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RECENT ADVANCES IN DIANION CHEMISTRY

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CONTENTS

I. Introduction

Over thirty years ago, Morgan and Harris[1] observed that the alkylation of the dipotassium salt of benzoylacetone occurred predominantly at the terminal methyl group and thereby ushered in the field of regioselective carbon-carbon bond formation via "dianions." [2] Since that report, dianions have become increasingly popular as strategic tools to the synthetic planner. This popularity has manifested itself in a wide array of reaction types ranging from the well-established β-dicarbonyl (acetoacetate-type) dianion to the ingenious, chiral, heteroatom-based dianion intermediates, many of which we will introduce in this review

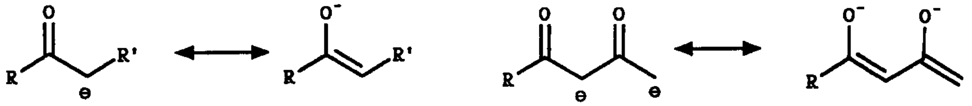
The word "dianion" conjures up a variety of meanings to different members of the chemical community and it is therefore appropriate first to describe and delimit this review accordingly Our goal is predominantly to serve readers who wish to use carbon-based dianions in synthetic maneuvers The 1980's witnessed a remarkable growth in the number of articles that exploit these reactive intermediates, and as a result we have adjusted the scope of this review to include only those dianion species that react at a carbanionic, second deprotonation site Such limits will necessarily exclude transition metal, electrochemically produced, aromatic species (i e , dianions that result in an aromatic compound) and heteroatom-only based dianions The material included herein is neither definitive nor exhaustive within the topic of carbon-based dianions but is intended to serve primarily as a guide to the most recent developments A consequence of the increased popularity of dianion chemistry is that many elaborate transformations involving their use are concealed either in total syntheses or in other studies and have escaped our attention We hope that such omissions may be found as cross references within our bibliography

To date, only a few reviews have covered the chemistry of dianions[3-10] and many of these reviews focus upon specific dianion types Our intention is to augment those excellent prior reviews with current contributions and to incorporate, where appropriate, some new applications to synthesis. Also, a recent ^{13}C and ^{17}O NMR examination provided excellent spectroscopic signatures for dianion detection that should be of great value [11]

If one assumes that the ultimate goal of generating a dianion is to create a new regiospecific carbon-carbon bond then the second deprotonation may be considered to occur solely at carbon Therefore, we shall represent and organize dianions by their primary deprotonation site For example, we distinguish carboxylate-containing from acetoacetate-type dianion species by virtue of the fact that the former undergoes primary deprotonation at an oxygen (O,C-type) whereas the latter is deprotonated first at carbon (C,C-type) In this manner, dianions may be grouped into C,C-, O,C-, N,C- and S,C-types with only slight additional distinction of the primary deprotonation site required (e g , hydroxy versus carboxylic -OH) to delineate further the varied dianion species within a section This approach is also consistent with related positional descriptors of dianions such as the α,α' definition.

In the literature many dianions are pictorially represented as both carbanion and enolate Although an enolate structure is preferred, we have chosen to depict the dianions at the sites of deprotonation than as the respective stabilized form to facilitate recognition of the reactive carbon and to discriminate among many different species under consideration Such depictions are more instructive than factual With this approach, this review stays consistent with a major previous treatise on carbanion chemistry [6] As a further distinction, we portray all carbanionic centers with a circled

minus charge (⊖) and the heteroatom deprotonation sites simply as a **minus charge** (-)



α-carbanion enolate α,α'-dianion dienolate

A primer of basic carbanion chemistry will aid the understanding of dianion methods and utility Although such a primer is beyond the scope of this review, readers may wish first to consult some excellent texts and reviews that survey basic carbanion chemistry [6,12-18]

Doubtless, two of the most important considerations in dianion chemistry are the evaluation of the equilibrium acidities (pKa's) of the sites to be deprotonated and the selection of the base. Carbanions stabilized by inductive or resonance effects have been converted to their conjugate bases and evaluated for their C-H acidities.[6] Unlike their mono-carbanion counterparts, dianions generally require more than a modest equilibrium composition to effect reaction In general, second deprotonations generally range in acidity from 20-35 pK_a units Thus, far stronger bases usually must be employed for dianion generation As will be evidenced in this review, no standard rules for the choice of base exist Still, prudent control over the relative base strength and the resulting nucleophilicity can lead to uniquely successful couplings and frequent avoidance of serious side reactions.

II. C,C-bis-deprotonations

II.(a) β-Dicarbonyl (α,α') dianions

Dianions generated from sequential deprotonations of β-keto esters and β-diketones have become routinely used in many synthetic strategies In this section, we update the coverage of these specific dianion types and include new and interesting variations on the β-dicarbonyl dianion theme. Typically, these dianions are generated either by the addition of 2 molar equivalents of an amide base or by initial addition of a base of modest strength (NaH, KH, etc.) followed by a stronger amide base (LDA, $NaNH_2$, etc)

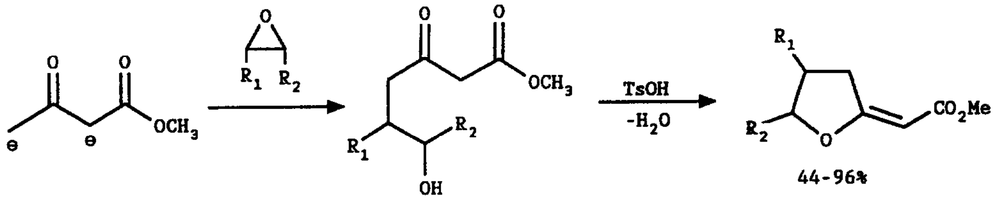
The alkylation of β-dicarbonyl dianions continues to be an attractive route to γ-substituted β-keto esters and their congeners. Typically, primary, allylic, and benzylic iodides, bromides and tosylates have been employed for optimum results although other variations have been successful We summarize some recent contributions in Table 1 [19-42]

Several features of this table are noteworthy As expected, the alkylation of β-dicarbonyl dianions proceeds most readily with primary and allylic-type iodides and bromides Intramolecular alkylation of β-keto ester dianions (entries 20-22) is a novel approach to macrocyclic lactones [32]

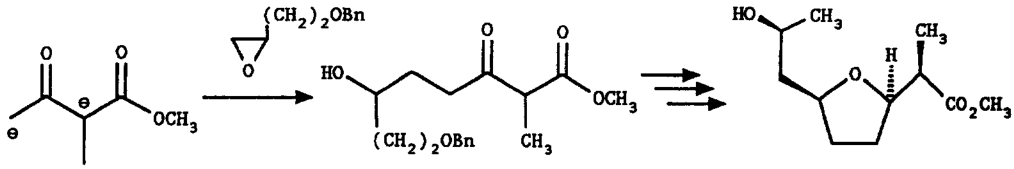
However, only tetra-, penta-, and hexadecanolides could be produced by the method; the lower homologues eliminated to the terminal alkene The *tert*-butyl ester (entries 12, 24) and thiolester (entries 43-46) have increased in use, with the latter envisioned as a synthetic equivalent to diketene.[40] The corresponding cyclic dianions (entries 29-37, 39-42, 47-49) also extend the overall scope

Additional applications not shown in the table include the alkylation of heteroatom-containing cyclic β-keto ester dianions[43] and an interesting alternative to the alkylation through enamine-isoxazole salts.[44]

Epoxides undergo reaction at the anion terminus of β-dicarbonyls. Clear advantages of these reactions include possible subsequent cyclization (centered at the resulting hydroxyl) to afford furans and furanones. Such processes report epoxide-opening with the dianion of *tert*-butyl acetoacetate in studies examining the synthesis of vernolepin.[45] Subsequent investigations revealed that the reaction may be promoted by addition of boron trifluoride etherate.[46] This latter study showed that the resultant hydroxy keto esters may be selectively dehydrated to furylidene acetates.



Lygo and co-workers have recently extended this epoxide-dianion combination to tolerate a variety of substituents[47] The preparations of methyl nonactate[48] and homononactates[49] further illustrate this useful transformation

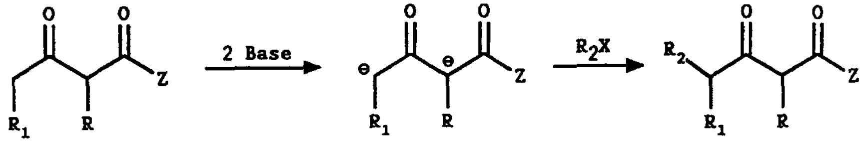


nonactic acid, methyl ester

Finally, an early report made dual use of this strategy A cyclic acetoacetate dianion was reacted with an epoxide to furnish a precursor en route to chalcogran[50]

β-Carbonyl dianions undergo condensation reactions. Besides establishing a regiochemically precise C-C bond connection, the product of condensations contains an additional hydroxyl group that may be synchronously utilized in either straightforward synthetic manipulations or to construct oxygen-containing heterocycles As this topic has been covered briefly in prior reviews,[3,5,6] this section on condensations will summarize recent advances in the reaction of β-dicarbonyl dianions with aldehydes,

TABLE 1. REPRESENTATIVE ALKYLATIONS OF β-DICARBONYL DIANIONS

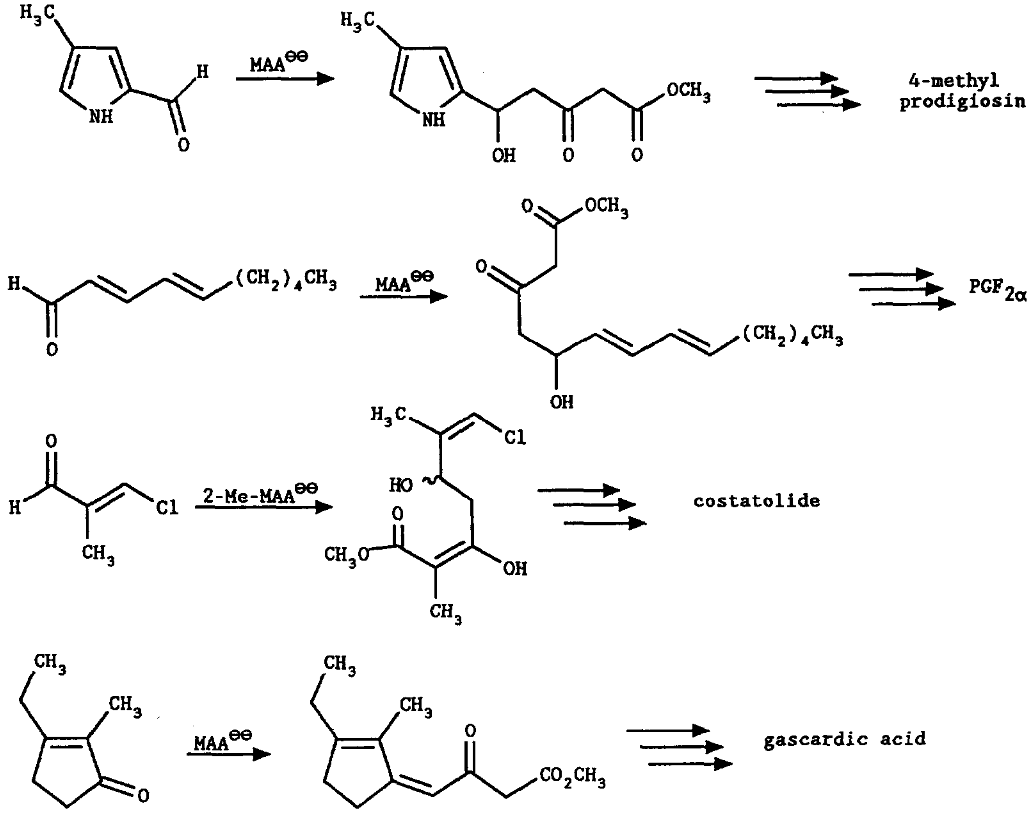


Entry	R	R_1	Z	Base	R_2X	Yield (%)	Ref
1	H	H	OMe	a	$Br(CH_2)_4Br$	26	19
2	H	H	OMe	a	$Br(CH_2)_5Br$	25	19
3	H	H	OMe	a	$Br(CH_2)_{10}Br$	39	19
4	H	H	OMe	a	(Z)-$ClCH_2CH=CHCH_2Cl$	18	19
5	H	H	OMe	a	$MeOCH_2Cl$	65	20
6	H	H	OMe	a	MeOCH(Cl)Me	89	20
7	H	H	OMe	a	EtOCH(Cl)Me	73	20
8	H	Me	OMe	a	$MeOCH_2Cl$	87	20
9	H	H	OMe	a	$Me_2C=CHCH_2Br$	79-85	21-23
10	H	H	OMe	a	1-bromomethylcyclohexene	70	24
11	H	H	OMe	a	geranyl-Br	61	25
12	H	H	OtBu	a	geranyl-Br	-	26
13	H	H	OMe	a	geranyl-Cl	82	27
14	H	H	OEt	a	allyl-Br	97	28
15	H	H	OMe	a	(E)-$CH_2=CHCH=CHCH_2Br$	70	29
16	H	H	OMe	a	(E)-$CH_2=CHCH=C(Me)CH_2Br$	50	29
17	H	H	OMe	a	(E,E)-$MeCH=CH\text{-}CH=C(Me)\text{-}CH_2Br$	53	29
18	H	H	OMe	a	farnesyl-Br	≥ 80	30
19	H	H	OMe	a	(E)-$Br(Me)C=CHCH_2Br$	-	31
20	H	H	$O(CH_2)_9Br$	b	-	43	32
21	H	H	$O(CH_2)_{10}Br$	b	-	45	32
22	H	H	$O(CH_2)_{11}Br$	b	-	49	32
23	H	H	OMe	a	1-tosylmethylcyclopentene	-	33
24	H	H	OtBu	c	4-iodomethyl-β-lactam	84	34
25	H	H	$N(Me)_2$	b/c	BnCl	92	35
26	H	$-CH_2CH_2-$		b	MeI	41	36
27	H	$-CH_2CH_2-$		b	allyl-Br	56	36
28	H	$-CH_2CH_2-$		b	BnBr	67	36
29	H	$-C(Me)_2CH_2-$		b	MeI	42	36
30	H	$-C(Me)_2CH_2-$		b	allyl-Br	57	36
31	H	$-C(Me)_2CH_2-$		b	n-PrBr	32	36
32	H	$-C(Me)_2CH_2-$		b	n-PrI	62	36
33	H	$-C(Me)_2CH_2-$		b	i-PrBr	75	36
34	H	$-C(Me)_2CH_2-$		b	i-PrI	78	36
35	H	$-C(Me)_2CH_2-$		b	cyclohexyl-Br	16	36
36	H	$-C(Me)_2CH_2-$		b	cyclohexyl-I	54	36
37	H	$-C(Me)_2CH_2-$		b	BuBr	70	36
38	H	H	Ph	b	EtI	-	37
39	$-CH_2CH_2-$		OMe	a	$CH_2=CHCH_2CH_2CH_2I$	89	38
40	W	$-CH_2CH_2-$		b	MeI	80	39
41	W	$-CH_2CH_2-$		b	n-PrI	69	39
42	W	$-CH_2CH_2-$		b	i-PrI	67	39
43	H	H	S-tBu	a	MeI	78	40
44	H	H	S-tBu	a	EtI	69	40
45	H	H	S-tBu	a	allyl-Br	70	40
46	H	H	S-tBu	a	$THPOCH_2CH_2I$	75	40
47	$-CH_2CMe_2-$		OMe	a	(E)-$CH_2=CHCH=CHCH_2CH_2I$	-	41
48	Me	$-CH_2-$		c	allyl-Br	50	42
49	Me	$-CH_2-$		c	n-pentyl-I	71	42

$W=CH_2CH_2OEt$
Base combinations a. NaH/BuLi b 2 LDA c 2 BuLi

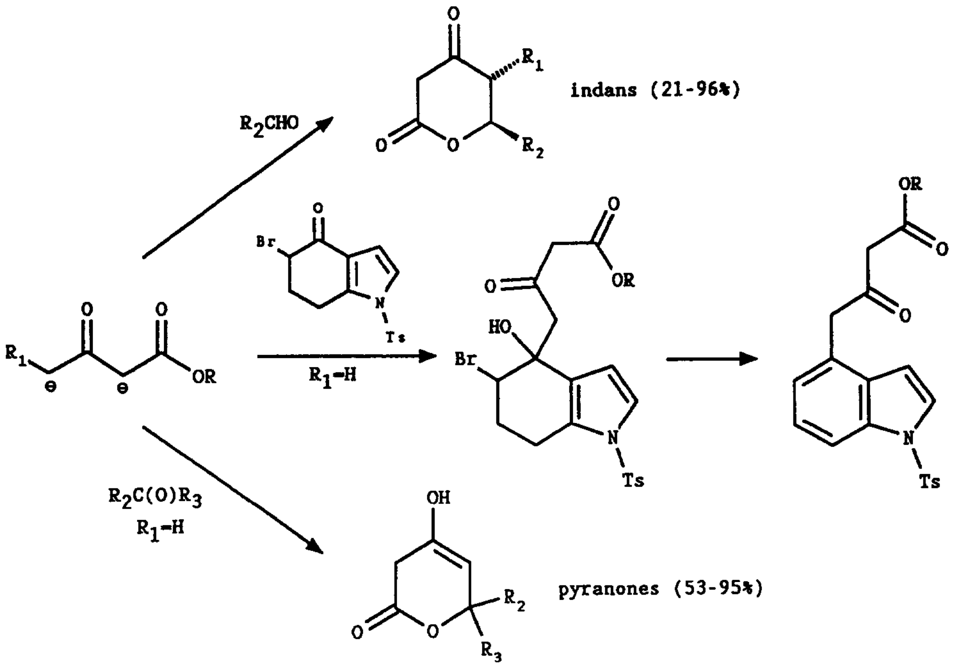
ketones and acylating agents (esters, amides, etc.). As with many of these reactions, self-condensation can frequently be a concern.

Probably because of their simplicity and reliable generation, the dianions of methyl acetoacetates have been the most widely employed in condensation reactions.[51] As testimony to this reliability, several groups have pursued lengthy syntheses incorporating the acetoacetate dianion condensation reaction at an early stage. Some examples include the preparation of 4-methyl prodigiosin,[52] prostaglandin $F_{2\alpha}$,[53] phytotoxin analogues,[54] costatolide,[55] dihydroxy vitamin D_3[56] and gascardic acid.[57]

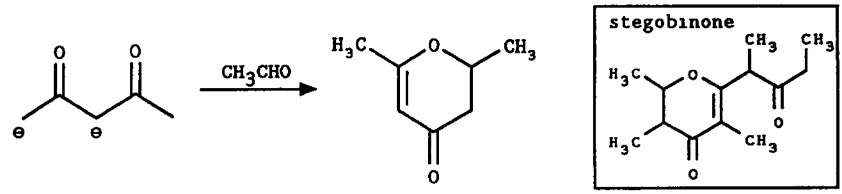


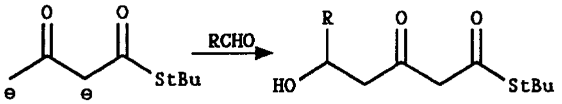
MAA⊖⊖ = methyl acetoacetate dianion 2-Me-MAA⊖⊖ = 2-methyl methylacetoacetate dianion

In a similar fashion, 4-substituted indoles,[58] indans,[59] and pyranones[60] have been prepared with acetoacetate dianion condensation methodology.



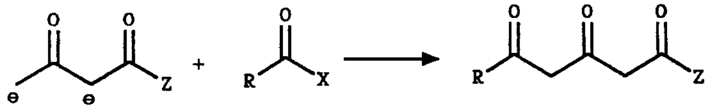
Variation in the carboxyl portion of the dianions has also been proven possible. β-Ketoamides,[35] β-diketones,[61] and acetyl thioacetates[40,62] have been converted to their corresponding dianions and condensed with carbonyls. The utility was noteworthy in the synthetic approaches to stegobinone[61] and milbemycin seco analogues[62]



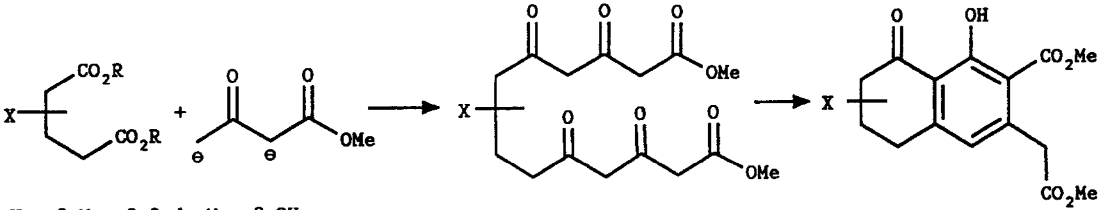


R	Yield
Ph	65%
CH_2=CH-	83%
C_3H_7-	84%
CH_2=CMeCH$_2$-	88% → milbemycin seco analogues

Dianions of β-dicarbonyl compounds react readily with acylating agents to furnish 1,3,5-tricarbonyl derivatives, a class to which the biologically important polyketides belong



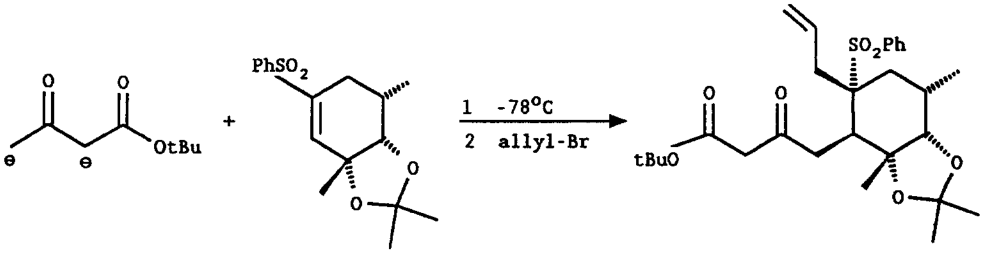
Yamaguchi and co-workers treated methyl acetoacetate dianions (2 molar equivalents) with various glutarates to obtain the intermediate polyketides in a biomimetic path to tetrahydronaphthalenes.[63] Later studies from this group found the bis-dimethylamide (R = NMe$_2$) to be a superior acylating agent in the presence of boron trifluoride etherate and that the sequence was amenable to succinamides and adipamides.[64]


X = 2-Me, 2,2-di-Me, 2-OH

A dramatic increase in the acylation of dianions (generated from 2 equivalents of LDA) by esters was effected by addition of 0.02 M TMEDA.[65] The problem of self-condensation may be circumvented by use of β-keto dialkylamide dianions.[35] Additionally, N-methoxy-N-methyl amides are reported to be superior electrophiles toward acylation.[66]

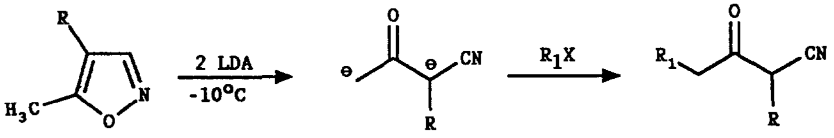
β-Diketone dianions have also been successfully acylated. Syntheses of xanthones[67] and stegibinone[68] are accomplished via this type of condensation.

Lastly, β-ketoester dianions have been shown to participate in the Michael reaction.[69] The dianion of *tert*-butyl acetoacetate adds to a vinyl sulfone to furnish the desired adduct after *in situ* capture with allyl bromide in 85% yield. This adroit investigation significantly adds to the reaction scope.

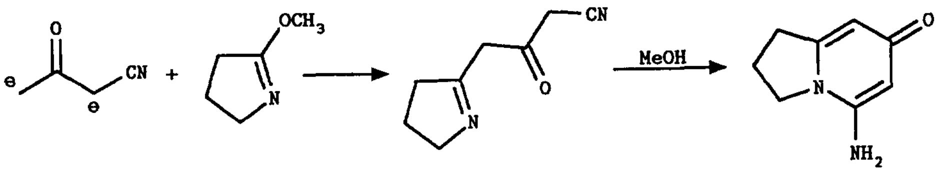


II.(b) α,α'-Dianions other than β-dicarbonyl

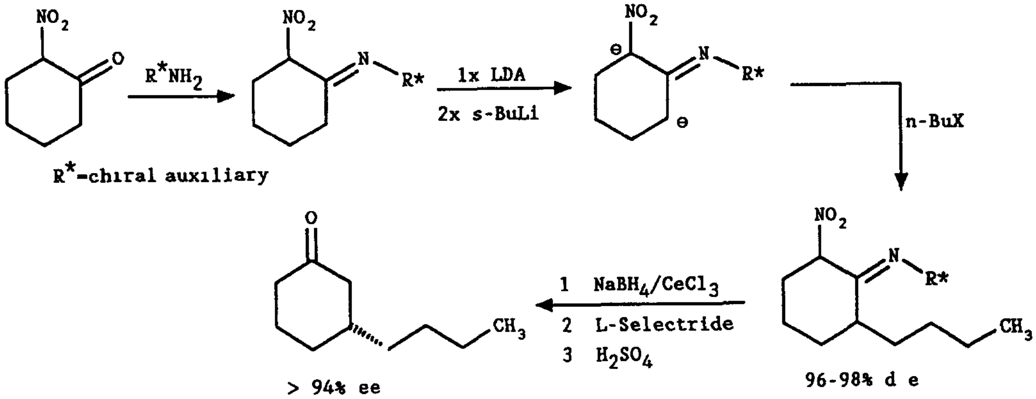
In this section, we briefly cover the character and utility of dianions resulting from α,α'-bis deprotonations in systems other than β-dicarbonyl. First, the dianions of the structurally similar β-ketonitriles are readily obtained although via an unusual starting material. Ring opening of methyl isoxazoles with two equivalents of LDA is reported to be the most convenient preparation.[70] Subsequent alkylation reactions gave good results



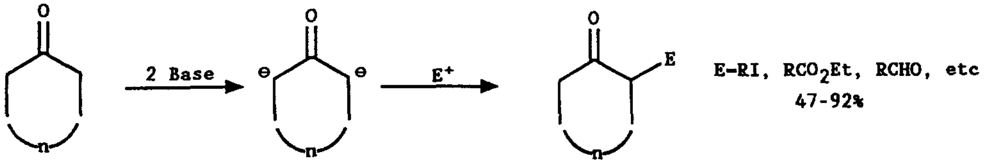
Reaction of this dianion with lactim ethers affords intermediate β-keto imines that upon reaction with methanol, cyclize to bicyclic pyridones.[71]



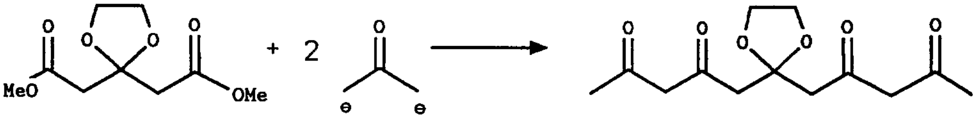
α-Nitro ketimines also may be bis-deprotonated in still another version of the α,α'-type dianion Denmark and co-workers used a chiral imine auxiliary to achieve stereoselective alkylation [72,73] This strategy marks a dramatic step in controlling asymmetric C-C bond formation via dianions



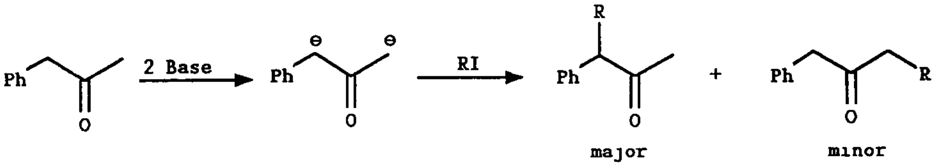
Bis-deprotonated ketones are commonly documented dianions Aliphatic cyclic and acyclic ketone dianions have been reacted with a variety of electrophiles in good to excellent yield [74]



The acetone dianion (with counterions, Li^+, K^+) has been used to prepare β-polycarbonyl compounds by the reaction with esters.[75,76]



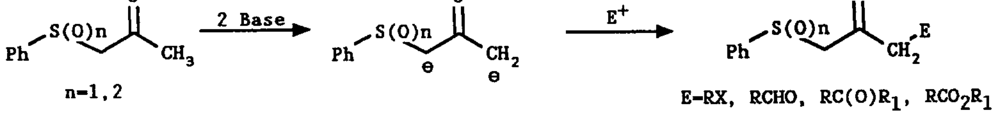
Ketone dianions that bear an α-phenyl substituent have been examined closely for their interesting anomalous behavior Trimitsis and co-workers[77,78] and Bays[79] showed that the phenylacetone dianion reacted predominantly at the benzylic position with most alkyl halides than at the expected terminal position akthough methyl iodide furnished an approximately equal product distribution



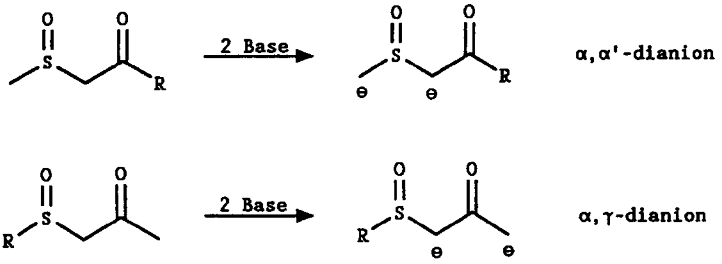
The 1,3-diphenylacetone dianion[80] and a benzylic congener[81] were examined for their oxidative and aromaticity properties, respectively

II.(c) β-Sulfinyl and β-sulfonyl dianions

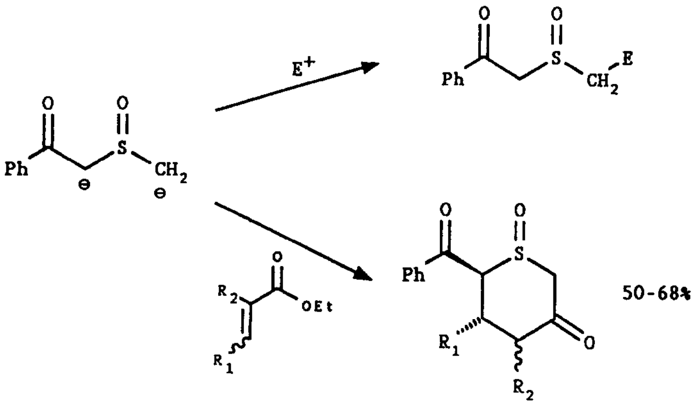
Sulfoxides and sulfones are capable of stabilizing α-carbanions similar to their isoelectronic, carbonyl counterparts Researchers began investigating dianions analogous to the acetoacetate and acetylacetone types that contain these heteroatom functional groups. Grieco *et al.* and Kuwajima *et al.* each showed that treatment of β-keto sulfoxides and sulfones with two equivalents of base leads to [α,α'] dianions that react at the second deprotonation site.[5,7] Both acyclic and cyclic versions were shown to be synthetically useful. We shall focus this section on some recent innovations in the field of β-keto sulfoxide and sulfone dianions, respectively



It is noteworthy that these dianions may be generated as either α,α'- (carbanion centers both α to sulfur group) or α,γ-(only one carbanion center juxtaposed to a sulfur moiety). Additional care therefore, must be taken in recognizing which nucleophilic species is intended for use.

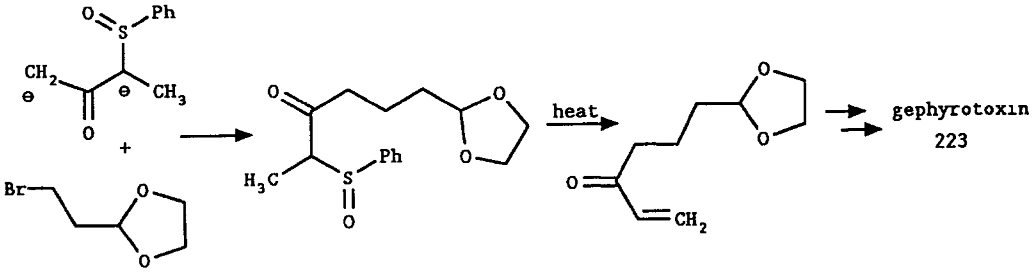


Tamura and co-workers have reported alkylation, acylation and condensation reactions of α,α'-ketosulfoxide dianions[82] Further studies with these dianions showed that Robinson-type annulation processes also were possible with α,β-unsaturated esters[83]



E	Yield
-Bn	95%
$-C(OH)Ph_2$	70%
-CH(OH)Ph	71%
-CH(Ph)NHPh	75%
-C(O)Ph	52%

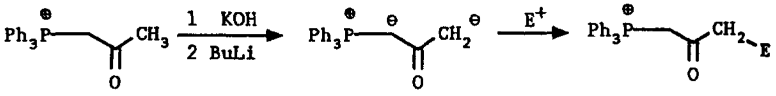
One major advantage of β-sulfinyl dianions over the acetoacetate congeners is a pyrolytic elimination of the sulfoxide moiety to furnish a latent alkene group Forbes[84] and Stevens[85] used this reaction combination in their synthetic efforts toward sceletium and gephyrotoxin alkaloids



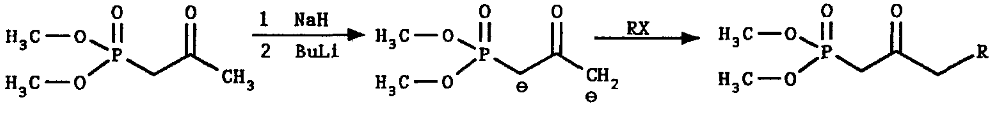
Dianions of β-ketosulfones have also been used in creative carbon-carbon bond forming tactics including an oxidative coupling (see also Section III.(b).)[86] and a stereospecific alkylation[87]

II.(d) β-Phosphonyl and β-phosphinyl dianions

Grieco and Taylor initiated studies that used bis-deprotonated β-keto phosphonates in synthetically useful ways.[5,88,89] Like the β-keto sulfone and sulfoxide dianions, β-phosphonyl carbonyl dianions are generated in either the α,α' or α,γ form. However, unlike the sulfur functional groups, certain phosphonates may be susceptible to attack by alkyllithium bases prompting the use of non-nucleophilic bases

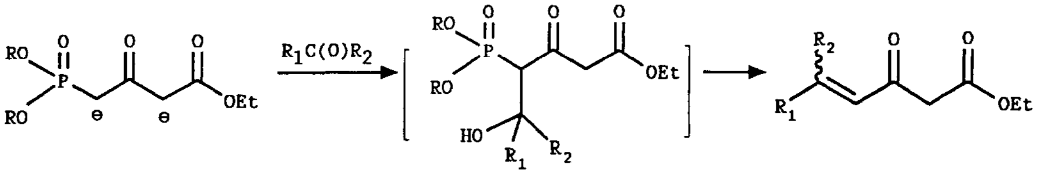


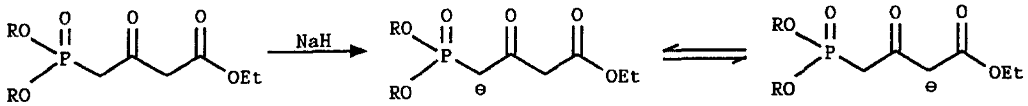
E	Yield
BnBr	44%
allyl-Br	52%
PhC(O)Ph	65%



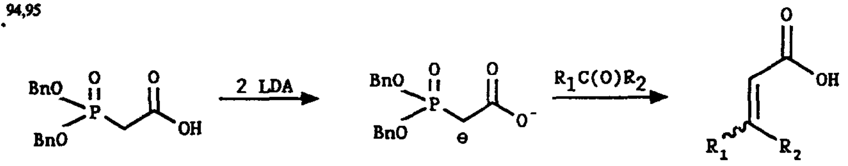
R=Me,n-Bu,iPr,Bn (65-75%)

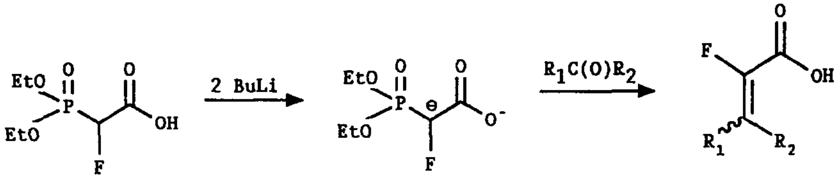
Interestingly, β-phosphonyl dianions have seen only sluggish growth A second point has been increased use of the 4-phosph(o)nyl-2-oxobutanate dianions, compounds that possess a third stabilizing functional group For example, the 4-phosphinyl dianions, generated by 2 equivalents of NaH, were used in condensation reactions Here, reaction occurs predominantly alpha to the phosphinyl moiety, then undergoes Horner-Emmon's expulsion of phosphine oxide to afford γ,δ-unsaturated β-ketoesters[90] Similarly devised phosphonate dianions condense with carbonyls[91-93] However, recent studies implied that 2 equivalents of NaH or KH used in earlier studies were insufficient for dianion generation[91] An equilibrium of monoanions was suggested as the attacking species



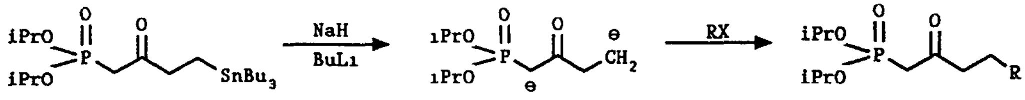


β-Phosphoryl carboxylic acid dianions add to carbonyl compounds to furnish alkenoic acids in good yield.[94,95]

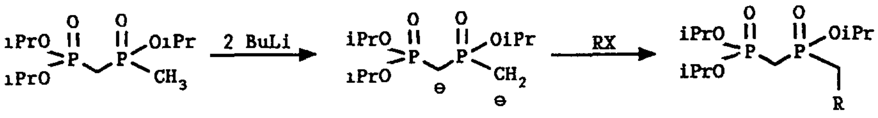




Tin-lithium exchange was used to prepare 1,4-(homoenolate)dianions of β-keto phosphonates These dianions were reacted with a variety of electrophiles to provide the 4-substituted adducts[96]



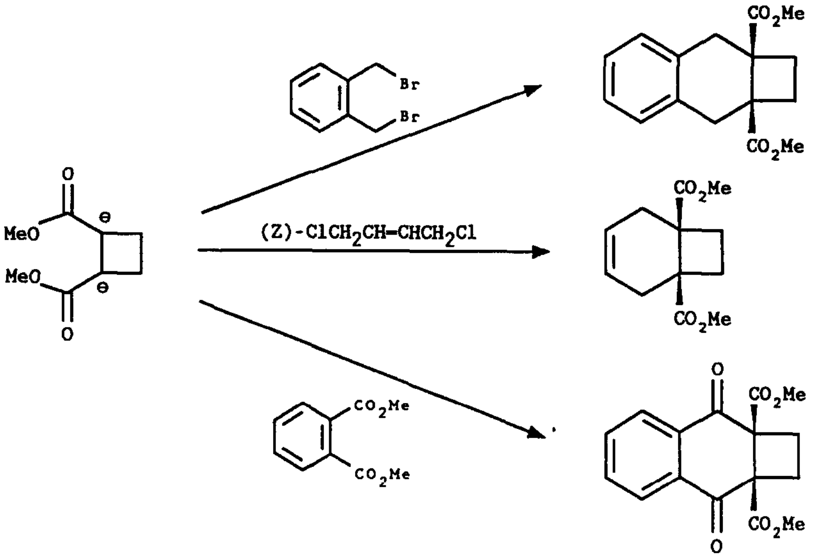
Last, the phosphonylphosphinyl dianion has been prepared (NaH, BuLi) and reacted with a variety of electrophiles[97]



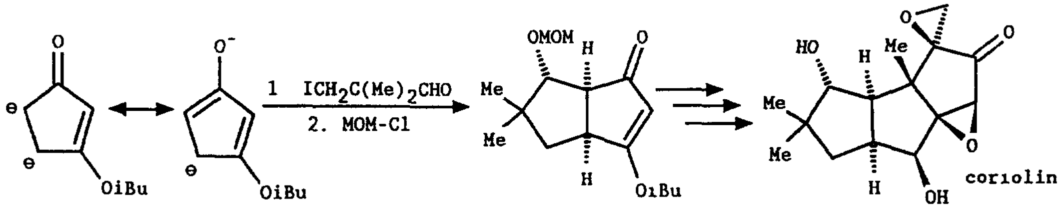
II.(e) Vicinal dianions

Suitably positioned electron withdrawing or stabilizing groups permit the formation of vicinal (α,β) dianions Vicinal dianions and geminal dianions (Section II.(f)) are subject to high levels of coulombic repulsion. However, despite this seemingly unfavorable factor, several investigators have recognized their potential and made excellent synthetic use of these intermediates We review these compounds by grouping them into the cyclic and acyclic versions (the former further focused by ring size). Sections II.(f), III.(a), IV.(a) and IV.(b) contain resonance delocalized dianions that also may exist, in the vicinal form

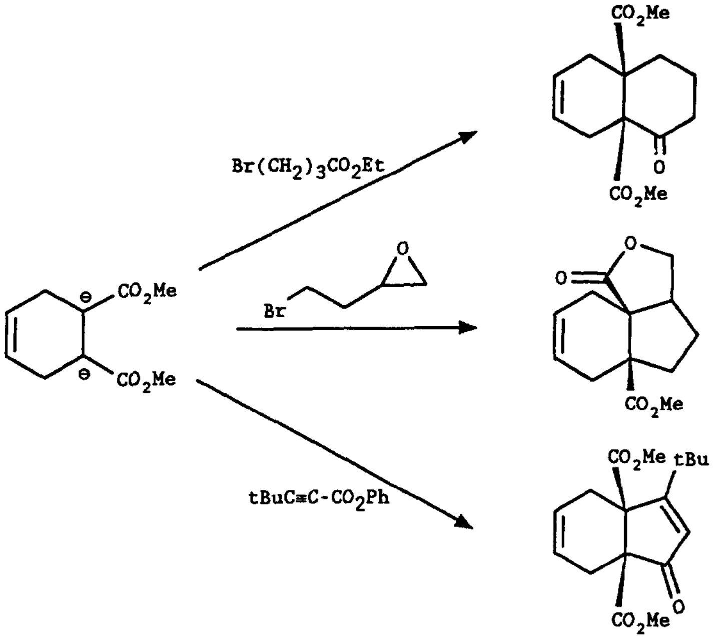
Generally, vicinal dianions are formed from the double deprotonation of vicinal diesters and related carbonyl compounds although related stabilizing groups will be briefly discussed Dimethyl cyclobutane-1,2-dicarboxylate dianion[98] reacts with 1,4-dihalides[99] and diesters[100] to give bi- and tricyclic products. The physical properties of the cyclobutene analog were studied.[101]



The corresponding vicinal dianion prepared from a five-membered ring was reacted with epoxy halides.[102] The increased stability of cyclopentadienyl carbanions prompted Ide[103] and Koreeda[104,105] to strategically exploit this particular dianion. The dianion of 3-isobutoxy-cyclopent-2-ene-1-one was utilized in the synthesis of coriolin [105]

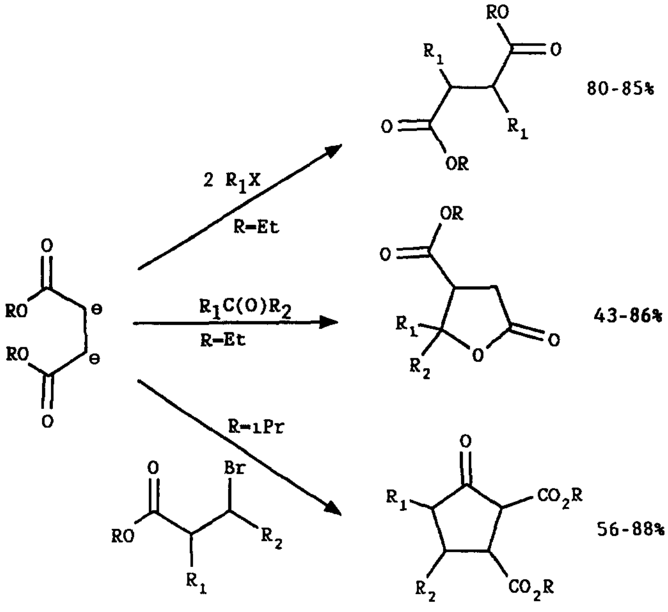


The most extensively employed cyclic, vicinal dianions are the six-membered rings. Garratt and co-workers reacted the dianion of dimethyl-4-cyclohexen-1,2-dicarboxylate with 3-bromo-esters (to furnish decalones),[106] bis-benzyl bromides,[107] 2-bromo-epoxides (to afford annulated lactones),[102] 1,4-dihalides (propellanes),[108] and alkynoates (via a novel mechanistic pathway) [109]



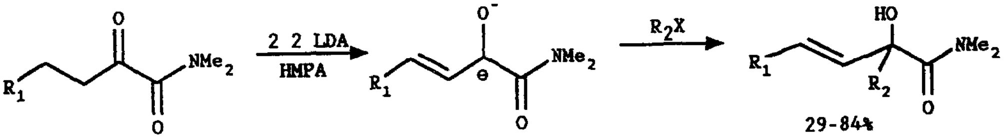
Cyclohexane-based vicinal dianions were used to synthesize valerane[110] Last among these cyclic vicinal species is the bicyclic succinimide dianion, which irrespective of initial exo or endo stereochemistry, alkylates predominantly from the exo face[111]

Acyclic vicinal dianions have been explored to a far lesser extent. The dianion of dialkyl succinates reacts with alkylating agents,[112] carbonyls,[112] and 2-halo esters[113] to yield functionalized rings

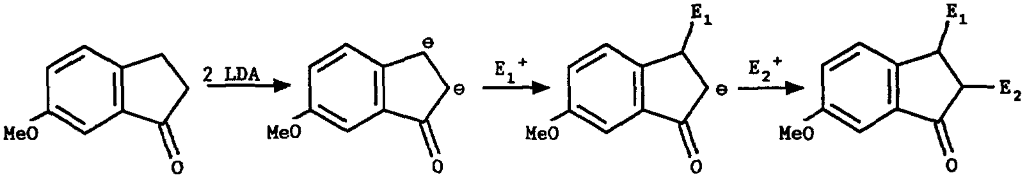


A bis-oxazoline dianion was reacted with a variety of dihalides to furnish cyclic and bicyclic compounds.[114]

Heteroatom-based vicinal dianions (also Sections III.(a), IV.(a) and IV.(b)) were explored by Koft and Williams. The dianion of an α-keto amide was alkylated yielding an α-amido tertiary alcohol.[115]

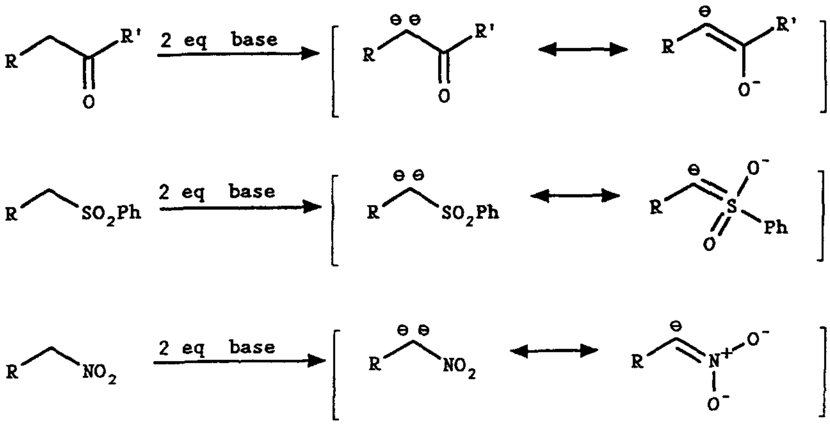


The dianion of 6-methoxy-1-indanone has been reported.[116] This vicinal-type dianion reacts predominantly at the 3-position with electrophiles. Since the product of the first reaction remains an enolate, subsequent substitution also was feasible



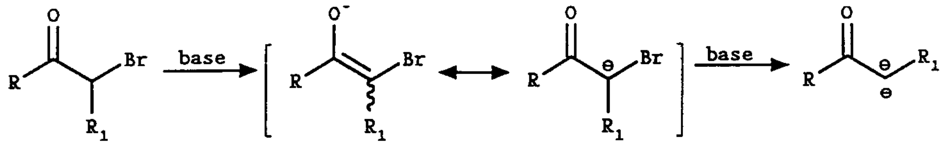
II.(f) α,α -(geminal) dianions

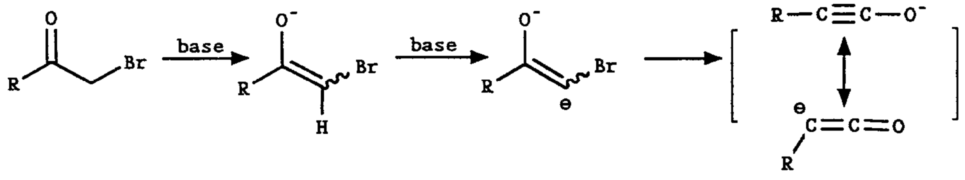
The α,α-dianions (geminal dianions) once an unrealized class of reactive intermediates, have been employed in transformations that primarily utilize the reactivity character and resultant chemoselectivity than the traditional regiochemical advantages of dianions Many geminal dianion intermediates bear carbonyl, sulfonyl and nitro as the dominant stabilizing groups Dianion structures in this section are depicted in both geminal carbanion and enolate-like forms for clarification since there is a preference for both



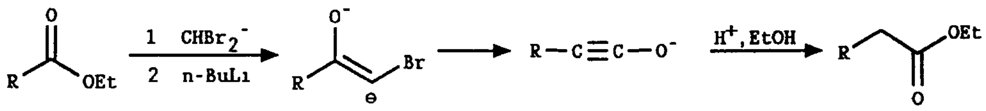
We have categorized this section by distinguishing each geminal dianion type by the requisite stabilizing group. Thus, we review the chemistry of carbonyl, sulfonyl, nitro, and related geminal dianions, respectively.

Prior to investigations by Kowalski and co-workers initiated in 1980,[117] only one α-keto(carbonyl) geminal dianion had been reported.[118] Since addition reactions would compete, these investigators cleverly utilized α-bromoketones. These compounds are deprotonated first by amide base to afford the lithio enolate followed by a metal-halogen exchange to yield the desired α-keto dianions Both cyclic and acyclic halo-ketones serve as precursors for this dianion. Reaction of these dianions with trimethylsilyl chloride to afford the disilylated enol ether and bis-α-deuteration provided strong evidence for geminal dianion existence Subsequent investigations established that geminal dianions react with ketones and aldehydes to yield alcohol products [119] It is noteworthy that highly hindered ketones were coaxed into reaction with geminal dianions [119] Under certain circumstances, addition of the second equivalent of alkyllithium base also was found to induce Hoffman-type rearrangement via deprotonation [120]



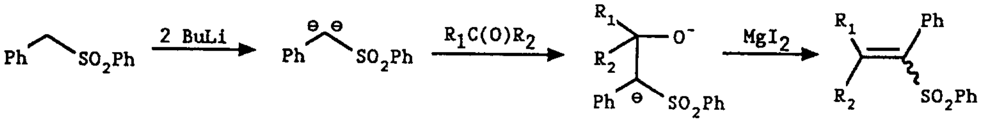


In interesting usages of this rearrangement reaction acyclic and cyclic esters may be homologated by one methylene[121] or converted to bromomethyl ketones.[122]

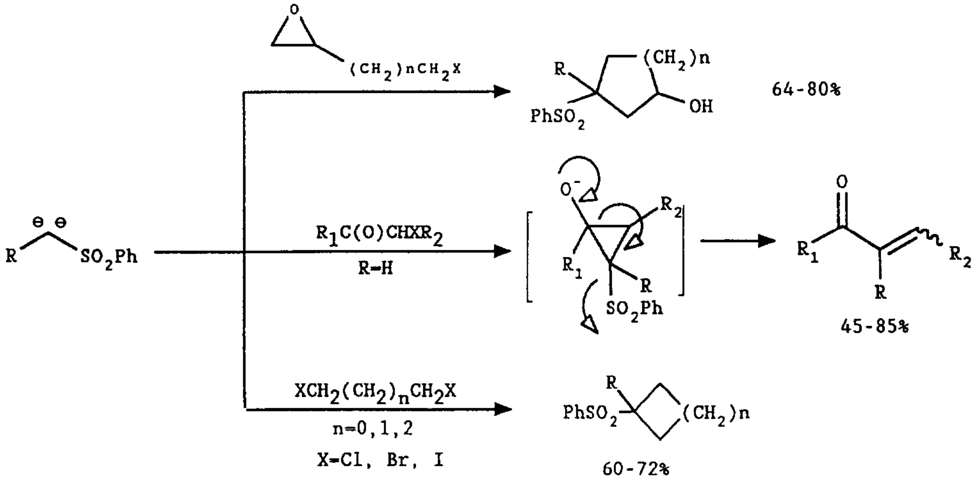


α-Keto dianions also may be prepared via the α-bromo enol acetates [123] A recent extension of this dianion methodology to the preparation of β-keto phosphonates, previously unavailable by Arbuzov-type chemistry, also has been reported.[124]

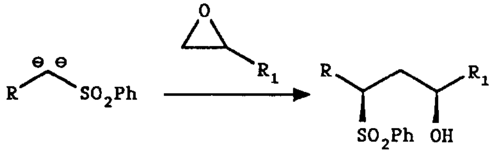
Unlike the inventive approach required for the carbonyl-stabilized geminal dianions, the corresponding α-sulfonyl intermediates are generated by straightforward reaction with two equivalents of alkyl-lithium reagent Two early reports illustrated this fact a an E_1cB mechanism induced by an α-sulfonyl dianion[125] and, b condensations of the gem-dianions with aldehydes and ketones to furnish intermediate β-alkoxide carbanions which when metallo-exchanged for magnesium, eliminated readily[126]



A variety of bifunctional organic substrates react with the dilithio-alkyl phenyl sulfones to provide carbocycles in a two-stage, nucleophilic displacement process[127-129] Slight variations on this theme using a second α-heteroatom functional group to stabilize the dianion makes possible the synthesis of carbonyl compounds[130] and vinyl sulfones,[131] the latter via a β-phosphono sulfone

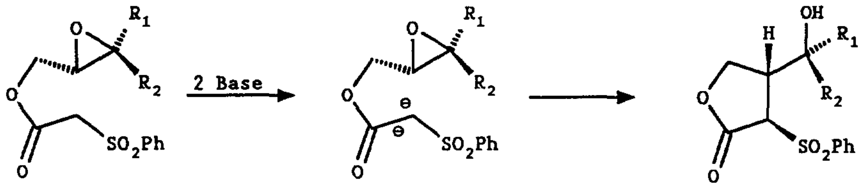


Sulfone stabilized geminal dianions react with epoxides diastereoselectively to form γ-hydroxysulfones in good yield[132]

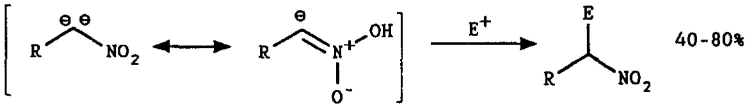


	Yield	de
R= $C(CH_3)$-CH_2, R_1=Ph	71%	99 1
R= $C(CH_3)$-CH_2, R_1=3-butene	90%	95 5
related	58-93%	

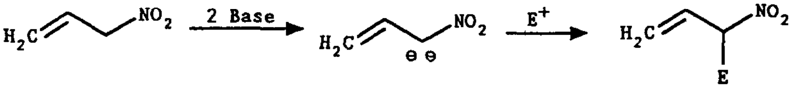
Last among α,α-sulfonyl dianions, McCombie and co-workers cyclized the dianion of a sulfonylacetate onto an epoxide to yield butyrolactones.[133]

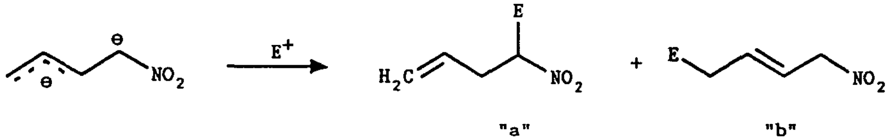


The nitro group, with its low α-pKa and resistance to attack by alkyllithium reagents provides the perfect marriage of features needed to function as a stabilizing moiety for geminal dianions In contrast to the carbonyl and sulfonyl groups, the nucleophilicity of a nitro stabilized α-carbanion is remarkably weak Geminal dianion formation was envisioned as a possible cure Seebach and co-workers found dramatically enhanced nucleophilicity of doubly deprotonated nitroalkanes toward esters, carbonates, aldehydes, ketones, and halides relative to the α-monoanion[134,135] The discovery that allylic nitronates provide the expected α-alkylation product whereas the homoallylic nitronate yields mixture of α- and δ-alkylation is noteworthy[136]



E=alkyl halide, ester, aldehyde, ketone, carbonate, anhydride

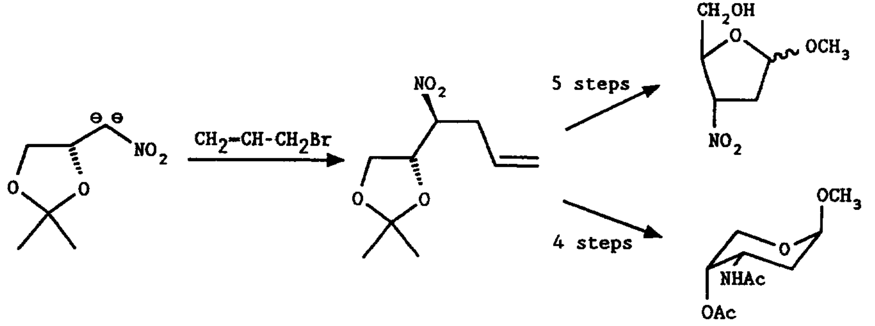




Ratio a b = 3:97 → 56 44
Overall yield 40-82%

Similar regiochemical outcomes were noted with nitro-stabilized geminal dianions that bear an additional stabilizing group at the β-position[135] Specific conditions to generate either the geminal or vicinal dianion of simple alkyl nitronates have been described[137]

Nitronate dianions that carry β-hydroxy or β-ether functionalities are stable toward elimination and condense with aldehydes and ketones to yield a diastereomeric excess of the *threo* (di)hydroxy nitronates in 75-95% yield[138] An enantiospecific synthesis of furanosides used a chiral, nitro stabilized geminal dianion.[139]



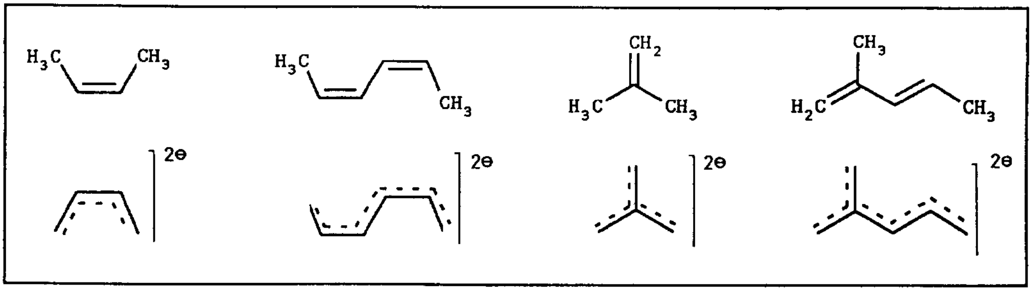
The α,α-dianion of 1,3-dithiepin was used to prepare a cyclic tetrathiaethylene unit[140]

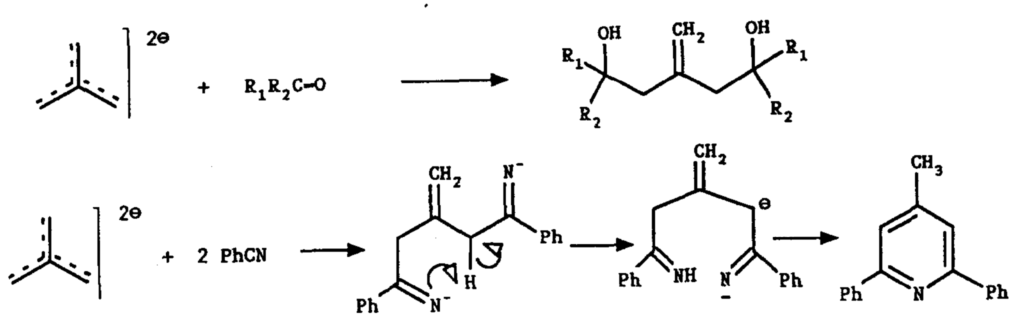
The existence of certain geminal dianions has been challenged Despite extensive experimentation that show geminal dianions react as such, ^{13}C NMR data suggests that the α,α-dianions of benzylnitrile ($PhCH_2CN$) and diethyl benzylphosphonate ($PhCH_2P(O)OEt_2$), are monoanions complexed with a second equivalent of base[141] These data imply sequential carbanion generation in carbon-carbon bond formation than the reaction of a resident α,α-dianion However, this study was in contrast to one that showed clear sulfonyl dianion formation.[142]

II.(g) Resonance-stabilized dianions[143]

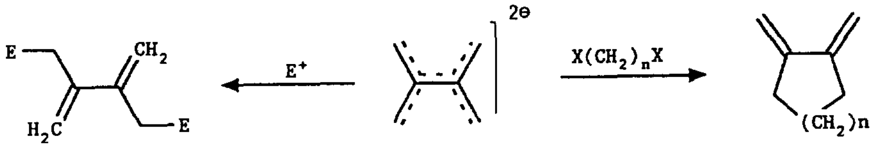
By virtue of a neighboring π-system, allylic positions may be readily deprotonated to furnish the carbanion Where possible, two such "allylic positions" may be deprotonated to give a dianion This section reviews such species with particular focus upon allylic and benzylic bis-deprotonations

Alkyl halides[144] and dihalides[145] react with the dianion of several simple alkenes and dienes (below) 2-Methyleneallyl dianion reacts twice with carbonyls and epoxides[146] Capitalizing on this propensity for bis-addition, 2-methyleneallyl dianion was reacted with nitriles to yield a new pyridine synthesis[147]

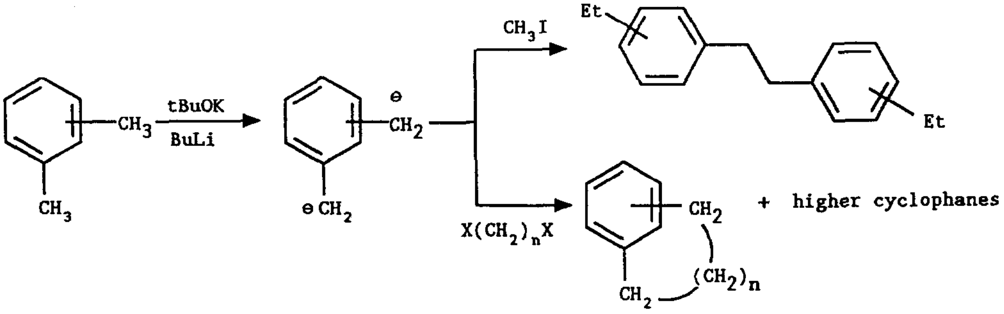




A novel investigative approach was taken with the 2,3-dimethylene butadiene dianion.[148] Reaction with monofunctional electrophiles led to bis-adducts,[149,150] while reaction with dihalides gave cyclic 1,2-dimethylene compounds.



Xylenes and lutidines are converted to their dianions.[151] Reaction with methyl iodide induced oxidative coupling but alkyl sulfates furnished alkylation products. Noteworthy was the production of cyclophanes by this method.

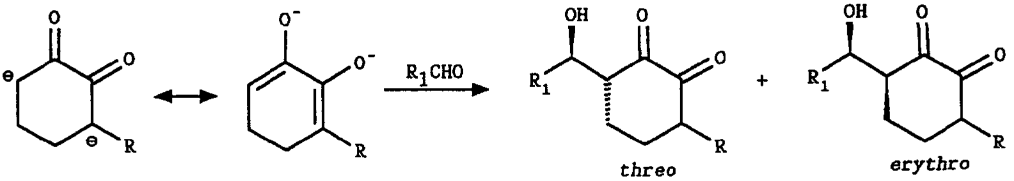


Also, symmetrical dimethylbiphenyls have been bis-deprotonated and reacted with alkylating agents in routes to cyclophanes.[152]

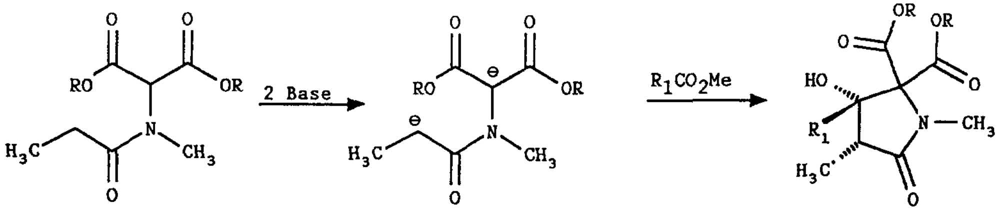
II.(h) Remote dianions

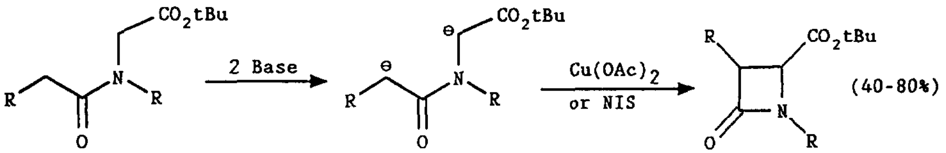
Dianions generated by stepwise C-H deprotonations occurring at positions on a molecule with at least two intervening atoms or functional groups (to aid distinction from α,α' and vicinal dianions for example) may be termed "remote." Remote dianions generated from initial deprotonation of a carboxylic acid will be covered later owing to their popular use (**Section III.(b)**). Here we review remote dianion discoveries where the functional groups used for stabilization are either carbonyls or sulfur-containing.

1,2-Cyclohexanedione dianions undergo the aldol reaction in high (80-99%) *threo* preference and good overall yield.[153] Presumably, a chair-like transition state accounts for the enhanced *threo* selectivity

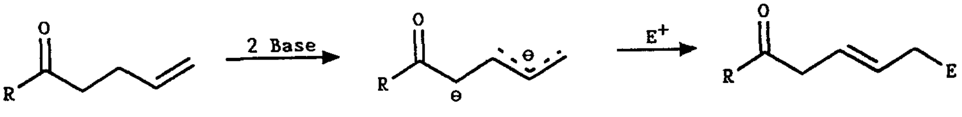


Remote dianions of carboxamides have been used to construct heterocycles Kende and co-workers took advantage of sequential condensation onto an ester by an amide-based remote dianion in route to neooxazolomycin [154] A structurally similar remote dianion was oxidatively cyclized by Hiyama to afford β-lactams [155]



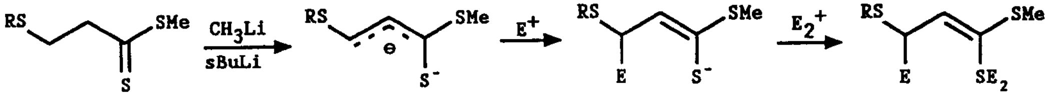


Seebach and co-workers investigated γ,δ-unsaturated carbonyl bis-deprotonations that yield the π-delocalized dianions shown below Reaction with electrophiles yields β,γ-unsaturated products making these dianions d^5-synthons [156]

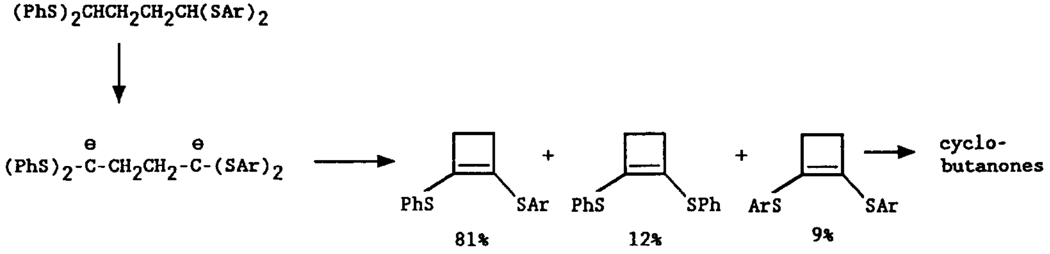


Sulfur-based stabilizing groups are a favorite among C-C remote dianion investigators Hirai *et al* have reacted the dianion of 2-propargylthiothiazoline with alkyl halides[157] and carbonyls[158] in route to squalene Dithioesters also may be bis-deprotonated and reacted with electrophiles at the β-[159] or δ-

position[160] (when an alkene is present).

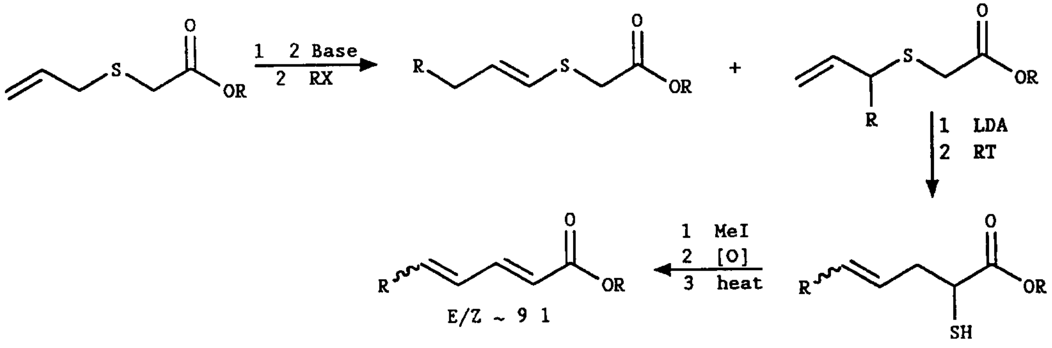


Thioacetal-based dianions were used as cyclobutanone[161] and trithiocarbonates[162] precursors

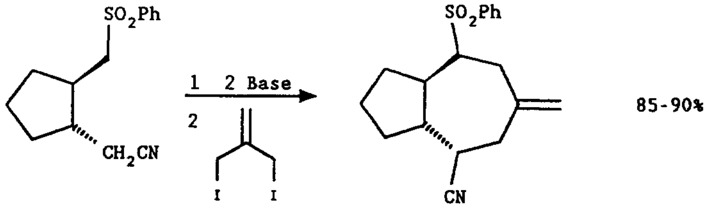


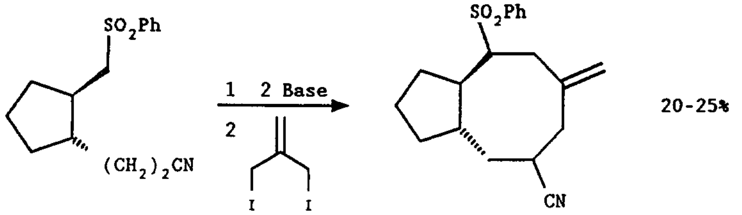
Tsuji and co-workers took an intriguing approach to their utilization of a sulfur stabilized dianion. In this study, a benzylic carbanion, additionally stabilized by a phenyl thioether, was generated [as part of a dianion] to control favorably the side chain orientation [163] The phenylthio group also served to block free rotation of the side chain needed for effective intramolecular cyclization

Alkylation of the dianion of (allylthio)acetate occurs readily and, after isolation and subsequent LDA treatment to induce a [2,3]-sigmatropic rearrangement, a dienoate is formed [164] The α/γ-alkylation ratios ranged from 7 3 to 93 7.



Remote dianions stabilized by a sulfoxide moiety have been used to synthesize prostanoids [165,166] The last remaining sulfur-containing remote dianions are the sulfone stabilized Hartman and Halczenko exploited the sulfone moiety for its bidentate chelating ability,[167] whereas Lansbury used this dianion type in an annulation process [168]





Also notable remote dianions are the 1,6-dianions of azines,[169] 1,8-dianions of ethyl-bridged dipyrazines,[170] and the dianion of dimethyl-2-carbomethoxy glutarate that was used in the synthesis of deethyleburnamonine [171]

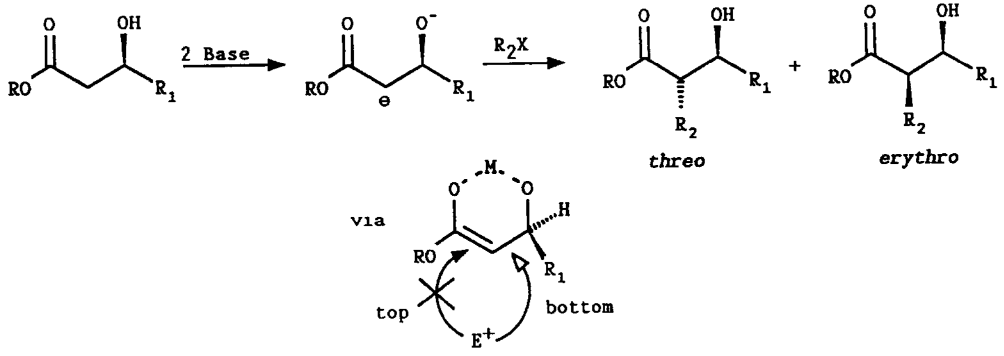
III. O,C-bis-deprotonations

Dianion generation that proceeds through first deprotonation at an OH functional group has achieved considerable attention The attractiveness and advantages of this process manifest primarily in circumventing lengthy protection-deprotection sequences. Also, protected hydroxyls and carboxyl esters occasionally appear precariously positioned and may undergo an eliminative pathway intended for carbanion-type reactions Thus, alkoxide- and carboxylate-based dianions may have grown in application systematically from both economy and strategy

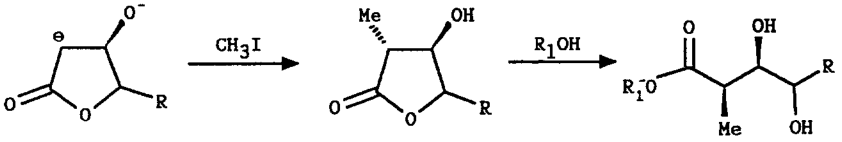
III.(a) Alkoxide and oxime-based dianions

The arrangement and inclusion of specific dianion types requires that diverse structures within a group be justified Whereas bis-deprotonations of β-hydroxy carbonyls and sulfonyls/sulfinyls, phenols, and related (remote and vicinal) hydroxy-containing intermediates are obvious choices for this section, we also include oxime-based deprotonations Notably, a previous review[5] assembled these species with other amine-containing dianions However, we make an organizational distinction in this review between deprotonations occurring at nitrogen (N-H) and oxygen (O-H) functional groups We hope that this slight departure from the previous review does not conceal any important dianion contributions

Herrmann and Schlessinger were among the first to report a successful alkylation of dianions derived from β-hydroxy esters.[172] Further studies investigating the stereochemical outcome showed that better than 90% stereoselectivity of *threo* products was obtained.[173-177] The observed diastereofacial preference was attributed to intramolecular chelation.[177]

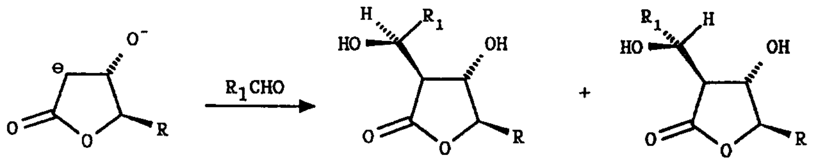


Hydroxy lactone dianions have been manipulated to provide 2,3-trans-oriented alkylation products[178-180] Recognition of these alkylated cyclic versions as the corresponding acyclic, *erythro* isomers furnished an inventive alternative in the preparation of this antipode[179]



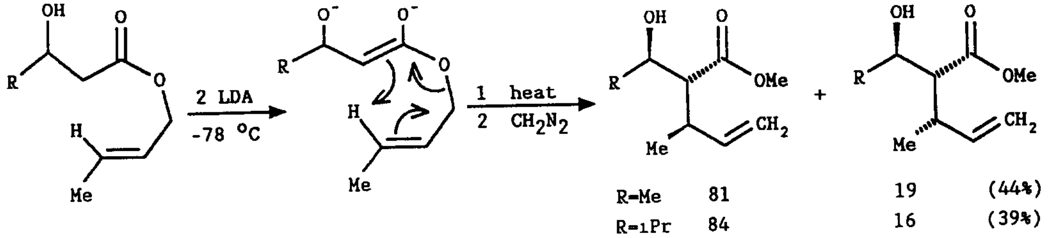
erythro ~ 90%

Hydroxy-lactone dianions also condense with aldehydes and ketones to give a range of stereoselectivities dependent largely upon the steric component.[178,180]

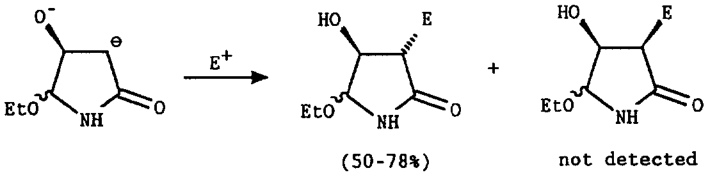


<u>R</u>	<u>R_1</u>	<u>*erythro*</u>	<u>*threo*</u>	<u>yield(%)</u>
H	t-Bu-	100	1	34
H	Bn-	1 3	1	45
H	Ph-	10	1	43
H	n-$C_{13}H_{27}$-	1	1	48
Me	Ph-	3	1	75
Me	n-$C_{13}H_{27}$-	1	1 5	60
Me	H-C≡C$(CH_2)_8CH_2$-	1	2	72

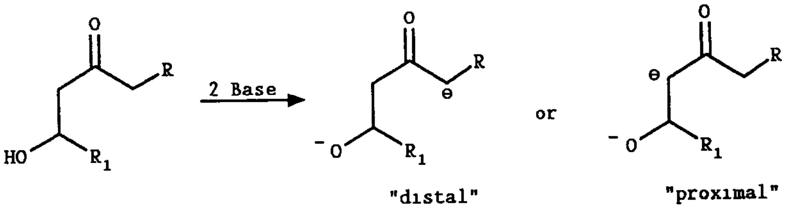
Chiral β-alkoxy ester dianions have also been utilized in Claisen rearrangements to provide stereocontrolled access to the corresponding α-allyl materials.[181-183] Chair-boat transition state selectivity was an important factor in the (E)-enolate enhancement. Application of this process to the preparation of the mycotoxin, botryodiplodin has been described.[182]



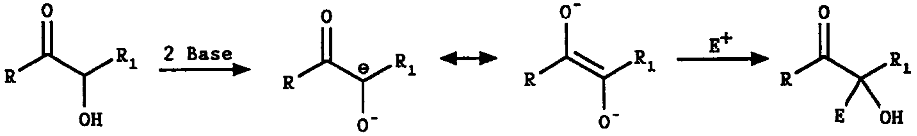
The diastereoselective alkylation of β-hydroxy lactams has also been reported.[184]



Another type of alkoxide-containing, carbonyl stabilized dianion is the "distal" enolate. Bis-deprotonation of certain β-hydroxy ketones furnishes kinetic enolates (as proven by TMS trapping) opposite to the alkoxide chain.[185,186] The resultant silyl [enol] di-ethers were used to prepare tetrahydropyranones. Distal dianions had also been directly used without conversion to the enol ether in the preparation of quinolones.[187]



The synthetic utility of α-alkoxy dianions has been evaluated. When deprotonation proceeds alpha to a carbonyl bearing a hydroxyl group, a class of intermediates known as the enediolates are formed. These dianions react at the α-position to furnish di-substituted α-hydroxy carbonyls.[188,189]

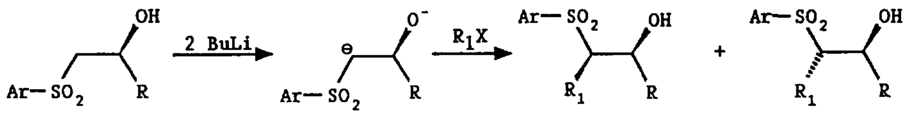


Similar stabilization by an alkyne to produce an α-alkoxy dianion was used in synthetic studies of milbemycin[190] and in the synthesis of oxoalkanenitriles.[191]

The "umpolung" dithiane moiety also may serve to stabilize the second deprotonation site in α-hydroxy dianions. Chain elongated saccharides were prepared by this process.[192,193]

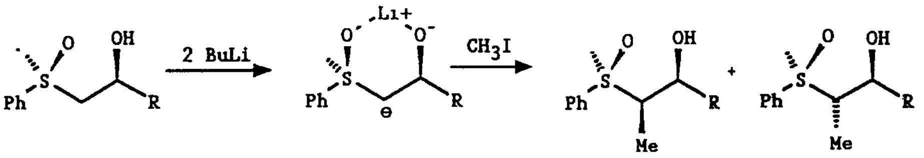
A similar experimental vantage point has been achieved with β-hydroxy sulfoxides and sulfones. Unlike the carbonyl-containing α-alkoxy dianions, sulfur moieties impart unique characteristics to both alkylation and condensation outcomes. The dianions of β-hydroxy sulfones and sulfoxides are generated by the addition of 2 equivalents of n-BuLi than LDA since they are not as sensitive to alkyllithiums.

Dianions of β-hydroxy sulfones react well with alkyl halides,[194-196,198] aldehydes,[194,197] and α-halo carbonyls.[194] A noteworthy observation in the simple alkylation reactions was that, as opposed to the carbonyl analogues, sulfonyl dianions furnish the more sterically demanding *erythro* products (50-100 % d.e.).[198] In two instances,[194,195] furanones were produced by subsequent cyclization, including an optically active synthesis that proceeded via a Bakers yeast reduction to furnish the precursor hydroxy sulfone.[195]



R	R_1X	*erythro*	*threo*	yield
Me	$CH_2=CH_2CH_2Br$	73	27	83%
Me	MeI	51	49	98%
i-Bu	MeI	78	22	72%
i-Bu	$CH_2=CH_2CH_2Br$	80	20	78%
Bn	$CH_2=CH_2CH_2Br$	98	2	69%

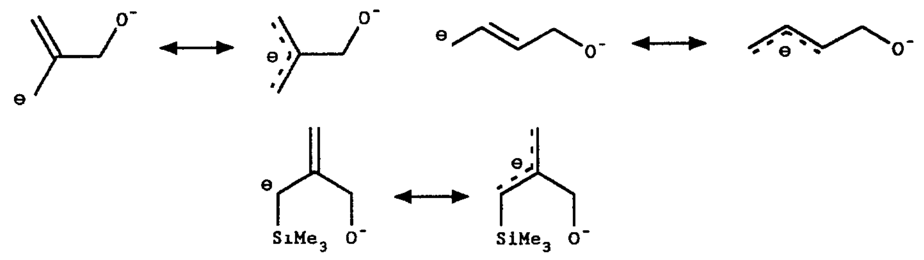
Tanikaga and co-workers contributed an exciting new addition to β-hydroxy-based dianions. β-Hydroxy sulfoxides, available via di-isobutyl aluminum hydride reduction of the corresponding ketones, are alkylated in good yields and diastereomeric excesses in *threo/erythro* ratios similar to those of the carbonyl companions.[199,200] Direct comparison to the sulfone derivative further showed the anomalous behavior of the aforementioned sulfone toward preferential *erythro* products[199] In part, such outcomes are due to chelation and steric effects.[201] The additional chiral center at the sulfoxide moiety also raises new and exciting possibilities for chiral molecule manipulation.



R	*erythro*	*threo*	Yield(%)
Me-	11	89	86
i-Bu-	4	96	96
n-C_9H_{19}-	5	95	70
Bn-	3	97	84

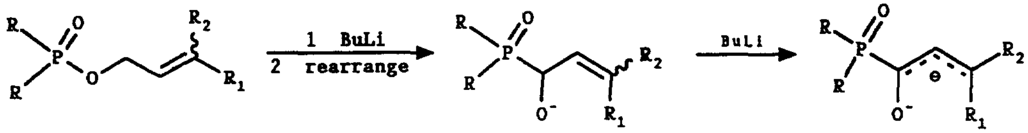
Alkoxide-containing dianions in which the second deprotonation occurs by abstraction of a proton from an allylic (or allylic-type) position have been investigated Dianions from methallyl alcohol,[202,203] crotyl,[204] silyl-substituted crotyl,[205] and related[206-208] materials have been used in synthetic schemes Alkylation and condensation reactions followed by oxidation of a hydroxyl yielded lactones[202,203] The presence of the allylic silyl moiety establishes a conjunctive reagent possessing both nucleophilic and electrophilic character[205]

Some representative alkoxide-based allylic dianions



Important to the production and utility of these dianions is concern with vinylic versus allylic deprotonation[207] Methallyl alcohol is metallated at the vinylic position with n-BuLi/HMPA in hexane[209] but is deprotonated at the allylic position with n-BuLi in ether or THF[210]

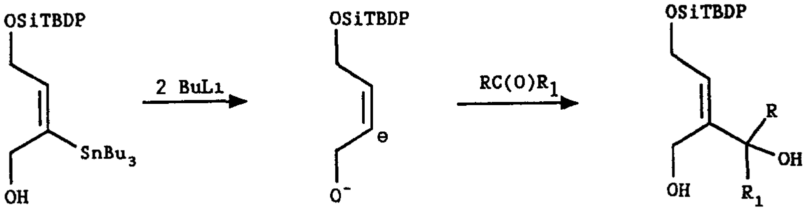
A somewhat indirect but nonetheless intriguing route to an alkoxide-containing allylic dianion proceeds via a phosphate-phosphonate rearrangement[211] Initial methylene deprotonation of an allylic phosphate induces transposition to the α-alkoxyphosphonate A second equivalent of base then furnishes the allylic dianion



The dianions of propargyl alcohol,[212,213] pyrroline-3-methanol,[214] and 4-biphenylmethanol[215] have been investigated.

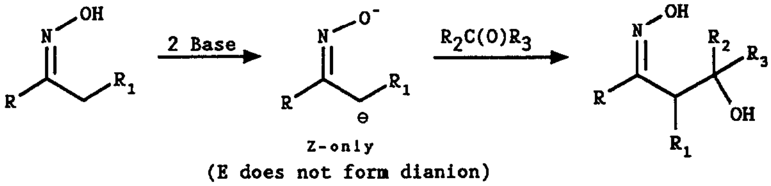
Dianions containing a phenolic group also may be first deprotonated at this site Although such processes would seem commonplace only a paucity of work has been reported Perhaps, such dianions are not duly advertised by the investigators avoiding reference collection Phenolic-based dianions deprotonated at enolate[216,217] or benzylic[218,219] positions have been reported as has an evaluation of cresol dianions [220]

An interesting path to alkoxide-based dianions uses lithium-tin exchange reactions The regiochemical installation of a vinyl carbanion provided an efficient route to substituted tetrahydrofurans [221] Similar transmetallation-based dianion creations prepared from alkanes have been reported[222,223] as well as lithium-halogen exchange routes [224]



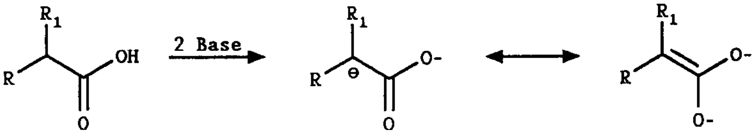
Cohen and co-workers investigated the unique properties of alkoxide thioacetal dianions [225,226] It was postulated that α-alkoxy thioacetal dianions behave as carbene-like[225] whereas more remote positioning of the anion centers results in more traditional reactivity profiles.

Last, we review some recent contributions utilizing oxime-based dianions Much of the preliminary work conducted in this area has been reviewed [5] Contemporary additions to the field have focused primarily upon the preparation of isoxazoles/pyrazoles,[227,228] azetidines,[229] and quinolines,[230] although interest continues in alkylation,[231,232] aldol,[232] and sulfenylation[233] reactions Importantly, only the Z-isomer of certain oximes forms a dianion and the aldol reaction of these intermediates is not diastereoselective [232] Use of the furan aldoxime dianion to furnish the 2,5-disubstituted heterocycle is a noteworthy addition [234]



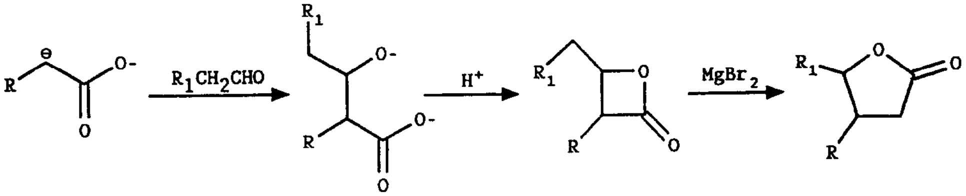
III.(b).1 Carboxylate-containing dianions

Because excellent reviews of α-carboxylic acid dianions already exist,[4,5,8,235] attention in this section is given to those articles appearing after 1982 α-Carboxylic acid dianions continue to be attractive intermediates for regioselective C-C bond formation, precursors for β-lactone ring formation, and other carbo- and heterocyclic ring-forming processes

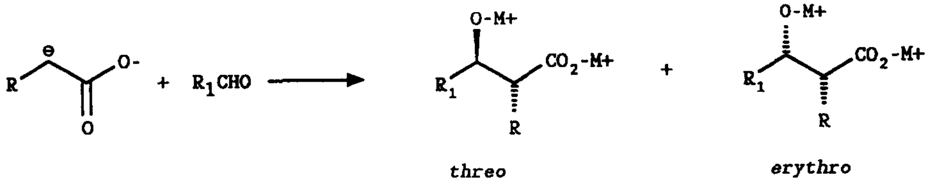


Simple α-carboxylic acid dianions (R=H, alkyl, aryl) appeared with new applications in the preparation of medicinally active compounds such as serine protease inactivators[236] and hypolipidemics[237]

Black and co-workers[238-242] made continued use of alkyl carboxylic acid dianions in studies of the dyotropic rearrangement Condensation of aliphatic α-carboxylic acid dianions with aldehydes affords, after cyclization, β-lactones Upon treatment with $MgBr_2$ rearrangement to butryolactones occurs

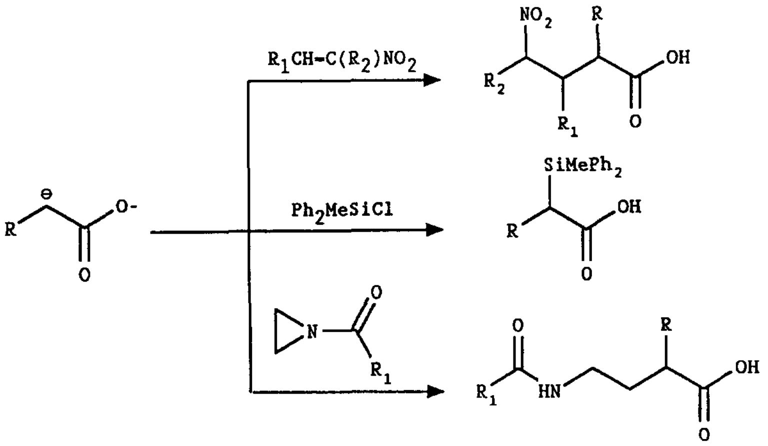


Mulzer elucidated specific stereochemical aspects of α-carboxylic acid dianion additions[243-245] Under kinetically controlled conditions, the dianions add to aldehydes to provide high *threo/erythro* product ratios when bulky substituents were present and a corresponding low *threo/erythro* ratio when a low charge/radius ratio of counterion (M+) was used[243] Such influences also were proved in additions to α,β-unsaturated aldehydes and ketones, the former materials being attacked

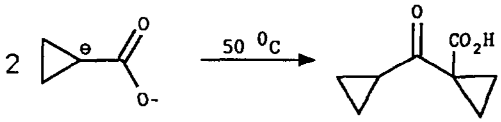


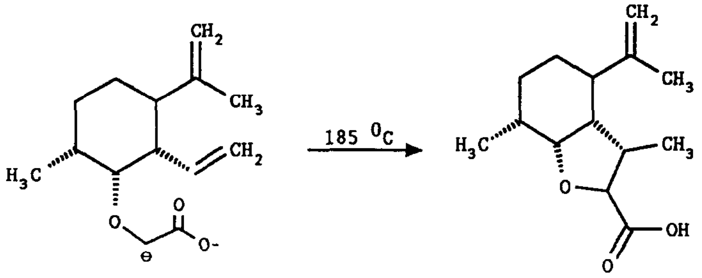
regiospecifically, and reversibly 1,2, whereas ketones react irreversibly by 1,2- and 1,4-processes[244] These experiments were used to advantage in the synthesis of some natural products.[245]

Some recent examples that have expanded the reaction repertoire of α-carboxylate dianions include addition to nitro-olefins,[246,247] diphenylmethylsilyl chloride,[248] and aziridines.[249]

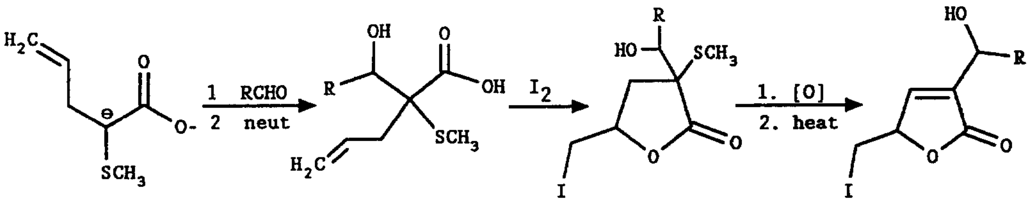


Two interesting reports describe the dimerization of the α-cyclopropyl carboxylic acid dianion[250] and an ene-type cyclization,[251] both of which are thermally induced

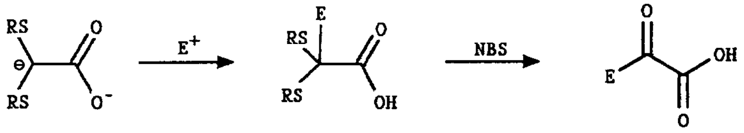




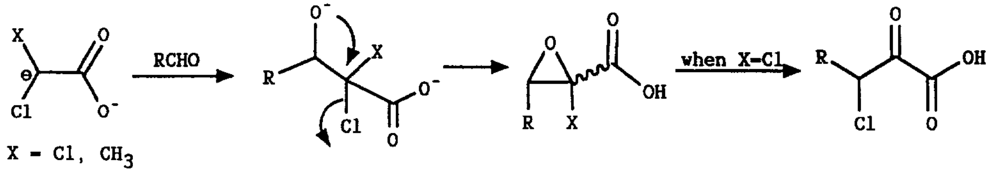
α-Heteroatom-substituted carboxylic acid dianions also increased in use Tanaka and co-workers found that α-methylthio based dianions react successfully with alkyl halides[252] and carbonyls.[253] Oxidation followed by thermal elimination of the sulfinyl moiety affords α,β-unsaturated lactones



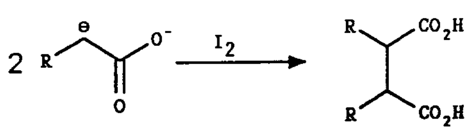
Bis-thioether α-carboxylic acid dianions react with alkyl halides, epoxides and aziridines[254,255] Thioacetal deprotection affords the α-keto acids

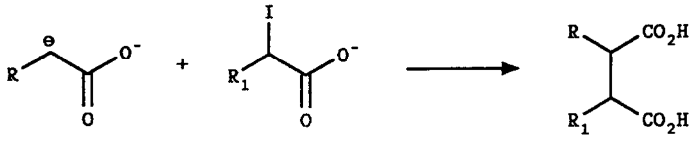


Similar alkylations of α-chloro and α,α-dichlorocarboxylic acid dianions have been reported[256,257] Reaction of either of these two species with aldehydes proceed through Darzens-type condensation to afford epoxides[256,258]



Belletire and co-workers uniquely utilized α-carboxylic acid dianions to form vicinal dicarboxylic acids via oxidative coupling A variety of substituents tolerate both dianion and oxidation steps making this approach ideal for the construction of symmetrical[259,260] and unsymmetrical[261] *vic*-diacids as well as natural products[262-264] Reaction of an α-iodo carboxylate with the α-carboxylic acid dianion was used in the construction of lignan prototypes[265] An adroit electrochemical investigation of dianion oxidation and pK_a's (approx 30) has also been reported[266]





Next, we will cover carboxylic acid dianions that react predominantly at positions other than alpha (including alkene-containing dianions). Difficulty in classifying these latter materials emerge since many factors influence the regioselectivity of their reaction. Such detailed coverage is beyond the scope of this review. In general, selective α-alkylation may be obtained from the lithio-dienolate and γ-alkylation with copper counterion.[8,267] Other examples that either alkylate or condense predominantly at the alpha position despite resonance delocalization have been reported.[268-270]

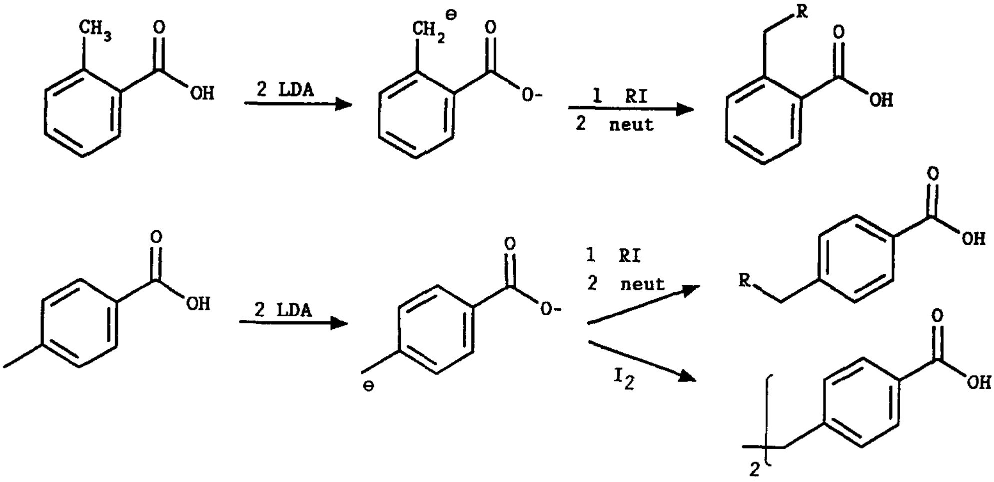
III.(b).2 Remote Carboxylic Dianions

This section describes the utility and reaction management of dianions prepared by initial deprotonation at a carboxylic-OH followed by carbanion generation at a site **other than alpha** to the carboxylate. These "remote" dianions occur because either the α-carboxylate position(s) is/are unavailable or a more acidic proton appears elsewhere in the molecule. These dianions proved to be important tools in diverse structure manipulation as well as C-C bond formation. Moreover, the carboxylate moiety is frequently suitably positioned for synchronous cyclization to yield heterocycles. Comprehensive details on specific dianion species in this class through 1982 are available.[8] Some duplication of reactions was necessary to illustrate certain examples.

Synthetic strategists have used a wide array of remote functional groups to serve as stabilizers for the second deprotonation site. As such, indirect information about the comparative [α-carboxylate to other] carbon acidities may be gleaned. The placement of a second anionic center at a position distal to a carboxylate should be energetically more favorable than concentrating two negative charges. However, α-carboxylate dianions are easily formed forcing a remote stabilizing group to furnish a more enhanced C-H(α) acidity. Although no systematic study has been conducted that evaluates competing remote vs. α-carboxylate deprotonations, we supply a variety of examples that will be instructive in illustrating this competition.

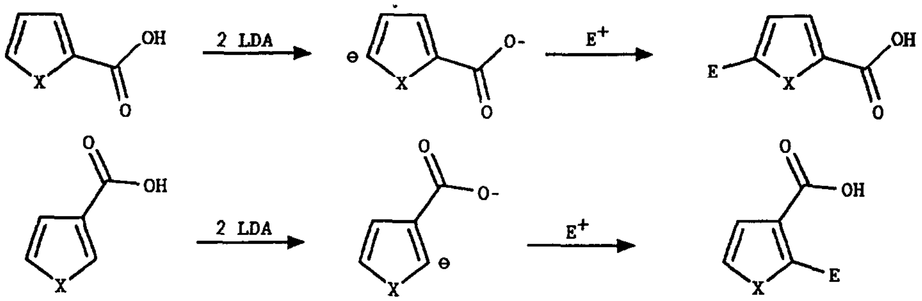
We will partition this next discussion into the choice of second stabilizing moiety. Examples of functional groups reviewed are: a. aromatic and heteroaromatic systems (metallation and lateral deprotonation), b. alkene, c. alkyne, d. carbonyl/carboxyl, e. sulfinyl and sulfonyl, and f. miscellaneous, respectively.

o,m,p-Toluic acid dianions have been generated, alkylated, and in the case of *para*, oxidatively coupled[271,272] As expected, the *ortho* and *para* isomer dianions formed far easier than the *meta* due to decreased resonance stabilization of the latter



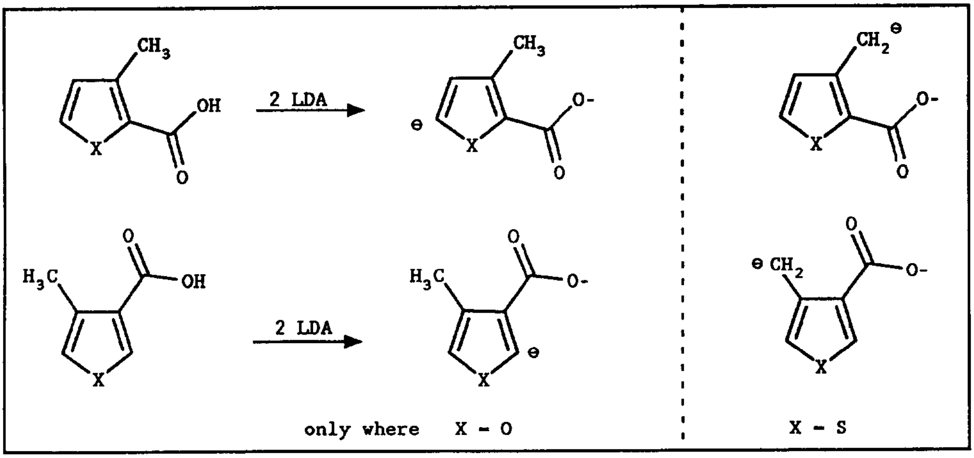
Remote carboxylic acid dianions tethered to five-membered heteroaromatics also have been investigated. Interesting regiochemical preferences for ring deprotonations have been observed In cases where the heteroaromatic nucleus bears an alkyl substituent, metallation or "lateral" (removal of an alkyl group proton) processes may predominate Specific examples of both are presented

Unsubstituted furan and thiophene 2-carboxylic acids are metallated predominantly at the 5-position whereas the corresponding 3-carboxylic acids are metallated at the 2-position[273,274]

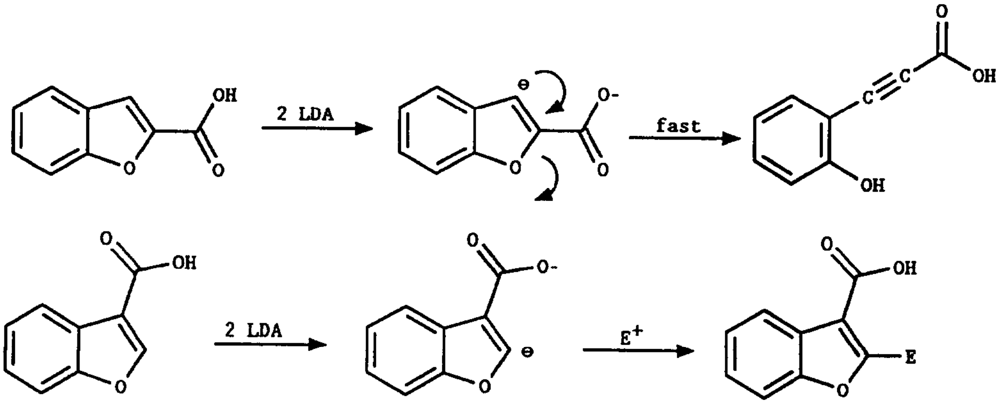


X = O, S   E = RI, RCHO, RC(O)R_1, TMS-Cl, etc

Thiophencarboxylic acid dianions were more reactive than the furoic counterparts [273] Reaction of the furoic acid dianions with a variety of electrophiles[273,274] proceeded smoothly as did the thiophencarboxylic acid dianions.[273,275] These model studies were used in the total synthesis of eudesmanolides[276,277] and wyerone.[278] Furan ring metallation occurs in the presence of an alkyl group[274] whereas alkyl substituted thiophene carboxylic acids undergo alkyl ("lateral")[279] deprotonation.[280] Similar lateral dianion generation methods have been observed for thiazoles/oxazoles[281] and isoxazoles[282] and exploited in the preparation of the guaiane sesquiterpene, gnididione.[283]

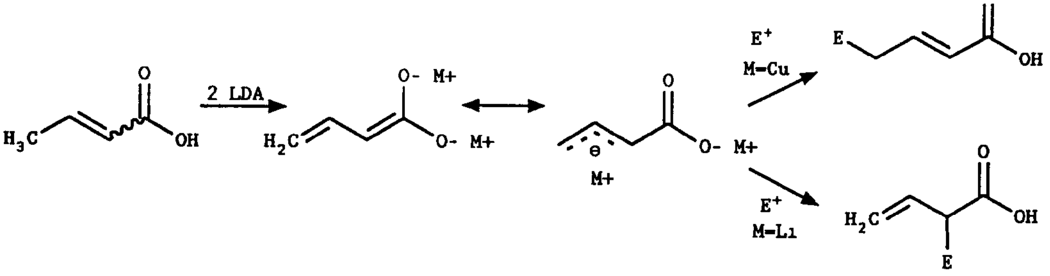


Extension of this approach to benzofurancarboxylic acids leads to sole secondary metallation of the heterocycle [284,285] The benzofuran-2-carboxylic acid dianion rapidly reorganizes to form 2-hydroxyphenylpropynoic acid Lateral deprotonation in the case of 3-methyl-2-benzofurancarboxylic acid and 2-methyl-3-benzofurancarboxylic acid overrides any benzene ring metallation.[284]



Certain compounds bridge the structural and reactivity gap of α-carboxylate and remote carboxylate dianion types. Dienolates derived from bis-deprotonation of crotonic acid derivatives serve as a useful starting example. For the most part, expert evaluations of α versus γ attack in carboxylate[8] and the related ester enolate systems[286] have been covered in pertinent reviews. It is instructive for this review to summarize certain points of interest to aid coverage of these related dianions

A comprehensive investigation of dienolates derived from α,β-unsaturated carboxylic acids showed that α-alkylation predominated when the counterion was lithium, but γ-alkylation occurred when the metals were exchanged for copper[287] Similar regioselectivity reversals were reported with HMPT as an additive[288-290] Rigid attenuation of these conditions were required to synthesize malyngolide[289] Under specific conditions 3-methyl-2-butenoic acid dianion reacts with total diastereoselection at the γ-position leading to the Z-configuration.[291] Carbon-13 nuclear magnetic resonance studies of this dianion suggest a delocalized structure with the metal located above the plane of the conjugated system[292]

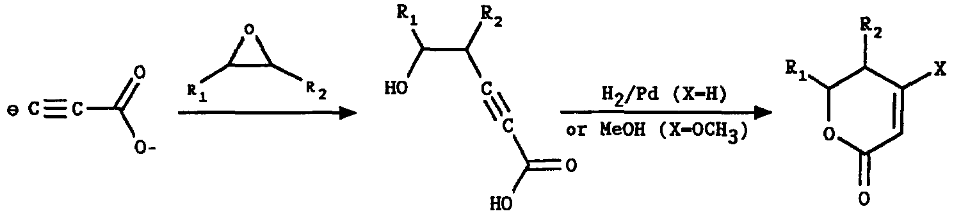


The dianions of tiglic and crotonic acid successfully condense with aldehydes and ketones, but at elevated temperatures reversal of the α-condensation reaction occurs[293]

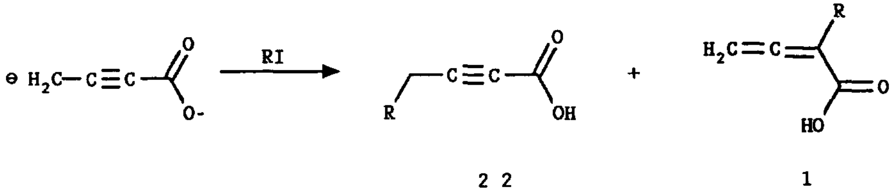
A synthesis of butenolides from 3-phenylthio-2-phenylthio-propenoic acid dianion was accomplished through γ-condensation[294]

In summary, a variety of conditions (sterics, temperature, solvent polarity, counterions, and additives) has been found to affect the regiochemistry of α,β-unsaturated carboxylic acid dianion reactions. Thorough consultation of the specific system under consideration will greatly aid future investigations

Carboxylic acids containing an alkyne moiety that bear the second carbanionic site at either the alkyne terminus (propynoic acid) or the propargylic methylene (2-butynoic acid) form dianions Propynoic acid dianions serve as acyl acetate equivalents in reactions with epoxides to furnish the δ-hydroxyacetylenic acids[295,296] Subsequent conjugate addition of methanol or reductive cyclization affords 5,6-dihydro-2H-pyran-2-ones that were further used successfully in the synthesis of pestalotin[295]

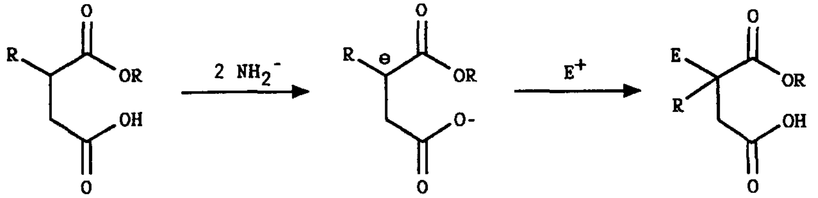


The propargylic carboxylate dianion of 2-butynoic acid reacts with electrophiles to provide a 2.2:1 mixture of alkyne-allene alkylation products[297,298] in a result not unlike that of the α,β-alkenoic acid dianions. Similar ratios were reported for condensations of this dianion with aldehydes and ketones.[299,300]

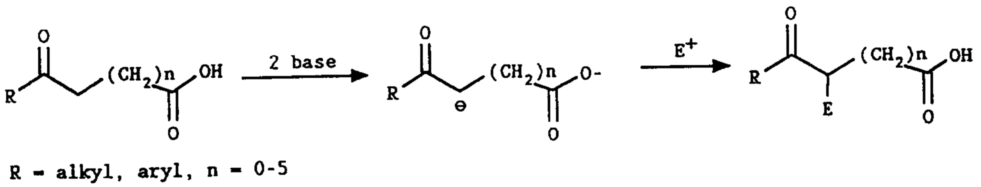


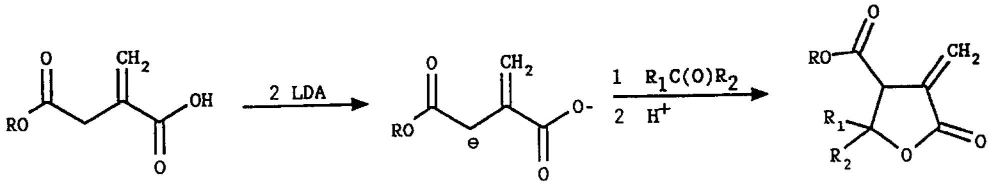
A second deprotonation site may be induced alpha to a carbonyl/carboxy moiety in the presence of the carboxylate. Esters, ketones, and amides stabilize remote carboxylate dianion formation. A few representative reports are included herein.

Monoesters of succinic acid are converted by lithium amide into β-carboxylate dianions that react readily with a variety of alkyl halides and carbonyl compounds in modest to good yield.[301]

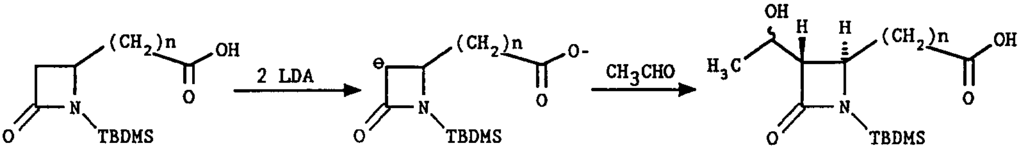


Extension of the intervening methylene chain to five carbons does not alter the success. An ε-carboxylate dianion was produced and successfully condensed with a cyclobutanone.[302] A recent report explored remote carboxylate dianions stabilized by ketones with insulating methylenes.[303] Itaconic acid monoesters are deprotonated alpha to the ester moiety.[304]

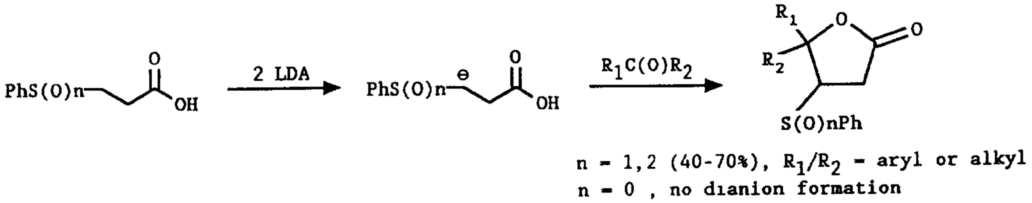




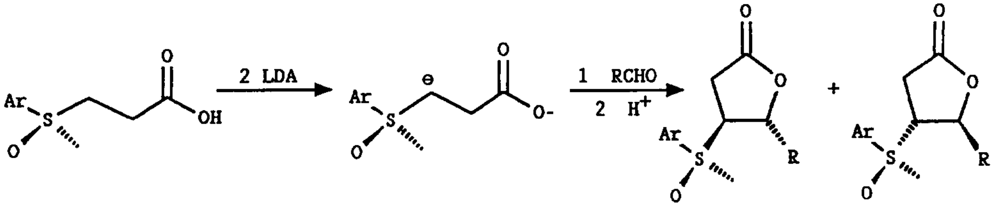
β-Lactam chemistry has also been pervaded by remote carboxylate dianion methodology Clever usage of the second amide deprotonation site initiated a carbon-carbon bond condensation required for the synthesis of thienamycin Notably, the amide stabilized dianions of both β-[305] and γ-dianions[306] were achieved with very little destruction of the β-lactam ring



Carboxylic acids with a remotely positioned sulfinyl or sulfonyl group are deprotonated adjacent to the oxidized sulfur rather than alpha to the carboxylate In a comparison of phenyl sulfenyl, sulfinyl, and sulfonyl propanoic acid dianions, Iwai *et al.* found that the sulfinyl and sulfonyl group assisted α-deprotonation whereas no evidence of α-phenylsulfenyl deprotonation occurred (elimination predominated)[307] The dianions derived from 3-phenylsulfinyl and sulfonyl propanoic acids were used in a butenolide synthesis



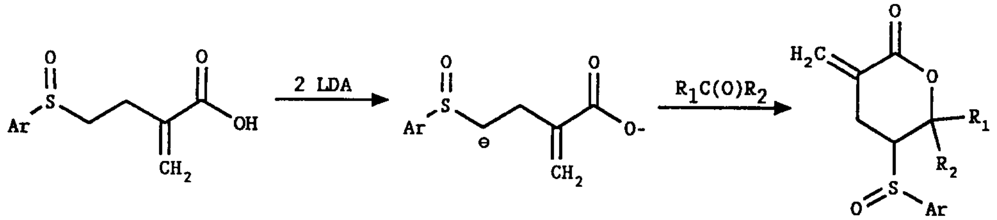
In a fine extension of this work, (+)-(R)-3-[4-methyphenyl)sulfinyl]propanoic acid was converted to its dianion and condensed with aldehydes to furnish chiral butanolides.[308] Pyrolytic elimination removed the chiral appendage to furnish the requisite chiral butenolides.



3 2 (65-90%)

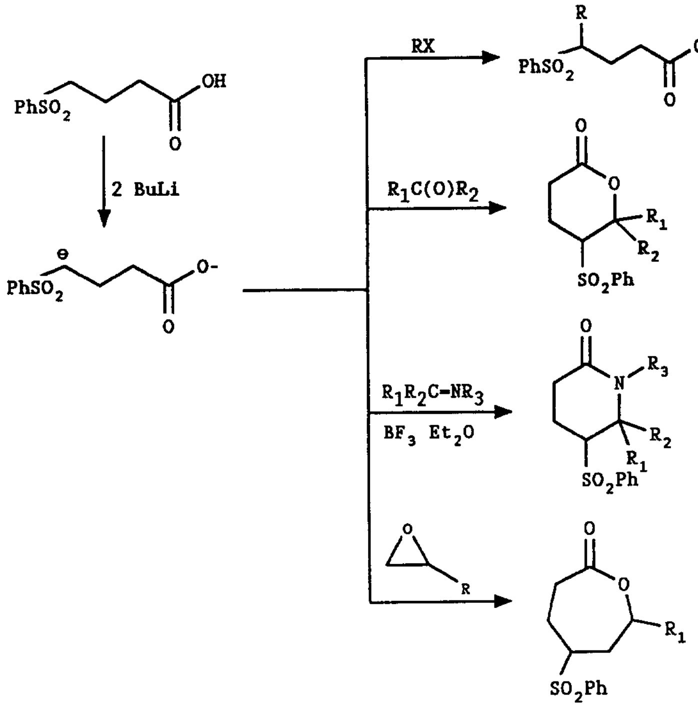
R = tBu, Ph

A subsequent study from the same laboratory formed the dianion of α-methylene-γ-(phenylsulfinyl)butyric acid and reacted it with aldehydes and ketones to afford α-methylene-δ-lactones [309]



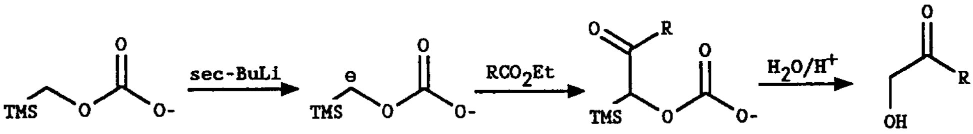
41-66%

Work in the authors laboratory has focused upon the structurally similar 4-(phenylsulfonyl)butanoic acid dianion Bis-deprotonation affords the remote dianion A study of the effect of bases revealed that 2 equivalents of n-BuLi were necessary for complete conversion to the dianion [310] Reaction of this dianion with alkyl halides,[311] aldehydes and ketones (which yield lactones after cyclization),[310,312] activated imines (to afford piperidinones),[313] and epoxides,[314] have been effected The phenylsulfonyl lactones react with 6% Na/Hg amalgam to provide γ,δ-unsaturated esters,[310] the equivalent of four-carbon homologation used successfully in the synthesis of a simple pheromone [315] The substituted piperidinones do not readily undergo reductive ring opening,[313] and have been applied to the synthesis of indolizidines,[316] and aza-spirocycles related to perhydrohistrionicotoxin [317]



In perhaps the largest distance between anionic sites, Julia and Badet reacted the dianion of 11-(phenylsulfonyl)undecanoic acid with alkyl halides in routes to exaltolide[318]

Last, although not strictly classified as a carboxylic acid dianion, is α-lithio trimethylsilyl lithium carbonate, which substitutes as a methanol dianion equivalent[319] Esters, amides, nitriles, and acyl halides all serve as electrophiles for this interesting reagent

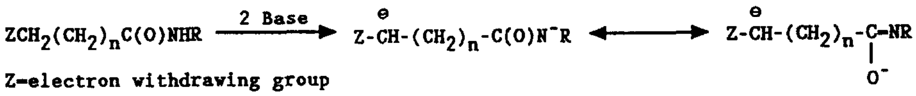


IV. N,C-bis-deprotonations

An excellent review includes dianions in this classification covering the literature through 1976[5] We shall include only reports that have appeared since 1976, or that were omitted from that review These dianions are generated by proton abstraction at nitrogen first followed by carbanion formation As with O,C-dianions, the ease of deprotonation or metallation varies greatly with the carbon and nitrogen substituents It is most convenient to group dianions of this type into three categories a amide based dianions, b amine based dianions and, c carbamate based dianions The amide subclass also includes thioamide and sulfonamide dianions Again, as this represents somewhat different organization than a prior review[5], we regret any resulting confusion

IV.(a) Amide-containing dianions

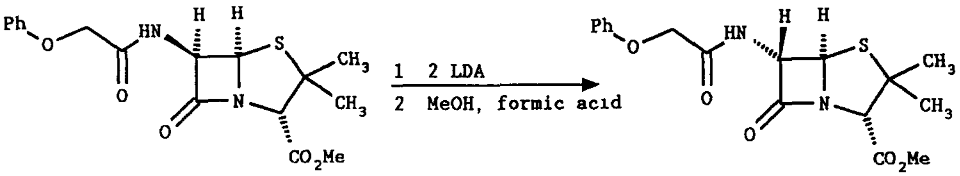
Amide dianions are of the general structure shown below.



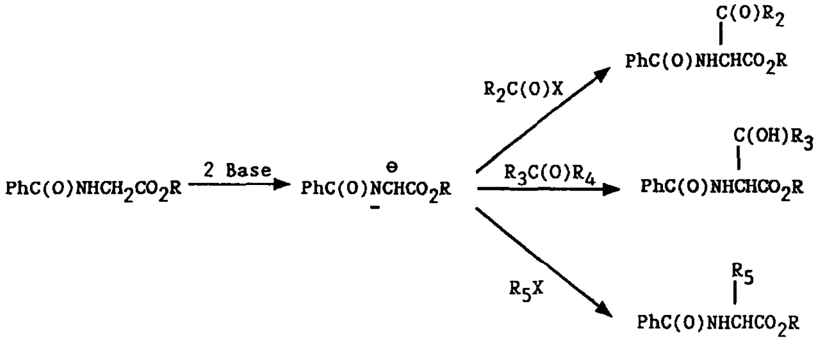
$$ZCH_2(CH_2)_nC(O)NHR \xrightarrow{2\ Base} Z\text{-}\overset{\ominus}{C}H\text{-}(CH_2)_n\text{-}C(O)N^{-}R \longleftrightarrow Z\text{-}\overset{\ominus}{C}H\text{-}(CH_2)_n\text{-}\underset{O^-}{C}{=}NR$$

Z=electron withdrawing group

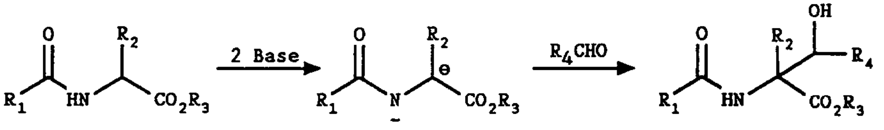
The synthetic use of vicinal dianions of amides has been the subject of many investigations In 1973, Koppel reported the direct C-6 epimerization of a penicillin via a dianion.[320]



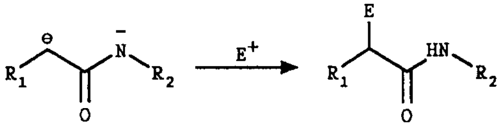
Regioselective alkylation of the dianion of ethyl hippurate was used to synthesize some α-amino acids[321] Acylation of this dianion with acid anhydrides forms α-aminoketones[322] The attempted acylation of the dianion with acetyl chloride failed, but was later reported to proceed under improved reaction conditions with the dianion of methyl hippurate[323] This latter report also asserts that other acid chlorides react in moderate yields when lithium hexamethyldisilazide is used as the base. Yet, condensation of the methyl hippurate dianion with aldehydes and ketones (to produce α-amino-β-hydroxy ester derivatives) proceeds in good yield and does not appear to be sensitive to the base used



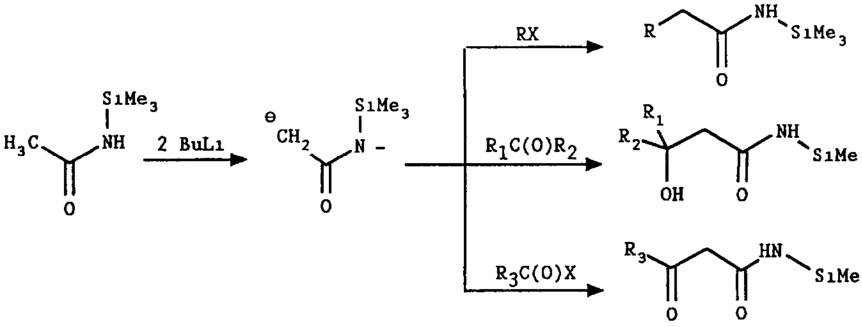
Finally, N-acyl-α-amino ester dianions have been used in the synthesis of substituted serine derivatives[324]



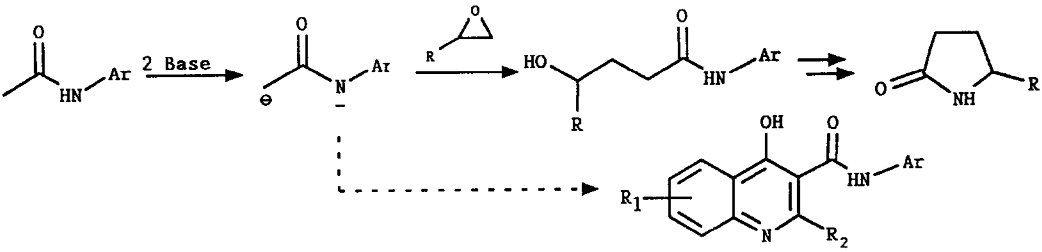
Another amide dianion is the α,α'-type similar to that found in α-carboxylate dianion systems (Sect **III.(b).1**). The regioselective alkylation of a β-lactam dianion led to β-lactam prostaglandins[325] The γ-alkylation of protected piperazinones employing a variety of electrophiles has been reported[326] as has the regioselective C-3 alkylation and 3,3-dialkylation of the dianion of oxindole This latter transformation shows the remarkable selectivity of dianions of this type with almost no N- or O-alkylation[327]



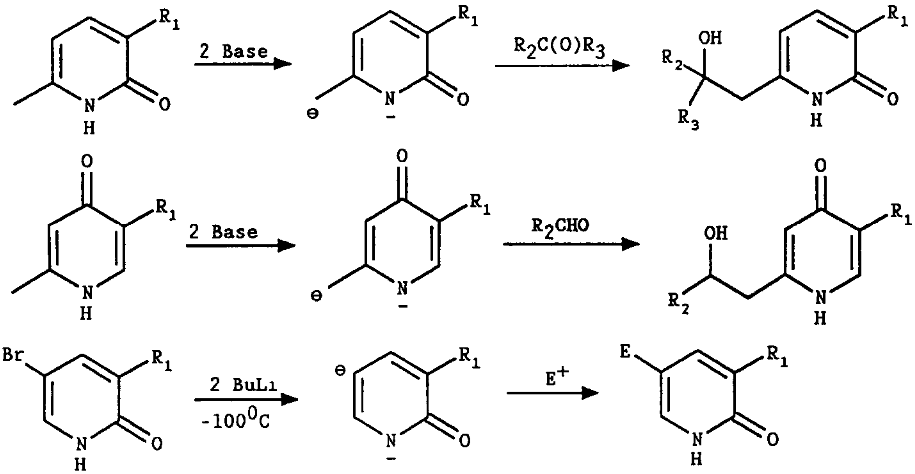
The dianion of N-(trimethylsilyl)-acetamide was reacted with a variety of electrophiles to give C-alkylation and acylation products in moderate yields[328] The use of the trimethylsilyl group lends solubility and stability to the acetamide in these transformations



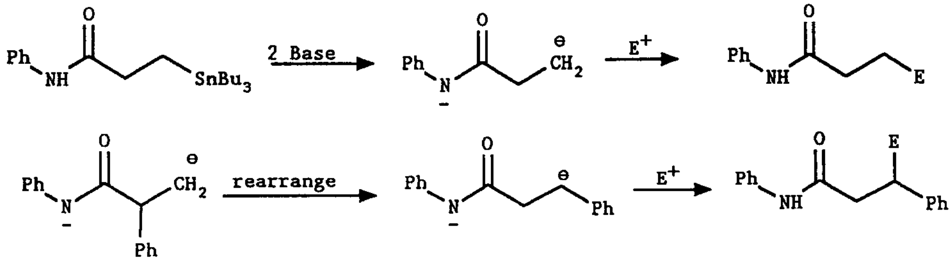
The α,α'-dianion of acetanilide was utilized by Takahata and co-workers in the synthesis of 5-alkyl-γ-lactams[329] The N-pyridyl- and N-thiazolyl-derivatives of this dianion have been employed in the synthesis of the antiarthritic and analgesic 4-hydroxy-3-quinolinecarboxamides[330]



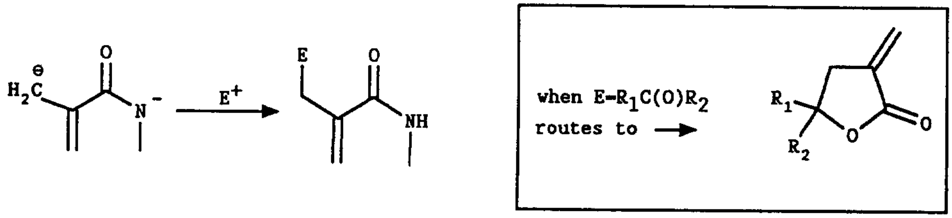
Domagala and co-workers have reported the generation and acylation of pyridone dianions (cyclic amides) as a route to pyridones with functionalized side chains[331] The synthetic uses of pyridone dianions to install 5-positional substituents have been investigated[332] The formation of an anion at the 5-position was facilitated through a halogen-lithium exchange at -100°C and provided selective substitution upon reaction with various electrophiles



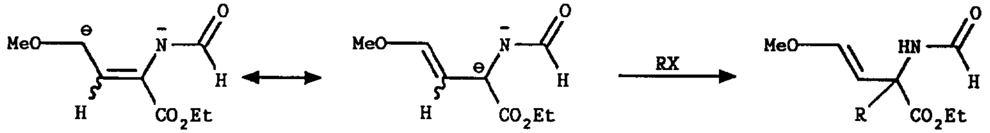
Tin-lithium exchange to form amide dianions has been used in an analogous manner to that previously discussed (Sect. **II.(d)**) Dianion reactions of N-phenyl- and N-methyl-3-(tri-n-butylstannyl)propionamide with electrophiles provide substituted amides[333] However, a second report[334] indicated that a phenyl substituent at the 2-position of the propionamide induced a rearrangement to the more stable 3-phenyl substituted dianion This rearrangement was slow at lower temperatures (below -40°C) presumably proceeding via a cyclopropane intermediate



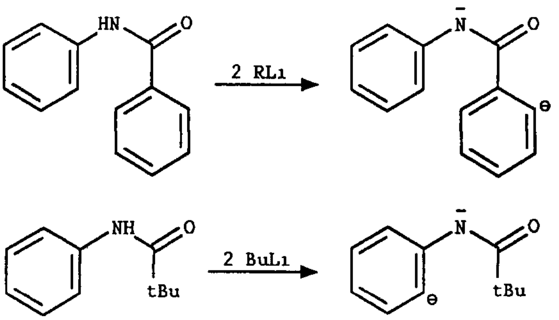
Reactions of the dianions of α,β-unsaturated amides with various electrophiles have been incorporated into many synthetic strategies. Fitt and Gschwend devised a synthetic route to α-methylene lactones and α-substituted acrylamides from the dianion of N-*tert*-butylmethacrylamide[335] Also, Tanaka and co-workers used the dianion of N-(*o*-methoxyphenyl)-2-methylpropenamide in the preparation of substituted α-methylene lactones.[336]



Isomerization and alkylation of (E)- and (Z)-2-formylamino-4-methoxy-2-butenoate were accomplished via the vicinal dianions.[337]

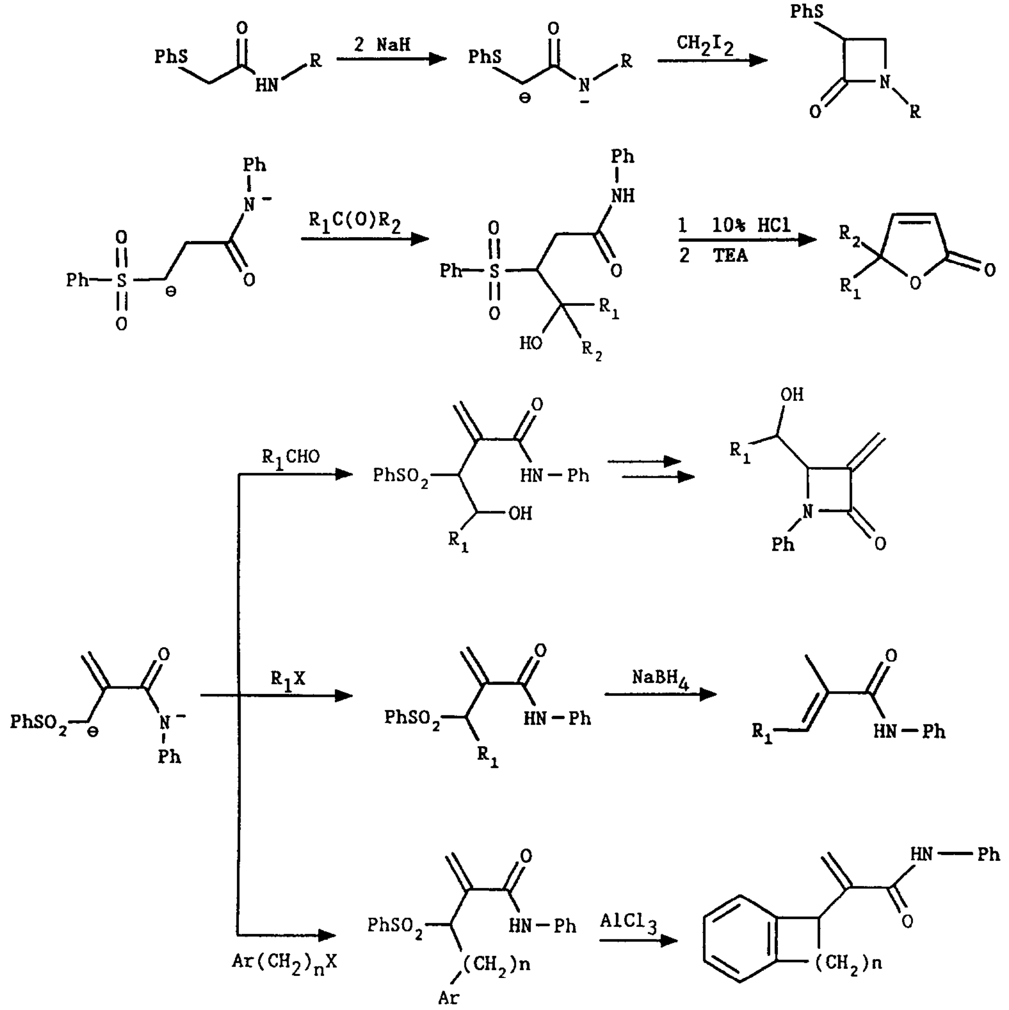


The added stability of aromatic substitution has played a role in the generation of several N,C-dianions The regioselective C-alkylation and C-acylation of the dianion of phenyl-(2-pivaloylamidophenyl)-methane has been employed in synthetic approaches to alkaloids[338] *Ortho*-lithiation of N-phenyl amides led to piperidinols from N-pivaloyl-4-chloroaniline[339] and the synthesis of ebselen from benzanilide[340] The main difference in the two *ortho*-lithiation approaches lies in the formation of a carbon anionic center *ortho* to the nitrogen in the former case and *ortho* to the carbonyl carbon in the latter case The preferential formation of the anion on the carbonyl-substituted ring as opposed to the nitrogen-substituted ring is presumably due to the electron-withdrawing effect of the carbonyl and chelation of the enolate

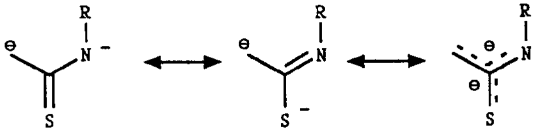


As with previously discussed dianions (Sect. II and III), sulfur and sulfone stabilization of the carbanion of amide dianions has been frequently integrated into synthetic strategies The addition of an α-phenylthioacetamide (1,3) dianion to diiodomethane provided substituted β-lactams[341] Remote sulfone stabilization of amide-based dianions yielded the reaction of N-monosubstituted-3-

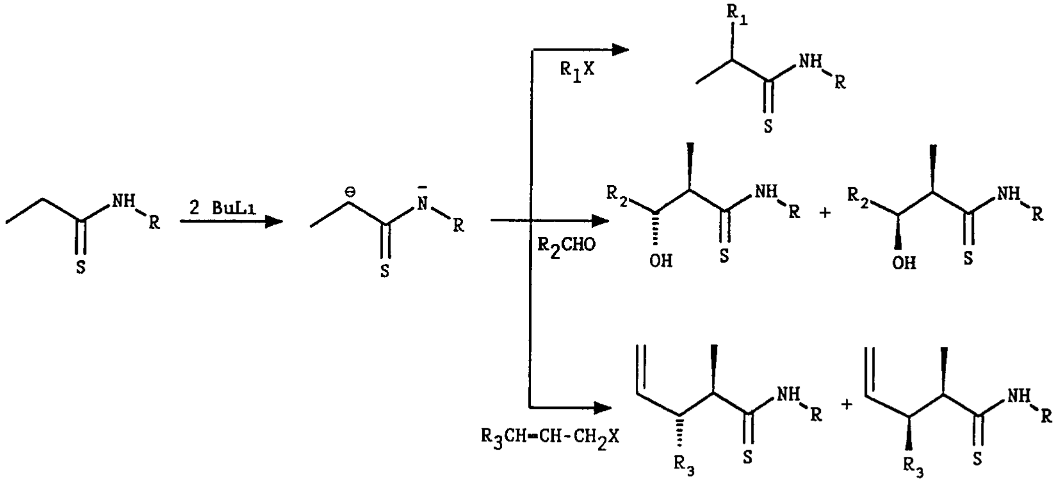
(phenylsulfonyl)-propanamides with carbonyl compounds to give γ-hydroxyamides (which were further elaborated to furanones).[342] The dianion derived from N-phenyl-2-(phenylsulfonylmethyl)-propenamide was used in the preparation of (*E*)-α,β-unsaturated amides,[343] 3,4-epoxy-2-methylenealkanoic acid derivatives,[344] α-methylene-β-lactams,[345] and α-methylenecarboxamides.[346] This dianion is very similar to the amide dianion previously noted[341] although the presence of the phenylsulfonyl moiety lends added stability

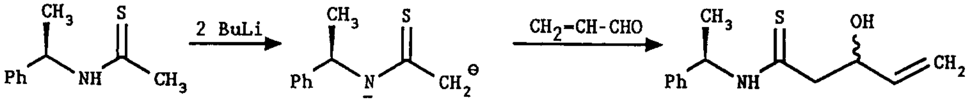


Dianions of thioamides are depicted as the resonance structures shown below α,α'-Dianions of

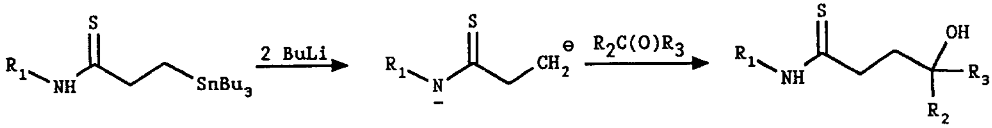


this type have been the subject of numerous recent investigations *Sec*-thioamide dianions react with alkyl halides,[347] aldehydes,[348] allyl halides,[349] and condense with aldehydes in high diastereoselectivity, giving *threo* products when the base was *i*-PrMgBr. The allylation reaction also proceeds with high diastereoselectivity, confirming the earlier assertion that these dianions exist primarily in the (*Z*)-enolic form An α-phenethylamine-derived thioamide dianion was reacted with acrolein to provide unsaturated β-hydroxythioamides in a synthesis of N-protected statine [350]

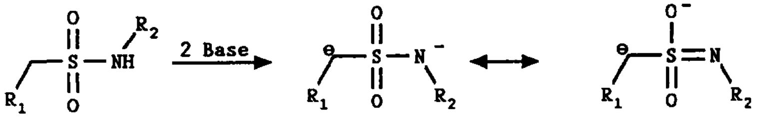




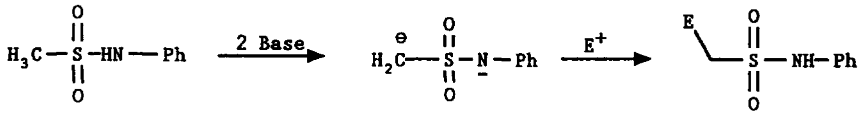
3-(Tri-*n*-butylstannyl)-thiopropionamide was transmetallated[333,334] and the dianion reacted with aldehydes and ketones to provide γ-hydroxythioamides [351] Reactions with α,β-unsaturated carbonyls gave lower yields, presumably due to some 1,4-addition The thioamide dianion provided higher yields of addition product than the corresponding amide dianion



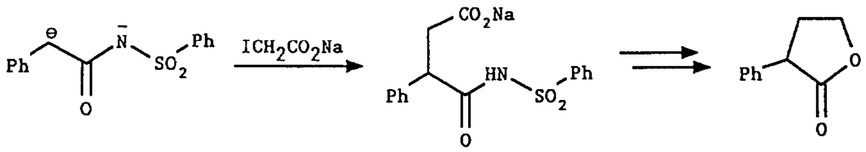
Sulfonamide dianions constitute the final sub-category of amide dianions and possess the basic structure indicated below This group is further separated into dianions of alkanesulfonamides and tosylhydrazones

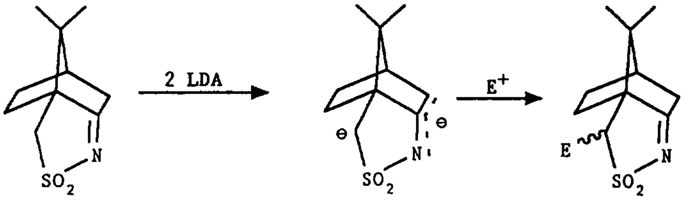


The dianion of N-protected methanesulfonamide reacts chemoselectively with various electrophiles[352] A subsequent investigation prepared β-ketosulfonamides that were elaborated into heterocycles[353]

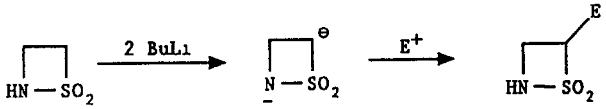


The unsymmetrical coupling of acylsulfonamide dianions with iodocarboxylates provides a unique synthesis of lactones[354] These dianions were used advantageously for the regioselective alkylation of (camphorylsulfonyl)imine dianion at the α-carbon[355]



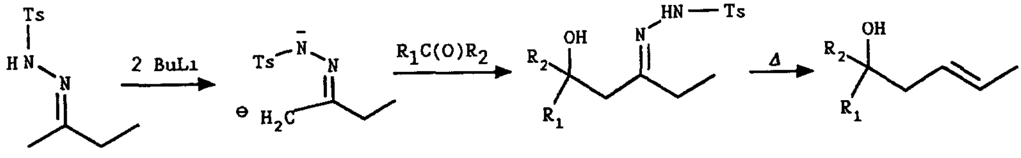


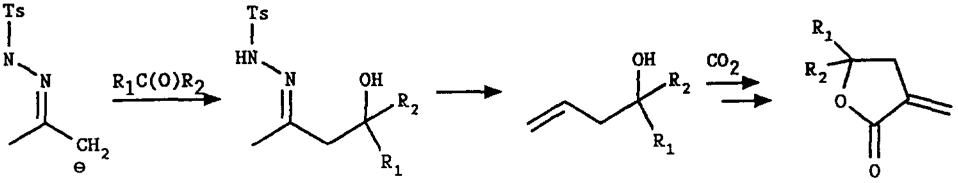
Generation of β-sultam dianions and reaction with a variety of electrophiles furnished an efficient method for side chain incorporation in the synthesis of β-sultam analogues of β-lactam antibiotics[356]



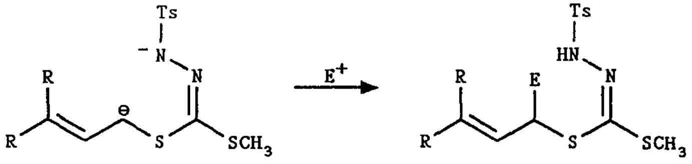
Investigations of the synthetic utility of tosylhydrazone dianions have continued. The Shapiro reaction,[357] the thermal decomposition of tosylhydrazone dianions to form olefins, has been frequently employed. The dianions are reacted with electrophiles followed by treatment with another equivalent of base for dianion regeneration and subjected to Shapiro thermal decomposition conditions For example, the reaction of tosylhydrazone dianions with aldehydes and ketones provided β-(hydroxy)-tosylhydrazones that were converted into homoallylic alcohols[358] Similarly, Adlington and Barrett reported the reaction of tosylhydrazone dianions with aldehydes and ketones in a synthesis of α-

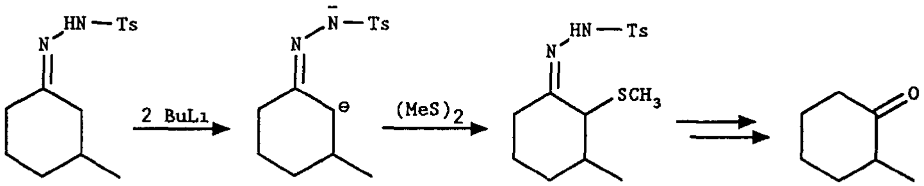
methylene-γ-lactones,[359] and ketene equivalents in a synthesis of dimethylene tetrahydropyranone and furanone derivatives[360]



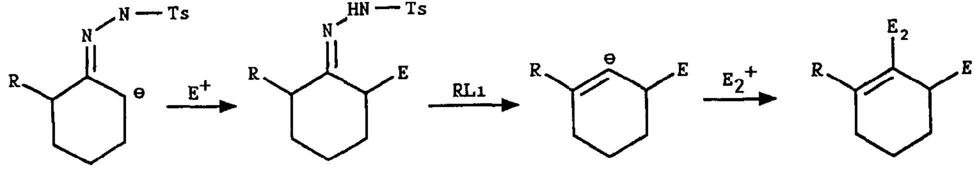


Allylic dithiocarbonate tosylhydrazone dianions were examined for the regioselectivity of alkylation[361] The same group also reported the use of the tosylhydrazone dianion to effect a 1,2-carbonyl shift[362]

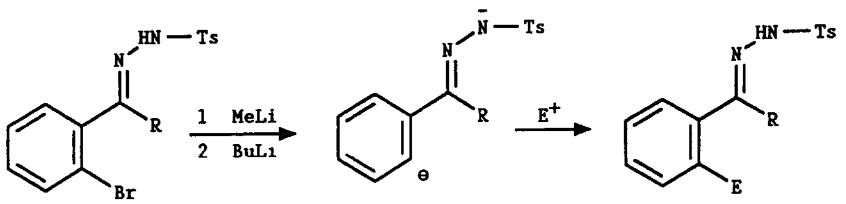




Under the Shapiro conditions, the alkylation of trisyl- and tosylhydrazone dianions furnished vinyl carbanions that were trapped by a variety of reagents[363]

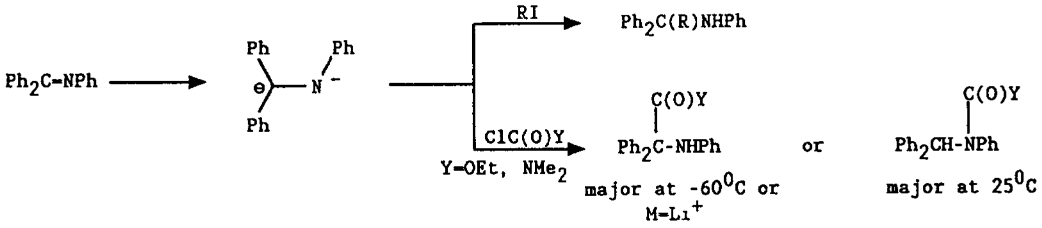


Finally, the *ortho*-lithiated dianion of benzophenone tosylhydrazone was generated via metal-halogen exchange and reacted with several electrophiles[364] Subsequent manipulations provided interesting heterocyclic compounds

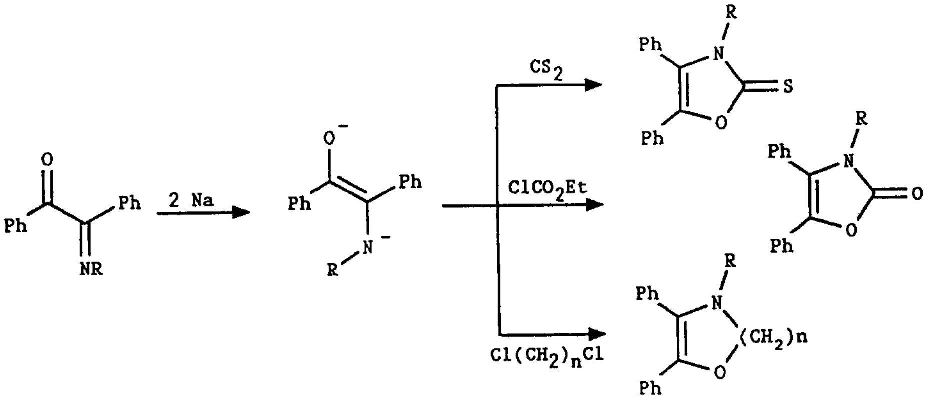


IV.(b) Amine-containing dianions

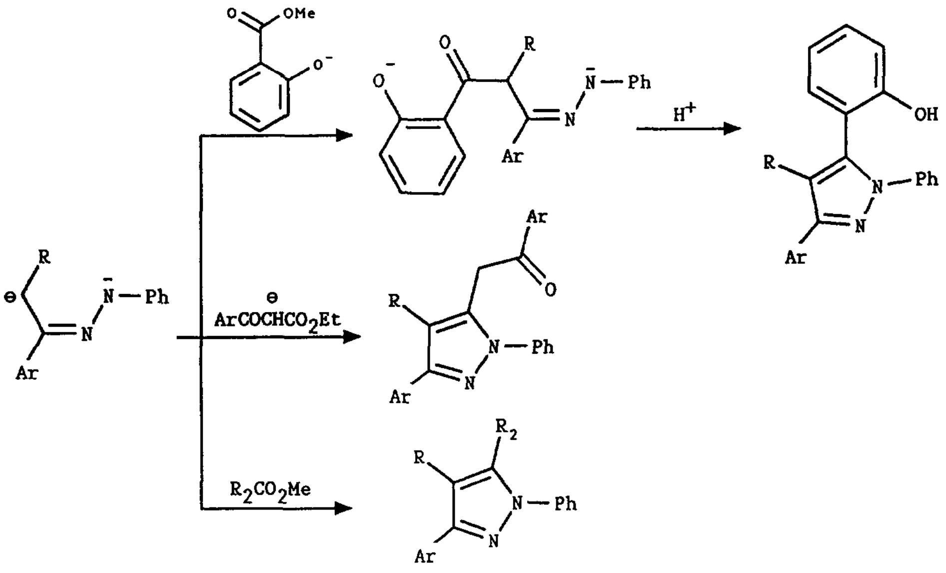
Vicinal dianions of benzophenone anil and related compounds have been the subject of many reports. While initial studies proved that alkylation with alkyl halides occurred primarily at carbon,[365] later reports found that reaction with acid chlorides was accompanied by rearrangement from C-acyl to N-acyl products[366-368] This rearrangement was found to occur with a variety of acylating agents, yet metallation with lithium than sodium resulted in clean C-acylation[367] Finally, alkylation studies with hindered alkylating agents gave evidence that the mechanism for this transformation may proceed via a single electron transfer step[369]



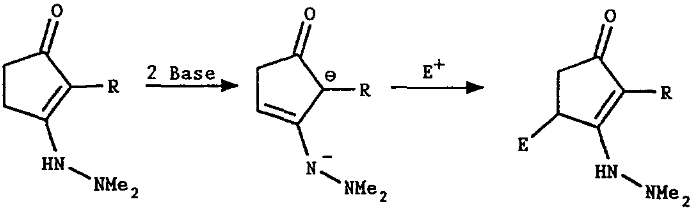
One additional dimetallated substrate of the amine vicinal dianion type was reported by Mehrotra[370] Although this interesting disodio compound does not fit the classical carbon-nitrogen dianion group, it is included here for completeness This dianion was reacted with carbon disulfide, ethyl chloroformate, and dihaloalkanes to form oxazolines, oxazocines, and oxazonines



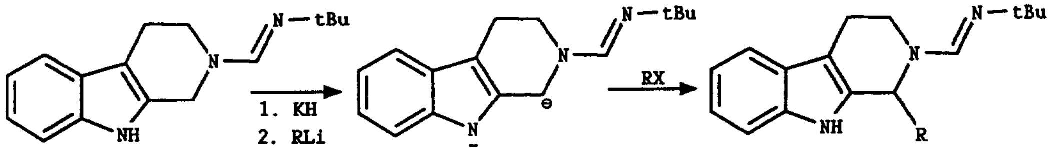
The dianions of phenylhydrazones continue to be attractive as heterocyclic building blocks Beam *et al.* added phenylhydrazone dianions to: a. lithiated methyl salicylate to provide hydroxyphenylpyrazoles,[227] b. lithiated ethyl benzoyl acetate to provide 5-phenacylpyrazoles,[228] and c aromatic and heteroaromatic esters to provide N-phenylpyrazoles [371]



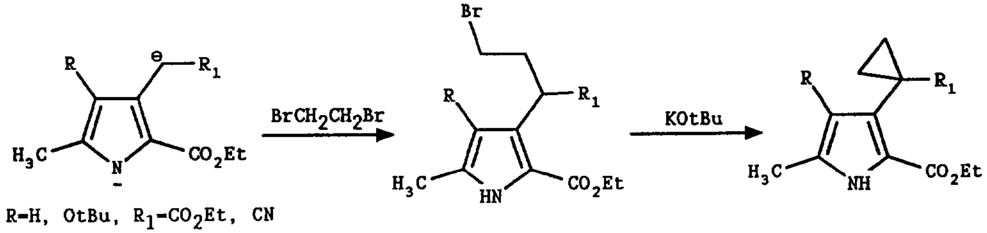
The synthesis of C-4 substituted, cyclic 1,3-diketones via the dianion of the monodimethylhydrazone takes advantage of the ability to form regioselectively the monohydrazone derivative, which in turn is alkylated [372]



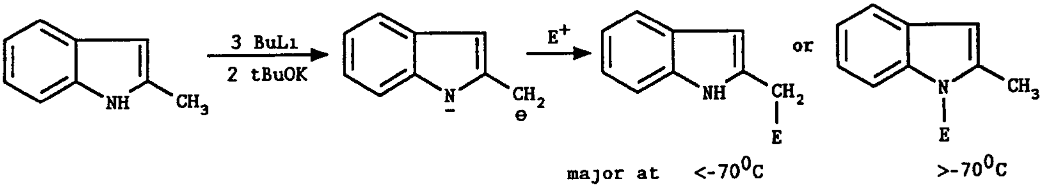
Another common group of amine dianions exploits the relative acidity of the pyrrole/indole nitrogen proton These dianions protect the nitrogen from alkylation while reacting at a remote carbon. Meyers and Loewe examined the C-1 alkylation of β-carboline formamidine,[373] finding that C-1 is inert to alkylation when the pyrrole nitrogen is lithiated, but is readily alkylated when the sodio- or potassio- salt is used This information led to the successful synthesis of tetracyclic systems when this dianion was reacted with bifunctional electrophiles



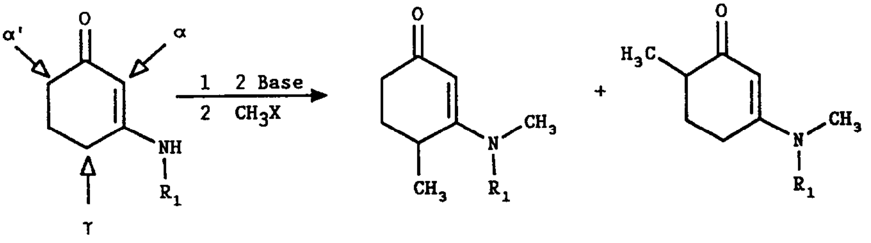
Pyrrole dianions have been utilized to avoid lengthy protection and deprotection of the pyrrole nitrogen during the synthesis of the B/C ring system of CC-1065 [374] This work yielded 3-cyclopropane-substituted pyrrole acetonitriles and pyrrole acetic acid esters

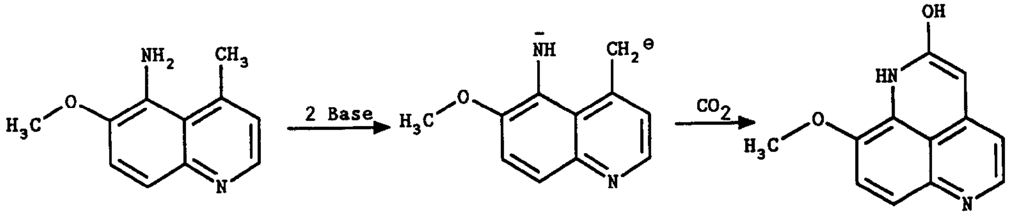


Inagaki *et al.* alkylated the dianion of 2-methylindole [375] The method requires a large excess of base (3 eq BuLi and 2 eq t-BuOK) but provides exclusive C-alkylation at low temperatures (below -70°C) At higher temperatures, both C- and N-alkylation were observed



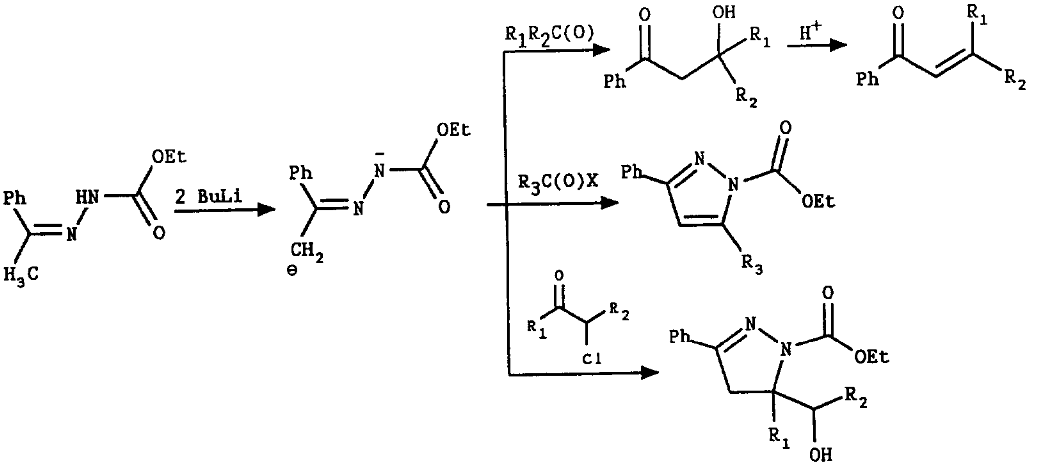
Various miscellaneous amine dianions also have appeared The dianion of (-)-3-oxovincadifformine was used to install a double bond in the synthesis of tabersonine [376] Regioselective dianion formation in β-(alkylamino)-α,β-unsaturated ketones has been investigated [377] The latter report indicates that the regiochemistry of dianion formation and alkylation depends upon the temperature, base, and reaction time Cook and Weber cleverly carbonylated the dianion of an aminoquinoline derivative to form the 1,6-diazaphenalene ring system [378]



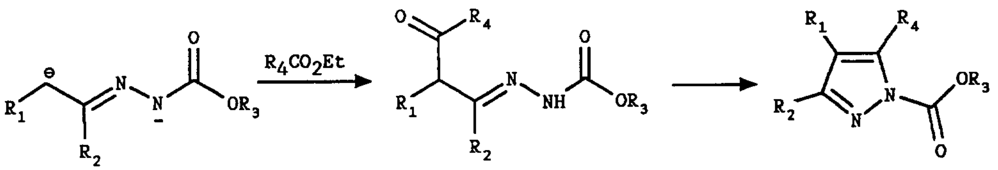


IV.(c) Carbamate-containing dianions

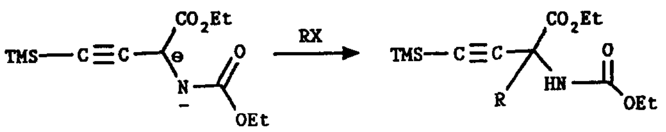
Carbamate dianions continue to be used, most commonly cited as carboalkoxy hydrazones Matsumura and co-workers added several carbonyl electrophiles to the 1,4-dianion of acetophenone N ethoxycarbonylhydrazone to form *β*-hydroxyketones, *α*,*β*-unsaturated ketones, and substituted pyrazoles.[379] The apparent advantage of using the carboalkoxy hydrazone over the hydrazone lies mainly in the ease of hydrolysis of the derivative into the corresponding carbonyl functionality Also reported was the reaction of the same dianion with *α*-chloroketones to yield pyrazoline derivatives[380]



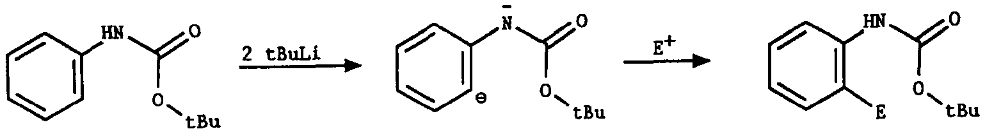
Acylation of carboalkoxy hydrazone dianions has been employed in the synthesis of substituted N-carboalkoxy pyrazoles[371] and 4-quinolinols[230]



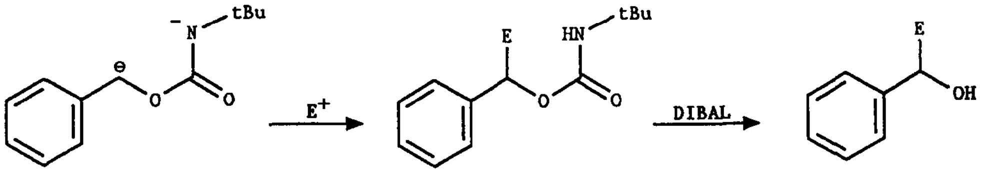
The vicinal dianion of trimethylsilylacetylene-N-carboethoxy glycinate was reacted with alkyl halides and methacrylate to prepare acetylenic amino acids.[381] The directing effect of the ester on alkylation site was also examined[382]



The *tert*-butyl carbamate of aniline was dilithiated (*ortho*-lithiation of the ring) and reacted with a variety of electrophiles to yield an array of *ortho*-substituted anilines.[383]



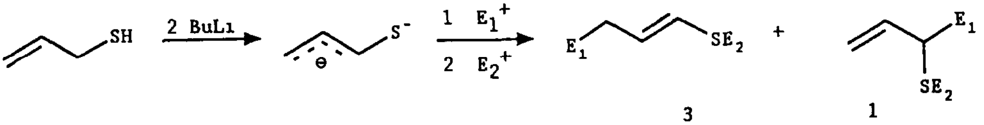
The use of N-*tert*-butyl benzylic carbamate dianions for the synthesis of secondary and tertiary benzylic alcohols has been explored[384]



V. S,C-bis-deprotonations

Since an excellent review is already available on this topic,[7] we shall summarize the recent and varied types of sulfur-carbon bis-deprotonations that lead to carbon-carbon bond formation

Suitably substituted thiols are converted to their respective dianions and react with electrophiles Allyl mercaptan (thioacrolein, *vide infra*) and isobutylene mercaptan, for example, are readily converted to dianions and successfully coupled with electrophiles Whereas the allyl mercaptan dianion gave greater than 3 1 mixtures of γ to α-attack,[385] the isobutylene congener reacts primarily at the α-carbon.[386]



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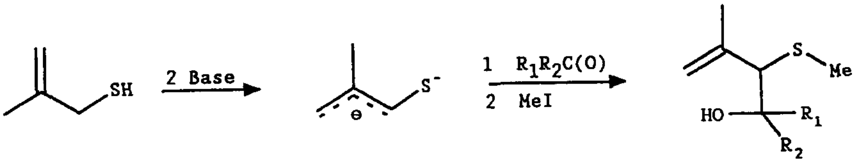
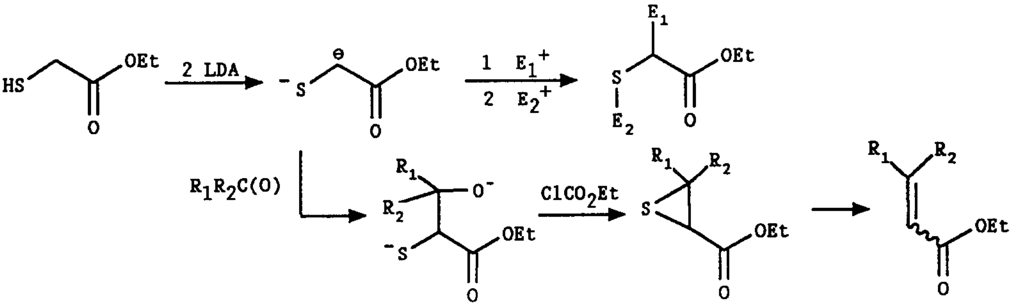
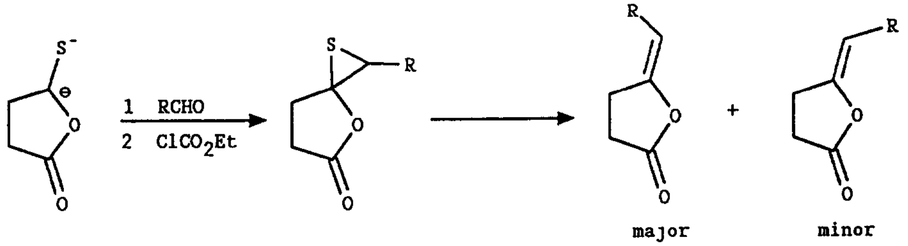


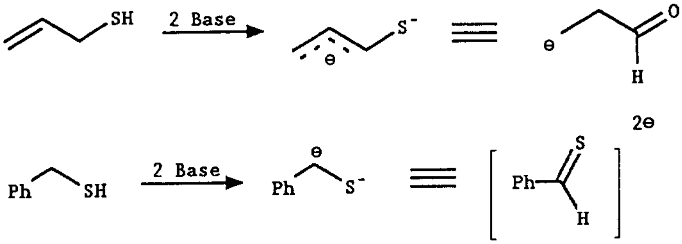
2-Mercaptoacetate was bis-deprotonated (2.2 equivalents of LDA) to afford a vicinal, heteroatom dianion that reacted with alkyl halides and carbonyls in good yield[387] Thiirane formation



and sulfur extrusion offer a new route to α,β-unsaturated esters[388,389] The cyclic homologue, α-mercapto-γ-butyrolactone, also reacts with alkyl halides[390] and carbonyls[391] As with the acyclic derivative, treatment of the intermediate mercapto-alkoxide carbonyl condensation product with ethyl chloroformate affords α-alkylidene butyrolactones[392] Aldehydes react to form the E-alkene predominantly



Seebach and co-workers described the formation of dianions of thiocarbonyl compounds Thiocarbonyls are generally only stable as neutral compounds at reduced temperatures For example, the dianions of allyl mercaptan and benzyl mercaptan are reliably generated These dianions alkylate as synthetic equivalents to the homoenolate aldehyde[393] and thiobenzaldehyde,[394] respectively



The thiobenzaldehyde nucleophile reacts with epoxides, carbonyls, and alkyl halides at the benzylic position to give good yields of adducts[385]

VI. Conclusions

The increase in the number of publications dedicated to dianions and their application to synthesis over the past decade bears testimony to the fact that these species are no longer relegated to the specialist Even with this dramatic surge in utility much room for further investigation still exists For example, the recent entry of dianions into stereospecific carbon-carbon bond forming reactions seems particularly fertile

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