst chiefly yields 1-acetylcyclooctene. The formation of the three depicted products was envisaged by Cantrell as proceeding *via* several carbenium ion processes. Chemical and spectral data lead to the assignment of the stereochemistry of the obtained compounds. Still, the $AlCl_3$ catalyzed reaction of 1,5-cyclooctadiene **1038** with AcCl gave *exo*-2-acetyl-6-chloro-*cis*-bicyclo[3.3.0]octane **1039** as the major product.

4.8. Oxidation

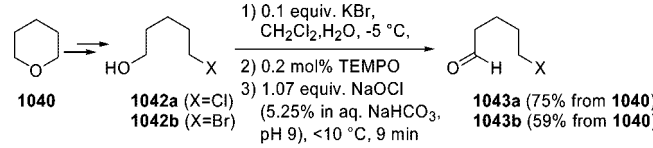
4.8.1. Oxidation of Halogenated Alcohols

4.8.1.1. Chromium-Based Oxidants. *Collins−Ratcliff Reagent.* As described in the section on γ-halogenated compounds, polychlorinated bicyclo[2.2.2]octan-2-one **801** has been prepared by Collins−Ratcliff oxidation of the parent alcohol (Scheme 203).[316]

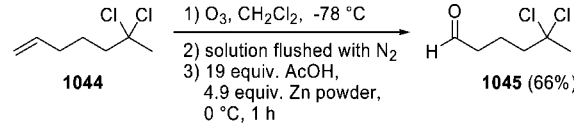
4.8.1.2. Non-chromium-Based Oxidants. *Swern Oxidation.* Hoffmann and co-workers published a high-yielding three-step synthesis of 5-chloropentanal **1043a**, starting from tetrahydropyran **1040** and involving a successful Swern oxidation of the parent alcohol **1042a** (Scheme 271).[397]

2,2,6,6-Tetramethyl-1-piperidinyloxy Radical (TEMPO). TEMPO-catalyzed oxidations have been proposed as a higher

Scheme 272



Scheme 273



yielding alternative to the Swern protocol, concurrently eliminating the obnoxious Me_2S odor.[398] This was exemplified by Brodfuehrer and co-workers in the synthesis of 5-bromopentanal **1043b** (Scheme 272). Chlorinated analogue **1043a**, however, was obtained in lower yield than *via* the Swern-protocol (Scheme 271). Still, the TEMPO-approach proved applicable on a fairly large scale, as **1043a** was prepared starting from 200 g of the parent alcohol. While chloro aldehyde **1043a** proved fairly stable, brominated analogue **1043b** was generally converted to its more stable dimethyl acetal without intermediate isolation.

Chlorine Gas. In an approach identical to the one of Hoffmann and co-workers (see Scheme 271), De Kimpe and co-workers prepared 5-chloropentan-1-ol **1062a** *via* ring-opening of tetrahydropyran **1060**.[399] This alcohol was subsequently oxidized and α,α,-dichlorinated in one step upon treatment with Cl_2 in DMF and $CHCl_3$ according to the method of De Buyck and co-workers,[400] thus furnishing 2,2,5-trichloropentanal in a straightforward three-step synthesis.

4.8.2. Oxidation of Olefins

In their enantioselective total synthesis of dolabellin, a cytotoxic metabolite from the sea hare *Dolabella auricularia*, Yamada and co-workers required 5,5-dichlorohexanal **1045** as a starting material (Scheme 280).[401] Ozonolysis of 6,6-dichloro-1-heptene **1044** was chosen as the preferred entry to this aldehyde, while the reductive workup of the ozonide was accomplished on treatment with zinc in AcOH (Scheme 273).

In the earlier described preparation of *exo*-9-chloro-*exo*-tricyclo[5.2.1.$0^{2,6}$]decan-3-one **822** *via* hydroboration−oxidation of a mixture of the parent dec-3-ene and dec-4-ene, two tricyclic δ-chlorinated ketones were formed as the other possible regioisomers (see the section on γ-halogenated ketones and aldehydes and also Scheme 211).[325]

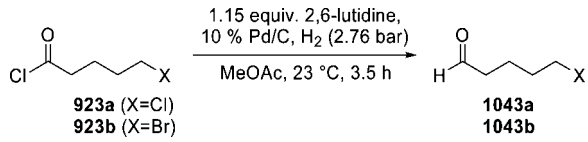
4.9. Reduction

Introduction

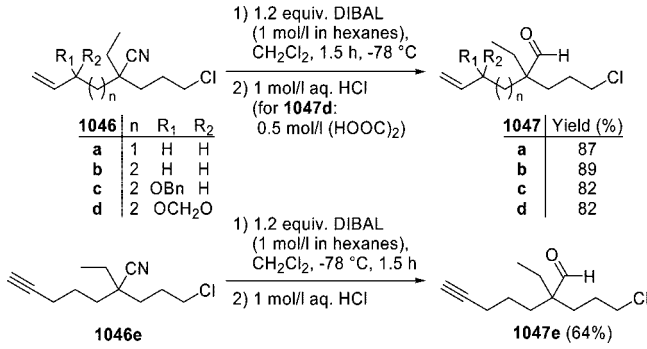
4.9.1. Reduction of Carboxylic Acid Derivatives

Brodfuehrer and co-workers evaluated the preparation of 5-bromopentanal **1043b** by Rosenmund reduction of 5-bromopentanoyl chloride **923b** (Scheme 274) as an alternative to the TEMPO-catalyzed oxidation of the corresponding alcohols (see the section on Oxidation and also Scheme 272).[398] The latter strategy was preferred, given the high cost of the required acid chlorides and the incomplete conversion *via* the reduction pathway.

Scheme 274



Scheme 275



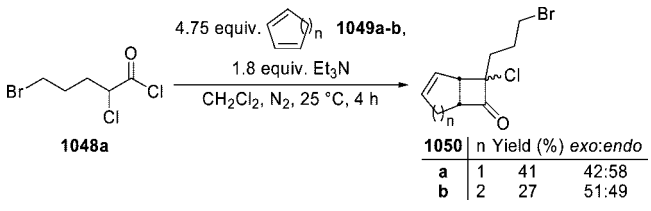
En route toward fused tricyclic amines, Coldham and co-workers synthesized several δ-halogenated alcohols from the corresponding nitriles *via* a DIBAL-mediated reduction (Scheme 275).[329] Yields were high for olefinic substrates **1046a−d**, whereas alkyne **1046e** only reacted with moderate success.

4.10. Pericyclic Reactions

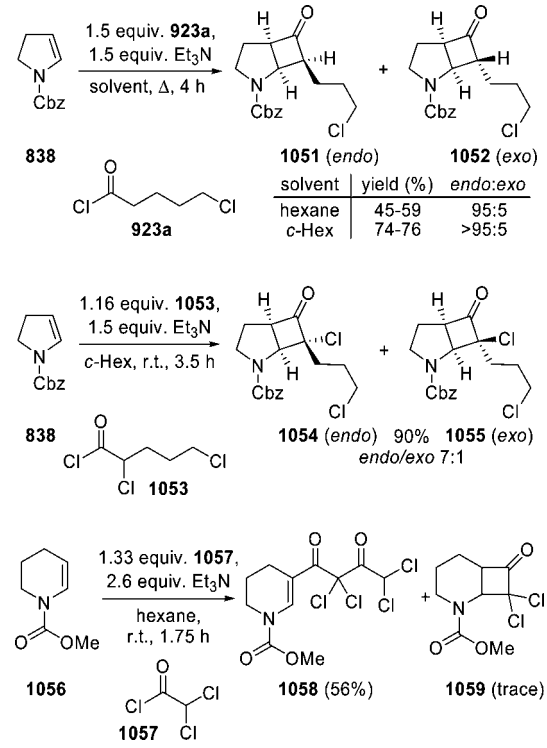
Cyclobutanones bearing a halogen atom at the δ-position can be prepared by [2 + 2] cycloaddition of a suitable, stabilized ketene to an active alkene.[402,403] This ketene cycloaddition is assumed to yield as the major adduct the product with the larger group at the *endo*-position. However, in their experiments, Dowd and co-workers obtained mixtures of *endo*- and *exo*-side chain products **1050a−b** (Scheme 276).[404]

As introduced in the section on γ-halogenated ketones and aldehydes, Correia and co-workers studied the [2 + 2]cycloaddition of five-membered endocyclic enecarbamates **838** to alkyl ketenes (Scheme 277).[333] Using 5-chloropentanoyl chloride **923a** as the ketene precursor in cyclohexane, bicyclic δ-chlorinated ketone **1051** could be obtained with good *endo*-selectivity. Remarkably, the putative kinetic product of the cycloaddition, *endo*-adduct **1051**, underwent extensive epimerization at C(7) in the presence of $Et_3N\cdot HCl$, when using solvents such as THF or CH_2Cl_2. Furthermore, 2,5-dichlorovaleryl chloride **1053** readily afforded an easily separable mixture of *endo*- and *exo*-2-azabicyclic cyclobutanones **1054** and **1055**, for which the position of the alkyl group was determined by NOE-experiments. Interestingly, six-membered endocyclic enecarbamates **1056** only provided the corresponding cycloadducts **1059** in trace amounts. For these substrates, the 3-acyl endocyclic enecarbamates **1058** were the main isolated reaction products.

Scheme 276



Scheme 277



5. Synthesis of ω-Halo Ketones and Aldehydes

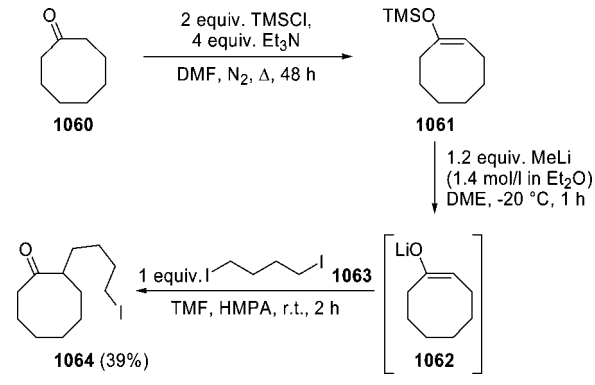
5.1. Nucleophilic Substitution

5.1.1. Enolate Alkylation

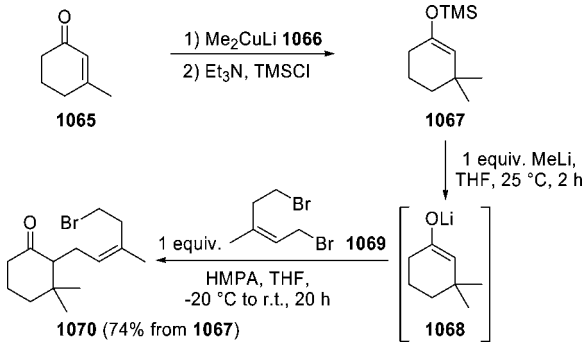
As described in the previous sections, enolate haloalkylation is one of the most obvious and straightforward manners to create ω-halogenated carbonyl compounds. Instead of generating a reactive enolate and trapping it *in situ* with an electrophile, in the context of this review generally an α,ω-dihaloalkane, it is sometimes preferable to isolate the nucleophile as a trimethylsilyl enolate. In this way, for example, Suginome and co-workers prepared 2-(ω-iodobutyl)cyclooctanone **1064** from the unsubstituted parent cycloalkanone (Scheme 278).[337] The intermediate trimethylsilyl enolate **1061** was isolated as such and, in a separate step, converted into its more reactive lithium counterpart upon treatment with MeLi. Likewise, 2-methylcyclohexanone was transformed into 2-(ω-iodobutyl)-2-methylcyclohexanone; only a few percent of the regioisomer was detected.

In a second notable example, Canonne and co-workers trapped the enolate, formed upon 1,4-addition of Me_2CuLi

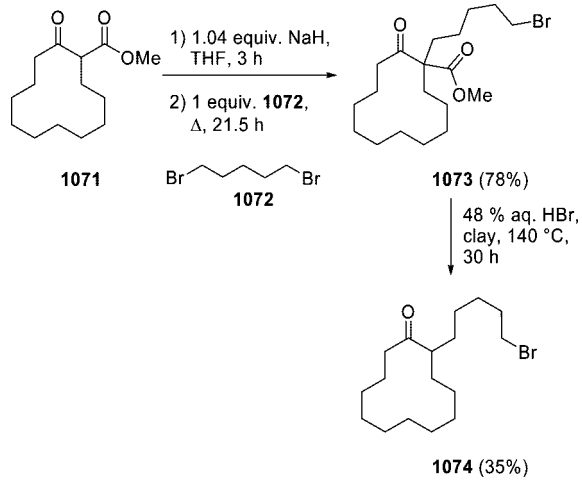
Scheme 278



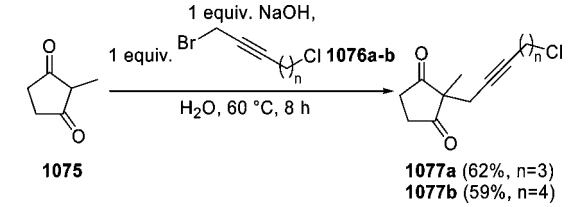
Scheme 279



Scheme 280



Scheme 281

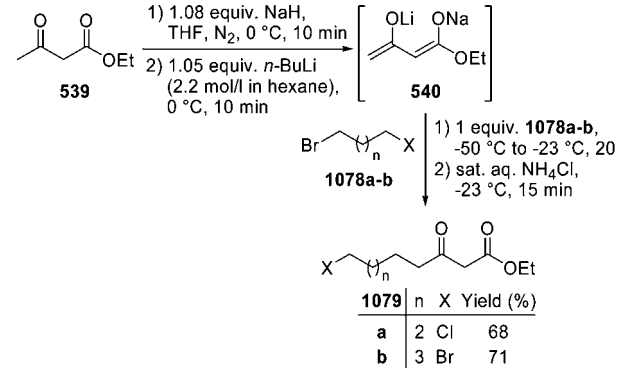


to 3-methylcyclohex-2-en-1-one **1065**, as silylated analogue **1067**. The latter species was converted into its lithium counterpart **1068**, which was subsequently alkylated with (*Z*)-1,5-dibromo-3-methylpent-2-ene **1069** (Scheme 279).[405] Examination of the reaction mixture revealed that substitution occurred with complete regioselectivity at the bromide in the allylic position.

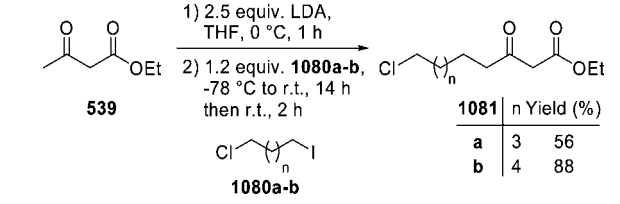
As described in the previous sections, the enolate is very often generated from an activated substrate. Hence, β-ketoesters such as ethyl acetoacetate[406] and 2-(ethoxycarbonyl)-1-tetralone[8,407] and ethyl cycloalkanone-2-carboxylates of different ring size[12,340,342,343,408] have been used in the reaction with α,ω-dihaloalkanes. If not desired in the end product, the ester moiety can be removed *via* a decarboxylation step. In the development of a route toward macrobicyclic allenes, Nickon and co-workers successfully alkylated 2-(methoxycarbonyl)cyclododecanone **1071** (Scheme 280).[409] A successive decarboxylation step transformed ketoester **1073** into the corresponding halogenated macrocyclic ketone **1074**.

In another example on the use of an activated substrate, Schick and co-workers generated the enolate of cyclic 1,3-diketone **1075**, employing NaOH as a base (Scheme 281).[410] Reaction of the thus obtained nucleophile with dihaloalkynes

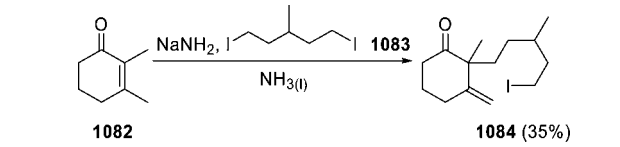
Scheme 282



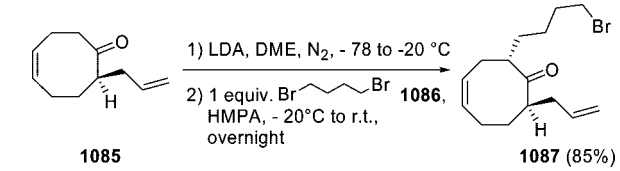
Scheme 283



Scheme 284



Scheme 285



1076a−b furnished ω-chlorinated diketones **1077a−b** in reasonable yield.

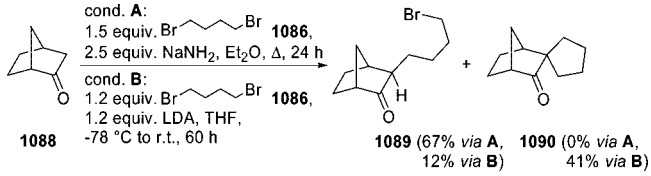
The regioselective γ-alkylation of β-ketoesters was introduced by Carrié and co-workers. Besides several γ- and δ-halogenated carbonyl compounds, whose synthesis was used to introduce this transformation in the previous sections, also ω-halogenated compounds **1079a−b** were prepared in this way (Scheme 282).[204]

Later on, Langer and co-workers used this methodology to synthesize direct analogues **1081a−b** in varying yields (Scheme 283).[344]

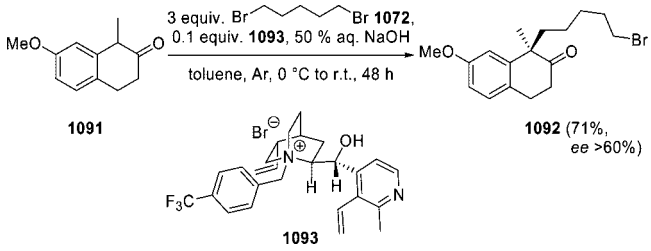
Furthermore, α,β-unsaturated carbonyl compounds can be deprotonated at the γ-position and will regioselectively deliver their α-alkyl-β,γ-unsaturated analogues upon treatment with a suitable electrophile. In this manner, Yoshikoshi and co-workers were able to alkylate 2,3-dimethylcyclohex-2-enone **1082** with 1,5-diiodo-3-methylpentane **1083**, using $NaNH_2$ in liquid NH_3 as a base (Scheme 284).[411]

Another way to enhance regioselectivity in this type of reactions consists of favoring the formation of the thermodynamic or the kinetic enolate. As such, 8-allylcyclooct-4-enone **1085** was regioselectively alkylated with 1,4-dibromobutane **1086** under kinetically controlled conditions by Mehta and co-workers (Scheme 285).[412] Furthermore, the reaction proved to be diastereoselective, as the more stable *trans*-dialkylated cyclooctenone **1087** was preferably formed.

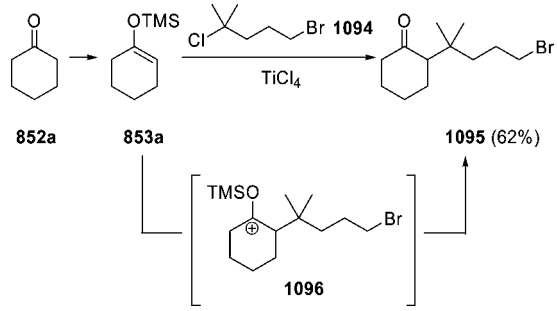
Scheme 286



Scheme 287



Scheme 288



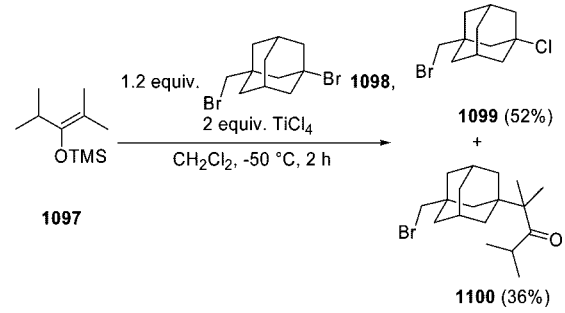
Diastereoselectivity has also been observed in several other enolate haloalkylation studies. In the development of a general method for the synthesis of spironorcamphor derivatives **1090** involving cycloalkylation of 2-norbornone **1088** with 1,4-dibromobutane **1086**, for example, 3-*exo*-(4-bromobutyl)norcamphor **1089** was identified as the sole intermediate (Scheme 286).[413] This was rationalized based on a selective *exo*-attack of the alkylating reagent **1086**. The lack of its *endo*-epimer implies a rapid cyclization of the enolate anion derived from **1089**, compared to the competing proton exchange reaction. As depicted in the scheme, selective formation of mono- or dialkylated compounds was highly dependent upon the reaction conditions.

Enantioselective alkylations have also been conducted. Vandewalle and co-workers, for example, investigated the alkylation of selected α-aryl substituted aliphatic carbonyl compounds by means of chiral phase transfer catalysis (Scheme 287).[414] Treatment of tetralone **1091** with 1,5-dibromopentane **1072** in the presence of cinchonidinium catalyst **1093** led to the formation of brominated ketone **1092** in moderate enantiomeric excess.

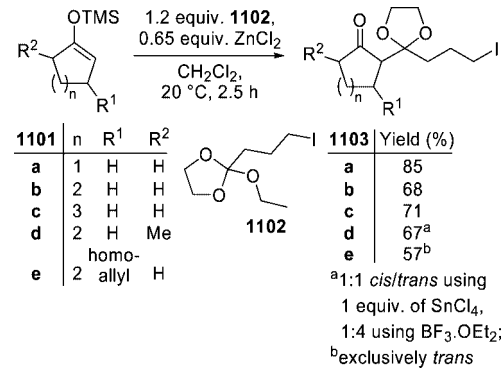
As discussed for γ-halogenated ketones and aldehydes, all but one electrophiles in the above depicted examples are unhindered primary halides. Hence, substitution proceeds *via* an S_N2 mechanism. However, for many secondary or tertiary alkylating reagents, a competing enolate-induced elimination reaction may be observed. A silyl enol ether, an electron-rich yet nonbasic nucleophile, constitutes a useful alternative in these cases.

This approach was used by Reetz for the alkylation of cyclohexanone **852a** with tertiary alkyl chloride **1094** (Scheme 288).[415] A rapid desilylation prevented oligomerization, while the regioselectivity of the transformation was

Scheme 289



Scheme 290

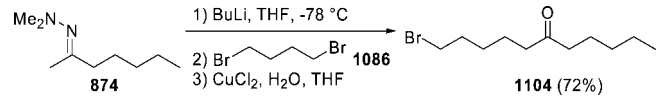


1101	n	R^1	R^2
a	1	H	H
b	2	H	H
c	3	H	H
d	2	H	Me
e	2	homo-allyl	H

1103	Yield (%)
a	85
b	68
c	71
d	67[a]
e	57[b]

[a]1:1 *cis*/*trans* using 1 equiv. of $SnCl_4$, 1:4 using $BF_3.OEt_2$; [b]exclusively *trans*

Scheme 291



controlled by the Lewis acid-induced formation of the most stable cation derived from the alkylating reagent. This was also observed by Asaoka and co-workers in a reaction with 5-bromo-3-bromomethyl-2-methylpent-2-ene, where the allylic cation was formed preferentially.[416]

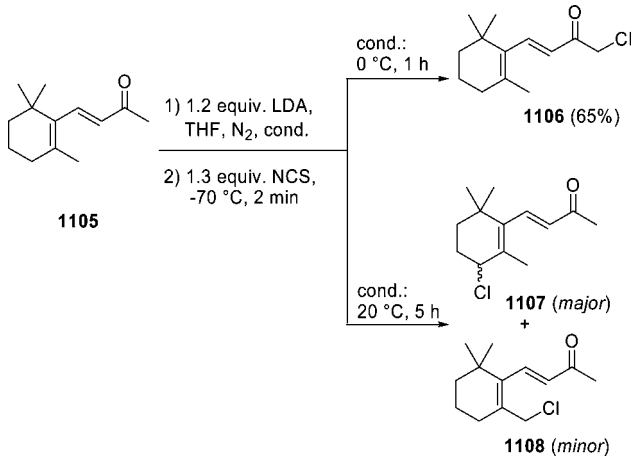
Also, Dubois and co-workers applied the method on more complex alkylating agents of the adamantane series (Scheme 289).[417] One of the target structures was an ω-halogenated carbonyl compound **1100**, which, however, was only obtained as a side product, with the primary reaction being a transhalogenation that afforded chloride **1099**.

In their investigations toward the establishment of a novel annelation protocol for the rapid preparation of a range of bicyclic enones, Markó and co-workers were able to synthesize ω-iodinated ketones **1103** by reacting trimethylsilyl enol ethers **1101** and orthoester **1102** (Scheme 290).[418] Although this is a well-documented transformation, the investigators observed that numerous Lewis acids were inefficient in promoting the reaction. However, the use of $ZnCl_2$, $SnCl_4$, or $BF_3 \cdot Et_2O$ proved to be successful, and good diastereocontrol was observed in some cases. Still, tetrasubstituted silyl enol ethers proved to be inert under these reaction conditions.

As discussed in the section on the preparation of δ-halogenated aldehydes and ketones, imines and hydrazones can be converted into their corresponding enamines since they possess acidic α-protons. Hence, ω-brominated ketone **1104** was prepared using the Corey−Enders hydrazone alkylation, followed by a $CuCl_2$-mediated hydrolysis step (Scheme 291).[347]

Furthermore, as described before (Scheme 231), β-lithiated enamines are readily prepared from enamines by successive

Scheme 292



bromination and halogen−metal exchange, and they yield ω-chloro carbonyl compounds upon reaction with 1-bromo-ω-chloroalkanes.[352]

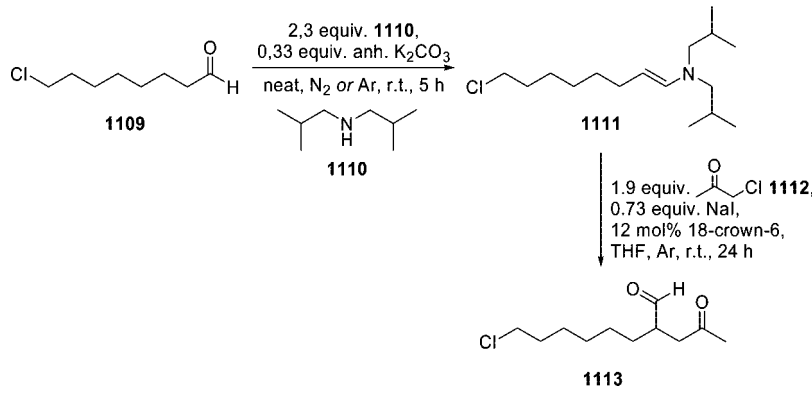
5.1.2. Enolate Halogenations

Analoguous to the haloalkylation of enolates, these carbon nucleophiles can also be reacted with electrophilic halogens. Again, the regioselectivity of the transformation can be controlled by favoring the formation of the thermodynamic or the kinetic enolate. As such, the α′-lithium enolate of β-ionone **1105** rearranges at room temperature to the thermodynamically more stable allylic form (Scheme 292).[419] Thus, upon quenching with NCS, the allylic chlorinated products **1107** and **1108** were formed, whereas α′-chlorination was observed at low temperature. It should be noted that the α-chloromethyl ketone **1106** proved to be fairly unstable.

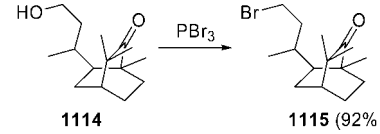
5.1.3. Reactions with Electrophilic Carbonyl Compounds

Instead of introducing the haloalkyl moiety through reaction of a dihalogenated electrophile with an enolate or its equivalent, the carbonyl group can also be part of the electrophile. Robertson and co-workers, for example, used chloroacetone **1112** as the electrophilic partner in a reaction with diisobutyl enamine **1111**, prepared from 8-chlorooctanal **1109** (Scheme 293).[420] NaI activation of the electrophile proved compulsory to obtain γ-ketoaldehyde **1113** in good yield.

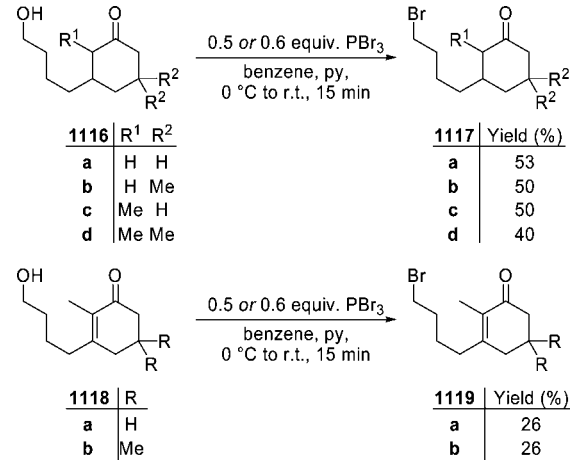
Scheme 293



Scheme 294



Scheme 295



5.1.4. Conversion of an Alcohol or Ether into an Alkyl Halide

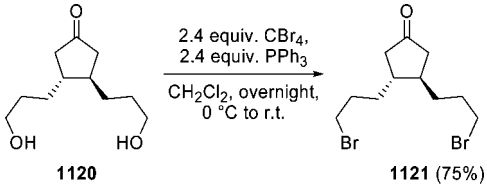
5.1.4.1. Substitution of Phosphoryl Activated Alcohols. As explained in the section on β-halogenated compounds, PBr_3 is a widely used agent for the nucleophilic displacement of hydroxyl groups. *Via* this approach, Danishefsky and co-workers were able to prepare bicyclic bromo ketone **1115** from the corresponding alcohol **1114** (Scheme 294).[421]

In a second example, Conia and co-workers employed PBr_3 in their synthesis of several 3-(ω-bromoalkyl)cyclohexanones **1117a**−**d**, which were obtained in rather modest yields (Scheme 295).[422] The reaction outcome was even less satisfying for α,β-unsaturated analogues **1119a**−**b**.

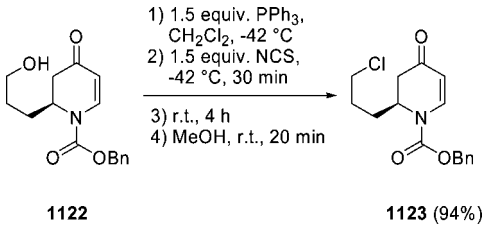
Another valuable method involving phosphoryl activation of alcohols is the Appel reaction, in which the substrate is treated with PPh_3 and CCl_4 or CBr_4 under mild conditions (Scheme 296).[423] Alternative halide sources for this transformation are I_2[353] and NCS (Scheme 297).[424]

Additionally, the Appel reaction is compatible with the presence of a stannyl group in the substrate, as demonstrated by Tsai and co-workers (Scheme 298).[354] Further details on this reaction were described in the section on δ-halogenated compounds.

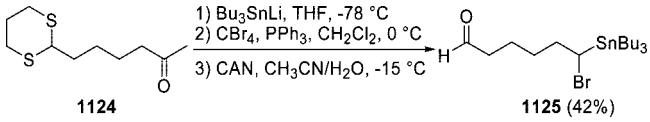
Scheme 296



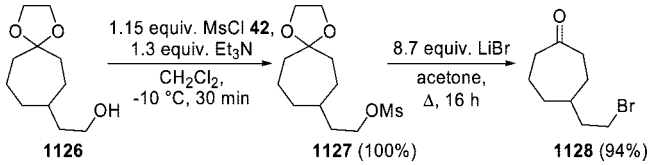
Scheme 297



Scheme 298



Scheme 299

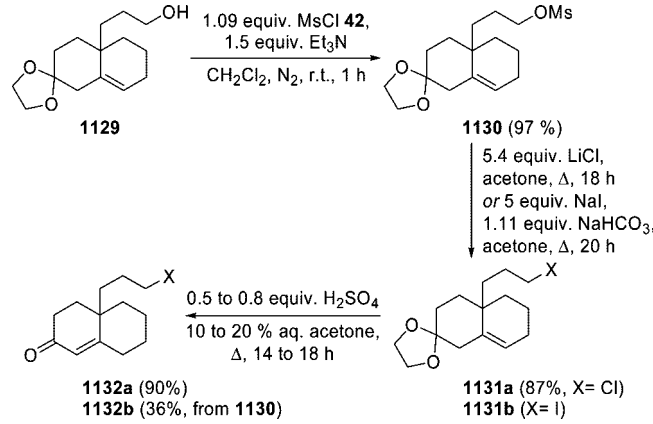


5.1.4.2. Substitution of Sulfuryl Activated Alcohols. As stated in the previous sections, esters of sulfonic acids are good leaving groups. Hence, alcohols are often activated toward nucleophilic substitutions by converting them into mesylates (Scheme 299).[425] In a typical procedure, the alcohol is treated with mesyl chloride **55** in dry CH_2Cl_2,[425,426] in the presence of a base such as Et_3N, at room temperature or below. This transformation usually proceeds in very high yield, if not quantitative. Subsequently, the mesylate **1143** is treated with LiCl or LiBr in warm acetone to furnish the respective alkyl halide **1144**.[359,425,426] In some cases, the halogenation step is performed in the presence of the sodium salt of the halide[427,428] or in another polar aprotic solvent such as DMF.[427] The example presented in Scheme 299 illustrates the possible occurrence of acetal hydrolysis under the conditions used to substitute the mesylate for a halide.

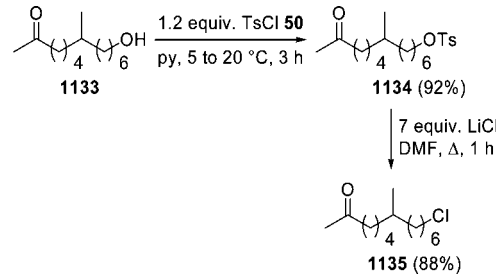
However, in other syntheses, mesylate substitution proceeds without concomitant hydrolysis of the acetal moiety, and an extra step is requisite to deprotect the carbonyl group. In one example, Piers and co-workers observed a simultaneous isomerization of the double bond of halo acetals **1131a−b** when subjecting these intermediates to the hydrolysis conditions depicted in Scheme 300.[429]

Another option to activate an alcohol toward substitution is its conversion into a *p*-toluenesulfonate **1134**. This methodology was employed by Joss and co-workers to convert ω-hydroxyketone **1133** into its chlorinated analogue **1135** (Scheme 301).[243] In general, these transformations proceed readily for primary tosylates, under similar conditions as those used in mesylation strategies.

Scheme 300



Scheme 301



5.2. Nucleophilic Addition

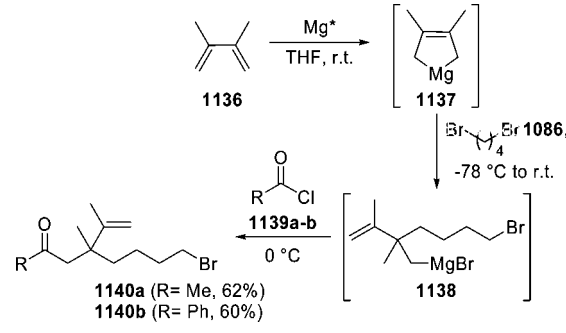
5.2.1. Addition of Organomagnesium Reagents

Complexes of 1,3-dienes and activated magnesium (Mg*) are interesting nucleophiles that can attack two different electrophiles in a stepwise fashion. Treatment of 2,3-dimethyl-2-butene-1,4-diylmagnesium complex **1137** with the 1,4-dibromobutane, a relatively soft electrophile, gives selective alkylation at the 2-position of the diene (Scheme 302).[430] Organomagnesium intermediate **1138** can then be reacted with other electrophiles, such as acid chlorides **1139a−b**. Hence, ω-bromo ketones **1140a−b**, the net "2,1-addition" products, were obtained in reasonable yield.

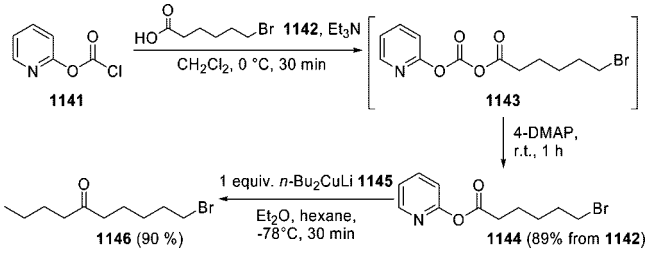
5.2.2. Addition of Organocuprate Reagents

ω-Halo ketones can be synthesized *via* reaction of lithium dialkylcuprates **1145** with 2-pyridyl esters **1144**. In this context, Kim and co-workers introduced 2-pyridyl chloroformate **1141** as a new reagent for the conversion of acids into the desired esters (Scheme 303).[431] Although complete exclusion of oxygen is required for the ketone synthesis, a variety of fuctional groups, such as bromide, ketone, and ester moieties, are tolerated. Of special synthetic significance

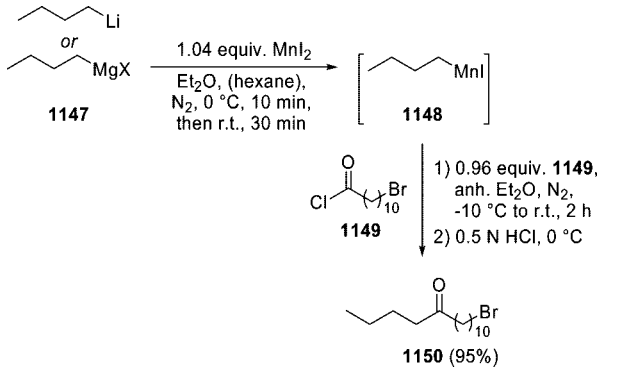
Scheme 302



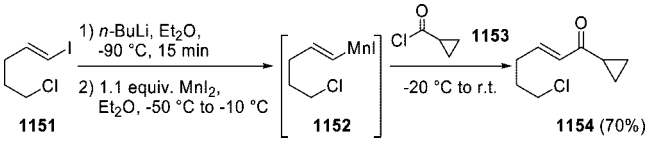
Scheme 303



Scheme 304



Scheme 305



is the essentially complete utilization of both alkyl groups of the organocuprate reagent in several of the investigated cases (though not for **1142**).

5.2.3. Addition of Organomanganese(II) Reagents

Organomanganous reagents are useful reagents for various synthetic purposes. Friour and co-workers, for example, showed that reaction of *n*-butylmanganese(II) iodide **1148** with ω-bromoacid chloride **1149** affords ω-bromo ketone **1150** in excellent yield (Scheme 304).[222]

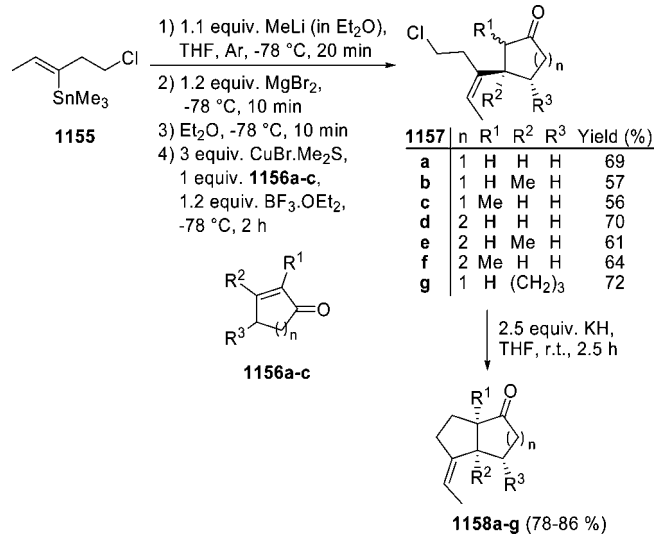
In the course of their investigation on the preparation and reactivity of functionalized alkenylmanganese halides, Knochel and co-workers prepared nucleophile **1152** *via* transmetalation of its organolithium precursor upon treatment with MnI_2 in Et_2O at −50 °C (Scheme 305).[223] This species was subsequently reacted with cyclopropanecarbonyl chloride **1153**, furnishing ω-chloro ketone **1154** in good yield.

5.3. Conjugate Additions

5.3.1. Organocuprate Additions

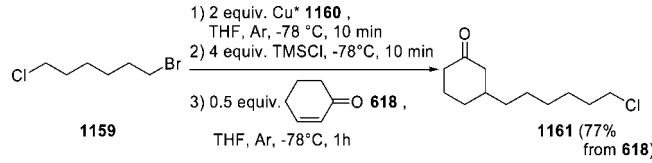
The remarkable softening effect of copper(I) salts on organometallic reagents has proven its invaluable importance in numerous syntheses. Contrary to Grignard reagents, which add to the harder C═O bond of an enone moiety, transmetalation to the organocopper equivalent redirects the attack to the softer C═C bond, as copper has larger, more diffuse orbitals than magnesium. The importance of this transformation was illustrated in the methylene[432,433] and ethylidene[434,435] cyclopentane and methylene cyclohexane[436,437] annulation sequences developed by Piers and co-workers, in which a suitable bifunctional cuprate reagent adds to an enone

Scheme 306



1157	n	R^1	R^2	R^3	Yield (%)
a	1	H	H	H	69
b	1	H	Me	H	57
c	1	Me	H	H	56
d	2	H	H	H	70
e	2	H	Me	H	61
f	2	Me	H	H	64
g	1	H	$(CH_2)_3$		72

Scheme 307

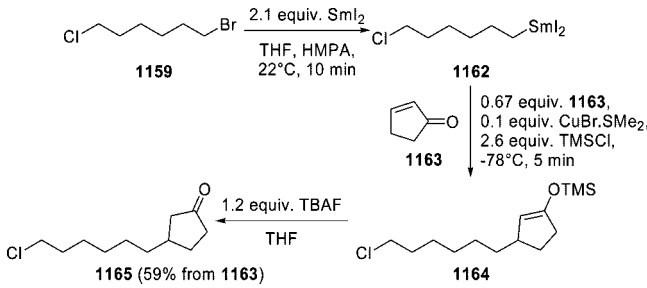


1156a−c (Scheme 306).[438] The use of $BF_3 \cdot Et_2O$ as a catalyst significantly improved the yield of conjugate addition products over similar reactions in the absence of the Lewis acid. As illustrated for the ethylidene variant, the thus obtained 3-[(*Z*)-3-(5-chloro-2-pentenyl)]cycloalkanones **1157a−g** readily undergo a subsequent ring closure toward exocyclic olefins **1158a−g**.

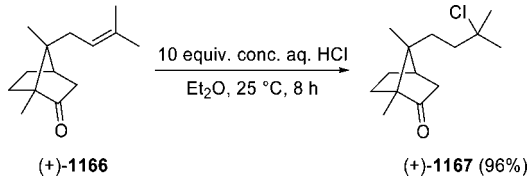
However, the traditional preparation of these organocopper reagents by transmetalation of an organomagnesium or organolithium precursor severely limits the functionality that may be incorporated into the organocopper reagent. This restriction was circumvented by Rieke and co-workers by using thienyl-based highly reactive zerovalent copper **1160**, which directly undergoes rapid oxidative addition to organic halides **1159**, thus creating stable functionalized organocopper reagents. Conjugate addition of these reagents to both cyclic and acyclic α,β-unsaturated ketones (here exemplified for cyclohexenone **618**) proceeds in excellent yields in the presence of TMSCl as a carbonyl activator (Scheme 307).[439] It appears that the complexing ligand plays a significant role in the reactivity of zerovalent copper, as phosphine-based activated copper yielded inferior results: ω-chloro ketone **1161** was obtained in a mere 52% yield by employing PBu_3.[440]

Alkylsamarium species **1162** can be generated in solution by SmI_2 reduction of the corresponding halides **1159**. Wipf and co-workers combined the unique features of samarium chemistry with the broad scope of organocopper reagents *via* a catalytic *in situ* transmetalation of these organosamarium reagents **1162** to copper(I) salts (Scheme 308).[441] In the presence of TMSCl and HMPA, the thus obtained cuprates react with α,β-unsaturated carbonyl compounds (exemplified here for cyclopentenone **1163**) to provide silyl enol ethers **1164**. Cleavage of these species with TBAF provides the corresponding ketones. *Via* this route, ω-chloro ketone **1165** was obtained in 59% yield.

Scheme 308



Scheme 309



5.4. Electrophilic Addition

In a synthesis of longiborneol and longifolene, Kuo and Money reported the Markovnikov addition of HCl across the double bond of (+)-campherenone **1166** in excellent yield (Scheme 309).[442]

5.5. Radical Reactions

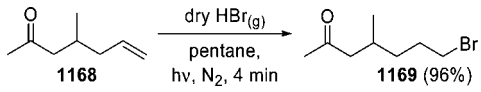
5.5.1. Hydrogen Halide Addition

As discussed in previous sections for their lower homologues, the light-initiated, radical addition of hydrogen halides to unsaturated ketones provides a straightforward entry to ω-halo ketones (Scheme 310).[27]

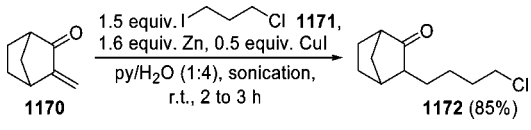
5.5.2. Conjugate Additions

Halogenated alkyl bromides and iodides (such as **1171**) add smoothly to α,β-unsaturated ketones (e.g., **1170**) in the presence of a Zn−Cu couple in an aqueous medium (Scheme 311).[443] The process is greatly enhanced by sonication and is compatible with several functional groups that would not be tolerated in other methods. The use of an aqueous medium makes the involvement of free organometallic species highly improbable; thus, a radical mechanism was proposed. Complete reaction inhibition by cumene substantiates this assumption. Further optimization of this novel organometallic reaction pointed out that the parameter of highest importance is the solvent composition, the optimum of which changes from primary to secondary and tertiary iodides.[444] This indicates a strong solvent participation in the determining step.

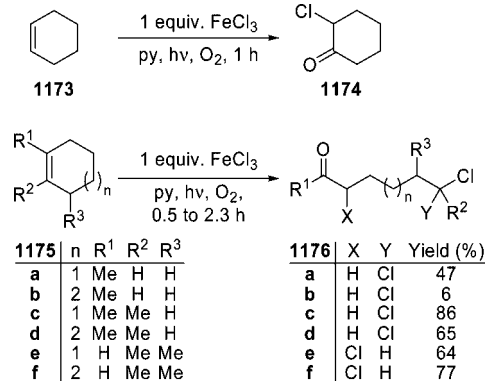
Scheme 310



Scheme 311



Scheme 312



1175	n	R^1	R^2	R^3
a	1	Me	H	H
b	2	Me	H	H
c	1	Me	Me	H
d	2	Me	Me	H
e	1	H	Me	Me
f	2	H	Me	Me

1176	X	Y	Yield (%)
a	H	Cl	47
b	H	Cl	6
c	H	Cl	86
d	H	Cl	65
e	Cl	H	64
f	Cl	H	77

5.5.3. Ring-Opening Reactions

Sato and co-workers developed a one-step synthesis of chlorinated ketones from olefins by photo-oxidation in the presence of $FeCl_3$ and O_2. Pyridine solutions of simple cyclohexenes **1173** give α-chloro ketones **1174** (or their vinylogues in the case of conjugated enones), whereas polyfunctionalized cyclohexenes **1175a−d** afford *gem*-dichloro ketones **1176a−d** *via* C−C-bond cleavage (Scheme 312).[445] α,ω-Dialkylcycloalkenes **1175e,f** produce α,ω-dichloro ketones **1176e,f** under identical conditions.[446] The process was interpreted in terms of an electron-transfer mechanism occurring within the coordination sphere of the iron ion, involving a β-chlorohydroperoxide as the primary product of photo-oxidation. Furthermore, the preparative utility of these transformations was illustrated in the syntheses of brevicomin, muscone,[446] D-solanone,[446,447] and *exo*-brevicomin.[448]

Ring-opening reactions involving the β-scission of alkoxy free radicals are well-documented in the literature and provide an interesting route toward a wide range of halo ketones. An overview of the most important reports on this transformation was given in the section on δ-halogenated ketones and aldehydes, where also the synthesis of several ω-halogenated analogues was discussed.[377,378,380]

5.6. Ring-Opening

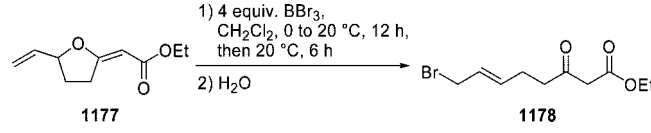
5.6.1. Enol Ethers

Cyclic enol ethers are common intermediates in organic synthesis that can undergo interesting ring-opening reactions. In one example, reaction of BBr_3 with 5-vinyl-2-alkylidene-tetrahydrofuran **1177** resulted in the nearly quantitative formation of ethyl 8-bromo-3-oxooct-6-enoate **1178** (Scheme 313).[257] This transformation proceeds *via* an S_N2' mechanism with migration of the double bond.

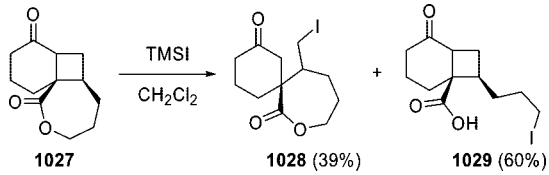
5.6.2. Lactones

Upon treatment with TMSI, tricyclic ketolactone **1027** furnishes ω-iodo ketone **1029** as the major product (Scheme 314).[393] To a lower extent, opening of the cyclobutane moiety furnished spiroketolactone **1028**.

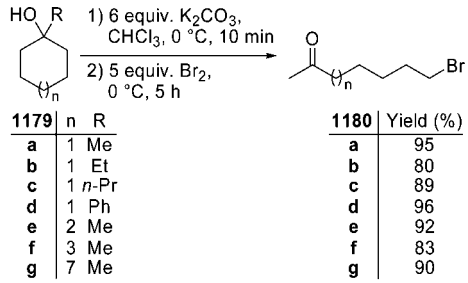
Scheme 313



Scheme 314

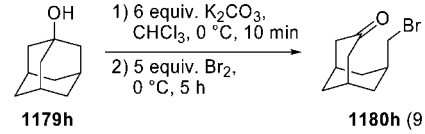


Scheme 315

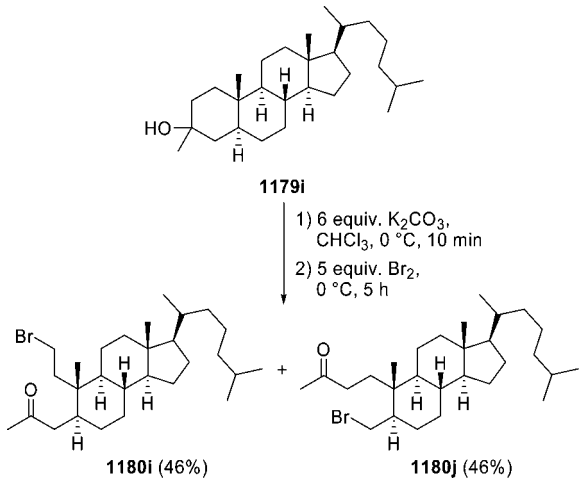


1179	n	R
a	1	Me
b	1	Et
c	1	*n*-Pr
d	1	Ph
e	2	Me
f	3	Me
g	7	Me

1180	Yield (%)
a	95
b	80
c	89
d	96
e	92
f	83
g	90



1179h 1180h (91%)

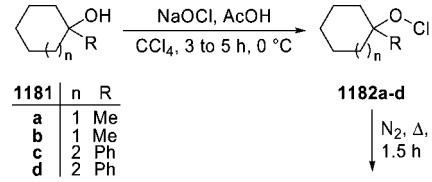


5.6.3. Cycloalkanols

The Barbier-type reaction is a fundamental transformation in organic chemistry. Althoug this metal-mediated carbon−carbon bond formation between alkyl halides and carbonyl compounds is well-established and extensively applied in synthesis, the reversed transformation has received much less attention. Yet, retro-Barbier type reaction of cyclic alcohols provides a convenient entry to ω-halo ketones. In one report, Li and co-workers investigated the scope of this process when applied to cyclic tertiary alcohols. Employing the optimized conditions depicted in Scheme 315, cycloalkanols of varying ring size and bearing different side chains (**1179**) were successfully converted into the corresponding ω-halo ketones **1180**.[395] Unfortunately, when the side chain (R) was a butyl group, an inseparable mixture of products was obtained.

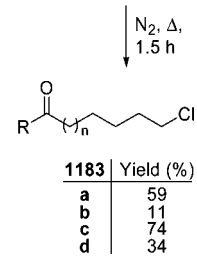
Closely related, Wilt and co-workers investigated the scope of the thermal rearrangement of *tert*-cycloalkyl hypochlorites.[394] The cleavage of six-membered rings proceeded in reasonable to good yields, whereas seven-membered rings gave poor results. Phenyl-substituted rings reacted significantly more slowly than rings bearing a methyl group.

Scheme 316



1181	n	R
a	1	Me
b	1	Me
c	2	Ph
d	2	Ph

1182a-d



1183	Yield (%)
a	59
b	11
c	74
d	34

Furthermore, the presence of oxygen in the reaction mixture had an inhibitory effect (Scheme 316).

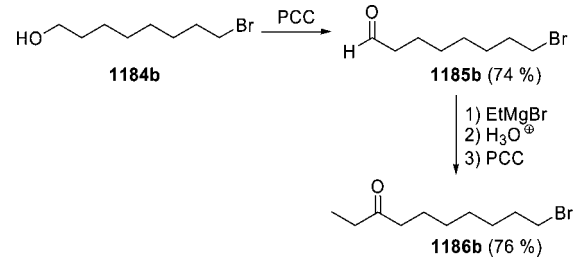
5.7. Oxidation

5.7.1. Oxidation of Alcohols

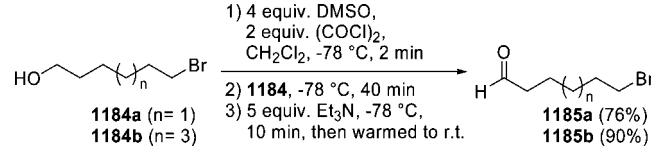
Pyridinium Chlorochromate (PCC). The oxidation of ω-bromoalkan-1-ols to the corresponding ω-bromo aldehydes by means of PCC is a widespread reaction, frequently employed in the synthesis of long-chain natural products. In one example of this approach, as a part of a synthetic route toward (±)-prosopinine, Stille and co-workers obtained ω-bromocaprylic aldehyde **1185b** in rather good yield (Scheme 317).[449] An identical result was reported by Wiley and co-workers during their investigation of Darmstoff analogues.[450] In the same way, Carballeira[451,452] and Bestmann,[453] respectively, obtained 10-bromodecanal and 7-bromoheptanal. Still, upon addition of EtMgBr to aldehyde **1185b** and following a second PCC-mediated oxidation step, Cook and co-workers obtained 10-bromodecan-2-one **1186b** in reasonable overall yield.

Swern Oxidation. When compared to the aforementioned PCC-mediated oxiditation reported by Stille and co-workers (Scheme 317),[449] Swern conditions proved to be superior for the conversion of 8-bromooctanol **1184b** into ω-bromocaprylic aldehyde **1185b** (Scheme 318).[454] Interestingly, the analogous hexanal **1185a** was obtained in significantly lower yield.

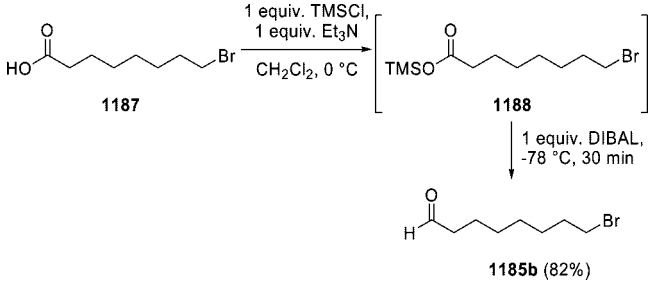
Scheme 317



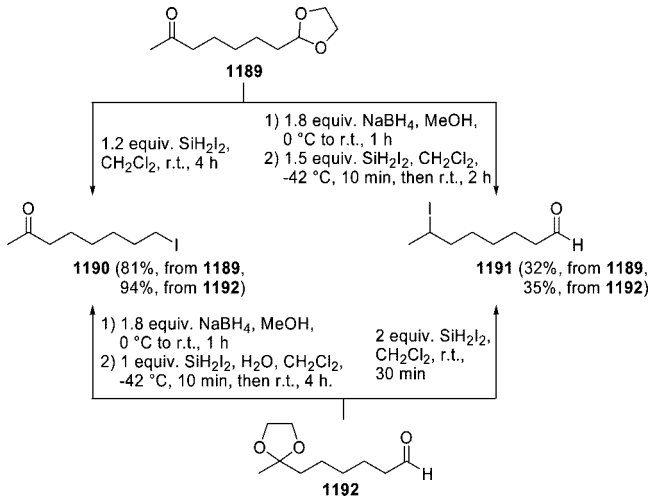
Scheme 318



Scheme 319



Scheme 320



5.8. Reduction

5.8.1. Reduction of Carboxylic Acid Derivatives

Although the aldehydes constitute an important class of organic compounds, their preparation *via* a direct reduction of carboxylic acids is rather poorly addressed. In the development of an olefin tolerant alternative to borane for this transformation, Chandrasekhar and co-workers prepared 8-bromooctanal **1185b** from 8-bromooctanoic acid **1187** *via* a one-pot chemoselective reduction of the *in situ* formed trimethylsilyl ester **1188** using DIBAL (Scheme 319).[455] No bromine reduction product was formed.

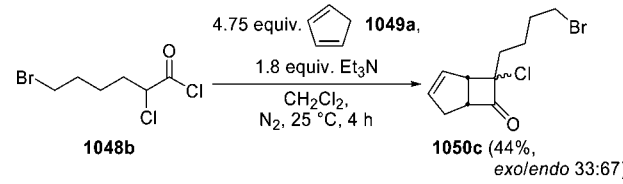
5.8.2. Miscellaneous

A remarkable case of chemoselectivity in the reduction of carbonyl groups was observed by Keinan and co-workers when using SiH_2I_2 (Scheme 320).[456] At low temperature, a catalytic amount of SiH_2I_2 provides a clean deprotection of various acetals, without apparent reduction of the obtained carbonyl moieties. Nevertheless, at temperatures above 0 °C, the reagent effectively reduces acetals to iodoalkanes, while unprotected ketones and aldehydes are inert. A direct comparison with the corresponding $NaBH_4$-mediated reductions was made.

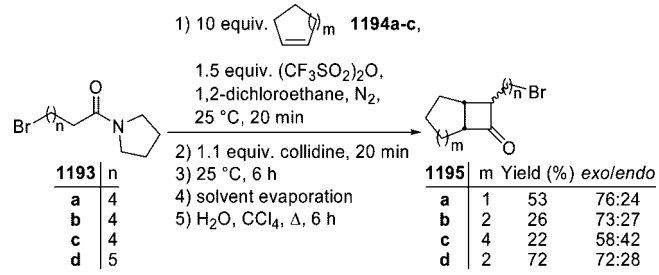
5.9. Cycloaddition Reactions

ω-Haloalkyl substituted cyclobutanones can be synthesized by [2 + 2] cycloaddition of a suitable, stabilized ketene to an active alkene.[457,458] Generally, the major adduct is expected to be the product with the larger group at the *endo*-position. Dowd and co-workers, however, obtained mixtures of *endo*- and *exo*-side chain products **1050c** in their experiments (Scheme 321).[459]

Scheme 321



Scheme 322



1193	n
a	4
b	4
c	4
d	5

1195	m	Yield (%)	*exo*/*endo*
a	1	53	76:24
b	2	26	73:27
c	4	22	58:42
d	2	72	72:28

In the same report, an alternative method toward these cyclobutanones was examined, consisting of a cycloaddition of ketiminium salts with alkenes (Scheme 322). These salts are more electrophilic than ketenes and, therefore, react with unactivated alkenes. Moreover, higher *exo*/*endo* ratios were obtained.

6. Conclusion and Outlook

The synthetic organic chemist is now presented with a myriad of routes for the preparation of halogenated aldehydes and ketones. The fact that essentially all classes of organic reactions have been employed to synthesize these substances—and are accordingly treated in this overview—further underlines the value of halogenated aldehydes and ketones.

The diverse chemistry encountered in the current overview encompasses both old, well-known, rather crude methods and more sophisticated regio-, chemo-, and stereoselective strategies developed in the last decades. Most of these approaches can be used for the synthesis of β-, γ-, δ-, as well as ω-halogenated aldehydes and ketones. The conjugate addition of a hydrogen halide to an enone and the electrophilic addition of an acyl chloride to an olefin, however, are convenient methods for the prepation of β-halogenated carbonyl compounds, but they are also necessarily confined to these β-analogues. Analogously, the hydrogen halide-mediated ring-opening of cyclopropyl ketones generally furnishes γ-halo ketones.

A large number of standard procedures and name reactions used in modern organic synthesis involve the intermediacy of a halogenated carbonyl compound, as was illustrated for the Dowd−Beckwith ring expansion methodology. Furthermore, an important share of the depicted halogenated ketones and aldehydes serve as structural analogues of valuable natural products or as synthetic intermediates in the total synthesis of the latter. Thus, one can conclude beyond any reasonable doubt that numerous novel synthetic methods will be expanded to the preparation of β-, γ-, δ-, ..., ω-halogenated ketones and aldehydes in the next decades.

7. Abbreviations

AIBN	azobisisobutyronitrile
BPO	dibenzoyl peroxide
BTEAC	benzyltriethylammonium chloride

CAN	cerium ammonium nitrate
Δ	reflux temperature
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DIBAL	diisobutyl aluminum hydride
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMP	Dess−Martin periodinane
DMSO	dimethylsulfoxide
ee	enantiomeric excess
HMPA	hexamethylphosphorus(V) triamide
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropyl amide
$LiAlH_4$	lithium aluminum hydride
MAPH	methylaluminium bis(2,6-diphenyloxide)
m-CPBA	*m*-chloroperbenzoic acid
MS	molecular sieves
MsCl	methanesulfonyl chloride
MW	microwave heating
NCS	*N*-chlorosuccinimide
PCC	pyridinium chlorochromate
PPTS	pyridinium *p*-toluenesulfonate
py	pyridine
rt	room temperature
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy radical
TES	triethylsilyl
THF	tetrahydrofuran
TMSBr	trimethylsilyl bromide
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TsCl	*p*-toluenesulfonyl chloride

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