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Reactions of conjugated haloenoates with nucleophilic reagents

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Contents

1. Introduction

Conjugated haloenoates contain trifunctionality—vinyl or alkyl halide moieties, activated α,β-double bonds and ester carbonyl groups—which potentially offer three sites for nucleophilic attack. Although 1,2-attack on the ester carbonyl carbon atom can occur with highly basic reagents, these compounds normally undergo conjugate (1,4-) addition as an initial step. However, since these reactions are frequently reversible, products of direct S_N2 or S_N2' reactions can be observed when γ- or ω-halogen atoms or α-haloalkyl groups are present. Because anionic 1,4-adducts are commonly generated in the initial conjugate addition step, a variety of inter- and intramolecular reactions can ensue. Appropriate functionality, which is present in either partner of the reaction, can participate in these intramolecular reactions. Such sequential reactions (sometimes called tandem, cascade or domino reactions) often involve the formation of new carbon–carbon bonds and thus may offer access to a variety of complex molecules in a one-pot process. Because of their intrinsic elegance and economy from the point of view of time, reagents and solvents,

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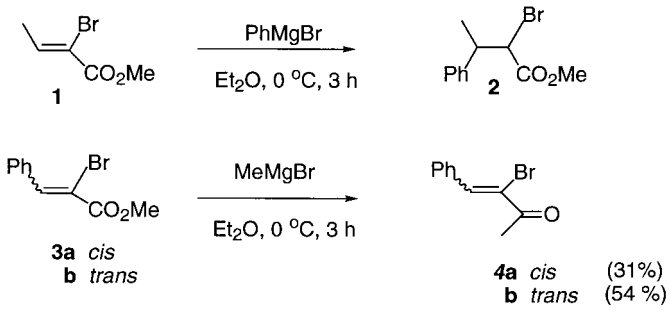


Scheme 1.

sequential reactions have been given an enormous amount of attention by synthetic organic chemists in recent years.[1–6]

This report will cover reactions of various types of conjugated haloenoates with anionic and neutral reagents ranging from highly nucleophilic organometallic reagents to weakly nucleophilic heteroatom electron donors. No attempt will be made to include reactions in which the starting haloenoate is initially converted into a conjugated metal halodienolate by deprotonation with bases such as lithium diisopropylamide (LDA),[7–10] or into a conjugated halometal dienolate by reductions with metals such as zinc (Reformatsky reactions),[11–13] other metals[14,15] or low valent metal salts.[16–19] Likewise, reactions in which haloenoates are involved as partners in various palladium-catalyzed coupling reactions (e.g. Heck couplings of alkenyl halides with alkenes,[20] Stille couplings of alkenyl and allylic halides with alkenyl and aryl tin compounds,[21–23] and Sonogashira couplings of alkenyl halides with alkynes[24]) will not be considered.

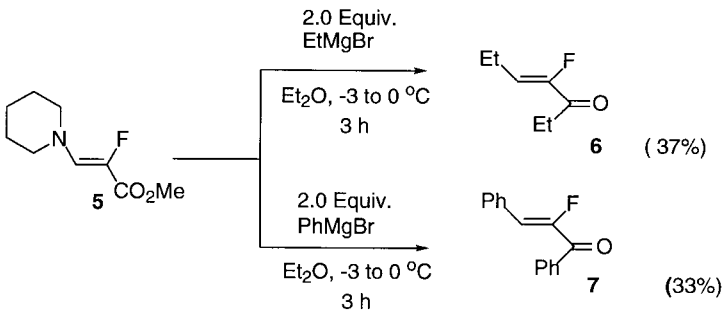
2. Reactions of conjugated α-haloenoates

2.1. With carbon nucleophiles

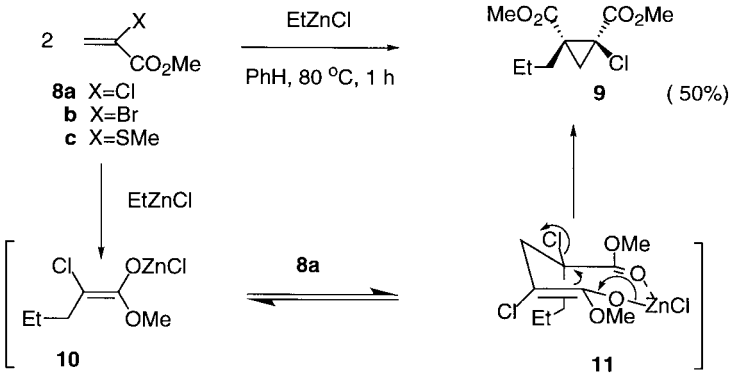
2.1.1. Organometallic reagents. The literature contains only a few examples of reactions of conjugated α-haloenoates with organometallic reagents. In general, β-unsubstituted and β-alkyl substituted systems participate predominately in 1,4-additions, while β-aryl substituted compounds usually undergo 1,2-additions. For example, Klein and Zitrin have shown that the reaction of methyl *trans*-α-bromocrotonate (**1**) with PhMgBr in ether gave a ca. 1:1 mixture of the *erythro* and *threo* 1,4-adducts **2** in approximately 70% yield.[25] Added CuCl or CoCl had no effect upon the course of this reaction. On the other hand, methyl *cis*- (**3a**) and *trans*-α-bromocinnamate (**3b**) reacted with MeMgBr in a 1,2-manner to give the corresponding methyl ketones **4a** and **4b** in 31 and 54% yields, respectively. Again, an added cuprous halide did not influence the course of the reaction. When treated with an excess of $LiMe_2Cu$ in ether at low temperatures, methyl *trans*-α-bromocinnamate (**3b**) and methyl *trans*-α-bromocrotonate (**1**) were converted into the corresponding α-Cu(I) derivatives with retention of configuration (Scheme 1).[26,27]

Ethyl *trans*-α-fluorocinnamate was found to behave similarly to **3b** upon treatment with Grignard reagents.[28] When treated with 2.0 equiv. of EtMgBr or PhMgBr, the vinylogous fluorocarbamate **5** underwent 1,2-addition with loss of OMe^- as well as 1,4-addition followed by elimination of the piperidino group to give the α-fluoro conjugated ketones **6** and **7** as the major products in low yields (Scheme 2).[28]

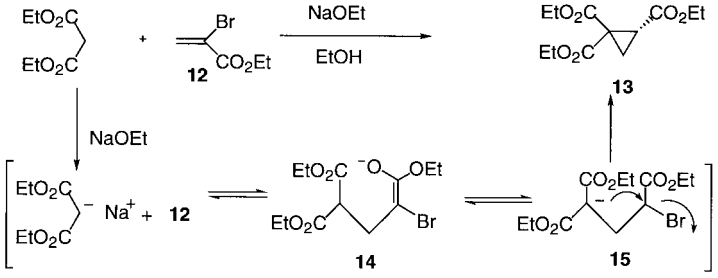
The reaction of EtZnCl with methyl α-chloroacrylate (**8a**) has been shown to give the cyclopropane derivative **9** in 50% yield.[29] This interesting sequential process appeared to involve irreversible addition of the organometallic reagent to the enoate to give the enolate **10**, reversible addition of this species to a second molecule of the enoate via a chelated eight-membered ring transition state to give a second enolate intermediate **11** and, finally, closure of the cyclopropane ring via intramolecular cyclization to give **9**. Chelation of the carbonyl groups by the Zn^{2+} cation in the transition state for the latter step would account for the formation of the cyclopropane derivative with the ester groups in a *cis* relationship. By the use of stereoselectively deuterium-labeled starting γ-bromoacrylate **8b** in a similar



Scheme 2.



Scheme 3.

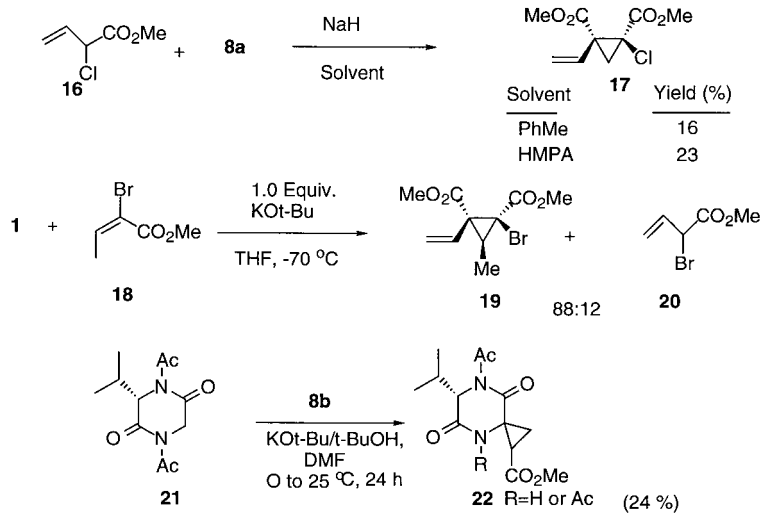


Scheme 4.

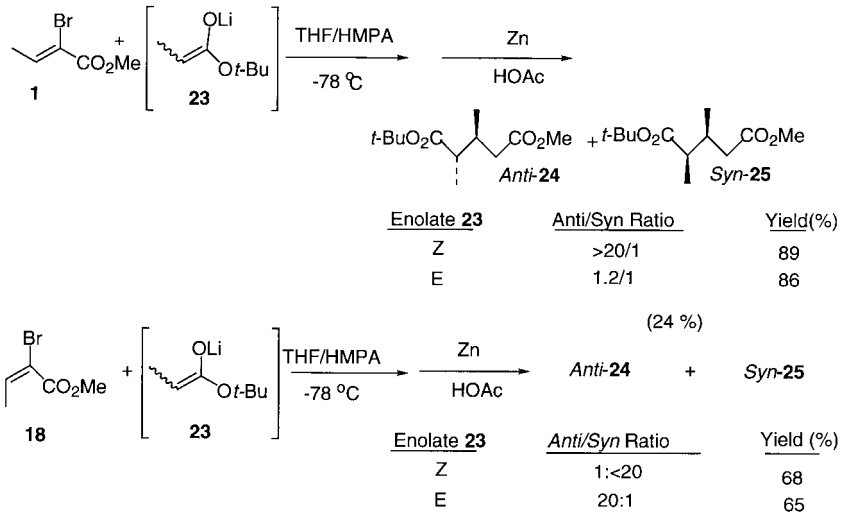
reaction, it was shown that rotation occurred about the new carbon–carbon bond in enolate **11** prior to the ring closure (Scheme 3).[30]

2.1.2. Metal enolates and related reagents. Michael reactions, specifically conjugate additions of metal enolates to conjugated carbonyl compounds, may be carried out in protic solvents containing a catalytic amount of a base under equilibrium conditions or by using preformed enolates in aprotic solvents at low temperatures under kinetic conditions.[31–33] The stereochemistry of the latter types of processes has been investigated extensively in recent years.[34] As is the case for other conjugated carbonyl compounds containing anion-stabilizing groups at the α-position,[35] α-haloenoates are good Michael acceptors in both the thermodynamically and the kinetically controlled reactions.[36,37] In an early study Michael himself found that a sequential reaction occurred to give the cyclopropane derivative **13** when the bromoacrylate **12** was treated with diethyl malonate in the presence of NaOEt/HOEt.[38] After the initial carbon–carbon bond formation step, the bromoester enolate **14** underwent a proton transfer reaction to give the more stable diester enolate **15**; intramolecular alkylation then yielded **13** (Scheme 4).

If the Michael donor contained only one acidic hydrogen atom, the simple Michael adduct was formed,[39,40] e.g. 2-methylcyclopentan-1,3-dione reacted in this manner



Scheme 5.

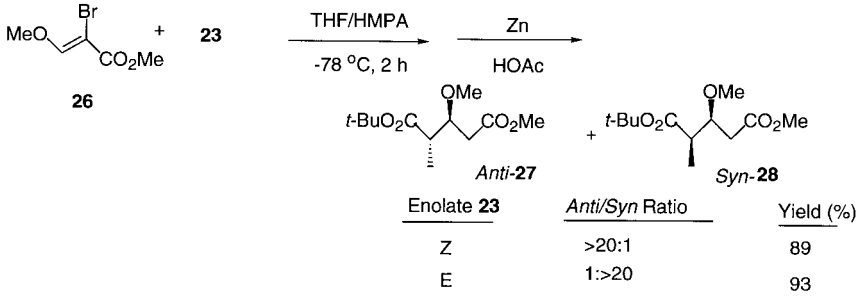


Scheme 6.

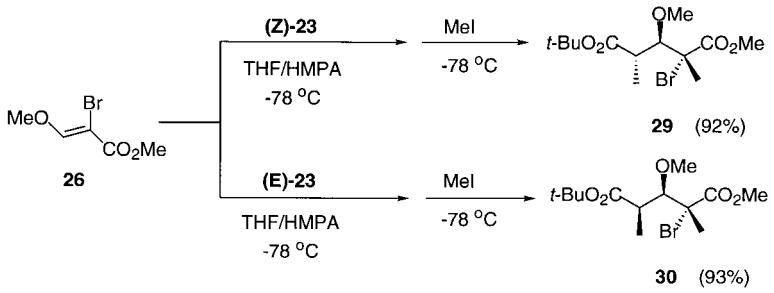
with α-chloroacrylate esters.[39] Other examples of the involvement of α-haloenoates in reactions leading to the formation of cyclopropane derivatives include: (1) the reaction of chloroester **8a** with the sodium dienolate of methyl 2-chloro-3-butenoate (**16**) in HMPA or PhMe to give the vinyl cyclopropane **17** in low yields,[41] (2) the self-condensation of a 75:25 mixture of bromoenoate **1** and methyl 2-bromoisocrotonate (**18**) using KO*t*-Bu in THF to give cyclopropane **19** and the deconjugated isomer of the starting material **20** in an 88:12 ratio,[42] and (3) the production of the spirocyclopropanes **22** from the reaction of the cyclic dipeptide **21** with the bromoacrylate **8b** using the same base.[43] The Michael acceptor **8b** has been generated in situ by dehydrobromination of methyl 2,3-dibromopropanoate. Thus, formyl cyclopropane derivatives were formed when mixtures of this dibromoester, various aldehydes and diethyltrimethylsilylamine were allowed to stand at room temperature in acetonitrile (Scheme 5).[44]

The stereochemistry of the addition of propionate ester enolates to α-bromocrotonate esters under aprotic conditions has been investigated rather extensively.[36,37] In general, the *anti*/*syn* adduct ratios of the glutarate products were similar to those observed for simple crotonate esters.[36] For example, the enolate (*Z*)-**23** of *tert*-butyl propionate reacted with the bromocrotonate acceptor **1** in 4:1 THF/HMPA to give a >20:1 ratio of the *anti*- and *syn*-glutarates **24** and **25**, respectively, after removal of the bromide with Zn/HOAc. Under the same conditions, acceptor **1** reacted with the enolate (*E*)-**23** to give approximately equal amounts of the diastereomeric adducts.[36] In the THF/HMPA solvent system, the stereochemical outcome of the additions was dependent upon the stereochemistry of the Michael acceptor. Thus, the bromoisocrotonate acceptor **18** reacted with (*Z*)-**23** to give the *syn* adduct **25** almost exclusively, while the use of (*E*)-**23** provided largely adduct **24**. However, in THF alone, the *syn* adduct **25** was the major product when (*E*)-**23** was treated with either acceptor **1** or **18**. Methyl or *tert*-butyl thiopropionate enolates were found to be less stereoselective than the corresponding *tert*-butyl ester enolates **23**. Also, the *tert*-butylthio derivative of acceptor **1** reacted with lower selectivity than the ester itself. In general, the results of these experiments were consistent with those expected for an addition step involving an eight-membered ring transition state, with the lithium cation bridging the carbonyl oxygen atoms of the donor and acceptor molecules (Scheme 6).

While methyl 3-methoxyacrylate failed to react, methyl 3-methoxy-2-bromoacrylate (**26**) was found to undergo facile Michael additions with the propionate enolates (*Z*)-**23** and (*E*)-**23** in THF/HMPA.[36] Surprisingly, Michael addition followed by alkoxide elimination was more of a problem when THF alone was used as the solvent. After the addition, the bromine atom was removed from the glutarate products reductively with Zn/HOAc. As predicted from the examination of the interactions in a chelated eight-membered ring transition state for the addition, enolate



Scheme 7.



Scheme 8.

(*Z*)-**23** gave almost exclusively the *anti*-methoxymethyl diester **27**, and the stereoisomer (*E*)-**23** gave the *syn* product **28** with high stereoselectivity (Scheme 7).

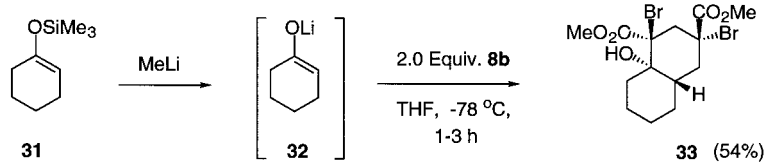
An extensive investigation of the manner in which changes in the structures of the two alkoxy groups of the acrylate Michael acceptor and the alkoxy group of the propionate enolate donor influenced the stereochemistry of the reaction led to the following general observations: (1) variations in the size of the alkoxyl group at C-1 or C-3 of the acceptor had no significant effect on the stereochemistry of the addition with either the *Z* or the *E* donor enolates **23**; (2) the steroselectivity of the addition was lower when *Z* or *E* enolates of the Michael donor containing groups more or less bulky than the *tert*-butoxy group were employed; and (3) moderate amounts of asymmetric induction were observed when propionate ester enolates containing chiral auxiliaries in the alkyl moiety were employed.[37]

When produced under aprotic conditions, Michael adducts of α-haloenoates are capable of being trapped inter- or intramolecularly with a variety of electrophilic reagents. Such sequential alkylation,[36,37] Michael,[3,44] aldol and Darzens reactions[45] allow the construction of rather complex molecules in a single synthetic operation. For example, trapping of the enolate intermediates derived from addition of enolates (*Z*)-**23** and (*E*)-**23** to haloenoate **26** with MeI gave alkylated adducts **29** and **30**, respectively, containing three new stereocenters in high yields (Scheme 8).[36]

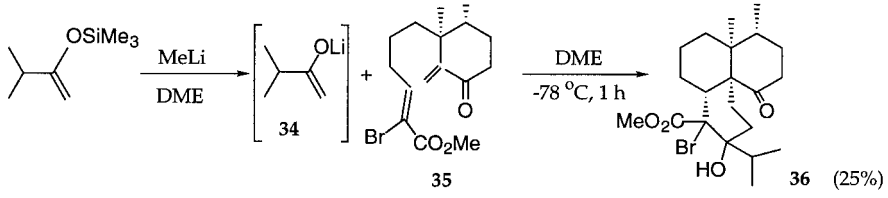
Posner and coworkers have reported that α-haloenoates participate in triply convergent, 2+2+2, Michael–Michael–aldol reactions (MIMIRC) to give polyfunctional cyclohexanol derivatives such as the decalone **33** from the reaction of the lithium enolate of cyclohexanone **32** (generated from the reaction of the trimethylsilyl enol ether of cyclohexanone with MeLi) with acrylate **12**.[3,45] Similar reactions have been carried out with acyclic and heterocyclic ketone enolates (Scheme 9).

Danishefsky and coworkers found that the bis-Michael acceptor **35** reacted with the acyclic lithium enolate **34** (generated from the reaction of 3-methyl-2-trimethylsiloxy-1-butene and MeLi in DME) to give the bromohydrin **36** in 25% yield.[46] This interesting bisannulation sequence involved (1) the initial addition of the enolate to the α-methylene ketone acceptor moiety, (2) Michael addition of the newly created cyclohexanone enolate to the α-bromoenoate side chain to close the first ring, and (3) closure of the second ring by addition of the bromoester enolate to the carbonyl group of the isopropyl ketone side chain. The influence of the presence of a methyl group at the γ-position of the bromoenoate side chain on the stereochemical course of the bisannulation process was also investigated in detail by Danishefsky and coworkers. This type of sequential reaction was used for the total synthesis of the indole alkaloid 3-desmethylflavinine (Scheme 10).[46]

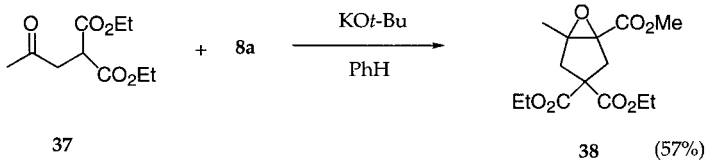
The epoxy triester **38** was obtained from the reaction of diethyl acetonylmalonate (**37**) and chloroenoate **8a** in KO*t*-Bu/PhH by a sequential process involving formation of the enolate of the diester, addition of this species to the



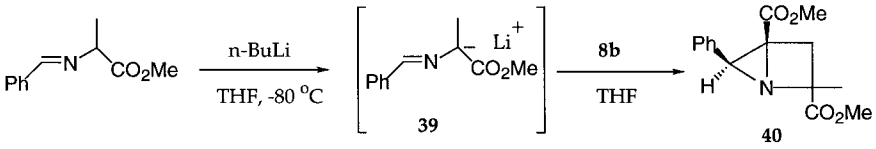
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

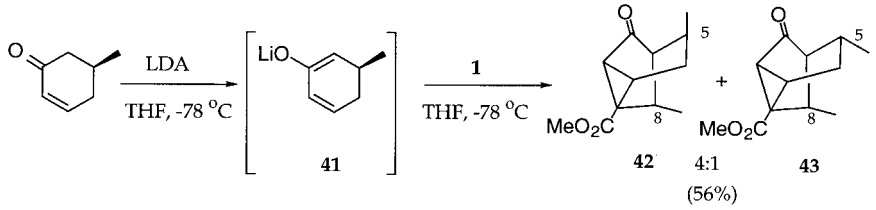
unsaturated ester and, finally, a Darzens reaction involving addition of the chloroester enolate product to the methyl ketone carbonyl group and epoxide formation (Scheme 11).[47]

α-Haloenoates reacted with imine-stabilized enolates to yield 1-azabicyclo[2.1.0]pentane derivatives;[48] e.g. the heterocycle **40** was formed in almost quantitative yield from the reaction of enoate **8b** and the enolate **39**. This interesting reaction involved a [2+3]-cycloaddition to form a bromopyrrolidine anion which underwent a 3-*exo*-cyclization with displacement of the Br^-. Related sequential reactions involving anions of *N*-benzylidene-α-aminoalkyl phosphonates and **8b** have also been reported (Scheme 12).[49]

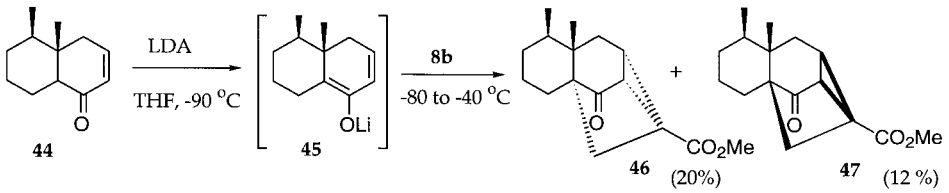
Kinetic dienolates of conjugated enones have been found to participate in sequential reactions with a variety of Michael acceptors in which the initially generated Michael adduct enolate underwent a second Michael addition to the enone system to give cyclic products.[34,50,51] A majority of examples of these reactions involve cross-conjugated dienolates of cyclohexanone derivatives which yield bicyclo[2.2.2]octane derivatives efficiently. The use of α-haloenoates as Michael acceptors in such reactions provided an added dimension in that the ketone enolate generated in the second step was capable of undergoing intramolecular alkylation to produce a cyclopropane ring.[52–57] Such MIMIRC reactions have been used to synthesize tricyclo[3.2.1.$0^{2,7}$]octane and tricyclo[4.4.0.$0^{1,5}$]-decane ring systems. For example, reaction of the kinetic dienolate **41** of 5-methylcyclohexenone with bromocrotonate **1** gave a mixture of the C-5 epimeric tricyclooctanones **42** and **43** in a 4:1 ratio in 56% yield.[53] The major product was derived from initial attack of the Michael acceptor on the side of the dienolate opposite the methyl group. A similar reaction involving the corresponding carvone dienolate was more selective because of the presence of the bulky isopropenyl group at C-5. The stereochemistry of the methyl groups at C-8 of these compounds was unspecified, but the reaction very likely involved an eight-membered chelated ring in the transition state for the second Michael ring closure. This would have been expected to yield the 8β-methyl compounds shown (Scheme 13).

A sequential dienolate–haloester reaction has been applied to the synthesis of the sesquiterpene ishwarane.[53] Treatment of the octalone **44** with LDA gave the dienolate **45** which reacted with bromoacrylate **8b** to give the tetracyclic products **46** and **47** in 20% and 12% yields, respectively. The major diastereomer **46** had the desired stereochemistry and was converted into ishwarane in three steps (Scheme 14).

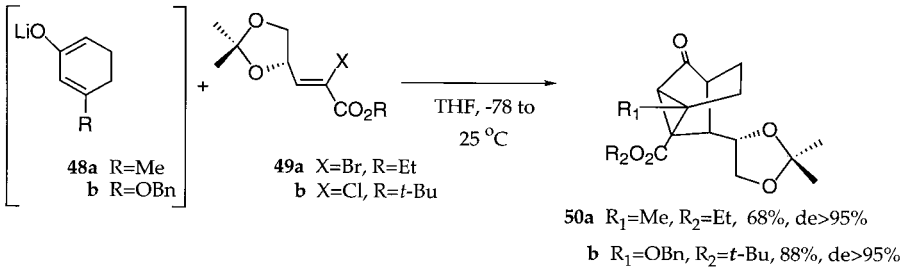
Another tricyclo[3.2.1.$0^{2,7}$]octanone prepared by an



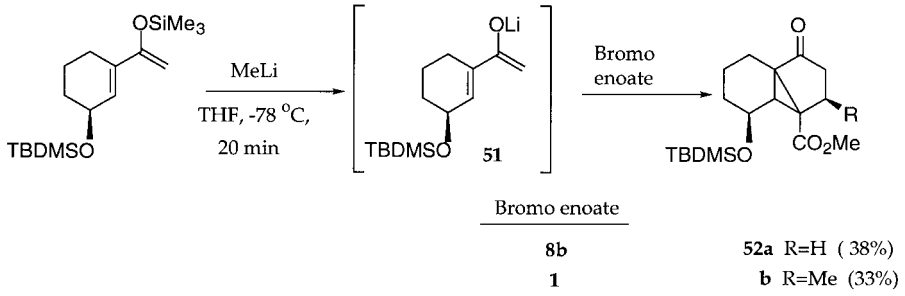
Scheme 13.



Scheme 14.



Scheme 15.



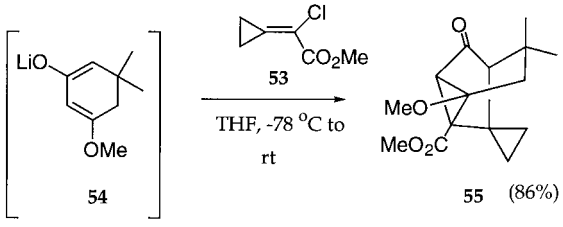
Scheme 16.

MIMIRC sequential process has been used as the starting material for a total synthesis of the natural product helminthosporal.[58] Enantiopure tricyclo[3.2.1.0^{2,7}]octan-6-ones such as **50** have been prepared in good yields by sequential reactions involving the corresponding cyclohexenone dienolates **48** and homochiral haloenoates **49**.[59–61] The 1-trimethylsilyl enol ether of 3,5,5-trimethylcyclohexen-1,4-dione has also been reacted with the bromoacrylate **8b** under the influence of Et_2AlCl to give the corresponding tricyclooctandione in a low yield (Scheme 15).[56]

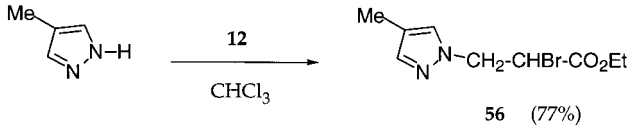
The use of kinetic dienolates of acyl cyclohexene derivatives in reactions with haloenoates provided a useful route to tricyclo[4.4.0.0^{1,5}]decane derivatives.[54,55] Such reactions have also been conducted with dienolates of acyl cyclopentenes and cycloheptenes. The starting dienolates are best prepared by cleavage of the corresponding trimethylsilyl enol ethers with MeLi in THF.[55] As an illustration of these reactions, fair yields of tricyclic products **52** were obtained when the lithium dienolate **51** was treated with bromoenoates **8b** and **1**. The stereochemical course of the reaction was explained by consideration of an eight-membered ring transition state with the Li^+ chelating the dienolate oxygen atom and the methoxycarbonyl group of the *s-cis* conformation of the enoate. The second Michael addition then occurred from the face of the molecule opposite the TBDMSO substituent. Interestingly, the geometric isomer of **1**, i.e. **25**, did not yield a tricyclic product when reacted with **51**, possibly because the 3-methyl group interfered with the formation of an eight-membered ring chelated transition state for the second Michael addition step.[55] Three new carbon–carbon bonds and two new rings were formed efficiently in these sequential reactions (Scheme 16).

It has recently been shown that these MIMIRC reactions proceeded smoothly when the chloroenoate Michael acceptor **8a** was generated in situ by the addition of methyl 2,3-dichloropropionate to a THF solution of an appropriate dienolate in the presence of 1.0 equiv. of lithium hexamethyldisilazide.[57] This technique allowed problems associated with the preparation and storage of the usual haloenoate Michael acceptors to be overcome.

Several lithium dienolates of cyclohexenone derivatives have been reacted with methyl 2-chlorocyclopropylidene acetate (**53**) to give the corresponding tricyclo[3.2.1.0^{2,7}]-octanes containing a spiro cyclopropane ring at C-8.[62–65] Better yields were obtained with 3-alkyl- and 3-alkoxy-substituted cyclohexenone dienolate donors than with the parent system.[64] The reaction of dienolate **54** with acceptor **53** provided an example of this reaction in which a high yield of the product **55** was obtained.[63] Haloenoates also served as acceptors for cross-conjugated lithium dienolates of cyclopentenone and cycloheptenone derivatives.[65] The 3-ethoxy derivative of the latter compound gave the expected tricyclo[4.2.1.0^{2,8}]nonane derivative containing a spiro cyclopropane ring. This compound was potentially useful as a starting material for the synthesis of the marine diterpene mediterranols (Scheme 17).[65]



Scheme 17.



Scheme 18.

2.2. With heteroatom nucleophiles

As well as carbon nucleophiles, conjugated α-haloenoates have been found to react with a variety of heteroatom nucleophiles—both neutral and anionic electron donor species. α-Chloroacrylate **8a** was converted into the corresponding α-SMe derivative **8c** in 60% yield upon heating with HSMe, $CaBr_2$, and Et_3N in DMF.[66] Under similar conditions α-bromocrotonate **1** reacted with HSEt to give a 5:2 *Z*/*E*-mixture of the corresponding α-SEt derivatives. Apparently, these reactions involved a three-step process of 1,4-addition of the mercaptan, S_N2 displacement of Br^- of the adduct by the thiolate anion and, finally, β-elimination of the mercaptan from the α,β-dithioalkyl intermediate.[66,67] Acrylate ester **12** underwent simple conjugate addition when reacted with 1.0 equiv. pyrazole[68] or methylpyrazole.[69] The latter reaction gave the bromoester **56** in 77% yield (Scheme 18).

As was true for carbon nucleophiles, heteroatom nucleophiles underwent MIMIRC reactions when treated with 2.0 equiv. of an α-haloenoate.[70,71] For example, lithium alkoxides **57** reacted with the corresponding bromoacrylate esters in THF to produce the bromocyclopropanes **58** in good yields.[71] The use of LiSEt or LiSPh as the donor also gave the related thiolates.[71] The formation of the cyclopropanes with the two ester groups *cis* followed from the involvement of an eight-membered ring chelated species in the transition state for the ring closure. Likewise, oxime and hydrazine anions participated in MIMIRC reactions with 2.0 equiv. of bromoacrylate **8b** (Scheme 19).[70]

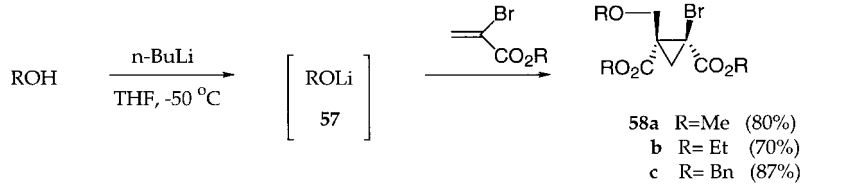
Benzamidine reacted with ethyl α-bromocinnamate and other α-haloenoates in the presence of Et_3N to give 2,6-disubstituted-4(3*H*)-pyrimidinones.[72] After the initial conjugate addition, the six-membered ring was formed by attack of the imine nitrogen atom on the carbonyl group with loss of the alkoxy group followed by elimination of HBr. However, aminothiazole **59** reacted with **8b** by a pathway involving the intramolecular displacement of the Br^- by the imine nitrogen of the adduct **60** to give the tetrahydroimidoazothiazole **61** in 69% yield (Scheme 20).[73]

4-Substituted-2-methylene-1,3-dithiolanes and 2-*N*-phenylsulfonylimino-1,3-dithiolanes were formed when alkali dimetal salts of 1,1-ethenedithiolanes and 2-*N*-phenylsulfonyldithiocarboimidic acids and bromoester **8b** were reacted in aqueous acid.[74] β-Phosphonoacrylates were obtained by a sequential conjugate addition followed by elimination of TMSBr when diethyl trimethylsilyl phosphite was treated with acrylate **8b** in CH_2Cl_2.[75] Other important classes of heterocyclic compounds have been synthesized from reactions of α-haloenoates with functionalized heteroatom nucleophiles. For example, treatment of the sodium salt **62** of 2(*N*-phenylformimidoyl)indole with **8b** in THF/HMPA led to sequential conjugate addition, intramolecular addition of the bromoenolate adduct to the imine side chain, and a Darzens-like ring closure to give the bisannulated aziridine **63** with a skeleton related to the mitomycin antitumor antibiotics (Scheme 21).[76]

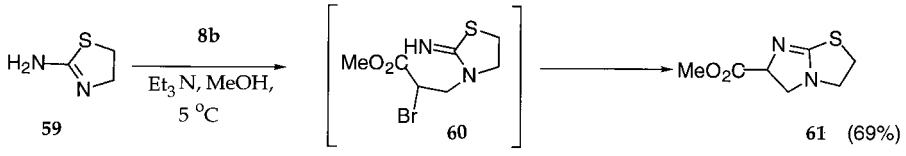
3. Reactions of conjugated β-haloenoates

3.1. With carbon nucleophiles

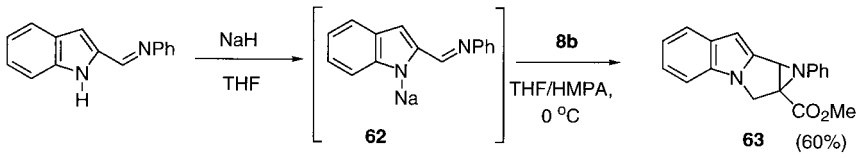
3.1.1. Organometallic reagents. Some years ago Decaux and Vessiere reported the reactions of *trans*- **64** and *cis*-β-halocrotonate esters **65** with EtMgBr in ether in the absence or presence of CuCl.[77] The salient results of this study were



Scheme 19.



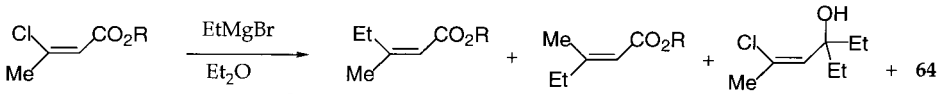
Scheme 20.



Scheme 21.

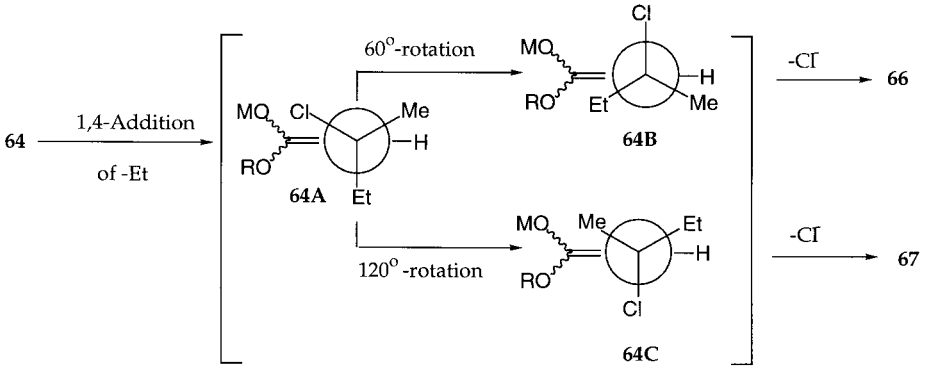
as follows: (1) the more hindered *s*-Bu esters were significantly less reactive than the corresponding ethyl esters; (2) the initial 1,2-addition processes which led ultimately to the tertiary alcohols **68** and **69** from the enoates **64** and **65**, respectively, were generally favored when no Cu(I) catalyst was present; and (3) when Cu(I) was present there was a preference for retention of configuration in the overall replacement of –Cl by –Et, but the steroeselectivity of the process was low. In the latter process metal enolate intermediates such as **64A** and **65A** presumably were generated by oxidative 1,4-addition of an organocopper intermediate to the enoate, followed by reductive elimination to form an sp^3 Et–β-C bond.[78,79] Elimination of Cl^- from such an enolate then led to the formation of the substituted enoate system. Rotation of 60° clockwise or 120° counter-clockwise about the α,β-C–C bond would allow the C–Cl bond to achieve an alignment parallel to the π electron system of the enolate, where stereoelectronically controlled loss of Cl^- would be facile. In these cases the rate of loss of Cl^- appeared to be slow enough that both the 60°-rotatomers, i.e. **64B** and **65B**, and the 120°-rotatomers, i.e. **64C** and **65C**, which do not differ significantly in energy, were populated prior to the elimination step (Schemes 22 and 23).

Jalander and Broms have found that the isomeric ethyl β-chlorocinnamates behave differently from each other and from the corresponding crotonates when treated with Grignard regents in the presence of CuI.[80] Some representative reactions of the *Z*-isomer **70** and the *E*-isomer **71** with reagents containing different classes of alkyl groups are shown below. Thus, substitution of –Cl by –R occurred with complete retention of configuration for compound **70**, but the product of inversion **72** was the major isomer from **71**. For the β-Ph-substituted compound there was probably a preference for the elimination of Cl^- to occur in a conformation of the enolate adduct having the ester group and the Ph group in an *anti* relationship. This would have allowed for better overlap of the extended π electron system of the incipient enoate to be achieved than in the conformer where the ester and Ph groups are *syn*. Conformation **70B** resulting from a 60°-rotation in the initial enolate adduct **70A** would fulfill this requirement and give the retention product **72** from **70**. On the other hand, enolate

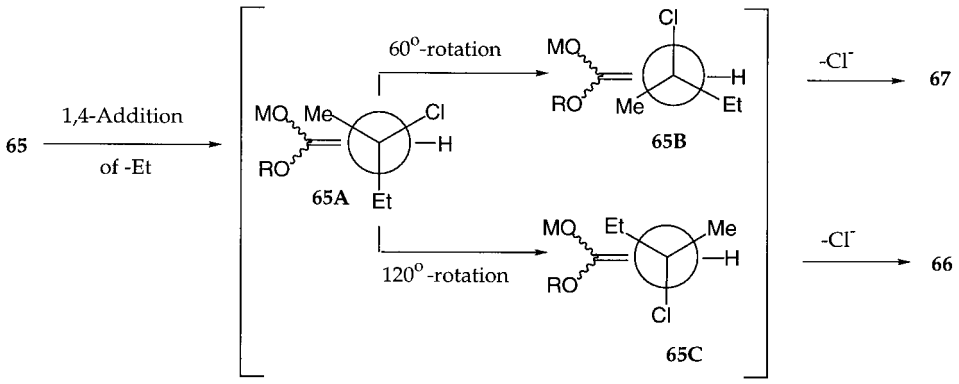


R-	Cat.	66	67	68	64
		Products (%)			
Et-	None	11	0	70	16
s-Bu	"	24	0	12	64
Et-	3 mol% CuCl	48	42	11	0
s-Bu	"	46	36	6	12

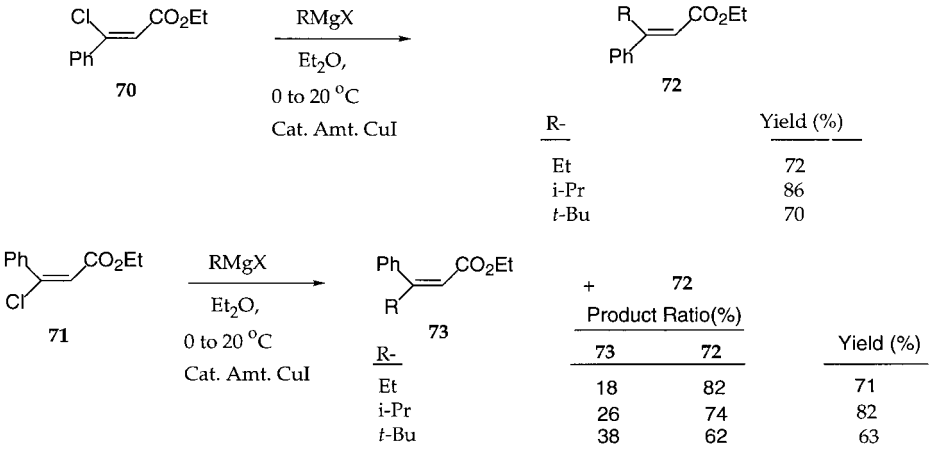
R-	Cat.	66	67	69	65
		Products (%)			
Et-	None	0	0	85	15
s-Bu	"	0	0	20	80
Et-	3 mol% CuCl	10	57	33	0
s-Bu	"	13	82	5	0



Scheme 22.



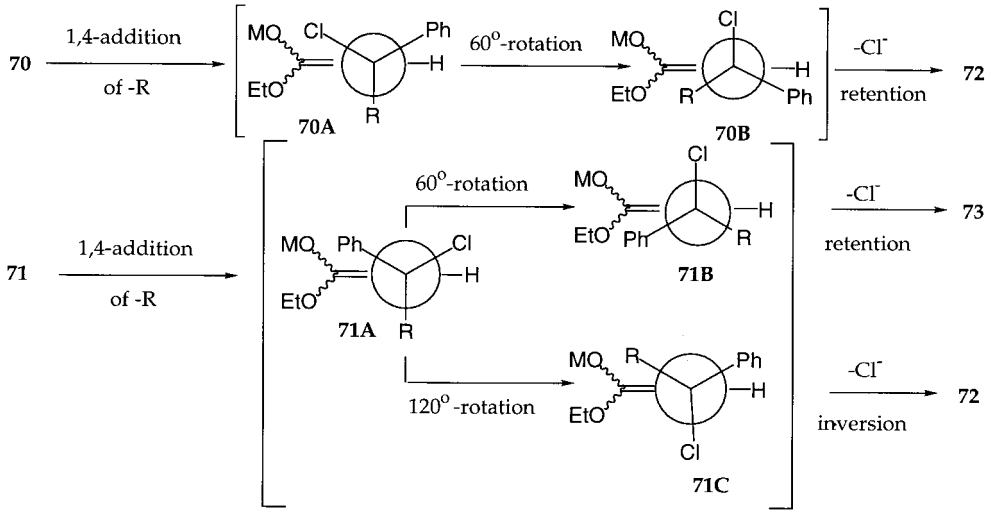
Scheme 23.



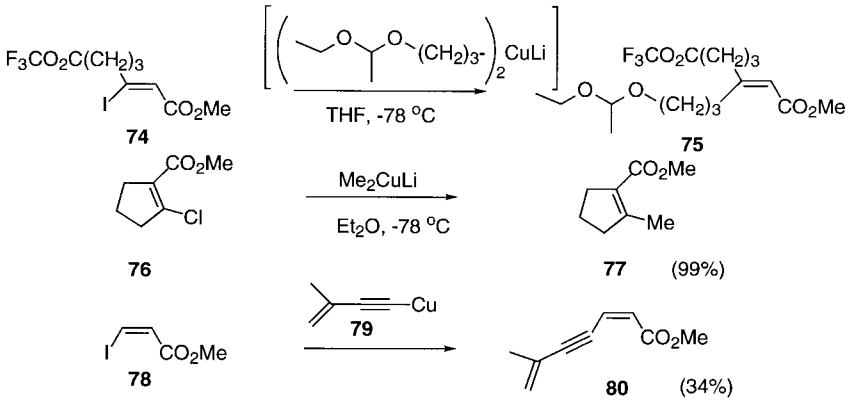
Scheme 24.

71A derived from the isomer **71** would have to undergo a 120°-rotation and give conformer **71C** for the achievement of optimum π electron overlap. This would have accounted for the preference for formation of the inversion product **72** from the *Z*-isomer **71**. However, elimination of Cl^- via the 60°-rotation conformer **71B**, which would have led to the retention product **73**, competed in this case. This was particularly true when a bulky alkyl group, which would have been expected to hinder the 120°-rotation about the C–C bond more than the 60°-rotation, was present (Schemes 24 and 25).

Reactions of β-haloenoates with stoichiometric quantities of lithium dialkylcuprates led to the substitution of the halogen by an alkyl group. The conversions of the iodoenoate **74** into the β,β-disubstituted compound **75**,[81] and the methyl 2-chlorocyclopentene carboxylate **76** into the corresponding



Scheme 25.

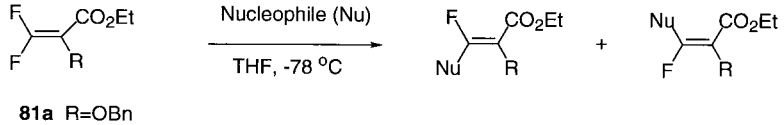


Scheme 26.

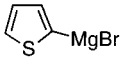
2-methyl derivative **77**,[82] provide examples of these reactions. Also, the alkynyl copper compound **79** reacted with the *Z*-iodoacrylate **78** to give the alkynyl dienoate **80** in a poor yield (Scheme 26).[83]

Recently, the manner in which α-substituents influence the regiochemistry of the substitution of the fluorine atoms of ethyl β,β-difluoroacrylates upon reactions with organometallic reagents and other nucleophiles has been investigated.[84,85] With organometallic reagents the α-benzyloxy- and α-trimethylsilylmethyl compounds **81a** and **81b** gave the results shown below (Scheme 27).

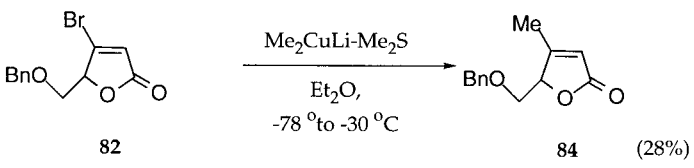
β-Bromobutenolides **82** and **83** have also been converted into the corresponding β-alkyl compounds **84** and **85**, respectively, with the appropriate lithium dialkylcuprate reagents. Compound **84** was obtained in poor yield from the reaction of butenolide **82** with Me_2CuLi.[86] Although the 2-aminobenzoyl butenolide **83** reacted smoothly with $(n\text{-}Bu)_2CuLi$ to give the substitution product **85a**, Olsen and coworkers reported that a poor yield of the 3-methyl butenolide **85b** was also obtained with Me_2CuLi.[88] After a considerable amount of experimentation, they found that a new boron-modified reagent (Me_2CuLi–MeLi–BF_3) provided the desired 3-methyl compound in a good yield.[88] Both the *cis* and *trans* isomers of ethyl β-bromoacrylate have been shown to undergo stereospecific substitution of the bromine when treated with copper(I) methyltrialkylborates.[89] Again, an addition–elimination mechanism was proposed for these reactions. Also, the α-(difluoromethylene)-γ-lactone **86** was found to undergo replacement of one or both of the fluorine atoms to give lactones **87** or **88** when treated with 1.0 equiv. of $PhCH_2MgBr$ or 2.0 equiv. of *n*-BuLi.[90] When γ,γ-disubstituted β-bromobutenolides were reacted with organolithium or organomagnesium compounds, 1,2-addition occurred.[87] The adducts were readily rearranged into the corresponding 3(2*H*)-furanones upon acid treatment. The related α,β-difluorobutenolides exhibited similar behavior.[91] These butenolides underwent substitution of the β-fluorine atom when treated with Grignard reagents under Cu(I) catalysis (Schemes 28 and 29).[91]



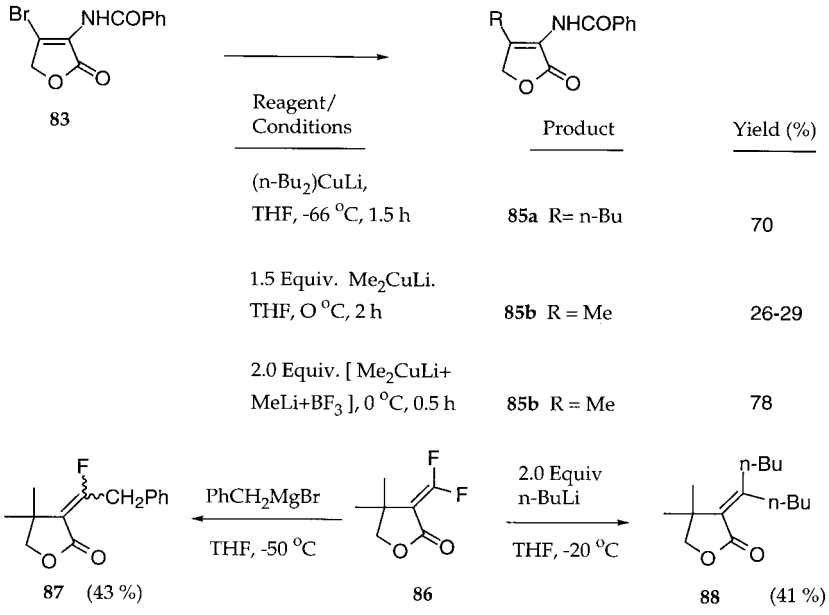
81a R=OBn
b R=CH_2SiMe_3

Reactant	Nu	Product Ratio (%)		Yield (%)
81a	Ph_2CuLi	90	10	90
	i-PrMgBr, CuBr	88	12	90
		16	84	84
81b	Me_2CuLi	100	0	86
	Ph_2CuLi	40	60	65

Scheme 27.



Scheme 28.

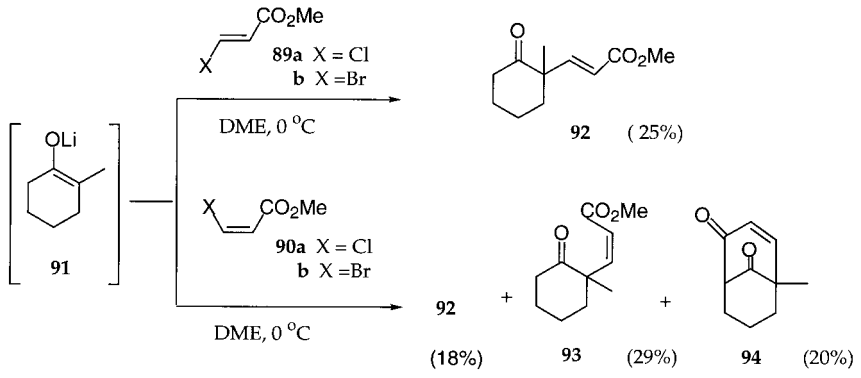


Scheme 29.

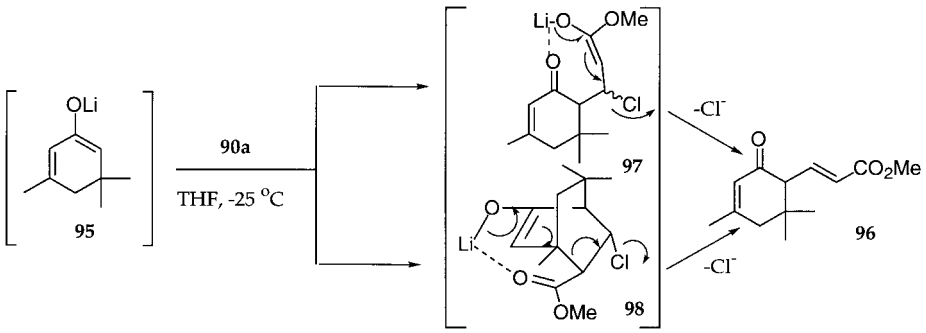
3.1.2. Metal enolates and related compounds. Metal enolates of carbonyl compounds and related nucleophiles generally behave as Michael donors in reaction with conjugated β-haloenoates. The Michael addition is followed by elimination of the halide ion from the enolate adduct. The overall substitution process generally occurs with retention of the configuration of the substrate.

A mixture derived from Michael additions involving C-2 and C-6 of 2-methylcyclohexanone was obtained in very low yield when methyl *trans*-β-chloroacrylate (**89a**) was treated with this ketone using KO*t*-Bu/HO*t*-Bu as the base/solvent system.[92] No addition–elimination product was obtained when the isomeric haloacrylate **90a** was employed as the potential Michael acceptor. Instead, a tertiary alcohol derived from dehydrohalogenation of the enoate to the propiolate ester and addition of its anion to the carbonyl group of the ketone was obtained.[92] On the other hand, the *preformed*, more substituted lithium enolate **91** of 2-methylcyclohexanone gave moderate to good yields of addition–elimination products with both **89a** and **90a** as Michael acceptors.[93] The retention product **92** was the only one obtained from the *trans* ester **89a**, and the retention/inversion ratio was 2.5 for the *cis* isomer **90a**. In the latter case, a portion of the retention product **93** was converted into the bicyclic diketone **94** by an in situ Dieckmann reaction (Scheme 30).

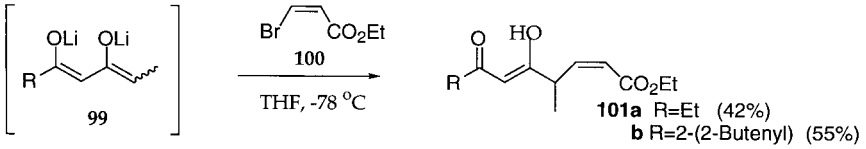
Reactions of cross-conjugated dienolates of cyclohexenone derivatives with conjugated enones and enoates have been widely investigated as a method to synthesize bicyclodecanone derivatives.[34,50] Ostensibly, such reactions may proceed via sequential Michael reactions or via a concerted Diels–Alder reaction. Evidence for the former pathway was obtained when it was found that the lithium dienolate of isophorone **95** gave the monocyclic unsaturated ester **96** when reacted with the chloroacrylate **90a**.[94] (It is not clear why inversion of the configuration of the starting ester occurred.) Apparently, the ester enolate Michael adduct, which most likely existed as the eight-membered ring lithium chelated structure **97**, lost Cl^- faster than it underwent an intramolecular Michael addition to give the bicyclic ketoester enolate **98**. However, the possibility cannot be ruled out that **98** was formed initially by a [4+2]-cycloaddition, but, because of ring strain, a retro-Michael reaction with concomitant elimination of Cl^- occurred



Scheme 30.



Scheme 31.



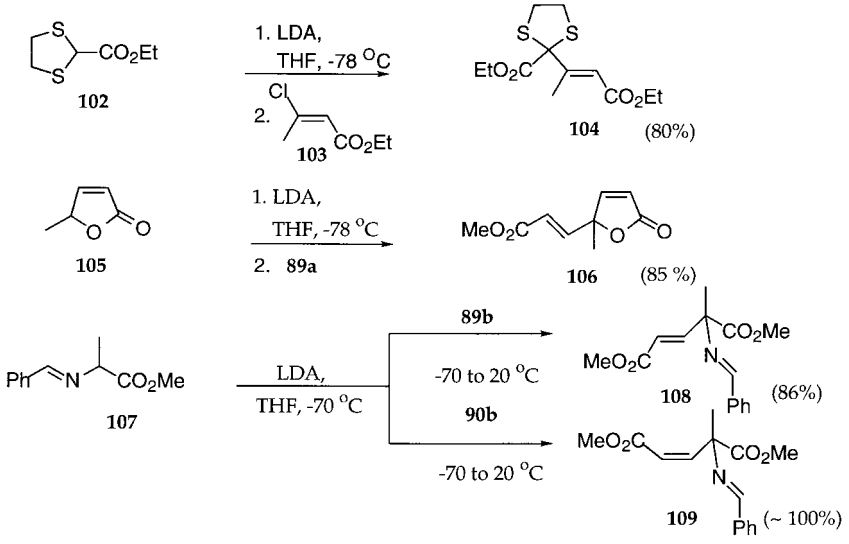
Scheme 32.

rapidly to yield the ring-opened ketoenoate product (Scheme 31).

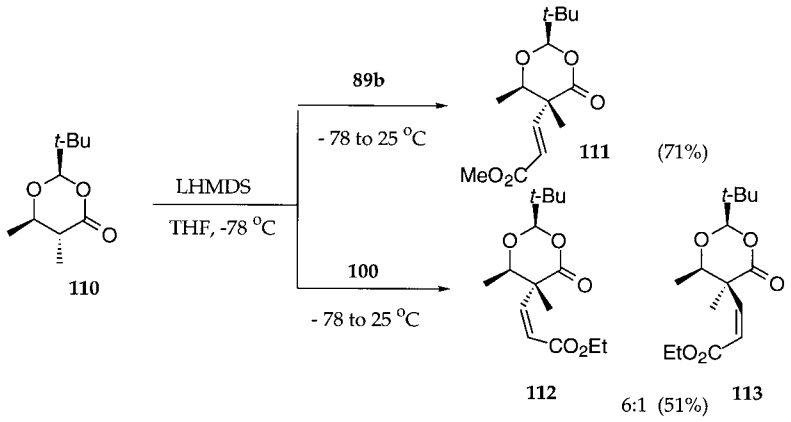
The expected sequential addition–elimination reactions occurred with retention of configuration to give diketoenoates such as **101** when dilithium dienolates **99** of 1,3-diketones containing terminal ethyl groups were reacted with ethyl *cis*-β-bromoacrylate (**100**).[95] With terminal methyl ketones the double bond of the initially formed conjugated enoate underwent rapid isomerization into conjugation with the enol form of the 1,3-diketone. Also, 2-substituted 1,3-diketones failed to react (Scheme 32).

Several examples of the reactions of stabilized ester enolates with β-haloenoates have been reported: (1) the lithium enolate of the carbonyl anion equivalent **102** reacted with the chlorocrotonate **103** to give the enoate **104** in 80% yield;[96] (2) the lithium dienolate of butenolide **105** served as a Michael donor at the γ-position and reacted with the chloroacrylate **89a** to give the butenolide enoate **106** in good yield;[97] (3) the lithium (or sodium) enolate of methyl *N*-benzylidenealanate (**107**) reacted with the bromoacrylates **89b** and **90b** to give the corresponding enoate products **108** and **109**;[98] and (4) the lithium enolate of the dioxanone **110** reacted with the *trans*-bromoacrylate **89a** or the *cis*-bromoacrylate **100** to give the addition–elimination product **111** or a 6:1 mixture of the corresponding products **112** and **113** (Schemes 33 and 34).[99]

Rapoport and coworkers have reported the reactions of *Z*/*E*-mixtures of the β-chlorocrotonate **114a** and the α-halo-β-chlorocrotonates **114b,c** with the sodium enolate of diethyl ethylmalonate (**115**) in DMF.[100] Compound **114a** underwent addition–elimination followed by extensive deconjugation of the double bond to produce a 1:4 mixture of **116a** and **117a**, while the dichloroenoate **114b** gave exclusively the deconjugated product **117b**. In the case of the α-bromo-β-chloro compound **114c**, the conjugated intermediate **116c**



Scheme 33.



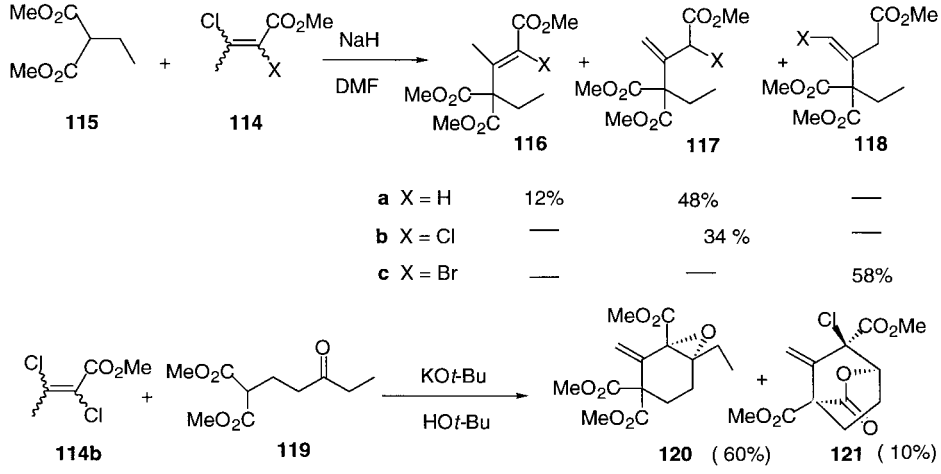
Scheme 34.

was unstable and underwent allylic rearrangement of the bromide followed by deconjugation to give the vinyl bromide **118c** as the only isolable product. Under basic conditions the dichloroenoate **114b** reacted with the functionalized malonate diester **119** to give the glycidic ester **120** plus other products, e.g. the lactone **121**, in variable yields. Compound **120** resulted from a sequential addition–elimination–deconjugation–intramolecular Darzens condensation process. For larger scale runs best results were achieved when KO*t*-Bu/HO*t*-Bu was employed as the base. Glycidic ester **120** was considered to be a useful synthon for ring A of aklavinone, which is the aglycone of the antitumor antibiotic aclacinomycin A (Scheme 35).[100]

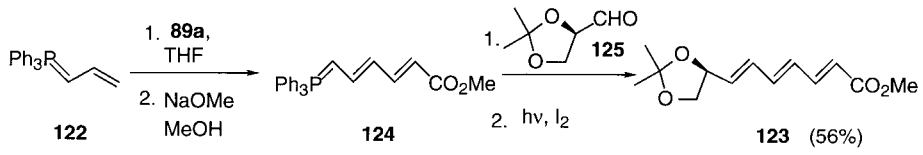
Allylidenetriphenylphosphorane (**122**) behaved as a nucleophile in reactions with β-haloenoates.[101] This provided a convenient route for the synthesis of stabilized ylides which were useful for the synthesis of conjugated polyenes. Recently, Mori and coworkers prepared the chiral trienoate **123**, a precursor of the macrolide antibiotic roxaticin, by this methodology.[102] Upon reaction of **122** with the chloroacrylate **89a** followed by base treatment, the stabilized ylide **124** was obtained in situ. Then, addition of the chiral aldehyde **125** and isomerization of the resulting 1:2 *E*/*Z* trienoate mixture with ultraviolet light in the presence of I_2 gave **123** in 56% yield (Scheme 36).

Schollkopf and Schroder have found that lithiated bislactims such as **126**, which are chiral enolate equivalents, reacted with β-haloenoates stereospecifically with respect to the configuration of the double bond and with a high degree of asymmetric induction.[103] Thus, enoates **127** and **128** were produced from chloroenoates **129** and **130**, respectively, in good yields and with at least 99.5% diastereomeric excess (Scheme 37).

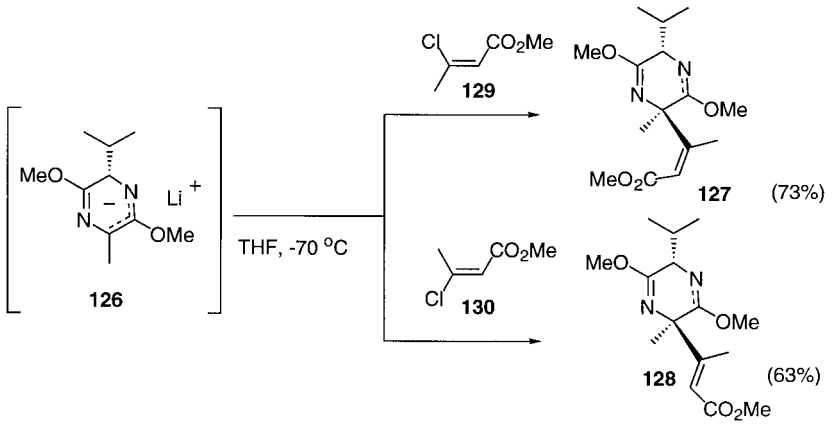
α-Substituted β,β-difluoroacrylates such as **81** undergo substitution of only one of the fluorine atoms when reacted



Scheme 35.



Scheme 36.



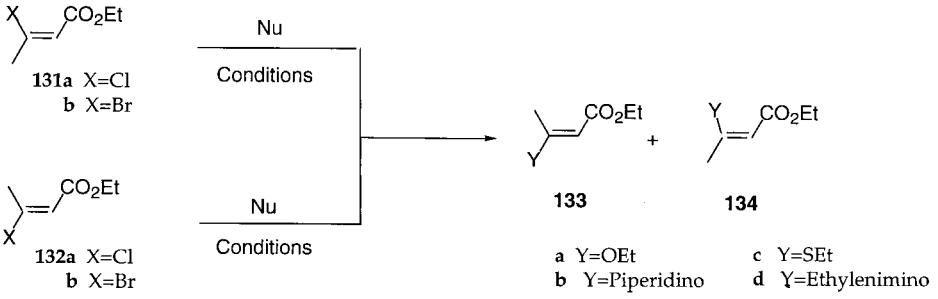
Scheme 37.

with metal enolates of simple ketones, esters, or β-diesters.[84,85] The α-benzyloxy compound **81a** gave *E*/*Z* mixtures in which the *E*-isomer was favored,[84] but the fluorine atom on the opposite side of the double bond was replaced by the nucleophile exclusively when the $-CH_2SiMe_3$ was present.[85] The latter result was attributed to the presence of a C–F–Si coordinative interaction in the transition state for the elimination of F^- from the Michael adduct enolate intermediate.[85]

3.2. With heteroatom nucleophiles

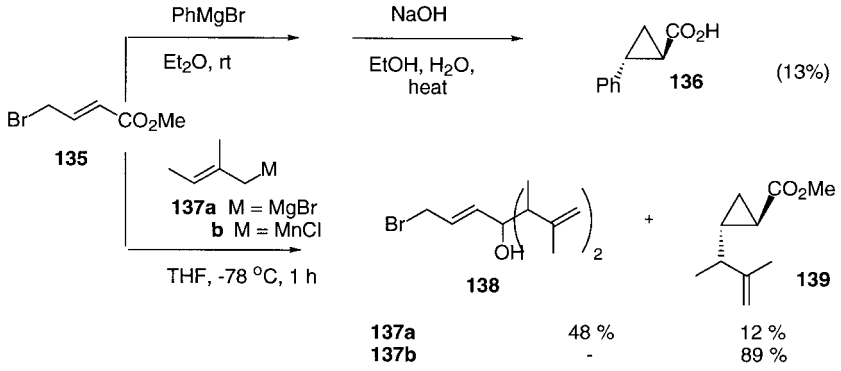
β-Haloenoates undergo substitution reactions with various anionic and uncharged nucleophiles by an addition–elimination mechanism.[104,105] Representative examples of such reactions with the isomeric chlorocrotonates **131a** and **132a** are listed below. Depending upon the nature of the nucleophile, complete stereoconvergence, or complete or partial retention of the configuration of the double bond has been observed. For example, the reaction of either **131a** or **132a** with OEt^-[106] or piperidine[107,108] produced exclusively the *cis* crotonate esters **133a** and **133b** with the ester and the heteroatom containing groups *trans*. In such compounds, n–π electron resonance could be more important than in compounds such as **134a** and **134b**, where there would probably be greater steric hindrance to coplanarity. Thus, in these cases elimination of the Cl^- apparently occurred in a rotamer of the enolate adduct, which would give the more stable product, i.e. **133**, although thermodynamic control could be involved as well (Scheme 38).

Predominant or complete retention of the configuration of the double bond was found when SEt^- or ethylenimine was employed as a nucleophile in reactions with the chlorocrotonates **131a** and **132a.** Stabilization of the substitution product by n–π resonance for compounds **133c** and **133d** would be less important than for the corresponding ethoxy or piperdino derivatives. In the thioalkyl system **133c**, the lone electron pair on sulfur occupies a 3p orbital so that n–π overlap would be poor, and release of electrons from

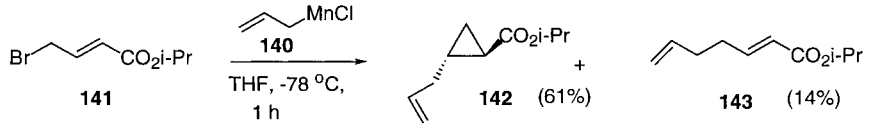


Reactant	Nu/Conditions	Product Ratio (%)		Yield (%)
131a	NaOEt, EtOH	100	0	87
132a	"	100	0	"
131a	Piperidine, Et_2O	100	0	92
132a	"	100	0	"
131a	NaSEt, EtOH, 0 °C	8	92	90
132a	"	85	15	89
131a	Ethylenimine	0	100	79
132a	"	100	0	87

Scheme 38.



Scheme 39.



Scheme 40.

nitrogen in the ethylenimino compound **133d** would lead to an increase in ring strain. When product stability did not provide a strong driving force for the reaction, elimination of Cl^- apparently occurred via a conformation resulting from a 60° rotation about the C–C bond in the initial enolate adduct.

The isomeric bromocrotonates **131b** and **132b** also reacted with nucleophiles such as SPh^- with retention of configuration of the double bond, but with OEt^-, dehydrobromination took place to yield an acetylenic ester from the *trans* ester **131b** and an allenic ester from the *cis* isomer **132b**.[109]

The stereochemistry of the substitution of doubly activated vinlylic halides, including β-haloesters, by nucleophiles with regard to the nucleofuge, the counterion, the nucleophile and other conditions has been widely investigated by Rappoport and coworkers, but coverage of their results is beyond the scope of this review.[110–113]

β-Chloro- and β-iodoacrylates have been found to undergo substitution with tributylstannylmetals, especially tributylstannylcopper in THF, with retention of the configuration of the double bond.[114] The functionalized vinyltin compounds that were formed are useful reagents for C–C bond formation via Stille coupling with vinyl halides and triflates.

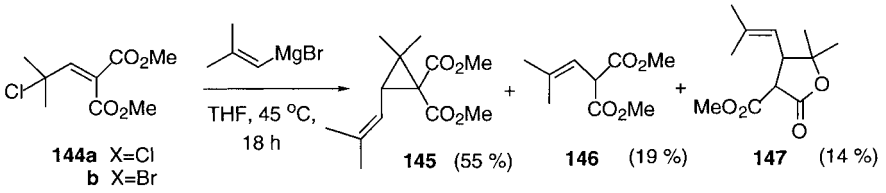
In reactions with 1-indolyllithium and diethylphosporylsodium, the difluoroacrylate **81b** underwent substitution of the fluorine atom opposite the $-CH_2SiMe_3$ group exclusively, while reactions of this compound with sodium phenoxide or sodium borohydride were nonregiospecific.[85] Isopropyl β,β-difluoroacrylate underwent amine-catalyzed 1,4-additions of nitroalcohols without elimination of F^-.[115]

4. Reactions of conjugated γ-haloenoates

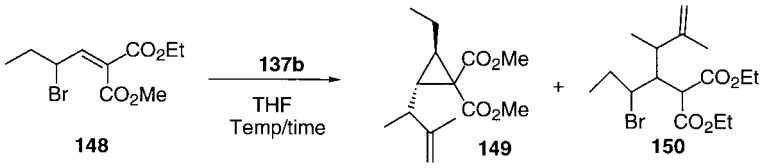
Nucleophiles may react with γ-haloenoates in four different ways: (1) 1,2-addition to the carbonyl carbon atom; (2) direct S_N2 displacement of the halide at the γ-position; (3) S_N2' displacement of the halide by attack at the α-position; and (4) 1,4-addition to the β-position to generate an ester enolate intermediate. Under certain conditions, this intermediate may be stable so that the simple 1,4-adduct is obtained upon workup of the reaction mixture. However, such adducts normally undergo intramolecular cycloalkylation to produce cyclopropanecarboxylic esters. This latter type of process, which has significant applications in the synthesis of cyclopropanes, has been termed a Michael Initiated Ring Closure (MIRC) by Little and Dawson.[116]

4.1. With carbon nucleophiles

4.1.1. Organometallic reagents. Various types of organometallic reagents are known to be capable of reaction with γ-haloenoates by one or more of the addition or substitution modes listed above. The MIRC product **136** was produced in a very low yield when PhMgBr was treated with methyl γ-bromocrotonate (**135**) and the ester intermediate hydrolyzed to the corresponding acid.[117] The allylic Grignard reagent **137a** reacted with **135** primarily by 1,2-



Scheme 41.



Temp/time	Products(%) 149	150
-78 °C, 2 h	55	28
-78 to 0 °C, 2 h	82	-

Scheme 42.

addition to give the tertiary alcohol **138**; the MIRC product **139** was also obtained, but in a very low yield. Allylic chloromanganese compounds have been found to promote MIRC reactions much better than the corresponding Grignard reagents.[118] For example, when the bromo ester **135** was treated with reagent **137b**, the cyclopropane derivative **139** was obtained in a high yield (Scheme 39).[118]

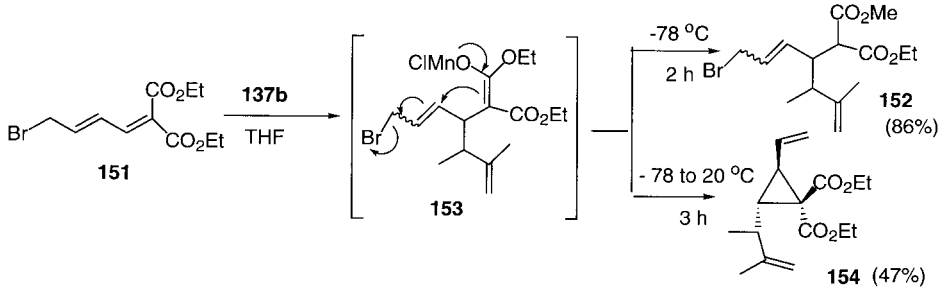
The course of the reaction of allylic chloromanganese compounds with γ-haloenoates was found to be significantly affected by the degree of substitution of the double bond of the organometallic reagent, the bulkiness of the alkoxyl group of the enoate, and the presence of alkyl groups at the α-, β-, or γ-positions of the enoate.[118] Unlike reagent **137b**, allyl manganese chloride (**140**) gave a considerable amount of the 1,2-addition product when reacted with enoate **135**. However, the use of the more hindered isopropyl ester **141** resulted in the production of a mixture of the MIRC product **142** and the direct subsitution product **143**. MIRC products were not formed at all when alkyl derivatives of ethyl γ-bromocrotonate were reacted with reagent **137b**: (1) the α-methyl compound gave a mixture of the simple 1,4-adduct and the direct substitution product; (2) the β-methyl derivative gave only the direct substitution product; and (3) the γ-*n*-pentyl derivative gave an enone resulting from the addition of 1.0 equiv. of the reagent to the carbonyl group and direct substitution at the γ-position.[118] The reactions of *n*-BuLi, PhLi and isobutenyllithium with *tert*-butyl *trans*-γ-chlorocrotonate in THF have been shown to give the corresponding *trans* 2-substituted cyclopropanecarboxylates in 22, 56 and 51% yields, respectively.[119] The bulky *tert*-butoxy groups of the enoate acceptor favored the MIRC pathway as opposed to 1,2-addition in these reactions (Scheme 40).

Because of the presence of two electron withdrawing groups on the double bond, alkylidene malonates are highly susceptible to 1,4-addition. Thus, MIRC products were obtained in high yields from reactions of γ-haloalkylidene malonates with vinyl Grignard reagents[120] and allylic manganese compounds.[118] Thus, when the chloro ester **144** was treated with 2-methyl-1-propenylmagnesium chloride a mixture of the cyclopropane derivative **145**, the dehalogenated product **146**, and the lactone **147** (another type of MIRC product) was obtained.[120] The yield of **145** was not improved by the use of bromine in place of chlorine in the substrate or by the addition of a catalytic amount of CuCl (Scheme 41).

Diethyl (2-bromobutylidine)malonate (**148**) gave the 3-ethylcyclopropane derivative **149** in 82% yield when treated with reagent **137b** at 0°C. However, if the temperature was kept low before the quenching of the reaction, the simple 1,4-adduct was also isolated, indicating that the ring closure step was somewhat slow (Scheme 42).

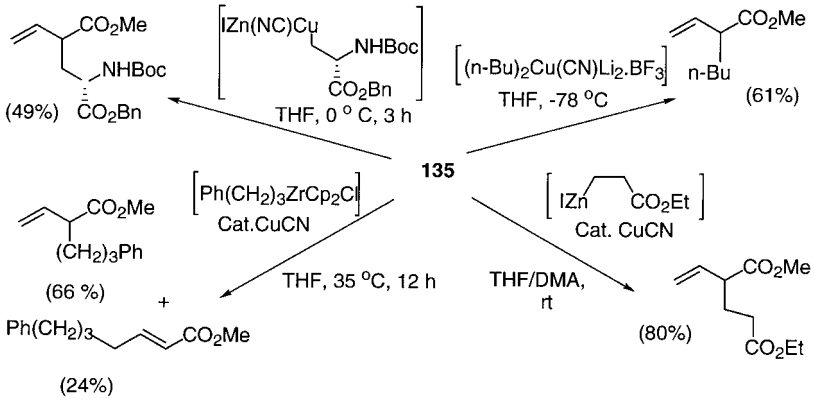
Diethyl (*trans*-4-bromo-2-butenylidine)malonate (**151**) reacted with reagent **137b** to give a 1:1 mixture of 1,4-adducts **152** at −78°C, but at higher temperature the malonate enolate intermediate **153** with a *cis* configuration of the double bond underwent cycloalkylation via an S_N2' mechanism to give the MIRC product **154**.[118] The mechanism of formation of the *cis* isomer of **153** is unclear (Scheme 43).

Several different organometallic reagents have been found to effect substitution rather than addition reactions with γ-haloenoates. A direct displacement of Br^- occurred when the copper complex **155** (prepared by the treatment of tricarbonyl-η^6-triisopropylsilylindole chromium(0) with 2.0 equiv. *n*-BuLi in TMEDA at −78°C and then addition of 1.0 equiv. of CuBr–SMe_2 at −23°C) was treated with the



Scheme 43.

Scheme 44.

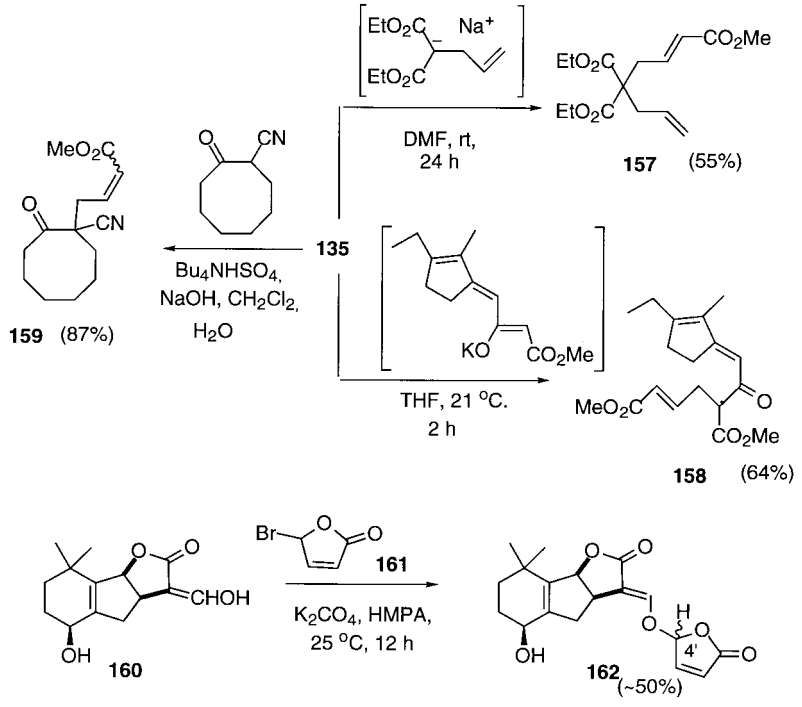


Scheme 45.

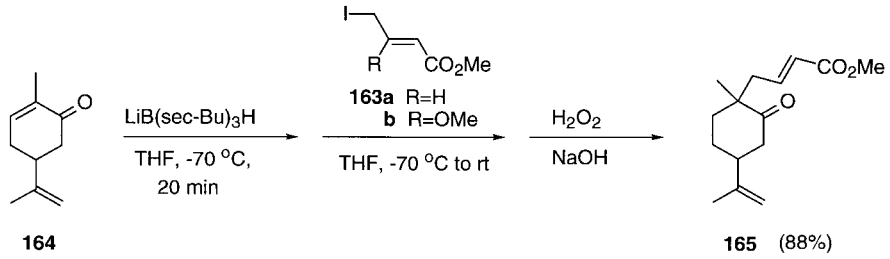
bromoenoate **135**. After decomplexation of the intermediate chromium(0) compound with air in the presence of ultraviolet light, the indole derivative **156** was obtained in approximately 35% yield (Scheme 44).[121]

As shown in the equations below, several organometallic reagents including higher order cuprates,[122] iodozinc reagents using CuCN as a catalyst,[123] stoichiometric zinc–copper reagents,[124] and alkylzirconium compounds[125] have been found to effect S_N2' displacement of the Br^- from enoate **135**. Several γ-substituted derivatives of enoate **135** also worked equally well with the higher order cuprate reagents (Scheme 45).[122]

4.1.2. Metal enolates and related reagents. Metal enolates are known to react with γ-haloenoates by direct S_N2 displacement or by MIRC processes.[126] The Michael addition step of the MIRC process is usually faster than the S_N2 reaction, but it is reversible. Therefore, in cases where the reactant enolate is more stable than the adduct ester enolate,



Scheme 46.



Scheme 47.

the concentration of the reactants may remain high enough that the slower S_N2 pathway predominates. Although a variety of factors—such as the nature of the leaving group of the electrophile, the counterion of the enolate, the solvent and the temperature—may affect the course of the reaction, it has generally been observed that enolates derived from β-diesters,[126–129] β-ketoesters,[127,130,131] hydroxymethylene lactones,[132] β-cyanoketones,[133] β-ketoamides,[134] and aliphatic ketones[135–137] react with γ-haloenoates via an S_N2 pathway. On the other hand, as will be discussed later, more basic enolates, such as those derived from esters, generally participate in MIRC reactions.

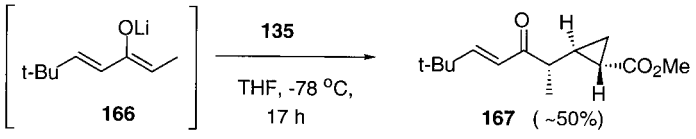
Some recent examples of reactions in which bromoenoate **135** was employed as the electrophile with the appropriate enolate to give the β-diester **157**,[128] the β-ketoester **158**,[131] and the β-cyanoketone **159**[133] are shown below. Compound **158** was an intermediate in the synthesis of a precursor of racemic gascardic acid.[131] The potassium enolate of the hydroxymethylene lactone **160** underwent O-alkylation when treated with γ-bromobutenolide **161** to give a ca. 1:1 mixture of strigol (**162**, C-4′Hβ) and its C-4′-epimer in ca. 50% yield (Scheme 46).[132]

γ-Iodoenotes such as **163** have been shown to be reactive enough in S_N2 displacements to effect regiospecific alkylations of lithium enolates of aliphatic ketones in THF in good to excellent yields.[135] The reductive alkylation of carvone (**164**) with enoate **163a** to give the derivative **165** provided an illustration of such a reaction (Scheme 47).[136,137] γ-Iodo-β-methoxyenoates such as **163b** were especially useful reagents for regiospecific alkylations of lithium enolates of cyclopentanones[138–144] and kinetic lithium dienolates of 3-ethoxycyclohexenones.[145] The presence of the β-methoxy substituent suppressed the tendency of this electrophile to undergo Michael additions. Reagent **163b** has been widely used for the synthesis of natural products and other highly fuctionalized molecules because the alkylation product contains a latent β-ketoester side chain.[138–145] The potassium enolate of isobutyraldehyde was also alkylated with methyl γ-bromo-β-methoxycrotonate.[146]

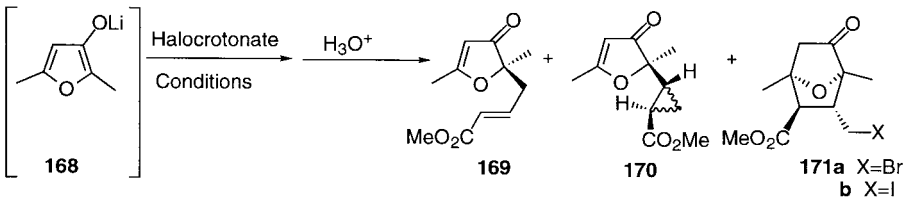
γ-Bromoenoates such as **135** would be expected to be less reactive than the corresponding iodides, e.g. **163a**, toward nucleophilic displacement. This presumably accounts for the fact that treatment of the acyclic lithium dienolate **166** with **135** led to the MIRC product **167** (which resulted from the formation of an *anti* haloenolate adduct and subsequent cyclopropanation) rather than the direct alkylation product (Scheme 48).[147]

The lithium dienolate **168** of 2,5-dimethyl-3(2*H*)-furanone provided an example of a nucleophile which exhibited trifurcate reactivity toward γ-halocrotonates.[148] In THF, the usual solvent for such reactions, dienolate **168** reacted with the bromoester **135** at −78°C to give a ca. 2:2:1 mixture of the direct substitution product **169**, a diastereomeric mixture of the MIRC products **170**, and the bromomethyl oxabicycloheptanone **171**, which presumably resulted from sequential Michael additions. At 0°C only a ca. 4:1 mixture of the two types of cyclization products was obtained, and at 25°C only the MIRC product was isolated. At −78°C it appeared that there was competition between the irreversible S_N2 and the reversible initial Michael step, which led to a mixture of the *anti* and *syn* ketoester enolate adducts **170A**. The *syn* species was capable of undergoing irreversible intramolecular cycloalkylation to give cyclopropane derivatives **170**, while the *anti* isomer of **170A** was able to undergo reversible intramolecular Michael addition to yield the bicyclic enolate **171A**. At higher temperatures the two possible cyclization modes of **170A** appeared to be fast enough to compete effectively with its reconversion to the reactants. This could explain why **169** was not produced at higher temperatures. Also, as was confirmed by a control experiment, the bicyclic enolate **171A** was capable of undergoing a retro-Michael addition to give the *anti* isomer of **170A**, which cyclized irreversibly to the *anti* isomer of cyclopropane **170** (Scheme 49).

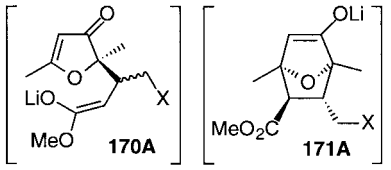
The results of previous studies, which will be described below, on the effect of solvent polarity on the course of the reactions of ester enolates with enoate **135**[126] led to an investigation of such a change in conditions on the reactions of dienolate **168**.[148] An increase in the polarity of the solvent by the introduction of the polar additive *N*,*N*′-dimethylpropyleneurea (DMPU) to the THF solution of



Scheme 48.



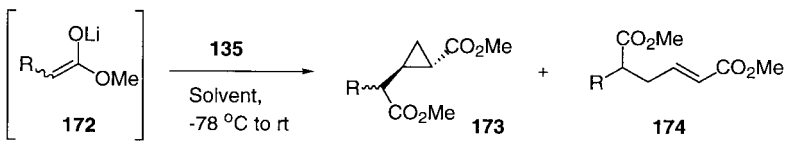
Halocrotonate	Conditions	Product Ratio(%)		
135	THF,-78 °C, 7 h	40	41	18
	THF, 0 °C, 1 h	-	82	18
	THF, 25 °C, 12 h	-	100	-
	THF+4.0 equiv. DMPU, -78 °C, 7 h	84	11	6
	3:1 THF:Cyclohexane -78 °C, 7 h	-	3	97
163a	THF, -78 to -40 °C, 1.5 h	95	5	-
	3:1 THF:Cyclohexane -78 °C, 7.0 h	8	5	88



Scheme 49.

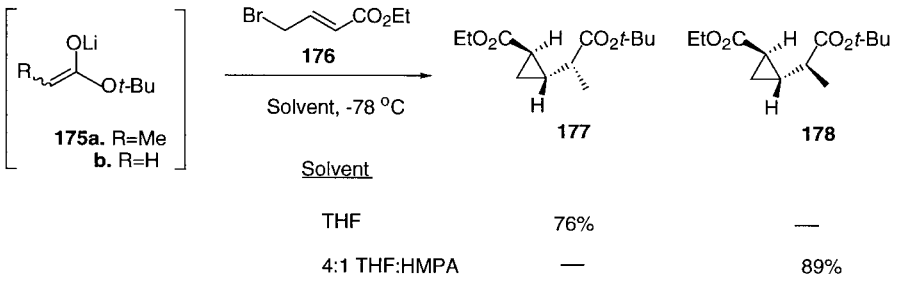
168 at −78°C gave a reaction mixture in which the simple alkylation product **169** was by far the major product. Under these conditions the stability of the initial Michael adduct would have been reduced because of less effective lithium chelation of the ester enolate and the furanone carbonyl oxygen. Thus the initial Michael step must have been sufficiently reversible to allow the S_N2 process to become much more important. On the other hand, the addition of the nonpolar solvent cyclohexane to the enolate solution before treating it with the electrophile was expected to increase the stability of **170A** by chelation. Under these conditions the bicyclic product **171a** was formed almost exclusively, indicating that the intramolecular Michael addition of **170A** was faster than the intramolecular cycloalkylation.

When the iodocrotonate **163a** was used as the electrophile, the direct S_N2 displacement of the iodide by the dienolate **168** to give **169** was the major reaction pathway, even in THF at low temperature. However, in the less polar medium, the sequential Michael process to form the bicylic iodomethyl compound **171b** was significantly favored. Although a sequential Michael addition pathway for the formation of **171a**,**b** has been suggested, a nonsynchronous one-step Diels–Alder reaction pathway has not been excluded.



Reactant	Solvent	Product Yields (%) 173	174
a. R=H	THF	37	-
b. R=CH_2CH_2Ph	THF	54	-
	20:1 THF:HMPA	54	10
c. R=Ph	THF	48	14
	20:1 THF:HMPA	-	66

Scheme 50.



Scheme 51.

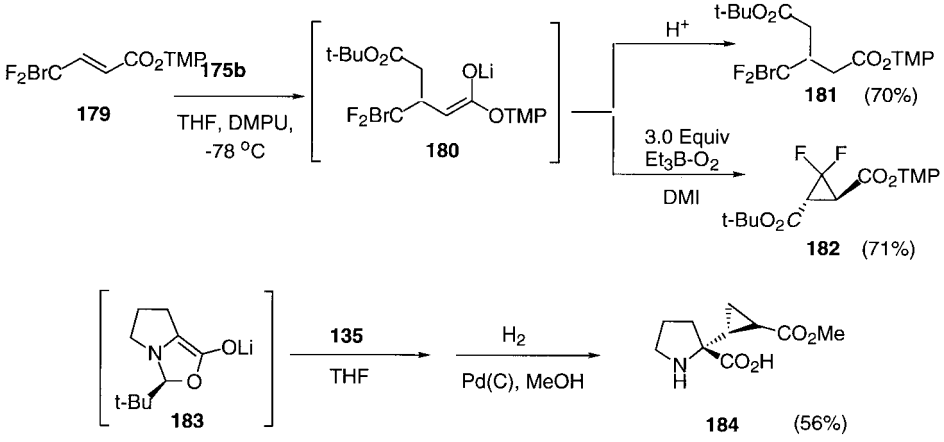
Lithium enolates of acetates and other α-alkyl-substituted esters are more reactive than the related ketone enolates. This feature, coupled with the favorable chelation of the initial Michael adduct, caused these nucleophiles to trigger MIRC reactions when treated with γ-haloenotes in THF solution.[126] For example, the lithium enolates of methyl acetate (**172a**) and methyl γ-phenylbutyrate (**172b**) gave only the MIRC products **173a** and **173b**, respectively, when reacted with enoate **135** in THF solution. α-Phenyl-substituted enolates such as **172c**, which are somewhat more stable than their α-alkyl-substituted counterparts, also reacted with enoate **135** to give primarily the MIRC products, e.g. **173c**. However, the direct S_N2 displacement product **174c** was also obtained in low yield. The use of a 20:1 mixture of THF/HMPA as the solvent had a significant effect upon the course of the reaction and the only product obtained under these conditions was the direct displacement product **174c**. The decrease in the stability of the Michael adduct and consequent reduction of the equilibrium constant for the Michael addition brought about by the more polar solvent allowed the irreversible S_N2 reaction to become the predominant process.[126] The stereochemistry of the cyclopropanes **173b** and **173c** was not determined, but the substituents on the ring were presumbly *trans* as indicated (Scheme 50).

trans-Cyclopropanes containing an extra chiral center have been obtained by the use of lithium enolates of propionate esters, such as **175a**, in MIRC processes with ethyl γ-bromocrotonate (**176**).[149] The stereochemical outcome of these reactions was strongly influenced by the solvent. Thus, the *E*-enolate (*E*)-**175a** obtained by deprotonation of the ester with LDA in THF gave the *syn* product **177** in 76% yield, while either (*E*)-**175a** or (*Z*)-**175a** reacted with **176** in a ca. 4:1 mixture of THF/HMPA to give the *anti* product **178** in 89% yield (Scheme 51).

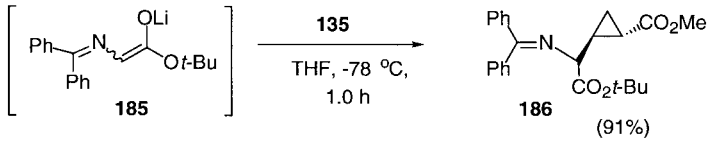
Lithium *Z*-enolates of α-methylaminoacetates have been shown to give *trans*-cyclopropanes with *anti* stereoselectivity upon reaction with bromocrotonate **135**.[150] On the other hand, lithium enolates of the corresponding amides (dimethylamino or pyrrolidino) showed *syn* stereoselectivity. Lithium enolates of both α-dialkylaminoacetates and amides showed *syn* stereoselectivites upon reaction with **135**.

2,4,6-Trimethylphenoxy (TMP)-γ-bromo-γ,γ-difluorocrotonate (**179**) was found to behave as a Michael acceptor for the lithium enolate of *tert*-butyl acetate (**175b**) in THF at −78°C.[151] The enolate adduct **180** did not undergo intramolecular cyclopropanation under these conditions and only the bromodifluorodiester **181** was formed upon workup of the reaction mixture. However, when enolate **180** was treated with $Et_3B–O_2$ and 10 vol.% of 1,3-dimethyl-2-imidazolidinone (DMI) was added, ring closure occurred to give the *gem*-difluorocyclopropane **182** in 71% yield along with a small amount of the simple adduct **181**. The lithium enolate **183**, derived from an optically pure proline derivative by treatment with LDA, gave the MIRC product **184** in 56% yield when treated with bromoester **135** in THF followed by hydrogenolysis of the *N*,*O*-acetal (Scheme 52).[152]

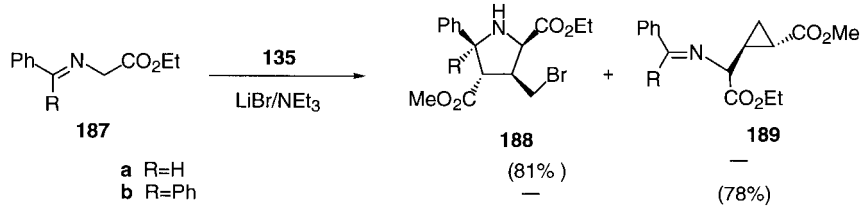
Lithium enolates of imine derivatives of α-aminoesters generally showed similar behavior to ordinary ester enolates in reactions with γ-haloenoates.[153–155] When THF was used



Scheme 52.



Scheme 53.



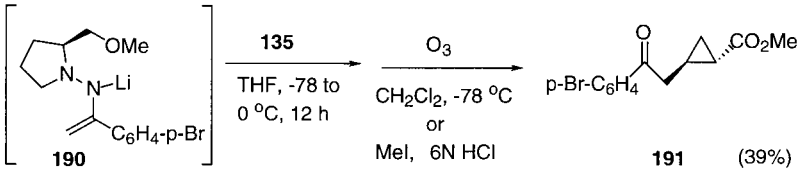
Scheme 54.

as the solvent for reactions of these species with bromoenoate **135**, MIRC products were observed, but direct substitution products were obtained when THF/HMPA mixtures were used under the same conditions.[153] As indicated by the reaction of the glycine-derived enolate **185** with the electrophile **135** to give the cyclopropyl glycinate **186**, these MIRC reactions normally occurred with complete diastereoselectivity. Chelation of the metal cation between the donor and acceptor carbonyl oxygen atoms in the transition state for the initial Michael addition provided an explanation for these results (Scheme 53).[154] When the γ,γ-dimethyl derivative of **135** was employed as the electrophile, an α-substituted ester arising from an S_N2' reaction was isolated.

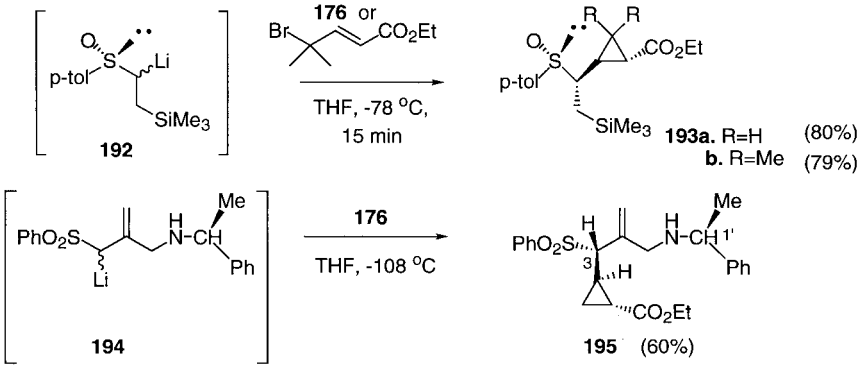
The degree of substitution of the imine double bond has been shown to influence the course of the reactions of imine glycinate enolates with compound **135**.[155] Thus, the benzaldehyde-derived compound **187a** gave the 1,3-dipolar cycloadduct **188** in a high yield when treated with enoate **135** using $LiBr/Et_3N$ as the base, but the more usual MIRC product **189** was also obtained in good yield when the benzophenone-derived glycinate **187b** was employed under the same conditions. It was suggested that the presence of a second Ph group in this compound created enough steric hindrance to prevent the occurrence of the 1,3-dipolar cycloaddition (Scheme 54).[155]

An MIRC reaction occurred with high diastereo- and enantioselectivity to give the (1*S*,2*R*)-bromophenacylcyclopropanecarboxylate **191** when the lithiated SAMP-hydrazone **190** was treated with bromoenoate **135** in THF and the product hydrazone cleaved by reaction with ozone or MeI followed by HCl (Scheme 55).[156,157]

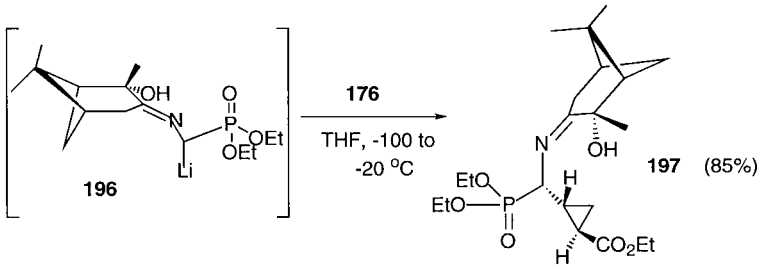
Like ester enolates, α-lithiated sulfones, sulfoxides and sulfides are highly reactive and undergo MIRC reactions with γ-haloenoates.[158–160] Cyclopropanecarboxylates such as **193** have been obtained with high stereoselectivity using the chiral lithiated sulfoxide **192** as the nucleophile



Scheme 55.



Scheme 56.



Scheme 57.

in reaction with bromeonoate **176** or its γ,γ-dimethyl derivative.[159] Note that the result of the reaction of the latter enoate was different from that of the corresponding methyl γ,γ-dimethyl-substituted ester with the ester enolate **185**, where an S_N2' reaction occurred. The remote chiral auxiliary in the allylic sulfone **194** also promoted asymmetric induction in an MIRC reaction with electrophile **176**, and the (3*S*,1′*S*) diastereomer **195** was favored over the (3*R*,1′*S*) isomer by a 9:1 ratio.[160] Chelation of the carbonyl group of the Michael acceptor to the lithium cation bridging a sulfone oxygen, the nitrogen atom of the amino group, and the Ph ring of the Michael donor was proposed to account for the stereoselectivity of the reaction (Scheme 56).

An MIRC reaction of the chiral lithiated phosphonoglycine equivalent **196** with the bromocrotonate **176** gave the cyclopropanecarboxylate **197** in 85% yield.[161] This product was converted into (2*S*,3*R*,4*R*)-ethoxycarbonylcyclopropyl phosphonoglycine in two steps (Scheme 57).

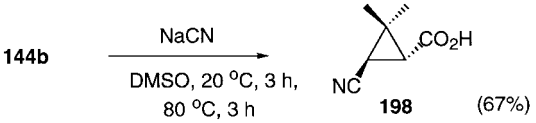
γ,γ-Disubstituted γ-bromoalkylidene malonates, which are excellent Michael acceptors and not prone to displacement of the halogen atom, have been shown to give *gem*-disubstituted cyclopropanecarboxylates when treated with KCN or NaCN in MeOH[162–164] or DMSO,[165] respectively. For example, the bromoendioate **144b** was converted into the cyanocyclopropanecarboxylic acid **198** in 67% yield by an MIRC reaction with excess NaCN in DMSO, followed by heating at 80°C to effect hydrolysis and decarboxylation (Scheme 58). Compound **198** is a precursor to the pyrethoid insecticide chrysanthemic acid. Under phase transfer conditions γ-bromocrotonates and γ-bromoalkylidene malonates have been converted into tribromomethyl cyclopropane derivatives by MIRC reactions triggered by Br_3C^-.[166]

4.2. With heteroatom nucleophiles

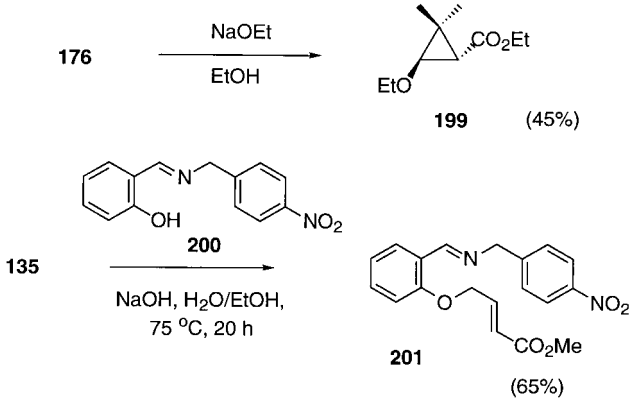
Enoates containing primary γ-halides such as **176** have been shown to undergo cyclopropanation reactions upon treatment with metal alkoxides.[167] For example, compound **176** reacted with NaOEt in EtOH to give *trans*-2-ethoxycyclopropanecarboxylate (**199**) in 45% yield. The diethoxy ester resulting from both S_N2 displacement of the bromide and conjugate addition was also isolated in 6% yield. Several groups have shown that less basic phenoxide ions participate in direct S_N2 reactions with γ-bromocrotonates such as **135** and **176**.[168–174] The treatment of haloenoate **135** with the phenol **200** in the presence of NaOH provided the phenyl ether **201** in a 65% yield (Scheme 59).[168]

As, expected, γ-haloalkylidene malonates such as **144b** have been found to undergo MIRC reactions with both alkoxides and phenoxides.[162,164,175] Examples of these reactions using MeOH or ether as the solvent are shown below.[164] Note that the initially formed methoxycyclopropane **202a** underwent opening of the cyclopropane ring to give the dimethoxy acetal **203** in the presence of 2.0 equiv. of NaOMe. Also, acetal **203** was formed in MeOH to a small extent when NaOPh was used as the base. However, compounds **202a** and **202b** were formed exclusively when NaOMe and NaOPh were reacted with **144b** in ether (Scheme 60). Walborsky and Topolski have proposed that, in MIRC reactions of this type, the closure of the cyclopropane ring—which required intramolecular substitution of a tertiary bromide—took place by a single electron transfer process.[175]

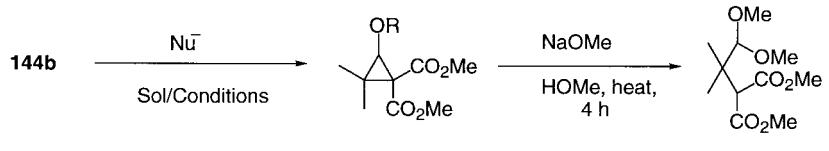
Chloroenoate **204**, which contains both a ketone and an ester activating group, underwent an MIRC reaction to give the cyclopropane derivative **205** upon treatment with 1.0 equiv. NaOMe at 0°C.[164] Upon being heated in MeOH at reflux, **205** underwent rearrangement to the dihydrofuran derivative **206**. Treatment of **204** with 2.0 equiv. of NaOMe in DME gave a 90:10 mixture of the cyclopropane derivative **207** and the dihydrofuran derivative **208**. The former compound apparently arose via deacetylation of the



Scheme 58.



Scheme 59.



202a. R=Me
b. R=Ph

203

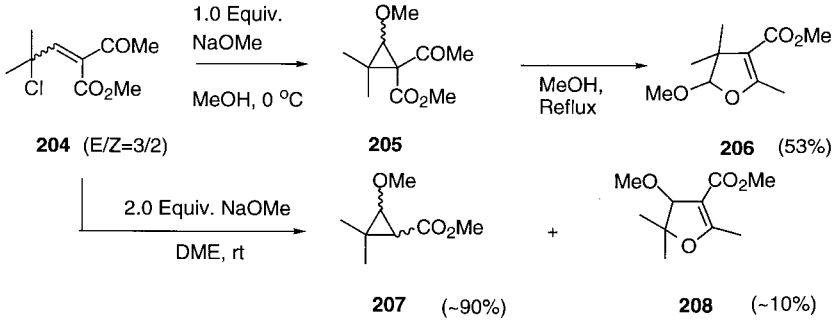
Nu⁻	Sol/Conditions	Products (%) 202	203
–	HOMe, Reflux, 2 h	100	–
2.0 Equiv, NaOMe	HOMe/Reflux, 4 h	–	100
1.0 Equiv. NaOMe	Ether, 12 h, rt	100	–
NaOPh	HOMe, Reflux, 2h	80	20
NaOPh	Ether, 12 h, rt	100	–

Scheme 60.

expected MIRC product, while the latter was probably generated by intramolecular *O*-alkylation rather than *C*-alkylation of the intermediate chloroenolate precursor of **207** (Scheme 61).

Weakly basic alkyl thiolates have been shown to undergo competitive MIRC and S_N2 displacement processes with haloenoates such as **135**.[116,176–178] In early studies with thiolate anions, Little and Dawson[116,176] found that one process or the other can be favored by the appropriate choice of the M^+ counterion and the solvent. As shown below, the use of Li^+ and solvents of low polarity (e.g. THF) favored the MIRC pathway to yield cyclopropanes such as **209**, while larger metal cations (e.g. K^+ or Na^+) or dipolar aprotic solvents favored direct displacement to give alkylthioenoates such as **210** or its deconjugated isomer **211**. Under the former conditions, where it would be expected to be strongly coordinated with the metal cation, the closure of the three-membered ring of the adduct ester enolate must have been faster than its reversion to the reactants, even though its concentration remained low. However, under the latter conditions the adduct enolate must have reverted to the reactants rapidly enough in comparison with the ring closure step that the direct S_N2 step became product-controlling. As expected, halodienoates such as **144b** gave exclusively MIRC products when treated with alkyl- or phenylthiolates in HOMe at room temperature (Scheme 62).[164]

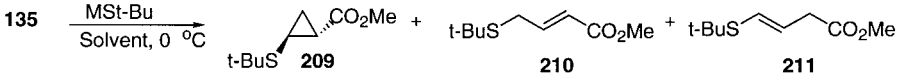
Use of the chiral γ-bromocrotonate ester derived from 10-dicyclohexylsulfamoyl-D-isoborneol as the acceptor in Michael reactions with Li*S*t-Bu in THF at ca. −70°C provided the MIRC product in 72–78% yield with 50–60% d.e.[177] The opposite diastereomer was produced in up to 33% d.e. if the reaction was run at higher temperatures. It was suggested that these results could be accounted for if



204 (E/Z=3/2) **205** **206** (53%)

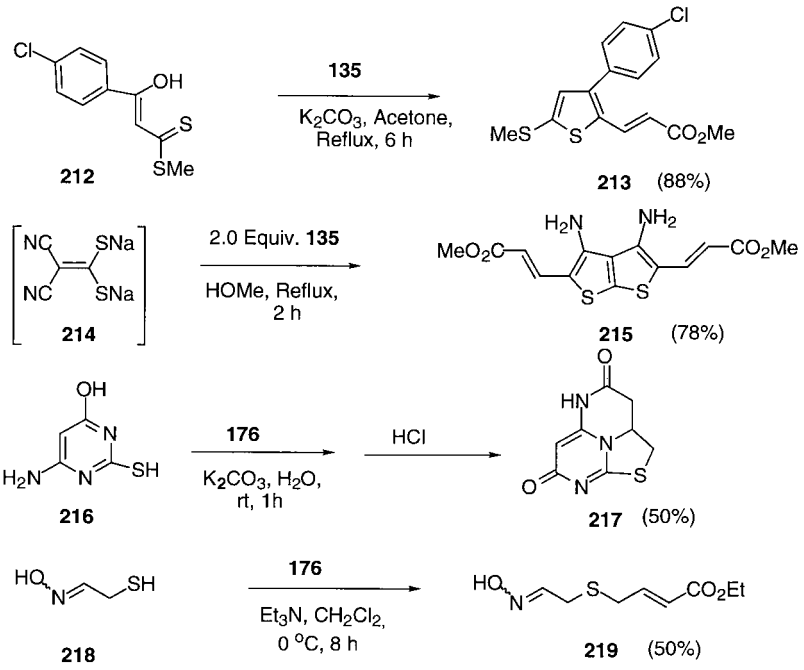
207 (~90%) **208** (~10%)

Scheme 61.



M	Solvent	Products (%) 209	210	211
Li	THF	65-85	15-35	–
K	THF	–	>90	–
Li	DME	–	80	20

Scheme 62.

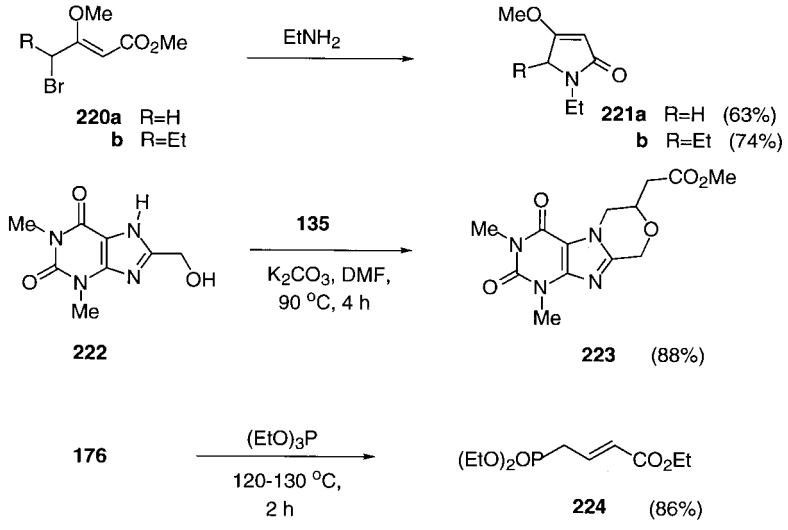


Scheme 63.

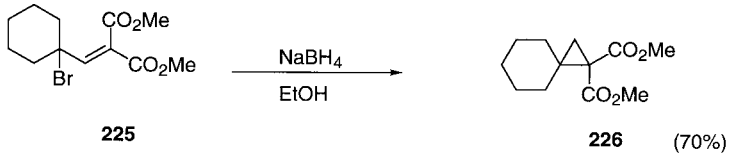
both the *s-cis* and *s-trans* conformers of the haloenoate were present in equilibrium, and if lowering the temperature shifted the equilibrium in favor of one of these conformers.[177]

The reported syntheses of the heterocyclic compounds **213**,[179] **215**,[180] and **217**[181] involved the direct displacement of Br^- from γ-bromoenoates such as **135** and **176** by a thio anion as the initial step. Mercaptoacetaldehyde oxime (**218**) was also reacted with enoate **176** in the presence of Et_3N to give the substitution product **219**.[182] Neutral sulfides such as dimethyl sulfide and methyl alkyl sulfides have been found to provide γ-thiomethyl- or γ-thioalkylcrotonates upon heating with enoates such as **176**.[183] These conversions involved the formation of a sulfonium bromide intermediate which lost MeBr upon heating (Scheme 63).

Benzylamine[184,185] and aromatic amines[174,186,187] (especially under Cu(0)/$Cu(ClO_4)_2$ catalysis) have been found to effect S_N2 displacement of Br^- from γ-bromocrotonates **135** or **176**. The bromomalonate **144b** has also been shown to react rapidly with primary and secondary amines.[188] Methoxypyrrolinones such as **221** have been prepared from methyl γ-bromo-β-methoxycrotonates **220** (or the corresponding ethyl esters) through displacement of Br^- by primary amines, followed by the lactamization of the γ-aminoester intermediates.[189] Lithium amides such as LDA have been shown to effect deprotonation rather than substitution or MIRC reactions of enoate **135**,[116] but a variety of anionic nitrogen nucleophiles, generated by reactions of the corresponding amino compounds with K_2CO_3, have been found to undergo simple alkylation when treated with **135** or the corresponding ethyl ester **176**. For example,

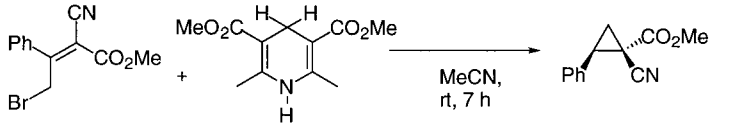


Scheme 64.



225 226 (70%)

Scheme 65.



228 227 229 (90%)

Scheme 66.

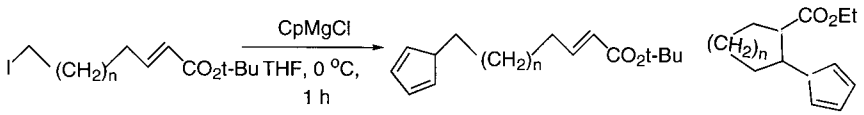
alkylations of 1,2,3,4-tetrahydroisoquinoline with **135**[190] and 2-pyridone with **176**[191] proceeded in 80 and 69% yields, respectively. Also, alkylation of 8-(hydroxymethyl)theophylline (**222**) with **135**, followed by intramolecular conjugate addition of the hydroxyl group to the enoate double bond, was found to give the tricyclic ester **223** in 88% yield.[192] Sodium succimide[193] and sodium azide[194] have been used as nucleophiles in the displacement of Br^- from enoate **222a** and its ethyl ester derivative. By a reaction with $(EtO)_3P$, γ-bromocrotonate **176** has been converted into the triethyl phosphonate (**224**) in 88% yield.[195] The β-methyl and β-methoxy derivatives of **224** have also been synthesized in a similar manner using the corresponding β-methyl[196] and β-methoxy[197] derivatives of **176**. Methyl γ-bromo-β-methylcrotonate as well as compound **176** have been converted into the corresponding phosphonium[198] and arsonium[199] salts by treatment with Ph_3P and Ph_3As, respectively. The conversion of these salts into the corresponding ylides, followed by reaction with various saturated and unsaturated carbonyl compounds, allowed the synthesis of the corresponding alkadienoic and trienoic esters (Scheme 64).

Hydride donors such as $NaBH_4$ have been found to cause MIRC reactions of γ-disubstituted alkylidene malonates such as **225** to give spiro products such as **226**.[200] The related alkylidene acetoacetates underwent cyclopropanation and reduction of the ketone carbonyl group under the same conditions.[200] $LiAlH_4$ effected cyclopropanation as well as reduction of the ester group of such compounds (Scheme 65).[201]

Hantzseh esters such as **227**, which are analogs of NAD(P)H, have been used to trigger an MIRC reaction by the donation of H^- to the β-carbon of ethyl (*Z*)-β-bromomethyl-α-cyanocinnamate (**228**).[202] The cyclopropane derivative **229** was obtained in 90% yield (Scheme 66).

5. Reactions of conjugated ω-haloenoates with nucleophiles

As is the case for γ-haloenoates, the related ω-halosystems have been shown to undergo S_N2 displacement and/or MIRC reactions, depending upon the nucleophilic reagent, the counterion and other reation conditions. Additionally, when the conjugate acid of a carbon nucleophile contains two acidic hydrogens, sequential alkylation–Michael addition reactions have been reported to take place to lead to carbocyclic compounds.[2] Primary amino compounds have been found to participate in similar reactions to yield nitrogen-containing heterocycles.[2,81] The MIRC and sequential alkylation–Michael addition processes have generally been used to prepare five-, six-, and seven-membered ring systems. The rates of closure of such rings have been found to be slower than those of three-membered rings in MIRC reactions of γ-haloenoates. A number of studies have led to the general conclusion that the pK_a of the conjugate acid of the nucleophile is of major importance in determining whether substitution or Michael addition occurs initially: nucleophiles with conjugate acids having a $pK_a < 16$ generally effect substitutions (which may be followed by intramolecular Michael reactions), while

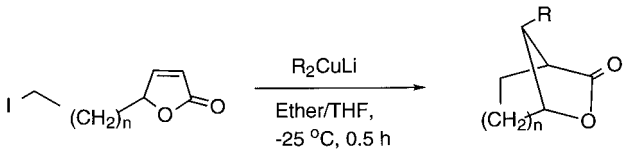


230 231 232

Products (%)

n	231	232
0	78	22
1	86	14
2	91	9

Scheme 67.



n	R	Product **234** (%)
1	Me	41
1	n-Bu	77
1	Ph	81
2	Ph	53

Scheme 68.

those with conjugate acids having a pK_a>16 generally lead to MIRC reaction products.[116,203,204]

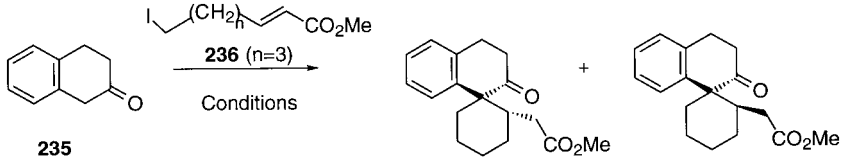
5.1. With carbon nucleophiles

5.1.1. Organometallic reagents. Stille and Grubbs have investigated the reactions of *tert*-butyl ω-iodoenoates such as **230** with CpMgCl.[205] The ratios of the substitution products **231** to the MIRC products **232** were determined by effecting subsequent intramolecular Diels–Alder reactions of the resulting ω-Cp enoates. For convenience, only the 1-alkyl-2,4-diene structures of both types of products are illustrated. However, in both cases these compounds underwent rearrangements to mixtures of the corresponding more substituted 1- and 2-alkyl-1,3-dienes under the initial reaction conditions, or during subsequent treatment to effect the intramolecular Diels–Alder reaction.[205] With the cyclopentadienyl nucleophile with a pK_a=16, the substitution process was significantly favored over the MIRC reaction (Scheme 67). Cuprate-induced MIRC reactions of butenolides such as **233** containing iodoalkyl groups at the γ-position have been used to synthesize oxabicycloheptanone **234** (n=1) and oxabicyclooctanone **234** (n=2) (Scheme 68).[206]

5.1.2. Metal enolates and related reagents. Relatively acidic carbonyl compounds have been found to react with ω-haloenoates such as methyl 7-iodo-2-heptenoate (**236**) (n=3) in the presence of excess Cs_2CO_3 to give spiro ketone derivatives via sequential alkylation–Michael processes.[203,204] Initial research by d'Angelo and coworkers led to synthesis of the spirocyclic homoerythrina alkaloid ring skeleton precursor **237** by reaction of 2-tetralone (**235**) with **236** (n=3).[203] When the same reagents were employed using NaH as the base, a ca. 50:50 mixture of **237** and its diastereomer **238** was obtained in ca. 68% yield. The Cs_2CO_3-catalyzed intramolecuar Michael addition step was found to occur under kinetic control. Its stereoselectivity was believed to result from the participation of Cs^+ counterion in chelation of the carbonyl group of the enoate acceptor side chain and the tetralone enolate donor in an eight-membered ring transition state for the ring closure step.[207,208] Later, Desmaele and Louvet reported that CsO*t*-Bu effected a similar reaction between **236** (n=3) and the 6,7-dimethoxy derivative of **235** in 80% yield (Scheme 69).[204]

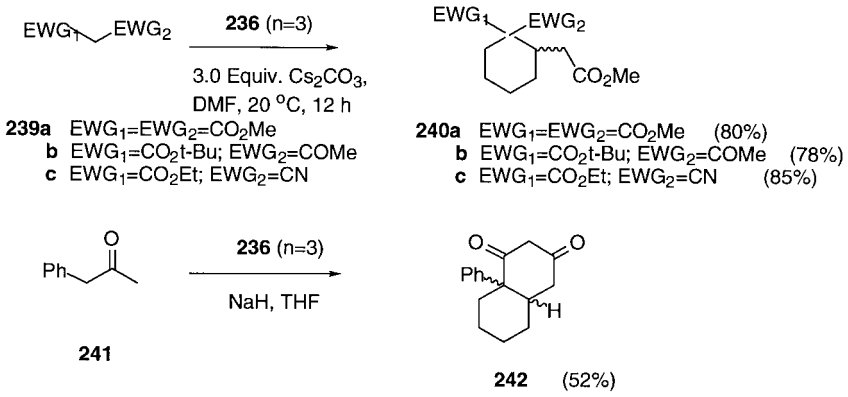
Also, using Cs_2CO_3 as the base, it was shown that dimethyl malonate (**239a**), *tert*-butyl acetoacetate (**239b**), and ethyl cyanoacetate (**239c**) gave the cyclohexane derivatives **240a–c** in good yields on reaction with iodoenoate **236** (n=3).[204] The Cs^+ salt of nitromethane also triggered an alkylation–Michael addition upon reaction with **236** (n=3).[204] In the presence of Cs_2CO_3, the less acidic phenylacetone (**241**), as well as acetylacetone and 1,3-cyclohexadione, underwent alkylation, but not a subsequent Michael addition step, with enoate **236** (n=3). However, NaH effected a reaction between **241** and **236** (n=3) to produce the bicyclic diketone **242** in 52% yield. This compound was formed by an alkylation followed by a sequential Michael addition and Claisen–Schmidt condensation (Scheme 70).[204]

Reactions involving simple acyclic aliphatic ketone enolates and ω-haloenoates do not appear to have been reported in the literature. However, Li^+ anions of chiral hydrazones[156,157] and Li^+ enolates of esters,[149] which are both more basic than the anionic nucleophiles discussed above, have been shown to participate in MIRC reactions with these electrophiles. Enders and coworkers have reported reactions which proceeded with excellent diastereo- and enantioselectivities using SAMP- and RAMP-hydrazones.[156,157] For example, the conversion with LDA of the SAMP-hydrazone **243** into its anion, followed by addition of methyl (*E*)-7-bromo-2-heptenoate (**244**), yielded the MIRC product **245**. After oxidative cleavage of the hydrazone, the *trans*-(1*S*,2*R*)-ketoester **246** was

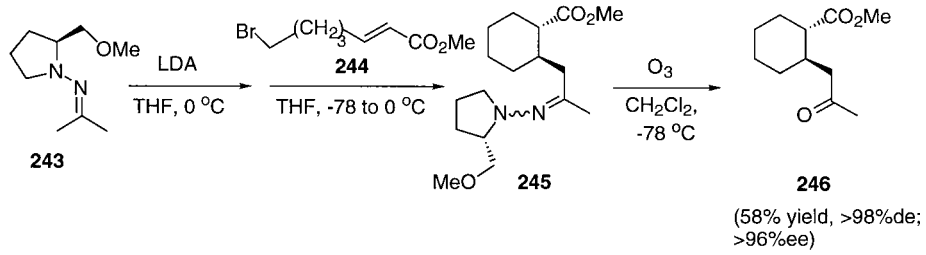


Conditions	Products (%)	
3.0 Equiv. Cs_2CO_3, DMF, 20 °C, 12 h	66%	-
NaH, THF, 20 °C, 12 h	~34%	~34%

Scheme 69.



Scheme 70.

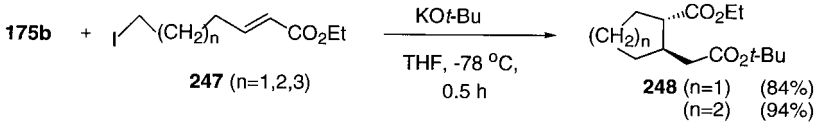


Scheme 71.

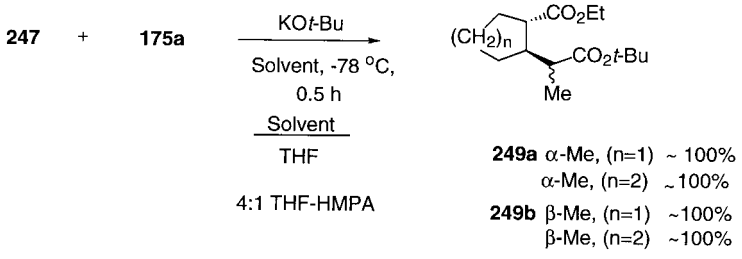
obtained in 58% yield with >95% diastereo- and enantioselective excess. As noted earlier, this method was applicable to the synthesis of optically active cyclopropane derivatives such as **191**. *trans*-(1*S*,2*S*)-Ketoesters containing cyclopentane and, in lower yields, cycloheptane rings were also available by this methodology. In addition, the corresponding *trans*-(1*R*,2*S*) diastereomers could be obtained by using the *Z*-isomer of enoate **244** (Scheme 71).

E-ω-Iodoenoates such as **247** show similar behavior to the corresponding γ-haloenoates upon reaction with Li^+ enolates of esters.[149] For example, enolate **175b** reacted with iodoenoates such as **247** (*n*=1, 2) to produce the corresponding *trans*-cyclopentane **248** (*n*=1) and cyclohexane **248** (*n*=2) derivatives in good yields. The addition of 1.0 equiv. of KO*t*-Bu was required to cause efficient completion of the cyclization step.[149] Using the corresponding octenoate **247** (*n*=3), much lower yields were observed, even under high dilution and vigorous reaction conditions (Scheme 72).

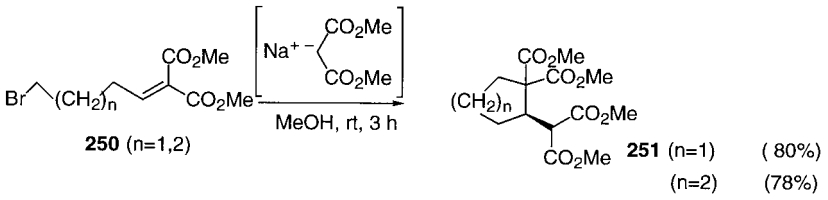
As was observed for γ-bromoenoates such as **176**, when propionate enolates, e.g. **175a**, were employed in reactions with acceptors such as **247**, the stereochemistry at the chiral center of the exocyclic side chain could be easily altered by the choice of the solvent. Thus, when the enolates were prepared and reacted in THF alone, *syn* isomers such as **249a** were obtained with >15:1 stereoselectivity in nearly quantitative yields. However, when 4:1 THF/HMPA was employed as the solvent, the corresponding *anti* isomers



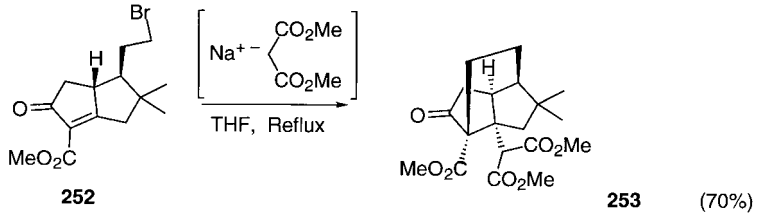
Scheme 72.



Scheme 73.



Scheme 74.



Scheme 75.

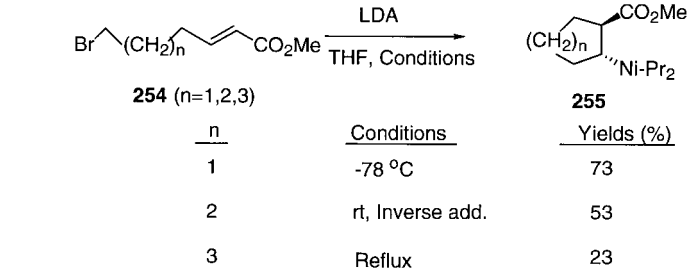
249b were formed in similar yields and levels of diastereoselectivity (Scheme 73).

When electron withdrawing substituents are present at the α-positions of ω-haloenoates, the equilibrium for the Michael addition of nucleophiles becomes more favorable for MIRC reactions, and they have been reported to occur with weakly basic nucleophiles such as malonate enolates and CN^-. The reactions of ω-bromoalkylidene malonates such as **250** (*n*=1,2) with dimethyl sodiomalonate in MeOH gave the cyclopentane **251** (*n*=1) and the cyclohexane triesters **251** (*n*=2) in good yields. KCN was also found to effect MIRC reactions of **250** (*n*=1, 2) in 73–80% yields under similar conditions (Scheme 74).[209]

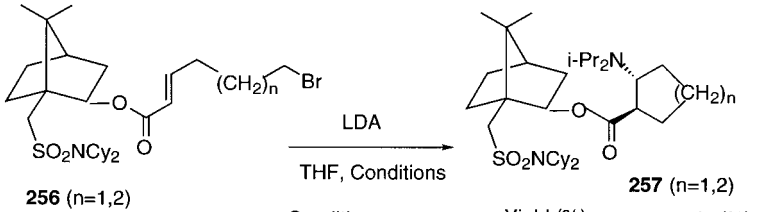
In a novel early experiment that made use of an MIRC reaction, the bromoenoate **252**, containing a carbonyl group at the α-position, was converted into the tricyclic keto triester **253** in 70% yield upon reaction with dimethyl sodiomalonate in THF.[210] This reaction was interpreted as proceeding via epimerization at the bridgehead γ-position prior to attack of the nucleophile from the side of the molecule opposite the bromoethyl side chain (Scheme 75).

5.2. With heteroatom nucleophiles

LDA, well known for its property as a strong base, was one of the first anionic compounds shown to be capable of inducing MIRC reactions with appropriate haloenoates.[116]

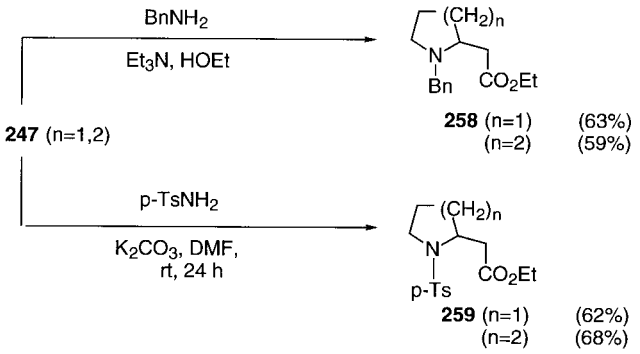


n	Conditions	Yields (%)
1	-78 °C	73
2	rt, Inverse add.	53
3	Reflux	23



n	Conditions	Yield (%)	de (%)
1	Inverse add., -68 to -72 °C. 4.3 h	62-64	60-62
2	Inverse add., -68 °C to rt	70-78	~95

Scheme 76.



Scheme 77.

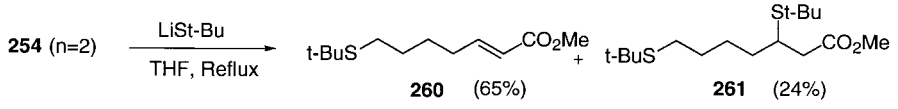
It was shown by Little and Dawson to provide *trans*-cycloalkane aminoesters **255** (n=1, 2, 3) upon reaction with the corresponding ω-bromoenoates **254** (n=1, 2, 3).[116] The yields were fair to good for the cyclopentane and cyclohexane derivatives but, presumably for entropic reasons, the cycloheptane derivative was obtained only in a very low yield. An attempt to form a cyclobutane derivative by using **254** (n=0) as the acceptor led only to the dienoate resulting from β-elimination of HBr. An attempt to use the less reactive chloroenoate corresponding to **254** (n=1) as the acceptor in a reaction with LDA led to a mixture containing 44% of the MIRC product **255** (n=1) and 30% of methyl *trans*-β-cyclopropylacrylate.[116] Upon reaction of chiral bromoenoates such as **256** (n=1, 2) with LDA, the MIRC reaction took place with asymmetric induction to give aminoesters **257** (n=1, 2) (Scheme 76).[177]

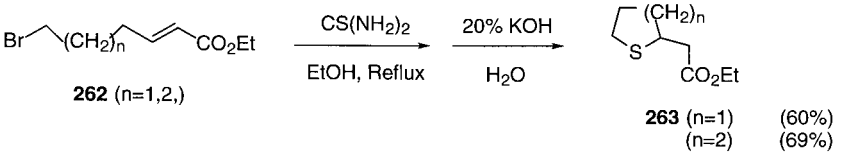
In contrast to amide ions, amines themselves have been found to participate in sequential alkylation–Michael addition reactions with ω-haloenoates.[81,211] For example, iodoenoates **247** (n=1, 2) were shown to react with n-$BuNH_2$ to give the corresponding heterocyclic compounds **258** (n=1, 2).[211] Also, $TsNH_2$, which forms a weakly basic anion in the presence of K_2CO_3, participated in similar reactions to give the pyrrolidine and piperidene derivatives **259** (n=1) and **259** (n=2) (Scheme 77).[212]

As discussed above, γ-haloenoates undergo MIRC reactions with Li^+ thiolates,[116,176] but ω-haloenoates primarily undergo substitution with these nucleophiles.[116] The reported conversion of the bromoenoate **254** (n=2) into a mixture of the substitution product **260** and the substitution-plus-conjugate-addition product **261** provided a typical example of this behavior.[116] Although reversible conjugate addition of the thiolate ion to the acceptor probably still occurred, the slower rate of closure of the six-membered ring compared with that of the three-membered ring caused the substitution process to be greatly favored. Sulfur heterocycles such as **263** (n=1, 2) have been prepared by reactions of bromoenoates **262** (n=1, 2) with thiourea followed by base-promoted hydrolysis of the isothiouronium salt intermediates (Scheme 78).[211]

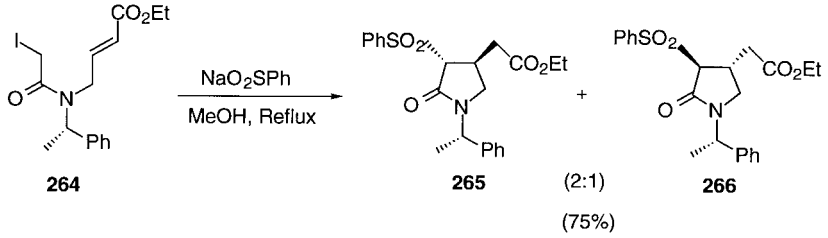
The highly functionalized iodoenoate **264** was shown to react with 2.0 equiv. $Na^+O_2SPh^-$ to give a 2:1 mixture of the pyrrolidinones **265** and **266** in 75% yield.[213] This reaction involved the substitution of the I^- by O_2SPh^- followed by O_2SPh^--catalyzed intramolecular Michael addition of the amidosulfone intermediate (Scheme 79).

As expected, activated bromoenoates such as **250** (n=1, 2) have been found to undergo MIRC reactions with Na^+ or Li*S*t-Bu to give the corresponding thiocyclopentane **267** (n=1) and cyclohexane derivatives **267** (n=2).[213] MIRC reactions of **250** (n=1, 2) involving H^- as the nucleophile have been effected with L-Selectride in THF at 0°C (Scheme 80).[209,214]

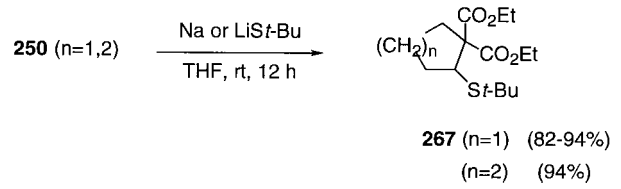




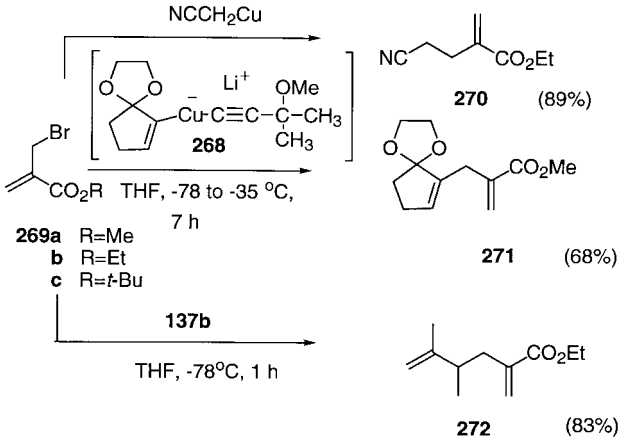
Scheme 78.



Scheme 79.



Scheme 80.



Scheme 81.

6. Reactions of conjugated α-halomethyl(alkyl)enoates

α-Halomethylenoates are highly useful reagents in organic synthesis.[13] The presence of the electron withdrawing carboxylate group increases the electrophilicity of these compounds compared with simple allylic halides. Thus, a major aspect of their chemistry involves their reactions with nucleophilic reagents. In general, these reactions occur via an addition–elimination mechanism, i.e. an overall S_N2' process.

6.1. With carbon nucleophiles

6.1.1. Organometallic reagents. The reactions of the α-bromomethylacrylates of the type **269** provided examples of reactions in which organometallic reagents behaved as nucleophiles. The conversions of **269b** into the cyanoenoate **270**[215] and **269a** into the cyclopentyl ketal enoate **271**[216] provided illustrations of the use of organocopper and organocupurate reagents in these reactions. Likewise, reaction of the chloromanganese compound **137b** with **269b** gave the dienoate substitution product **272** (Scheme 81).[118]

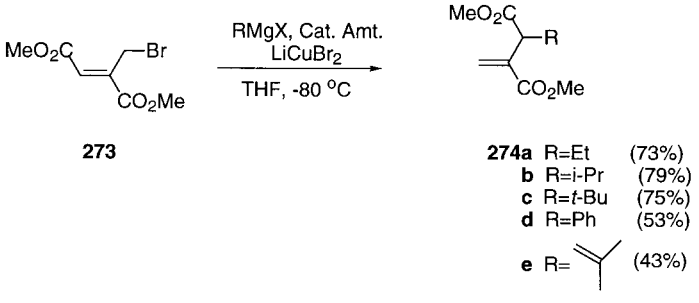
Several substituted dimethyl itaconates such as **274** were obtained in satisfactory yields when primary, secondary, and tertiary alkyl, as well as vinyl and aromatic, Grignard reagents were reacted with dimethyl γ-bromomesoconate **273** in THF in the presence of a catalytic amount of $LiCuBr_2$ at −80°C (Scheme 82).[217]

Knochel and coworkers have reported the use of a variety of functionalized Zn–Cu alkyl, vinyl, and aromatic reagents as nucleophiles in reactions with bromoenoates such as **269b** and **269c**. The scope of these reactions, which provide routes to a plethora of α-functionalized acrylates, has been thoroughly reviewed elsewhere.[13,218]

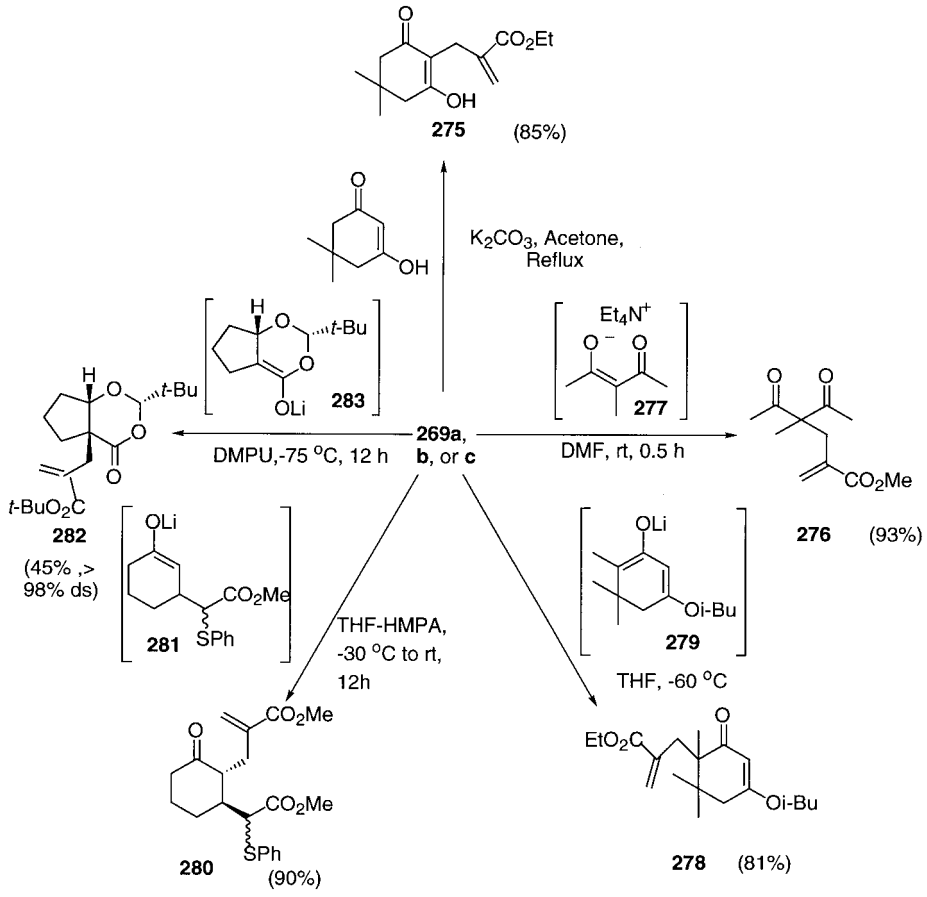
6.1.2. Metal enolates and related reagents. Enolates of cyclic[219,220] and acyclic[221] β-diketones, enol ethers of cyclic β-diketones,[222] β-ketoesters,[227–230] simple ketones,[223–228] esters,[229–232] and bicylic dioxanones[233] have been alkylated with bromoethylacrylates such as **269** and related compounds. As shown below, these reactions have been used in the synthesis of numerous highly functionalized compounds. It was proposed that the alkylation product **275** derived from dimedone was obtained by an initial *O*-alkylation followed by a Claisen rearrangement, although a direct *C*-alkylation by an S_N2' mechanism was not ruled out.[219] The enolate **277** was prepared by treatment of the corresponding diketone with the tetrabutylammonium enolate of 2-pyrrolidinone;[221] the dienolate **279** was prepared by kinetic deprotonation of the corresponding β-alkoxyenone with LiHMDA;[222] the Li^+ enolate **281** was prepared by conjugate addition of the Li^+ enolate of methyl phenylthioacetate to cyclohexenone[227,228] and the dioxanone enolate **283** was prepared by the reaction of the corresponding bicylic dioxanone with LDA (Scheme 83).[233]

Enoate **269b** has been shown to undergo sequential substitution–Michael addition reactions with 1,3-diphenylacetone (**284a**) and 1,3-dicarboethoxyacetone (**285b**) to give cyclohexanone derivatives **285a** and **285b**, respectively, upon treatment with 1.0 equiv. NaOEt in EtOH.[226] When 2.0 equiv. of the base were employed oxobicyclononanes such as **286a** and **286b** were obtained. An adamantandione tetraester **288** was produced in 50% yield when 2,4,4,6-tetracarbomethoxycyclohexanone (**287**) was treated with **269b** under similar conditions.[226] In this case, a Dieckmann condensation took place in the final step to form the third ring (Scheme 84).

The regiochemistry of the reaction of ethyl (*Z*)-2-bromomethyl-2-alkenoates such as **289** with Na^+ enolates of

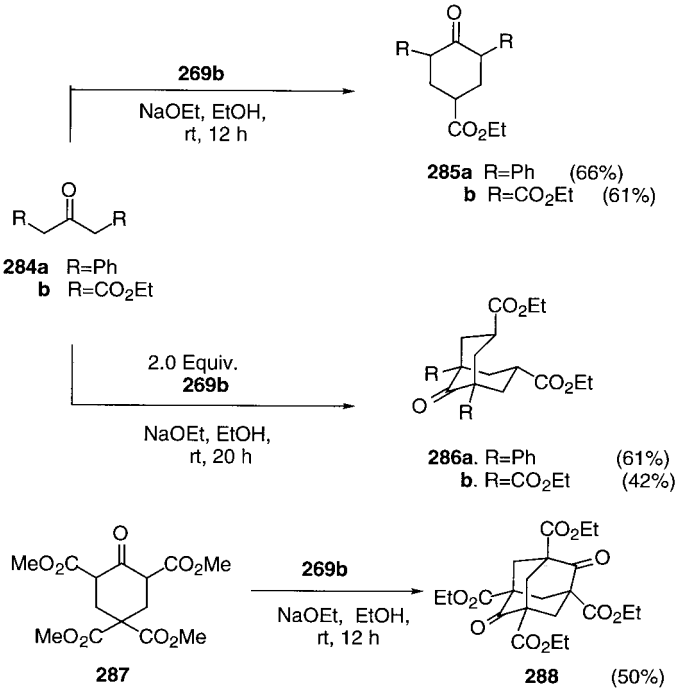


Scheme 82.

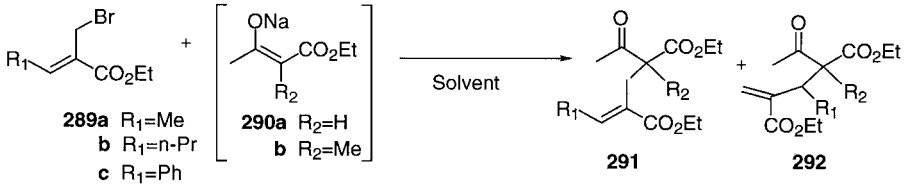


Scheme 83.

β-ketoesters such as **290** has been investigated.[233] Products such as **291** resulting from allylic attack at C-3′ and **292** resulting from vinylic attack at C-3 were obtained. Some of the data regarding substituent and solvent effects that were obtained are shown below. The allylic attack products **291** were favored by increasing the size of the substituents within the electrophile and the nucleophile and by increasing the polarity of the solvent from THF to EtOH. It was



Scheme 84.



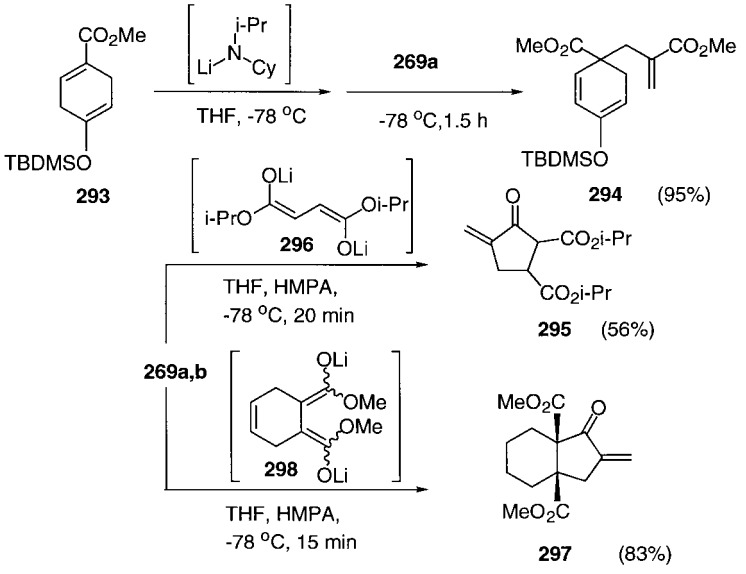
Reactants	Solvent	Product ratio(%)	
289a + **290a**	THF	32	68
"	EtOH	72	28
289a + **290b**	THF	30	70
"	EtOH	100	0
289b + **290a**	THF	50	50
"	EtOH	85	15
289b + **290b**	THF	65	35
"	EtOH	100	0
289c + **290a**	THF	50	50
"	EtOH	90	10
289c + **290b**	THF	88	12
"	EtOH	100	0

Scheme 85.

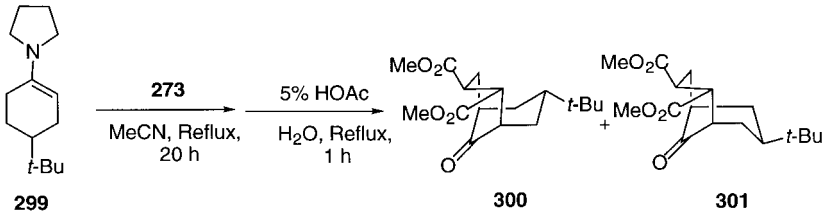
suggested that the nonpolar solvent THF favored a bimolecular Michael addition as the initial step, while in the more polar solvent EtOH an S_N1 mechanism obtained, with attack being favored at the primary position of the allylic carbocation intermediate. The behavior of **289c** having a Ph group at C-3 supported this explanation, as did the influence of the electronic effects of *para* substituents on the Ph ring. The expected trends in product distribution were also observed when the iodo- and chloroenoates related to **289** were employed as electrophilic partners in such reactions (Scheme 85).[224]

Several ester enolates or dienolates have been alkylated with α-bromomethylenoates.[229–232] Treatment of the Li^+ enolate of ethyl 3-dimethylaminopropionate with **269b** gave the expected C-2 alkylation product,[229] and reaction of the Li^+ enolate of methyl dihydrobenzoate (**293**) with **269a** provided the dihydrobenzene derivative **294** in an excellent yield.[231] α,α-Diallylation occurred when *S-n*-butyl selenothionoacetate was treated with enoate **269b**.[232] Dilithium dienolates **296** and **298**, derived from diisopropylsuccinate[234] and dimethyl 4-cyclohexene-1,2-dicarboxylate,[235] have been shown to undergo sequential substitution–Dieckmann cyclization reactions when treated with bromoenoates **269a** and **269b**, respectively. The α-methylene ketodiesters **295** and **297** were formed in these reactions (Scheme 86).

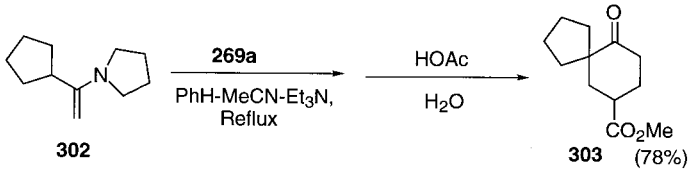
Enamines were among the first nucleophilic reagents employed in reactions with α-halomethylenoates.[236–244] Monoalkylated ketones derived from alkylation and hydrolysis of enamines have been obtained in solvents of lower polarity such as dioxane[241] and acetone.[243] However, the more interesting uses of these reactions have been for α,α′-annelations which occurred when solvents such as MeCN were employed. Lawton and coworkers have



Scheme 86.



Scheme 87.



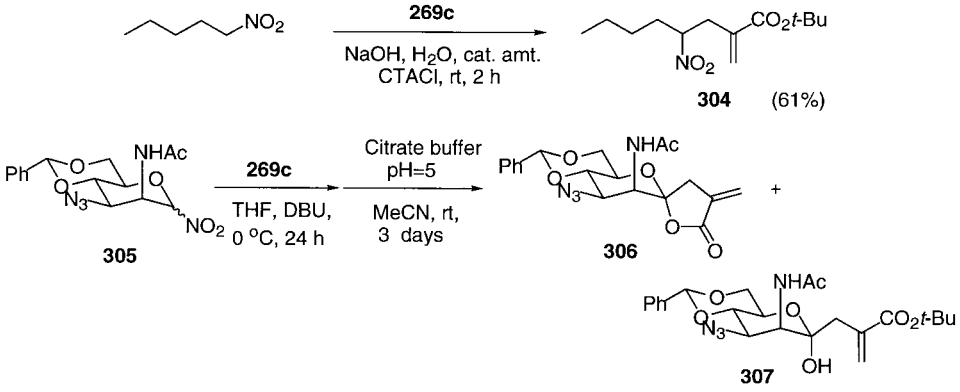
Scheme 88.

proposed that these reactions proceeded via alkylation of the enamine, proton transfer to reform an enamine, followed by intramolecular Michael addition, and, finally, protonation and hydrolysis of the zwitterionic iminium–enolate intermediate.[236–239] These workers initially reported that the oxobicyclononanone **301** was the major product of the reaction of the pyrrolidine enamine of 4-*t*-butylcyclohexanone (**299**) with bromodiester **273**. However, a later investigation of the stereochemistry of this reaction by Peters and coworkers revealed that a mixture containing **300** and **301** in a 5:1 ratio was obtained.[242] They proposed that the major product arose by axial alkylation of the half-chair conformation of the enamine with the *t*-butyl group equatorial. Then, after proton transfer and intramolecular Michael addition, protonation occurred from the *exo*-face of the bridged iminium–enolate intermediate to give the major isomer. These same authors also reported that the pyrrolidine enamine of cyclohexanone and its 4-alkyl derivatives including **299** were annelated with **269a** to give mixtures, with the analogs of **300** and **301** being produced in ca. 60:40 ratios in 81–89% yields. With **269b** as the electrophile, the α,α′-annelation sequence was also applied to the pyrrolidine enamine of 4-methoxycyclohexanone (Scheme 87).[244]

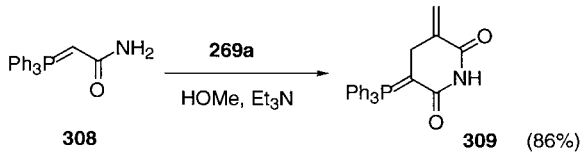
The spirocyclic ketone **303** was produced in 78% yield when the pyrrolidine enamine of acetylcyclopentane (**302**) was refluxed with the haloenoate **269a** in PhH–MeCN–Et_3N and the reaction mixture hydrolyzed with aqueous HOAc.[239] Similarly, spirocyclic ketones were formed when the α,α′-annelation process was applied to the enamines of 1-acetyl-2-methylcyclopentane and acetylcyclohexane (Scheme 88).[239]

Moderately acidic nitroalkanes have been observed to undergo base-promoted Michael addition–elimination reactions with α-bromomethylacrylates.[245] α-Substituted acrylates such as **304** which are versatile synthetic intermediates have been obtained by the reaction of nitropentane with **269c** in a two-phase system with dilute NaOH as the base and cetyl trimethylammonium chloride (CTACl) as a cationic surfactant. Nitromannose derivatives have also been shown to be capable of alkylation with electrophiles such as **269**.[246,247] The conversion of the nitromannose derivative **305** into a mixture of the butenolide **306** and the hydroxyenoate **307** was accomplished by reaction with **269c** in the presence of DBU in THF followed by hydrolytic removal of the nitro group. The ring-opened hydroxyketone isomer of **307** was also present (Scheme 89).

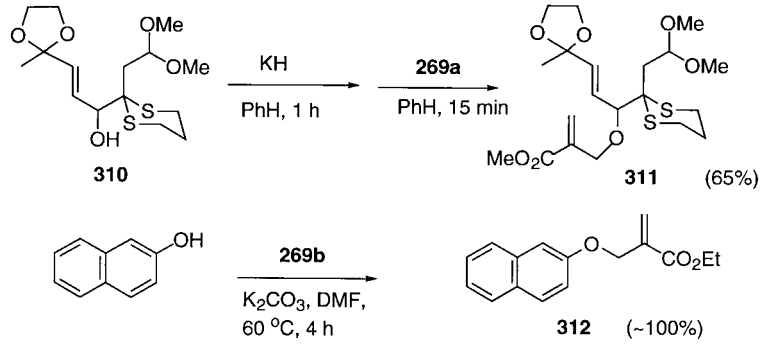
The α-methylene glutarimide ylide **309** was prepared in 86% yield using triphenyl phosphoranylidene acetamide as the nucleophile in a reaction with bromoenoate **269a**.[248] Ylide **309** was found to be useful for the synthesis of glutarimide nucleosides (Scheme 90).



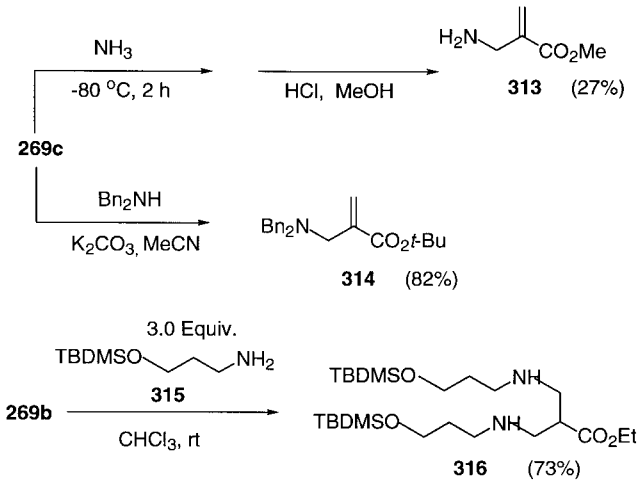
Scheme 89.



Scheme 90.



Scheme 91.



Scheme 92.

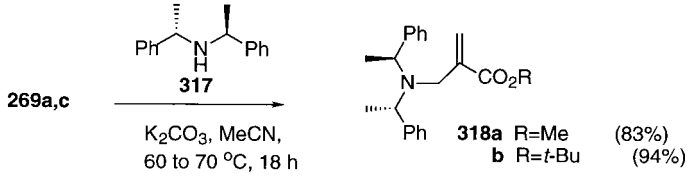
6.2. With heteroatom nucleophiles

The synthesis of acrylates containing alkoxy or aryloxy substituents at the α-position has been accomplished by reactions of α-bromomethyl acrylates with metal alkoxides[249,250] and aryloxides.[251–253] For example, the synthesis of allylic ether **311** was carried out by treating the K^+ alkoxide of the alcohol **310** with the enoate **269a**,[250] and the naphthyl ether **312** was obtained from the reaction of β-naphthol with enoate **269b** in the presence of K_2CO_3.[251] Although the exact sequence of steps was unclear, esters of β-bromo-α-bromomethylacrylate were reported to yield α-diphenoxymethylacrylates in 85–87% yields upon reaction with phenol in the presence of NaH (Scheme 91).[253]

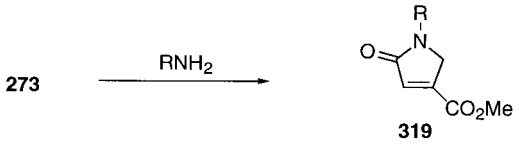
Ammonia[254] and primary and secondary amines[255–261] have been used as nucleophiles in reactions with α-bromomethylacrylates **269** and the bromomesoconate **273**. Illustrations of these types of reactions include the preparation of the α-methylene-β-alaninate **313** from the reaction of **269c** with NH_3 followed by transesterification with HOMe,[254] and the synthesis of the aminoenoate **314** upon reaction of **269c** with *n*-Bu_2NH.[255] The diaminoester **316**, the product of displacement of Br^- and conjugate addition, was obtained when **269b** was treated with an excess of the primary amine **315**.[256] Compounds **314** and **316** were employed in synthetic studies related to ptilomycalin A (Scheme 92).[255–257]

Bromoenoates **269a** and **269c** gave the chiral substitution products **318a** and **318b** in excellent yields when reacted with the chiral C_2 symmetrical secondary amine **317**.[262] Asymmetric syntheses of chiral β-amino acid derivatives were accomplished by Michael additions to these chiral compounds (Scheme 93).

The bromomesoconate **273** has been reacted with a variety of secondary amines.[258] While many of these, e.g. *i*-Pr_2NH, gave S_N2' substitution products (presumably via an addition–elimination mechanism), the less sterically hindered ones, e.g., Me_2NH and MePhNH, were found to react by two consecutive S_N2'-type processes, and the more hindered ones, e.g., 2,2,6,6-tetramethylpiperidine, gave only the direct substitution product.[259] The reaction of **273** with primary amines yielded pyrrolin-2-ones such as **319** by substitution followed by intramolecular cyclization



Scheme 93.



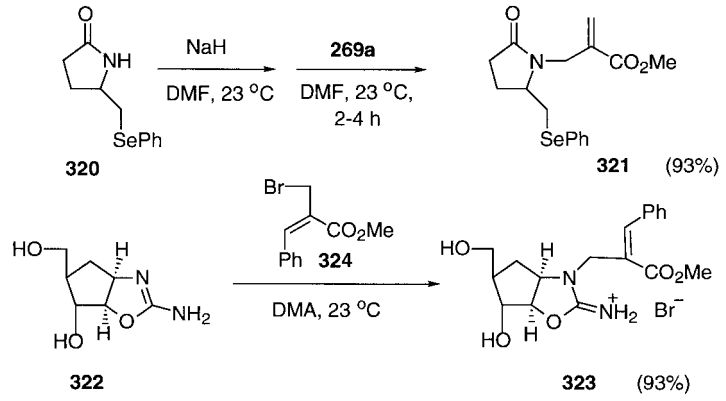
Scheme 94.

(Scheme 94).[257] An attempted Reformatsky reaction of bromoenoate **269b** with substituted piperidones led instead to the substitution of Br^-, with the N atom of the piperidone behaving as the nucleophile.[260]

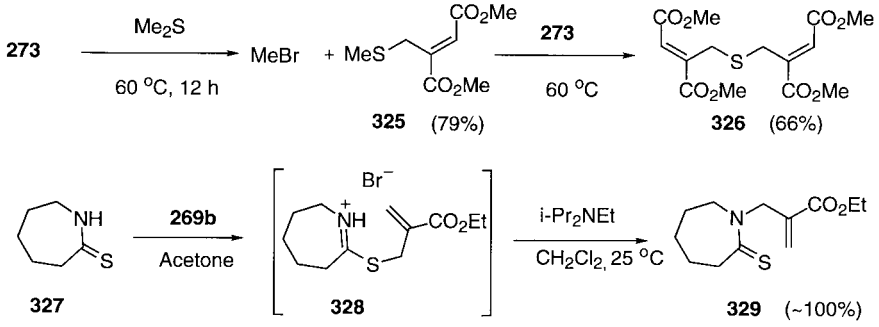
The phenylselenolactam **320** underwent *N*-alkylation to give the lactam **321** upon conversion to its Na^+ salt with NaH, followed by addition of the electrophilic reagent **269a**.[261] The K^+ salt of phthalimide was also *N*-alkylated with **269a**.[262] Amidines[263] and aminooxazolines[264] behave as nucleophiles in reactions with α-halomethylenoates to give the corresponding salts. For example, the arabino-aminooxazoline **322** gave the bromonium salt **323** in 93% yield upon treatment with methyl α-(bromomethyl)cinnamate (**324**) (Scheme 95).[264]

α-Thiophenylacrylates have been reported to be readily prepared by substitution reaction of α-bromoacrylates such as **269** with NaSPh.[265,266] The base-sensitive bromomesoconate **273** has been converted into the corresponding methyl sulfide **325** by heating with Me_2S to form the corresponding sulfonium salts which underwent demethylation with the loss of MeBr.[183] Upon heating of the sulfide **325** with 1.0 equiv. of enoate **273** for an extended time period, the symmetrical sulfide **326** was obtained. Upon reaction of the haloenoates **269a** and **289a**,**c** with NaSMe at 40°C, the expected substitution products were obtained.[267] The latter two unsymmetrical compounds reacted primarily by direct S_N2 displacement. Thiocaprolactam (**327**) underwent *S*-allylation with bromoenoate **269b** to give the salt **328**.[268] Upon the addition of *i*-Pr_2NEt to the salt solution, deprotonation followed by a facile thio-Claisen rearrangement occurred to give the *N*-substituted thiolactam **329** (Scheme 96).

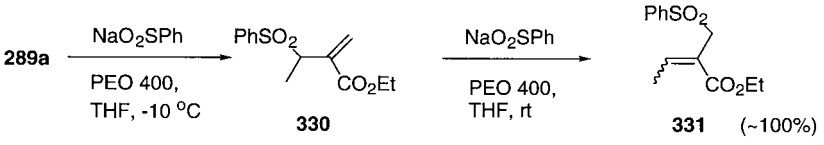
Bromoenoate **289a** was found to yield the addition–elimination product **330** upon reaction with NaO_2SPh in THF under kinetic control using polyethylene oxide 400 (PEO 400) as a cation complexing agent.[269] In the presence of an excess of the nucleophilic reagent, the more thermodynamically stable product **331**, apparently the result of direct S_N2 displacement, was obtained (Scheme 97).[269]



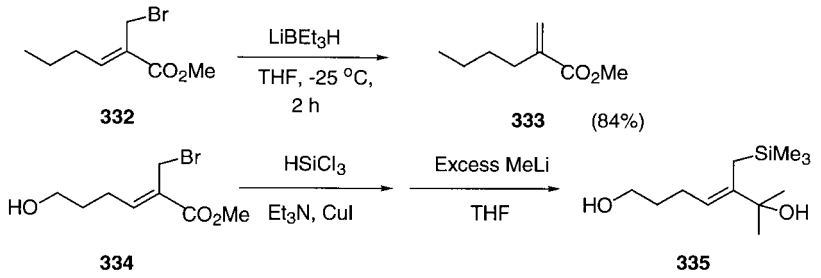
Scheme 95.



Scheme 96.



Scheme 97.



Scheme 98.

Other heteroatom nucleophiles such as H^- and $SiCl_3^-$ have been found to effect displacement of Br^- of bromomethylenoates.[270] The reaction of the α-bromomethylenoate **332** with $LiBEt_3H$ proceeded via an S_N2' mechanism to give the α-*n*-butylacrylate **333**. On the other hand, α-bromomethylenoate **334** underwent direct S_N2 attack by $SiCl_3^-$ to give the trimethylsilyldiol **335** after treatment of the initial product with excess MeLi (Scheme 98).[270]

7. Conclusions

Reactions of conjugated haloenoates with nucleophilic reagents provide important methods of constructing molecules containing new carbon–carbon and carbon–heteroatom bonds. Although the nucleophile may attack the carbonyl carbon of the enoate or directly displace the halogen if it is not attached directly to the double bond, conjugate addition is usually the preferred mode of reaction. When anionic carbon or heteroatom nucleophiles are involved, the initially formed ester enolate intermediate may participate in a variety of intramolecular reactions, e.g., elimination if a halogen atom is present at the β-position, or intramolecular cyclization reactions if a suitably disposed electrophilic site is present. The latter types of reaction have been widely used to synthesize functionalized cycloalkane (especially cyclopropane) derivatives and bridged ring systems. Intermolecular trapping reactions of ester enolate intermediates are also well known. Enantioselective reactions have been observed when the acceptor enoate or the donor nucleophile contain an appropriate chiral auxiliary. The use of haloenoate–nucleophile reactions for the efficient synthesis of complex acyclic and cyclic molecules is a potentially rich field of investigation for the future.

Acknowledgements

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Biographical sketch

Drury Caine was born in Selma, Alabama, 9 June 1932. After high school, he attended the University of the South, Sewanee, Tennessee, and Vanderbilt University, Nashville, Tennessee, for undergraduate work, and received a B.A. degree in chemistry from Vanderbilt in June 1954. He also received a M.S. degree in organic chemistry from Vanderbilt in 1956. His masters' thesis was under the joint direction of Professors Donald E. Pearson and Lamar Field. After two years of military service, he enrolled in the graduate program at Emory University, Atlanta, Georgia, and received his PhD in organic chemistry in August 1961. His PhD dissertation was under the direction of Professor Leon Mandell. From 1961 to 1962, he was an NIH postdoctoral fellow in Professor Gilbert Stork's laboratory at Columbia University, New York. He was appointed to the faculty at Georgia Institute of Technology, Atlanta, GA, in August 1962 and remained there until March 1983. Then, he became Chairman of the Department of Chemistry at the University of Alabama, Tuscaloosa, AL, and occupied that position until August 1995. He continued as Professor of Chemistry at Alabama until August 1999 when he officially retired. During his career he was a Visiting Professor in the Department of Chemistry at the University of California, Berkeley, CA, and in the Department of Biochemistry and Molecular Genetics at the University of Alabama at Birmingham, Birmingham, AL. His research interests have included the total synthesis of natural products, reactions of metal enolates and homoenolates, and photochemical rearrangements of cross-conjugated cyclohexadienones.