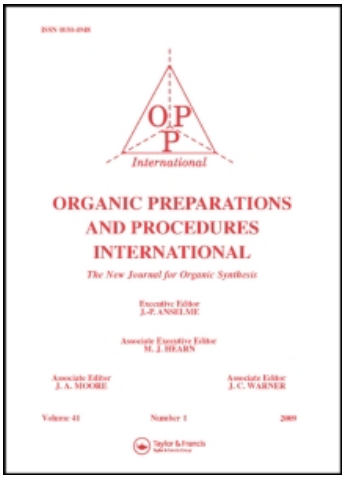

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MICHAEL ADDITION OF ORGANOLITHIUM COMPOUNDS. A REVIEW

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INTRODUCTION

The addition of carbanions to Michael acceptors continues to be one of the cornerstones for carbon-carbon bond formation in organic synthesis. While a plethora of methods have been developed and widely utilized in organic chemistry addressing this type of transformation,[1] one area which has slowly developed and only recently shown promise is the conjugate addition of organolithium reagents to Michael acceptors.

Prior to 1978, the literature was sparse in this area due to studies indicating that hard nucleophiles have a propensity to add 1,2- versus 1,4- to Michael acceptors.[2] Some studies involving manipulation of standard reaction conditions were encouraging indicating that the ratio of 1,4- versus 1,2-addition could be enhanced, but still 1,2-addition products predominated. During this time, the majority of work targeting conjugate addition of organolithium reagents entailed the generation of cuprates from the desired RLi precursor.[1] This technique, while effective, has been limited by the conditions necessary for the generation of the cuprate reagents, thus precluding the use of certain electrophilic functional groups contained on the transfer ligand.[3]

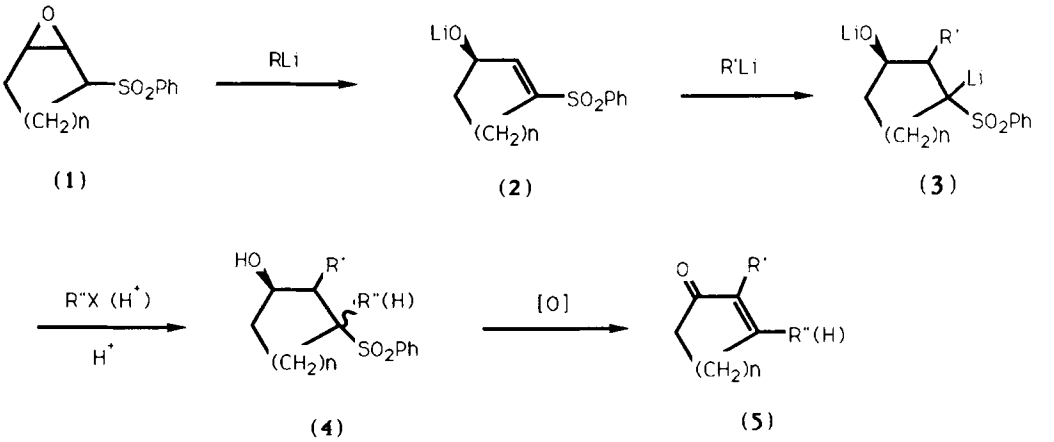
The advent of highly functionalized organolithium reagents,[4] coupled with a more thorough understanding of the mechanisms involved in the reaction of organometallic reagents with Michael acceptors,[5] has renewed interest in conjugate addition reactions with organolithium compounds during in the past decade. This review has been undertaken in order to address the advances made in this important area of

organic synthesis, focusing primarily on non-enolate system work reported in the literature during the last fifteen years up to the end of 1988.

I. REACTION OF ORGANOLITHIUM REAGENTS WITH VINYL SULFONES AND VINYL SULFOXIMINES

The first description of the Michael-type reactivity of α,β-unsaturated sulfones toward organometallic reagents was recorded over fifty years ago by Kohler and Potter.[6] These studies focused on the addition of Grignard reagents to the unsaturated sulfone moiety and indicated that Michael additions were the predominant reaction pathway. Vinyl sulfone reactivity toward cuprates was investigated in the late seventies by Posner[7] and Fiandanese,[8] with results once again indicating the 1,4-addition mode predominated. It was not until 1978 that reports surfaced on the reaction of reaction of vinyl sulfones with organolithium reagents.

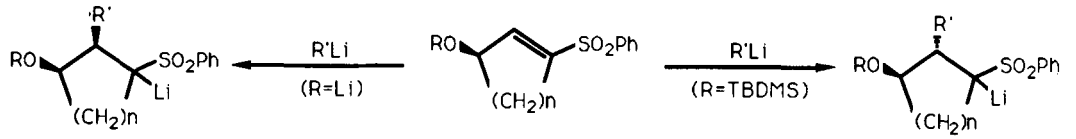
Initial reports[9] focused on the addition of simple organolithium reagents to γ-oxido-α,β-unsaturated sulfones of the type (**2**), followed by electrophilic quenching of the intermediate anion (**3**) to give the elaborated cycloalkanol (**4**). Chromate oxidation and elimination of the sulfone moiety gives 2,3-disubstituted cycloalkanones (**5**) in good yields. The utility of this method is demonstrated by the minimal manipulation required (2-pot sequence) without necessary isolation of the intermediates.



(**1**) (**2**) (**3**) (**4**) (**5**)

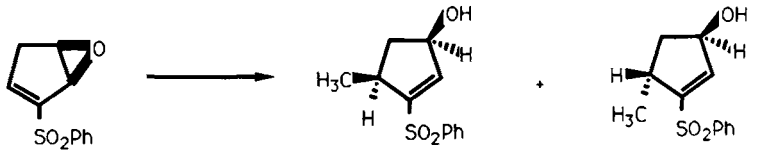
In order to further define the scope of this reaction sequence, subsequent studies

concentrated on factors responsible for the stereochemical outcome of the introduction of the organometallic reagent to the β-position. This work revealed that the stereochemistry of the incoming organometallic reagent could be controlled by the judicious selection of the γ-oxygen substitutents.[10] The influence exerted by the γ-oxygen has been attributed to complex-mediated directing effects of the lithium alkoxide to give the cis product (**7**) versus steric directing effects for the trans product (**8**). Additionally, the structure of the sulfone group plays a crucial role in conjugate addition versus metallation α- to the sulfone.[11]

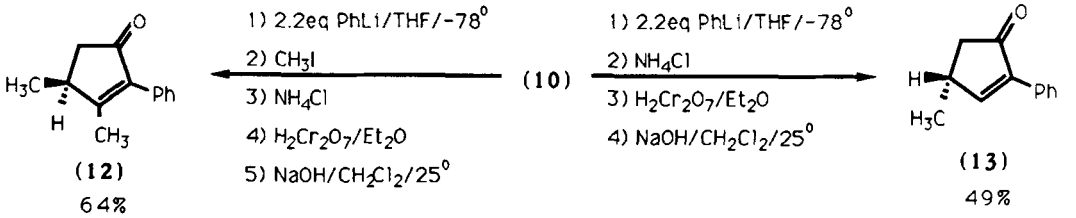


(**7**) (**6**) (**8**)

This general procedure serves as a cornerstone for the enantiospecific preparation of γ-substituted enones (**12**,**13**) via epoxy vinyl sulfones (**9**).[12]



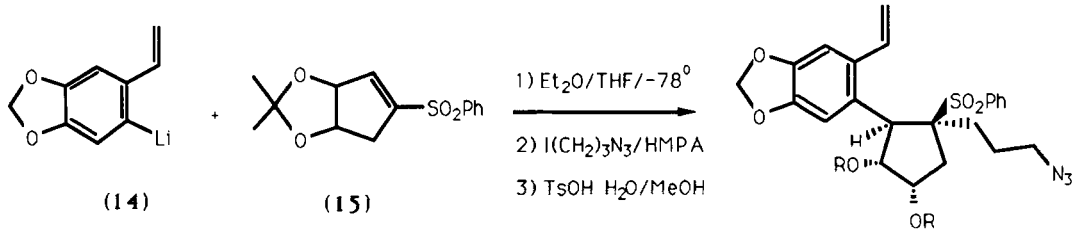
(**9**) (**10**) 65% (**11**) 15%



(**12**) 64% (**13**) 49%

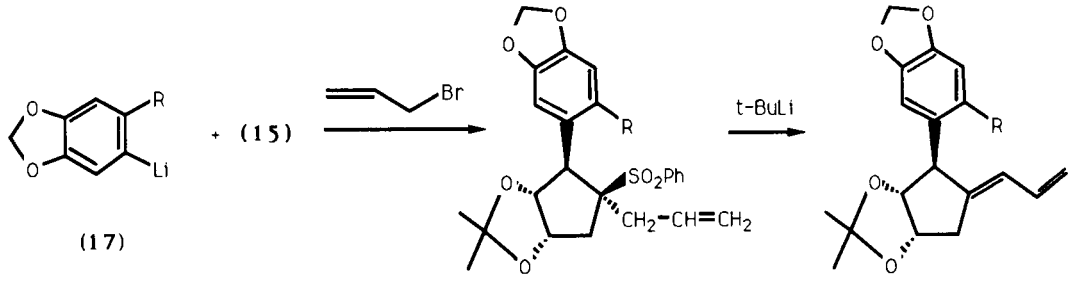
Extensions of this technique have been applied to the preparation of more complex systems by the use of highly functionalized organolithium reagents. For example, condensation of aryllithium reagent (**14**) with vinyl sulfone (**15**) afforded an α-sulfonyl anion which was alkylated with 3-iodopropyl azide to give the triply converged

adduct (16).[13]



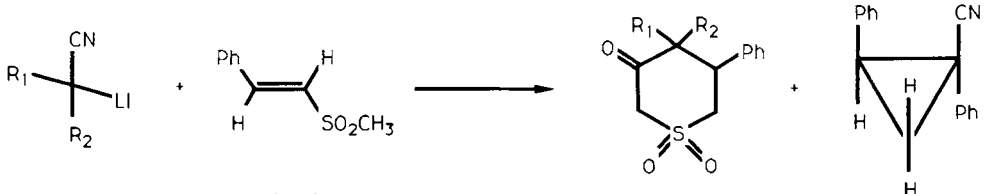
(14) (15) (16)

A further example of the utility of this method involves the loss of the sulfone group as a facile route to 1,3-dienes (19).[14]



(17) (18) (19)

Michael addition of organolithium reagents to vinyl sulfones has proven to be an excellent procedure for the construction of cyclic products. Agawa applied this technique to the preparation of 3-oxathian-1,1-dioxides (22) and cyclopropane derivatives (23) in good yields.[15] Takaki has utilized the condensation of methyl styryl sul-

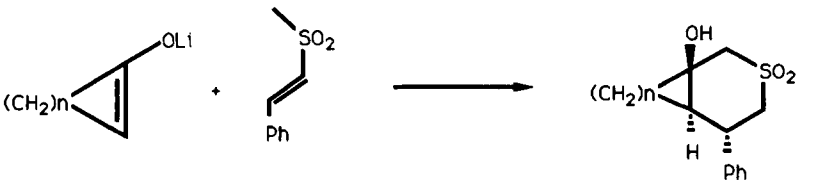


(20) (21) (22) (23)

a: $R_1=R_2=H$ - 51%
b: $R_1=H$, $R_2=Me$ -76%
c: $R_1=R_2=Me$ -80%
d: $R_1=H$, $R_2=Et$ -89%

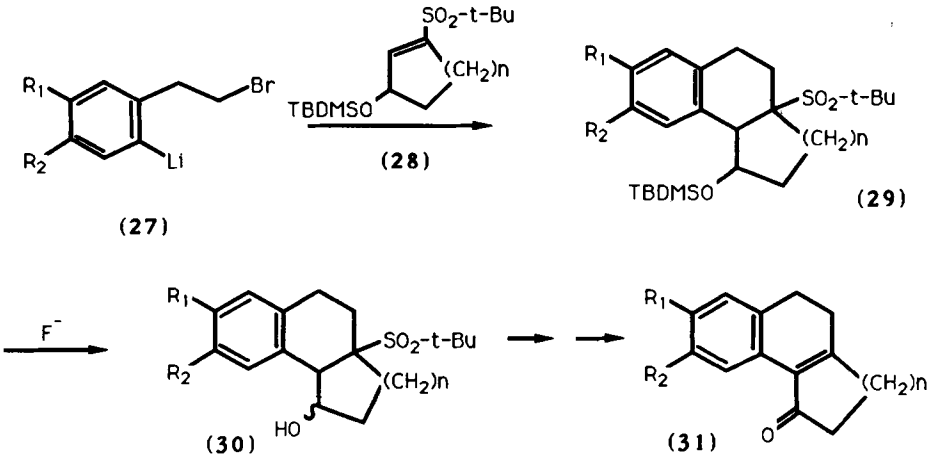
68%

fones (25) with lithium enolates as a method for the preparation of cyclic sulfones (26).[16]



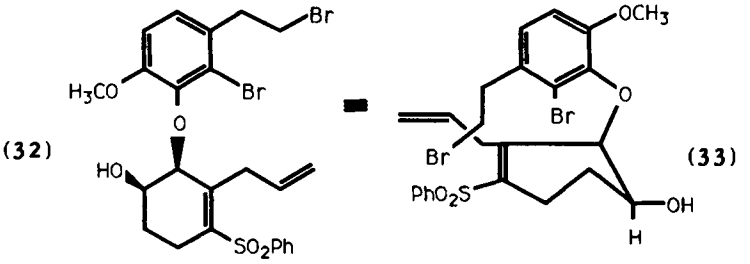
(24) (25) (26)

Helquist and Fuchs have shown that functionalized aryllithium reagents of the type (27),[4a] formed by the low temperature metal-halogen exchange of the corresponding aryl bromide, react with cyclic vinyl sulfones (28) to give tricyclic ring systems (31) after appropriate transformations.[17]

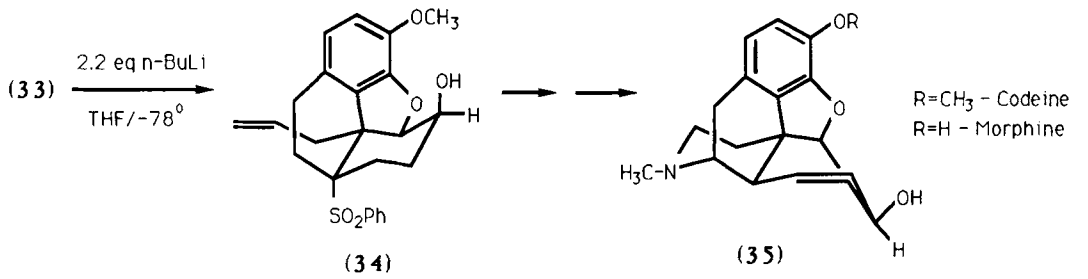


(27) (28) (29) (30) (31)

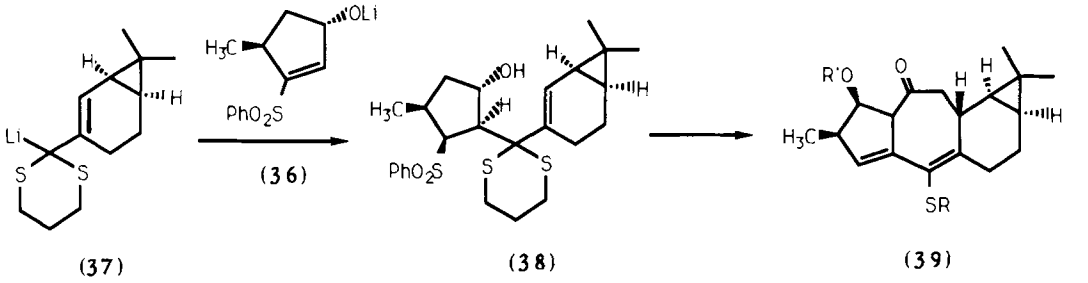
This annulation methodology has culminated in the use of these reactions as key steps in the stereoselective synthesis of natural products. A prime example of the use of this technique is the elegant synthesis of (d,l)-morphine (35), with the key step utilizing an intramolecular Michael addition of the aryllithium derivative from (33) to give the tetracycle (34).[18]



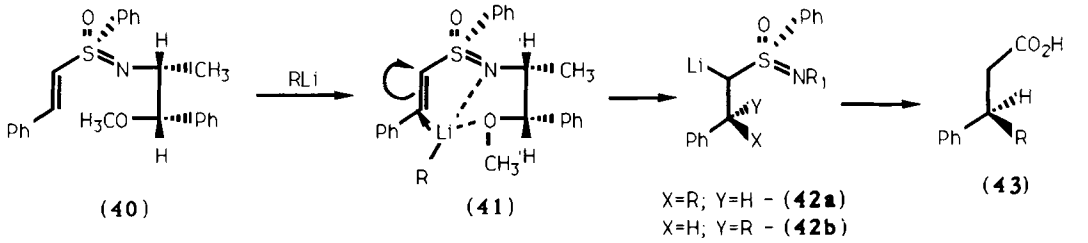
(32) (33)



The wide applicability of the vinyl sulfone condensation method is also revealed through the preparation of a chiral tetracyclic synthon (**39**) of the lanthrane diterpenes via the key intermediate (**38**).[19]



Based on analogy with the addition behavior of vinyl sulfones, Pyne has investigated the use of chiral sulfoximines (**40**) as Michael acceptors for asymmetric conjugate addition.[20] The high degree of asymmetric induction observed during the con-



jugate addition step can be attributed to the intramolecular chelation of the organometallic reagent (**41**). Thus, the corresponding phenyl propionic acids (**43**) prepared by this route have >90% e.e.

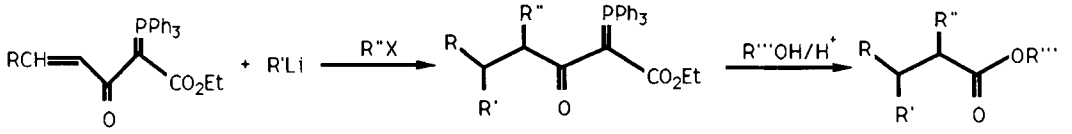
II. CHARGE-DIRECTED CONJUGATE ADDITIONS WITH UNSATURATED ACYL DERIVATIVES OF (CARBOETHOXYMETHYLENE)TRIPHENYLPHOSPHORANE

Attempts at carrying out 1,4-additions to Michael acceptors generally require the

use of weak or highly stabilized nucleophiles, or hard nucleophiles converted to soft nucleophiles by chemical transformation (i.e., RLi to R_2CuLi). Procedures have also been devised which entail select nucleophiles or Michael acceptors based on size (i.e., steric bulk prohibiting 1,2-addition; vide infra) or requisite softening of a donor molecule.

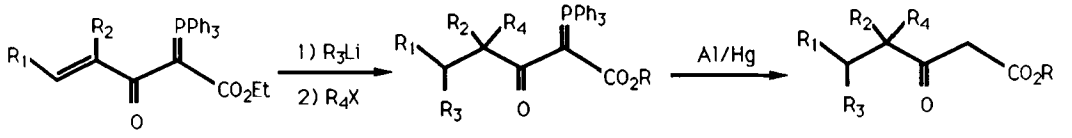
Charge-directed conjugate addition involves the preparation of an unsaturated carbonyl deactivated system possessing latent functionality enhancing the receptivity of the unsaturation site toward nucleophilic attack giving a stable, yet reactive dianionic species. The deactivating moiety, after elaboration of the parent system, can then be removed by simple chemical methods. Cooke's group has extensively developed this methodology during the past decade. This technique has proven to be an equivalent to formal conjugate addition of hard nucleophiles to α,β-unsaturated carbonyl systems without additional elaboration of the nucleophile.

The stabilizing group meeting these requirements for the Michael acceptor is the acylphosphorane[21] based on studies indicating that this group renders the carbonyl unit resistant to attack by nucleophiles and has the ability to stabilize the resulting carbanionic center, which can then be elaborated by nucleophiles.[22] This technique is amenable to a series of transformations on the triphenylphosphoranylidene group

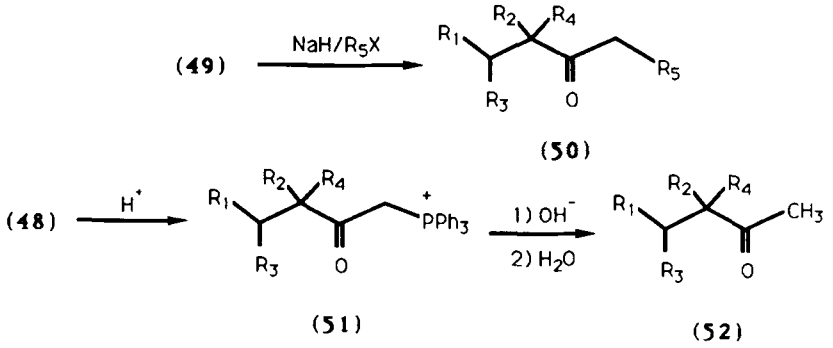


(44) (45) (46)

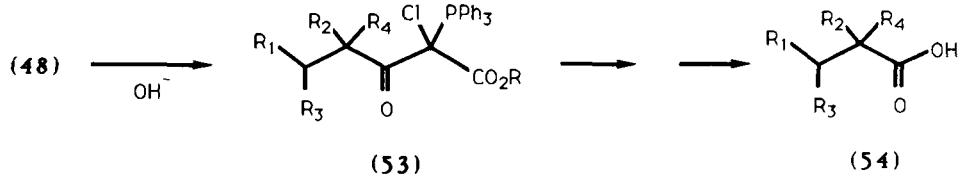
after conjugate addition and subsequent alkylation of the resulting carbanion to give rise to ketones (**48-50,52**).[23,24] Oxidative hydrolysis of the triphenylphosphoranylidene (**48**) with alkaline NaOCl in either THF or acetonitrile gives the corresponding



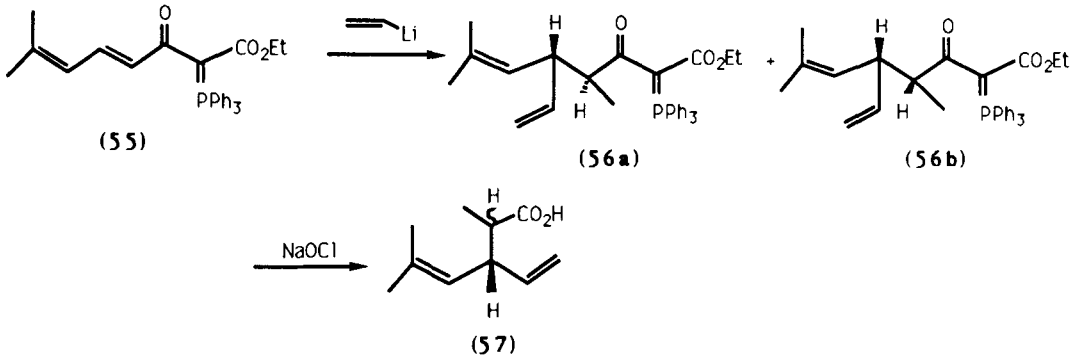
(47) (48) (49)



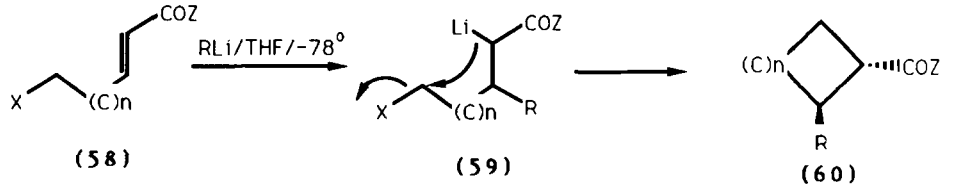
carboxylic acid (**54**). The overall reaction is the synthetic equivalent of a Michael addition to acrylic acid. This method has been applied to a facile synthesis of epi-santo-



linate (**57**) from the acylphosphorane (**55**).[25]

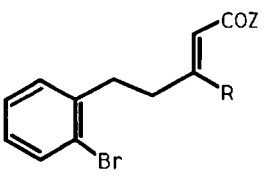


A useful extension of this method involves addition of an organolithium reagent to the functionalized acylphosphorane (**58**), followed by trapping of the intermediate carbanion (**59**) with an internal electrophile to give cyclized products of the type (**60**).[26] The exclusive formation of the trans isomer suggests a high preference for

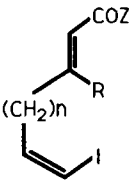


the cyclization of (**59**) by attack of the nucleophile from the face least hindered by the β-substitutent onto the electrophilic center.

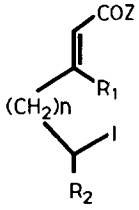
Cooke and Widener have extended this general technique to include lithium-halogen exchange-initiated intramolecular conjugate addition reactions of unsaturated acylphosphoranes of the type (**61**).[27] Critical to the success of the reaction is halide



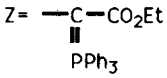
(**61a**)



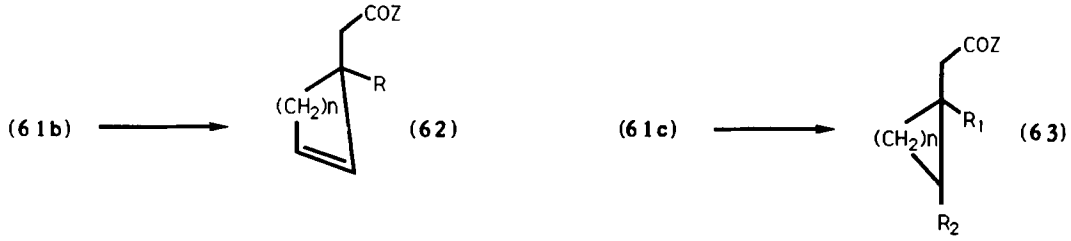
(**61b**)



(**61c**)

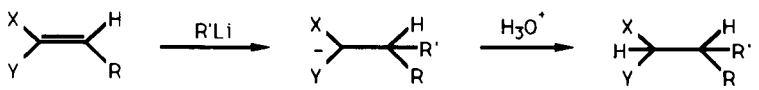


type, chain length, and the substitution pattern of the Michael acceptor portion of the molecule. Exchange reactions for compounds of the type (**61a**) were found to be too slow with respect to competitive side reactions, while three to six membered ring carbocycles of the type (**62**) and (**63**) are formed in good to excellent yields from (**61b**) and (**61c**) respectively.



III. HETEROCONJUGATE ADDITION

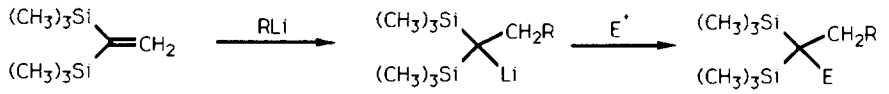
Compounds with second or third row atoms directly bonded to a carbon-carbon double bond have proven to be Michael-type acceptors toward organolithium reagents. Isobe has coined the term "heteroconjugate addition" for the reaction of organometallic reagents with trisubstituted olefins of the type (**64**), where X and Y are groups containing the necessary heteroatoms.[28,29] While this is the formal defini-



(**64**) (**65**) (**66**)

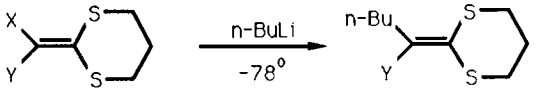
tion of heteroconjugate addition, it is clear that there are several heteroatom-facilitated Michael acceptors that could be similarly catagorized. An example of this would be the addition of organometallics to vinyl sulfones or sulfoximines.

Examples of heteroconjugate addition using vinyldisilanes (67) were first described by Seebach.[30]



(67) (68) (69)

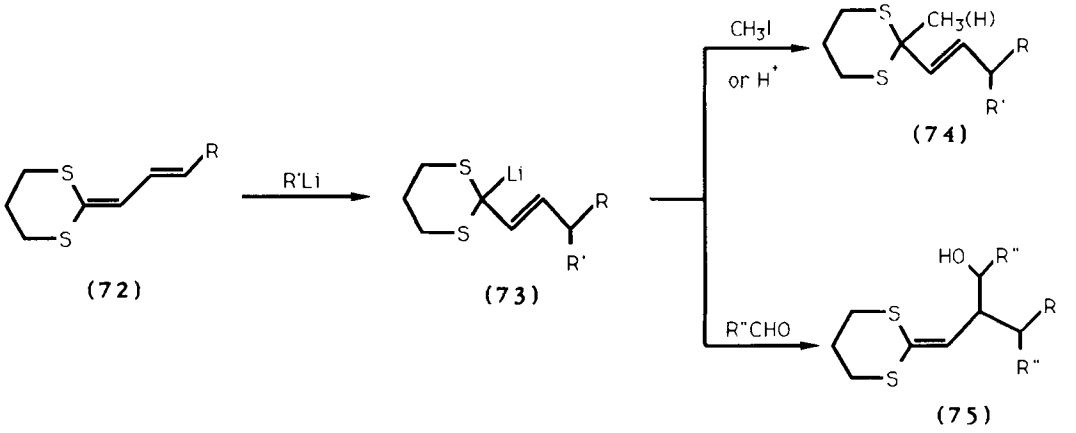
Andersen applied the general concept of heteroatom-mediated carbanion stabilization to the reaction of organolithium and Grignard reagents with substituted ketene dithioacetals (70) via an 1,4-addition-elimination.[31] The reaction fails in cases where X or Y=aryl, alkyl, or H due to the formation of transmetallation products.



(70) (71)

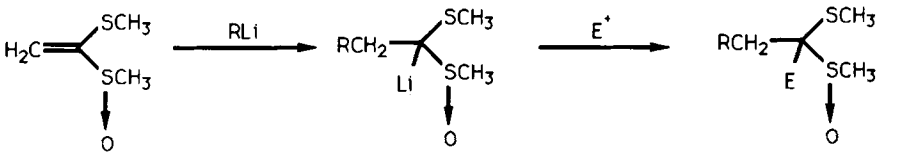
X=Y=Cl

A few isolated cases where non-halogenated ketene thioacetals have proven of value as Michael acceptors are reactions of (70) (X,Y=H) with various alkyllithium reagents[32,33] and reactions of (70) (X=Ph,Y=H; lacking allylic hydrogens for metallations) with t-butyllithium.[34] Vinylogous extensions of the type (72) do undergo



(72) (73) (74) (75)

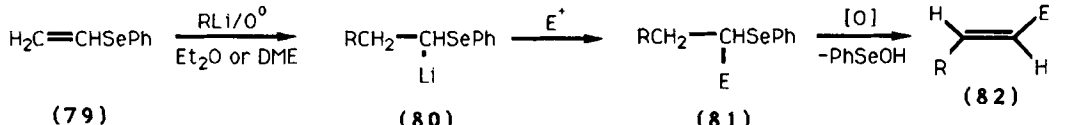
conjugate additions via the intermediate stabilized carbanion (73).[34,35] An alternative to the use of ketene thioacetals is the use of the corresponding dithioacetal monoxides, demonstrated by the elaboration of (76).[36]



(76) (77) (78)

75-98%

Similar methodology was used by Raucher and Koolpe in their studies of the addition of organolithium reagents to vinyl phenyl selenide (79).[37] Oxidative elimination of the elaborated selenide (81) gives the *E*-alkene stereospecifically in excel-

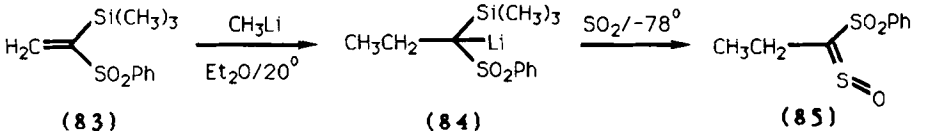


(79) (80) (81) (82)

72-97%

lent yields. This is a rather rare case whereby organolithium reagents are reactive toward a Michael acceptor, while cuprate and Grignard reagents are unreactive.

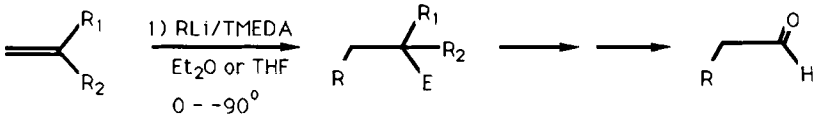
Van der Leij used a similar concept to prepare sulfines of the type (85) from vinyl silanes (83) by Michael addition of RLi.[38]



(83) (84) (85)

74%

Ager has reported the addition of alkyllithium compounds to phenylthioethene (86a), trimethylsilylethene (86b), and 1-phenylthio-1-trimethylsilylethene (86c) in

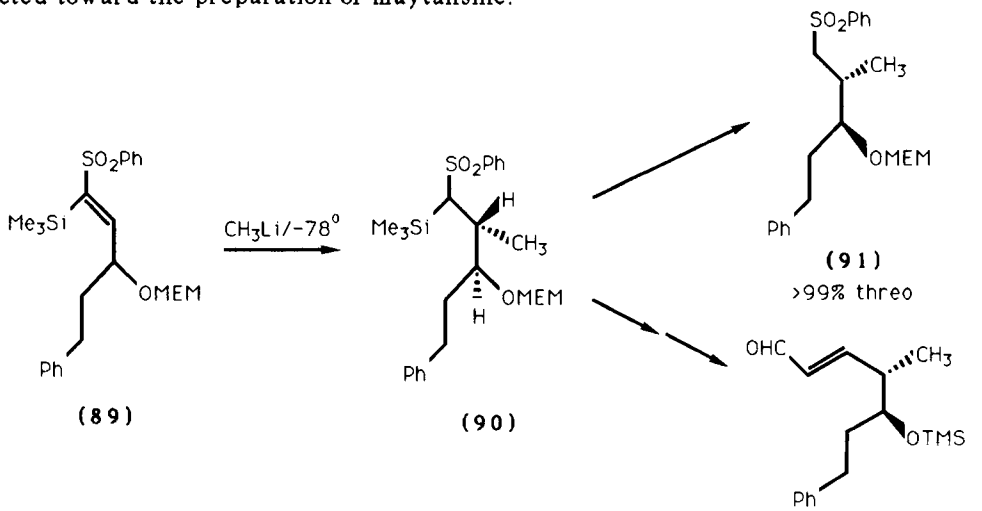


(86) (87) (88)

a: R_1=SPh; R_2=H; E=$SiMe_3$
b: R_1=$SiMe_3$; R_2=H; E=SPh
c: R_1=SPh; R_2=$SiMe_3$; E=H

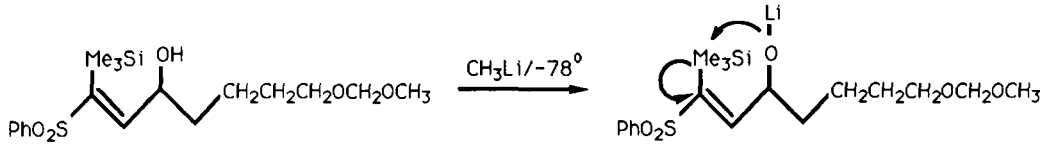
the presence of TMEDA as a general route to 1-phenylthio-1-trimethylsilylalkanes (87).[39] These compounds can be readily converted to aldehydes.

Isobe has elegantly utilized the heteroconjugate addition concept to prepare a variety of chiral products in high preparative yields and enantiomeric purities. With hetero-olefins of the type (64) containing an asymmetric center in the R group, a remarkable degree of asymmetric induction is observed in the Michael addition product. This is aptly demonstrated by the preparation of the chiral intermediate (90) directed toward the preparation of maytansine.[28]

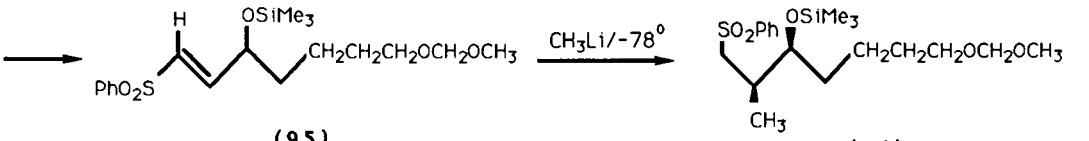


The asymmetric induction observed in this case did not hold when applied to compounds containing higher functionality during Isobe's studies concerning the preparations of chiral acyclic synthons for macrolide synthesis. The rationale given for this observed shortcoming was the principal chelation effect of the MOM group, which became competitive when other ether moieties were present in the molecule. This problem was addressed by employing an intramolecular silicon-to-oxygen migration from the alkoxide (94) to give a γ-silyloxy vinyl sulfone of the type (95), which gave rise to good yields of Michael adducts (96) with high degrees of asymmetric induction. These studies indicated that use of a free hydroxy group gave rise to the best asymmetric induction, presumably due to the higher degree of lithium com-

plexation with the lithium alkoxide group.[40]



(93) (94)

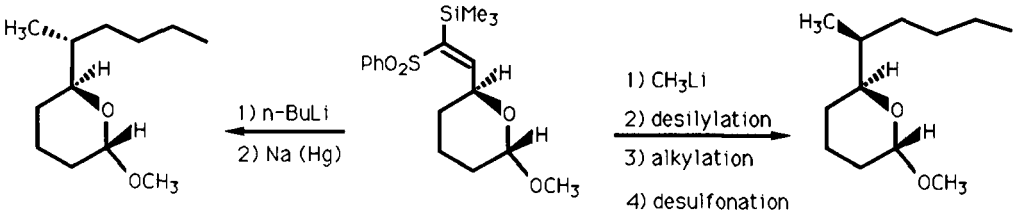


(95) (96)

95%

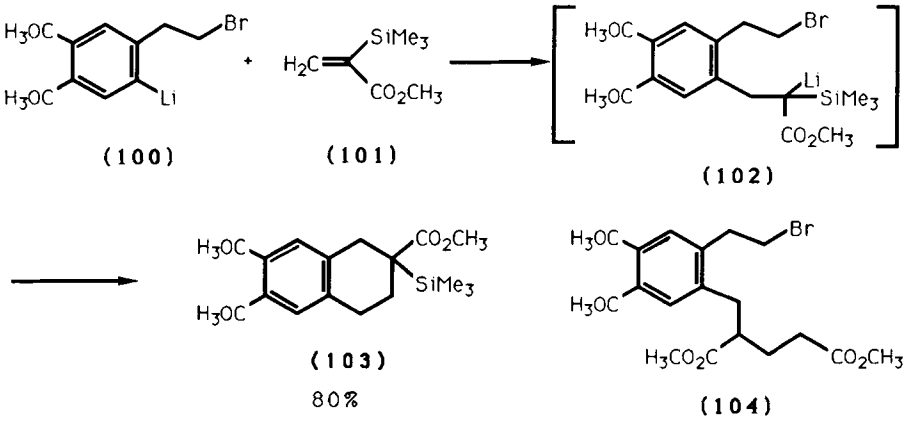
(>99:1 threo/erythro)

Further evolution of this procedure has resulted in the ability to conduct diastereoselective syntheses of either anti (**98**) or syn (**99**) diastereomers based on workup conditions of the Michael adduct resulting from the addition of organolithium reagents to the hetero-olefin (**97**).[41]



(98) (97) (99)

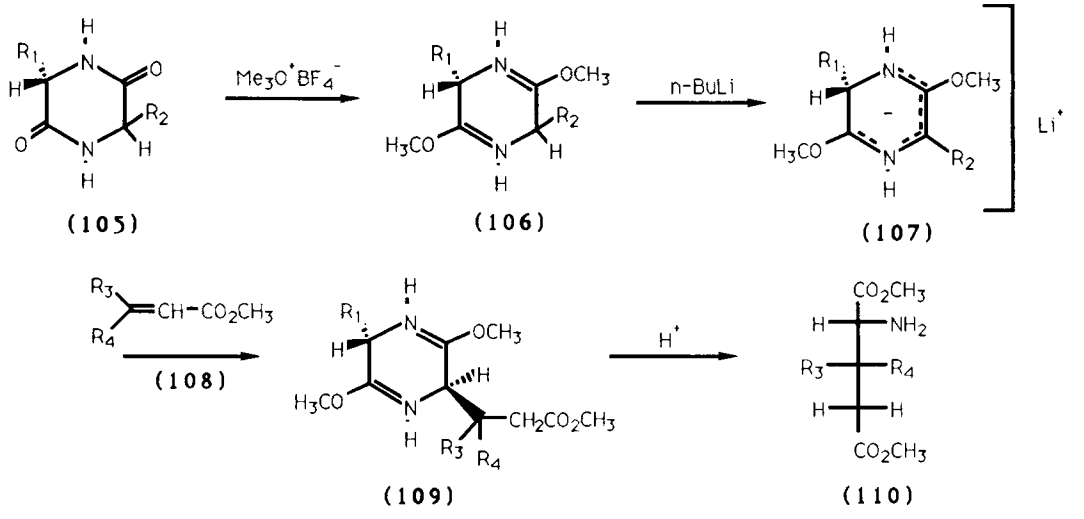
Yet another example of heteroconjugate addition entails the use of (α-trimethylsilyl) acrylic acid esters of the type (**101**) as the Michael acceptor.[42] Thus, the use of ester (**101**) to prepare cyclization products (**103**) from functionalized aryllithium reagents[4a] was rationalized in terms of stabilizing the carbanion (**102**) in order to retard anionic polymerization of the Michael adduct. As a comparison test case, attempts at using methyl acrylate as the Michael acceptor in the reaction scheme gave 25% of (**103**), along with the bis-adduct (**104**).



(100) (101) (102) (103) 80% (104)

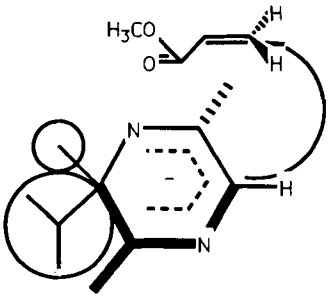
IV. bis-LACTIM ETHERS

Schöllkopf's group has recently developed a highly efficient strategy for the asymmetric synthesis of a variety of substrates via the addition of highly stabilized metallated bis-lactim ethers (107) to electrophiles, including Michael acceptors, to give C-alkylated products of the type (109) in yields often exceeding 95% with high degrees of asymmetric induction.[43] The elaborated bis-lactim ethers can then be hydrolyzed to provide good yields of chiral amino acid derivatives (110). The starting bis-lactim ethers (106) can be easily prepared by treatment of the corresponding 2,5-diketopiperazine (105) with either Meerwein's salt or methyl triflate.

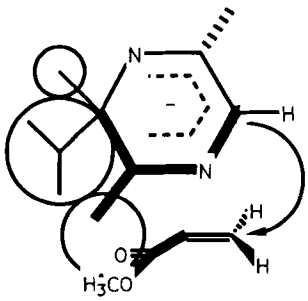


(105) (106) (107) (108) (109) (110)

The high degree of asymmetric induction in the 1,4-addition has been attributed to spacial requirements necessary for the approach of either of the two enantiotopic faces of the Michael acceptor to the planar anion which contains a bulky R group (**111**,**112**). This rationale is reinforced by the high diastereofacial selectivity of the methyl 2-alkenoates (**108**) with respect to the planar bis-lactim anion (**107**) [(2R):(2S)›140-200:1]. This result cannot be solely attributable to the size of (**108**), since this is a relatively compact electrophile. The postulate which has been put forward is that a π-complex is formed (**111**,**112**) which is stabilized by HOMO-LUMO attractions



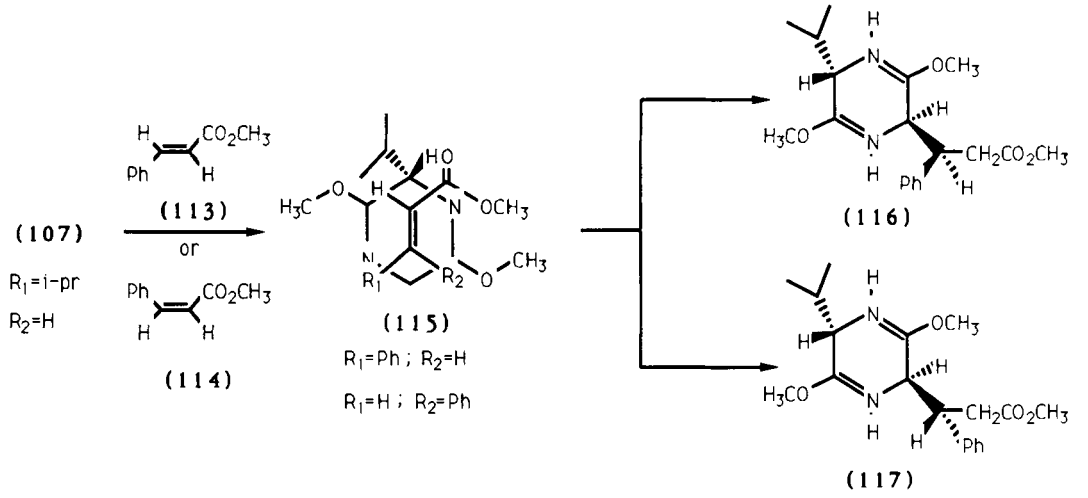
(**111**)



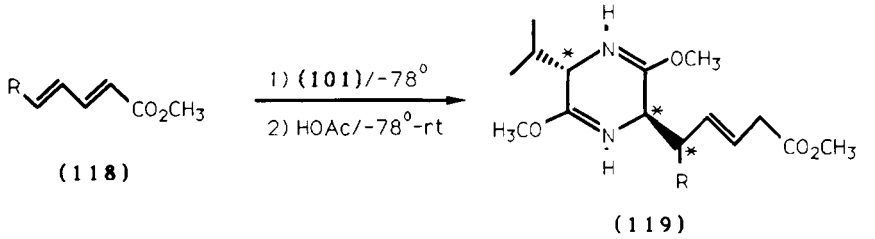
(**112**)

or charge transfer interactions. In these π-complex transition states, the entering Michael acceptor approaches the immediate vicinity of the chiral-inducing center of the planar anion, thus creating two widely different transition states with respect to energy. The "top-side" transition state (**111**) is less sterically hindered and hence of significantly lower energy than the corresponding "bottom-side" transition state (**112**).[43,44]

Stereochemistry of the adduct (**109**) is also dependent on the configuration of the double bond of the Michael acceptor. For example, reaction of the trans-cinnamate (**113**) with anion (**107**) gives mainly the (2R,1'S) adduct (**116**), while the cis-cinnamate (**114**) gives mainly the (2R,1'R) adduct (**117**).[45] This stereochemical dependency based on the olefin configuration has been attributed to the structure of the transition state (**115**), which is stabilized by oxygen coordination to the N-1 lithium cation of the diazapentadienyl anion (presumably the location of the lithium cation).

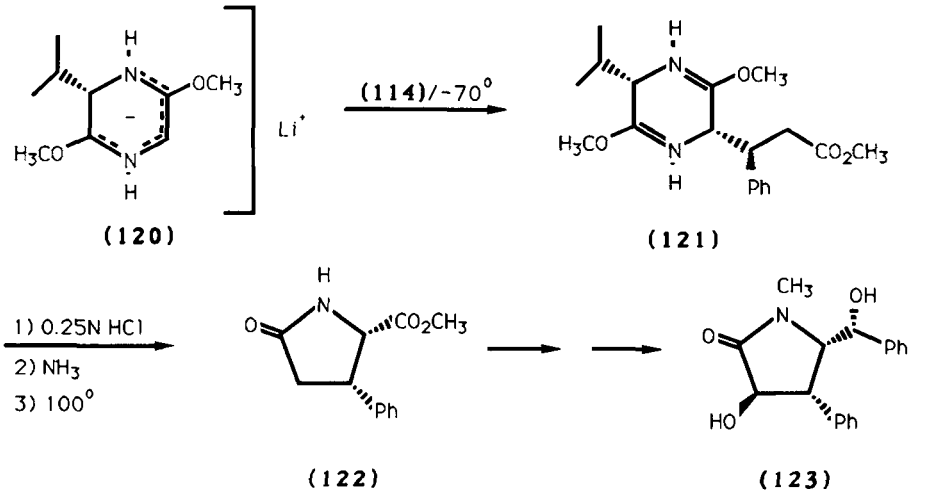


Methyl 2,4-pentadienoates (**118**) have also been shown to react with (**107**) regioselectively in an 1,6-addition to give good yields of products of the type (**119**) with a



high degree of diastereoselectivity. Out of a possible four diastereomers, virtually only one is formed as detected by nmr spectroscopy.[46] Subsequent transformations of (**119**) similar to those previously outlined provide a route to complex amino acid derivatives of high chiral purity.

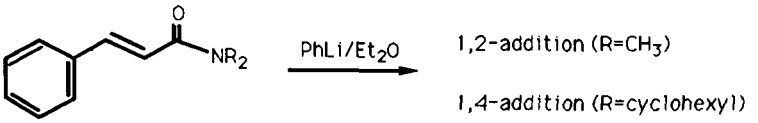
The bis-lactim ether strategy has recently been employed by Hartwig and Born in the total synthesis of the hepatoprotective agent clausenamide.[47] Thus, condensation of anion (**120**) with the cis-cinnamate ester (**114**) gives the optically pure adduct (**121**) in 73% yield. Hydrolysis of the heterocyclic unit, followed by heating furnished the optically pure pyrrolidinone (**122**) in 56% yield, which was then converted to (+)-clausenamide (**123**).



(120) (121) (122) (123)

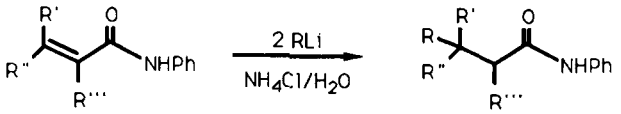
V. CONJUGATE ADDITION OF ORGANOLITHIUM COMPOUNDS TO α,β -UNSATURATED AMIDES AND THIOAMIDES

The first report on the Michael-type reactivity of α,β -unsaturated amides was described in 1957 by Gilbert and Aycock.[48] These reactions were performed at ambient temperature, and demonstrated the steric effect of substitution on the amide nitrogen toward Michael reactivity. It was not until 1980 that studies of reactivity of α,β-un-



(124)

saturated amides toward hard organometallics were again undertaken by Baldwin and Dupont.[49] The studies focused on additions of simple organolithium reagents to acrylanilide anions derived from (125), and revealed that fair to good yields of Michael ad-

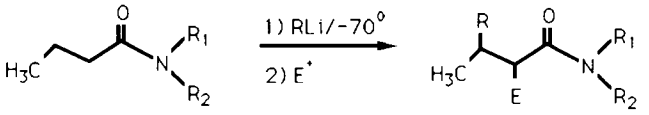


(125) (126)

ducts (126) could be obtained.

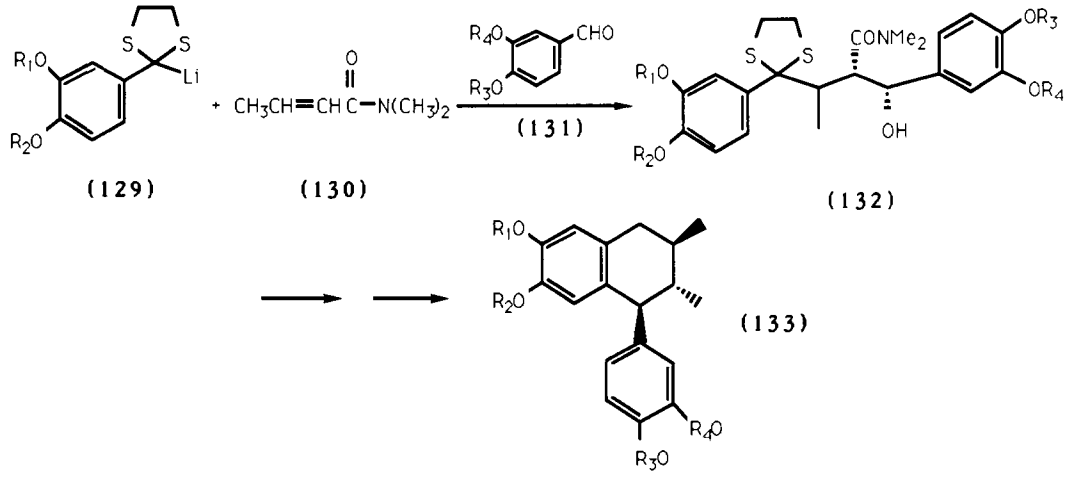
Snieckus further defined the scope of the reaction during the development of a

tandem conjugate addition-α-alkylation technique.[50] The reaction was found to be broad in scope with respect to either secondary or tertiary amides, with good yields of the elaborated Michael adducts (**128**) obtained. Certain systems, however, were found



(**127**) (**128**)

which do not behave as Michael acceptors. These include β,β-dialkylated tertiary[49,51] and α-alkylated secondary[52] unsaturated amides. Snieckus further demonstrated the synthetic utility of this method through the synthesis of 1-aryltetralin ligands (**133**), with the crucial step involving condensation of the lithiodithiane (**129**) with amide (**130**).[53]

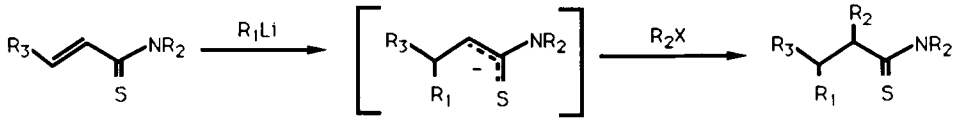


(**129**) (**130**) (**131**) (**132**) (**133**)

In a similar vein, Klein and Aminadav have reported cursory investigations on the effects of functional groups on the Michael addition of organometallic reagents to derivatives of phenyl- and methylpropiolic acids.[54] As might be expected, the reactivity and reaction product distribution from the condensation of derivatives of phenylpropiolic acid with methyllithium versus methylmagnesium bromide are different. The acid, its salt, and the primary amide did not react with methyllithium, while the methyl ester gave products arising from 1,2-addition. However, the mono-

and dimethyl amide derivatives gave the 1,4-addition product exclusively in moderate to good yields.

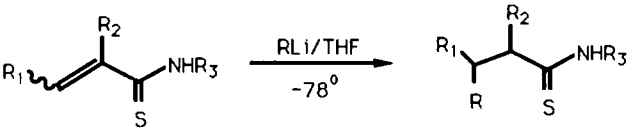
Much of the work which spurred the investigation of the Michael behavior of the α,β-unsaturated amides can be attributed to the Yoshida group's investigations on the behavior of unsaturated thioamides toward organolithium and Grignard reagents. The first report concerning the behavior of tertiary unsaturated thioamides[55] revealed that Michael reactivity is quite general in nature, and the reactions were suprisingly clean in light of the behavior of other thiocarbonyl compounds toward organometallic reagents.[56-62] The reaction is amenable to a variety of cyclic or acyclic thioamides. The Michael adduct can be elaborated by quenching the intermediate S-stabilized anion (**135**) with an electrophile to give good to excel-



(**134**) (**135**) (**136**)

lent yields of elaborated products (**136**). These studies also indicated that hard carbanions show conjugate addition as the major reaction pathway, whereas softer carbanions, such as those derived from dimethyl malonate, show either nonreactivity or give several products, depending on the nature of the unsaturated thioamide. This methodology has been extended to lithium enolates, which add in a 1,4-fashion to unsaturated thioamides in good to excellent yields.[63]

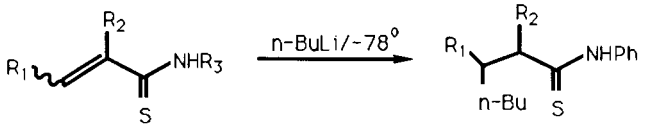
These studies had been conducted with unsaturated tertiary thioamides, and subsequent work indicated unsaturated secondary thioamides (**137**) possessed similar character to their tertiary counterparts toward reaction with organolithium reagents.[64]



(**137**) (**138**)

In this case, however, only organolithium reagents undergo the 1,4-addition, with

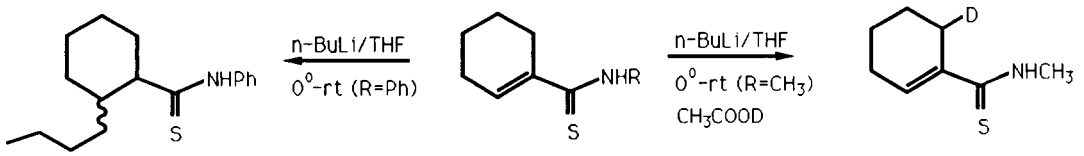
Grignard reagents being totally unreactive. For the unsaturated secondary thioamides, N-substitution exerts a more profound effect on the Michael addition. For example, treatment of N-methylthiocrotonamide (**139**) or N-methylthio-α-methacrylamide (**140**) gave decomposition products upon treatment with 2.2 equivalents of n-butyllithium at -78°, whereas the corresponding N-phenyl analogs (**141**,**142**) gave



R_1=CH_3; R_2=H; R_3=CH_3 - (**139**)
R_1=H; R_2=CH_3; R_3=CH_3 - (**140**)
R_1=CH_3; R_2=H; R_3=Ph - (**141**)
R_1=H; R_2=CH_3; R_3=Ph - (**142**)

R_1=CH_3; R_2=H - (**143**)
R_1=H; R_2=CH_3 - (**144**)
degradation products from (**139**,**140**)

good to excellent yields of the Michael adducts (**143**,**144**). In addition to the observed sensitivity for acyclic cases, effects of N-substitution on secondary thioamides directly bonded to an unsaturated cycloaliphatic ring system as in (**145**) also exert a profound effect toward reactivity with organolithium reagents. The N-phenyl derivative (**145**), upon treatment with 2.2 equivalents of n-butyllithium undergoes conju-



(**147**)

R = Ph (**145**)
R = CH_3 (**146**)

(**148**)

gate addition to give (**147**) in good yield, while the corresponding N-methyl derivative (**146**) is apparently unreactive, based on 80% recovery of starting material. Further investigation of the reaction through quenching experiments with d_1-acetic acid revealed that allylic metallation was occurring to give (**148**).

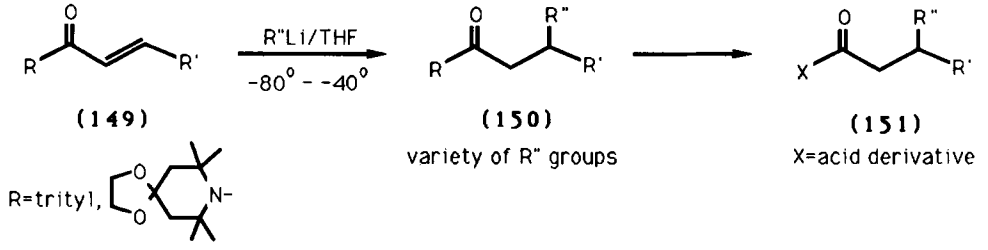
Investigations of the reaction of allyllithium reagents with unsaturated thioamides revealed that the addition products and yields are sensitive to solvent and reaction temperature, and the regioselectivity of the addition (kinetic versus thermodynamic) can be controlled by varying the reaction conditions.[65] This phenomena will be dis-

cussed in further detail in the following section.

VI. STRUCTURAL, THERMODYNAMIC, AND SOLVENT EFFECTS IN CONJUGATE ADDITION REACTIONS OF ORGANOLITHIUM REAGENTS

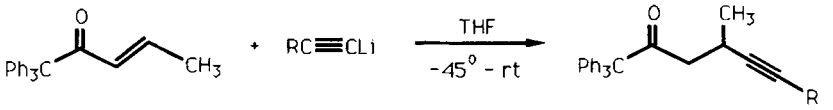
The three major factors which control the regioselectivity of nucleophilic addition to Michael acceptors are: 1) steric, 2) electron transfer,[5b] and 3) charge direction.[5a] Additionally, it has now been established that 1,2-addition can be reversible such that by controlling reaction conditions, kinetically favored 1,2-addition products or intermediates can be converted to the thermodynamically favored 1,4-adduct. The conjugate addition reactions which have been discussed up to this point have primarily focused on the charge direction capabilities of the Michael acceptor. In this section, discussions will focus on the manipulation of steric factors, conditions related to electron transfer, and thermodynamics in the development of synthetic methods for the conjugate addition reaction of organolithium reagents with Michael acceptors.

Examples of bulky substituent effects on the conjugate addition reactions of organolithium reagents to α,β-unsaturated amides[48] and thioamides[64] have already been discussed. As early as 1965, it was known that steric hindrance of the carbonyl group of the Michael acceptor can alter the reactivity of enones by shifting the regioselectivity of attack of the nucleophile to the β-position.[66] More recently, studies by the Seebach group have better defined this effect, known as enforced a^3 reactivity.[67] Thus, addition of a variety of hard nucleophiles such as organolithium reagents to a hindered enone (**149**) gives good to excellent yields of the Michael adduct (**150**; R=trityl), which can be converted to the corresponding carboxylic acid derivative (**151**).



(149) **(150)** variety of R" groups **(151)** X=acid derivative

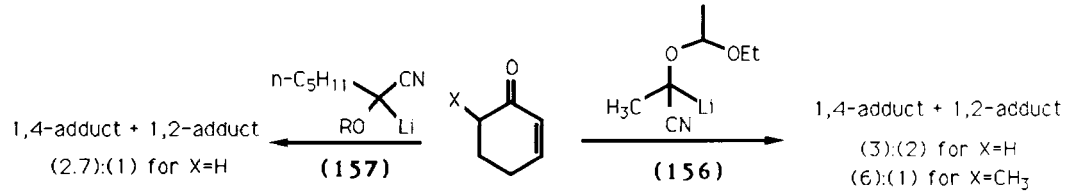
This reaction scheme is also applicable to Grignard reagents. Locher and Seebach extended this concept to a facile preparation of 4-alkyne-1-ones (**154**) via the addition of lithium acetylides (**153**) to propenyl trityl ketones (**152**).[68] This reaction is an ex-



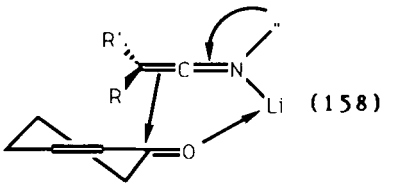
(**152**) (**153**) (**154**)

ample of pure steric control, independent of mechanism,[69] nucleophile structure,[70] solvent effects,[71] and temperature effects.[72]

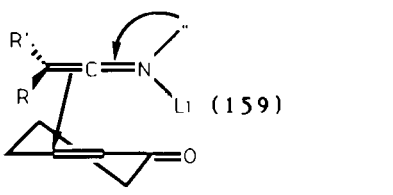
Stork and Maldonado have demonstrated that steric effects of both the nucleophile and enone can exert an effect on the regioselectivity of Michael addition.[73] This work is exemplified by the addition of lithium cyanohydrin anions (**156**,**157**) to cyclic enones. Thus, anion (**157**) is more sterically hindered compared to its counterpart (**156**), giving a higher ratio of 1,4:1,2-addition to enone (**155**; X=H). In addition, a steric effect can also be exerted by the Michael acceptor. α-Methyl substitution of enone (**155**) enhances the 1,4-addition of anion (157) when compared to the parent case (**155**; X=H). These data indicate that the structure of the transition state is markedly affected by the size of the substituents of the cyanohydrin. When the R groups



are large, C-C bond formation is more sterically encumbered about the carbonyl carbon, thus favoring the transition state depicted by (**159**), while relatively small R groups would tend to favor the transition state (**158**).

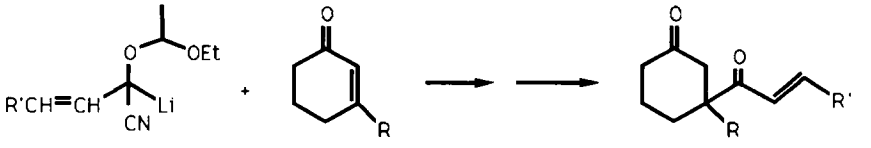


(**158**)



(**159**)

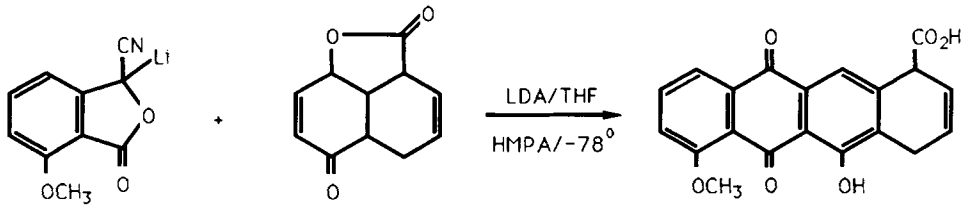
In the same study, it was also revealed that by altering certain structural features of the attacking anion, good to excellent yields of the thermodynamic Michael addition products could be obtained by making the kinetically favored 1,2-addition reversible. This is illustrated by the addition of anions derived from α,β-unsaturated aldehydes (**160**) to cyclohexenone (**161**; R=H). This finding also holds for cases with



(**160**) (**161**) (**163**) 70-85%

substitution at the 3-position of the enone (**161**; R=CH_3). This is one of the initial reportsconcerning factors governing kinetic and/or thermodynamic control on the addition of organolithium reagents with Michael acceptors.

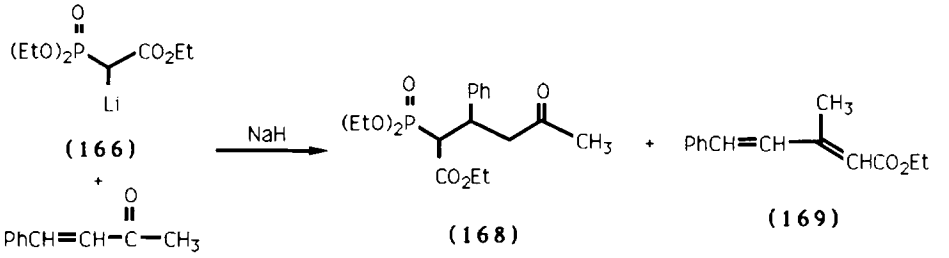
Li and Walsgrove have applied these findings toward the synthesis of the aklavi-



(**163**) (**164**) (**165**)

none ring system (**165**) via reaction of the lithiocyanophthalide (**163**) with the enone lactone (**164**).[74]

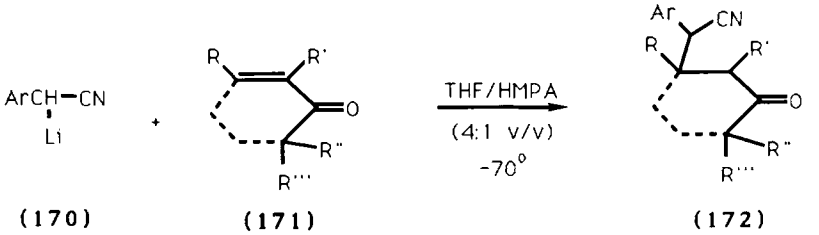
It is now widely recognized that there are several cases of kinetic versus thermodynamic control governing the addition of organolithium compounds to Michael acceptors. The common theme in these cases lies in the net stabilization of the carbanion via substitutent effects. One of the earliest reports of kinetic/thermodynamic control involves the addition of lithium phosphonates of the type (**166**) to benzylidene acetone (**167**).[75] While the Michael adduct (**168**) was reported to form more rapidly, the product arising from 1,2-addition (**169**) predominated with longer reaction times. When an excess of the stabilized carbanion (**166**) was used in the re-



(166) + (167) → NaH → (168) + (169)

action sequence, the 1,4-adduct (**168**) predominated. This reaction behavior is a clear example of 1,4-kinetic and 1,2-thermodynamic control of addition. More recently, Cohen's group has shown that the regioselectivity in nucleophilic addition to α,β-unsaturated enones is highly dependent on temperature and ion pairing effects, with low temperatures favoring kinetic 1,4-addition over 1,2-addition.[76]

In contrast, the majority of organolithium compounds exhibiting controlled addition chemistry have been shown to proceed 1,2-kinetically and 1,4-thermodynamically. The previously cited work of Stork and Maldonado is an example of 1,4-thermodynamic addition. Likewise, the Michael addition of lithiophenylacetonitriles (**170**) to substituted enones or α,β -unsaturated aldehydes (**171**) has been demonstrated to proceed under thermodynamically controlled conditions.[70,77-80] The reaction proceeds regiospecifically for enones to give the 1,4-addition products of the type (**172**) in THF/HMPA, while a product mixture is obtained for unsaturated aldehydes under the same reaction conditions. For the enones studied, the formation of allylic alcohols, products of 1,2-addition, is reversible in the solvent mixture, and 1,2-addition products predominate when the reaction is conducted in THF alone.

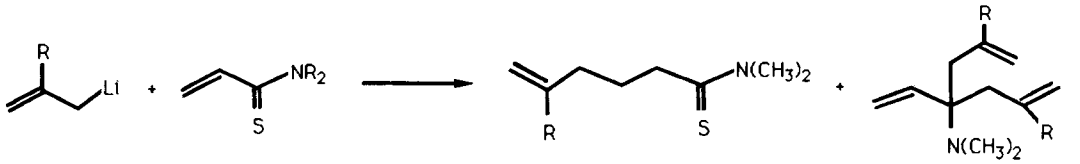


(170) + (171) → THF/HMPA (4:1 v/v) -70° → (172)

These studies also revealed that in some cases, kinetic control of 1,4-addition was ob-

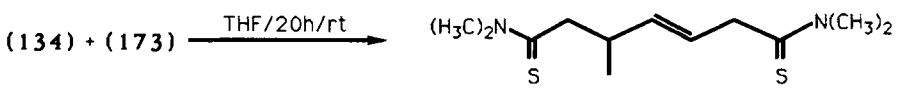
served. The factors governing the observation of kinetic versus thermodynamic control of 1,4-addition as well as the rates of formation of 1,4-addition products were highly dependent on aryl substitution, which affected the nucleophile HOMO. Steric sensitivities were also noted for these cases, which indicated that the approach of the organolithium reagent to the C=C bond is governed by the less hindered face, accounting for the observed stereoselectivities.

Another example of the ability to control kinetic and/or thermodynamic driven conjugate addition reactions by adjustment of temperature, solvent, and reaction time is the condensation of allylithium compounds (**173**) to α,β-unsaturated thioamides (**134**; R=CH_3, R_3=H).[65] Thus, allylithium (**173**) with the unsaturated thioamide (**134**) in THF at -78° gives excellent yields of the thermodynamically controlled Michael



(**173**) (**134**) (R=CH_3) (**174**) (**175**)

product (**174**) exclusively, whereas reaction at ambient temperature for 0.5 hours gives excellent yields of the kinetically controlled 1,2-addition product (**175**) exclusively. Conducting the same reaction at ambient temperature for 20 hours gives the thermodynamically controlled product (**176**) in excellent yield. Studies with lithium enolates and thiosorbamides are also reported and indicate thermodynamic regiocontrol for the 1,6-addition and kinetic control for the 1,4-addition with yields ranging from fair to excellent.

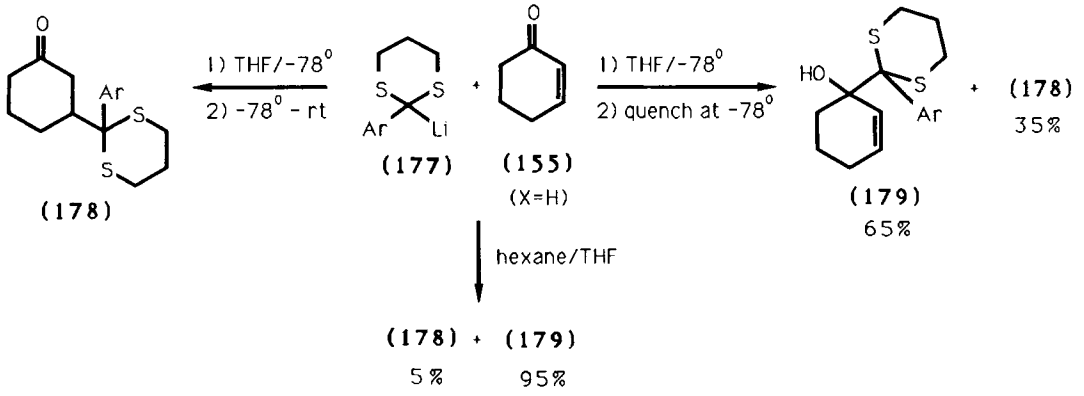


(**176**)

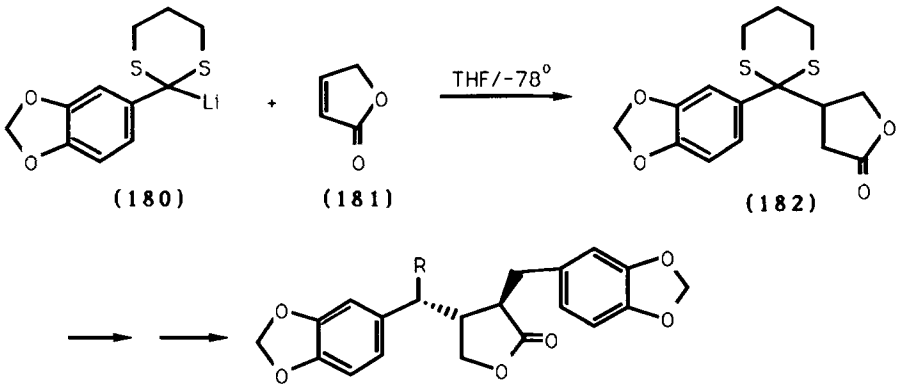
Schultz has also reported thermodynamic and kinetic conditions for the addition of lithium ester enolates to cyclohexenone, and has demonstrated that subtle structur-

al effects of the anion play a crucial role on the regioselectivity of the addition reaction with respect to product distribution.[81]

Lithiodithianes have been intensively investigated with regard to thermodynamic and kinetic product distribution in reactions with a variety of Michael acceptors. Early work with these acyl anion equivalents and other sulfur-substituted organolithium compounds indicated that reactions occur readily with enones to give only the 1,2-addition products in the absence of further chemical modification or solvent effects.[82-90] The earliest report demonstrating the 1,4-addition behavior of highly stabilized sulfur-substituted organolithium compounds toward α-enones was the 1975 work of Manas and Smith with tris(phenylthio)methyllithium.[91] The first work indicating that structural effects play a crucial role in the Michael behavior of enones toward lithiodithiane anions was reported by Ostrowski and Kane in 1977.[92] This work indicated that condensation at ambient temperature of lithiophenyldithianes (**177**) with enones gives excellent yields of 1,4-addition products (**178**), while reaction at -78° with concomitant low temperature quenching of the intermediate anion gives a mixture of 1,2 (**179**) and 1,4-additon products (**178**). Additionally, dilution of the low temperature reaction mixture with hexane followed by low temperature quenching gives the 1,2-addition product (**179**) in 95% yield. These results indicate that the 1,2-addition product arises via a kinetic process, and the 1,4-product is the result of a thermodynamic process.



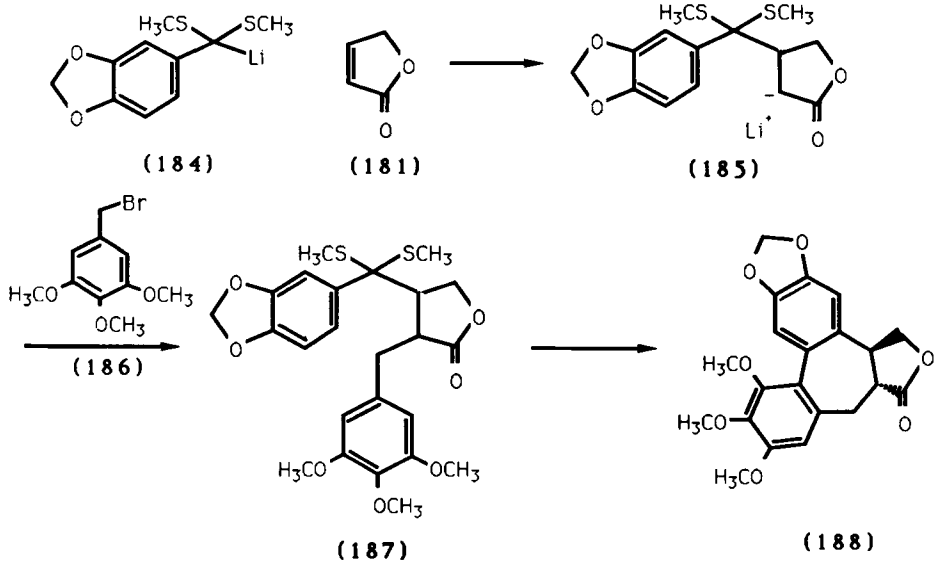
These investigations into the regioselective nature of the addition of aryldithiane anions to Michael acceptors have led to elegant applications of this methodology to natural product synthesis. Asano, Kamikawa, and Tokoroyama have reported the efficient preparations of (±)-parabenzyllactone (**183**; R=OH) and (±)-hinokinin (**183**; R=H) through the Michael addition of the lithium dithiane (**180**) to 2-butenolide (**181**).[93]



(**180**) (**181**) (**182**)

(**183**)

A similar procedure was employed for the highly efficient preparation of (±)-isostegnane (**188**) by quenching the lithium lactone enolate (**185**), formed by the Mi-



(**184**) (**181**) (**185**)

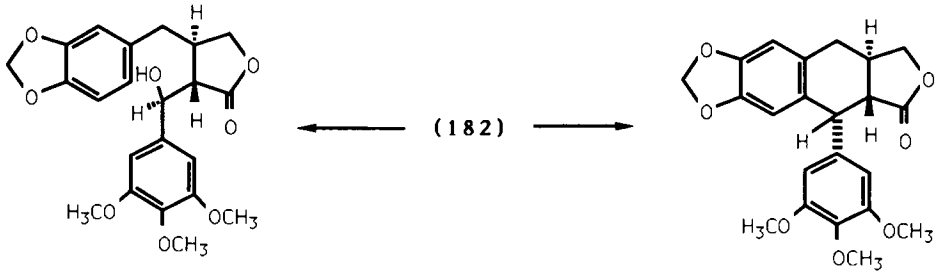
(**186**)

(**187**) (**188**)

chael addition of the thioalkyl acetal anion (**184**) to 2-butenolide (**181**), with the ben-

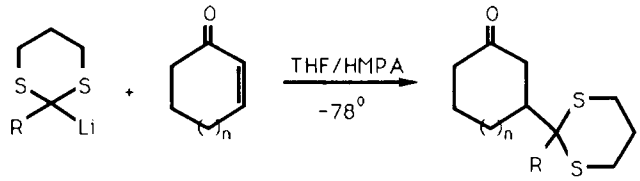
zyl bromide (**186**) at -78° to give the elaborated lactone (**187**).[94] Biaryl coupling results in (±)-isostegnane (**188**) in 55% overall yield.

Ziegler and Schwartz have incorporated a conjugate addition of the stabilized aryldithiane anion (**180**) to 2-butenolide (**181**) in the synthesis of two lignan lactones.[95] Subsequent trapping of the resultant lactone lithium enolate of (**182**) with the appropriate benzaldehyde provides an entry to the lignan lactones (±)-podorhizol (**189**) and (±)-isopodophyllotoxone (**190**). The Michael addition product (**182**) is obtained in 88% yield when the anion derived from the dithiane (**180**) was employed, whereas yields of the corresponding Michael adduct derived from thioalkylacetal anions are reported to be appreciably lower (50%).



(**189**) (**190**)

Brown and Yamaichi later reported that regioselectivity of the addition of lithium alkyldithianes (**191**) to Michael acceptors like (**192**) could be controlled by the use of a THF/HMPA cosolvent system, thus resulting in a "true" conjugate addition to give (**193**).[96] This observation is reinforced by experiments indicating that addition of HMPA to solutions of the lithium salt of the 1,2-addition product derived from the reaction of (**191**) with (**192**) in THF gives no 1,4-addition product after 24 hours at room temperature.

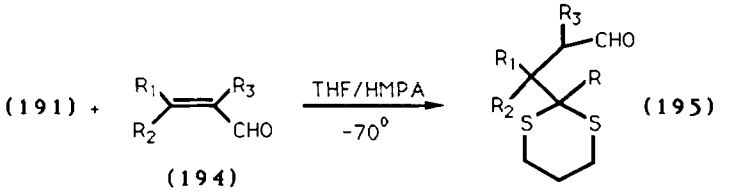


(**191**) (**192**) (**193**)

The findings of Ostrowski and Brown were confirmed and extended through the

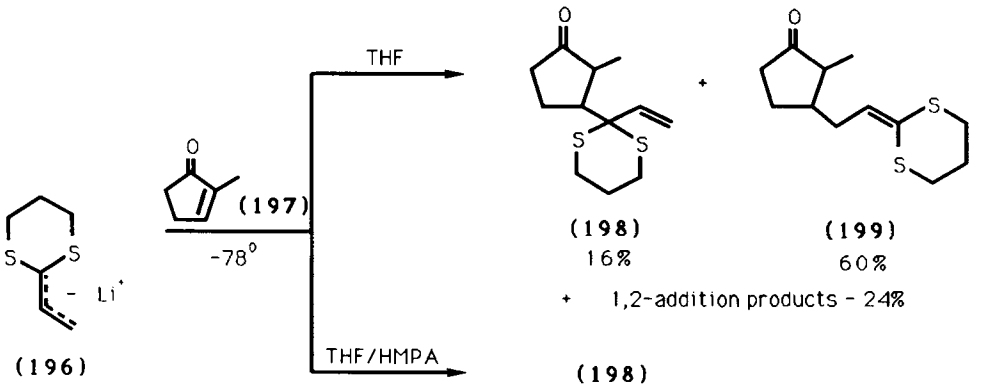
work of Lucchetti, Dumont, and Krief.[97] Their investigations indicated that in addition to lithiodithianes, bis(phenylthio)alkyllithiums and bis(methylseleno)alkyllithium reagents add 1,4 to enones if HMPA is present as a cosolvent prior to the addition of the enone to the anion. This work, along with the findings described by Brown, serves to reinforce the point that in these particular cases, reactions are occuring under the auspices of kinetic control as evidenced by the inability to convert the alkoxide resulting from 1,2-addition to its 1,4-regioisomer.

Further investigations into the nature of the reaction of lithiodithianes (**191**) with α,β-unsaturated aldehydes (**194**) demonstrated similar effects of the THF/HMPA cosolvent system,[72] with the 1,4-addition being kinetically controlled as evidenced by



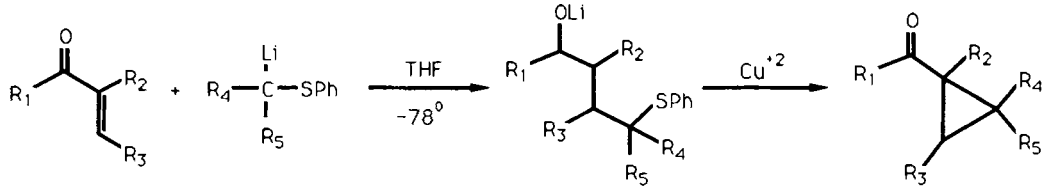
the inherent stability of the lithioalcoholates in the mixed solvent system. Additionally, structural effects of both the nucleophile and Michael acceptor as well as orbital interactions[80] are described as major factors influencing the observed regioselectivity.

Ziegler and Tam have reported the addition of ketene dithioacetal anions to cyclic enones and have found that regioselctivities are influenced by both solvent and



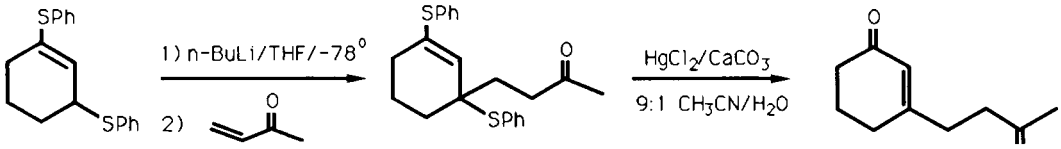
counterion.[98] The lithium anion of 2-ethylidene-1,3-dithiane (**196**) demonstrates regioselectivity for 1,4-γ-substitution (**199**), whereas addition of HMPA to the solvent system demonstrates a significant reversal of selectivity as evidenced by the sole formation of (**198**).

Recently, Cohen and Myers have demonstrated the synthetic utility of sulfur-stabilized organolithium compounds in Michael additions with α,β-unsaturated ketones. The first report demonstrated a technique for the one-pot preparation of cyclopro-



(**200**) (**201**) (**202**) (**203**)

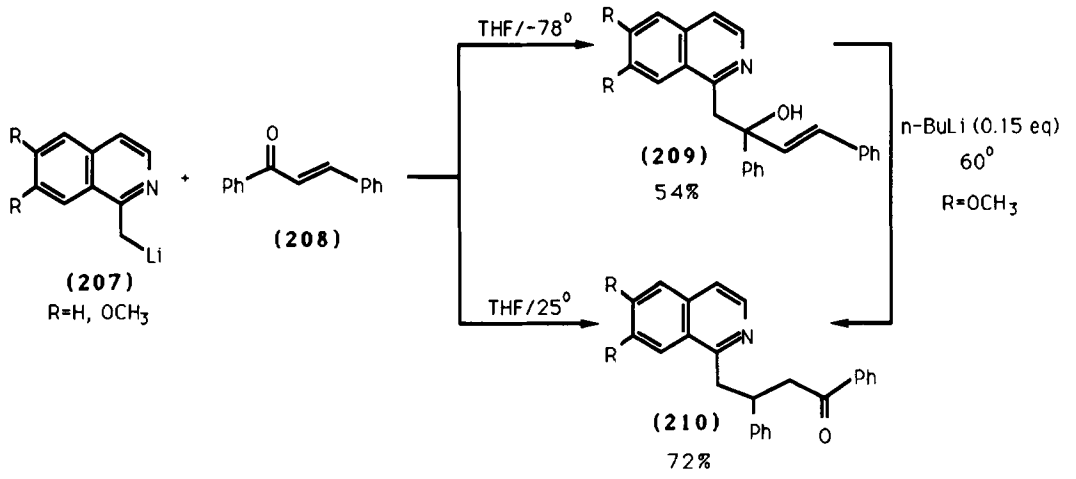
pyl ketones via the addition of sulfur-stabilized organolithiums of the type (**201**) with enones (**200**).[99] Extensions of this work revealed that organolithium compounds stabilized by two phenylthio groups add in the Michael fashion to α,β-unsaturated ketones at low temperatures in the absence of HMPA.[100] An interesting example of this technique is illustrated by the addition of the vinylogous bis(thiophenyl)-stabilized-anion derived from (**204**) to methyl vinyl ketone giving the product (**205**), which is readily converted to the elaborated cyclohexenone (**206**).



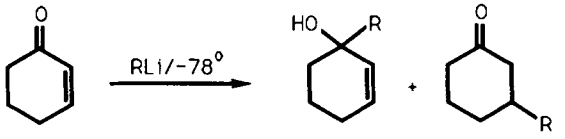
(**204**) (**205**) (**206**) 88%

Kaiser, Knutson, and McClure have reported that organolithiums stabilized only by a nitrogen heterocycle add to enones by reversible 1,2-kinetic control and 1,4- by thermodynamic control.[101] This finding is illustrated by the addition of the lithiomethylisoquinoline (**207**) to chalcone (**208**) in THF. At ambient temperature, the 1,4-addition product (**210**) predominates, while the 1,2-addition product (**209**) predomin-

ates at a reaction temperature of -78°. Further proof of thermodynamic control is indicated by the catalyic conversion of (209) to (210) with n-butyllithium at 60°.



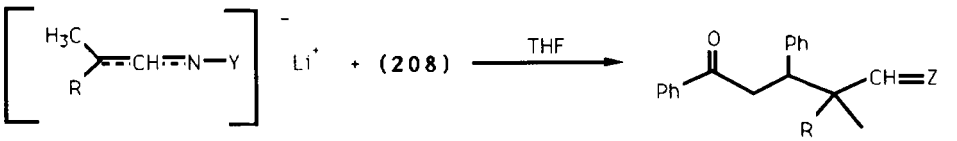
Still and Mitra have reported investigations of the addition of organolithium reagents and Group IV anions to cyclohexenones with respect to solvent effects on regioselectivity.[102] Their findings indicate that results are qualitatively opposite to predictions made on the basis of the HSAB theory.[103-105] Thus, the 1,4-addition product (212; R=t-butyl) predominates in strongly ionizing media where counterion effects are minimized via the addition of the hard t-butyl anion to the soft β-enonic



Solvent	Product Distribution	
Et_2O	100%	-
THF	95%	5%
THF/5% HMPA	65%	35%
THF/20% HMPA	10%	90%

site. These data support the rationale for the Michael addition being an electron transfer process based on the electrode potential for the oxidation of the t-butyl group and reduction potential of 2-cyclohexenone.[5b]

Gorrichon-Guigon and Hammerer have studied the condensation of metallated imines and hydrazones (**213**) with enones and have shown that regioselectivities are sensitive to both reaction times and temperatures.[106] Thus, longer reaction times and higher temperatures favor the 1,4-addition product (**214**), while 1,2-addition products

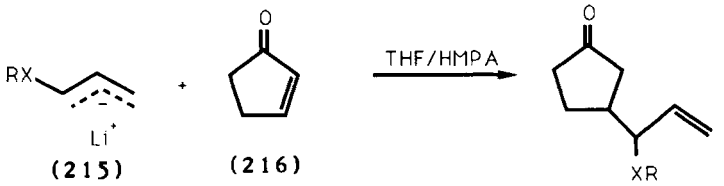


(**213**)
R=CH_3, H
Y=t-Bu, $N(Me)_2$

(**214**)
Z=N-R; O

predominate at lower temperatures indicating thermodynamic control of addition is possible in these cases. Additional evidence for thermodynamic control is the observation of reversible addition to the carbonyl group of chalcone, parallel to the findings reported by Kaiser for the case of lithiomethylisoquinolines.

Binns, et. al. have studied the effects of HMPA on the conjugate addition of alkyl- and phenylthioallyl anions (**215**) to cyclopentenone (**216**).[107] These studies revealed that addition of one equivalent of HMPA to the THF solvent induces Michael addition

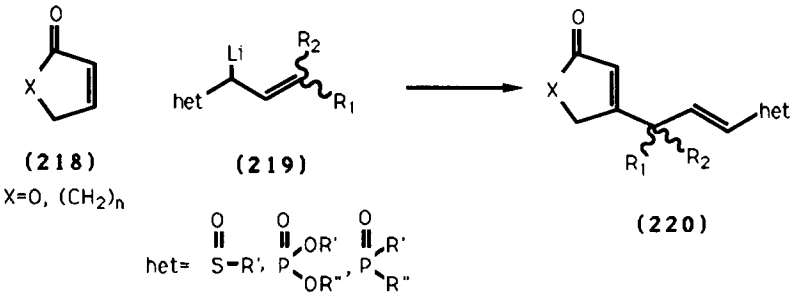


(**215**)
R=alkyl, aryl
X=S

(**216**)

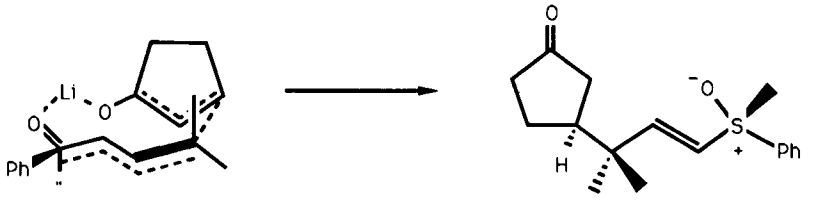
(**217**)

of anions of the type (**215**) through the α-position in good yields to give products of the type (**217**), whereas in THF alone, irreversible 1,2-addition occurs to give product mixtures arising from attack of either terminus of the ambident nucleophile. Attempts to rearrange the intermediate lithium alkoxides of resulting from the 1,2-addition products to provide the 1,4-regioisomers failed, indicating that all products obtained result from kinetic addition. Extensions of these studies focused on the conjugate addition of allyllithium reagents bearing various polar groups (**219**) to cyclic enones (**218**).[108] These reactions were found to proceed in good yield with high



(218) X=O, $(CH_2)_n$ (219) (220)

diastereoselectivities to give products of the type (**220**), with HMPA exerting no regiochemical influence on the addition. The transition state structure plays an important role in the high efficiencies of these reactions. The formation of planar lithiated reagents where the lithium cation is bound to the oxygen attached to the sulfur or phosphorous of the polar group permits the formation of a transition state, depicted by (**221**), in which the reagent assumes an endo orientation over one face of the enone, similar to Stork and Maldonado's proposed mechanism.[73]



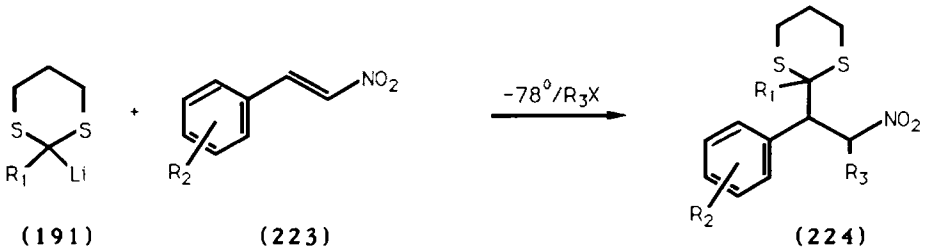
(221) (222)

VII. MISCELLANEOUS MICHAEL ACCEPTORS FOR ORGANOLITHIUM REAGENTS

There are several cases of Michael acceptors for organolithium reagents which have recently been reported in the literature that do not formally fall into any of the prior categories which have thus far been discussed. This section is included as a brief survey of some of these areas, many of which are in initial stages of investigation.

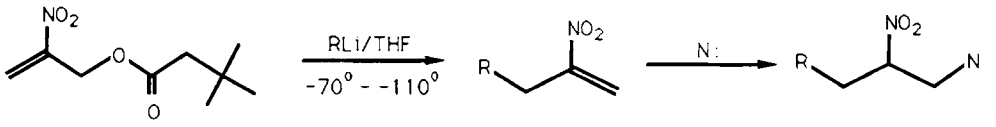
Nitroalkenes have recently shown promise as Michael acceptors toward organolithium reagents, although very limited use of these compounds have been reported. Early work by Seebach and Leitz described the efficient regioselectivities observed for the reaction of 2-lithio-1,3-dithianes (**191**) with substituted ω-nitrostyrenes

(223).[109]



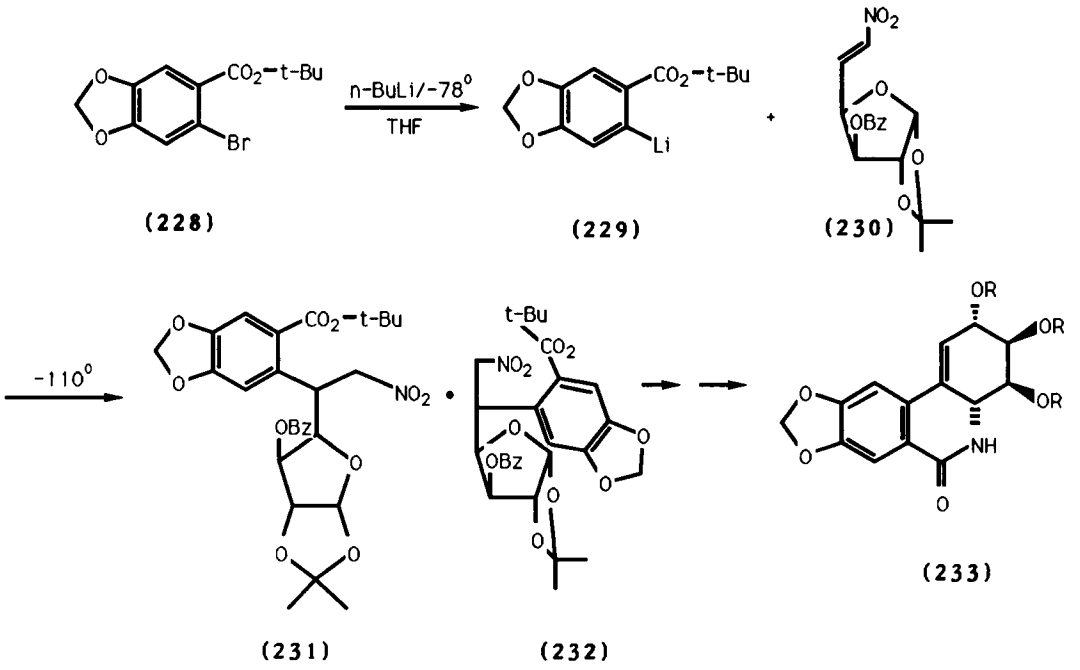
(191) (223) (224)

Knochel and Seebach have developed a novel reagent which behaves as a dual Michael acceptor based on the reactivity of nitroalkenes.[110] The compound, 2-nitro-3-pivaloyloxy-1-propene (NPP; **225**) reacts in a 1,4-fashion with concomitant formal loss of the t-butyl ester moiety to give the nitroalkene (**226**), which can then be subjected to a second nucleophile to give products of the type (**227**) in excellent yields. The first addition is receptive to a variety of nucleophiles, such as alkyl and aryllithium compounds, giving rise to the elaborated nitroalkene (**226**). This intermediate, which is isolable, can then be subjected to yet another Michael addition. A softer nucleophile is necessary for the second addition based on observations that hard nucleophiles do not normally add cleanly to nitroolefins with a terminal double bond.[111] A SET mechanism for this observed reactivity is not likely, based on retention of configuration of products derived from reaction of (**225**) with cis-1-heptenyllithium.[112-113] A mechanism for this reaction has since been proposed.[114]

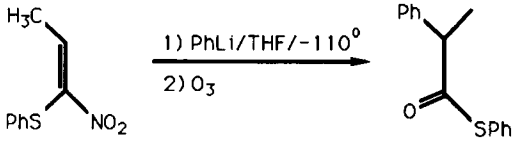


(225) (226) (227)

Paulsen and Stubbe have described the condensation of a functionalized aryllithium reagent (**229**)[4a,115] with a nitroolefin (**230**) as a key step in the total synthesis of (+)-lycoricidine (**233**).[116] The reaction affords a mixture of the ido-component (**232**) and the gluco-product (**231**) in 77% overall yield, both of which are used in subsequent steps.



Barrett, Graboski, and Russell have recently investigated the Michael receptivity of α-thiophenyl nitroalkenes (**234**) with select organolithium reagents, followed by ozonolysis of the stabilized intermediate nitronate salt in situ as a method to generate



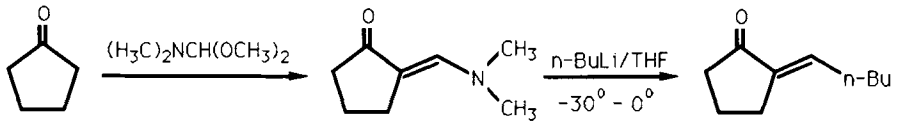
thioesters of the type (**235**) in moderate yields.[117]

Work described by Severin, Scheel, and Adhikary demonstrates that directed conjugate addition occurs upon reaction of simple Grignard or stabilized organolithium

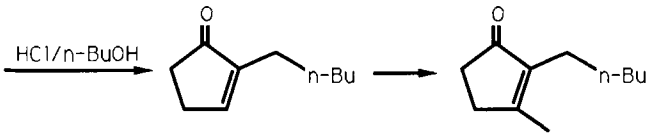
reagents with nitroenamines of the type (**236**) to give highly substituted nitroalkenes (**237**) through an addition-elimination sequence with yields ranging from 60-

85%.[118]

A similar type of 1,4-addition-elimination has been observed for the reaction of β-acylenamines of the type (**239**) with alkyllithium reagents as a general method for the conversion of ketones (**238**) to substituted enones (**241**) in yields ranging from 60-85%. This procedure is exemplified by its use in the preparation of dihydrojasmone (**242**).[119]



(**238**) (**239**) (**240**)



(**241**) (**242**)

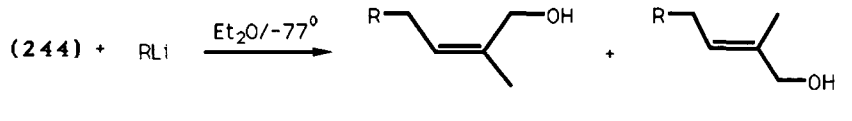
Another electrophilic system which has been sparsely investigated with respect to the 1,4-addition behavior of organolithium reagents is vinyl epoxides. One of the earliest reports in this area detailed investigations of regioselectivities for the addition of organometallics to alkenyl oxiranes as a method to prepare 1,4- and 1,5-alkadienes.[120,121] While these studies focused on cuprate and copper-catalyzed addition of

(**243**) (**244**) (**245**)

vinyl organometallics (**243**) to alkenyl oxiranes (**244**), a single entry describes the addition of (**243**; M=Li) to (**244**) to give a moderate yield of 1,4-alkadiene (**245**) in an *E/Z* ratio of 4:1. The yield and stereoselectivity were reported to be sensitive to solvent (THF versus diethyl ether).

A short report by Netland describes a stereoselective approach to *Z*-allylic alcohols (**246**) in excellent yields by the selective reaction of alkyllithium reagents with

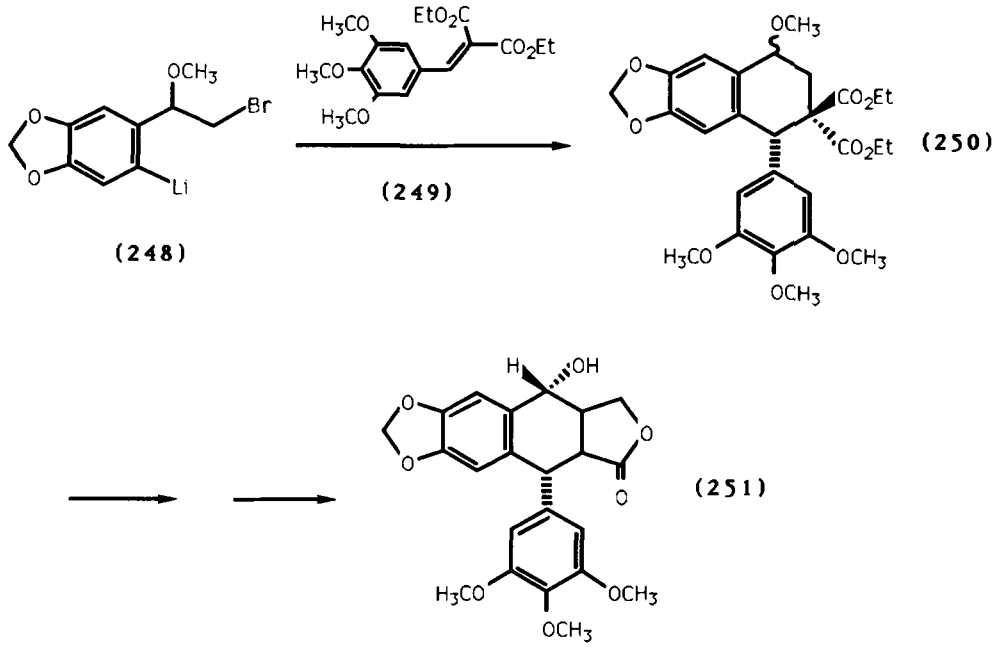
(244).[122] The observed *E/Z* ratios were 16:84 for R=n-butyl and 13:87 for R=t-butyl.



Z (246) E (247)

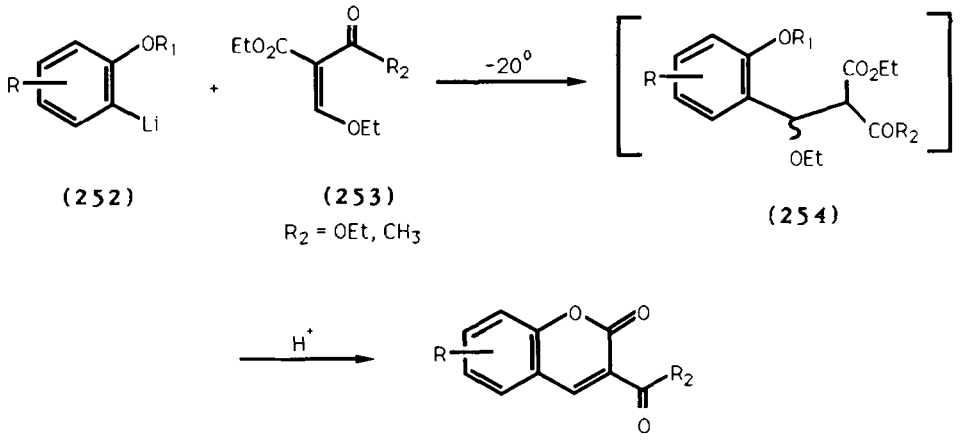
The addition of either HMPA or TMEDA did not improve product yields, and no mention was made concerning solvent effects on ratios or yields.

The use of inter- and intramolecular Michael additions to esters or lactones via rapidly formed organolithium reagents as a method for forming cyclized products has a great deal of potential in organic synthesis as evidenced by recent reports from the Kende, Kraus, and Cooke groups. Kende has reported the use of this method (**249-250**) as a key step in the total synthesis of (±)-4'-demethyl-4-epipodophyllotoxin (**251**).[123] The cyclization gave the annulated product (**250**) in 88% as a mixture of diastereomers.



Kraus and Pezzanite have described the conjugate addition of the aryllithium reagents (**252**) to either ethyl ethoxymethyleneacetoacetate or the corresponding malo-

nate (253) as a method for the preparation of oxygenated coumarins (255) in fair yields.[124]

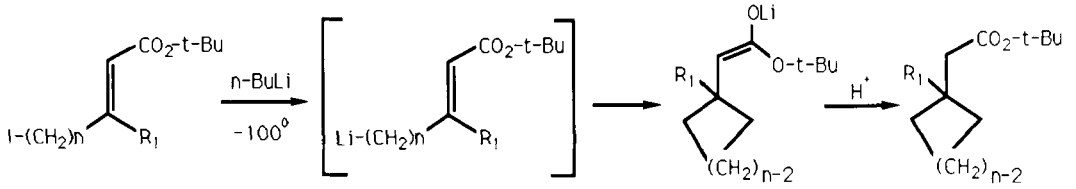


(252) (253) (254)

R_2 = OEt, CH_3

(255)

Cooke has recently studied carbocycle formation via intramolecular conjugate addition of internal unstabilized nucleophilic centers formed through rapid halogen-lithium exchange of ω-iodo-α,β-unsaturated esters (256).[125] The cyclization reaction is conducted in THF and yields are sensitive to temperature, the organolithium reagent used in the exchange reaction, and substrate substituent effects. While this procedure permits a facile entry to cyclobutanes and cyclopentanes, the cyclizations



(256) (257) (258) (259)

leading to larger ring systems have proven less successful. These studies indicate the possibility of executing the construction of variety of annulated products based on rate differences between halogen-lithium exhange and direct reaction of the metallating agent with an internal electrophilic center.[126]

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