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Acylvinyl and Vinylogous Synthons†

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Contents

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Carmen Nájera was born in Nájera (La Rioja) and was graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays with Prof. D. Seebach at the ETH (Zurich), Prof. J. E. Baldwin at the Dyson Perrins Laboratory (Oxford), Prof. E. J. Corey at Harvard University, and Prof. J.-E. Bäckvall at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and full Professor in 1993 at the University of Alicante. Her current research interest is focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis, peptide coupling reagents and solid-phase synthesis.

I. Introduction

The functionality $-(CH{=}CH)_nCO-$ is an important structural feature in many naturally occurring compounds such as oxopolyenoic acids, lactones, and polyenamides.[1] Consequently, considerable efforts have been dedicated to the development of synthetic methods capable to achieve the preparation of this important moiety. Thus, Wittig-based methodologies have been profusely applied, but an obvious synthetic approach consists of the use of reagents able to act as acylvinyl or vinylogous synthons (Figure 1).[2]

General structures of the acyclic and cyclic series of such synthons are shown in Figure 1, the asterisk representing a positive or negative charge. The figure

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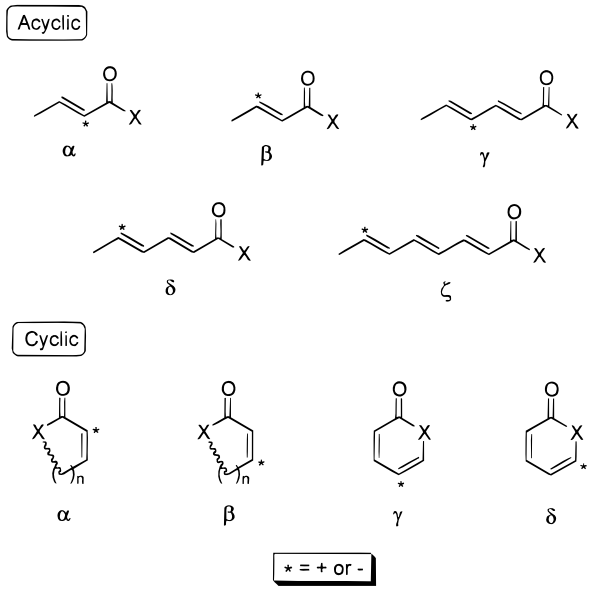


Figure 1.

shows how, according with the distance between the carbonyl group and the sp^2 carbon bearing the charge in the vinylic or polyenic structure, these entities can be clasified into acyclic and cyclic α-, *β*-, *γ*-, ..., *ω*-acylvinyl or polyenyl synthons.

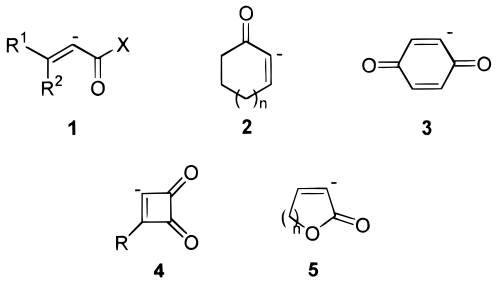
The most direct precursors of cationic acylvinyl and vinylogous synthons of these type would be reagents with a leaving group attached to the sp^2 carbon α, *β*, *γ*, ..., relative to the carbonyl, whereas direct precursors of their anionic counterparts would be the corresponding organometallic compounds. These precursors would react with nucleophilic or electrophilic species, respectively, allowing the incorporation of the acyl-vinylic or polyenic moiety.

A vast array of these reagents has been developed to cover important synthetic necessities, and special attention has been devoted to anionic α- and, especially, *β*-acylvinyl synthon precursors. The present revision presents a general view of these different reagents that have been used as precursors of anionic and cationic acylvinyl and vinylogous synthons. Thus, carbonyl-protected and unprotected species will be presented, together with reagents considered as synthetic equivalents where the vinylic or polyenic structure is not seen at the first glance. Moreover, not only nucleophilic or electrophilic systems with the ability to carry out a direct substitution reaction will be considered but also transition metal-catalyzed coupling reactions. The Heck reaction will be excluded, since a polar group is not present at the vinylic position of the unsaturated carbonyl system.

Throughout this review, Seebach's *d*/*a* (donor/acceptor), notation for anionic and cationic synthons[3] together with the more informal plus/minus, will be used.

II. α*-Acylvinyl Anionic Synthons*

The α-anions of acylvinyl moieties can also be seen as synthons donors of electrons of the type d^2 following Seebach's nomenclature,[3] presenting "normal" reactivity. In this section, species which are α-acylvinyl anions of type **1**−**5** will be considered. Com-

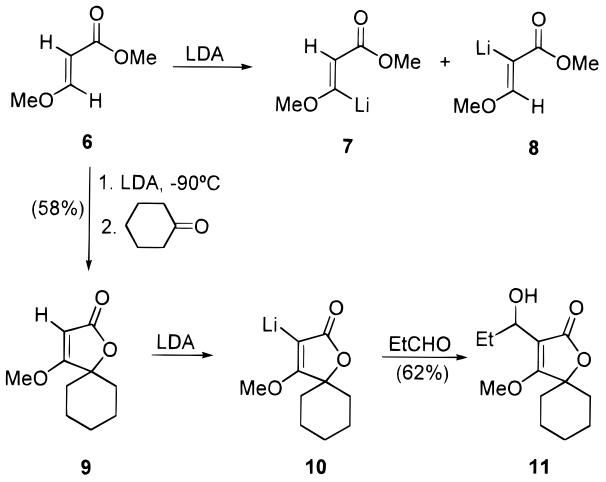


pounds used as precursor of these species have been divided in two groups depending if the carbonyl group remains free without any protection as is the case of carboxylic acid derivatives or has to be previously protected as is usually the case of aldehydes or ketones. In addition, synthetic equivalents of the α,*β*-unsaturated carbonylic system will also be considered.

A. α,*β*-Unsaturated Unprotected Carbonyl Compounds

The most direct approach to a synthon of type **1** would be the direct α-lithiation of an acrylic acid derivative using strong bases and low temperatures.[4] However, such conditions favor kinetic *β*-metalation, the α-lithiation being a thermodynamic process. This has been shown extensively with *β*-functionalized substituted acrylic acid derivatives, analyzing the influence of polarity effects and intramolecular complexation[5] and solvation.[6,7] For example, under kinetic control the lithiation of methyl *β*-methoxyacrylate (**6**) leads exclusively to the *β*-lithiated species **7**; however, under thermodynamic control a 1:1 mixture of the α- (**8**) and *β*-lithiated (**7**) species is generated (Scheme 1).[6a,7] Therefore, **6** can be regarded as a

Scheme 1

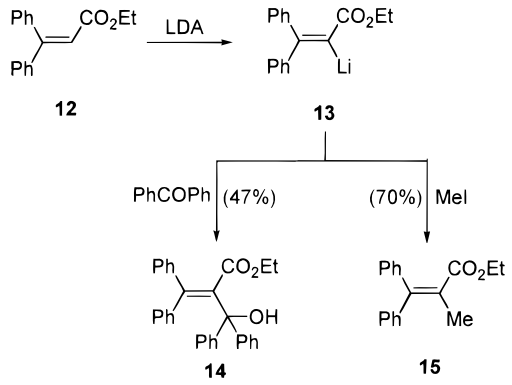


functionalized building block for the synthesis of cyclopentenones, butenolides, and tetronates,[8−10] as shown in Scheme 1 for the synthesis of tetronate **11** from α-organolithium reagent **10** which behaves as a synthon of the type **5**.[9]

Obviously, only when there is no *β*-hydrogen, the α-lithiation is exclusively achieved. Thus, ethyl *β*,*β*-

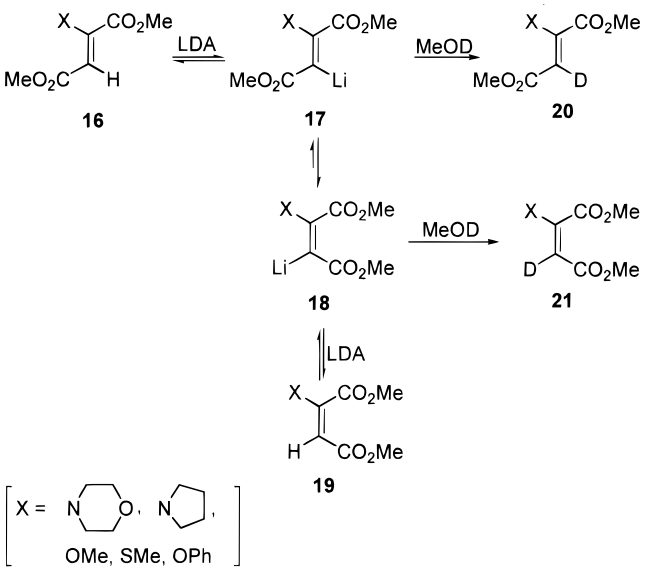
diphenylacrylate (**12**) can be deprotonated with lithium diisopropylamide at low temperature giving the vinyl carbanion **13** which reacts with electrophiles such as benzophenone and methyl iodide in addition and substitution reactions, respectively (Scheme 2).[11]

Scheme 2



The configurational stability of these types of vinyllithium compounds affects the final stereochemical result of the reaction with an electrophile. Such stability depends of several factors, such as ion-pairing characteristics, effect of the medium, and substituent effects.[12−15] Higher configurational stability is achieved with intense ion-pair contact. In addition, substituents such as the carbonyl group, which stabilize carbanions by delocalization, decrease the configurational stability of the corresponding vinyllithium compound. On the other hand, an electron-donating β-substituent situated at a *trans* position to the vinyl carbanion on the methyl ester of α-lithiated fumaric acid **17** decreases the configurational stability probably due to the formation of an allenolate intermediate and also increases the nucleophilic reactivity compared with the lithiated maleic acid derivative **18**.[12,15] This has been shown by quenching the formed lithium derivatives with electrophiles such as deuterated methanol, the main compound obtained being **21** probably due to internal

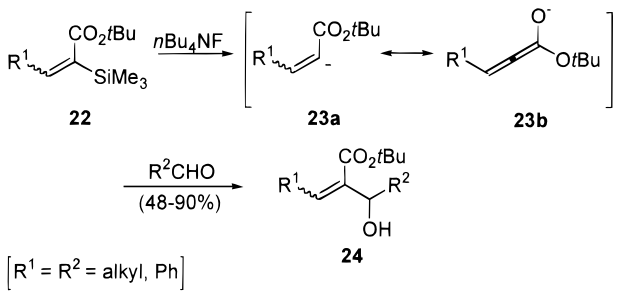
Scheme 3



complexation[5] of the lithium intermediate with the substituent X (Scheme 3).

α-Lithio derivatives of α,β-unsaturated acid salts have also been prepared from halogen−metal exchange of the corresponding α-bromo acids with butyllithium at very low temperature.[16,17] Moreover, formation of the α-carbanions of *tert*-butyl 2-alkenoates **23a** has been achieved by fluoride ion-induced desilylation of *tert*-butyl 2-trimethylsilyl-2-alkenoates **22**. When the desilylation takes place in the presence of an aldehyde, *tert*-butyl 2-(1-hydroxyalkyl)-2-alkenoates **24** are obtained (Scheme 4).[18]

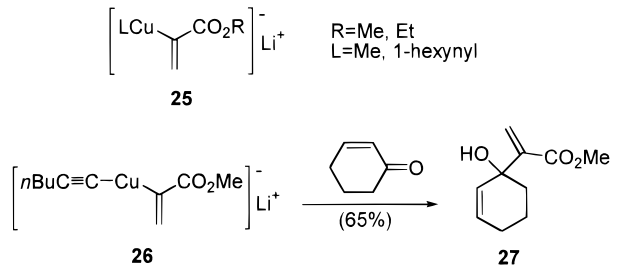
Scheme 4



However, the *Z*/*E* ratios of products **24** differ considerably from those of the starting compounds **22**, suggesting that the intermediate anion exists in a ketene acetal form **23b** rather than in a form **23a**.

α-Carboalkoxyvinyl cuprates such as **25**, obtained from the corresponding vinyl bromides by reaction with lithium cuprates, are direct synthetic equivalents of the acrylic α-anion **1** (X = OR).[19−22] These cuprates can be used in alkylation[19] and addition reactions to ketones.[20] α,β-Unsaturated ketones show a totally different reactivity than when their carbonyl-protected counterparts were used (see below). For instance, reaction of cuprate **26** with cyclohex-2-enone gives a 1,2-addition instead of the typical 1,4-addition (Scheme 5).[20] On the contrary, it has been

Scheme 5

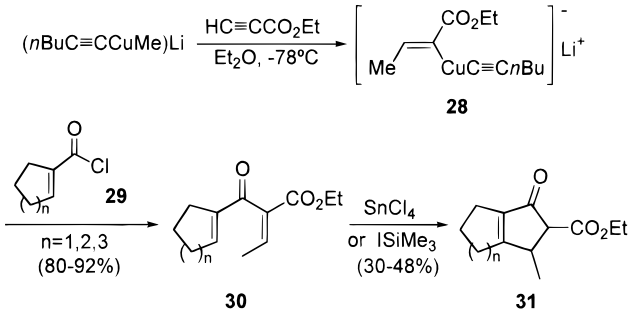


reported that this type of organocopper reagent adds preferentially in a 1,4 manner to the monoepoxide of 1,3-cycloheptadiene.[21] The unusual reactivity of these organocopper reagents could be also explained by the formation of an allenoate.[22]

These cuprates have been used for reaction with α,β-unsaturated acid chlorides, a process that takes place without concomitant conjugate addition.[22] In this case, the prepared [α-(carboethoxy)vinyl]cuprate such as **28** is obtained by conjugate addition of mixed alkyl cuprates to ethyl propiolate. Trapping of these organocopper reagents with acid chlorides **29** from cyclic α,β-unsaturated acids affords α,α′-dienones

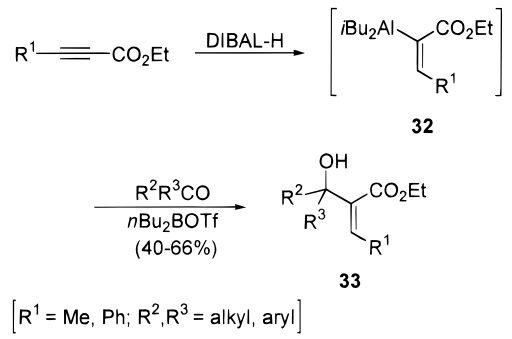
such as **30** which are converted into synthetically interesting ring-fused cyclopentenones **31** by a Lewis acid-mediated Nazarov-type cyclization (Scheme 6).[22]

Scheme 6



Related to all these acrylate-derived organocuprate reagents are the anionic β-substituted [α-(alkoxycarbonyl)vinyl]aluminum intermediates **32**.[23] These species are formed by reacting DIBAL-H with β-substituted propiolate and react with aldehydes and ketones in the presence of a catalytic amount of a Lewis acid to give only the (*Z*)-isomer of β-substituted α-(hydroxyalkyl)acrylates **33** (Scheme 7).[23b] These reagents

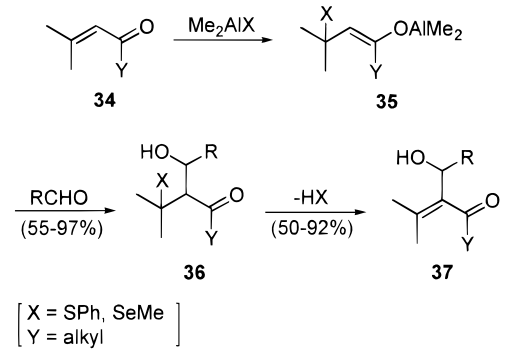
Scheme 7



also react with activated ketones, such as α-keto esters, α-acyl cyanides, and α-acetylenic ketones now in the absence of Lewis acid.[23c]

A similar process where the overall transformation provides an access to an α-acylvinyl anion adding to an aldehyde component is outlined in Scheme 8. In

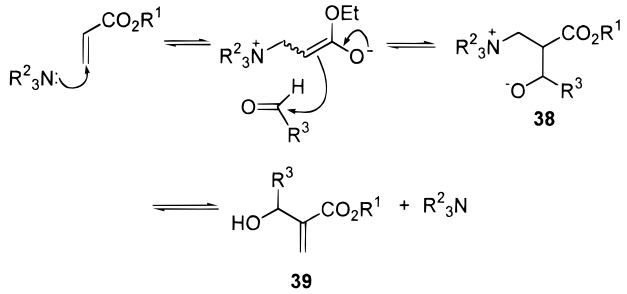
Scheme 8



this case, Me_2AlSPh or $Me_2AlSeMe$ add to α,β-unsaturated ketones in a 1,4-fashion. The resulting aluminum enolates **35** react with aldehydes affording adducts **36** which give final products **37** after final spontaneous or oxidative ($NaIO_4$ or H_2O_2) PhSH or MeSeH elimination.[24a] However, Me_2AlSPh was not effective with α,β-unsaturated esters or lactones, the use of the ate complex $Me_3Al^-SPhLi^+$ being necessary.[24a] This reaction is closely related to a previously reported addition of phenylthiomagnesium iodide to α,β-unsaturated carbonyls.[24b]

The tertiary amine-catalyzed Baylis−Hillman condensation reaction between an acrylate and an aldehyde to give α-(hydroxyalkyl)acrylates, such as the simplest methyl α-(hydroxymethyl)acrylate,[25a] is briefly cited here because it could be considered a process where an apparent α-acrylate anion is involved.[25b,26] However, the mechanism implies Michael addition of the amine catalyst (generally DABCO) to the acrylate followed by an aldol addition and subsequent elimination giving the final substituted acrylate and regenerating the catalytic nucleophile (Scheme 9). One of the shortcomings of this

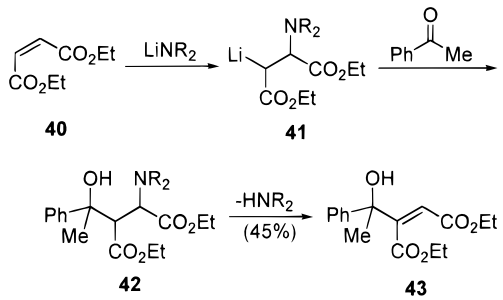
Scheme 9



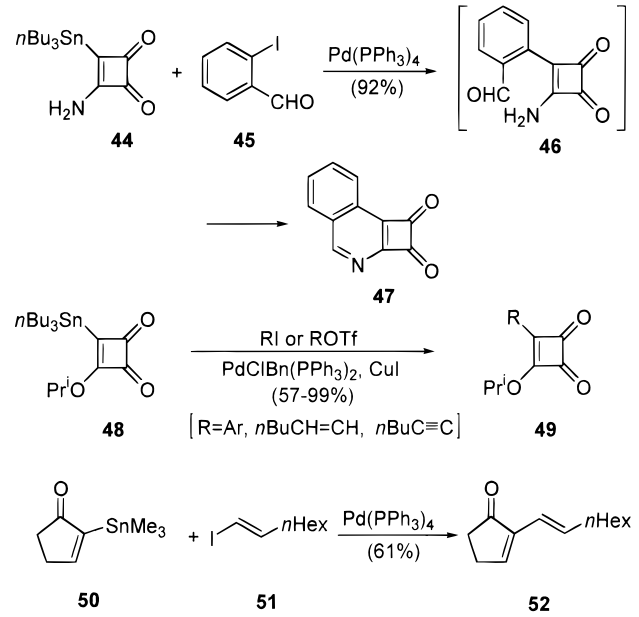
otherwise simple reaction is its very slow reaction rate, often requiring 2 or more weeks for completion. Moreover, it is not applicable to β-substituted alkenes, and extreme reaction conditions are necessary for ketones. However, due to the high synthetic utility of the obtained α-methylene-β-hydroxy esters **39**, an increasing interest has been focused on this reaction, and also asymmetric versions have been developed using optically pure amine[27] or even phosphine[28] catalysts and chiral substrates such as aldehydes[29] and acrylic derivatives.[30]

In addition, when diethyl maleate (**40**) and acetophenone are added to a solution of a lithium amide from benzylamine or tetramethylpiperidine, the maleate derivative **43** was the major product obtained. The reaction proceeds resembling previous examples: Michael addition of the nucleophile-acting amide anion, followed by condensation of **41** with the ketone and final elimination of the amine (Scheme 10).[31]

Scheme 10



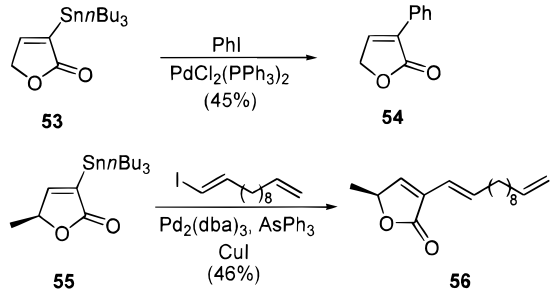
Scheme 11



α-Trialkylstannyl α,β-unsaturated carbonyl compounds can be considered as α-acylvinyl anions when the well-known Stille cross-coupling reaction with vinyl or aryl halides is considered, a powerful methodology which eliminates the need for protection/deprotection strategies necessary with most organometallic reagents.[32] Following this strategy, synthons **1**, **2**, **4**, and **5** have been coupled with sp^2-hybridized halides. For example, palladium-catalyzed reaction of 3-amino-4-(tri-*n*-butylstannyl)cyclobut-3-en-1,2-dione (**44**) with *o*-iodobenzaldehyde provides the product **46** which spontaneously dehydrated to the very unstable pyridine-fused cyclobutenedione **47** (Scheme 11).[33] Tri-*n*-butylstannyl isopropyl squarate (**48**) has been used in studies which showed a dramatic improvement in the rate of the cross-coupling Stille reaction when copper(I) iodide was added as cocatalyst.[34] In these studies, the tri-*n*-stannylcyclobutenedione **48** couples with aryl, alkenyl, and alkynyl iodides under palladium−copper catalysis affording the cyclobutenediones **49**. Attempted extension of this cross-coupling procedure to aryl triflates fails, but proves successful when vinyl triflates in the presence of $ZnCl_2$ and other additives are used.[34] This Stille coupling has also been carried out with compound **48** using solid-supported aryl halides.[35] In addition, 2-(trimethylstannyl)cyclopent-2-enone (**50**) reacts smoothly with (*E*)-1-iodooct-1-ene (**51**) under palladium catalysis affording α-alkenylated enone **52** (Scheme 11).[36]

The 3-tri-*n*-butylstannylfuran-2(5*H*)-one (**53**) can act as a precursor of synthon of the type **5** for the direct introduction of the furanone moiety to suitable functionalized substrates by Stille coupling, particularly for the preparation of pharmacologically active arylfuran-2-(5*H*)-ones. Thus, stannylfuranone **53** is prepared by ipso radical desulfurative stannylation of the corresponding phenylsulfanylfuranone and undergo palladium-catalyzed cross-coupling reaction with aryl iodides such as iodobenzene to give 3-arylfuranones such as **54** (Scheme 12).[37a] This Stille coupling reaction using a similar chiral (*S*)-5-methyl-

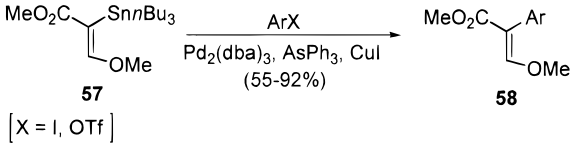
Scheme 12



3-tri-*n*-butylstannylfuran-2-(5*H*)-one (**55**) and (*E*)-1-iodododeca-1,11-diene has been employed in the total synthesis of (+)-hamabiwalactone B (**56**).[37b]

(*Z*)-2-Tri-*n*-butylstannyl-3-methoxypropenoate **57** has been used as a reagent for the direct introduction of a β-methoxypropenoate unit, important for the activity of some fungicides, into substituted aromatic derivatives affording compounds **58**. The method is based in the palladium/copper cocatalyzed cross-coupling reaction between aryl iodides or aryl triflates and the stannyl derivative **57** (Scheme 13).[38]

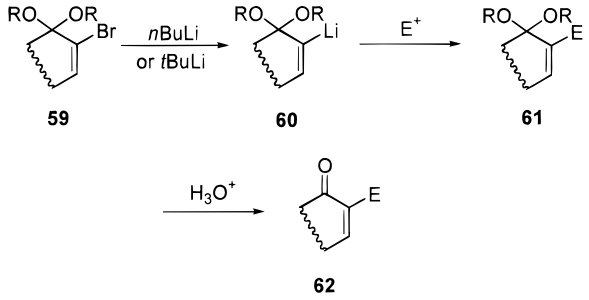
Scheme 13



B. α,β-Unsaturated Protected Carbonyl Compounds

The most direct approach for the construction of a variety of α-substituted α,β-unsaturated ketones directly from the parent enone without the use of the thermodynamic dienolate is illustrated in Scheme 14.

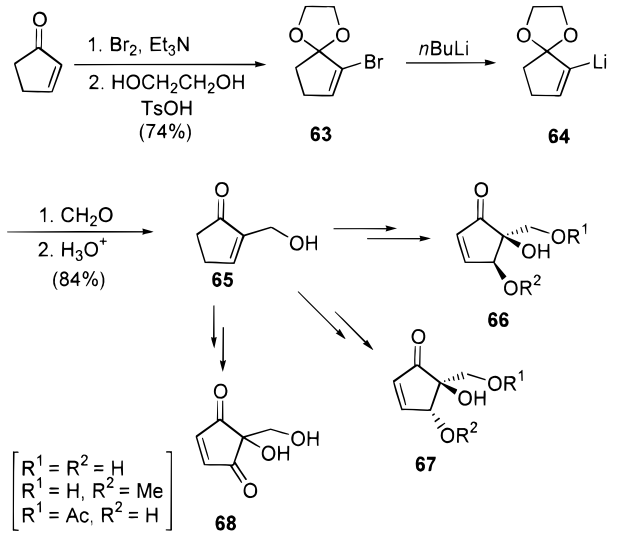
Scheme 14



The procedure employs metalation of ketals of α-bromo-α,β-enones **59**, prepared by bromination-dehydrobromination-ketalyzation of the enone, as a method of creation of a latent equivalent of a α-ketovinyl anion synthon of type **2**. Usually, the protection of the carbonyl group is necessary in the case of organolithium compounds, which generally are prepared by this halogen−lithium exchange. Subsequent electrophilic capture of the lithiated species **60** and hydrolysis of the ketal furnishes the final product **62**.

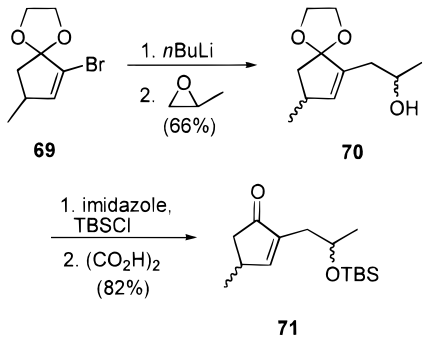
All kinds of electrophiles have been employed with these equivalents,[39−44] which have been used, for example, in the stereospecific total synthesis of cyclopentanoid antibiotics (±)-pentenomycins I−III

Scheme 15



(**66**), their epimers (**67**), and dehydropentenomycin I (**68**) via alcohol **65**[40] as common synthetic precursor[45,46] (Scheme 15). Also, α-bromoketal **69** can be lithiated and treated with propylene oxide affording alcohol **70**, which is transformed into enone **71** (Scheme 16), an intermediate in the synthesis of the

Scheme 16

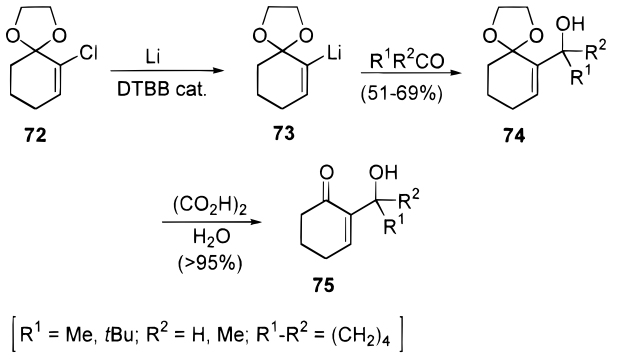


macrocyclic diterpenes (±)-*epi*-jatropone and (±)-jatropone.[47]

Recently, the equivalent lithiated ketal from cyclohexenone has been used in a nucleophilic substitution reaction with an alkyl iodide for the formal synthesis of the cytotoxic arenarol derivative popolohuanone E.[48a] In addition, these carbanions have been added to (−)-menthone for asymmetric cuprate conjugate addition reactions.[48b] The preparation of this type of ketalyzed α-lithiated α,*β*-unsaturated ketones is not limited to the use of α-bromo precursors, but it is also possible to prepare these α-acylvinyl anion equivalents by chlorine/lithium exchange but now using a 4,4′-di-*tert*-butylbiphenyl (DTBB)-catalyzed lithiation of the corresponding chlorinated precursors. Thus, reactions of chloroketals such as **72** with an excess of lithium powder and a catalytic amount of DTBB (4−5%) in THF at low-temperature results in intermediate **74**, which can be treated with electrophiles such as aldehydes or ketones affording, after hydrolysis, the expected enones **75** (Scheme 17).[49]

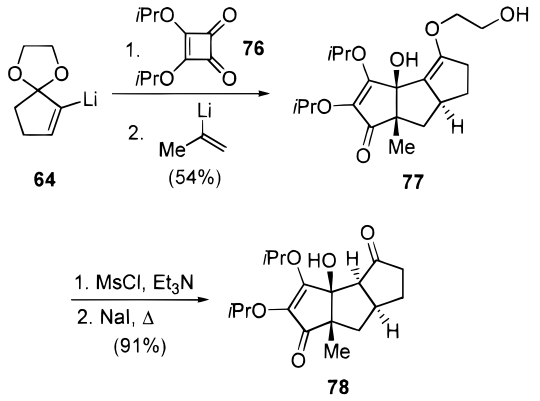
These carbonyl-protected α-acylvinyl anions have been used recently during the conversion of squarate

Scheme 17



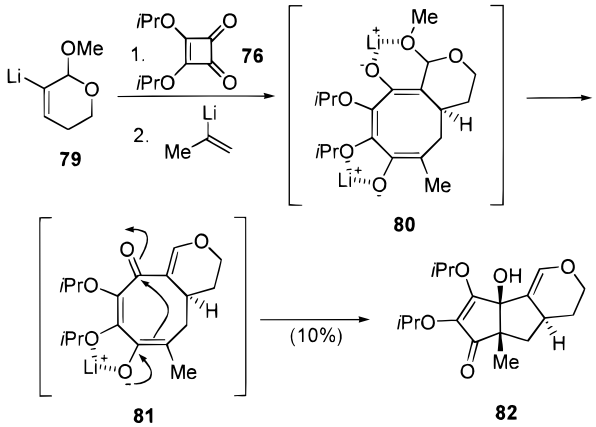
esters into complex polyquinanes.[50] Thus, lithiated species **64** (from bromine/lithium exchange with *tert*-butyllithium) was added to diisopropyl squarate (**76**). Subsequent introduction of 2-lithiopropene gave tricyclic enone **77** which was transformed into triquinane **78** after removing the 2-hydroxyethyl side chain by conversion to the mesylate and heating with sodium iodide in acetone (Scheme 18).[51]

Scheme 18



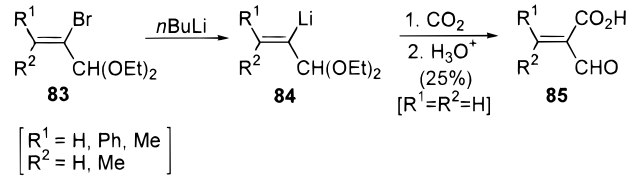
The dihydropyranyl anion **79** could be considered as a masked aldehyde-derived α-acylvinyl anion equivalent. This species, prepared from the bromine derivative by treatment with *tert*-butyllithium, reacts as before with diisopropyl squarate in combination with 2-propenyllithium arriving at bisenolate **80**. From this compound, triquinane **82** is isolated in low yield via intermediate **81** (Scheme 19).[51]

Scheme 19



Organolithium compounds from an acrylate unit with masked carbonyl moiety have been developed as synthons type **1** using the well-known bromine/lithium exchange. In this way, treatment of 2-bromo-3,3-diethoxyprop-1-ene (**83**) with *n*-butyllithium at low temperature allowed the generation of vinyllithium intermediates **84**, which react with electrophiles such as carbon dioxide to give, after hydrolysis, the corresponding α-functionalized acrylic acid **85** (Scheme 20).[52] An analogous lithiated intermediate,

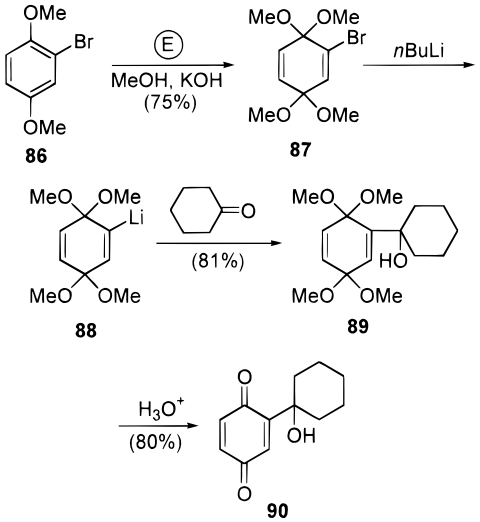
Scheme 20



2-lithio-3,3-dimethoxyprop-1-ene, has also been used for the synthesis of triquinanes following a similar protocol than in Schemes 18 and 19.[51]

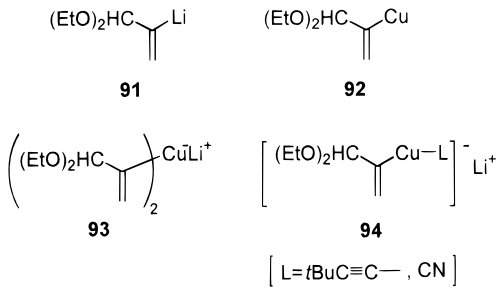
A quinone carbanion synthon type **3** has been obtained through bromine/lithium exchange from bromoquinone diketal **87**, which was prepared by anodic methoxylation of 2-bromo-1,4-dimethoxybenzene. This bromodiene **87** readily metalates with *n*-butyllithium at −70 °C and further reaction of the created organolithium reagent with various carbonyl compounds such as cyclohexanone afforded the corresponding adduct **89** which is hydrolyzed to the substituted quinone **90** (Scheme 21).[53] However,

Scheme 21



these types of lithiated quinone derivatives do not give acceptable results when activated halides are used as electrophiles. Instead, the corresponding organocopper derivatives, prepared by treatment of lithiated ketals such as **88** with cuprous iodide and dimethyl sulfide, react with alkyl halides and are used for the synthesis of different isoprenoid systems.[54]

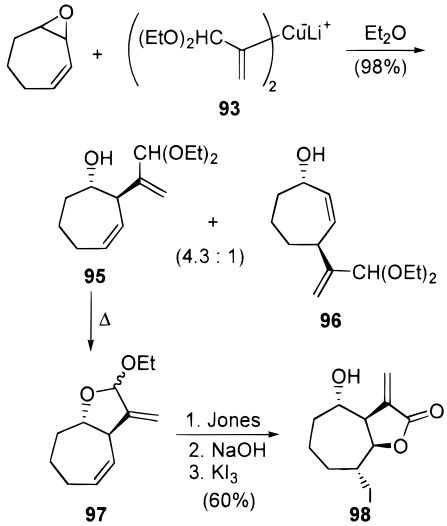
The 2-lithio-3,3-diethoxyprop-1-ene **91** (R^1=R^2=H) has also been used as precursor of organocopper acrolein-derived reagents. Thus, copper reagent **92** is prepared from the reaction of **91** with 1 equiv of



cuprous iodide,[55] while homocuprate **93** is obtained after treatment of 2 equiv of **91** with the 1 equiv of cuprous bromide as the dimethyl sulfide complex.[56] Moreover, mixed acetylenic isopropenyl cuprate **94** (L=*t*BuC≡C−) is prepared by initial generation of copper *tert*-butylacetylide from cuprous iodide and lithium *tert*-butylacetylide followed by addition of the lithium compound **91**,[56] whereas reagent **94** (L = CN) was obtained from cuprous cyanide and **91**.[55]

All these cuprates have been used in different reactions such as Michael additions to cyclic enones[56] or regio- and stereospecific ring opening of 3,4-epoxycycloalkenes.[55] For example, the isopropenyllithium derivative **91** proved ineffective for the opening of different epoxides whereas organocopper reagents **92**−**94** underwent *trans*-1,2 and -1,4 additions to monoepoxides of cycloalkadienes. The 1,2 addition is maximized with the use of ether as the solvent for the synthesis of compounds such as *trans*-hydroxy-*cis*-α-methylene-γ-butyrolactone **98**, a system found in the antitumor natural product helenalin, from the 1,2 opening of the monoepoxide of 1,3-cycloheptadiene (Scheme 22).[55]

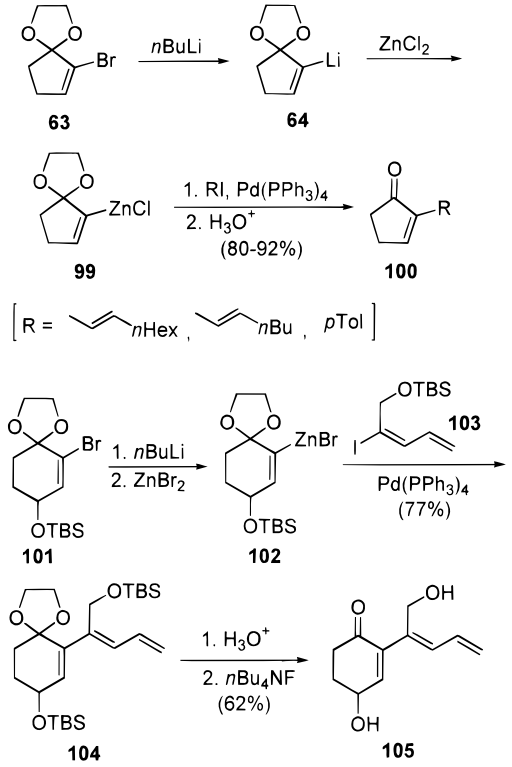
Scheme 22



The protected α-ketovinyl anion equivalent represented by the mentioned ketalyzed vinyllithium intermediate **64** has also been used as precursor in the Negishi palladium(0)-catalyzed coupling[32] for the α-alkenylation or arylation of the organozinc derivative of 2-cyclopentenone. The methodology involves sequential treatment of the organolithium **64** with zinc chloride, followed by palladium(0)-catalyzed cross-coupling reaction between the generated organozinc intermediate **99** and (*E*)-alkenyl iodides or aryl

iodides, in the first case with essentially complete retention (>98%) of geometry in the final α-alkenylated enone **100** (Scheme 23).[57] This coupling meth-

Scheme 23

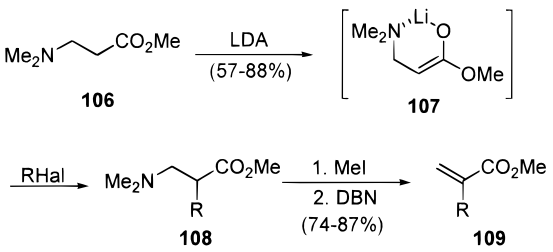


odology has also been used in the synthesis of the marine natural product nakienone B (**105**) starting from bromoketal **101**.[58] Lithiation of **101** and zincation with zinc bromide, followed by Negishi cross-coupling with vinyl iodide **103**, affords nakienone B after removal of the protecting groups (Scheme 23).

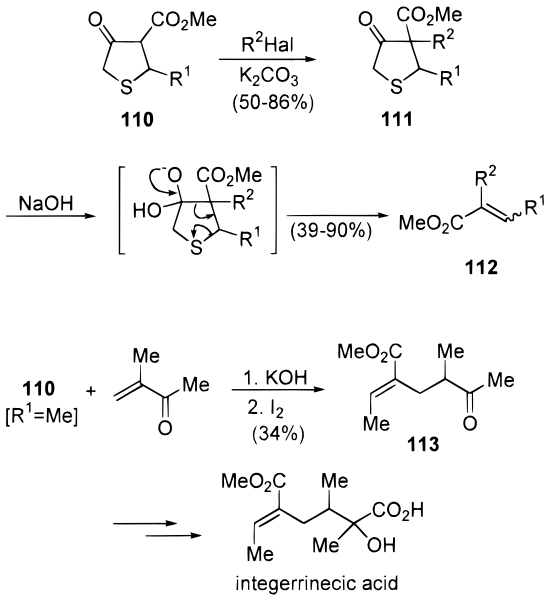
C. Synthetic Equivalents of α,β-Unsaturated Carbonyl Compounds

The lithium enolate **107** of methyl 3-(dimethylamino)propionate (**106**) has been developed as a synthetic equivalent of the α-anion of acrylic ester. This enolate, obtained by treatment of the free ester **106** with lithium diisopropylamide, is very stable, probably due to internal chelation, and is alkylated with alkyl halides giving products **108** which may be considered as protected acrylate esters. Unmasking is accomplished by quaternization with methyl iodide followed by 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)-induced elimination affording acrylates **109** (Scheme 24).[59a]

Scheme 24



Scheme 25



The same type of reaction was reported starting from methyl hydracrylates after alkylation and dehydration.[59b]

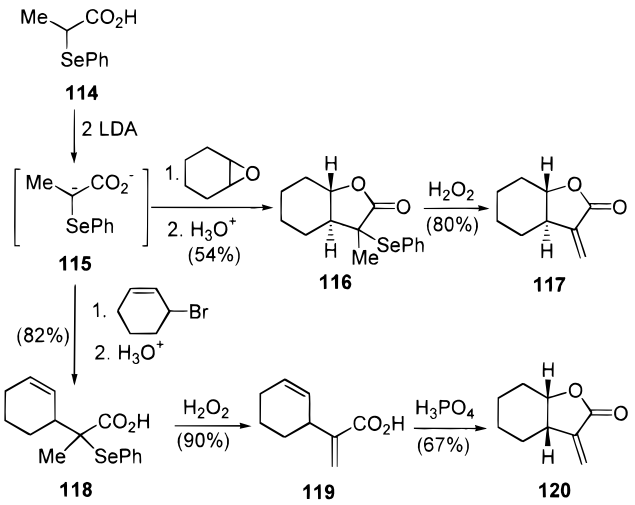
The α-anions of methyl 4-oxothiolane-3-carboxylates **110** can act as masked synthetic equivalents of α-acrylate ($R^1 = H$) and α-crotonate ($R^1 = Me$) anions for the preparation of α-substituted acrylic esters. The procedure involves a tandem of reverse Dieckmann−Michael reactions strategy, starting from alkylation of **110** with activated and unactivated alkyl halides and potassium carbonate and further treatment of alkylated compounds **111** with aqueous sodium hydroxide. Under these conditions, probably the fragmentation shown in Scheme 25 takes place affording final α-substituted acrylates and crotonates **112**.[60,61] This methodology using the crotonate equivalent of **110** ($R^1 = Me$) and isopropenyl methyl ketone in the presence of potassium hydroxide and after iodine-mediated isomerization has been applied to the direct preparation of **113** which constitutes a formal synthesis of the integerrinecic acid.[61]

2-Phenylselenopropanoic acid (**114**) has been used as a synthetic equivalent of the α-anion of acrylic acid synthon **1** (X = OH) for the stereoselective synthesis of *cis* and *trans*-fused α-methylene lactones. When acid **114** is treated with 2 equiv of LDA, the dianion **115** is obtained. Further reaction with cyclohexene oxide or 3-bromocyclohexene gives, after selenoxide elimination, *trans*- or *cis*-fused α-methylene lactones **117** or **120**, respectively (Scheme 26).[62a] Although an α-methyl-α-thiolactone can be obtained directly from the epoxide using a similar starting 2-phenylthiopropanoic acid,[62b] this route circunverts the rather laboriuos sequence to convert the thiolactone into the α-methylene derivative. This selenium-based methodology has been applied to the synthesis of allergenically active lactone sesquiterpene (±)-frullanolide.[63]

III. α-Acylvinyl Cationic Synthons

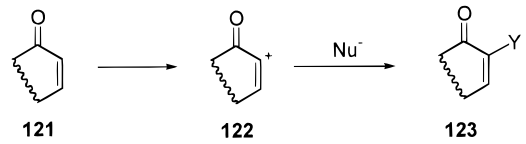
A complementary process to the use of α-acylvinyl anionic synthons (see Section II) for the introduction

Scheme 26

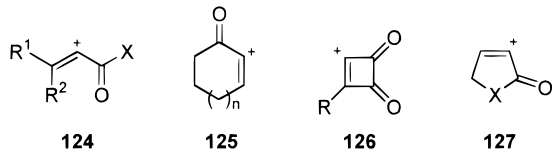


of carbon substituents on the α-carbon of an α,β-unsaturated compound such as **121**, with preservation of the unsaturation, is the use of their cationic counterparts. Consequently, the procedure would involve a reverse polarity (umpolung)[64] strategy with the generation of α-acylvinyl cationic synthons **122** (Scheme 27), which would be considered electronic

Scheme 27

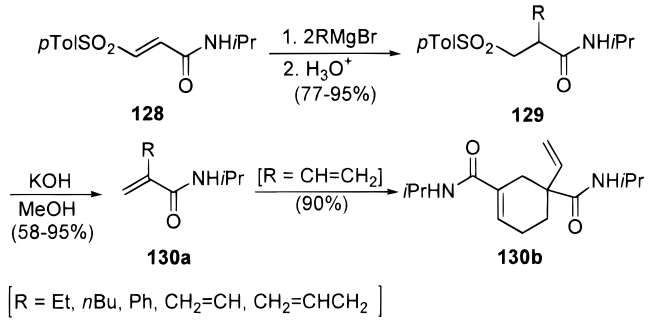


acceptors of the type *a*[2].[3] The present section deals with methods for the preparation and examples of reactivity of cationic α-acylvinyl synthons mainly of the type **124**−**127**.



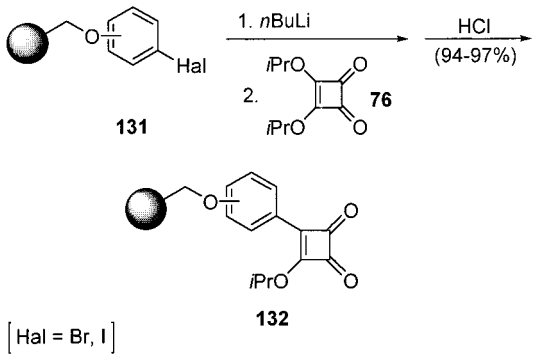
Contrary to the many cases found on the use of α-acylvinyl anion equivalents in the synthesis of α-substituted acrylates (see Section II), the synthetic use of cationic acrylic synthons of the type **124** is not so common, palladium catalyzed coupling reactions being the most used strategy (see below). One example is (*E*)-*N*-isopropyl-3-tosylacrylamide (**128**), easily available from the corresponding acrylamide through an iodosulfonylation-dehydroiodination sequence, which can be considered as a synthon of the type **124** (X = NHPr^i, R^1 = R^2 = H). Thus, reaction of the sulfone **128** with nucleophiles such as organomagnesium reagents and further basic elimination of the sulfone group on amide **129** afforded α-substituted acrylamides **130a** (Scheme 28).[65] In the case of using vinylmagnesium bromide, acrylamide **130a** (R = CH=CH$_2$) suffered spontaneous Diels−Alder dimerization reaction to achieve mikanecic acid diisopropylamide (**130b**).[65]

Scheme 28



Diisopropyl squarate (**76**) can also be considered a synthetic equivalent of synthon **126** when reacted with lithiated solid-supported aryl halides **131**, prepared by reaction of halogenated phenols to Wang resin (Scheme 29),[35] a methodology which has been

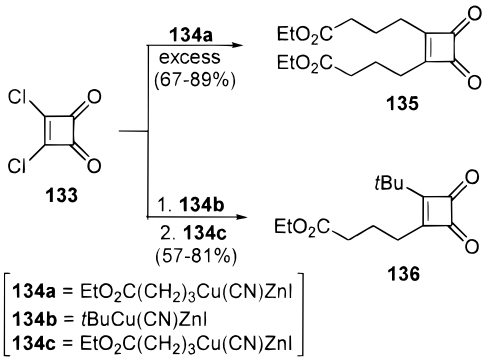
Scheme 29



previously described in liquid phase.[66a,b] The supported squarates **132** have been used in studies toward multiple core structure libraries. This is an example of the difficulty of the direct displacement of a leaving group lying on the α-position of an α,β-unsaturated carbonyl compound, something that only takes place, as in the present case, if the leaving group is also situated in a β-position relative to other carbonyl group.

Similarly, 3,4-dichlorocyclobut-3-en-1,2-dione (**133**) has shown an α (and β-)-acylvinyl cationic behavior when reacted with zinc−copper organometallics **134** for the preparation of functionalized symmetrical and mixed 3,4-disubstituted cyclobutene-1,2-diones of type **135** and **136**, as shown in Scheme 30.[66c]

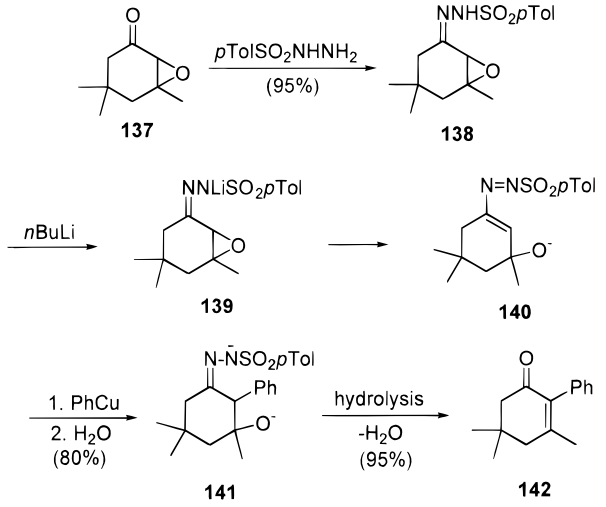
Scheme 30



A developed synthetic equivalent of a synthon type **125** is the α,β-epoxytosylhydrazone **138** from iso-

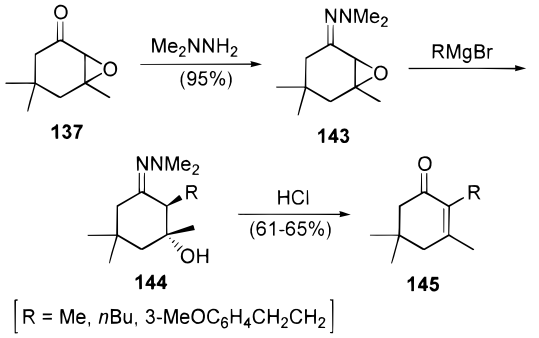
phorone oxide **137**, its use being based on the α-alkylation of α,β-epoxyketones.[67] The base (and acid-)-catalyzed fragmentation of **138** proceeds via an azoene intermediate **140** which, generated in the presence of phenylcopper, can be intercepted to yield α-phenyl-β-hydroxytosylhydrazone **141**. Dehydration and hydrolysis produces the desired enone **142** (Scheme 31).[68]

Scheme 31



Similarly, the *N*,*N*-dimethylhydrazone of the isophorone oxide (**137**) can be used as a synthon type **125**. The sequence is illustrated in Scheme 32 also

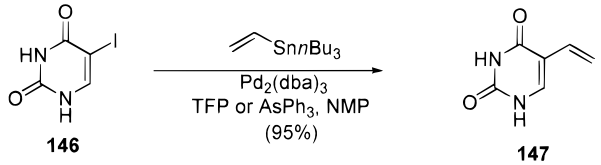
Scheme 32



with isophorone oxide: treatment of **137** with *N*,*N*-dimethylhydrazine gives epoxyhydrazone **143**. Ring opening reaction of this compound with Grignard reagents, followed by elimination afford α-substituted enones **145**.[69]

The already mentioned palladium-catalyzed cross-coupling synthetic methodologies[32] can obviously be oriented in a different way, exchanging the role of the α,β-unsaturated carbonyl compound and the vinyl or aryl species. Thus, if a halogen is now at the α-position of the carbonyl component and the appropriate metal lies on the vinyl or aryl species, the α-halo-α,β-unsaturated carbonyl compound can be considered precursors of α-acylvinyl cationic synthons. However, sometimes the rather low reactivity and certain instability of α-haloenones[37] have made it necessary to introduce improvements in the typical methodology. One example is the Stille coupling reaction between 5-iodouracil (**146**) and vinyl tri-*n*-butyltin (Scheme 33). Modifications include changes

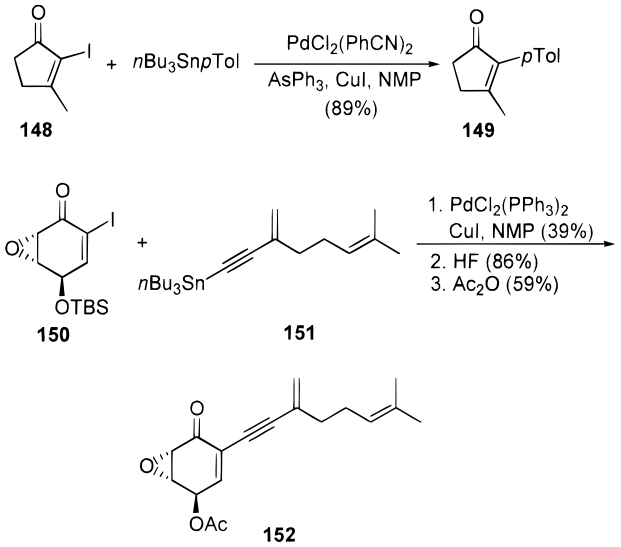
Scheme 33



to highly polar solvents [*N*-methylpyrrolidinone (NMP) instead of THF] and in the catalyst ligands [soft tri-2-furylphosphine (TFP) or triphenylarsine instead of triphenylphosphine], which achieved large reaction rate accelerations.[70a] Under these conditions, 2-aryl and 2-alkenyl-3-alkoxy-cyclohexenones have been prepared starting from 2-bromo-3-methoxycyclohex-2-enone[70b] These conditions have also been employed in couplings of α-bromoenones used in studies toward the synthesis of dynemicin A.[70c] Recently, even a silica-supported palladium catalyst has been used for alkenylation of iodouridine.[70d]

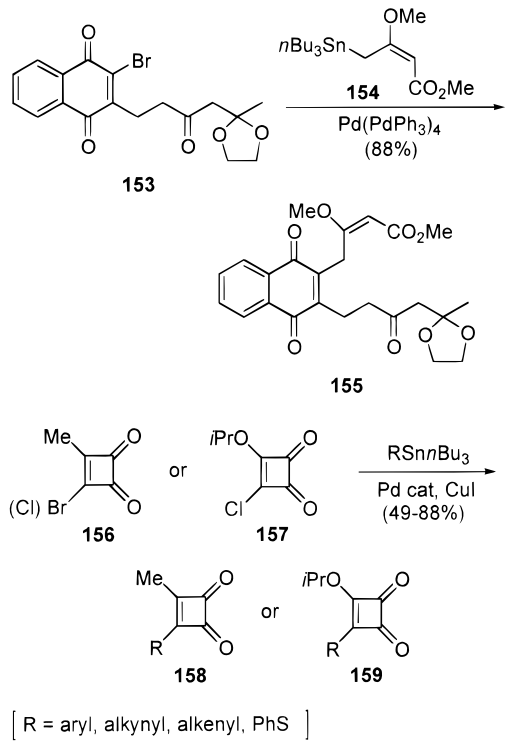
These modified Stille conditions, together with the mentioned observation that copper(I) iodide cocatalyzes Stille coupling[35,71] provided an efficient route to α-vinyl and α-aryl substituted enones starting from α-haloenones. Examples of this cross-coupling reaction are the synthesis of 3-methyl-2-*p*-tolylcyclopent-2-enone (**149**) from 2-iodo-3-methylcyclopent-2-enone (**148**)[72] (Scheme 34) or α-arylcyclohexenones

Scheme 34



from 2-iodocyclohex-2-enones.[73] The first mentioned iodoenone has been recently coupled with vinyl and arylstannanes for the synthesis of a series of fungicides.[74] Moreover, acetylenic stannanes have also been used under these reaction conditions, as is shown in the coupling reaction between iodoenone **150** and stannane **151**, for the synthesis of the enynylcyclohexenone antimitotic (−)-tricholomenyn A (**152**) (Scheme 34).[75] Other similar enynylcyclohexenones with anti-cancer properties such as harveinone and *epi*-harveinone have been prepared following this methodology[76] and also an angucycline oligoketide precursor **155** from bromonaphthoquino-

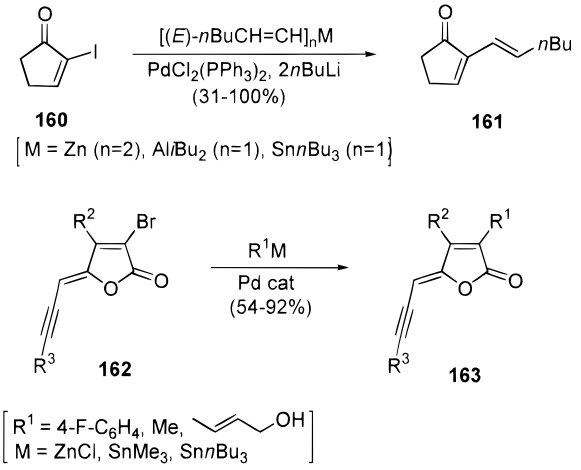
Scheme 35



ne **153** and allylstannane **154** (Scheme 35).[77] In addition, 3-chloro or 3-bromo-4-substituted cyclobut-3-en-1,2-diones **156** or **157** have been coupled with different stannanes under copper cocatalyzed Stille conditions (Scheme 35).[71]

Cyclic α-iodoenones (and also α-trifluoromethanesulfonyloxyenones) can react not only with vinylstannanes but also with alkenylmetal derivatives containing zinc or aluminum under palladium catalysis yielding the corresponding α-alkenylenones, as shown in Scheme 36 for 2-iodocyclopent-2-enone (**160**).[36a]

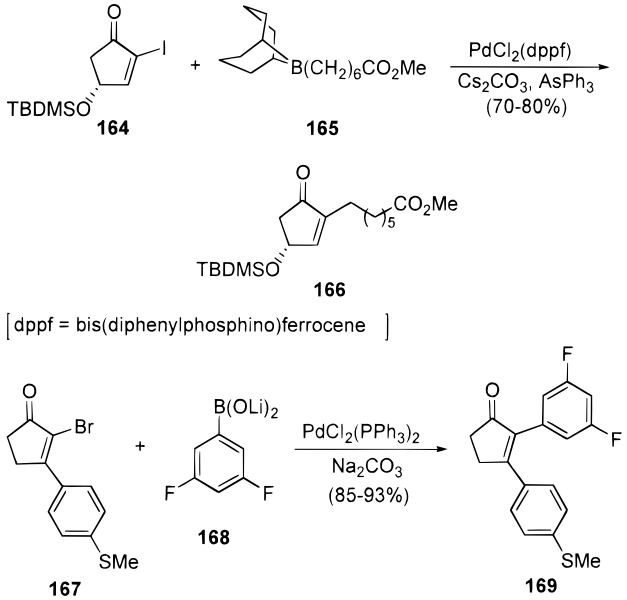
Scheme 36



The use of a polar solvent such as DMF, DMSO, or NMP proved to be essential, and the active palladium catalyst is generated in situ by treating thermally stable $PdCl_2(PPh_3)_2$ or $PdCl_2[P(2\text{-furyl})_3]_2$ with *n*-butyllithium. Furthermore, (*Z*)-3-bromo-alkylidenebutenolides **162** are able to undergo these palladium-catalyzed cross-coupling Negishi reactions with arylzinc halides,[32] and also tetraalkylstannanes or alkenylstannanes, providing the corresponding 3-substituted (*Z*)-5-ylidene-(5*H*)-furan-2-ones **163**[78] (Scheme 36).

The Suzuki reaction for the palladium(0)-catalyzed cross-coupling of boronic acids or alkylboranes with aryl or alkenyl halides[32] has been applied to the case of α-iodoenones.[73,79] An example is the preparation of α-substituted enone **166**, which is a precursor of PGE_1 and is obtained by coupling between the α-iodocyclopent-2-enone **164** and the borane **165**[79a] (Scheme 37). Recently, α-bromoenone **167** has been

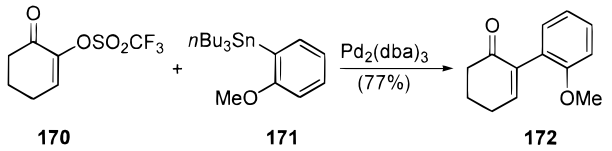
Scheme 37



coupled with boronate salt **168** to afford diarylcyclopent-2-enone **169** (Scheme 37), which after oxidation of the sulfide group to the corresponding sulfone, displays high selectivity and potency against cyclooxygenase-2, an enzyme responsible for the elevated production of prostaglandins during inflammation.[79b]

In some cases, α-trifluoromethanesulfonyloxyenones couple smoothly with arylstannanes in typical Stille conditions, although the use of *N*-methylpyrrolidinone as solvent was necessary. This has been shown in the reaction of vinyl triflate **170** with stannane **171** (Scheme 38).[80a] The same triflate **170**

Scheme 38

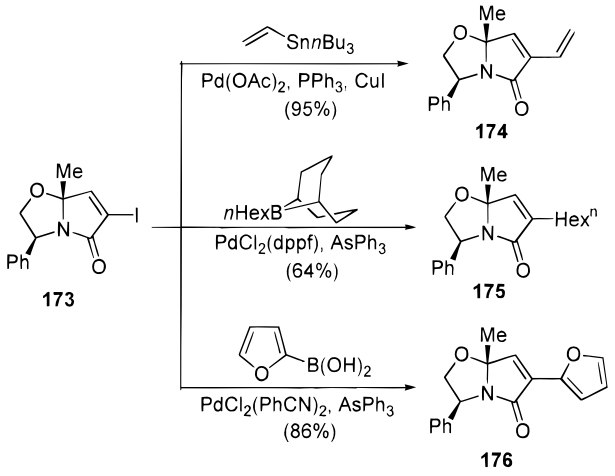


has been used in the synthesis of the allyltrimethylsilane derivative by cross-coupling with in situ generated tris((trimethylsilyl)methyl)aluminum catalyzed by palladium(0).[80b]

α-Halo-α,β-unsaturated bicyclic lactams, such as **173**, undergo conversion to a variety of coupled products when the above-mentioned modified Stille

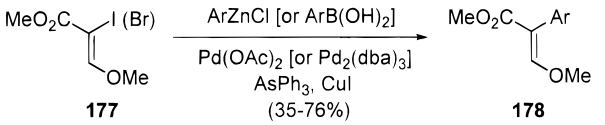
and Suzuki conditions are used.[81] Examples of these transformations are shown in Scheme 39.

Scheme 39



The direct introduction of the agrochemically important β-methoxypropenoate unit into aromatic derivatives have also been achieved by Negishi or Suzuki cross-coupling reactions[32] between arylzinc chlorides or arylboronic acids and methyl (*Z*)-2-iodo-3-methoxypropenoate or (*Z*)-2-bromo-3-methoxypropenoate **177**, respectively, affording (*E*)-2-aryl-3-methoxypropenoates **178** (Scheme 40).[82a] Moreover,

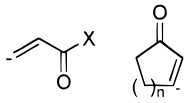
Scheme 40



organozinc halides have been coupled recently with α-diketone-derived nonaflates.[82b] In addition, α-bromoacrylates have been coupled with acetylenic compounds under palladium(0) catalysis[82c] (Sonogashira coupling[32]).

IV. β-Acylvinyl Anionic Synthons

β-Acylvinyl anions of the type **179** or **180** can be considered as sp^2-hybridized umpoled synthons of the



type d^3 [3] and are appropriate intermediates to provide a β-bonded α,β-unsaturated functionality when reacted with electrophiles, the *E* final stereochemistry being generally obtained in the case of **179**. Precursors of these synthons have been divided, similarly to the case of α-acylvinyl anion synthons, into carbonyl-unprotected systems (usually carboxylic acid derivatives), carbonyl-protected systems (from aldehydes, ketones, and even esters), and the corresponding equivalents.

A. α,β-Unsaturated Unprotected Carbonyl Compounds

Carbanionic intermediates of type **179** can be prepared by direct deprotonation of acrylic systems but always at low temperature in order to avoid side reactions, most notably rearrangement to the thermodynamically most stable α-acylvinyl anion (see Section IIA).[4,6,7] The presence of an electron-donating or -withdrawing group at the β-position of the starting α,β-unsaturated carbonyl compound is convenient to achieve stabilization. Thus, lithium intermediates of the type **181** can be considered as sp^2-hybridized

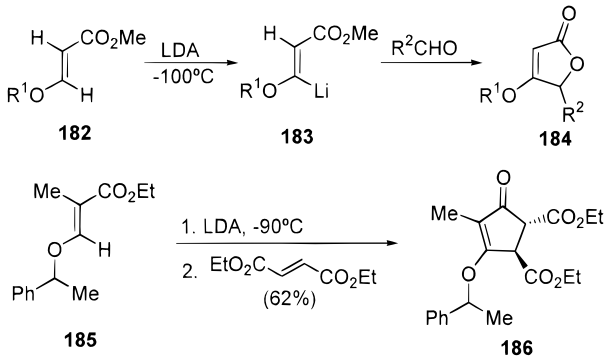
181

[X = H, R, RO, RS, R_2N, Cl, Br, RSO, RSO_2 ; Z = CO_2Li, CO_2R, CONLiR, $CONR_2$, CN]

homoenolate equivalents and are prepared in general by deprotonation of the corresponding activated precursors, containing usually the carboxylic acid derivatives functionality. Of course, further substitution on the α-position of reagents of the type **181** ensures an efficient β-deprotonation.

Therefore, direct deprotonation to achieve acrylic or acrylate reagents type **181** (X = OR, SR; Z = CO_2-Li or CO_2R) followed by reaction with electrophilic−nucleophilic species, as for instance with aldehydes, ketones, α,β-unsaturated carboxylates, or epoxides, represents an access to butenolides, tetronates, cyclopentenones, or δ-lactones, respectively.[9,83−86] Examples of these types of reagents are β-C-lithiated acrylates **183**, which are intermediates for the synthesis of tetronates **184** after reaction with aldehydes (Scheme 41).[8,10,12,87,88] Using α-chloroaldehydes, *erythro*-

Scheme 41

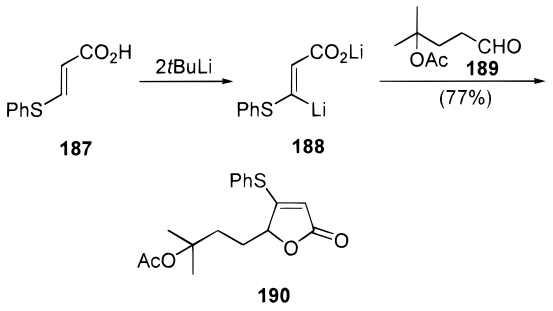


dihydroxycarboxylic acid lactones have been prepared starting from dianion **181** (Z = CO_2Li, X = SEt).[83] The synthesis of tetronates using this methodology has been made diastereoselective by using chiral β-alkoxy[89−91] or even β-amino[89] acrylate derivatives and has been employed, for example, for the synthesis of a (−)-vertinolide precursor.[91] However, the use of systems such as racemic **185** for the preparation of cyclopentenones **186** afforded rather low stereocontrol (2:1 diastereomer ratio) (Scheme 41).[92]

Similarly, β-lithiated β-amino-substituted acrylate derivatives type **181** (X = R_2N; Z = CO_2Me or CO_2-Et) have also been employed for the synthesis of tetronates,[93] butenolides,[94] and cyclopentenones,[94] as well as β-lithiated β-amino-[95,96] or thio-substituted[97] acrylamides. Even (*E*)-cinnamic esters (**181**, X = Ph; Z = CO_2Et) can be metalated at the β-position with

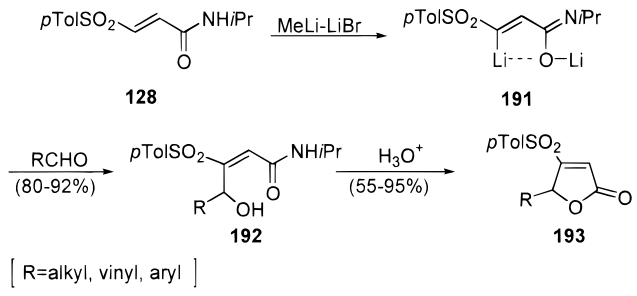
lithium diisopropylamide and react stereoselectively with electrophiles.[11] In addition, (*E*)-*β*-substituted nitriles (**181**, X = R_2N, OR, SR; Z = CN) can be kinetically lithiated at low temperature (<−100 °C) at the *β*-position.[6,7] Another interesting example of the use of these reagents is the preparation of lactone **190**, an intermediate in the total synthesis of the pheromone (±)-eldanolide, by reaction of metalated *β*-phenylthio acrylic acid **188** with aldehyde **189**[98] (Scheme 42).

Scheme 42



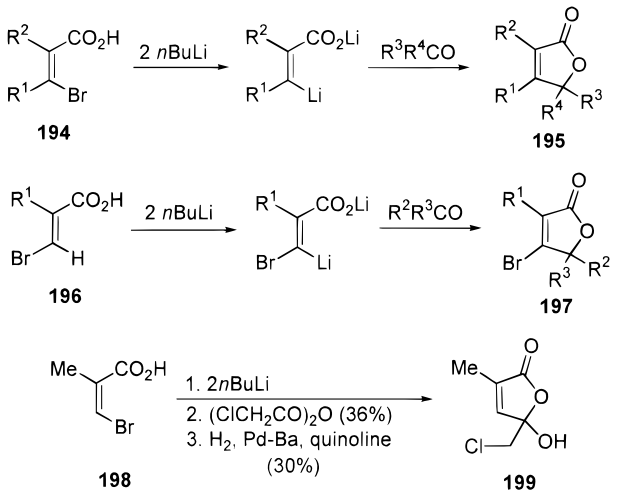
(*E*)-*N*-Isopropyl-3-(*p*-toluenesulfonyl)acrylamide (**128**), prepared as mentioned previously from *N*-isopropylacrylamide by a tandem iodosulfonylation-dehydroiodination reaction,[99] could give a reagent type **181** (X = *p*-$TolSO_2$; Z = CONLiR) which uses the stabilizing and directing effect of the sulfonyl group in metalation reactions. Thus, reaction of vinyl sulfone **128** with methyllithium−lithium bromide complex gives regio- and stereoselectively the dianion **191**, which by treatment with aldehydes yields alcohols **192**. These compounds are transformed into 4-substituted-3-(*p*-toluenesulfonyl)-α,*β*-butenolides **193** by acid hydrolysis. The total retention of configuration observed in alcohols **192** is probably achieved by intramolecular complexation in dianion **191** (Scheme 43).[100]

Scheme 43

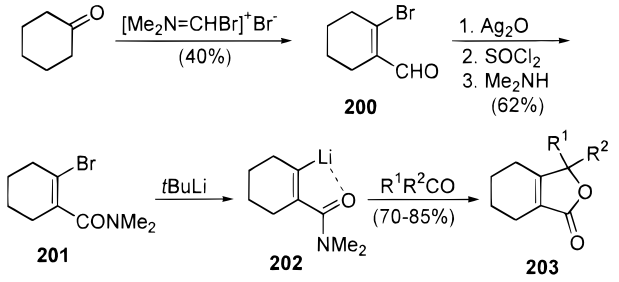


Lithium (*Z*)-*β*-lithioacrylates (**181**, X = H, R; Z = CO_2Li) or lithium (*E*)-*β*-bromo-*β*-lithioacrylates (**181**, X = Br, Z = CO_2Li) have been prepared from halogen−metal exchange of the corresponding (*Z*)-*β*-bromo acids **194** with 2 equiv of butyllithium or by deprotonation of (*E*)-*β*-bromoacrylic acids **196** under similar reaction conditions. In the later case, stabilization of the lithium anion by the carboxylate system accounts for achieving deprotonation instead of halogen−lithium exchange. Further reaction with aldehydes or ketones afforded butenolides **195**[101] and *β*-bromo-butenolides **197**[102] (Scheme 44), a methodology used in the synthesis of some bromobutenolide antibiotics.[103,104] When anhydrides where used as electrophiles, *γ*-hydroxybutenolides were obtained, which as been applied, for example, to the synthesis of the antibiotic lepiochlorin (**199**) (Scheme 44).[105] Moreover, fused bicyclic butenolides **203** have also been prepared by bromine−lithium exchange, but starting from bromo amide **201**. This compound was obtained by condensation of cyclohexanone with the bromo Vilsmeier reagent, followed by oxidation and amidation. Subsequent reaction of the lithio derivative **202** with aldehydes and ketones yielded the final α,*β*-unsaturated lactones **203** (Scheme 45).[106]

Scheme 44

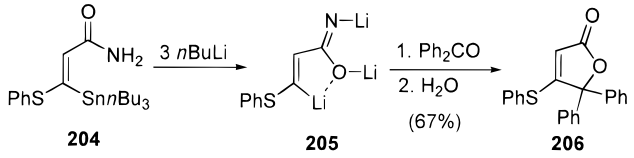


Scheme 45



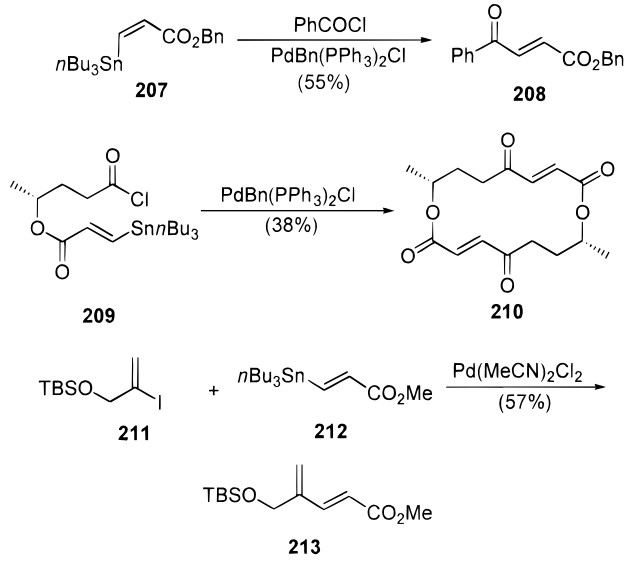
Stable *β*-lithioacrylamide reagents type **181** (X = OEt, SPh; Z = $CONLi_2$, CONLiR) have been prepared by tin−lithium transmetalation and used for the construction of functionalized butenolides. Thus, *β*-(tri-*n*-butylstannyl)acrylamides such as **204**, obtained by reaction of chlorosulfonyl isocyanate with phenyl 1-(tri-*n*-butylstannyl)vinyl thioether followed by treatment with sodium hydrogen sulfite,[107] undergo transmetalation with butyllithium with generation of the tri-anion **205** which was both regio- and configurationally stable, presumably due to the formation of a chelated intermediate. Reaction of this intermediate with a carbonyl compound such as benzophenone gave butenolide **206** (Scheme 46).[108,109] Even bis-stannylacrylates have been explored, although without success, as synthetic equivalents of the acrylate *β*,*β*-dianion.[110] In addition, an alkenylstannane has been recently used in a copper(I)-mediated coupling with an iodoalkene in the synthesis of the hypocholesterolemic agent 1233A.[111]

Scheme 46



Obviously, instead of a tin−lithium transmetalation, β-stannyl substituted α,β-unsaturated carbonyl compounds can be used to introduce an acylvinyl moiety in electrophilic centers by the well-known Stille palladium-catalyzed reaction.[32] One example is the coupling of β-stannyl acrylate **207** with benzoyl chloride to give (*E*)-β-benzoylacrylate **208** (Scheme 47).[112] The vinyl group transfers with retention of the

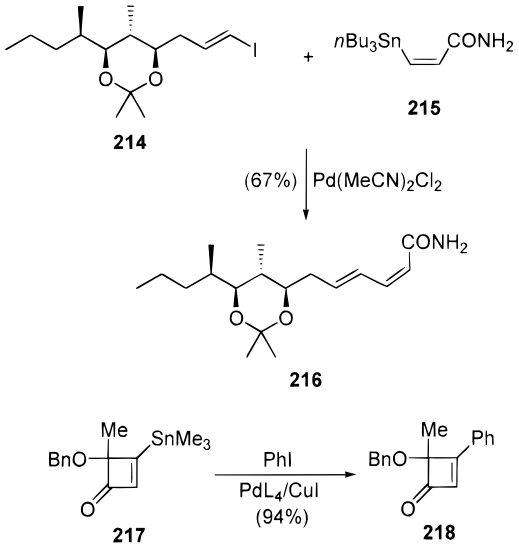
Scheme 47



geometry at the double bond; however, isomerization of the α,β-unsaturated ketone takes place rapidly and the thermodynamic product ultimately is observed in the coupling product. This kind of coupling between β-stannyl alkenoates and acid chlorides has been employed intramolecularly for the synthesis of α,β-unsaturated γ-oxo-macrolides,[112−115] as shown in Scheme 47 for the final step in the asymmetric synthesis of antifungal antibiotic macrodiolide (−)-(*R*,*R*)-pyrenophorin **210**.[115] Moreover, these stannyl derivatives have been cross-coupled with vinyl iodides[116] such as **211** yielding acrylate **213**, which is a precursor in the synthesis of a metabolite of the α-amino acid hypoglycin (Scheme 47).[117] There are also reported examples of coupling with aryl iodides[109] as well as with vinyl triflates.[118]

(*Z*)-Tributylstannyl acrylamide **215** has been coupled with vinyl iodide **214** to give dienamide **216**, in a key step for the total synthesis of the enantiomer of naturally occurring antifungal antibiotic YM-47522 (Scheme 48).[119] On the other hand, β-trimethylstannylcyclobutenones undergo facile coupling with aryl halides,[120] which has been recently employed in the synthesis of 4-substituted cyclobutenone **218** from the trimethylstannyl derivative **217** and iodobenzene (Scheme 48).[121a] Recently, 3,4-bis(tributylstannyl)−(5*H*)-furanones have been used in highly regioselec-

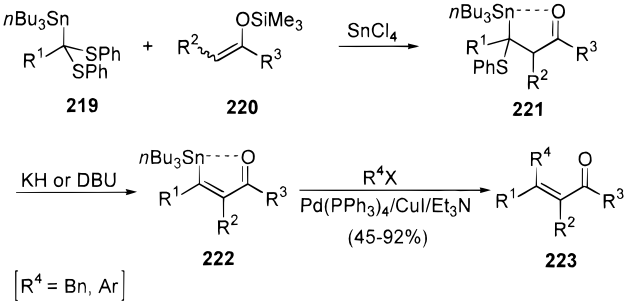
Scheme 48



tive Stille reactions to give 3-(tributylstannyl)-4-aryl-(5*H*)-furan-2-ones.[121b]

β-Tributylstannyl-α,β-unsaturated ketones **222** have been coupled with benzyl or aryl halides using the palladium(0)/copper(I) catalytic mixture, giving tri- and tetra-substituted enones **223** with high stereoselectivity, the yields being improved in the case of aryl iodides with the presence of triethylamine as additive (Scheme 49).[122] The starting materials **222**

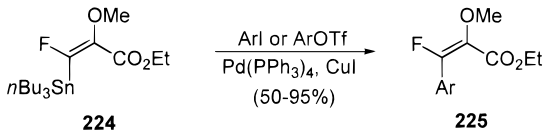
Scheme 49



were prepared by tin(IV) chloride-promoted coupling reaction of α-tributylstannylthioacetals **219** with silyl enol ethers followed by treatment with base.[123]

(*Z*)-β-Substituted β-fluoro-α-methoxyacrylates **225**, which are precursors of biologically interesting β-fluoro-α-ketoacids, have been obtained by reaction of the corresponding stannyl derivatives **224** with aryl iodides or triflates and also a vinyl triflate under palladium(0)/copper(I)-cocatalyzed conditions (Scheme 50).[124]

Scheme 50

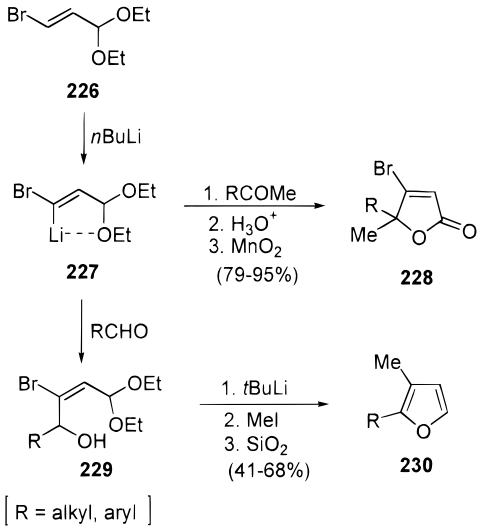


B. α,β-Unsaturated Protected Carbonyl Compounds

Other methodologies toward the preparation of synthetic equivalents of β-acylvinyl anionic synthons

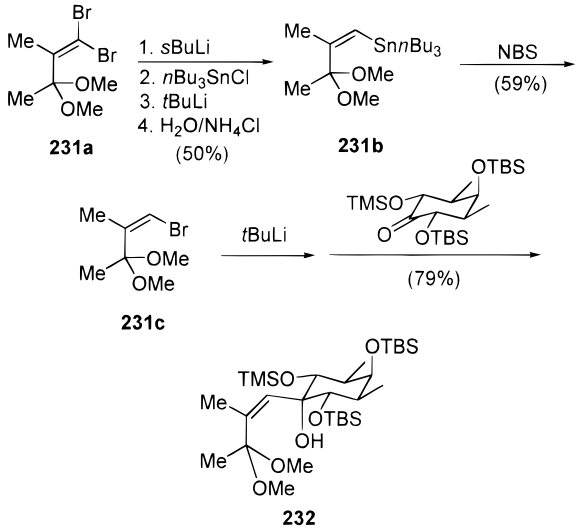
follow a "defensive" strategy, that is, the temporary masking of the carbonyl group as ketals, acetals, or ortho esters in order to avoid side reactions as in the case of α-acylvinyl anionic synthons (Section IIB.) These methodologies have been applied mainly in the case of aldehyde or ketone-derived β-acylvinyl anions. One example is the diethyl acetal of 3-bromoacrolein **226**, which when treated with *tert*-butyllithium at low temperatures (−120 °C), suffer halogen−metal exchange, whereas the use of *n*-butyllithium and higher temperatures led to proton abstraction at the β-position. Subsequent reaction of the later lithiated species **227** with aldehydes or ketones yielded unsaturated bromolactols which were oxidized to bromobutenolides **228**. On the other hand, treatment of intermediate **227** with aldehydes gave the corresponding alcohols **229** which, after halogen−metal exchange and alkylation with methyl iodide, can be transformed into furans **230** after hydrolysis and dehydration (Scheme 51).[125] Moreover, bromine−

Scheme 51



lithium exchange on bromo ketal **231c**, prepared from the corresponding β,β-dibromo enone ketal **231a** by a metalation-stannylation-metalation-protonation se-

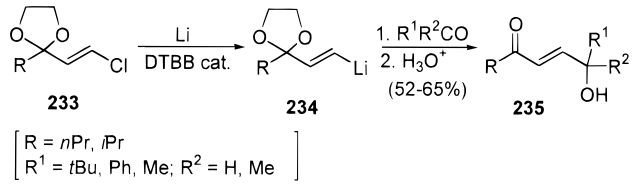
Scheme 52



quence followed by treatment with *N*-bromosuccinimide, have been used for the synthesis of alcohol **232**, which is an intermediate in the total synthesis of the tetramic acid antibiotic (±)-tirandamycin A (Scheme 52).[126]

The above-mentioned deprotonation vs debromolithiation competition in protected β-bromo α,β-unsaturated carbonyl compounds has been overcomed by the total chlorine−lithium exchange starting from (*E*)-chloroketals **233**. The metalation process can be achieved by using lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) as electron carrier at −90 °C, giving carbonyl-protected lithiated intermediate **234**, which reacted with different electrophiles yielding (*E*)-β-substituted ketones **235**, after hydrolytic deprotection (Scheme 53).[127] The

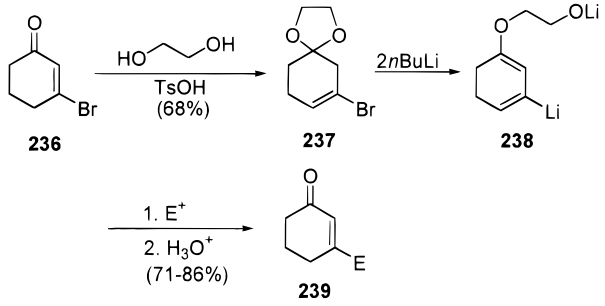
Scheme 53



same methodology has been used starting from a similar ketal from 3-chlorocyclohex-2-enone[49] and also has been applied to 3-bromo-2-methyl-2-cyclopentenone ketal as well as to five- and six-membered 3-bromocycloenone dithioketals.[128]

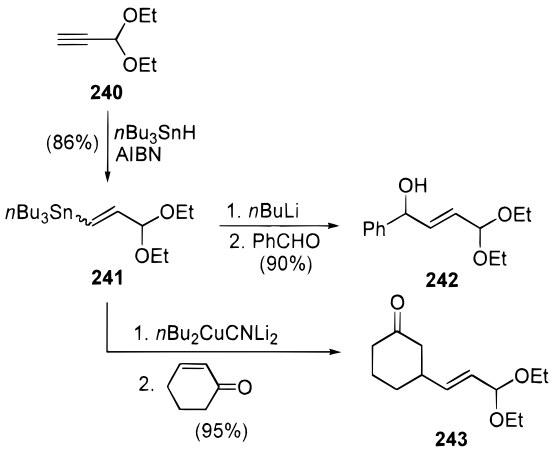
Synthetic equivalents of the β-vinyl carbanion synthon of cyclohexenone **180** are also available from treatment with 2 equiv of *n*-butyllithium of 3-bromocyclohex-3-enone ketal **237**, obtained after ketalization of enone **236**. This process afforded after β-elimination lithiated conjugated diene intermediate **238**, which undergoes reaction with aldehydes, ketones and reactive alkyl halides giving 3-substituted cyclohexenones **239** after hydrolytic workup (Scheme 54).[128,129]

Scheme 54



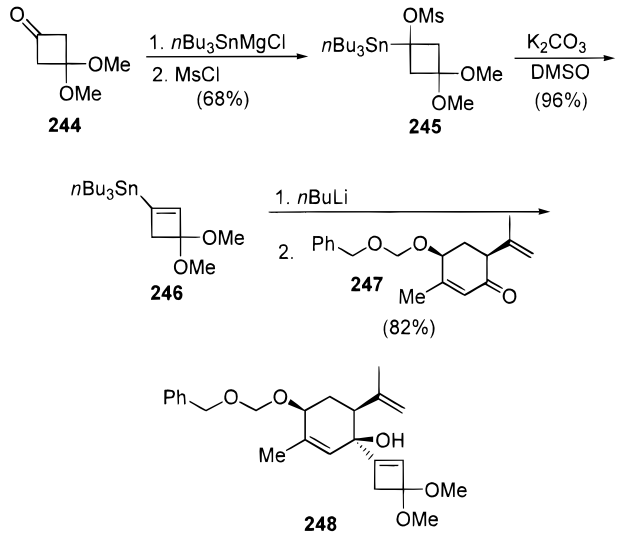
The tin−lithium exchange has also been used for the preparation of masked β-acylvinyl anion equivalents, as shown in Scheme 55 for the transmetalation of 1-tributylstannyl-3,3-diethoxyprop-1-ene (**241**), obtained with a *Z*:*E* = 16:84 ratio by radical hydrostannylation of 3,3-diethoxypropyne (**240**).[130a] Alternatively, compound **241** can be prepared cleanly as a pure *E* or *Z* isomer by treatment of 3,3-diethoxyprop-1-yne with Lipschutz reagent [$Bu_3SnCu(Bu)CNLi_2$][130b,c] or titanium isopropoxyde followed by hydrolysis,[130d] respectively. Treatment of the stannyl acetal **241**

Scheme 55



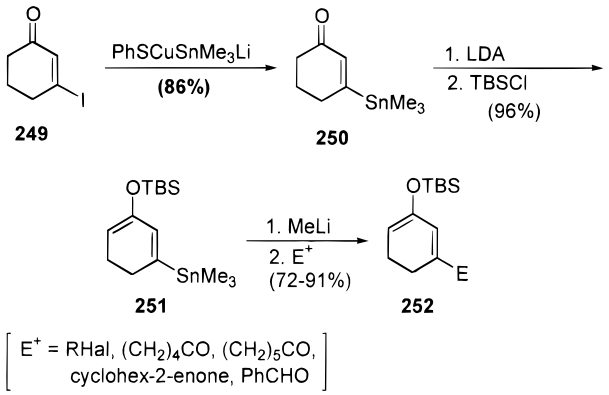
with *n*-butyllithium at −120 °C followed by reaction with electrophiles such as benzaldehyde afforded (*E*)-alcohol **242** as a direct precursor of a *β*-substituted acrolein.[130a] Interestingly, transmetalation of the starting acetal **241** with $Bu_2CuCNLi_2$ gave access to a vinyl cuprate reagent stable to room temperature ready for the introduction of a *β*-formylvinyl anion equivalent to α,*β*-enones such as cyclohexenone (Scheme 55).[130a] This tin−lithium transmetalation has also been used in the case of cyclobutenyltin reagent **246**, prepared from ketal **244**. Lithiation of **246** and addition of the enone **247** gave coupled adduct **248**, a key intermediate in the synthesis of cytotoxic germacranolide eucannabinolide (Scheme 56).[131]

Scheme 56



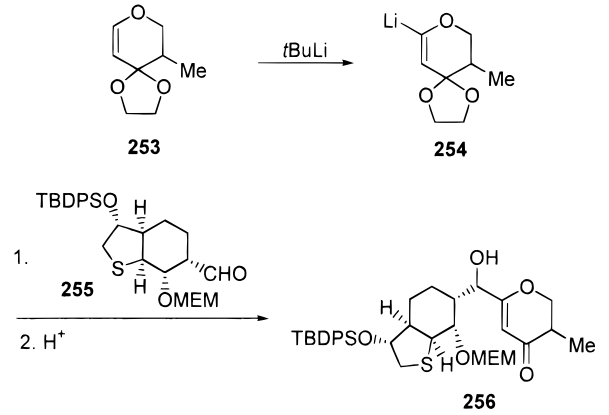
β-Iodoenones such as *β*-iodocyclohex-2-enone **249** can be transformed into the corresponding *β*-trimethylstannyl derivatives **250** by reaction with phenylthio(trimethylstannyl)cuprate. Treatment of **250** with lithium diisopropylamide followed by addition of *tert*-butyldimethylsilyl chloride afforded the silyl enol ether **251**. Transmetalation of this compound with methyllithium and reaction with electrophiles afforded substituted 1,3-cyclohexadienes **252**, which are direct precursors of *β*-substituted 2-cyclohexenones (Scheme 57).[132]

Scheme 57



Direct deprotonation on racemic dihydropyran **253** using *tert*-butyllithium afforded vinyllithium derivative **254**, which reacted with aldehyde **255** to give compound **256**, an intermediate in the total synthesis of (±)-breynolide, an aglycon derivative of the potent, orally active hypocholesterolemic glycoside breynin A (Scheme 58).[133]

Scheme 58

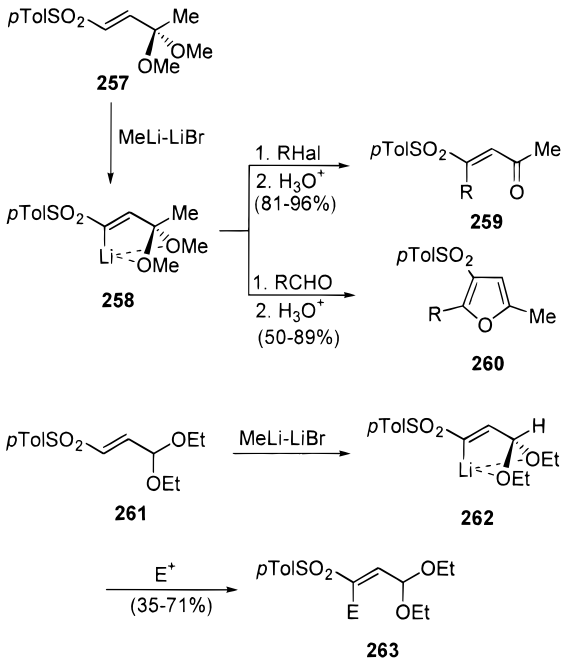


Kinetic *β*-deprotonation of *β*-sulfonyl-substituted protected enones such as (*E*)-4-(*p*-toluenesulfonyl)-butenone dimethyl ketal (**257**), takes place in a stereoselective manner with formation of stabilized (*E*)-vinyllithium **258**. Reaction of this intermediate with different alkyl halides gave stereoselectively the corresponding *E*-sulfonyl enones **259** after acid hydrolysis, whereas the reaction with aldehydes yielded 3-sulfonylfurans **260** or even monoprotected enediones when acyl chlorides or isocyanates were used (Scheme 59).[134] Similarly, sulfonyl acetal **261** acts as a precursor of a *β*-formylvinyl anion equivalent, affording the lithiated vinylic sulfone **262** according to Scheme 59. Electrophilic trapping of **262** with aldehydes, methyl iodide, and acyl chlorides afforded the expected substituted vinylic sulfones **263**.[135]

2-Alkyl-3-phenylthiofurans **266** have been prepared following a protocol that involves deprotonation of vinyl sulfide **264** with *sec*-butyllithium to give intermediate **265**. Quenching this anion with an appropriate aldehyde and final acid treatment affords the desired 3-(phenylthio)furans **266** (Scheme 60).[136]

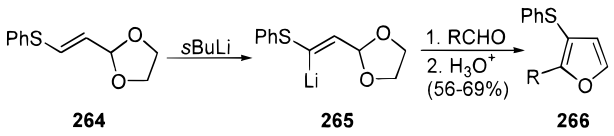
1-Vinyl-4-methyl-2,6,7-trioxabicylo[2.2.2]octane derivatives **268** can be considered as carboxylate-protected equivalent of the *β*-acrylate anion synthon.

Scheme 59



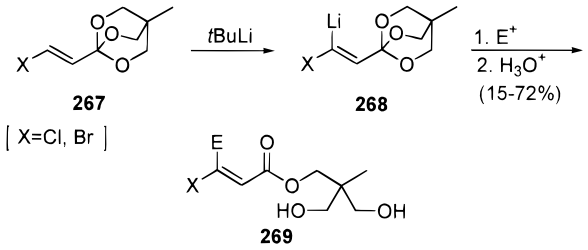
Thus, ortho ester **267** was metalated producing an unsaturated homoenolate anion equivalent **268** which stereoselectively intercepted electrophiles such as

Scheme 60



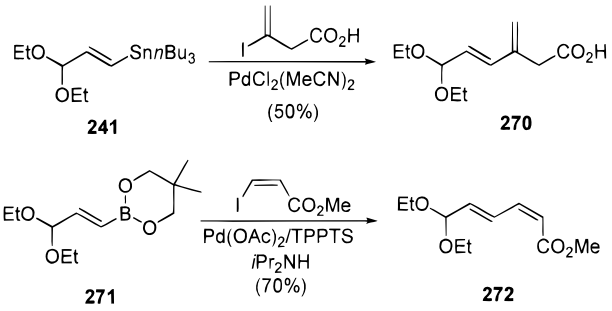
alkyl halides, aldehydes, ketones, and lactones to afford, after hydrolysis, β-substituted acrylate esters **269** (Scheme 61).[137] The higher yields were obtained using the bromo derivative of **267**.

Scheme 61



The mild experimental conditions of the palladium-catalyzed Stille cross-coupling reaction,[32] has been exploited in the reaction of 3-iodobut-3-enoic acid with acrolein vinylstannane derivative **241**, which affords conjugated dienic aldehyde precursor **270** without polymerization (Scheme 62).[138a] 1-Tributylstannyl-3,3-diethoxyprop-1-ene (**241**) has also been used in coupling reactions with aryl bromides[130] and in acylation and sulfonylation reactions.[135] In a related area, Suzuki cross-coupligs[32] have been done with the corresponding vinylboronates or vinylboronic acids.[138b–d] An example is shown in Scheme 62 with the cross-coupling of boronic ester **271** and methyl (*Z*)-3-iodoacrylate conducted with a in situ

Scheme 62

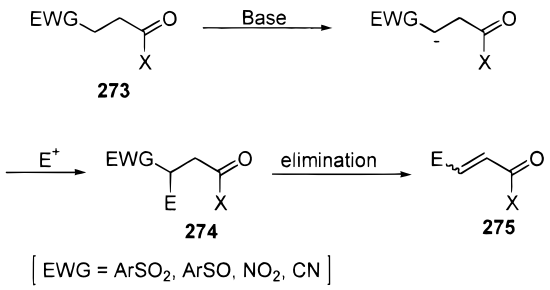


generated water soluble catalyst formed mixing palladium acetate and *m*-trisulfonated triphenylphosphine (TPPTS).[138b]

C. Synthetic Equivalents of α,β-Unsaturated Carbonyl Compounds

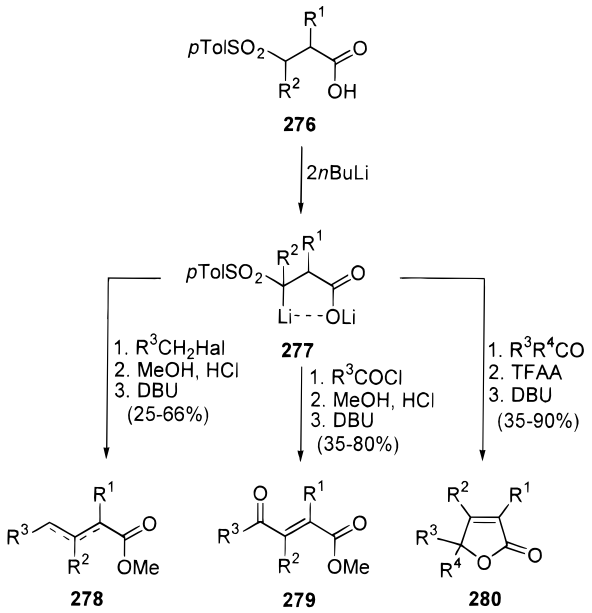
An alternative strategy for β-acylvinyl anionic synthons is the use of saturated carboxylic acids, esters, or amides **273** bearing an electron-withdrawing function at the β-position. These systems can be deprotonated with bases to give the corresponding homoenolates and therefore react with electrophiles to afford 3-substituted carbonyl compounds **274**, which could yield β-substituted α,β-unsaturated acrylic systems **275** after elimination of the electron-withdrawing group (Scheme 63).

Scheme 63



There are examples of this type of synthetic methodology using systems **273** (X = OH) bearing sulfone[139,140] or sulfoxide groups.[139,141,142] The sulfone group can be introduced by conjugated addition of a sulfinic acid to an α,β-unsaturated carbonyl compound[140] or by oxidation of 3-phenylthiopropionic acid,[139] whereas the sulfoxide group is created also by oxidation of the corresponding sulfide[139] or by substitution using a lithiated methyl sulfoxide.[141,142] The sulfone group can be finally removed by base-mediated elimination,[140] whereas pyrolysis can be used for the elimination of the sulfone and sulfinyl groups.[139,141,142] Example of the use of these systems is the anion **277** as synthon type **179** (X = OH), prepared by dilithiation of 3-(*p*-toluenesulfonyl)-propanoic ($R^1 = R^2 = H$ or $R^1 = Me$, $R^2 = H$) and butanoic ($R^1 = H$, $R^2 = Me$) acids **276**, which react with alkyl and acyl halides to give the corresponding 3-substituted unsaturated esters **278** and **279**, respectively, after esterification with methanol/hydrogen chloride and elimination of the sulfonyl group with DBU (Scheme 64).[140] When carbonyl compounds are used as electrophiles, α,β-butenolides **280** are

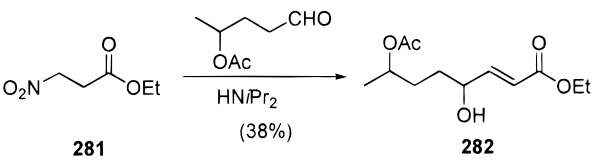
Scheme 64



obtained after in situ lactonization with trifluoroacetic anhydride (TFAA) and base-promoted elimination.[140] This methodology has been applied to the synthesis of interesting butenolides as a precursor of rosefuran, a derivative of (±)-umbelactone and (±)-andirolactone.[140b] The acylation process gives 1,4-enedicarbonyl compounds **279** used, for instance, in the synthesis of a precursor of the seco-acid of pyrenophorin (**210**).[140b] The usefulness of the sulfonylpropionic acid **276** ($R^1 = R^2 = H$) as butenolide precursor, has also recently been demonstrated when used in a key step for the synthesis of an analogue of the dioxabicyclo[3.2.1]octane core structure of the squalestatins (zaragozic acids).[143] This type of furan-2-ones **280** have also been obtained following the same method but starting from the dianion of *N*-monosubstituted 3-(phenylsulfonyl)propanamides.[144]

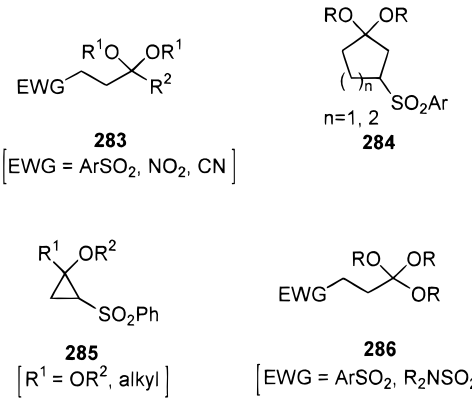
The nitro function can also be used as electron-withdrawing group for the strategy shown in Scheme 63, as it has been demonstrated in the aldol reaction of ethyl *β*-nitropropionate (**281**) with 4-acetoxypentanal in the presence of diisopropylamine. Spontaneous elimination of nitrous acid gave the corresponding *β*-substituted acrylate **282**, which has been employed in the synthesis of a mixture of D,L and meso forms of pyrenophorin (Scheme 65).[145a] Related

Scheme 65



with this methodology is the reported preparation of 4-hydroxy-2-cyclopenten-1-ones using 3-nitropropionyl chloride.[145b] Even the cyano group has been used as activating-leaving group, in this case from ketones.[146]

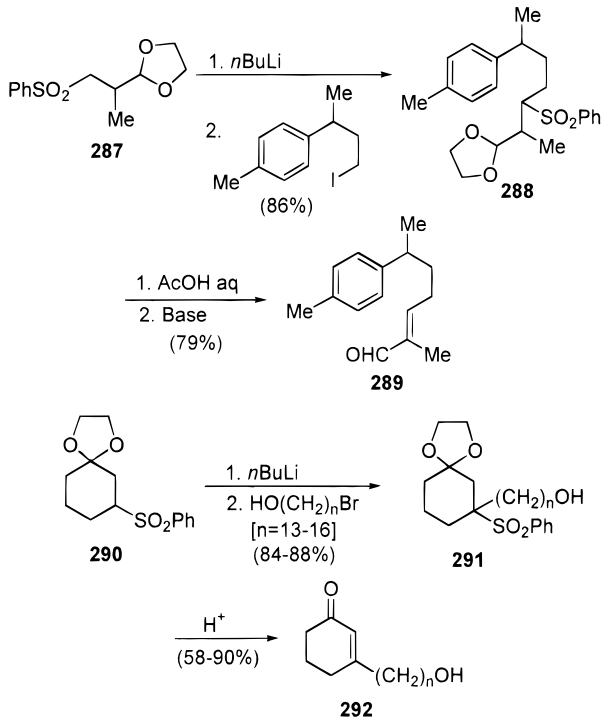
Ketone, aldehyde, and ester-protected compounds bearing an homoenolate anion stabilized by an easily removable group by *β*-elimination have been used frequently as *β*-acylvinyl anion equivalents. In that sense, ketals from acyclic (**283**, R^2 = alkyl) or cyclic ketones **284**, as well as acetals (**283**, R^2 = H), cyclopropyl sulfones **285** and ortho esters **286** have



been employed for the same previously shown deprotonation-reaction with electrophile-elimination strategy, just adding a deprotection step prior to *β*-elimination.

The sulfone group has been by far the most frequently used carbanion stabilizing function[147] in these *β*-acylvinyl anion equivalent precursors type **283**,[148–161] **284**,[155,162,163] **285**,[164–166] or **286**.[167–171b] Thus, for example, treatment of type **283** carbonyl-protected sulfone **287**, as synthon of methacrolein anion, with *n*-butyllithium and the alkyl iodide shown in Scheme 66 afforded sulfone **288**, which was deprotected with

Scheme 66

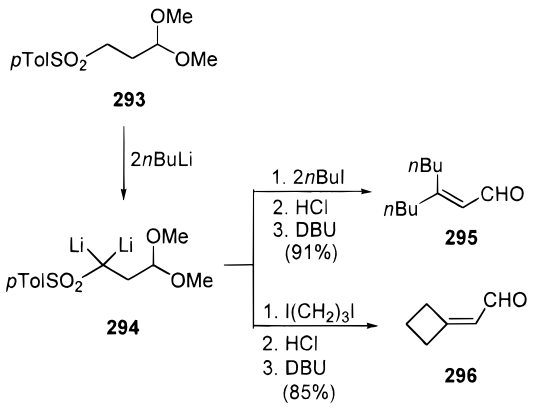


aqueous acetic acid and desulfonylated with base to give (±)-nuciferal (**289**).[148b] This reaction using carbonyl-protected cyclic ketosulfones such as **290**, as synthon **180** (n = 2), and a α,*ω*-bromoalkanol as electrophile allowed the synthesis of cyclohexenonic

long chain fatty alcohols **292**, compounds exhibiting influence on neurite outgrowth (Scheme 66).[163]

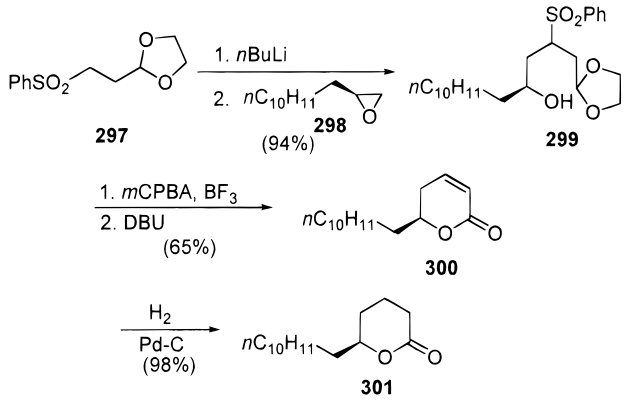
In addition, formal dialkylation at the β-position of acrolein have been achieved by using the still speculative dilithiated 1,1-dimethoxy-3-*p*-toluenesulfonylpropane **294** as a β-acylvinyl dianion equivalent in the reaction with mono- and dielectrophiles, giving dialkylated compounds such as **295** or carbocyclic derivatives such as **296** after base-induced elimination (Scheme 67).[161]

Scheme 67



Another recent example of the synthetic use of acetalic sulfones type **283** as β-acylvinyl anion equivalents is the opening of optically active epoxide **298** after lithiation of sulfone **297**. Deprotection, oxidation of the aldehyde, cyclization, and further DBU-induced elimination of the sulfone group afforded 5-hexadecanolide **301**, a pheromone of the queen of the oriental hornet *Vespa orientalis*, after catalytic hydrogenation (Scheme 68).[160]

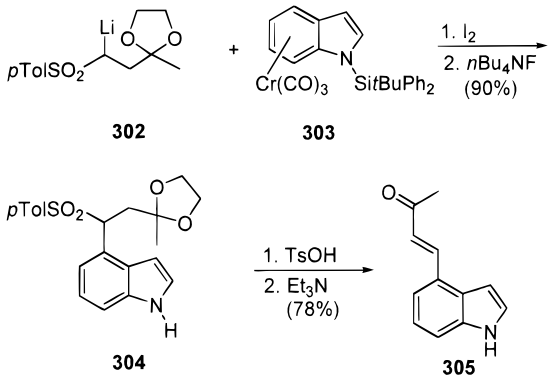
Scheme 68



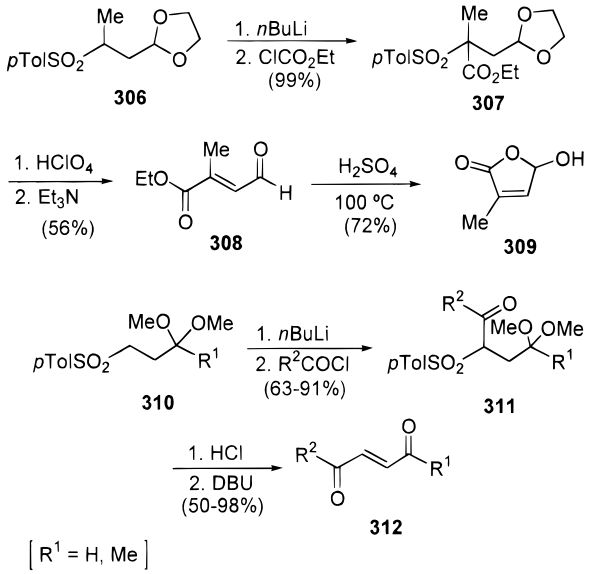
Selective nucleophilic substitution in indoles such as the tricarbonyl chromiun complex **303** has been achieved using the lithiated sulfone **302**, a methyl vinyl ketone anionic synthon. Oxidative quenching with iodine, desilylation, and final acid and base treatment gives the 3-substituted enone **305**, which is a precursor of the indole alkaloid clavicipitic acid (Scheme 69).[158]

Protected γ-oxosulfones such as **306** have also been used in acylation reactions of their corresponding lithium anions with ethyl chloroformate[157] for the synthesis of **309**, which is the γ-hydroxybutenolide moiety of strigol, a potent natural seed germination stimulant (Scheme 70).[152] Also lithiated compound

Scheme 69



Scheme 70

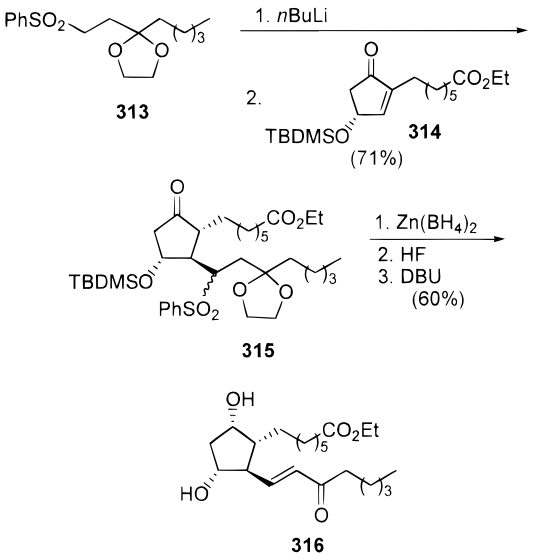


310 has reacted with acyl chlorides for the synthesis of ene-1,4-dicarbonyl compounds **312**.[159]

Michael addition of the lithium anion of protected ketosulfone **313** to substituted cyclopentenone **314** has been used for the stereocontrolled synthesis, after deprotection and elimination, of 15-oxoprostaglandin F_1 (**316**) (Scheme 71).[153] Moreover, reaction of lithiated reagents type **283** with aldehydes and ketones has been developed as a method for the preparation of α,β-butenolides **318** as is exemplified in Scheme 72. Thus, metalation of acetal **293** and reaction with the carbonyl compound followed by hydrolysis afforded cyclic acetal **317**, which was transformed to butenolides **318** after oxidation with Jones reagent and DBU-induced elimination of the sulfone group.[159] In addition, these sulfonyl carbanions have been used for the synthesis of 4-hydroxycyclopent-2-enones[149] or 3-substituted furans **321**,[151] the last process being illustrated in Scheme 72 and including two consecutive α-deprotonations with α-alkylation and addition to formaldehyde.

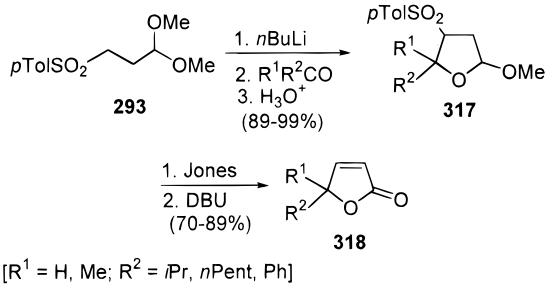
The nitro group has also been used as a carbanion stabilizing group in reagents type **283**. Thus, ni-

Scheme 71



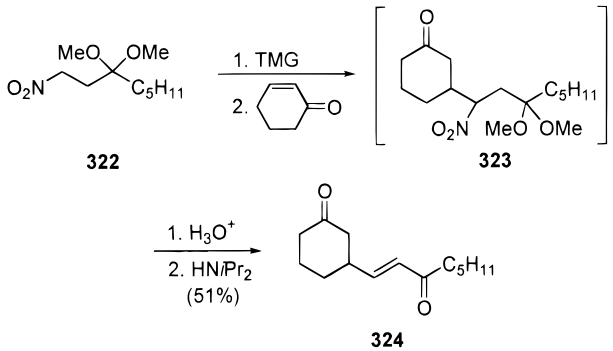
troketal **322** was deprotonated with tetramethylguanidine (TMG) and reacted in a 1,4-addition fashion with

Scheme 72



cyclohex-2-enone affording β-substituted enone **324** after in situ induced elimination with diisopropylamine (Scheme 73).[145a] Even there are examples on

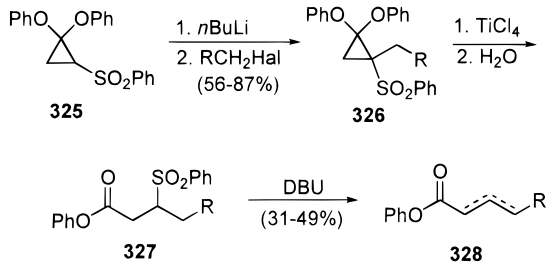
Scheme 73



the use of phosphonium[172a,b] and arsonium[172c] ylides as β-formylvinyl anion equivalents.

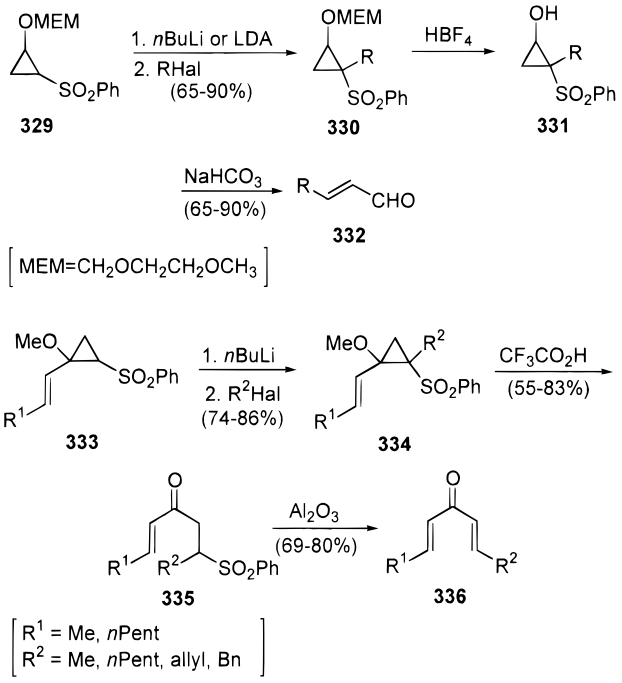
A protected sulfonyl-substituted cyclopropanone reagent type **285** has been used as a β-anionic acrylic ester synthon **179** (X = OPh). In this way, 2,2-diphenoxy-1-(phenylsulfonyl)cyclopropane (**325**) can be α-lithiated and reacts with alkyl halides to give alkylated cyclopropyl sulfones **326**, which were subjected to hydrolysis with titanium tetrachloride followed by elimination of the phenylsulfonyl group with DBU affording α,β-unsaturated esters **328** together with a certain amount of their β,γ-unsaturated isomers (Scheme 74).[164]

Scheme 74



The carbanion of 2-[(2-methoxyethoxy)methoxy]-1-phenylsulfonylcyclopropane (**329**) has been employed as acrolein β-anion synthon for the synthesis of β-alkyl substituted α,β-unsaturated aldehydes. In this procedure, the starting sulfone **329**, prepared by oxidation of the corresponding sulfide, is lithiated and reacts with alkyl halides to give cyclopropanes **330**. Hydrolysis of the MEM-protecting group with aqueous tetrafluoroboric acid afforded cyclopropanol **331**, which after treatment with sodium bicarbonate yields *trans*-β-substituted α,β-unsaturated aldehydes **332** (Scheme 75).[165] Similarly, 2-alkenyl-2-methoxycyclo-

Scheme 75

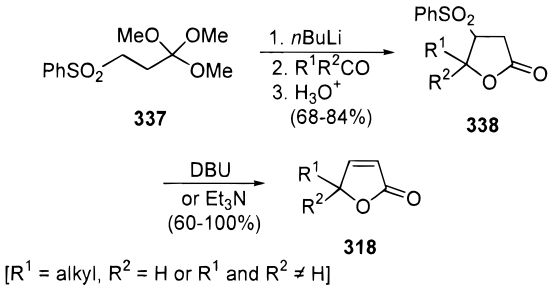


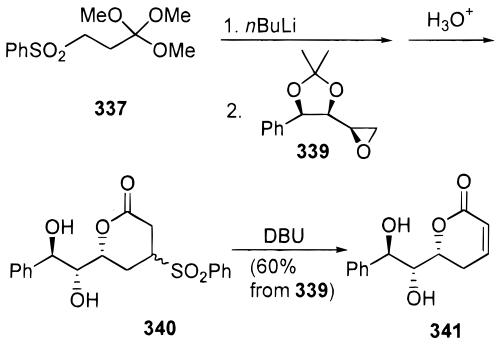
propyl phenyl sulfones **333** can be converted to unsymmetric dialkenyl ketones **336**, suitables for Nazarov reaction, by ring opening of the correspond-

ing alkylated cyclopropanes and alumina-induced elimination of the phenylsulfonyl group (Scheme 75).[166]

The homoenolate derived from methyl 3-phenylsulfonyl orthopropionate (**337**) can be considered also as a synthetic equivalent of a β-anionic acrylate synthon **179** (X = OMe), useful for the synthesis of butenolides. Thus, ortho ester **337** is metalated and reacts with aldehydes and ketones to yield, after hydrolysis, β-phenylsulfonyl γ-lactones **338**, which are transformed into butenolides **318** by base-induced elimination (Scheme 76).[167] This homoenolate has

Scheme 76

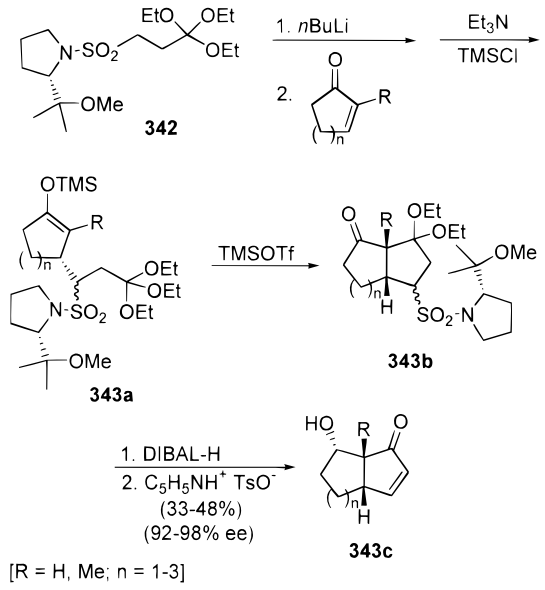




also been used in an acylation reactions for the synthesis of cytotoxic styryl lactones[168,169] and also in reaction with epoxides for the synthesis of α,β-unsaturated-δ-lactones.[170a] An example is the reaction with chiral epoxide **339** for the synthesis of the α,β-unsaturated-δ-lactone unit of (+)-gonodiol **341** (Scheme 76).[170b] The same homoenolate has been used for cyclopentannulation reactions with cyclic enones.[171a] A highly enantioselective version of this process has been recently developed using the chiral sulfonamide **342** as electron-withdrawing group on an ortho ester type **286** (Scheme 77).[171b] Thus, reaction of metalated sulfonamide ortho ester from **342** with cyclic enones and quenching with trimethylsilyl chloride give silyl enol ethers **343a**. These compounds suffered stereocontrolled trimethylsilyl triflate-induced cyclopentannulation affording ketones **343b**, which are transformed into enantiomerically enriched bicyclic cyclopentenones **343c**, after reduction, hydrolysis and elimination of the sulfonamide moiety.

There are a number of allylic reagents which, after metalation, can act as equivalents of the important acrolein β-anion synthon. These compounds can be represented as species of the type **344** (Scheme 78) and are characterized by the presence of groups capable of further stabilization of a carbanionic center

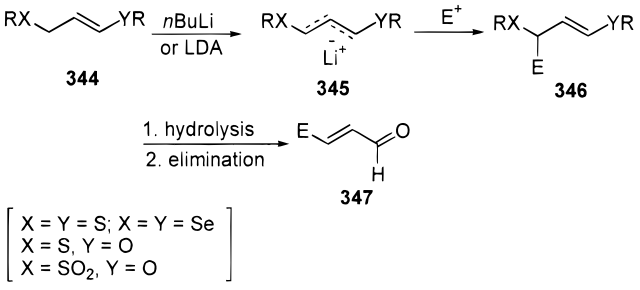
Scheme 77



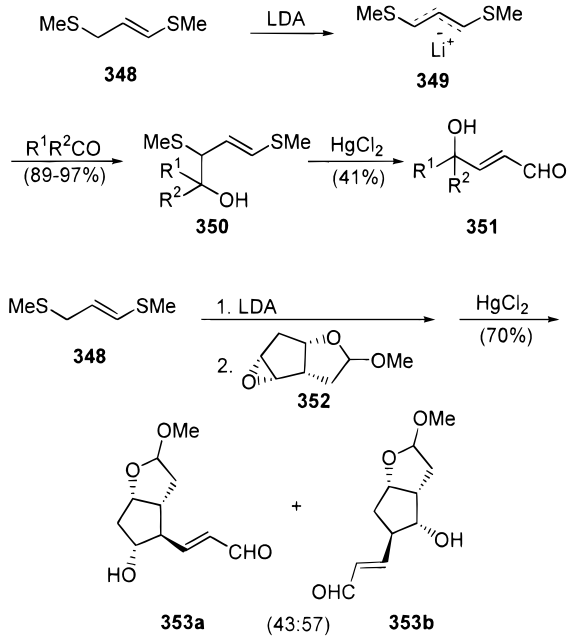
(bearing S, Se, or SO_2).[173] In addition, after the reaction of the created stabilized anion **345** with an electrophile, they show a vinylic system (**346**), which can be hydrolyzed to a carbonyl function. Further elimination of the carbanion-stabilizing group allows the final synthesis of β-substituted acroleins **347**.

The first developed reagent of type **344** (X = Y = S) was 1,3-bis(methylthio)propene (**348**), prepared by reaction of epichlorohydrin with sodium methylthiolate, methylation of the hydroxy group, and elimination of methanol by lithium diisopropylamide (LDA). Reaction of **348** with lithium diisopropylamide furnishes an anion **349** which can be stored in solution in a refrigerator without decomposition. Treatment of this lithio reagent with aldehydes or ketones, followed by mercuric ion promoted hydrolysis and elimination of methanethiol afforded γ-hydroxy-α,β-unsaturated aldehydes **351** (Scheme 79).[174] This lithiated reagent has also been used for epoxide ring opening reactions,[174,175] in key steps for the total synthesis of prostaglandins,[176,177] as shown in Scheme 79 in the synthesis of aldehydes **353** by opening of epoxide **352**. Compound **353a** has been used in the total synthesis of prostaglandin $F_{2\alpha}$.[176] Similar 1,3-bis(phenylthio)alkene derivatives (**344**, XR = YR = SPh) have been prepared by treatment of α,β-unsaturated aldehydes and ketones with triphenyl thioborate, a procedure which failed in the case of acrolein and methyl vinyl ketone.[178] These derivatives have been deprotonated and used as β-acylvinyl

Scheme 78



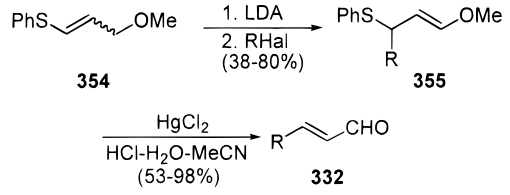
Scheme 79



anion equivalents.[178] Moreover, the phenylseleno equivalent of compound **344** (XR = YR = SePh), obtained by reaction of 1,3-dichloropropene with benzeneselenolate, has also been employed for the preparation of β-substituted α,β-unsaturated aldehydes after metalation, reaction with electrophiles, followed by unmasking with hydrogen peroxide.[179]

3-Methoxy-1-phenylthiopropene (**354**), obtained by reaction of epichlorohydrin with sodium phenylthiolate and further ring opening with sodium hydride followed by quenching with methyl iodide, can be lithiated and alkylated exclusively at the α-position of the sulfur atom. The resulting products afford α,β-unsaturated aldehydes after the above shown hydrolysis in the presence of mercuric chloride (Scheme 80).[180] The lithio anion of this allylic starting material

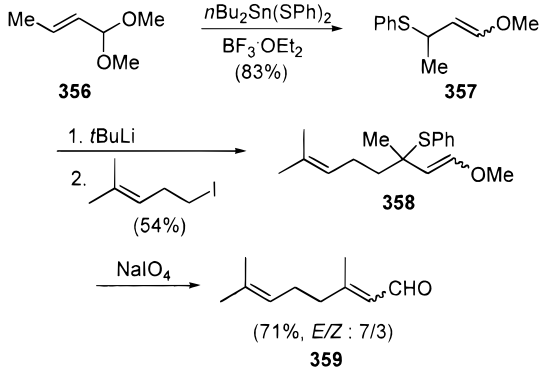
Scheme 80



354 has also been used for the ring opening of epoxides such as (*S*)-epoxypropane driving to the final preparation of 2*H*-pyran-2-ones such as parasorbic acid.[181]

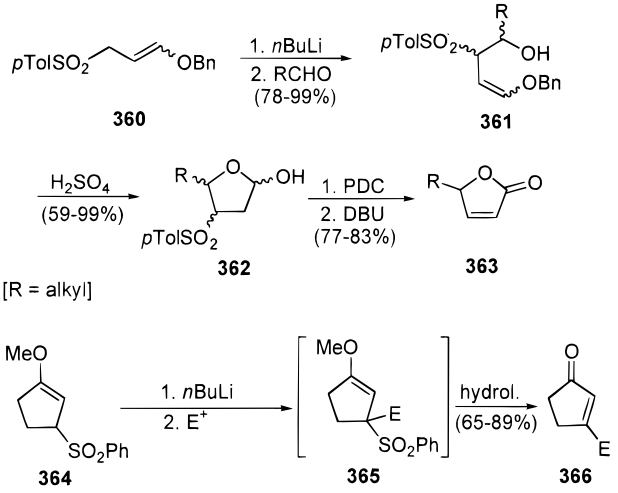
Sulfenylation of α-enal acetals has shown to be a route to the preparation reagents of type **344** (X = S, Y = O). Thus, acetals such as **356** proved susceptible of S_N2' attack affording γ-alkoxyallyl sulfide **357**. These types of compounds can act as equivalents of the acrolein β-anion synthon by *tert*-butyllithium-promoted alkylation and oxidative hydrolysis, as shown in Scheme 81 for the synthesis of citral (**359**).[182] Using a similar reagent, (±)-nuciferal (**289**) has also been obtained.[182]

Scheme 81



Reagents of the type **344** bearing an electron-stabilizing sulfone group (X = SO_2, Y = O) have also been prepared to serve, after deprotonation, as acrolein β-anion synthon. Thus, 1-benzyloxy-3-(*p*-toluenesulfonyl)propene **360**, obtained as a ca. 3:1 *Z*:*E* mixture by reaction of (diethylphosphonyl)lithio(*p*-toluenesulfonyl)methane with 2-benzyloxyethanal followed by isomerization, can be lithiated and reacts with aldehydes to give alcohols **361**. Sequential hydrolysis-cyclization, oxidation and DBU-mediated elimination gives substituted butenolides **363** (Scheme 82).[183,184] These kind of allyl sulfones have been also

Scheme 82

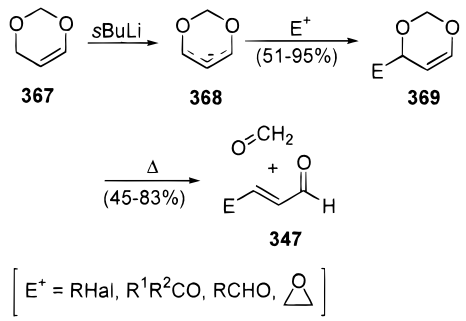


employed for the synthesis of substituted furans.[185,186] In the cyclic version of this type of allylic sulfones, a γ-methoxyallyl sulfone **364** undergoes metalation, followed by alkylation and hydrolysis to afford β-substituted cyclic cyclopentenones **366**.[187−189a] In addition, a reagent type **344** (X = SO_2, Y = S) has also been used for the synthesis of β-mono- and β,β-disubstituted α,β-unsaturated aldehydes,[189b] and γ-chloroallyl sulfoxides have been employed as latent α,β-unsaturated carbonyl compounds.[189c]

An equivalent of the acrolein β-anion synthon is the allyl anion **368**, obtained by allylic deprotonation of 4*H*-1,3-dioxin (**367**) with *s*-butyllithium. Reaction of this anion with different electrophiles such as alkyl halides, epoxides, ketones, or aldehydes provides monosubstituted dioxins **369**, which can be thermally converted to formaldehyde and the desired α,β-unsaturated aldehydes by a retro Diels−Alder reac-

tion (Scheme 83).[190] Further alkylation of monoalky-

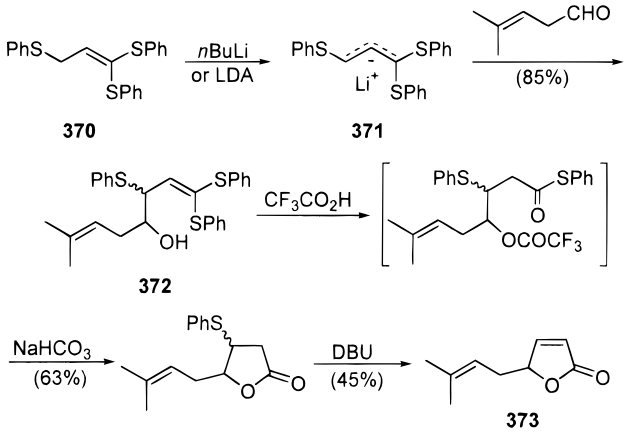
Scheme 83



lated dioxins **369** gives also access to (*E*)-alkenones.[191]

The incorporation of an additional phenylsulfonyl group to an allylic reagent type **344** (X = Y = SPh) promotes high γ-regioselectivity in the reaction of their ambidentate anion with both "hard" and "soft" electrophiles. Thus, the anion **371** of 1,1,3-tris-(phenylthio)propene (**370**), which can be considered as a β-lithioacrylic acid equivalent, reacts with electrophiles to give the γ-substituted adducts. Hydrolysis of the intact dithioacetal moiety serves to release the latent carboxylate function and elimination of thiophenol generates the corresponding β-substituted acrylic acids.[192,193] In the case of the reaction with aldehydes or ketones, cyclization and elimination of thiophenol generates the corresponding butenolides, as shown in Scheme 84 outlining the preparation of

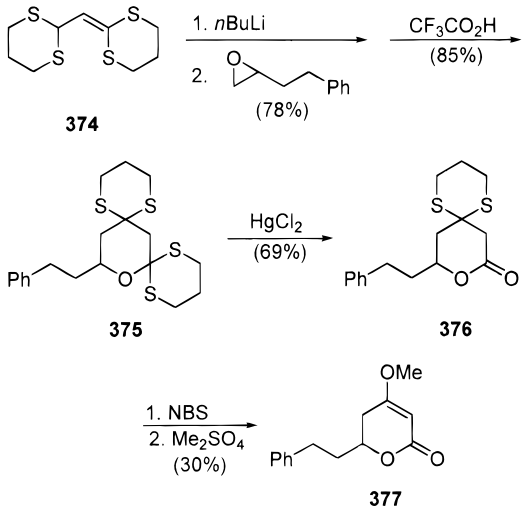
Scheme 84



butenolide **373**, which has been used as a precursor of the pheromone (±)-eldanolide.[193] Even chemically similar 1,1,3,3-tetraalkylthio-substituted propenes such as 2-(1,3-dithian-2-ylidenemethyl)-1,3-dithiane (**374**) can be lithiated and used now as an equivalent of the β-hydroxy-β-lithioacrylic acid for the synthesis of (±)-dihydrokawain (**377**) following the route outlined in Scheme 85.[194]

The lithio derivative **381** of 2-diethylamino-4-phenylthiobut-2-enenitrile (**380**) is also a practical β-lithioacrylic acid equivalent. This reagent is prepared by conversion of the amide **378** into the corresponding *S*-methylthioamide **379** followed by addition of potassium cyanide and elimination of methanethiol upon heating (Scheme 86). γ-Lithiation of the obtained cyanoenamine **380** followed by treat-

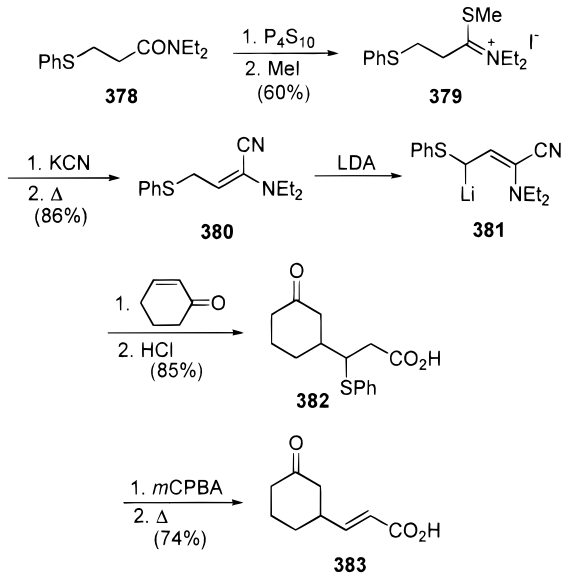
Scheme 85



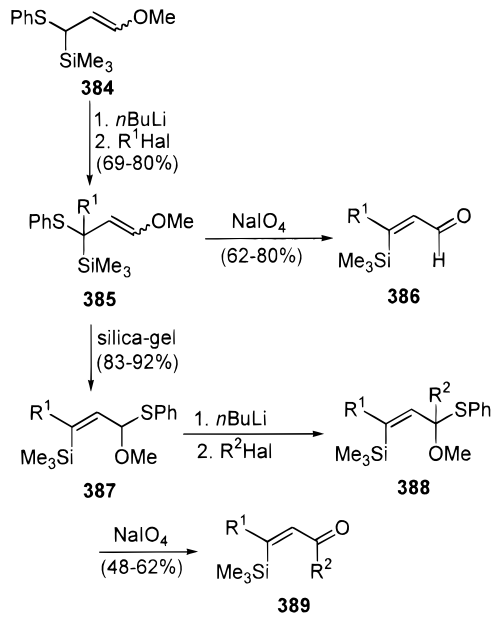
ment with an electrophile such as cyclohex-2-enone afforded the 1,4-addition product, which is converted into the 3-phenylthio-substituted acid **382** after hydrolysis. Oxidation to the sulfoxide and thermolysis gives the corresponding α,β-unsaturated acid **383** (Scheme 86).[195a] A related method, but using a phenyl sulfone, has also been published.[195b]

β-Trimethylsilyl-α,β-unsaturated carbonyl compounds are prepared via allylic sulfide **384**, which are considered as a precursor of a α-silylated β-acylvinyl anion. Alkylation of compound **384** results in an exclusive formation of α-adduct **385**, which is converted into **386** on treatment with sodium periodate by a [2.3]-sigmatropic rearrangement. In addition, silica gel-promoted thioallylic rearrangement of **385** followed by α-alkylation of resultant **387** enables incorporation of two electrophiles in different positions of **384**. Final oxidation of crude **388** allows the synthesis of enones **389** (Scheme 87).[196] Furthermore, α-methoxyallyl sulfides are used as a similar homoenolate dianion equivalents,[197] whereas 1-trimethylsilyl-1,3-bis(phenylthio)propene can be employed also as a silylated β-acylvinyl anion equivalent for

Scheme 86



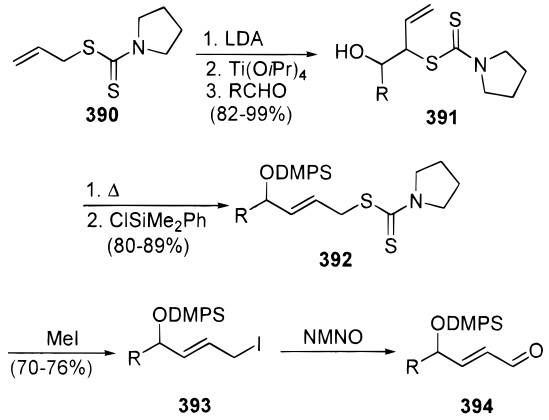
Scheme 87



the preparation of functionalized α,β-unsaturated acylsilanes.[198]

Allyldithiocarbamates have been used for the synthesis of α,β-unsaturated aldehydes.[199] For example, allyldithiocarbamate **390** has been employed as precursors of a acrolein β-anion synthon transforming aldehydes into 4-oxygenated alk-2-enals. The procedure involves deprotonation of compound **390** followed by reaction with aldehydes in the presence of titanium isopropoxyde at the α-site of **390**. The obtained compounds **391** are transformed into **392** upon heating and silylation. Reaction of the compounds **392** with methyl iodide affords the corresponding iodides **393**, which are oxidized to the enals **394** by treatment with *N*-methylmorpholine-*N*-oxide (NMNO) (Scheme 88).[199b] These types of enals have

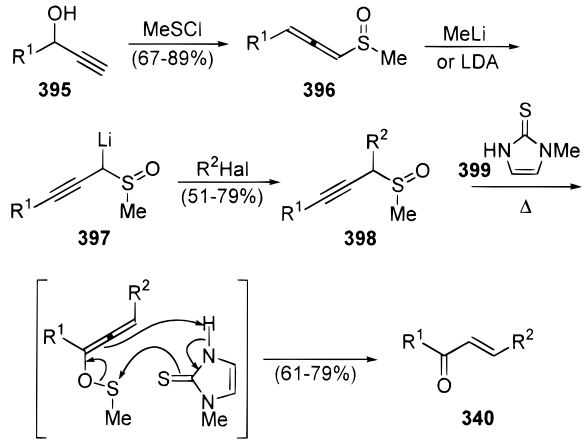
Scheme 88



been used as starting materials for the synthesis of coriolic and dismorphecolic acids.[199b]

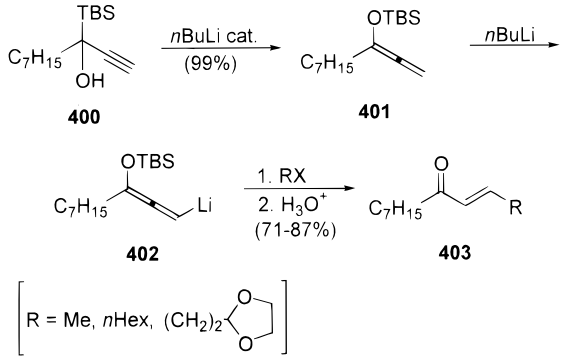
(*E*)-Enones can be prepared from different propargylic alcohols. One procedure involves transformation of propargyl alcohol **395** into γ-monosubstituted allenic methyl sulfoxides **396**, followed by deprotonation with methyllithium or lithium diisopropylamide and reaction with alkyl halides to give substituted propargylic sulfoxides **398**. Desulfurization of **398** using 2-mercapto-1-methylimidazole (**399**) furnished the corresponding final conjugated enones **340** (Scheme 89).[200] Another procedure involves 3-(*tert*-

Scheme 89



butyldimethylsiloxy)allenyllithium **402**, generated from a 1-silylpropargyl alcohol **400** (Scheme 90). The

Scheme 90

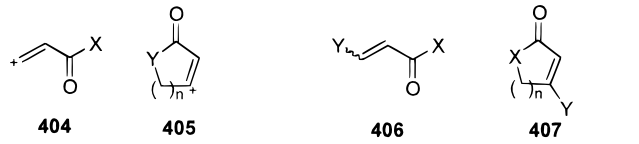


procedure implies conversion of alcohol **400** to silyloxyallene **401** under the influence of a catalytic amount of butyllithium. Addition of a stoichiometric amount of this organolithium reagent to **401** yields the silyloxyallenyllithium **402**, which reacts with alkyl halides to give (*E*)-α,β-unsaturated ketones **403** after hydrolysis.[201a] The use of other related alkoxyallene[201b–f] and *N*-propargylphosphoramide[201g] reagents have also been described previously as β-formylvinyl anion equivalents.

V. β-Acylvinyl Cationic Synthons

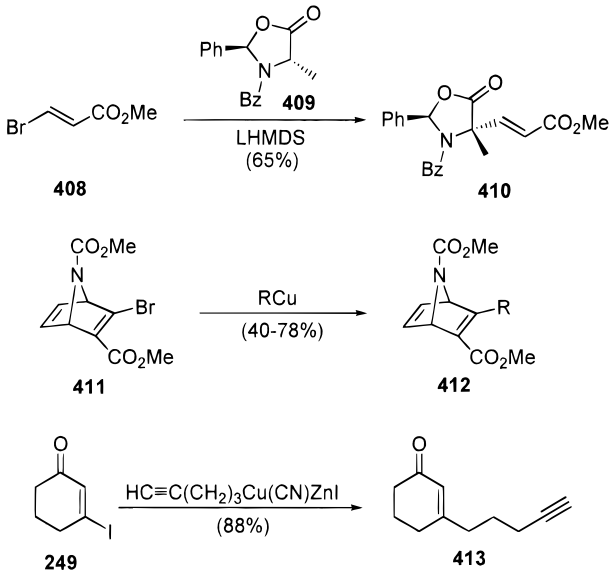
The β-acylvinyl cationic synthons **404** or **405** belong to the category of the considered unsaturated reagents of type *a*[3 3] and therefore can be attacked by nucleophiles providing β-substituted α,β-unsaturated compounds. Precursors of these synthons are compounds of the general formula **406** and **407**, in which a potential leaving group is attached at the β-position of the α,β-unsaturated system. This strategy has been traditionally used for the β-functionalization of α,β-unsaturated carbonyl compounds. These types of systems can undergo reactions with nucleophiles to achieve 3-substituted conjugated carbonyl compounds following two different pathways. Generally, a vinylic

substitution reaction by a 1,4-addition−elimination mechanism takes place, although a 1,2-addition to the carbonyl group followed by hydrolysis of the vinylic function and dehydration is also possible, specially starting from aldehydes or ketones of the type **406** or **407** with X = OR or NR_2.



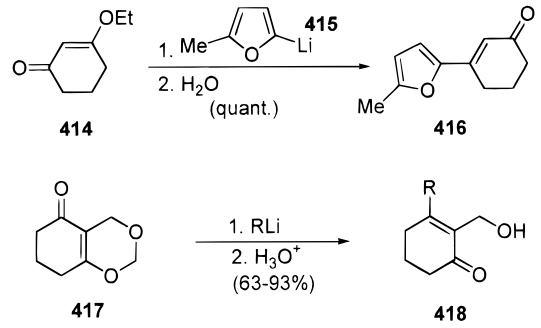
Thus, the conjugate addition−elimination of nucleophiles to activated vinyl halides is known for many years,[202] and the final configuration of the vinyl halide is retained in many cases. The starting halides type **406** can be prepared by addition of hydrogen halides to conjugated ethynyl systems as exemplified in the synthesis of methyl (*E*)-3-bromopropenoate (**408**),[203a] whereas cyclic α,*β*-unsaturated ketone halides type **407** are obtained usually by addition−elimination of halides to enones.[203b] Some selected recent examples on the use of these vinyl halide reagents **406** as equivalents of *β*-acylvinyl cations of type **404** are shown in Scheme 91. Thus, compound

Scheme 91



408 reacts with the lithio anion of alanine-derived chiral imidazolidinone **409** affording diastereomerically enriched α,*β*-unsaturated ester **410** (>98% *de*), which is a α-methyl-α-amino acid derivative employed in the preparation of some isotype-selective antagonists for metabotropic glutamate receptors.[204] Cuprates have also been employed for these reactions,[205a] for example azabicyclic compound **411** reacts with alkyl and aryl cuprates to give products **412** in studies toward the synthesis of epibatidine analogues.[205b] An example of the synthon type **405** (X = CH_2, *n* = 2) is *β*-iodocyclohexenone (**249**), which undergoes reaction with zinc cuprates containing functional groups[206−208a] to give *β*-substituted enones such as **413**.[208a] *β*-Iodocyclohexenones and iodocyclopentenones have also been used in reaction with phenylthio(trimethylstannyl)cuprate for the synthesis of *β*-trimethylstannyl-α,*β*-unsaturated ketones.[208b]

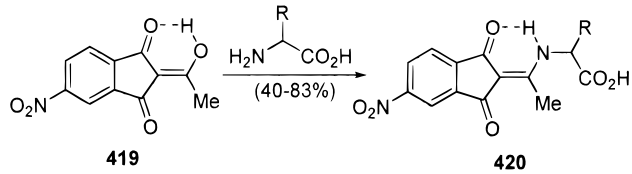
Scheme 92



Enol ethers of cyclic *β*-diketones can react with nucleophiles in a 1,2-fashion and subsequent hydrolysis of the enol function followed by dehydration yields *β*-substituted cyclic enones.[73a,209−215] This process can be seen as an apparent nucleophilic substitution of an oxygenated moiety. Recent examples of the use of this methodology are the reaction of 3-ethoxycyclohexenone (**414**) with lithiated 2-methylfuran (**415**), which yields the corresponding α,*β*-unsaturated ketone **416**, in the first step toward the synthesis of sesquiterpenolide (±)-decipienin A[209b] or the reaction of 1,3-dioxin **417** with organolithium compounds[214a] (Scheme 92). There is also a reported example with a cyclobutenone derivative.[215a] Related with this methodology is the reaction of organometalic reagents with *β*-phenylseleno-α,*β*-unsaturated carbonyl compounds followed by acid hydrolysis.[215b]

An example of substitution reaction, but now the hydroxyl acting as a leaving group, is the condensation of amino acids with indanone derivatives such as **419**, a methodology that has been recently used for protection strategies in solid-phase synthesis of peptides (Scheme 93).[216]

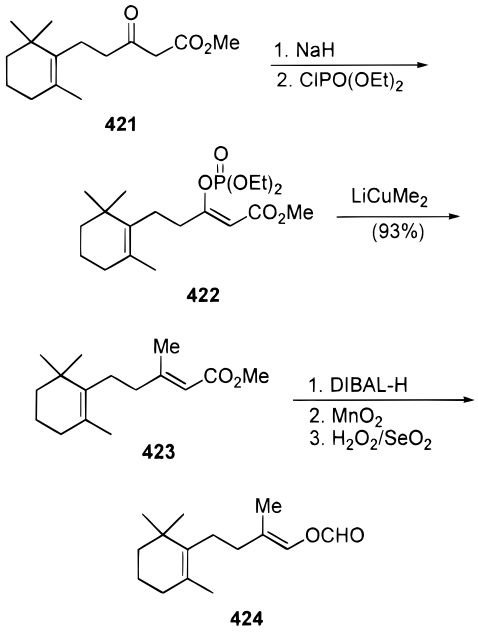
Scheme 93



The phosphate group is also used as leaving group in cationic synthons of the type **404**[217−219] and **405**.[205a] The synthetic equivalents are prepared by deprotonation of *β*-keto esters such as **421** and quenching with diethylphosphorochloridate affording enol phosphates such as **422**. These types of compounds can be treated with lithium dimethylcuprate giving alkyl (*E*)-3-methylalk-2-enoates such as **423** (Scheme 94), a compound used for the total synthesis of *Latia neritoides* luciferin (**424**).[217] The isoprenoid mokupalide has also been prepared using this methodology.[218]

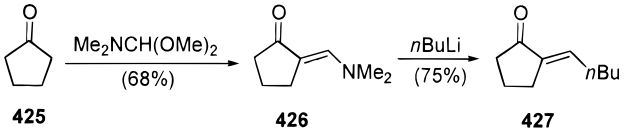
Enaminones[220] (**406**, X = R_2N, Y = R) are known to react similarly with organomagnesium and organolithium reagents acting thus as cationic synthons of the type **404** (the so-called Benary reaction).[221,222] The reaction proves to be general, offering an access

Scheme 94



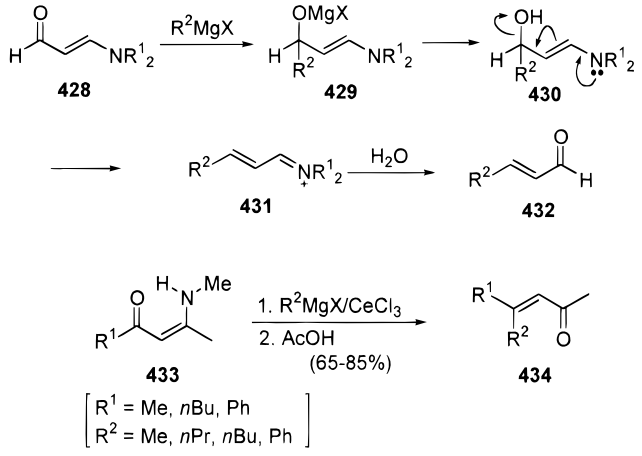
not only to α,β-unsaturated ketones but also to α,β-unsaturated aldehydes and esters, being also rather stereoselective.[221b] In the case of β-amino vinyl ketones, the reaction seems to proceed through a 1,4-addition−elimination mechanism.[221b] Example of the use of this reaction is the preparation of β-alkyl enone **427** from enaminone **426**, intermediate in the total synthesis of dihydrojasmone (Scheme 95).[223]

Scheme 95



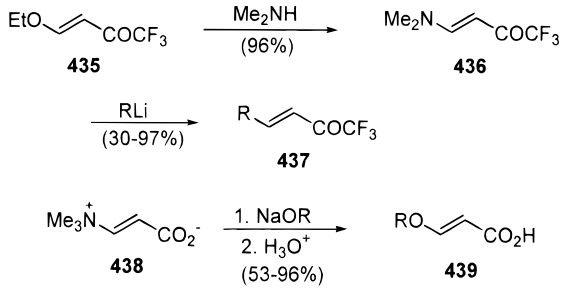
However, β-aminopropenals seems to react with organomagnesium and organolithium compounds mainly in a 1,2-fashion at the carbonyl group, as depicted in Scheme 96.[221b] The use of toluene as

Scheme 96



solvent when using Grignard reagents has proved to increase the yield of the obtained final enones in these type of reactions.[224] In addition, improved

Scheme 97

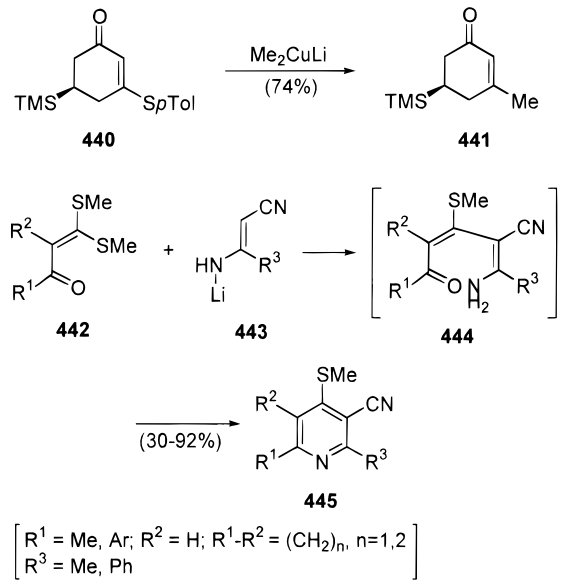


stereoselectivities in the synthesis of α,β-unsaturated ketones have been achieved when the reaction is carried out with Grignard reagents in the presence of cerium(III) chloride, the starting enaminone **433** bearing a secondary amine framework (Scheme 96).[225] In this case, a *trans* relationship between the introduced substituent and the carbonyl group is predominantly observed in final enone **434**, probably induced by a mechanism involving cerium oxygen−nitrogen complexation and 1,2-addition followed by 1,3-carbonyl shift.

Trifluoromethyl enaminoenones **436**, which can be prepared by reaction of β-trifluoroacetylvinyl ethers **435** and sulfides with amines such as dimethylamine,[226] react with lithium derivatives of aromatic or heteroaromatic compounds affording stereoselectively the corresponding trifluoromethyl enones **437**[227] (Scheme 97). Moreover, the betaine **438**, prepared from ethyl propiolate and trimethylamine, reacts with sodium salts of primary and secondary allylic alcohols affording (*E*)-3-(allyloxy)acrylic acids **439**, suitable for Claisen rearrangements (Scheme 97).[228]

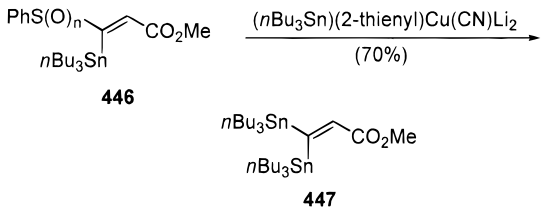
Sulfur-containing functions have also been used as leaving groups in α,β-unsaturated carbonyl compounds for addition−elimination reactions with nucleophiles. Thus, the reaction of lithium dimethyl cuprate with vinylsulfide **440** affords the β-methylcyclohex-2-enone **441**, which is an intermediate in the total synthesis of (+)-α-cuparenone (Scheme 98).[229]

Scheme 98



Similarly, oxoketene dithioacetals such as **442** un-

Scheme 99

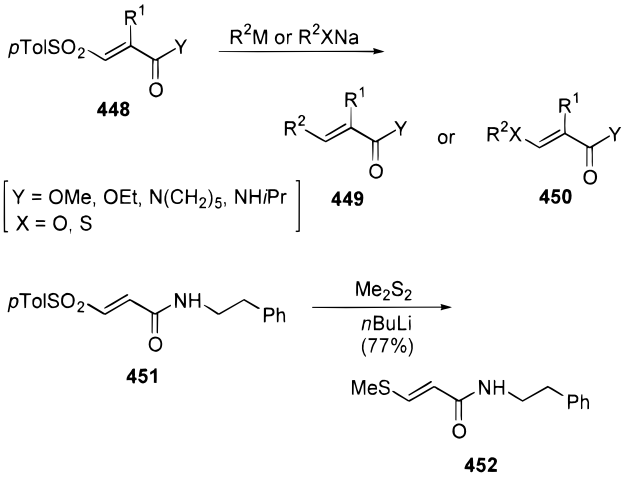


dergo vinylic substitution reaction with some nucleophiles,[230a−235] as illustrated in Scheme 98 for the reaction of α,β-unsaturated β-lithioaminonitrile **443** with the compound **442**, which allowed the synthesis of pyridines **445** *via* cyclization of the intermediate **444**.[231] Moreover, ketene dithioacetals having electron-withdrawing groups at the α position substitute a methylthio group by a nucleophile[232] and related oxoketene *N*,*S*-acetals have been employed for these addition−elimination reactions.[230a] Even β-oxovinylsulfonium salts have been described for nucleophilic displacement reactions using alcoholates and phenolates.[230b]

There are also examples of nucleophilic displacements of the sulfoxide group in a 1,4-fashion, as illustrated in Scheme 99 with the reaction of vinylsulfoxide **446** ($n = 1$) with a high order tin cuprate, affording the geminal bis-stannane **447**.[236] This reaction could be also carried out starting from vinyl sulfone **446** ($n = 2$).[236]

The sulfone group has been a frequently used sulfur-containing leaving group for these type of 1,4-addition−elimination reactions.[237] The usual high stability of these sulfones makes them easy to handle starting materials. Accordingly, β-(*p*-toluenesulfonyl)-α,β-unsaturated esters and amides **448** react regio- and stereoselectively with organomagnesium compounds and sodium malonate[238a] or even sodium alcoholates or thiolates[238b] to yield β-substituted α,β-enoates or enamides **449** or **450**, respectively (Scheme 100). This methodology has been applied to the

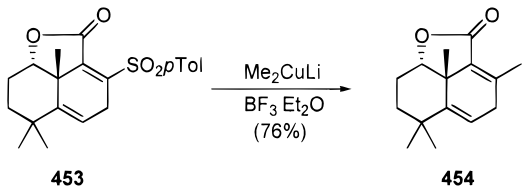
Scheme 100



synthesis of natural antifungal sinharine **452**, starting from sulfonyl acrylamide **451** (Scheme 100).[238b] Examples of this type of substitution reaction on dialkyluracils[238c] and cyclic systems such as 3(2*H*)-thiophenone 1,1-dioxides[238d] have also been reported.

Alkyl cuprates have been used as nucleophiles for the substitution of the sulfonyl group in α,β-unsaturated esters, as shown in Scheme 101 for the prepara-

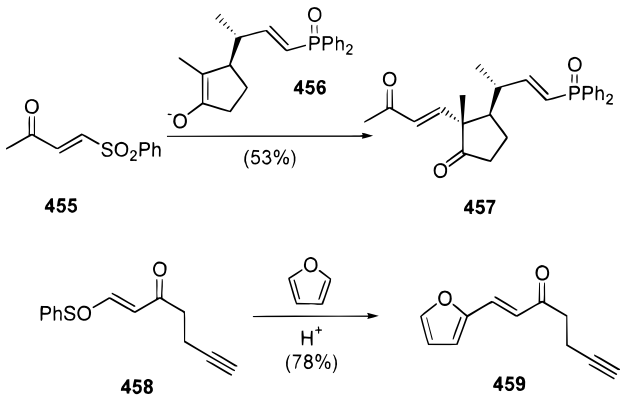
Scheme 101



tion of tricyclic lactone **454**, an intermediate in the total synthesis of the diterpenoid (±)-forskolin.[239] Furthermore, functionalized copper−zinc organometallics have also been employed in substitution reactions on (phenylsulfonyl)methylidenemalonates.[240]

β-Sulfonylvinyl ketones have been used as equivalents to vinyl ketones in substitution reactions by heteronucleophiles[100] and in Robinson annelation reactions for the synthesis of hydrindanones.[241−243] Thus, the sulfone **455** reacts with enolate **456** giving unsaturated diketone **457**, which is a precursor of an hydrindanol related to Vitamin D (Scheme 102).[242]

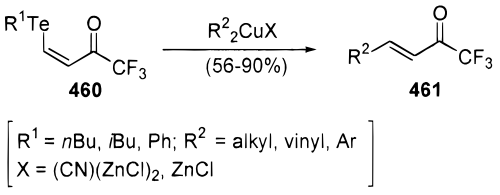
Scheme 102



In addition, vinyl sulfoxides undergo acid-catalyzed addition−elimination reactions with five-membered heterocyclic compounds to give (*E*)-4-arylbut-2-en-2-ones such as **459**, a methodology that has been employed as key step for the synthesis of naturally occurring furanocoumarin psoralen, starting from sulfoxide **458** and furane (Scheme 102).[244]

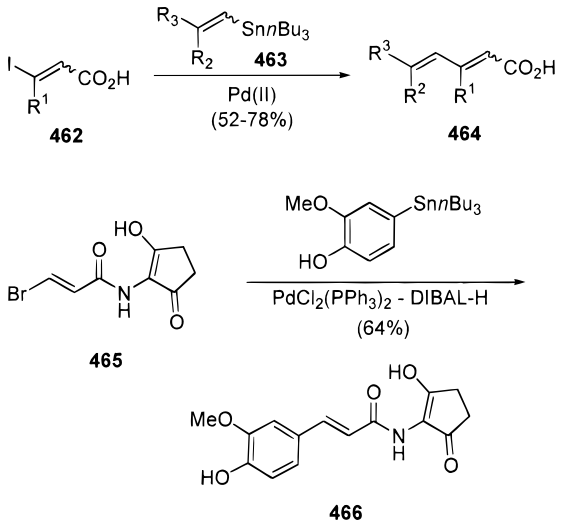
Even alkyl- and aryltellurates can act as leaving groups in 1,4-addition−elimination reactions. Thus, (*Z*)-β-trifluoroacetylvinyltellurides **460** have been found to react with zinc cuprates affording α,β-unsaturated trifluoromethyl ketones **461** with (*E*)-configuration (Scheme 103).[245]

Scheme 103



The palladium-catalyzed cross-coupling reaction[32] between β-acylvinyl halides of the type **406** or **407**

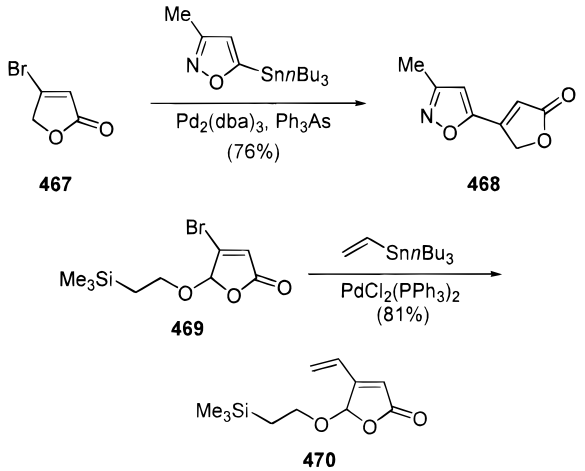
Scheme 104



462 463 464 465 466

and all the previously commented array of tin-, boron-, or zinc-containing counterparts, is another way of using these compounds as synthetic equivalents of synthons of the type **404** or **405**, the order of reactivity being I > Br ≫ Cl. The Stille coupling reaction[32] is probably the most common of these palladium-mediated reactions. Thus, (2*E*,4*E*)- or (2*Z*,4*E*)-dienoic acids **464** can be obtained through palladium-catalyzed coupling of (*E*)- or (*Z*)-3-iodoprop-2-enoic acids **462** with vinyltin reagents (Scheme 104).[246−249] This approach has been applied intermolecularly, for the synthesis of some natural occurring dienamides,[1c,248,249] even amide bond-anchored polyethylenglycol (PEG) derivatives,[250] or intramolecularly for the synthesis of polyene macrolides such as macrolactin A.[251] Similarly, it has been employed for the synthesis of some *Streptomyces* metabolites such as 2880-II (**466**) from cross-coupling between alkenyl bromide **465** and an aryl stannane (Scheme 104).[252] A further example is the coupling of *β*-bromobutenolide **467** with vinylic[253] and heterocyclic[254] stannanes for the preparation of furanones such as **468** (Scheme 105). Recently, a Stille reaction between a protected

Scheme 105

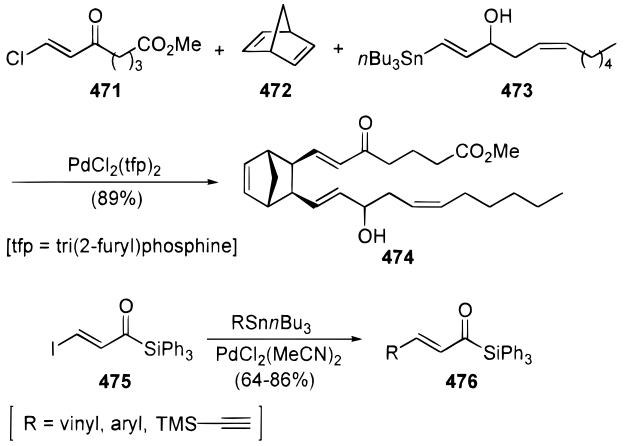


467 468 469 470

β-bromo-*γ*-hydroxybutenolide **469** and tributylvinylstannane has been used as one of the steps in the total synthesis of the nonsteroidal anti-inflamatory sesquiterpene manoalide (Scheme 105).[255]

A racemic 5,12-DiHETE−8,9-cyclopentadiene Diels−Alder adduct **474**, which is a potential precursor of a member of the leukotriene families, has been prepared by palladium-catalyzed ternary coupling between *β*-chloroenone **471**, vinylstannane **473**, and norbornadiene **472** (Scheme 106).[256] In addition,

Scheme 106

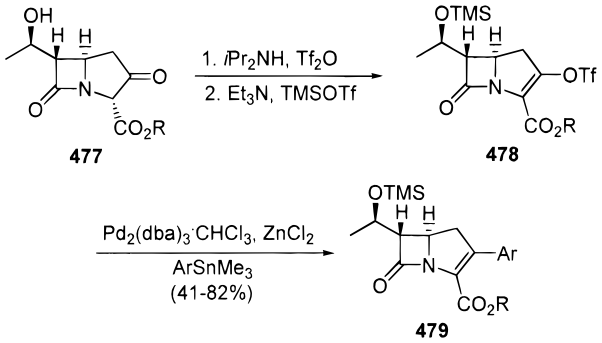


471 472 473 474 475 476

polyunsaturated acylsilanes **476** can be prepared by coupling of (*E*)-3-iodosilane **475** with vinyl, aryl, and alkenyl stannanes (Scheme 106).[257]

The Stille coupling, but now using vinyl triflates instead of vinyl halides, has also been used for the synthesis of different 2-substituted carbapenems[258] or 3-vinylcephems.[259] Example is the enol triflate **478**, prepared from the *β*-keto ester **477**, which coupled in situ with aryl stannanes to give carbapenems **479** (Scheme 107).[258] In addition, 1,4-dicarbonyl-1,3-buta-

Scheme 107

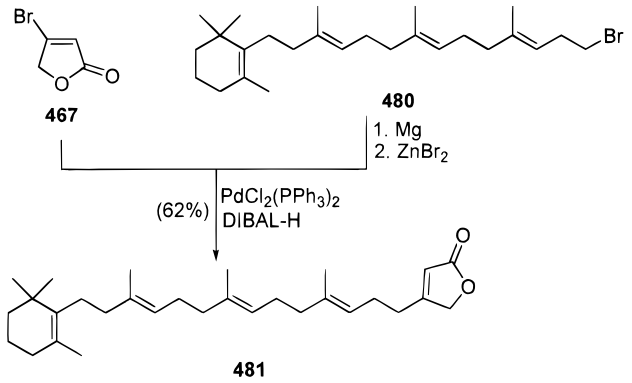


477 478 479

dienes have been obtained by the coupling of enol triflates with α,*β*-unsaturated carbonyl compounds,[260] whereas these triflates reacted also with functionalized organozinc reagents under copper(I)-catalysis.[261]

The Negishi coupling reaction[32] between alkylzinc derivatives and *β*-halogeno-α,*β*-unsaturated carbonyl derivatives have been employed as a stereoselective route to butenolides of terpenoid origin, such as mokupalide (**481**).[262] The synthesis involves treatment of the Grignard reagent of the homoallylic bromide **480** with zinc bromide producing in situ a homoallyl zinc derivative. Palladium(0)-catalyzed coupling of this derivative with 4-bromofuranone **467** afforded mokupalide **481** (Scheme 108). Recently, a

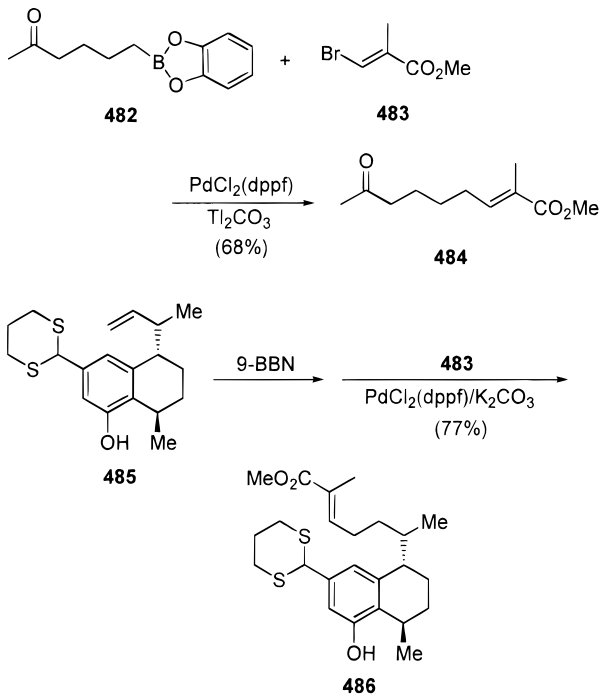
Scheme 108



two step Negishi alkylation-alkynation of α,β-dibromoacrylates has been shown to proceed first at the β-position.[82c]

Suzuki's cross-coupling reaction of organoboron derivatives and organic halides under palladium(0) catalysis,[32] has allowed the employment of β-bromo-α,β-unsaturated carbonyl compounds as β-acylvinyl cationic synthons.[263,264] One example is the reaction of boronic ester **482**, prepared by hydroboration of the corresponding olefin, with methyl β-bromomethacrylate **483** in the presence of a base such as thallium(I) carbonate to give stereoselectively ketoester **484** (Scheme 109). Similarly, when coupling

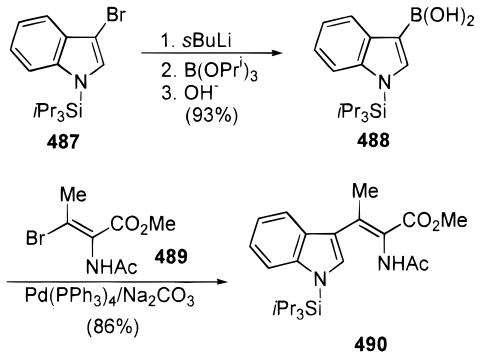
Scheme 109



(*E*)-β-bromoacrylamides with alkenyl- and alkylboronates, biologically active unsaturated amides such as dehydropipernonaline or pipernonaline were prepared.[265] Furthermore, this reaction has been employed in the preparation of ester **486**, which is an intermediate in the synthesis of the anti-inflamatory and analgesic diterpenoid (±)-dihydroxyserrulatic acid.[266] The preparation of this compound involves the hydroboration of the olefin **485**, followed by palladium(0)-catalyzed coupling with methyl β-bromomethacrylate (Scheme 109). Recently, 4-aryl-(5*H*)-furan-2-ones have been prepared by Suzuki coupling of bromobutenolides such as **468** with arylboronic acids, a strategy employed in the total synthesis of the marine antibiotics rubrolides C and E.[267]

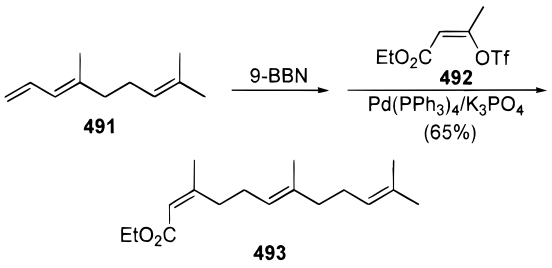
The asymmetric hydrogenation reaction of (*Z*)-didehydro-β-methyltryptophan (**490**) has been a recent way of preparation of (2*R*,3*S*)-β-methyltryptophan.[268] The synthesis of the starting didehydroamino acid derivative **490** involves a key Suzuki coupling of boronic acid derivative **488**, prepared from bromide **487**, and (*Z*)-vinyl bromoacetamidocrotonate **489** (Scheme 110).

Scheme 110



This palladium-catalyzed cross-coupling reaction can also be carried out using vinyl and aryl triflates instead of halides, the order of reactivity being I > Br > OTf. An example is shown in Scheme 111 for

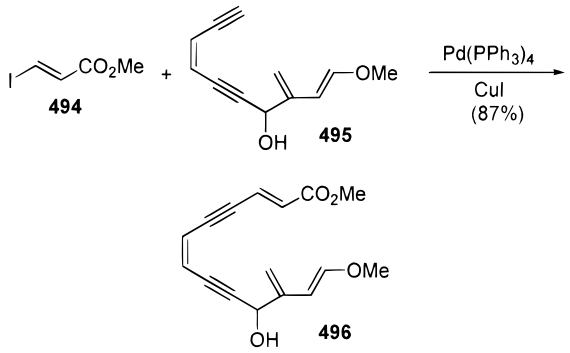
Scheme 111



the reaction of β-trifluoromethanesulfonyloxy crotonate **492** with the organoboron derivative obtained by hydroboration of olefin **491** with 9-BBN.[269] The use of aluminum derivatives for the coupling of β-trifluoromethanesulfonyloxy-α,β-unsaturated esters has also been reported.[80b]

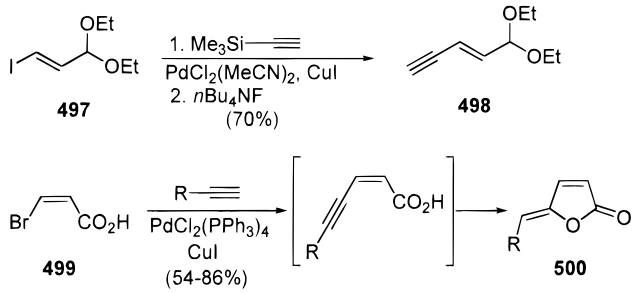
The Sonogashira palladium(0)-catalyzed coupling reaction[32] of terminal acetylenes such as carbinol **495** and vinyl halides, such as methyl (*E*)-β-iodoacrylate (**494**), has been used in synthesis directed toward the bicyclic core of the antitumor agents esperamicin and calichemicin (Scheme 112).[270] In addition, it has been employed in the synthesis of natural anti-cancer epoxycyclohexenone harveynone[76a] or in the preparation of enynal **498** from iodoacetal **497** and trimethylsilylacetylene (Scheme 113).[271] Moreover, this type of cross-coupling reaction with a β-iodocyclopent-2-enone has been used in the synthesis of PGB_1 analogues[272a] or, using (*Z*)-β-bromoacrylic acid (**499**),

Scheme 112



as a route to (*Z*)-γ-alkylidenebutenolides **500** (Scheme 113).[272b] The mechanism involves formation of yneno-

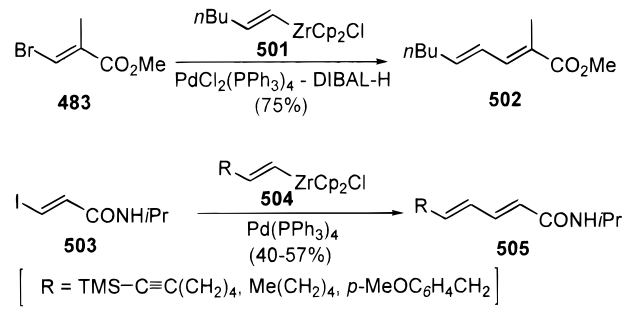
Scheme 113



ic acid intermediate, followed by palladium(II)-mediated *trans*-addition of the carboxylate anion across the carbon−carbon triple bond and final reductive elimination. γ-Alkylidenebutenolides such as rubrolides A, C, D, and E have been similarly prepared by palladium-catalyzed coupling of (*Z*)-β-aryl-β-iodoacrylic acids and alkynyl zinc derivatives, which were obtained by lithiation of terminal alkynes followed by addition of zinc bromide[273a] following a previously reported methodology.[273b] Recently, β-(1′-alkynyl)butenolides have been prepared by coupling of β-halobutenolides with terminal alkynes,[273c] whereas (*E*)-γ-tributylstannylmethylidene butenolides have been prepared by coupling of tributylstannyl 3-iodopropenoate derivatives with tributyltinacetylene.[273d]

Vinylzirconium derivatives have also been used as organometallic counterparts in palladium-catalyzed cross-coupling reactions with β-halo-α,β-unsaturated carbonyl compounds. Thus, (*E*)-1-alkenylzirconium compound **501**, prepared by reaction of the corresponding acetylene with Schwartz's reagent ZrH(Cl)-Cp_2, undergoes in situ coupling with vinyl bromides such as methyl (*E*)-β-bromomethacrylate (**483**) to

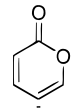
Scheme 114



afford conjugated dienic ester **502** (Scheme 114).[274] This type of coupling reaction has also been employed in the preparation of naturally occurring dienamides **505**, starting from (*E*)-β-iodoacrylamide **503** (Scheme 114).[275,276]

VI. γ-Acyldienyl Anionic Synthons

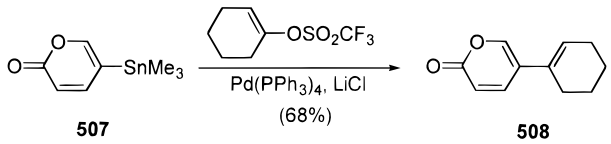
At least an example can be related to such d^4 synthons, corresponding to an equivalent of the cyclic anion **506** and involving a Stille coupling reaction.



506

Thus, 5-(trimethylstannyl)-2*H*-pyran-2-one (**507**) reacts with the enol triflate from cyclohexanone under palladium(0)-catalysis affording pyran-2-one derivative **508**, (Scheme 115) a methodology which has been employed for the synthesis of cardiotonic agents lucibufagins and bufadienolides.[277]

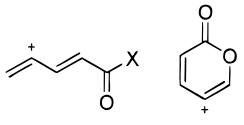
Scheme 115



VII. γ-Acyldienyl Cationic Synthons

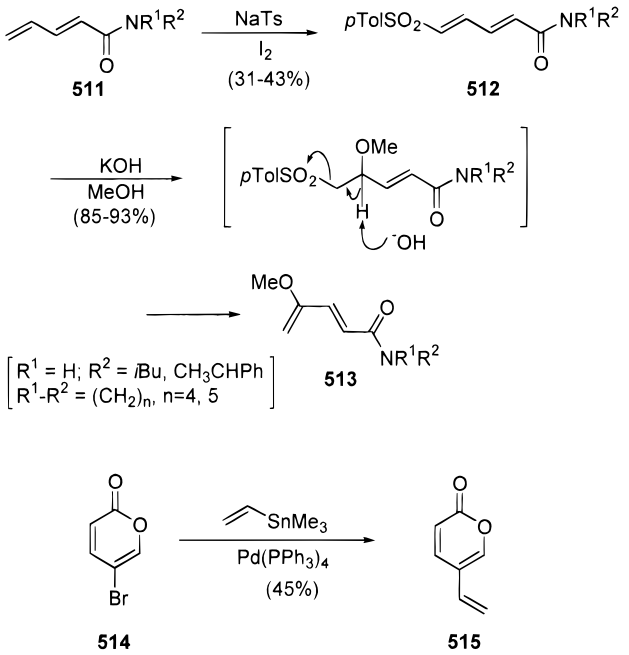
Few reports exist on the use of synthetic equivalent of the γ-acyldienyl cationic umpolung synthon type a^4 such as **509**, sulfonyldienamides **512** being an interesting case. These sulfones are stereoselectively prepared from (2*E*)-pentadienamides **511** by an in situ iodosulfonylation-dehydroiodination procedure, and react with potassium hydroxide in methanol to afford (2*E*)-4-methoxy-2,4-pentadienamides **513** resulting from the Michael addition of the methoxide anion to the vinyl sulfone moiety followed by dehydrosulfinylation (Scheme 116).[278a] These final dienamides behave as electron-rich dienes in Diels−Alder reactions giving highly functionalized adducts.

5-Bromo-2*H*-pyran-2-ones such as **514** can be considered synthetic equivalents of the γ-acyldienyl cationic synthon **510**. These systems have been used



in palladium-catalyzed coupling reactions such as the Stille coupling between compound **514** and vinyltrimethyltin (Scheme 116).[278b] These bromopyran-2-ones have also been used in Negishi palladium-catalyzed cross-couplings with alkylzinc reagents for the synthesis of supellapyrone a sex pheromone of the brownbanded cockroach *Supella longipalpa*,[278b]

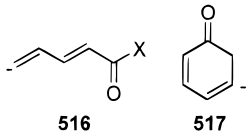
Scheme 116



as well as in Suzuki couplings with arylboronic acids.[278c]

VIII. δ-Acyldienyl Anionic Synthons

As seen above, the *β*-acylvinyl anions of the type **179** are interesting carbanionic intermediates with umpolung reactivity. Consequently, the *δ*-acyldienyl equivalents of cyclic and acyclic vinylogous anions **516** or **517** would be considered as d^5 synthons with

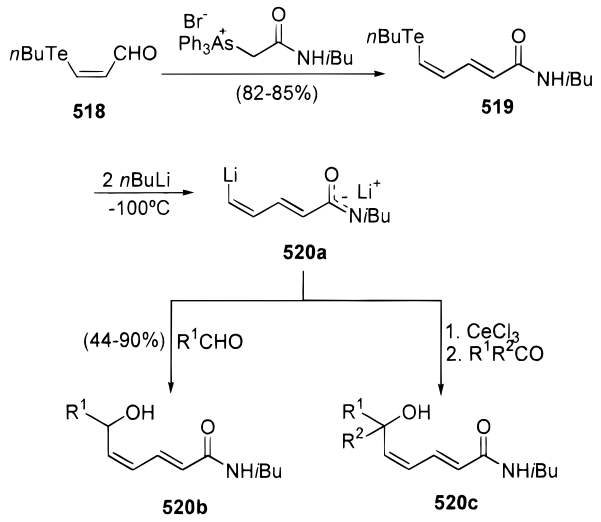


umpolung reactivity,[3] suitable to transfer an α,*β*,*γ*,*δ*-diunsaturated functionality to electrophilic reagents.

The generation of a *δ*-anion on a *δ*-acyldienyl system has only been recently achieved by transmetalation of a dienic organotelluride.[279a] Thus, (2*E*,4*Z*)-5-telluropentadienamide **519** was prepared by condensation of (*Z*)-*β*-butyltelluroacrolein **518** with a triphenylarsonium bromide amide derivative and was treated with butyllithium at −100 °C to provide dilithiated intermediate **520a**. This species reacted with aldehydes to give the corresponding (2*E*,4*Z*)-hexadienamides **520b**. When the lithiated intermediate **520a** was treated with cerium chloride, the created organocerium reagent was able to react also with ketones (Scheme 117).

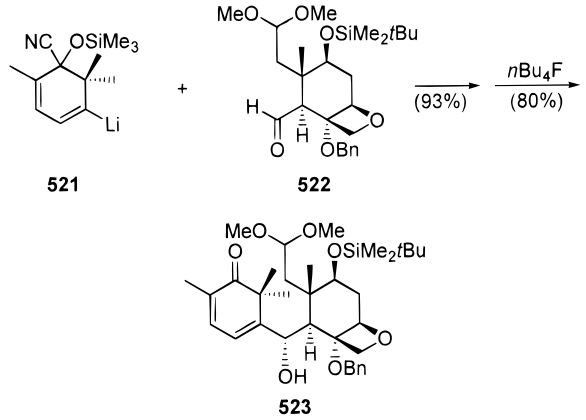
A masked cyclic *δ*-acyldienyl anionic synthon of the type **517** has been used in one of the total synthesis of taxol. Thus, the lithiated diene **521** reacts stereoselectively with aldehyde **522** to give, after desilylation-cyanide elimination, conjugated dienone **523**

Scheme 117



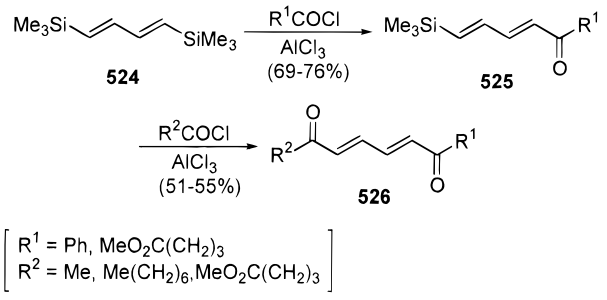
which bears rings A, C, and D of the taxol skeleton (Scheme 118).[279b,c]

Scheme 118



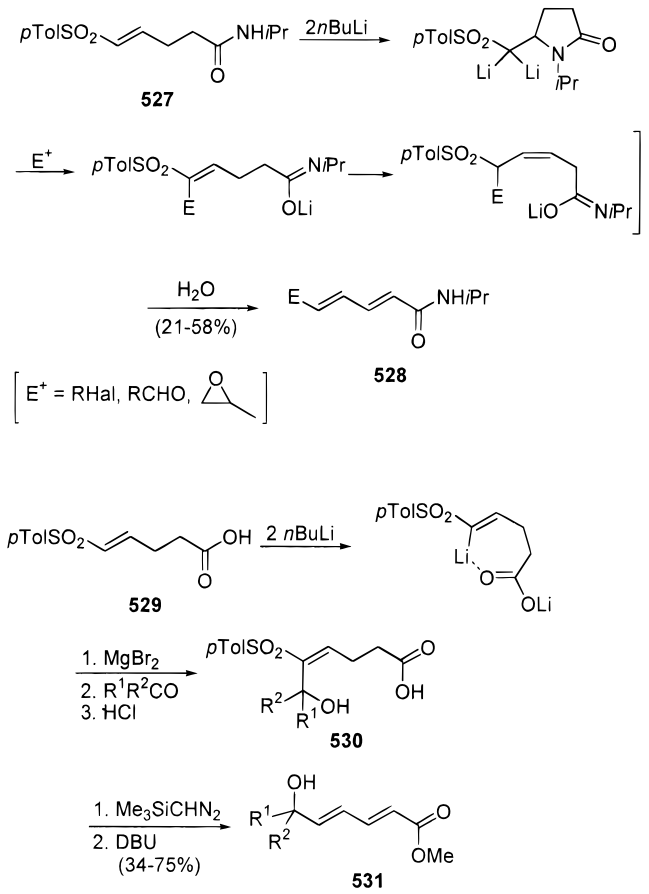
(1*E*,3*E*)-1,4-Bis(trimethylsilyl)buta-1,3-diene (**524**) can be used for the preparation of *δ*-silylated dienones **525** by electrophilic substitution reaction with acyl chlorides in the presence of aluminum trichloride. These obtained dienones **525** are synthetic equivalents of the synthon **516** and react similarly with acyl chlorides to afford 1,6-dicarbonyl compounds **526** with a conjugated diene structure (Scheme 119)[280a,b] and other polyenes.[280c]

Scheme 119



(*E*)-*N*-isopropyl-5-(*p*-toluenesulfonyl)pent-4-enamide (**527**), prepared from pent-4-enoic acid by stereoselective iodosulfonylation-dehydroiodination and fur-

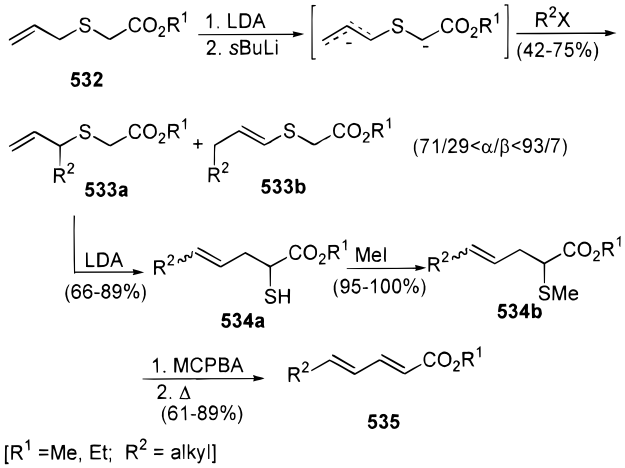
Scheme 120



ther amidation, has been used as precursor of a δ-acyldienyl anion equivalent of the type **516** (X = NH*i*Pr). The procedure implies intramolecular Michael addition of deprotonated vinyl sulfone **527** to give a lactam dianion intermediate which reacts at the α-position relative to the sulfone group with electrophiles such as aldehydes, alkyl halides, and epoxides. Further ring opening, double bond isomerization, and final δ-dehydrosulfinylation afford regio- and stereoselectively (2*E*,4*E*)-dienamides **528** (Scheme 120).[281] A related starting material, (*E*)-5-(*p*-toluenesulfonyl)-pent-4-enoic acid (**529**), also acts as δ-acyldienyl anion equivalent after lithiation at the vinylic position and reaction with carbonyl compounds. The obtained acids **530** have been transformed into methyl (2*E*,4*E*)-6-hydroxy-2,4-dienoates **531** by esterification with trimethylsilyldiazomethane followed by dehydrosulfinylation with DBU (Scheme 120).[282]

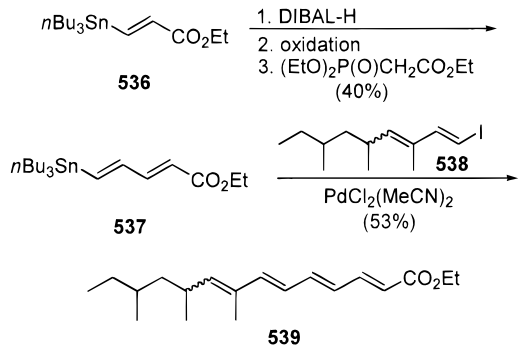
The dianions derived from (allylthio)acetates **532** have been also used as precursors of the δ-acyldienyl anion synthon **516**. Thus, treatment of the allylic system **532** with lithium diisopropylamide and *sec*-butyllithium, followed by further reaction with alkyl halides, gave α- and γ-monoalkylated products **533a** and **533b**. Reaction of the α-isomer **533a** with lithium diisopropylamide resulted in [2,3]-sigmatropic rearrangement and formation of the 2-mercaptocarboxylic esters **534a**, which are treated with methyl iodide giving 2-(methylthio)carboxylic esters **534b**. Oxidation of **534b** with *m*-chloroperbenzoic acid and thermal dehydrosulfenylation afforded (2*E*,4*E*)-dienoates **535**, which are precursors of dienamides (Scheme 121).[283]

Scheme 121



Dienylstannanes have been used in Stille palladium-catalyzed cross-coupling reactions with vinyl iodides[284a] or bromides[284b] as δ-acyldienyl anions. Scheme 122 shows the preparation of dienic ester **537**

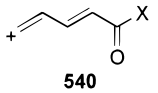
Scheme 122



from (*E*)-β-stannylacrylate **536**. Subsequent palladium-catalyzed coupling with iodide **538** yielded a mixture of tetraene double bond isomers **539**, the all-*E* being the C9−C25 fragment of the B2 selective bradykinin inhibitor L-755,807.[284a] Carbonyl-protected dienyl stannanes have also been employed in palladium-catalyzed coupling reactions,[271] whereas 5-trimethylstannyl-substituted dienic esters have been reported to suffer copper(I) chloride-mediated oxidative homocouplings.[284c]

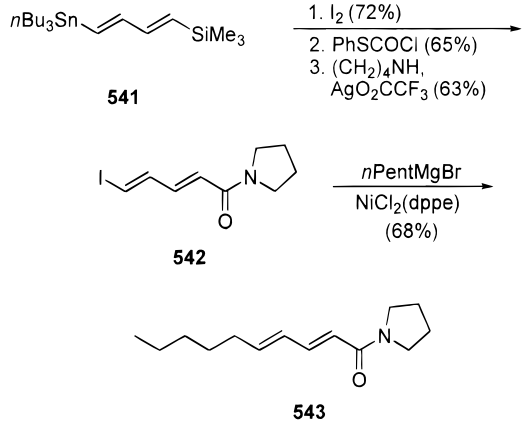
IX. δ-Acyldienyl Cationic Synthons

The possibility of a nucleophilic vinylic 1,6-substitution on conjugated dienic carbonyl compounds bearing a potential leaving group at the δ-position would allow the consideration of these kinds of compounds as equivalents of the δ-acyldienyl cationic a^5 synthon **540**.[3] For example, δ-iododienamides such



as **542**, prepared from stannylsilylbutadiene **541** following the sequence outlined in Scheme 123, react

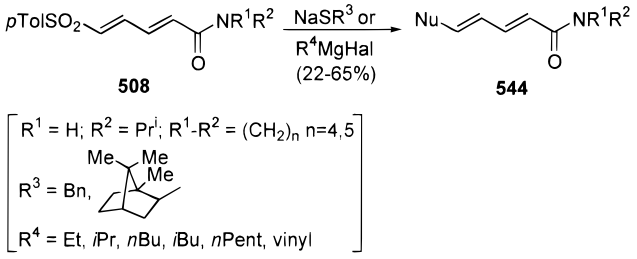
Scheme 123



with Grignard reagents such as *n*-pentylmagnesium bromide in the presence of a nickel catalyst to afford naturally occurring dienamides such as sarmentine (**543**).[1c,285a] Moreover, δ-chlorodienyl ketones have been employed in this type of substitution reaction with sodium sulfide,[285b] whereas the sulfide group has also been used as leaving group in substitution reaction with amines[285c−e]

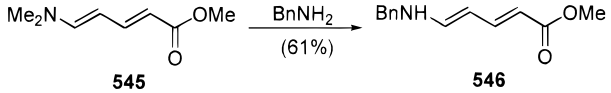
The sulfonyl group on dienamides has also been used as a leaving group in addition−elimination vinylic substitution reactions. Thus, the already mentioned sulfonyldienamides **508**, which can also act as a γ-acyldienyl cationic equivalent (see Section VI), suffer nucleophilic substitution by sodium thiolates and Grignard reagents to give regio- and stereoselectively (2*E*,4*E*)-dienamides **544**. This methodology has been applied to the synthesis of sarmentine and an *Achillea* amide[286a] (Scheme 124). In

Scheme 124



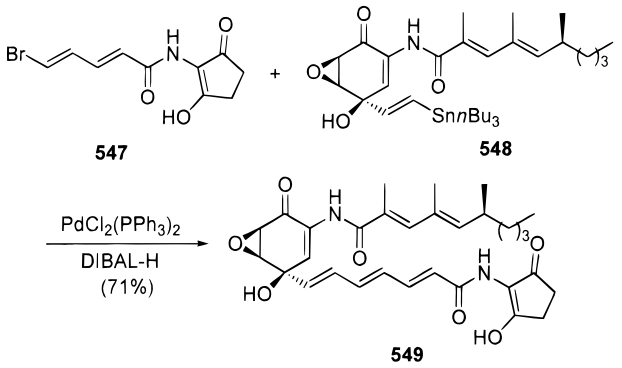
addition, organocuprates have been used as nucleophiles in this vinylic 1,6-disubstitution reaction with phosphate,[286b] trimethanesulfonyloxy,[286b] and *n*-butyltelluride[286c] acting as leaving groups, whereas selenium dienoates reacted with organolithium compounds to give dienic aldehydes and ketones in an apparent 1,5-carbonyl transposition sequence.[215b] δ-Aminodienylesters such as **545** react with benzylamine producing interchange of the amine moiety, which allows the isolation of dienic esters such as **546** (Scheme 125).[287]

Scheme 125



The above seen palladium(0)-catalyzed cross-coupling reactions[32] using halogenated equivalents

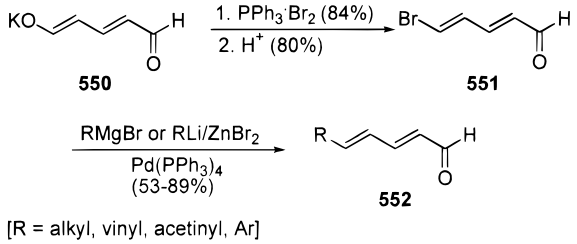
Scheme 126



of the β-acylvinyl cationic synthon **404** can be extended using δ-haloacyldienyl systems.[247,288] Thus, the Stille coupling reaction between a δ-iododienamide and a vinylic stannnyl compound has been used in the total synthesis of antiviral and antitumor natural product onnamide A,[1c,288b] whereas δ-iododienoic acids have been used for the preparation of retinoic acids with all-trans stereochemistry.[288c] This reaction, but employing δ-bromodienamide **547** and different vinylic stannanes, has been used as a method for the synthesis of naturally occurring polyenamides.[161,252,289,290] For example, compound **547** has been coupled with stannane **548**, with a prereduced palladium catalyst for the preparation of the (+)-enantiomer of the antibiotic manumycin A (**549**) (Scheme 126),[291] some of its analogues,[289,292] and also the *Streptomyces*-produced biosynthetic precursor of the antibiotic triamide asuka-*m*ABA.[252,290]

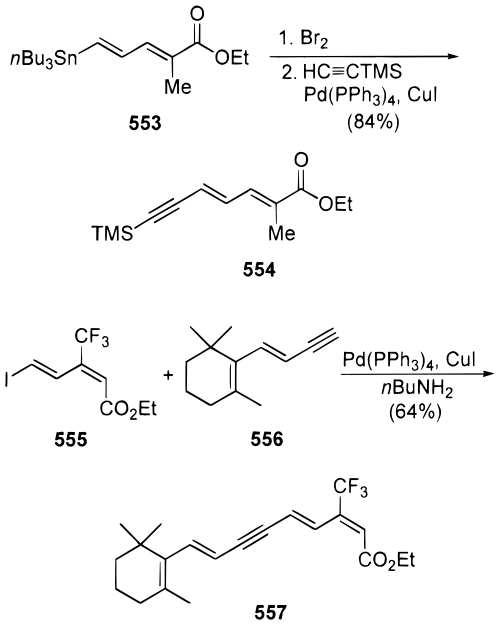
Negishi's palladium-catalyzed coupling of vinyl halides and organozinc reagents[32] have been employed as an access to (2*E*,4*E*)-dienals.[293] using a synthon type **540**. Thus, (2*E*,4*E*)-5-bromopenta-2,4-dienal (**551**), which can be efficiently prepared by bromination of gluconaldehyde potassium salt (**550**) and acid-mediated thermodynamic equilibration, reacts with in situ prepared organozinc compounds to achieve stereoselectively dienals **552** (Scheme 127).

Scheme 127



In addition, Suzuki cross-coupling between ethyl (2*E*,4*E*)-5-iodo-3-methylpenta-2,4-dienoate and vinylboronic acids has been used for the preparation of different retinoids.[294a] Furthermore, Sonogashira coupling of the δ-bromoester obtained from dienylstannane **553** and trimethylsilylacetylene afforded dienic ester **554**, which has been employed in the total synthesis of the polyene 6,7-dehydro-stipiamide, a compound which reverses the multidrug resistance (MDR) of human breast cancer cells (Scheme 128).[294b] Recently, Stille and Sonogashira cross-coupling reactions have been used for the stereoselective synthesis

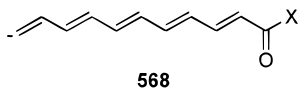
Scheme 128



of ethyl (13*E*)-trifluoromethylretinoate and analogues such as **557** starting from ethyl (2*E*,4*E*)-5-iodo-3-trifluoromethylpenta-2,4-dienoate (**555**) as shown in Scheme 128 with a Sonogashira reaction.[294c]

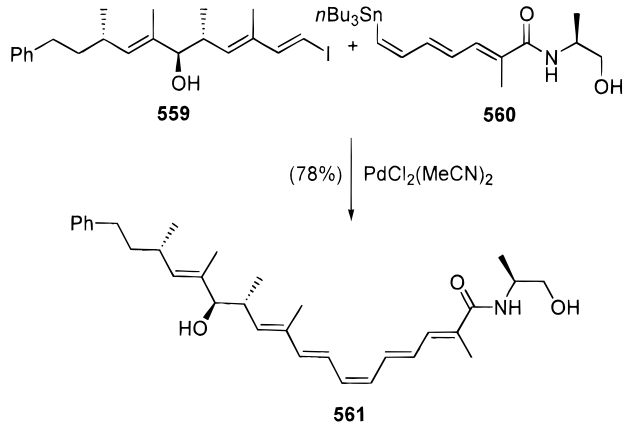
X. ζ-Acyltrienyl Anionic Synthons

References on the use of synthetic equivalents of the ζ-acyltrienyl anionic synthon type d^7 **558** are very



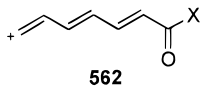
scarce. Thus, (6*Z*)-stannylated trieneamide **560** has been stereoselectively coupled with (*E*)-dienyl iodide **559** under Stille palladium-catalyzed conditions in the final step of the total synthesis of (−)-stipiamide (**561**) (Scheme 129).[294a]

Scheme 129



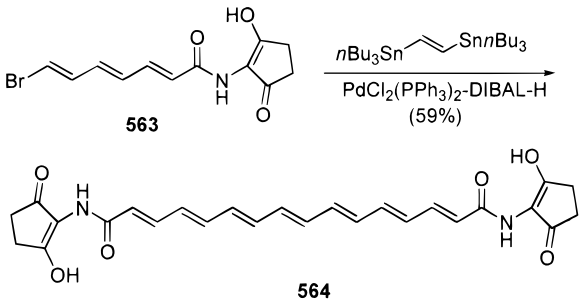
XI. ζ-Acyltrienyl Cationic Synthons

Similarly as the case of the above seen ζ-acyltrienyl anionic synthon, references to the cationic counterpart type a^7 **562**, are rare and centered in the preparation of acyltrienylhalides for the Stille reac-



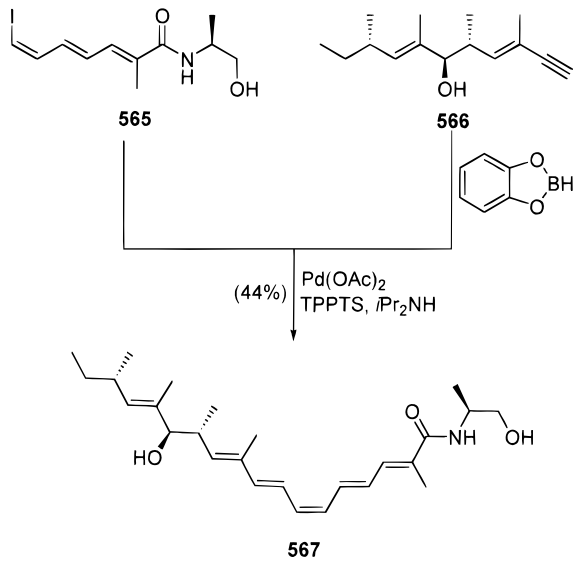
tion. Thus, the synthesis of the antiviral bis-2-amino-3-hydroxycyclopentenone diamide limocrocin (**564**) has been achieved by palladium prereduced-catalyzed cross-coupling reaction of 2 equiv of ζ-bromotrienamide **563** with (*E*)-1,2-bis(tributylstannyl)ethene (Scheme 130).[252,290] Moreover, stannane **560** when

Scheme 130



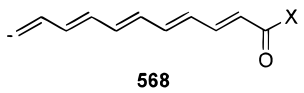
reacted with iodine afforded the corresponding iodotriene **565** which has been used in a Suzuki coupling reaction for the synthesis of polyene antibiotic myxalamide A (**567**) (Scheme 131).[295]

Scheme 131



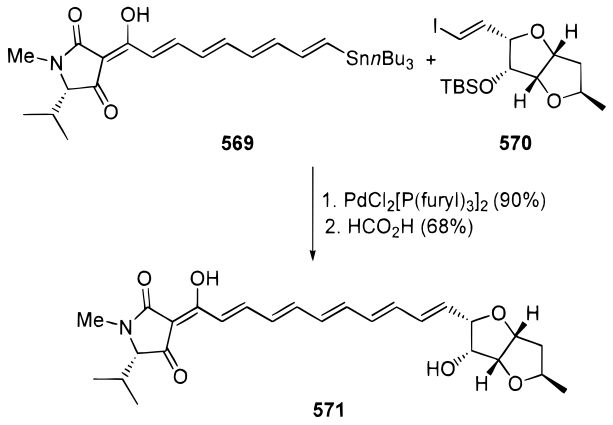
XII. Other Acylpolyenyl Synthons

ω-Halogeno polyenol ethers have been metalated and reacted with aldehydes and ketones to afford different polyenals, the lithiated species being equivalents of different acylpolyenyl anion synthons.[296] Recently, an acyltetramic acid polyene tributylstannyl derivative **569** has been employed in a Stille coupling reaction with iodoalkene **570** (Scheme 132).[297] This polyene could be considered a synthetic equivalent of a κ-acylhexaenyl anionic synthon type d^{11} **568**.



Final deprotection using neat formic acid afforded

Scheme 132



polienoyltetramic acid erythroskyrine (**571**), a mycotoxin which exhibits antibiotic action against some *Staphylococcus* species. A similar polyene tin derivative has been employed in the synthesis of the plasmodial pigment physarorubinic acid by Stille coupling.[298]

XIII. Conclusions

This review has shown how extensive the search for methodologies able to transfer the important acylvinyl and vinylogous moieties has been, with a special attention devoted to α- and β-acylvinyl anionic synthons. Generally, all these systems allow achieving high stereocontrol in the final conjugated system, especially in the acyclic series. Moreover, the development of a series of palladium-catalyzed cross-coupling reactions, which avoid carbonyl protection-deprotection steps, has expanded enormously the use of all these synthons beyond the traditional substitution reactions. However, the use of acylpolyenyl synthons able to transfer this moiety for the synthesis of a vast array of natural products is still rare compared with their acylvinyl counterparts. Substantially more work in this field is warranted to develop new reagents and methodologies capable to give response to many synthetic challenges.

XIV. Acknowledgments

The general financial support by the Spanish Ministerio de Educación y Cultura is gratefully acknowledged. We thank the referees for their interesting suggestions.

XV.References

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