Cyclization Reactions of Dianions in Organic Synthesis†

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Contents

† Dedicated to Professor Dr. Dr. h. c. mult. Dietmar Seyferth.

1. Introduction

Dianions are reactive organic intermediates containing two negative charges.[1] In this article dianions are more specifically defined as species that (a) possess a lithium, sodium, potassium, or magnesium counterion and (b) undergo at least one carbon−carbon bond formation in their reaction with electrophiles. The generation of dianions often requires the use of a strong base, such as lithium diisopropylamide (LDA) or *n*-butyllithium (*n*BuLi) and may be achieved by deprotonation, reduction, or metal−halide exchange.

The goal of the present article is to provide a review of cyclization reactions of dianions. A number of excellent reviews of the chemistry of dianions have been published.[1] More specific reviews of the cyclization of 1,3-dicarbonyl dianions with 1,2-dielectrophiles[2a] and of dianions with oxalic acid-bis(imidoyl)-dichlorides have been recently published.[2b] A number of cyclization reactions are included in earlier reviews. For the sake of comprehensiveness, those reactions are included herein.[1,2] We focus on selected examples of cyclization reactions that follow either a 1:1 stoichiometry of dianion and electrophile or an oxidative pathway. A variety of domino cyclizations of dianions are known that follow a 2:1 stoichiometry. This type of transformation, which includes for example the elegant work of Harris related to 1,3-dicarbonyl dianions,[3] is not included in this review. The cyclization reactions reported herein include, at least one, formation of a carbon−carbon bond. For reasons of comparison, we have included a few transformations that involve the formation of a carbon−silicon rather than a carbon−carbon bond.

Much work in dianion chemistry has been concentrated on the synthesis of open-chained products by reaction of dianions with monofunctional electrophiles and subsequent addition of water. Despite their simplicity and synthetic usefulness, cyclization reactions of dianions are relatively rare, compared to the formation of open-chained products. This can be explained by the fact that both dianions and many dielectrophiles represent highly reactive compounds, which results in a low reactivity matching. In addition, dielectrophiles are often rather labile, and reactions with strong nucleophiles can result in polymerization, decomposition, formation of open-chained products, elimination, or SET processes. Although these problems are present particularly in reactions of dianions with 1,2-dielectrophiles, they

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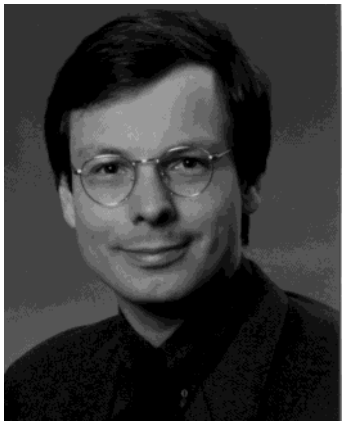


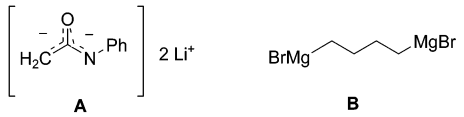
Peter Langer was born in Hannover (Germany) in 1969. He studied chemistry at the University of Hannover and at the Massachusetts Institute of Technology (MIT) and received his Diploma under the guidance of Prof. Dietmar Seyferth in March 1994. In February 1997, he obtained his Dr. rer. nat. for a synthetic work on *Cinchona* alkaloids under the supervision of Prof. H. Martin R. Hoffmann at the University of Hannover (summa cum laude). During a postdoctoral period with Prof. Steven V. Ley, FRS (Cambridge, UK), he worked on the synthesis of oligosaccharides. In 1998, he moved to the University of Göttingen where he started his independent research (related to cyclization reactions of dianions) associated to Prof. Armin de Meijere. He completed his habilitation in July 2001 and was appointed Privatdozent. In April 2002, he took a permanent position as a full professor (C4) at the University of Greifswald, which is located in the northeast of Germany close to the Baltic Sea. Prof. Langer is coauthor of currently 107 research papers (June 2004). His research is focused on the development of new synthetic methods and their application to the synthesis of biologically relevant ring systems and natural products. This includes regio- and stereoselective cyclization reactions of dianions and electroneutral dianion equivalents (1,3-bis-silyl enol ethers), transition metal and Lewis acid catalysis, domino reactions, allene and isothiocyanate chemistry, and heterocyclic chemistry. His awards and scholarships include Studienstiftung des deutschen Volkes (1992–94), Fonds der Chemischen Industrie (1995–96), Feodor-Lynen scholarship (1997–98), Liebig scholarship (1999–2001), and Heisenberg scholarship (2001).

Walter Freiberg was born in 1938 in Mitau. He studied chemistry at the University of Greifswald (1959–1964), Germany, and received his Ph.D. for studies related to the physical organic chemistry of 1,2,4-triazoles under the supervision of Prof. C. F. Kroeger (1968). In 1985, he completed his habilitation (studies on the basicity of ketones) and took a permanent position as a Privatdozent at the University of Greifswald. Very recently, Dr. Freiberg retired from active duty.

also occur in cyclizations with other 1,*n*-dielectrophiles. Two ways to overcome these intrinsic limitations are possible: (a) a proper tuning of the reactivity of dianion and dielectrophile and (b) the use of electroneutral dianion equivalents (masked dianions) in Lewis acid catalyzed reactions. Masked dianions, which are not included in this review, represent important synthetic building blocks. For example, tetradonor-substituted allenes can be regarded as masked malonic ester dianions.[4] The chemistry of masked 1,3-dicarbonyl dianions has recently been reviewed.[2c]

A common classification of dianions is based on the distance between the two negative charges of the dianion (1,*n*-dianions, $n = 1, 2, 3...$).[1] Among these groups, ambident dianions (one or two delocalized negative charges) can be distinguished from nonambident dianions (no delocalized negative charge). Typical examples are the 1,3-dianion of acetic anilide **A** and 1,4-di(bromomagnesio)butane **B** (Chart 1). Ambident dianions are particularly interesting, due

Chart 1. Ambident and Non-Ambident Dianions



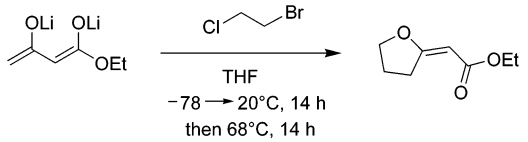
A B

to the high regioselectivity often observed in their reaction with electrophiles.

Three general mechanistic pathways are possible for cyclization reactions of dianions.

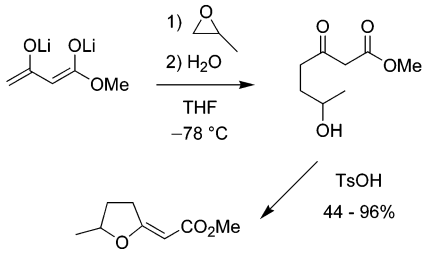
(1) Mechanism A: two nucleophilic centers of the dianion react with two electrophilic centers of a bis-electrophile. For example, the cyclization of the 1,3-dianion of ethyl acetoacetate with 1-bromo-2-chloroethane results in the formation of a 2-alkylidenetetrahydrofuran (Scheme 1).

Scheme 1. Cyclization Reaction of a 1,3-Dicarbonyl Dianion Following Mechanism A



(2) Mechanism B: the dianion reacts as a mononucleophile with a monofunctional electrophile. One negative charge is transferred from the dianion to the electrophile. A functional group of the former dianion moiety is subsequently attacked by the monoanion thus formed. For example, the cyclization of the dianion of methyl acetoacetate with propenoxide afforded an open-chained product, which was subsequently transformed into a 2-alkylidenetetrahydrofuran by treatment with acid (Scheme 2). The

Scheme 2. Cyclization Reaction of a 1,3-Dicarbonyl Dianion Following Mechanism B

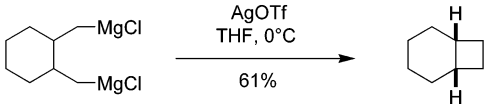


cyclization proceeds by attack of the epoxide derived hydroxy group onto the ketone and subsequent elimination of a water molecule.

The overall cyclization of dianions with electrophiles can be carried out in either one or two steps. In the first case, the cyclic product is directly formed in one step without the need of the isolation of an intermediate (Scheme 1). In the second case, an open-chained intermediate has to be isolated, and the cyclization is carried out in a separate synthetic operation (Scheme 2).

(3) Mechanism C: Two centers of the dianion are coupled by an oxidative cyclization. In these reactions, no electrophile is required. For example, bicyclo[4.2.0]octane was prepared by a silver(I) triflate-mediated oxidative cyclization (Scheme 3).

Scheme 3. Oxidative Cyclization of a 1,4-Dianion (Mechanism C)



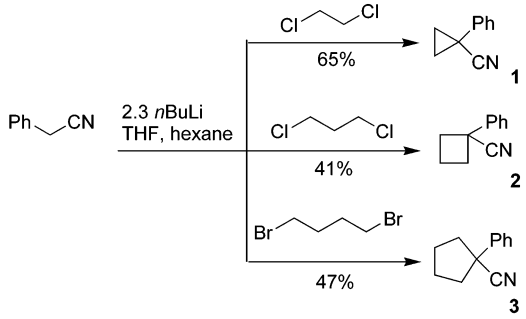
2. Cyclizations of 1,1-Dianions

2.1. Nitrile Dianions

Treatment of arylacetonitriles with 2 equiv of strong base, such as LDA or *n*BuLi, has been reported to give formal dianions.[5] It has been shown by crystal structure analyses that, in many cases, a true dianion is not generated in these reactions.[6,7] In contrast, a monoanion is formed that resides in the form of a lithiated ketenimine associated to a molecule of the base. Specific dilithiated nitriles have been reported to exist as true α,α-dianions.[8]

The reaction of dilithiated phenylacetonitrile with 1,2-dichloroethane, 1,3-dichloropropane, and 1,4-dibromobutane afforded the 3−5-membered rings **1**, **2**, and **3**, respectively (Scheme 4).[9] The best yields were

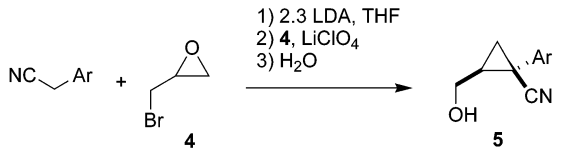
Scheme 4. Cyclization of Dilithiated Phenylacetonitrile with Dihalides (Mechanism A)



obtained for the formation of cyclopropane derivative **1**, presumably due to stereoelectronic reasons. The cyclizations proceeded by mechanism A.

The cyclization of arylacetonitriles with epibromohydrin (**4**) afforded the functionalized cyclopropanes **5** in good yields (Scheme 5).[10] The formation of **5** can

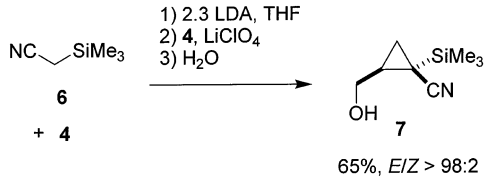
Scheme 5. Cyclization of Dilithiated Arylacetonitriles with Epibromohydrin (Mechanism A)[a]



[a] Ar = C_6H_5, 2-MeC_6H_4, 3-MeC_6H_4, 3-(MeO)C_6H_4, 4-MeC_6H_4, 4-(MeO)C_6H_4, 1-naphthyl, 2-thienyl, 2-(*N*-methyl)pyrrolyl, 34−83%.

be explained by chemoselective attack of the dianion onto the carbon attached to the bromine atom and subsequent cyclization via the central carbon atom of the epoxide (mechanism A). Alternatively, an attack of the dianion onto the epoxide and a subsequent Payne rearrangement is possible. The products are formed with good diastereoselectivity, which can be explained by steric reasons.

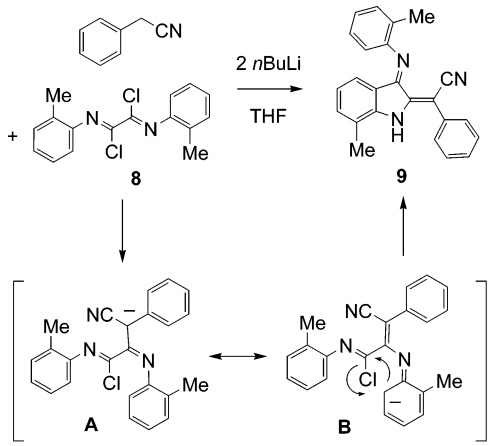
Scheme 6. Cyclization of Dilithiated Trimethylsilyl-Acetonitrile with Epibromohydrin



The cyclization of dilithiated trimethylsilyl-acetonitrile **6** with epibromohydrin afforded the TMS-substituted cyclopropane **7** with excellent diastereoselectivity (Scheme 6).[11,12] Treatment of **7** with NaH (2 equiv) and benzylic bromide resulted in benzylation and desilylation.

The reaction of dilithiated phenylacetonitrile with oxaldiimidoyl dichloride **8** afforded the 2-alkylidene-3-iminoindole **9** in good yield and with very good regio- and *E*-diastereoselectivity (Scheme 7).[13,14] The

Scheme 7. Cyclization of Dilithiated Phenylacetonitrile with Oxalic Acid-Bis(imidoyl) dichlorides (Mechanism A)

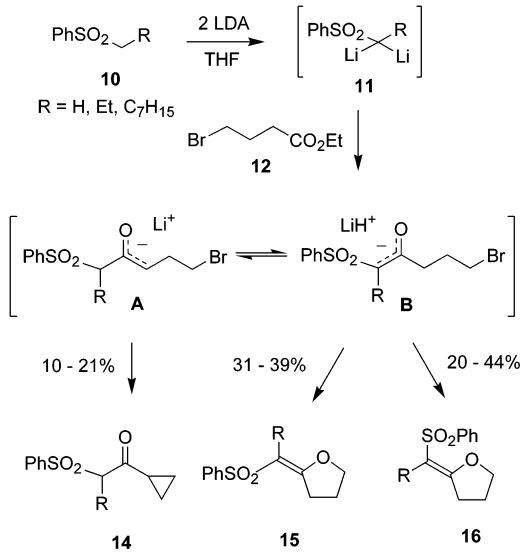


product, which can be regarded as a protected 2-alkylidene-3-oxindole, was formed by attack of the dianion onto the first imidoyl chloride group to give the anionic intermediate **A**. The second imidoyl chloride moiety was subsequently attacked by the *ortho* carbon of the arylimino group and a 1,3-proton shift finally afforded **9**. The high *E*-diastereoselectivity is a result of the steric interaction between the bulky arylimino and the phenyl group. The preparative scope of the cyclization reaction was extended to the synthesis of a great variety of 2-alkylidene-3-iminoindoles.[15−17] A number of substituents could be introduced both at the exocyclic double bond and at the indole moiety by variation of the substituents of the nitrile and of **8**, respectively.

2.2. Sulfone Dianions

Structure. Phenyl sulfones are known to form true dianions: the lithiation occurs at the CH_2 group and at the *ortho* position of the phenyl group. At elevated temperature the α,*o*-dianion undergoes a rearrangement to an α,α-dianion. At low temperature, the first attack of the α,*o*-dianion onto the electrophile occurs at the α-carbon atom and subsequent rearrangement affords an α-monoanion, which subsequently reacts

Scheme 8. Cyclization Reactions of Sulfone Dianions with Ethyl 4-Bromobutanoate



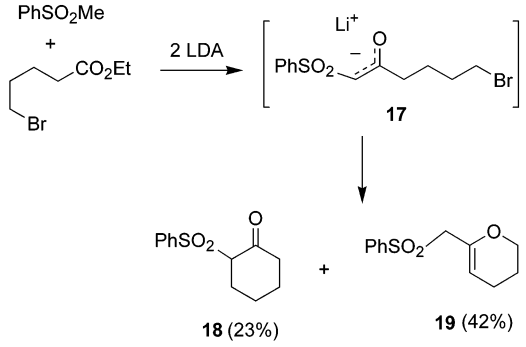
with the second equivalent of the electrophile to give an α,α-difunctionalized sulfone.[18−20]

Craig and co-workers have reported the stereoselective synthesis of functionalized tetrahydrofurans, pyrrolidines, and piperidines by cyclizations of sulfone monoanions and dianions with aziridines and other electrophiles.[21]

The sulfone dianion **11** was generated from **10** by means of LDA (2 equiv). Treatment of **11** with ethyl 4-bromobutanoate (**12**) resulted in formation of separable mixtures of cyclopropane derivatives **14** and of the 2-alkylidenetetrahydrofurans **15** and **16** (mechanism A, Scheme 8).[22] The product distribution was dependent on the substituents and on the reaction conditions. The first attack of the dianion onto **12** occurred regioselectively at the ester group to give the enolate **A**, which subsequently rearranged into the enolate **B**. The tetrahydrofurans **14** and **15** were formed from enolate **B** by attack of the oxygen atom onto the bromide (5-*exo*-*tet* cyclization). The cyclopropanes were formed by 3-*exo*-*tet* cyclization of **A**. The regioselectivity of cyclization can be explained by stereoelectronic considerations (Baldwin irules).

The reaction of dilithiated phenylmethyl sulfone with ethyl 5-bromopentanoate resulted in formation of cyclohexanone **18** and 2,3-dihydropyran **19** in 23 and 42% yields, respectively (Scheme 9).[22] The first

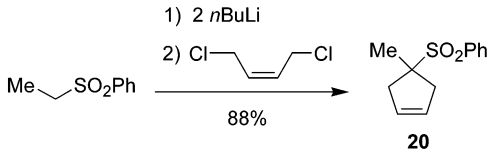
Scheme 9. Cyclization of the Dianion of Methylphenyl Sulfone with Ethyl 5-Bromopentanoate



attack of the dianion onto the dielectrophile again occurred regioselectively at the ester group to give intermediate **17**. The regioselectivity of cyclization (*O*- versus *C*-attack) was lower compared to the formation of the corresponding five-membered ring, due to stereoelectronic reasons.

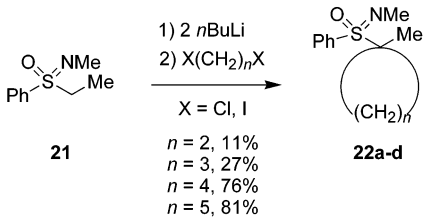
The cyclization of *cis*-1,4-dichloro-2-butene with the dianion of ethylphenyl sulfone, generated by *n*BuLi, afforded the cyclopentene **20** in 88% yield (Scheme 10, mechanism A).[23]

Scheme 10. Cyclization of the Dianion of Ethylphenyl Sulfone with 1,4-Dichloro-2-butene



The reaction of the dianion of iminosulfoxide **21** with 1,*n*-dihaloalkanes ($n = 2-5$) afforded the corresponding cyclization products **22a**−**d** (Scheme 11, mechanism A). The best yields were obtained for the synthesis of five- and six-membered rings.[24]

Scheme 11. Cyclization Reactions of the Dianion of an Iminosulfoxide



The cyclization of the dianion of methylphenyl sulfone with 1,2-dichloroethane, 1,4-diiodobutane, 3-chloro-1,2-epoxypropane, 4-bromo-1,2-epoxybutane, 5-bromo-1,2-epoxypentane, 4-bromobutanenitrile has been reported to give the corresponding cyclization products in good yields (mechanism A).[25] The reactions of the dianion with the haloepoxides afforded the cycloalkanols of maximum ring size. These results indicate that the first attack occurred onto the expoxide rather than onto the carbon-halide group, due to stereoelectronic reasons.

2.3. Other 1,1-Dianions

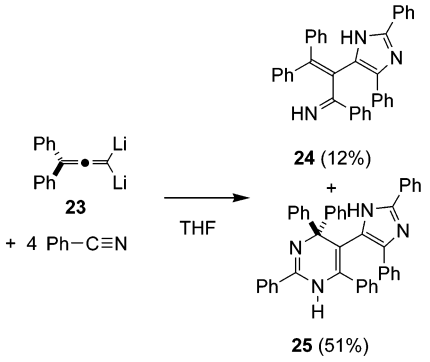
The cyclization of the dianion **23** of 1,1-diphenylallene with nitriles has been reported to result in the addition of up to four nitrile molecules onto the allene and formation of substituted imidazoles.[26a,b] For example, the reaction of **23** with benzonitrile afforded a separable mixture of the imidazoles **24** and **25** (Scheme 12).

3. Cyclizations of 1,2-Dianions

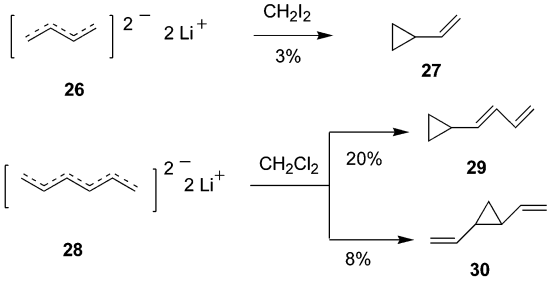
3.1. Dianions of Hydrocarbons

The reaction of diiodomethane with dilithiated 2-butene (**26**), generated by metal−halide exchange, afforded vinylcyclopropane (**27**), albeit in only 3%

Scheme 12. Cyclization Reaction of the Dianion of 1,1-Diphenylallene with Benzonitrile



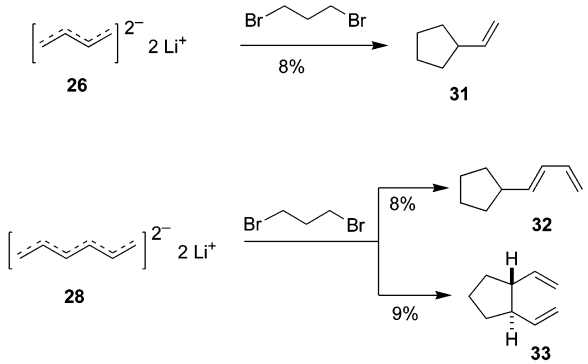
Scheme 13. Cyclization of 1,2-*C*,*C*-Dianions with 1,1-Dihalomethanes (Mechanism A)



yield (Scheme 13). The cyclization of dichloromethane with ambident dianion **28** gave a separable mixture of cyclopropanes **29** and **30** in low yield (mechanism A).[27] The main isomer was formed by attack of the terminal carbon of the dianion onto the dielectrophile.

The cyclization of dianions **26** and **28** with 1,3-dibromopropane gave low yields of vinylcyclopentane (**31**) and of a mixture of the cyclopentane derivatives **32** and **33**, respectively (Scheme 14, mechanism A).

Scheme 14. Cyclization of 1,2-*C*,*C*-Dianions with 1,3-Dibromopropane (Mechanism A)

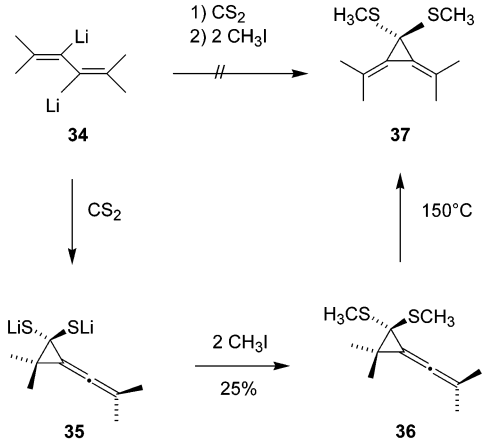


The reaction of dilithiated butadiene **34** with carbon disulfide and subsequent addition of methyl iodide afforded the allenylidene-cyclopropane **36** via intermediate **35** (Scheme 15, mechanism A). The thermolysis of **36** afforded the cyclopropane **37**.[28]

3.2. Dianions of 1,4-Diesters

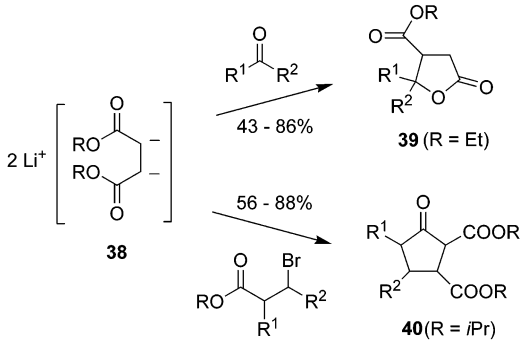
A number of cyclization reactions of dianions of succinic diesters have been reported. The reaction of

Scheme 15. Cyclization of 1,2-*C*,*C*-Dianions with Carbon Disulfide (Mechanism A)



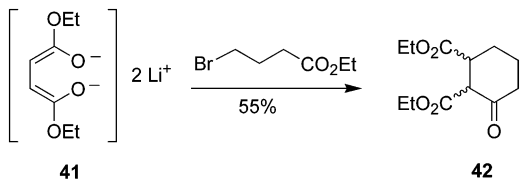
ketones with dianion **38**, generated by deprotonation of the diester, afforded the lactones **39** by attack of the dianion onto the ketone to give an alkoxide and subsequent attack of the latter onto the ester group (mechanism B). The cyclization of **38** with *β*-bromocarboxylic esters proceeded by mechanism A and afforded the cyclopentanones **40** (Scheme 16).[29,30]

Scheme 16. Cyclization of 1,4-Diester Dianions with Ketones and *β*-Bromocarboxylic Esters



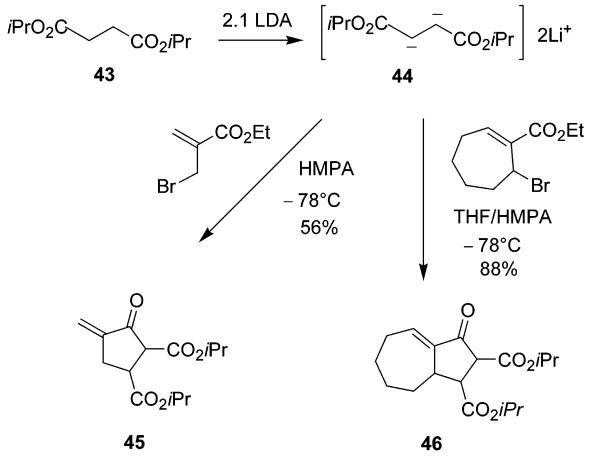
The cyclization of the dianion **41** with ethyl 4-bromobutanoate was equally successful and gave the cyclopentanone **42** as a mixture of diastereomers (Scheme 17, mechanism A).[31]

Scheme 17. Cyclization of 1,4-Diester Dianions with Ethyl 4-Bromobutanoate (Mechanism A)

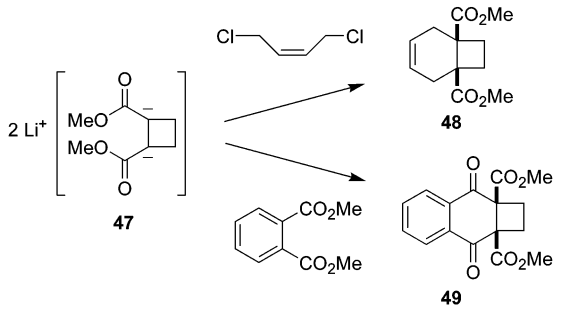


In many cases, the use of the more stable di*iso*propyl succinate **43** proved advantageous in terms of yield. For example, the reaction of the dianion **44** with open-chained and cyclic *β*-bromo-α-alkylidenecarboxylic esters afforded the cyclic and bicyclic products **45** and **46**, respectively (Scheme 18).[30]

Scheme 18. Cyclization of 1,4-Diester Dianions with β-Bromo-α-alkylidenecarboxylic Esters (Mechanism A)



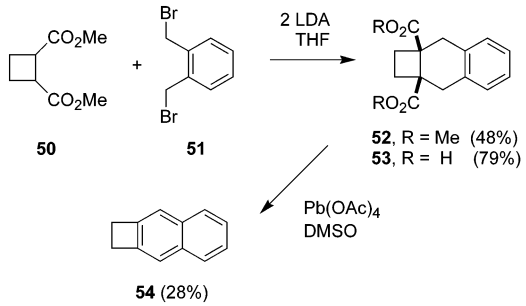
Scheme 19. Cyclization of the Dianion of Dimethyl Cyclobutane-1,2-dicarboxylate with 1,4-Dichloro-2-butene and Diethyl Phthalate (Mechanism A)



Cyclization reactions of dianions of cyclic 1,4-diesters have also been reported (Scheme 19). The reaction of the dianion of dimethyl cyclobutane-1,2-dicarboxylate (**47**), generated by means of 2 equiv of LDA, with *cis*-1,4-dichlorobut-2-ene afforded the bicyclo[4.2.0]octene **48**. The cyclization of **47** with dimethyl phthalate afforded the 1,3-ketoester **49** (mechanism A).[32,33]

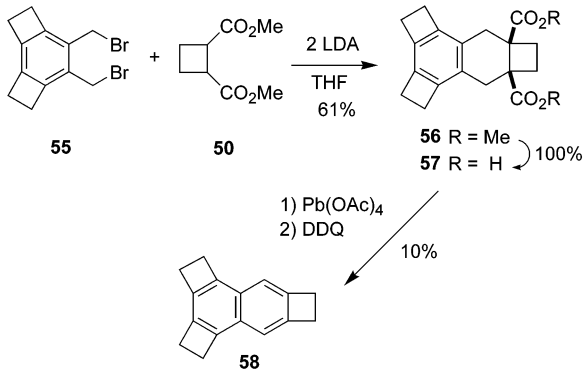
The cyclization of the dianion **47** with 1,2-bis-(bromomethyl)benzene (**51**) gave the diester **52**, which was transformed into the dicarboxylic acid **53** (Scheme 20, mechanism A). Treatment of the latter

Scheme 20. Cyclization of the Dianion of Dimethyl Cyclobutane-1,2-dicarboxylate with 1,2-Bis(bromomethyl)benzene (Mechanism A)



with $Pb(OAc)_4$/DMSO resulted in oxidation and decarboxylation to give the interesting naphthalene

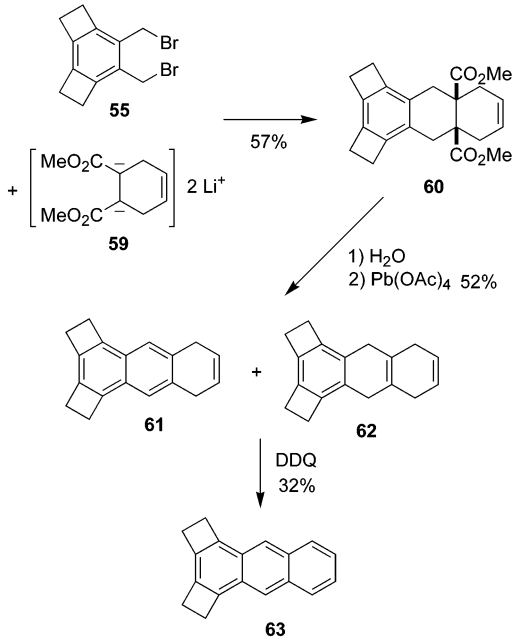
Scheme 21. Synthesis of Naphthalene 58 (Mechanism A)



derivative **54**. Likewise, naphthalene **58** was prepared by cyclization of the dianion of **50** with dibromide **55** and subsequent oxidation (Scheme 21).

The reaction of the dianion of dimethyl 1,2-cyclohexene dicarboxylate (**59**) with dibromide **55** gave the diester **60**, which was transformed into the anthracene derivative **63** by decarboxylation and subsequent oxidation (Scheme 22).[34]

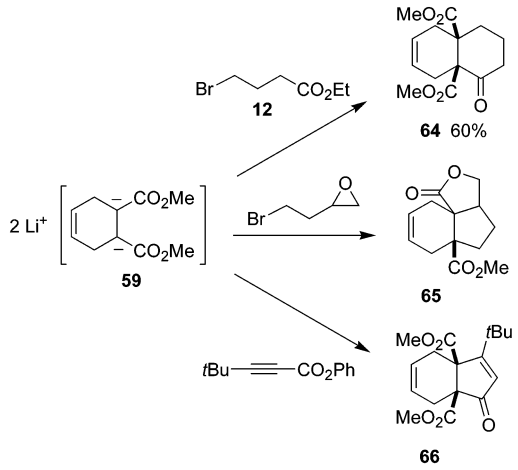
Scheme 22. Cyclization of the Dianion of Dimethyl 1,2-Cyclohexene Dicarboxylate with 1,2-Bis(bromomethyl)benzene (Mechanism A)



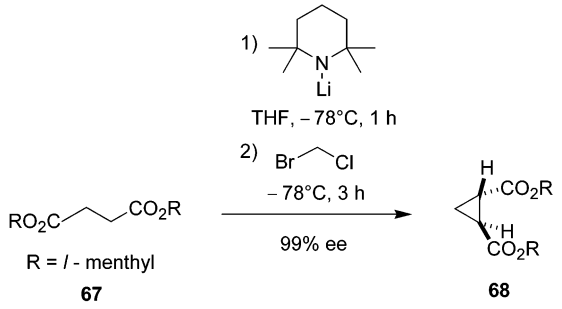
The cyclization of dianion **59** with ethyl 4-bromobutanoate (**12**) resulted in formation of the decalin-1-one **64** (Scheme 23, mechanism A). The reaction of **59** with 1-bromo-3-butenoxide afforded the lactone **65** by cyclization (mechanism A) and subsequent lactonization of the epoxide-derived alkoxide with the ester group. Employment of phenyl alkynoate afforded the cyclopentenone **66** by conjugate addition and nucleophilic attack of the dianion onto the ester group (mechanism A).[35−37]

The reaction of bromochloromethane with the dianion of the bis(*l*-menthyl) succinate **67**, generated

Scheme 23. Cyclization Reactions of Dianion 59 (Mechanism A)



Scheme 24. Cyclization of Dilithiated Bis(*l*-menthyl) Succinate with 1-Bromo-1-chloromethane (Mechanism A)



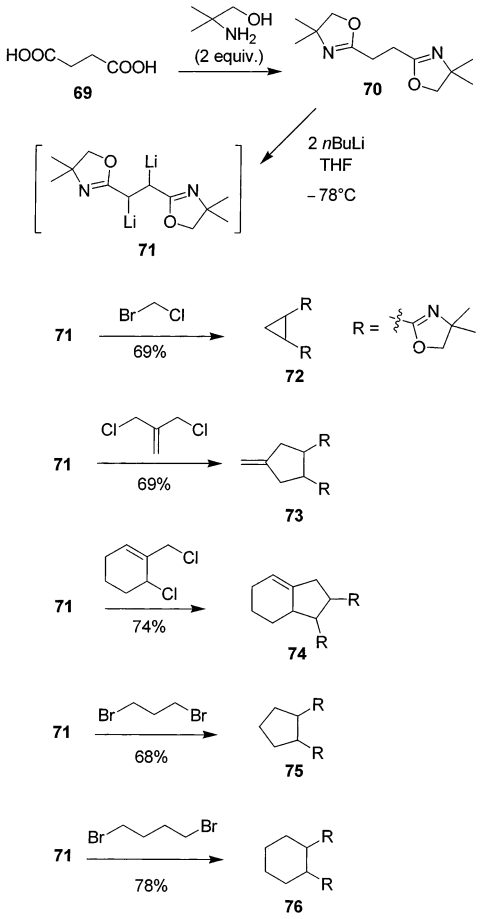
by deprotonation (LiTMP), afforded the cyclopropane derivative **68** with very good *E*-diastereoselectivity and enantioselectivity (99% *ee*). Excellent selectivities were obtained also for other cyclization reactions.[38] Succinic acid was transformed into the bis-oxazolidine **70**, a protected diacid, which could be transformed into the dianion **71** by deprotonation (*n*BuLi). The reaction of **71** with a number of dihalides afforded the corresponding cyclization products **72**−**76** in good yields (Scheme 25, mechanism A). The oxazolidine protective group could be removed by treatment with sulfuric acid.[39]

The cyclization of dianion **71** with ethyl 3-bromopropanoate afforded the five-membered ring **77**, which resides in the enamine tautomeric form. Likewise, the reaction of **71** with bromoester **78** afforded the product **79** (Scheme 26, mechanism A).

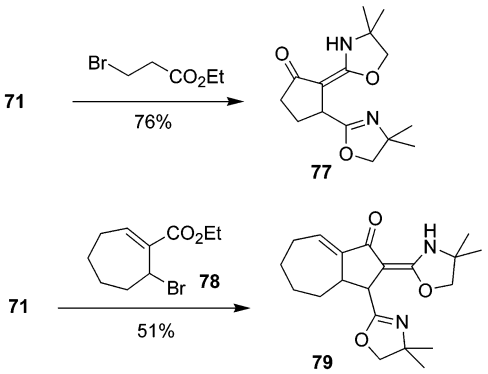
3.3. Other 1,2-Dianions

The dianion of 3-*iso*butoxycyclopent-2-en-1-one **80** was generated by deprotonation (LDA). The reaction of **80** with 3-iodo-2,2-dimethylpropanal (**81**) and subsequent addition of methoxymethyl chloride (MOMCl) resulted in formation of the bicyclo[3.3.0]-oct-2-en-1-one **82** by cyclization (mechanism A) and subsequent protection of the aldehyde derived alkoxide (Scheme 27).[40] Product **82** was transformed into the natural product coriolin.

Scheme 25. Cyclization of Dianion 71 with Dielectrophiles



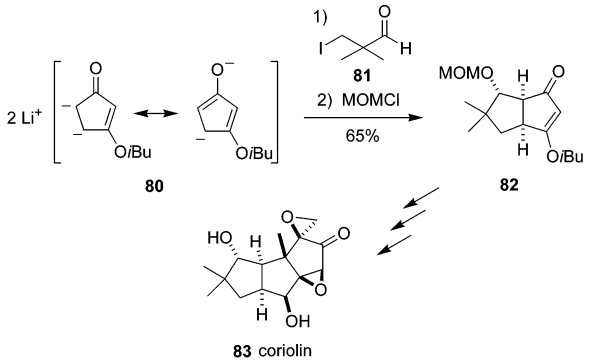
Scheme 26. Cyclization of Dianion 71 with *β*-Bromoesters



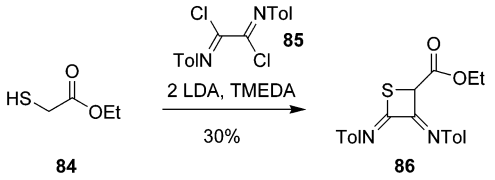
The reaction of the dianion of ethyl thioglycolate (**84**)[41] with oxalic acid-bis(imidoyl)dichloride **85** afforded the 2,3-diiminothietane **86**, which underwent a ring expansion reaction upon treatment with dimethyl acetylenedicarboxylate (Scheme 28).[42]

The influence of the heteroatoms of the 1,2-dianion on the regioselectivity was studied. The reaction of **85** with the dianion of ethyl hippurate (**87**)[43] afforded the 6-imino-6*H*-[1,3]oxazine **88** by cyclization via the carbon and the oxygen atom of the dianion (Scheme 29). The regioselectivity of this reaction can be explained by the higher electron density at the oxygen rather than at the nitrogen atom of the dianion or, alternatively, by initial

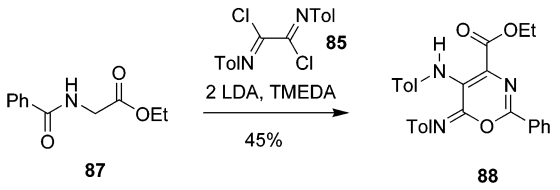
Scheme 27. Cyclization of Dianion 80 with 3-Iodo-2,2-dimethylpropanal (Mechanism A)



Scheme 28. Cyclization of the Dianion of Ethyl Thioglycolate with 85 (Mechanism A)



Scheme 29. Cyclization of the Dianion of Ethyl Hippurate with 85 (Mechanism A)



formation of a four-membered ring and subsequent ring-expansion.

4. Cyclizations of 1,3-Dianions

4.1. 1,3-*C*,*C*-Dianions

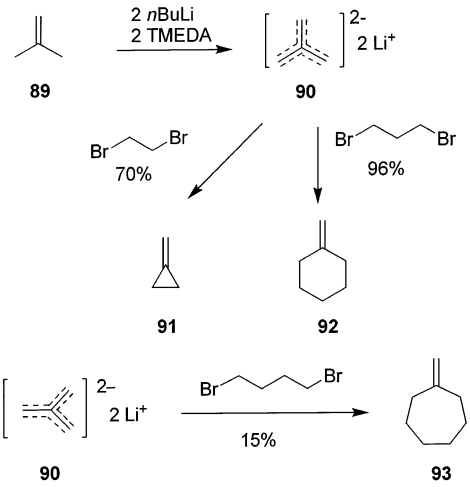
4.1.1. Allylic Dianions

Trimethylene Methane Dianion. A variety of reactions of the Y-shaped trimethylene methane dianion **90**, generated from **89** by deprotonation with *n*BuLi, were studied by Bates et al. The reaction of **90**, which was isolated in crystalline form, with 1,2-dibromoethane afforded methylidenecyclopropane (**91**) by oxidative cyclization of the dianion and reduction of the dielectrophile (mechanism C).[44a] Treatment of **90** with 1,3-dibromopropane resulted in a cyclization to give methylidenecyclohexane (**92**) in high yield (mechanism A). The cyclization of **90** with 1,4-dibromobutane afforded methylidenecycloheptane (**93**), however, in only 15% yield. The reaction of dianion **90** with phthalic dialdehyde resulted in formation of a separable 1:1 mixture of the open-chained condensation product **95** and of the desired cyclization product **96** in low yield (Scheme 31).[44b]

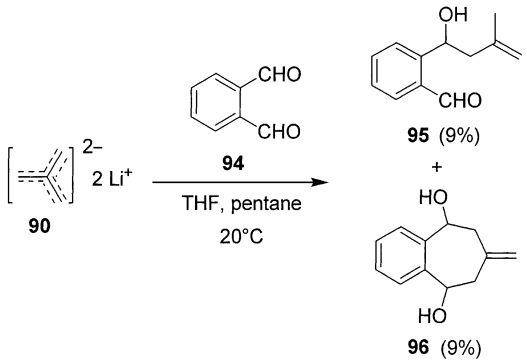
The reaction of **90** with benzonitrile (2 equiv) afforded the pyridine derivative **99** by addition of two nitrile molecules, subsequent cyclization and extrusion of NH_3 (Scheme 32).[44c]

The dianion **101** of triphenyl-trimethylenemethane was generated by deprotonation of **100**. Similar to

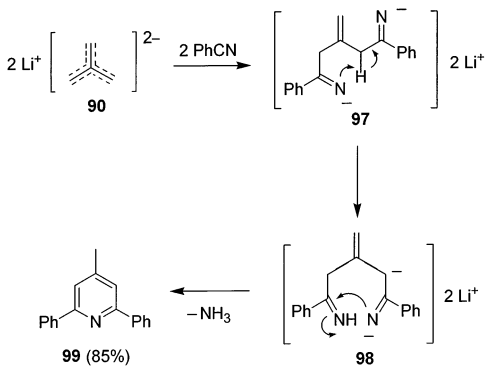
Scheme 30. Reaction of the Trimethylene Methane Dianion with Dibromides



Scheme 31. Reaction of the Trimethylene Methane Dianion with Phthalic Dialdehyde (Mechanism A)



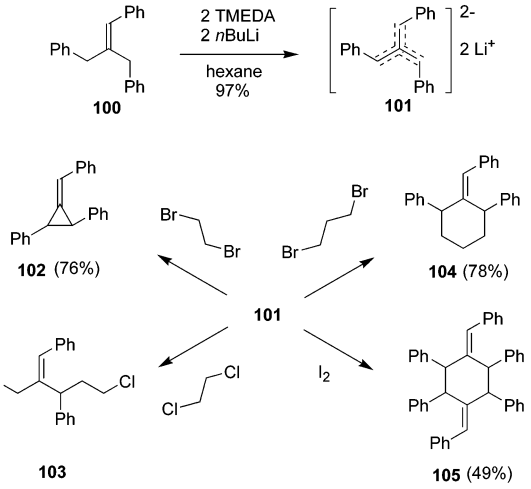
Scheme 32. Reaction of the Trimethylene Methane Dianion with Benzonitrile



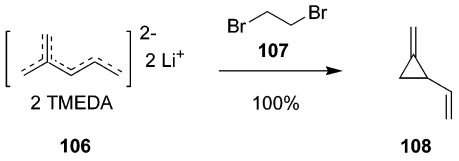
the reaction of the parent dianion **90**, the addition of 1,2-dibromoethane to **101** resulted in oxidation of the dianion (Scheme 33, mechanism C).[90a] The cyclopropane derivative **102** was formed in good yield. In contrast, the use of 1,2-dichloroethane afforded the open-chained condensation product **103**. The reaction of **101** with 1,3-dibromopropane gave the six-membered ring **104** (mechanism A). The addition of iodine afforded **105** by oxidative dimerization.[90a]

Vinyltrimethylenemethane Dianion. The dianion **107**, generated by deprotonation with *n*BuLi, can be regarded as a vinyl-substituted trimethylenemethane dianion (Scheme 34). Treatment of **106** (isolated in crystalline state) with 1,2-dibromoethane

Scheme 33. Reactions of the Triphenyl-trimethylenemethane Dianion



Scheme 34. Oxidative Cyclization of the Vinyl-trimethylenemethane Dianion (Mechanism C)

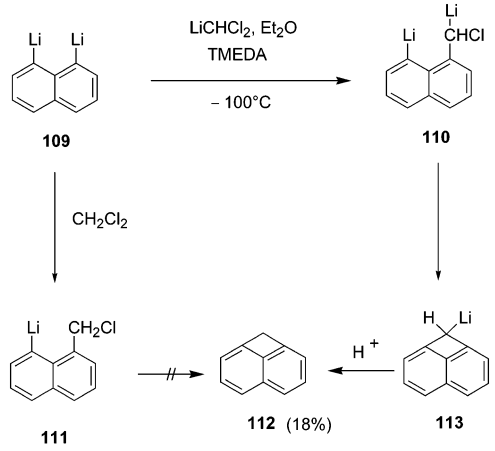


resulted in oxidative cyclization and formation of the cyclopropane **108** in quantitative yield (mechanism C).[44a]

4.1.2. Arene-Dianions

Dilithiated naphthalene **109** was generated by metal−halide exchange. The reaction of **109** with dichloromethane gave the open-chained product **111** rather than the desired strained cyclobutene derivative **112** (Scheme 35). However, the latter could be

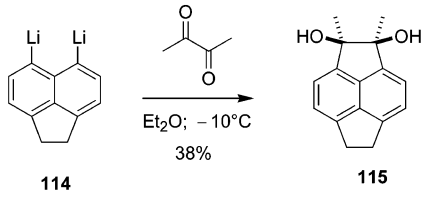
Scheme 35. Cyclization Reactions of Dilithiated Naphthalene (Mechanism A)



prepared by TMEDA-mediated reaction of **109** with lithiated dichloromethane and subsequent protonation of the lithiated intermediate **113**.[45]

The reaction of dilithiated naphthaline derivative **114** with 2,3-butanedione afforded the desired five-membered ring **115** in 38% yield (Scheme 36). The

Scheme 36. Cyclization of 1,3-Dianion 114 with 2,3-Butanedione (Mechanism A)

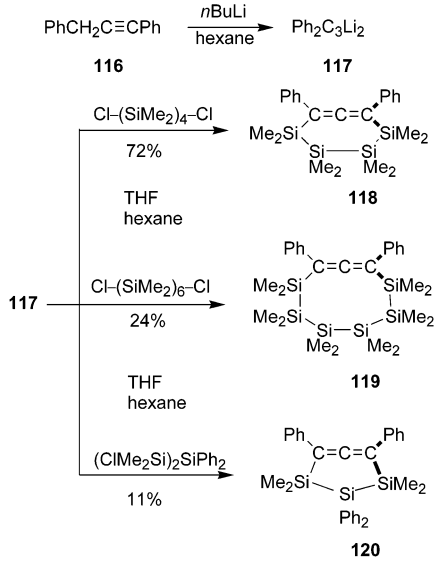


1,2-diol was formed with very good *cis*-diastereoselectivity (mechanism A).[46]

4.1.3. Allene Dianions

It was demonstrated by West and others that polylithio compounds can be readily generated by deprotonation of alkynes.[47a] For example, 1,3-dilithio-1,3-diphenylallene (**117**) could be generated by deprotonation of the alkyne **116** (Scheme 37). The cycliza-

Scheme 37. Cyclization of Dilithiated Allene 117 with 1,*n*-Dichlorosilanes (Mechanism A)



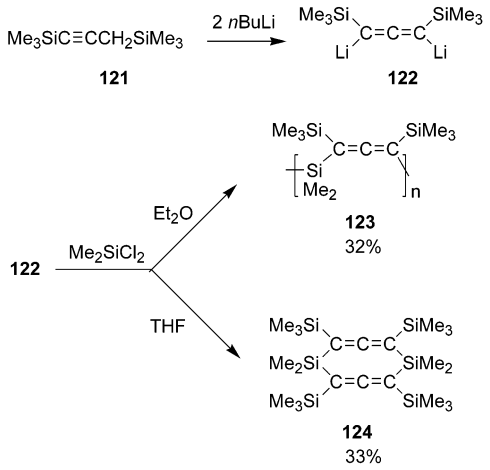
tion of **117** with dichlorosilanes afforded the cyclic allenes **118**−**120** (mechanism A). These cyclizations are included in this review, although no carbon−carbon bonds were formed. The best yield (72%) was obtained for the seven-membered ring **118**. The yield of the nine-membered ring **119** was significantly lower. Due to the greater size of the silicon relative to the carbon atom, the strained six-membered ring **120** was successfully obtained, albeit in only 11% yield.[47b]

The reaction of 1,3-dilithio-1,3-bis(trimethylsilyl)-allene (**122**), generated by deprotonation of **121**, with dimethyldichlorosilane resulted in the formation of open-chained oligomers **123** when the reaction was carried out in ether. In contrast, the eight-membered cyclic bis-allene **124** was formed by a 2:2 cyclization when THF was used.[48]

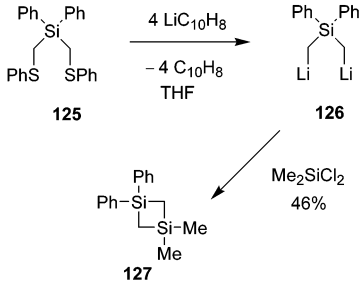
4.1.4. (2-Silapropane) Dianions

Strohmann and co-workers reported the generation of a variety of silicon containing 1,3-dianions which represent useful building blocks in the synthesis of

Scheme 38. Cyclization of Dilithiated Allene 122 with Dimethyldichlorosilane (Mechanism A)



Scheme 39. Formation and Cyclization of 1,3-Dianion 126 (Mechanism A)



silacycles. The dianion **126** was generated by reduction of the bis-thioether **125** with lithium naphthalide (Scheme 39). The cyclization of **126** with dimethyldichlorosilane gave the disilacyclobutane **127** (mechanism A).[49]

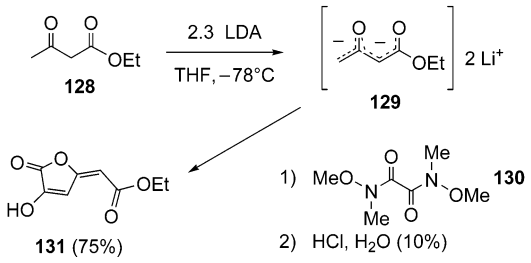
4.2. 1,3-Dicarbonyl Dianions

Oxygen-containing ambident 1,3-dianions are frequently used in organic chemistry. Among these, 1,3-dicarbonyl dianions are probably most common. 1,3-Dicarbonyl compounds can be metalated twice by the action of 2 equiv of LDA or by the use of NaH/*n*-BuLi.[50] The terminal carbon atom of the dianion can be regioselectively reacted with 1 equiv of an electrophile to give a monoanion, which is subsequently trapped by addition of a second electrophile. Monoanions may be alkylated twice by a double deprotonation-alkylation sequence. However, the regioselectivities of reactions of monoanions and dianions generally differ greatly. For example, 1,3-dicarbonyl monoanions are generally alkylated at the central carbon or at the oxygen atom, whereas the formation of dianions allows the functionalization of the terminal carbon atom. An exception are reactions of highly stabilized 1,3,5-tricarbonyl compounds that contain two (rather than only one) highly C−H acidic groups. The product obtained by sequential alkylation of a stabilized carbanion can be identical to that prepared from the respective dianion.

4.2.1. Reactions with Oxalic Acid Dielectrophiles

***N,N′*-Dimethoxy-*N,N′*-dimethylethanediamide.** The reaction of dilithiated ethyl acetoacetate **129** with simple oxalic acid dielectrophiles, such as oxalyl chloride and oxalic diethylester, resulted in the formation of complex mixtures.[51] The problem was recently solved by the use of *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide **130**,[52] a bis-Weinreb amide, which is available from oxalyl chloride in one step. The cyclization of the dianion with **130** afforded the γ-alkylidenebutenolide **131** in 75% yield (Scheme 40).[53] The success of this transformation relied on the

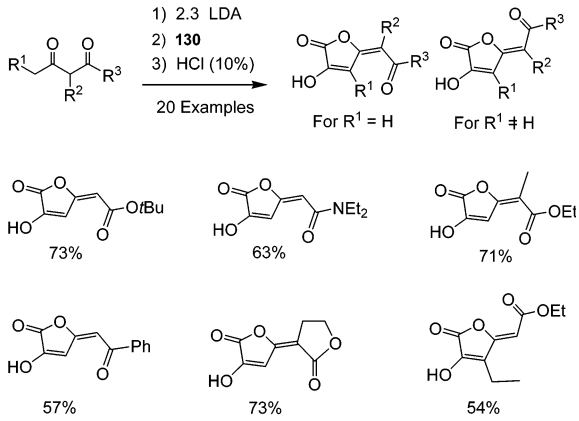
Scheme 40. Cyclization of 1,3-Dicarbonyl Dianions with *N,N′*-Dimethoxy-*N,N′*-dimethylethanediamide (Mechanism A)



proper reactivity tuning of the dielectrophile and the formation of a chelate complex, which is cleaved upon addition of hydrochloric acid (10%). The reaction proceeds by regioselective attack of the terminal carbon of the dianion onto **130** and subsequent regioselective cyclization *via* the oxygen atom of the dianion (mechanism A). The regioselectivity can be explained by stereoelectronic considerations.[54] The *E*-configured exocyclic double bond was formed with very good selectivity, which can be explained by the dipole−dipole repulsion of the oxygen atoms of a nonchelated enolate intermediate[55] and by the higher thermodynamic stability of the *E*-configured γ-alkylidenebutenolide.[56]

Variation of the substituents allowed the preparation of a variety of γ-alkylidenebutenolides (Scheme 41).[57] All reactions proceeded with very good *E*-

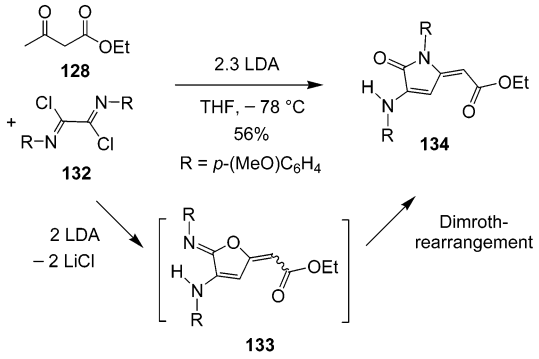
Scheme 41. Synthesis of Butenolides: Preparative Scope



diastereoselectivity for substrates containing a hydrogen atom at the terminal carbon of the 1,3-dicarbonyl compound ($R^1 = H$). Due to steric reasons, the selectivity changed from *E*- to *Z*-configuration for substrates containing a terminal substituent ($R^1 \neq H$).

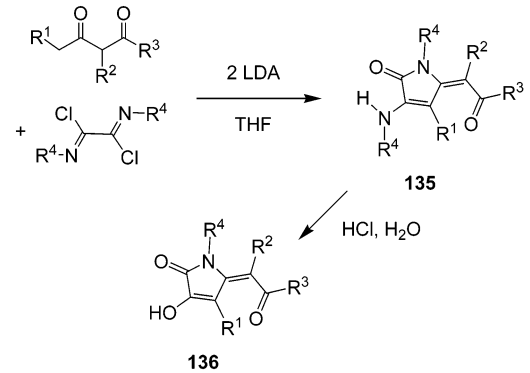
Oxalic Acid-bis(imidoyl)dichlorides. The reaction of dilithiated ethyl acetoacetate with oxalic acid-bis(imidoyl)chlorides **132**, which can be regarded as azanalogues of oxalyl chloride, resulted in regioselective formation of 5-alkylidene-5*H*-pyrrol-2-one **134** (Scheme 42).[58] The cyclization proceeds by regioselective attack of the terminal carbon atom of the dianion onto **132**, regioselective cyclization (mechanism A) to give intermediate **133** and subsequent Dimroth rearrangement of the latter. Due to the stereodirecting effect of the aryl group, the exocyclic double bond was formed with excellent *E*-selectivity. The 5-alkylidene-5*H*-pyrrol-2-one system is of biological relevance and occurs in a number of natural products.

Scheme 42. Cyclization of 1,3-Dicarbonyl Dianions with Oxalic Acid-Bis(imidoyl)dichlorides (Mechanism A)



The preparative scope of this reaction was studied. A variety of 5-alkylidene-5*H*-pyrrol-2-ones were prepared from the corresponding 1,3-dicarbonyl compounds. The exocyclic double bond was influenced by the substituent R^1 (*E*-configuration for $R^1 = H$) and *Z*-configuration for $R^1 \neq H$). The enamine moiety could be hydrolyzed in very good yield to give the 5-alkylidene-3-hydroxy-5*H*-pyrrol-2-ones **136**.

Scheme 43. Synthesis of 5-Alkylidene-5*H*-pyrrol-2-ones 135 and 136[a]

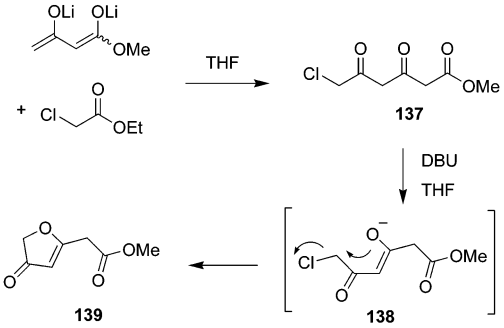


[a] R^1, R^2 = alkyl, R^3 = Me, Ph, OMe, OEt, NHTol, R^4 = aryl.

4.2.2. Reactions with Carboxylic Acid Derivatives

α-Chloroacetic Esters. The reaction of the dianion of methyl acetoacetate with ethyl α-chloroacetate afforded the triketide **137**. Treatment of **137** with DBU resulted in regioselective cyclization and formation of the functionalized 3(2*H*)furanone **138** (Scheme 44). Two other derivatives were prepared by this approach.[59]

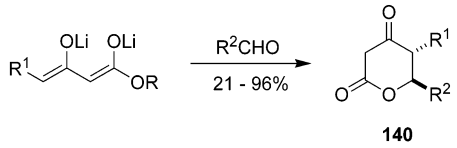
Scheme 44. Cyclization of 1,3-Dicarbonyl Dianions with Ethyl α-Chloroacetate (Mechanism A)



4.2.3. Reactions with Aldehydes and Ketones

Aldehydes. The reaction of 1,3-dicarbonyl dianions with aldehydes afforded the δ-lactones **140** by attack of the terminal carbon atom of the dianion onto the aldehyde and subsequent cyclization by attack of the aldehyde derived oxygen atom onto the ester group (Scheme 45, mechanism B).[60] A single example of the reaction of a 1,3-dicarbonyl dianion with bromoacetic aldehyde has been reported. However, the open-chained product has not been used for cyclization reactions.[61]

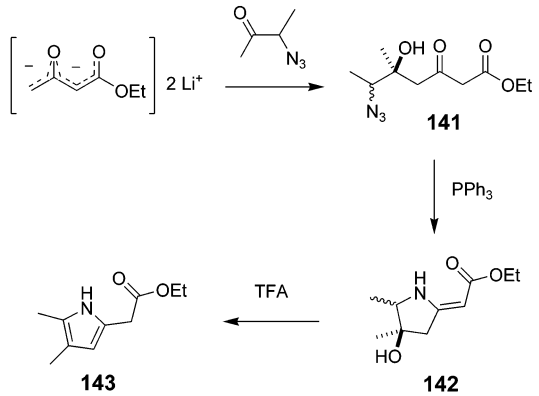
Scheme 45. Cyclization of 1,3-Dicarbonyl Dianions with Aldehydes (Mechanism B)[a]



[a] R^1, R^2 = alkyl.

α-Azidoketones. The cyclocondensation of 1,3-dicarbonyl dianions with α-azidoketones, which can be considered as masked α-aminoketones, provides an efficient and regioselective approach to functionalized 2-alkylidenepyrrolidines and pyrroles (Scheme 46).[62] The condensation of dilithiated ethyl acetoacetate with 2-azidobutan-3-one afforded the alcohol **141** in good yield. Treatment of **141** with PPh_3 afforded the 2-alkylidenepyrrolidine **142** by a domino

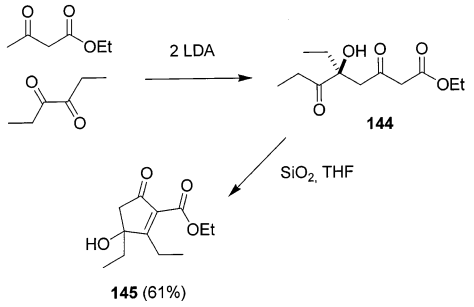
Scheme 46. Reaction of 1,3-Dicarbonyl Dianions with α-Azidoketones



Staudinger-aza-Wittig reaction with subsequent migration of the double bond. Treatment of a CH_2Cl_2 solution of **142** with TFA gave the desired alkyl-substituted pyrrole **143** by elimination of water and migration of the exocyclic double bond. For cyclizations of α-azidoaldehydes, the corresponding acetals were more efficiently reacted with 1,3-bis-silyl enol ethers.

1,2-Dicarbonyl Derivatives. Cyclizations of 1,3-dicarbonyl dianions with 1,2-diketones have been successfully carried out (Scheme 47). For example,

Scheme 47. Cyclization of 1,3-Dicarbonyl Dianions with 1,2-Butanedione (Mechanism A)

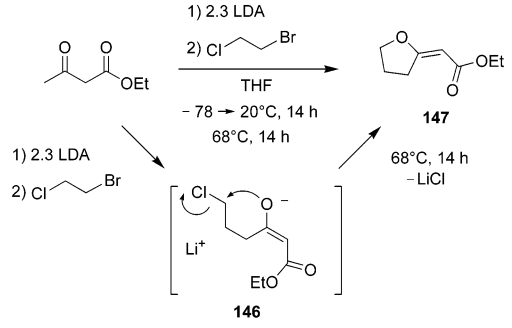


the reaction of the dianion of ethyl acetoacetate with 3,4-hexanedione gave the open-chained product **144**. Subsequent silica gel-mediated cyclization and dehydration afforded the cyclopentenone **145** in 61% overall yield.[63]

4.2.4. Reactions with Functionalized Halides and Cyclic Sulfates

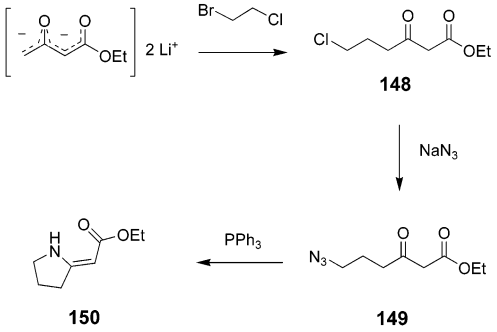
1-Bromo-2-chloroethane. The reaction of 1,3-dicarbonyl dianions with 1,2-dibromo- or 1,2-diiodoethane has been reported to result in oxidation of the dianion and formation of ethylene.[64] Open-chained oxidation products were obtained in the presence of catalytic amounts of CuCl, however, in only 25−33% yield.[65] The elimination became the main reaction pathway when 1,2-dichloroethane was used.[65] The problem was solved by the use of 1-bromo-2-chloroethane (Scheme 48).[66] The cyclization reactions afforded the tetrahydrofurans **147** with very good *C*/*O*-regio- and *E*-diastereoselectivity. The cyclization proceeded by attack of the terminal carbon of the dianion onto the bromide to give intermediate **146** and, upon heating, attack of the enolate oxygen onto the less reactive chloride group (mechanism A).[67]

Scheme 48. Cyclization of 1,3-Dicarbonyl Dianions with 1-Bromo-2-chloroethane (Mechanism A)



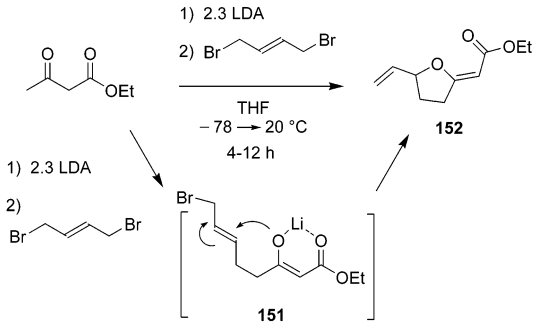
The reaction of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane at low temperature and subsequent treatment of the product with sodium azide afforded azidoesters, such as **149** (Scheme 49). Treatment of the latter with PPh_3 resulted in the formation of 2-alkylidenepyrrolidines **150** by Staudinger-aza-Wittig reactions (mechanism B).[67]

Scheme 49. Synthesis of 2-Alkylidenepyrrolidines



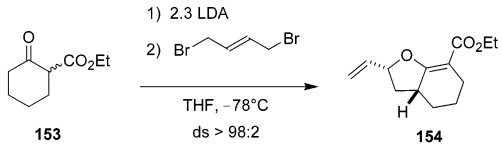
1,4-Dibromo-2-butene. The reaction of 1,3-dicarbonyl dianions with 1,4-di*chloro*-2-butene has been reported to give a mixture of open-chained products in low yield.[68] In contrast, a cyclization could be successfully carried out when 1,4-di*bromo*-2-butene was used (Scheme 50).[69,70] The product, 2-alkylidene-5-vinyltetrahydrofuran **152**, was formed by a S_N/S_N' displacement reaction with very good regio- and *Z*-diastereoselectivity (mechanism A). A rearrangement of **152** into the thermodynamically more stable *E*-configured isomer was observed upon standing.

Scheme 50. Cyclization of Open-Chained 1,3-Dicarbonyl Dianions with 1,4-Dibromo-2-butene (Mechanism A)



The reaction of 1,4-dibromo-2-butene with dianions of cyclic 1,3-dicarbonyl compounds, such as ethyl cyclohexanone-2-carboxylate **153**, resulted in formation of 2-vinyl-2,3,3a,4,5,6-hexahydro-2,3-benzofurans, such as **154**. The products were formed with very good 1,2- and 1,3-diastereoselectivity (Scheme 51)[69b]

Scheme 51. Cyclization of Cyclic 1,3-Dicarbonyl Dianions with 1,4-Dibromo-2-butene (Mechanism A)

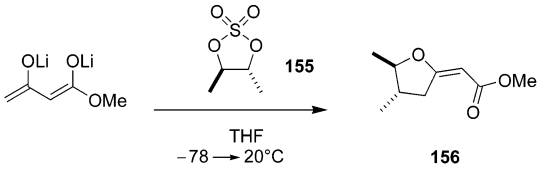


and could be efficiently transformed into the isomeric bicyclo[3.2.1]octan-8-ones by a palladium(0)-catalyzed rearrangement. This reaction proceeds by initial ring-

opening, formation of a π-allyl palladium complex and recyclization by nucleophilic attack of the carbon atom of the enolate onto the π-allyl palladium complex.[71]

Cyclic Sulfates. The reaction of 1,3-dicarbonyl dianions with cyclic sulfates **155** has been reported to give the 2-alkylidenetetrahydrofurans **156** (Scheme 52).[72a] The isomers containing the thermodynamically

Scheme 52. Cyclization of 1,3-Dicarbonyl Dianions with Cyclic Sulfates (Mechanism A)

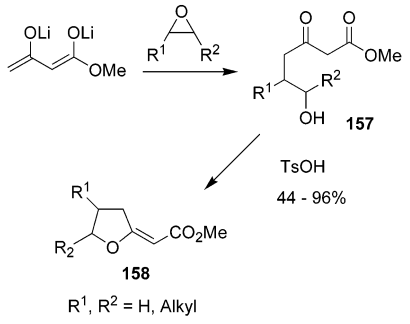


favorable *E*-configured double bond were formed. The cyclizations proceeded by double inversion of the configuration of the starting material which can be explained by two subsequent S_N2 reactions (mechanism A).

4.2.5. Reactions with Epoxides and Aziridines

Epoxides. A number of reactions of 1,3-dicarbonyl dianions with epoxides have been reported. These transformations give open-chained products in most cases. For example, an open-chained precursor to (*R*,*R*)−(−)-pyrenophorin has been enantiospecifically prepared by reaction of the dianion of *tert*-butyl acetoacetate with (*R*)−(+)-propylene oxide and subsequent aqueous quench of the resultant open-chained monoanion.[73] Cyclization reactions of epoxides with 1,3-dicarbonyl dianions have been carried out in two or in one steps. They proceed by attack of the terminal carbon atom of the dianion onto the sterically less hindered carbon of the epoxide (Scheme 53) to give the open-chained products **157**. These

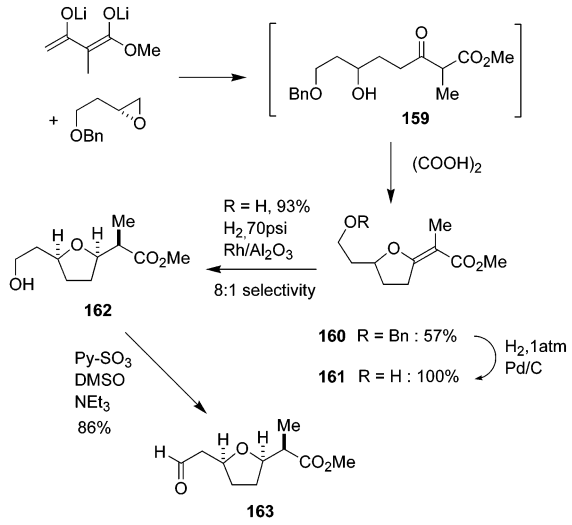
Scheme 53. Cyclization of 1,3-Dicarbonyl Dianions with Epoxides (Mechanism B)



products were transformed into 2-alkylidenetetrahydrofurans **158** by acid-catalyzed attack of the hydroxy group onto the ketone and subsequent extrusion of water (mechanism B).[74]

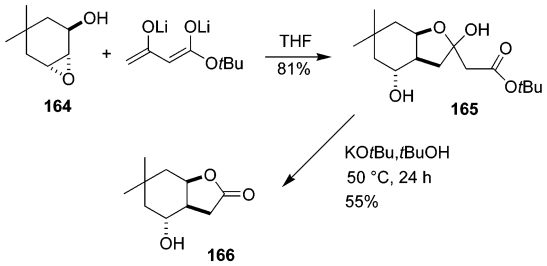
This reaction has been successfully applied to the synthesis of (±)-methyl homononactate and related natural products (Scheme 54).[74b] The 2-alkylidenetetrahydrofuran **160** was prepared from the dianion of methyl 2-methylacetoacetate. The benzyl group was removed to give **161**. Hydrogenation of the latter afforded the tetrahydrofuran **162** with good diastereoselectivity. Oxidation of the alcohol group gave the aldehyde **163**, which represents a key building block for further transformations.

Scheme 54. Synthesis of Nonactinic Acid Derivatives



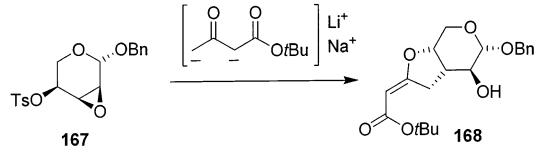
Functionalized Epoxides. The reaction of the dianion of *tert*-butyl acetoacetate with the cyclic epoxide **164** has been reported to give the semiaminal **165**. Treatment of the latter with base aforded the lactone **166** by fragmentation (Scheme 55).[75]

Scheme 55. Cyclization of 1,3-Dicarbonyl Dianions with Cyclic Epoxides (Mechanism B)



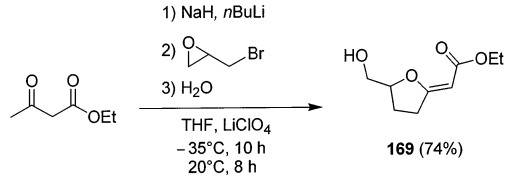
The reaction of 1,3-dicarbonyl dianions with carbohydrate-derived epoxy tosylates and triflates has been reported by Voelter et al. to result in formation of bicyclic products.[76] The regioselectivity was efficiently controlled by the choice of the leaving group. The reaction of the dianion of *tert*-butyl acetoacetate with epoxytosylate **167** afforded **168** by attack of the dianion onto the epoxide and subsequent cyclization via the tosylate (Scheme 56). The use of the corresponding triflate resulted in formation of the regioisomeric product by attack of the dianion onto the triflate and subsequent cyclization.

Scheme 56. Cyclization of 1,3-Dicarbonyl Dianions with Epoxytosylates (Mechanism A)



We and others have recently reported the cyclization of 1,3-dicarbonyl dianions with epibromohydrin.[77,78] This reaction resulted in the formation of 2-alkylidene-5-hydroxymethyltetrahydrofurans **169** (Scheme 57). A thorough optimization of the conditions (temperature, counterions of the dianion, presence of the Lewis acid $LiClO_4$) was important to obtain good yields and high chemo- and regioselectivities. The reaction yielded in most cases the thermodynamically less stable *Z*-diastereomers, which slowly isomerized into the corresponding *E*-configured products. The *Z*-diastereoselectivity can be explained by chelation of the oxygen atoms with a Li^+-ion during the reaction.

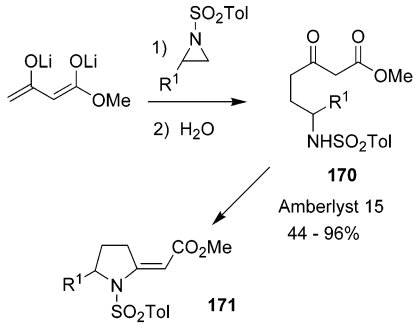
Scheme 57. Cyclization of 1,3-Dicarbonyl Dianions with Epibromohydrin (Mechanism A)



The Pd/C catalyzed hydrogenation of 2-alkylidene-5-hydroxymethyl-tetrahydrofurans afforded *syn*-configured functionalized tetrahydrofurans in good yields and with good diastereoselectivity.[77b] Due to steric reasons, the hydrogenation occurred from the sterically less encumbered side of the molecule.

Aziridines. The reaction of 1,3-dicarbonyl dianions with *N*-tosyl aziridines has been reported to give open-chained products that could be transformed into substituted pyrrolidines by treatment with acidic Amberlyst 15 resin (Scheme 58, mechanism B).[79]

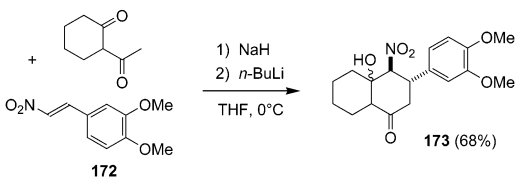
Scheme 58. Cyclization of 1,3-Dicarbonyl Dianions with Aziridines (Mechanism B)



4.2.6. Reactions with Nitro-alkenes

The cyclization of 1,3-dicarbonyl dianions with nitro-alkenes was reported by Seebach et al. to give functionalized cyclohexanones (Scheme 59).[80] For example, the Michael addition of the terminal carbon of the dianion of 2-acetylcyclohexanone with nitroalkene **172** and a subsequent aldol reaction gave the decalone **173** with very good 1,2-diastereoselectivity (mechanism B).

Scheme 59. Cyclization of 1,3-Dicarbonyl Dianions with Nitro-olefins (Mechanism B)

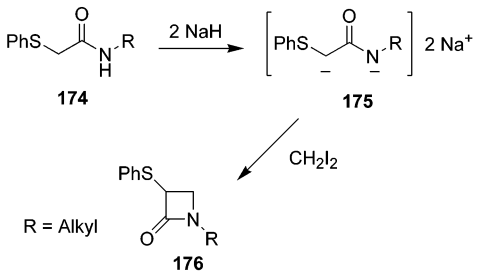


4.3. 1,3-*C*,*Het*-Dianions

4.3.1. 1,3-C,N-Dianions

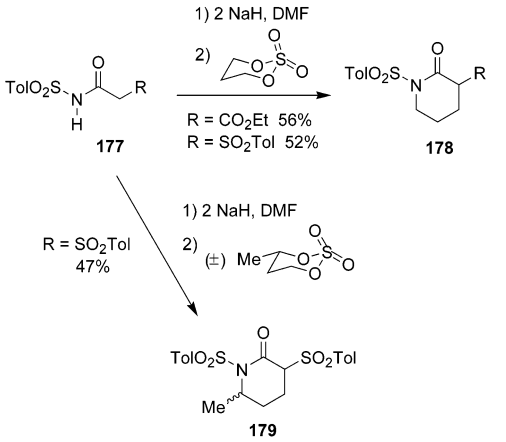
Amide Dianions. The dianions **175** of 2-thiophenyloxycarboxylic amides **174** were generated by treatment with sodium hydride (2 equiv). The cyclization of **175** with diiodomethane afforded the *β*-lactams **176** (Scheme 60).[81] The presence of the sulfide group was necessary for a successful cyclization. The first attack of the dianion onto the electrophile occurred from the carbon atom of the dianion. The cyclization proceeded via the nitrogen rather than the oxygen atom (mechanism A). The selectivity can be explained by the higher nucleophilicity of the nitrogen compared to the oxygen atom.

Scheme 60. Cyclization of Amide Dianions with Diiodomethane (Mechanism A).



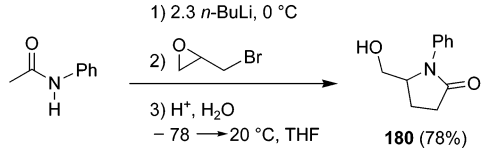
Amides **177** can be regarded as 1,3-dicarbonyl compounds or as *β*-ketosulfones (Scheme 61). The cyclization of the dianions of **177**, generated by NaH, with cyclic sulfates afforded the *δ*-lactams **178** and **179**.[82] The cyclization proceeded regioselectively via the carbon and the nitrogen atom of the dianion.

Scheme 61. Cyclization of Amide Dianions with Diiodomethane (Mechanism A).



The cyclization of the dianion of acetic anilide with epibromohydrin afforded 5-hydroxymethylpyrrolidin-4-one (**180**).[83] The formation of **180** can be explained by regioselective attack of the carbon atom of the dianion onto the bromide group and subsequent attack of the nitrogen atom onto the epoxide (mechanism A). Alternatively, the reaction can proceed by

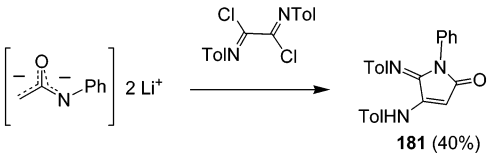
Scheme 62. Cyclization of Dilithiated Acetanilide with Epibromohydrin



attack of the dianion onto the epoxide and subsequent Payne rearrangement (Scheme 62). The regioselectivity is again a result of the higher nucleophilicity of the nitrogen compared to the oxygen atom. The preparative scope of the reaction was successfully extended to the use of other 1,3-amide dianions. This includes *N*-trimethylsilylacetic amide, propionic anilide, and thioacetic anilide. In addition, axially chiral γ-butyrolactams were prepared in racemic form.[83b−e]

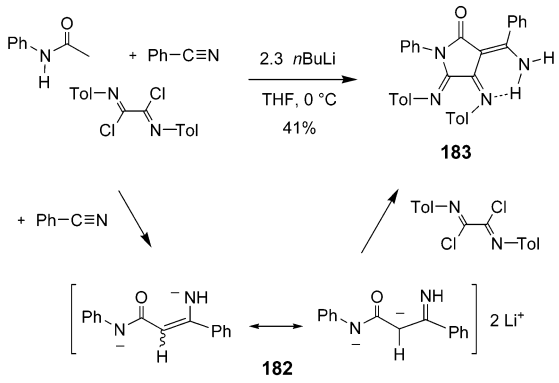
The cyclization of amide dianions with oxalic acid-bis(imidoyl)dichlorides afforded γ-iminotetramic acid amides (Scheme 63) by regioselective *C*,*N*-cyclization (mechanism A).[84a]

Scheme 63. Cyclization of Dilithiated Acetanilide with Bis(imidoyl)dichlorides



On the basis of the results shown in Scheme 61, one-pot reactions of amide dianions with nitriles and oxalic acid-bis(imidoyl)chlorides were developed. The reaction of dilithiated acetanilide with benzonitrile and subsequent cyclization with oxalic acid-bis(*p*-tolylimidoyl)dichloride regioselectively afforded the radialene-shaped pyrrole **183**.[85] The formation of **183** can be explained by attack of the dianion onto the nitrile to give intermediate **182**. A regioselective *C*,*N*-cyclization subsequently afforded the final product (Scheme 64). During the reaction, the CH_3 group of

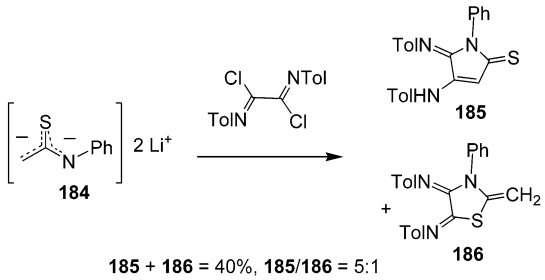
Scheme 64. One-Pot Reactions of Amide Dianions with Nitriles and Oxalic Acid-bis(imidoyl)chlorides (Mechanism A)



the amide was transformed into a sp^2-hybridized quaternary carbon atom.

Thioamide Dianions. The cyclization of the dianion of thioacetic anilide (**184**) with oxalic acid-bis(*p*-tolylimidoyl)dichloride afforded a mixture of the regioisomers **185** and **186**, which were formed by

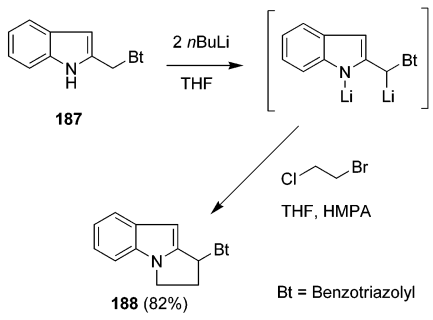
Scheme 65. Cyclization of the Dianion of Thioacetanilide with Oxalic Acid-bis(imidoyl)dichlorides (Mechanism A)



C,*N*- and *S*,*N*-cyclization, respectively (Scheme 65, mechanism A).[84b] The formation of **186** can be explained by the high nucleophilicity of sulfur.

Indole Dianions. Very recently, Katritzky et al. reported an efficient approach to fused [1,2-*a*]indoles based on the reaction of an indole derived dianion with 1-bromo-2-chloroethane (Scheme 66).[86a] The

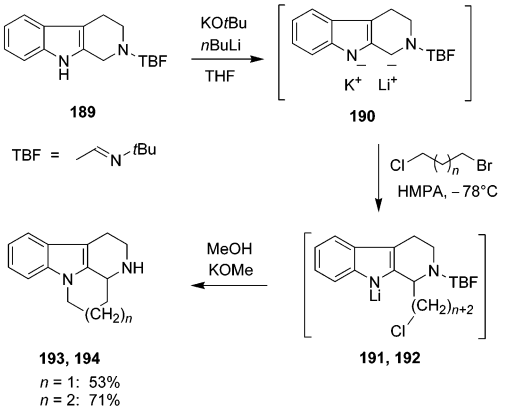
Scheme 66. Cyclization Reaction of the Dianion of a 2-Methylindole (Mechanism A)



dianion of **187** was generated by *n*BuLi. The cyclization required the presence of HMPA as a cosolvent and afforded the product **188** in good yield.

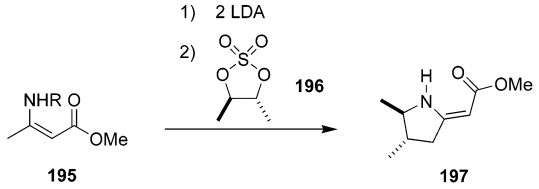
The dianion **190** of tetrahydrocarbazole **189** was generated by Schlosser base. The stepwise cyclization of **190** with 1-bromo-3-chloropropane and 1-bromo-4-chlorobutane afforded the tetracyclic products **193** and **194**, respectively (Scheme 67).[86b]

Scheme 67. Cyclization Reactions of the Dianion of Tetrahydrocarbazole (Mechanism A)



3-Aminocrotonate Dianions. The cyclization of dilithiated 3-aminocrotonates **195** with cyclic sulfates **196** has been reported to give the 2-alkylidenepyrrolidines **197** (Scheme 68).[72b] The isomers containing

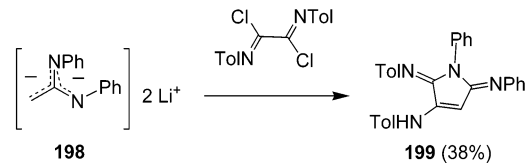
Scheme 68. Cyclization of 3-Aminocrotonate Dianions with Cyclic Sulfates (Mechanism A)



a *Z*-configured double bond were formed. The latter is thermodynamically favored, due to formation of an intramolecular hydrogen bond N−H···O. During the cyclization a double inversion of the configuration of the sulfate occurred. This led to the assumption that the cyclization proceeded by two subsequent S_N2 reactions (mechanism A).

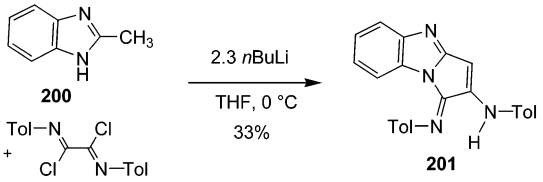
Amidine Dianions. The regioselective *C,N*-cyclization of dilithiated amidine **198** with oxalic acid-bis(*p*-tolylimidoyl)dichloride resulted in the formation of **199** (Scheme 69, mechanism A).[84]

Scheme 69. Cyclization of an Amidine Dianion with Oxalic Acid-bis(*p*-tolylimidoyl)dichloride



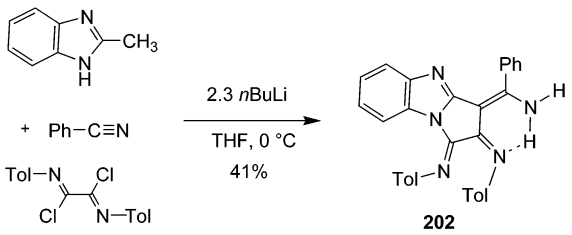
The regioselective *C,N*-cyclization of the dianion of 2-methylbenzimidazole **200**, generated by means of *n*BuLi, with oxalic acid-bis(*p*-tolylimidoyl)dichloride afforded the pyrrolo[1,2-*a*]benzimidazole **201** (Scheme 70, mechanism A).[85]

Scheme 70. Cyclization of the Dianion of 2-Methylbenzimidazole with Oxalic Acid-bis(*p*-tolylimidoyl)dichloride



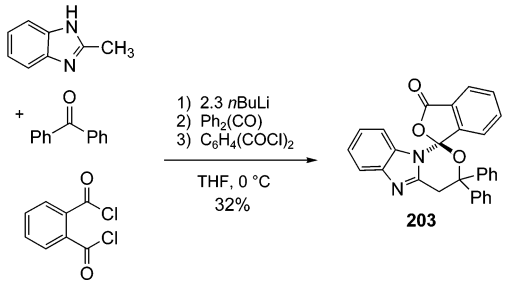
The reaction of the dianion of **200** with nitriles and subsequent cyclization with oxalic acid-bis(imidoyl)-chlorides regioselectively afforded the radialene-shaped pyrroles **202** (Scheme 71). Similar to the formation of **183**, the formation of **202** can be explained by initial attack of the dianion onto the nitrile and subsequent regioselective *C,N*-cyclization.[85]

Scheme 71. Cyclization of the Dianion of 2-methylbenzimidazole with Oxalic Acid-bis(*p*-tolylimidoyl)dichloride



The reaction of the dianion of 2-methylbenzimidazole with ketones and subsequent cyclization with phthaloyl dichlorde afforded the spiroacetals **203** (Scheme 72).[87] The formation of **203** can be explained

Scheme 72. Cyclization of the Dianion of 2-Methylbenzimidazole with Benzophenone and Phthaloyl Dichloride

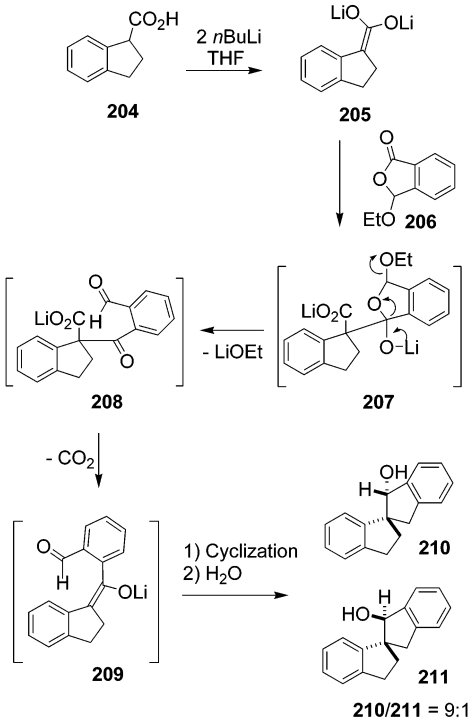


by initial attack of the dianion onto the ketone, attack of the ketone derived oxygen atom onto *iso*-phthaloyl dichloride and subsequent cyclization (mechanism A). The *iso*-phthaloyl dichloride was generated from phthaloyl dichloride during the reaction.

4.3.2. 1,3-C,O-Dianions

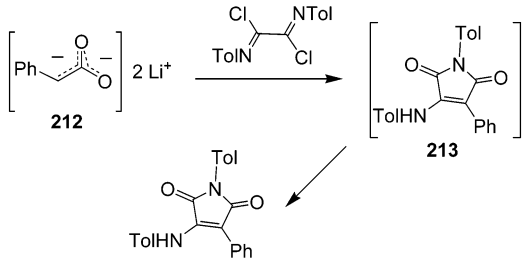
Carboxylic Acid Dianions. The cyclization of the cyclic acetal **206** with the dianion **205** of indane-1-carboxylic acid, generated by *n*BuLi, afforded a spirocyclic product as a mixture of the diastereomers **210** and **211** (mechanism A). The formation of **210/211** can be explained by attack of the carbon atom of the dianion onto the lactone and subsequent attack of the same carbon onto the aldehyde group formed by cleavage of the acetal (Scheme 73).[88]

Scheme 73. Cyclization of the Dianion of Indane-1-carboxylic Acid with Acetal 206 (Mechanism A)



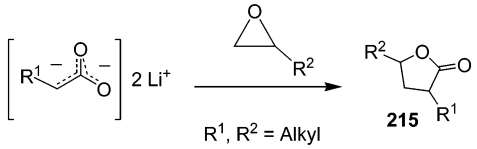
The cyclization of the dianion **212** of phenylacetic acid with oxalic acid-bis(*p*-tolylimidoyl)dichloride afforded the maleic imide **214** by initial *C*,*O*-cyclization (to give intermediate **213**) and subsequent Dimroth rearrangement (mechanism A, Scheme 74).[85]

Scheme 74. Cyclization of the Dianion of Phenylacetic Acid with Oxalic Acid-bis(imidoyl)dichlorides (Mechanism A)



The reaction of dilithiated carboxylic acids with epoxides has been reported to give γ-lactones **215** (Scheme 75).[89] The cyclization proceeds by attack of

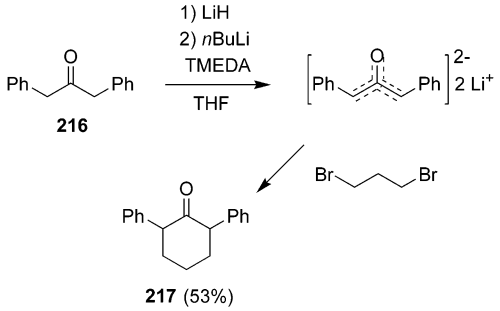
Scheme 75. Cyclization of Dilithiated Carboxylic Acids with Epoxides (Mechanism B)



the carbon atom of the dianion onto the sterically less encumbered site of the epoxide and subsequent lactonization (mechanism B).

Ketone Dianions. The cyclization of the dianion of 1,3-diphenylacetone (**216**) with 1,3-dibromopropane afforded 2,6-diphenylcyclohexanone (**217**) by regioselective *C*,*C*-cyclization (mechanism A, Scheme 76).[90a]

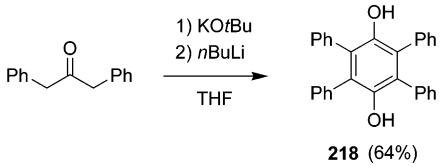
Scheme 76. Cyclization of the Dianion of 1,3-Diphenylacetone with 1,3-Dibromopropane (Mechanism A)



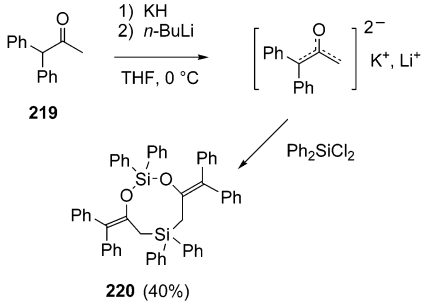
The oxidative cyclization of the dianion of **216** by iodine afforded the 1,4-dihydroquinone **218** in good yield (mechanism C, Scheme 77).[90b]

The reaction of the dianion of 1,1-diphenylacetone (**219**) with diphenyldichlorosilane resulted in the regioselective formation of the eight-membered silacycle **220** by 2:2-cyclization (Scheme 78).[91] The cyclization proceed by attack of the carbon atoms of two dianion molecules onto the dichlorosilane and subsequent cyclization by attack of the oxygen atoms of

Scheme 77. Oxidative Cyclization of the Dianion of 1,3-Diphenylacetone (Mechanism C)



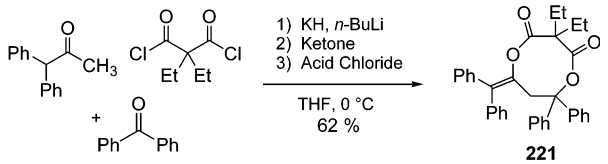
Scheme 78. Cyclization of the Dianion of 1,1-Diphenylacetone with Dichlorosilanes



the enolates thus formed onto a second molecule of diphenyldichlorosilane. The reaction of the dianion of **219** with diphenyldifluorosilane resulted in the formation of a different regioisomer.

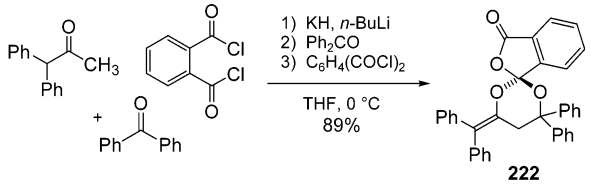
The reaction of the dianion of 1,1-diphenylacetone with benzophenone and subsequent addition of diethylmalonic dichloride afforded the eight-membered [1,5]dioxocane-2,4-dione **221** (Scheme 79).[92]

Scheme 79. One-Pot Reaction of the Dianion of 1,1-Diphenylacetone with Benzophenone and Diethylmalonyl Dichloride



The reaction of the dianion of 1,1-diphenylacetone with benzophenone and subsequent addition of phthalic dichloride afforded the spiro-annulated [1,3]-dioxane-2,1′-isobenzofuran-3′-one **222** in 89% yield (Scheme 80). The formation of the isobenzofuranone

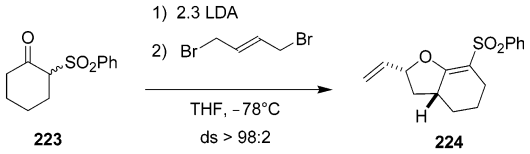
Scheme 80. One-Pot Rreaction of the Dianion of 1,1-Diphenylacetone with Benzophenone and Phthalic Dichloride



rather than the isomeric nine-membered ring can be explained by thermodynamic reasons and presumably involves the formation of *iso*-phthalic dichloride.

***β*-Ketosulfone Dianions.** The reaction of 1,4-dibromo-2-butene with the dianion β-ketosulfone **223** resulted in formation of 2-vinyl-2,3,3a,4,5,6-hexahydro-2,3-benzofurans **224** with very good diastereose-

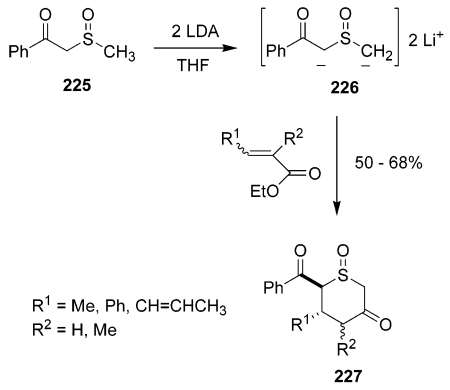
Scheme 81. Cyclization of Cyclic β-Ketosulfone Dianions with 1,4-Dibromo-2-butene (Mechanism A)



lectivity (Scheme 81).[69b] A number of related derivatives were successfully prepared. The products could be efficiently transformed into isomeric bicyclo[3.2.1]-octan-8-ones by palladium(0)-catalyzed rearrangements.

***β*-Ketosulfoxide Dianions.** The cyclization of the dianion of β-ketosulfoxide **225** with ethyl acrylates afforded the cyclic sulfoxides **227** (Scheme 82). The

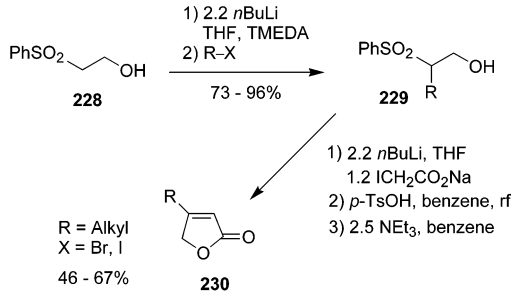
Scheme 82. Cyclization of the Dianion of *β*-Ketosulfoxide 225 with Ethyl Acrylates (Mechanism A)



products were formed by regioselective attack of the terminal carbon atom of the dianion onto the ester group and subsequent cyclization via the central carbon of the dianion (mechanism A).[93]

The reaction of the 1,3-dianion of β-hydroxysulfone **228** with alkyl halides afforded the substituted β-hydroxysulfones **229** (Scheme 83). Treatment of the

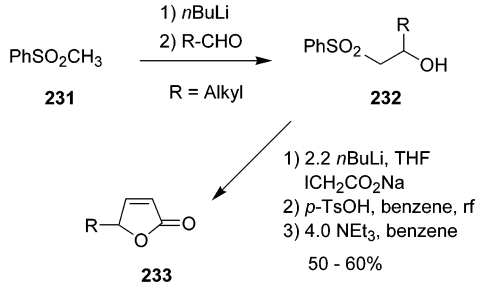
Scheme 83. Synthesis of Butenolides 230 from the Dianions of *β*-Hydroxysulfones 228



dianions of these compounds with the sodium salt of iodoacetic acid afforded open-chained condensation products. Sequential treatment of the latter with *p*-toluenesulfonic acid and triethylamine resulted in cyclization and cleavage of the sulfonyl group to give the butenolides **230**.

The regioisomeric substituted butenolides **233** were prepared by a slightly modified strategy (Scheme 84). The reaction of lithiated methylphenyl sulfone with

Scheme 84. Synthesis of Butenolides 233 from Dianions of *β*-Hydroxysulfones 232

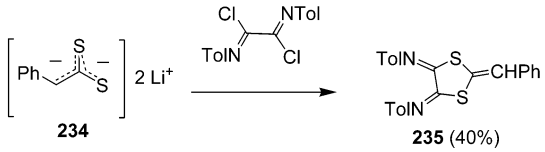


aldehydes afforded the β-hydroxysulfones **232**. The dianions of these compounds were transformed into butenolides **233**.[94]

4.3.3. 1,3-C,S-Dianions

The cyclization of oxalic acid-bis(*p*-tolylimidoyl)-dichloride with the dianion of phenyldithioacetic acid, generated from carbon disulfide, afforded the dithiolane **235** by regioselective *S*,*S*-cyclization (Scheme 85, mechanism A).[85]

Scheme 85. Cylization of Oxalic Acid-bis(*p*-tolylimidoyl)dichloride with the Dianion of Phenyldithioacetic Acid (Mechanism A)



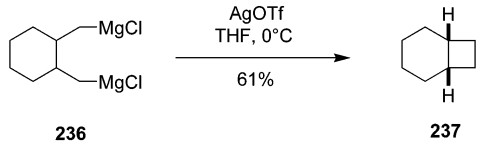
5. Cyclizations of 1,4-Dianions

5.1. 1,4-*C*,*C*-Dianions

5.1.1. 1,4-Butane Dianions

The AgOTf-mediated oxidation of bis-Grignard reagent **236**, which can be regarded as a 1,4-dianion, has been reported to give bicyclo[4.2.0]octane (**237**) (Scheme 86, mechanism C).[95]

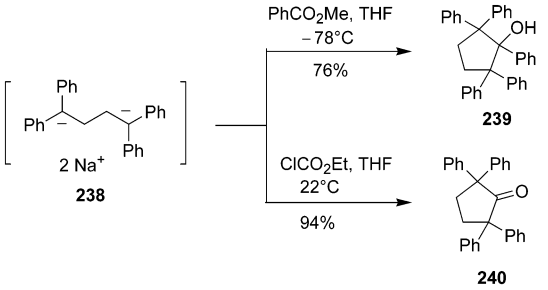
Scheme 86. Oxidative Cyclization of 1,4-Dianion 236 (Mechanism C)



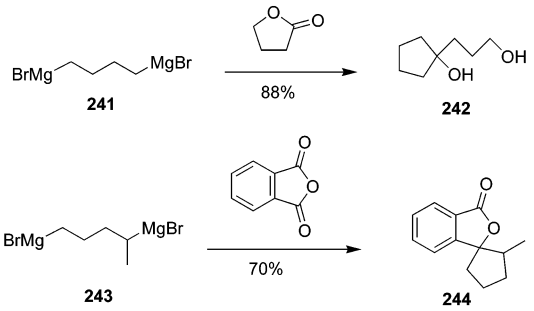
The reaction of the disodium salt of 1,1,4,4-tetraphenylbutane (**238**) with methyl benzoate afforded 1,2,2,5,5-pentaphenylcyclopentan-1-ol (**239**) in 76% yield (Scheme 87). The product was formed by attack of the dianion onto the ester and subsequent cyclization by attack of the dianion onto the ketone. The reaction of dianion **238** with ethyl chloroformate gave 2,2,5,5-tetraphenylcyclopentan-1-one (**240**) in 94% yield (mechanism A).[96]

The reaction of the symmetrical 1,4-dianion **241**, generated from 1,4-dibromobutane, with γ-butyrolactone afforded the cyclopentanol **242** (Scheme 88). The product was formed by attack of the dianion onto the lactone, ring cleavage, and cyclization by attack

Scheme 87. Cyclization Reactions of 1,4-Dianion 238 (Mechanism A)



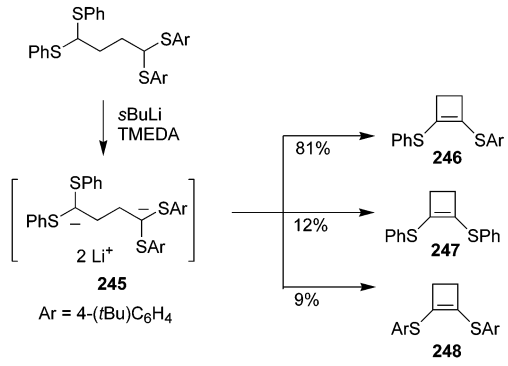
Scheme 88. Cyclization of the 1,4-Dianions 241 and 243 with γ-Butyrolactone and Phthalic Anhydride (Mechanism A)



of the dianion onto the carbonyl group (mechanism A). The reaction of the unsymmetrical dianion **243** with phthalic anhydride afforded the spiro-compound **244** by attack of the sterically less encumbered carbon atom of the dianion onto the anhydride, attack of the second carbon of the dianion onto the keto group formed, and subsequent lactonization.[97]

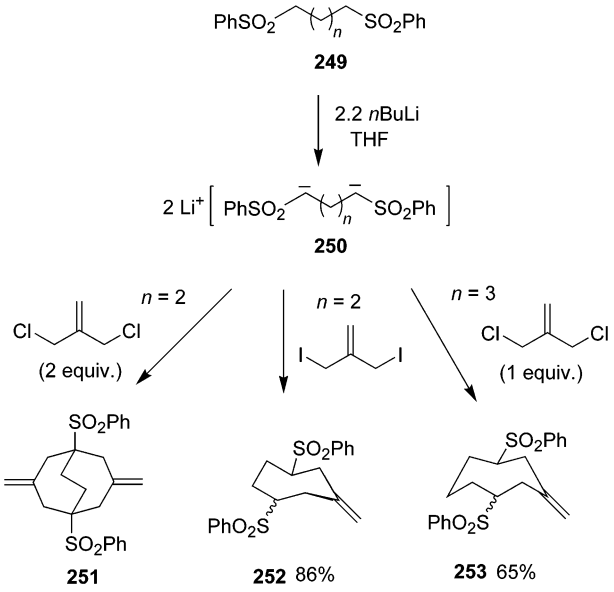
The dianions **245** of unsymmetrical 1,1,4,4-tetrathioaryloxybutanes were generated by deprotonation. Cyclization and subsequent elimination afforded the unsymmetrical cyclobutene derivatives **246** as the main products (mechanism A). Symmetrical cyclobutenes (**247**, **248**) were formed as side-products (Scheme 89).[98]

Scheme 89. Generation and Cyclization of 1,4-Dianion 245 (Mechanism A)



The dianion **250** of bis-sulfone **249** was generated by means of 2 equiv of *n*BuLi. The cyclization of **250** with dichloroisobutene resulted in a 2:1 reaction and formation of the bridged product **251** (Scheme 90). In contrast, the cyclization of **250** with diiodoisobutene resulted in a 1:1 reaction and formation of the monocyclic product **252** (mechanism A). The

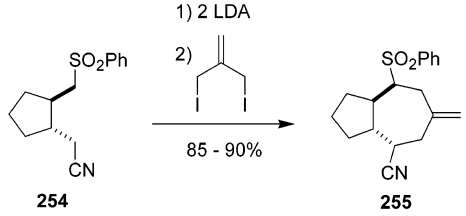
Scheme 90. Generation and Cyclizations of the 1,4-dianion 250 (Mechanism A)



cyclization of dichloroisobutene with the corresponding 1,5-dianion afforded the monocyclic product **253**.[99]

The dianion of the cyclic 1,4-cyanosulfone **254** was generated by means of 2 equiv of LDA. The cyclization of **254** with diiodoisobutene resulted in formation of the bicyclic product **255** (Scheme 91). The *trans*-

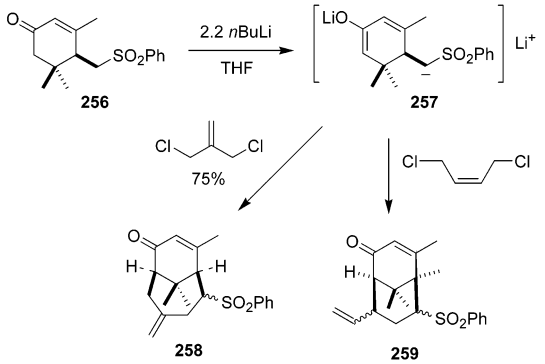
Scheme 91. Cyclizations of the Dianion of 1,4-Cyanosulfone 254 (Mechanism A)



configuration of the starting material was also present in the product (mechanism A).[99]

The dianion **257** of the cyclic ketosulfone **256** was generated by *n*BuLi. The dianion can be regarded both as a 1,4- or as a 1,6-dianion. The reaction of **257** with dichloro*iso*butene resulted in formation of the bridged cyclization product **258** in good yield (Scheme 92). The cyclization of dianion **257** with

Scheme 92. Cyclizations of 1,4-Ketosulfone Dianion 257 (Mechanism A)

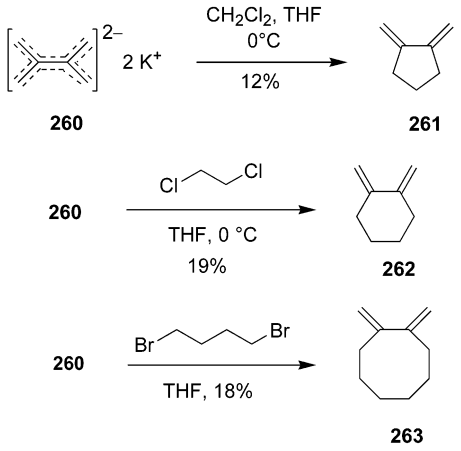


cis-1,4-dichlorobutene afforded the vinyl-substituted product **259** by a S_N/S_N'-cyclocondensation (mechanism A).[99]

5.1.2. 2,3-Dimethyl-1,3-butadiene Dianions

The cyclization of ambident 1,4-dianion **260** with dichloromethane afforded the 1,2-bis-methylidenecyclopentane **261**, however, in only 12% yield (mechanism A, Scheme 93).[100] The cyclization of **260** with

Scheme 93. Cyclization of 1,4-Dianion 260 with Dihalides (Mechanism A)

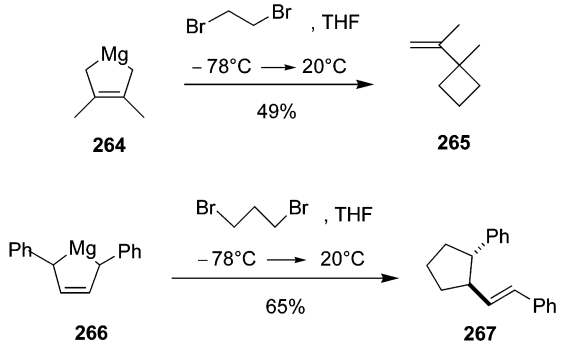


1,2-dichloroethane and 1,4-dibromobutane afforded the cyclohexanes **262** and **263** in low yields.

5.1.3. 2,3-Butene Dianions

Magnesacyclopentene **264** can be regarded as a 2,3-butene dianion and was formed by reduction of 2,3-dimethyl-1,3-butadiene with activated magnesium. The cyclization of dianion **264** with 1,2-dibromoethane afforded 1-*iso*propenyl-1-methylcyclobutane (**265**) in 49% yield (mechanism A, Scheme 94). The reaction

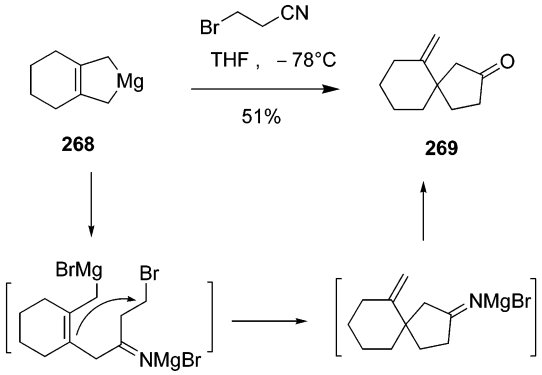
Scheme 94. Cyclizations of 1,4-Dianions 264 and 266 with Dibromides (Mechanism A)



of 1,3-dibromopropane with the related dianion **266**, which was generated from 1,4-diphenyl-1,3-butadiene, afforded the cyclopentane derivative **267**. In the formation of **267**, metallacyclobutene **266** reacted as a 1,2- rather than as a 1,4-dianion.[101]

The cyclization of the magnesacyclopentene **268** with 1-bromo-2-cyanoethane afforded the spiro[5.4]-cyclodecanone **269** (Scheme 95). The formation of **269**

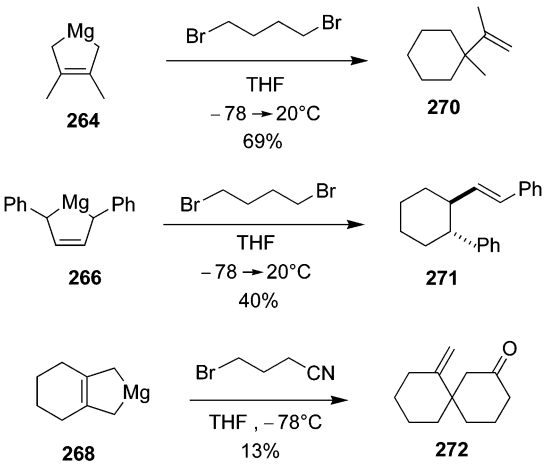
Scheme 95. Cyclizations of Dianion 268 with 1-Bromo-2-cyanoethane (Mechanism A)



can be explained by attack of the dianion onto the nitrile and subsequent cyclization via the bromide. In the formation of **269**, dianion **268** reacts as a 1,2- rather than as a 1,4-dianion (mechanism A).[102]

The cyclization of 2,3-butene dianions with 1,4-dielectrophiles was studied. The cyclization of dianions **264** and **266** with 1,4-dibromobutane afforded the functionalized cyclohexanes **270** and **271** (mechanism A, Scheme 96). During the formation of these

Scheme 96. Cyclization Reactions of Dianions 264, 266, and 268 with 1,4-Dibromobutane and 1-Bromo-3-cyanopropane (Mechanism A)



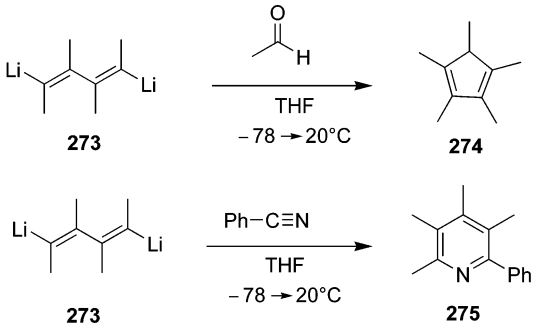
products, the dianions again reacted as 1,2- rather than as 1,4-dianions. The cyclization of dianion **268** with 1-bromo-3-cyanopropane afforded the spiro[5.5]-cycloundecanone **272**, albeit in low yield.[101,102] The formation of **270**−**272** can be explained by mechanisms related to that depicted in Scheme 95.

5.1.4. 1,3-Butadiene Dianions

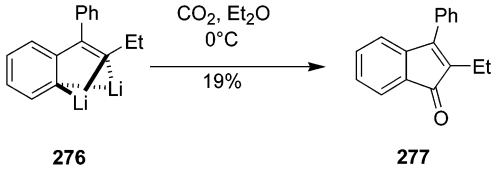
Dilithiated 1,2,3,4-tetraalkyl-1,3-butadienes were generated from the corresponding diiodides by metal−halide exchange (Scheme 97).[103] The cyclization of dianion **273** with ketones afforded the cyclopentadienes **274** (mechanism A). The cyclization of **273** with benzonitrile resulted in the formation of pyridine **275**.[104]

The cyclization of carbon dioxide with dianion **276**, which can be regarded as a dilithiated styrene, afforded the benzocyclopentenone **277** (mechanism A, Scheme 98).[105]

Scheme 97. Cyclizations of Dilithiated 1,3-Butadiene 273

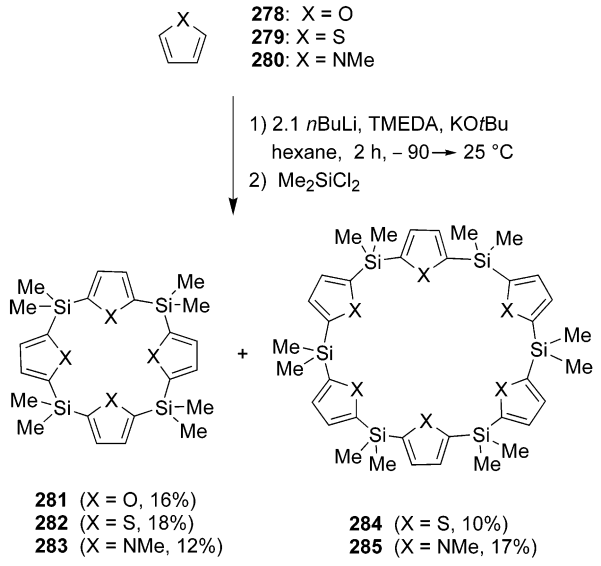


Scheme 98. Cyclization of Dianion 276 with Carbon Dioxide (Mechanism A)



The cyclization of dilithiated furan **278**, thiophene **279**, and *N*-methylpyrrole **280** with dimethyldichlorosilane afforded mixtures of macrocyclic products containing four or six heterocyclic moieties (Scheme 99, mechanism A).[106] For example, the silicon-bridged

Scheme 99. Cyclization of Dilithiated Furan, Thiophene, and *N*-Methylpyrrole with Dimethyldichlorosilane (Mechanism A)

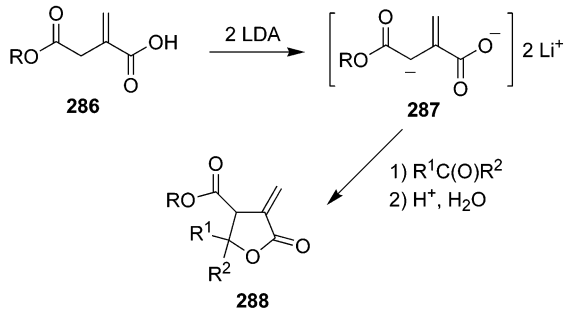


macrocycles **281**−**283** and **284**−**285** were obtained, however, in low yields.

5.2. 1,4-*C*,*O*-Dianions

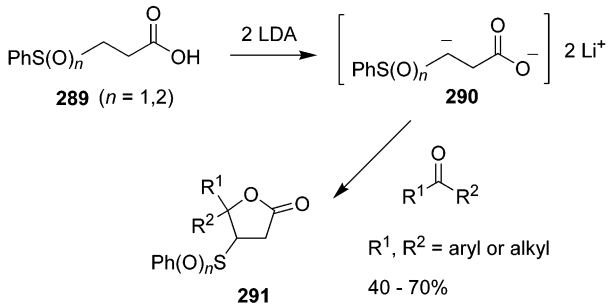
The dianion **287** of **286** was generated by LDA. The cyclization of **287** with ketones afforded the α-methylidene-γ-butyrolactones **288** (Scheme 100). The reaction proceeded by attack of the carbon atom of the dianion onto the ketone and subsequent lactonization (mechanism B).[107]

Scheme 100. Cyclization of Succinate 1,4-Dianion 287 with Ketones (Mechanism B)



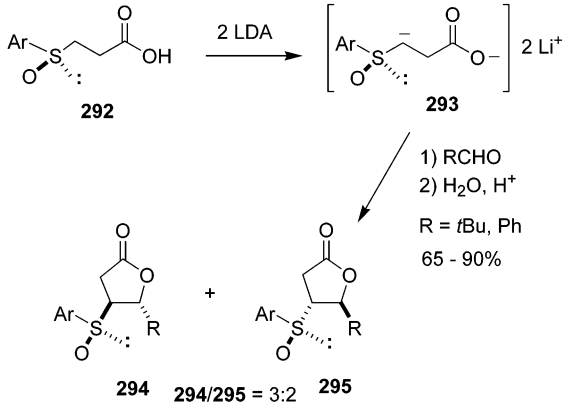
The cyclization of ketones with the dianions **290** of β-sulfonylcarboxylic acids **289** resulted in formation of the sulfonyl substituted γ-butyrolactones **291** (Scheme 101, mechanism B).[108]

Scheme 101. Cyclization of Succinate 1,4-Dianion 290 with Ketones (Mechanism B)



The dianions **293** of β-sulfoxide substituted carboxylic acids **292** were generated by LDA (Scheme 102). The cyclization of **293** with aldehydes afforded the γ-butyrolactones **294** and **295**, however, with high *trans*-diastereoselectivity, but low enantioselectivity (mechanism B).[109]

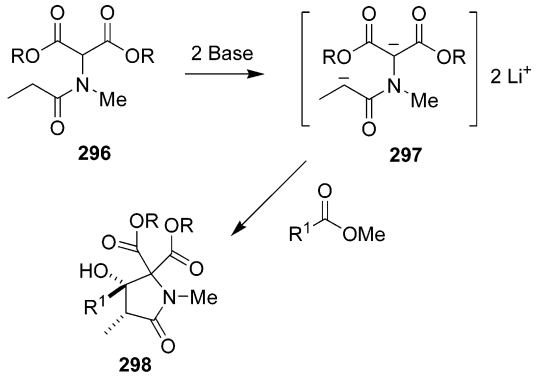
Scheme 102. Cyclizations of β-Sulfoxide Substituted Carboxylic Acids 292 (Mechanism B)



5.3. 1,4-*C*,*N*-Dianions

The ambident 1,4-dianion **297** was generated from amide **296**. The reaction of **297** with carboxylic esters afforded the γ-lactams **298** by attack of the carbon atom of the dianion onto the ester and subsequent

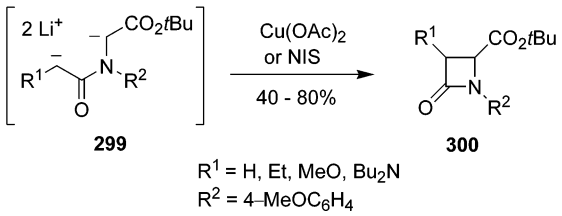
Scheme 103. Cyclization of 1,4-*C,N*-Dianion 297 with Esters (Mechanism A)



cyclization by attack of the malonate carbon atom onto the ketone (Scheme 103, mechanism A).[110]

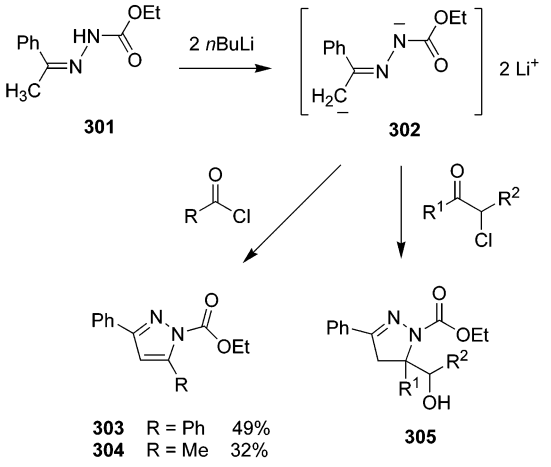
Treatment of the amide derived dianions **299** with copper(II) acetate afforded a variety of β-lactams **300** by oxidative cyclization (Scheme 104, mechanism C).[111]

Scheme 104. Oxidative Cyclizations of 1,4-*C,N*-Dianions 299 (Mechanism C)



The dianion **302** of hydrazone **301** was generated by *n*BuLi. The reaction of **302** with acid chlorides afforded the pyrazoles **303** and **304** by attack of the carbon atom of the dianion onto the acid chloride and subsequent cyclization by attack of the nitrogen atom onto the carbonyl group and elimination of water (Scheme 105, mechanism A). The reaction of **302** with

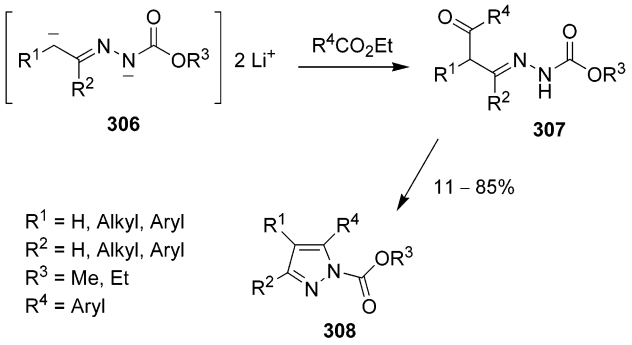
Scheme 105. Cyclization Reactions of Hydrazone 1,4-Dianion 302 (Mechanism A)



α-chloroketones afforded the pyrazolidine **305** by attack of the dianion onto the ketone and cyclization via the nitrogen atom (mechanism A).[112,113]

The condensation of dilithiated hydrazones **306** with esters and subsequent cyclization afforded the pyrazoles **308** (Scheme 106).[114]

Scheme 106. Cyclization of Hydrazone 1,4-Dianions 306 with Esters

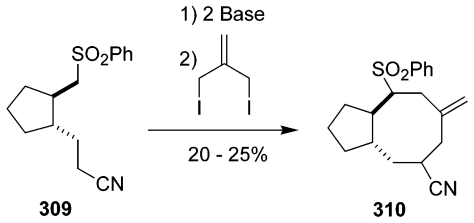


6. Cyclizations of 1,5-Dianions

6.1. 1,5-*C,C*-Dianions

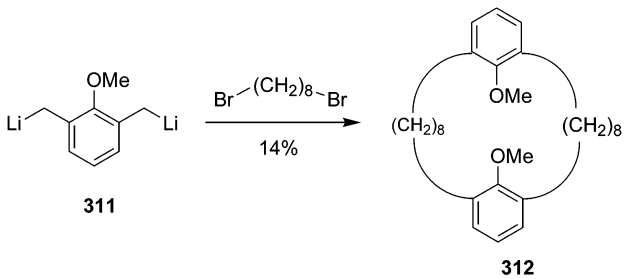
The reaction of the dianion of cyanosulfone **309**, generated by deprotonation, with a number of dielectrophiles was studied. The cyclization of **309** with 2-methylidene-1,3-diiodopropane afforded the eight-membered ring **310**, albeit in low yield (Scheme 107, mechanism A).[115]

Scheme 107. Cyclization Reaction of the 1,5-*C,C*-Dianion of 309 (Mechanism A)



The reaction of the dianion of 2,6-dimethyl-1-methoxybenzene **311** with 1,8-dibromooctane afforded the macrocyclic cyclophane **312**, however, in low yield (Scheme 108, mechanism A). Cyclizations of **311** with other dielectrophiles have also been reported.[116]

Scheme 108. Cyclization Reaction of the 1,5-*C,C*-Dianion 311 (Mechanism A)

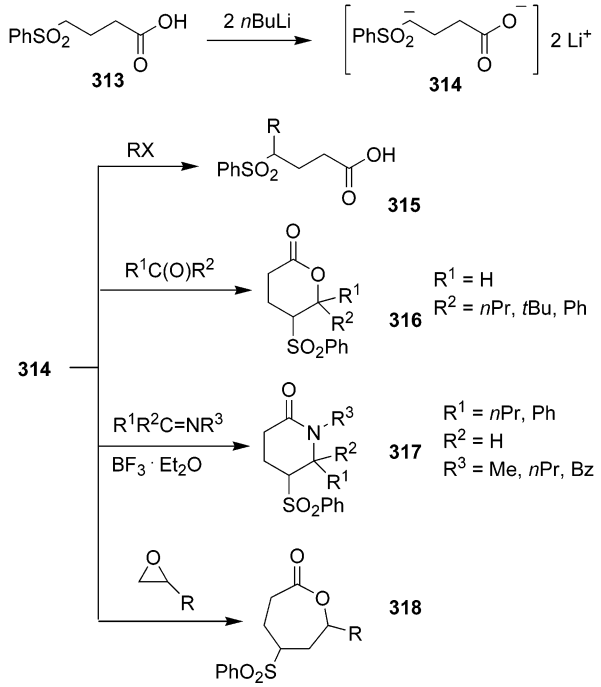


6.2. 1,5-*C,O*-Dianions

The dianion **314** of γ-sulfonylcarboxylic acid was generated by treatment of **313** with *n*BuLi. Treat-

ment of **314** with alkyl halides resulted in attack of the carbanion onto the electrophile and formation of the carboxylic acids **315**. The reaction of **314** with ketones proceeded with the same regioselectivity: δ-Lactones **316** were formed by attack of the carbanion onto the ketone and subsequent cyclization via the acid moiety (mechanism B, Scheme 109). Like-

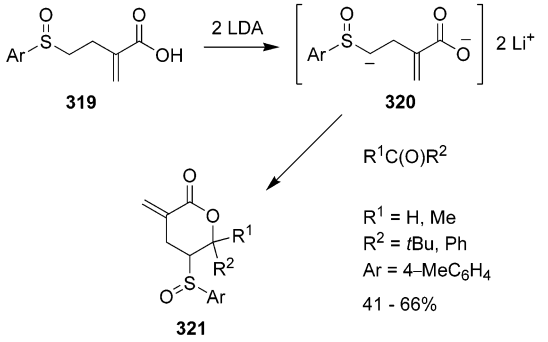
Scheme 109. Cyclization Reactions of the Dianion of γ-Sulfonylcarboxylic Acid 313 (Mechanism B)



wise, δ-lactams **317** were prepared by reaction of **314** with imines. The reaction of **314** with epoxides afforded the ϵ-lactones **318**.[117−122]

The cyclization of dianion **320**, generated from γ-sulfonylcarboxylic acid **319**, with ketones gave the methylidene-substituted lactones **321** (Scheme 110, mechanism A).[123]

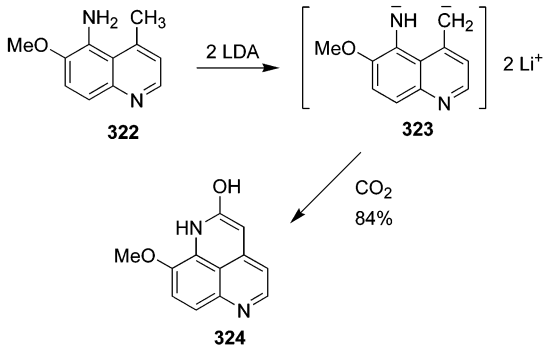
Scheme 110. Cyclization Reactions of the Dianion of γ-Sulfonylcarboxylic Acid 319 (Mechanism B)



6.3. 1,5-*C*,*N*-Dianions

The dianion **323** of amino-substituted quinoline **322** was generated by means of LDA. The cyclization of **323** with carbon dioxide afforded the tricyclic product **324** (mechanism A, Scheme 111).[124]

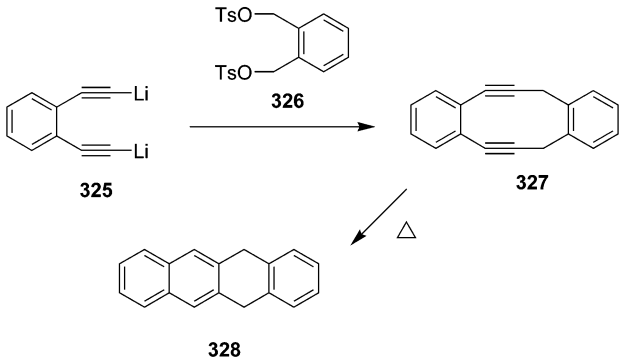
Scheme 111. Cyclization Reaction of the 1,5-C,*N*-Dianion 323 (Mechanism A)



7. Cyclizations of 1,6-Dianions

The cyclization of dilithiated 1,2-bis(ethinyl)benzene **325**, generated by deprotonation (LDA), with bis-tosylate **326** afforded the cyclic bis-alkyne **327** (Scheme 112). The latter underwent a Bergman

Scheme 112. Cyclization of the Dianion of Bis-alkyne 325 with Bis-tosylate 326

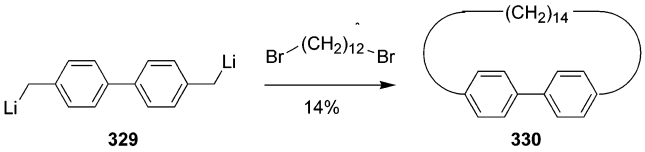


cyclization upon heating to give the tetracyclic product **328**.[125]

8. Cyclizations of 1,10-Dianions

The reaction of dilithiated hydrocarbon **329** with 1,12-dibromododecane afforded the cyclophane **330** in 14% yield. The synthesis of related cyclophans containing a biphenyl moiety have also been reported (mechanism A, Scheme 113).[126]

Scheme 113. Cyclization Reaction of 1,10-*C*,*C*-Dianion 329 (Mechanism A)



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