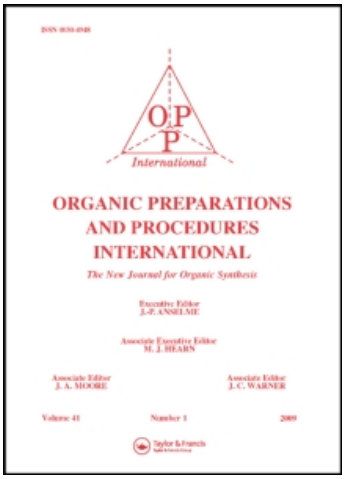

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ORGANOTIN ENOLATES IN ORGANIC SYNTHESIS. A REVIEW

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ORGANOTIN ENOLATES IN ORGANIC SYNTHESIS. A REVIEW

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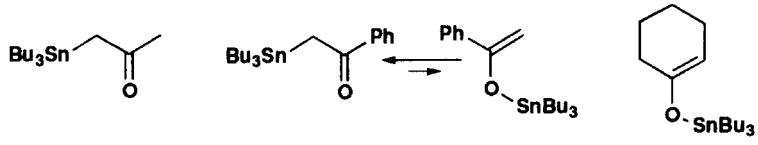
INTRODUCTION

Organotin compounds are widely used in organic synthesis.[1-4] Organotin enolates act as carbon nucleophiles to generate carbon-carbon bonds.[5] Tin enolates are more reactive than silyl enol ethers but less basic than lithium enolates. Compared with silyl enol ethers, tin enolates are used in narrower fields because of the difficulty in handling these moisture sensitive-reagents. However, the synthetic utility of organotin enolates has been developed in recent years because the enolates enable chemoselective and stereoselective reactions. This review will be concerned with the synthetic use of organotin(IV) enolates.

Several methods are available for the preparation of organotin enolates. The most conventional methods are the transesterification of enol acetates, the transmetallation of lithium enolates and the hydrostannation of α,β-unsaturated ketones.[5] Beside these methods, various other procedures for the generation of tin enolates have been reported and are described in this review.

Organotin enolates consist of C-stannyl derivatives and/or the O-stannyl enolates,[6] whose ratio depends on the substituents. ^{119}Sn-NMR spectra indicate the ratio measured at 50°.[7] For example, the ratio of tri-*n*-butyltin derivatives is as follows (Fig.1).



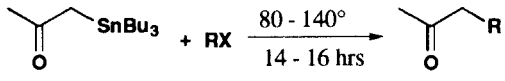
(100:0) (80:20) (0:100)

Fig. 1

I. COUPLING REACTION OF ORGANIC HALIDES

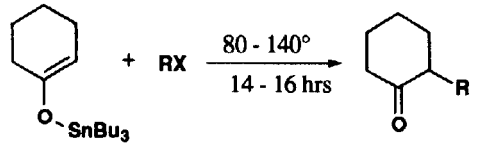
1. Reaction with Reactive Halides

Organotin enolates generated from ketones react with various reactive halides to give the alkylated ketones.[8] Alkyl iodides, α-halo esters, allyl bromides are used as reactive halides. Relatively severe reaction conditions are required such as above 80° (Eqs. 1 and 2). The α-alkylation of aldehydes can be achieved similarly (Eq. 3).[9]



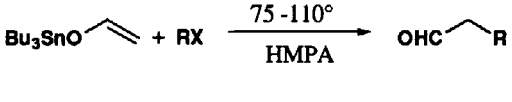
RX	Yield
MeI	60%
$EtCO_2CH_2Br$	50%
$MeOCH_2Cl$	63%

(1)



RX	Yield
MeI	90%
AllylBr	65%

(2)



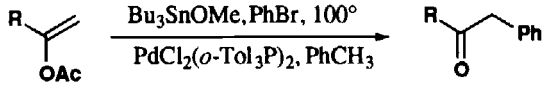
RX	Yield
MeI	61%
AllylBr	41%
BnBr	68%

(3)

The alkylation of tin enolates with propagylic bromide has been utilized in the preparation of methyl jasmonate[10] and prostaglandins.[11]

2. Palladium-catalyzed Coupling Reaction

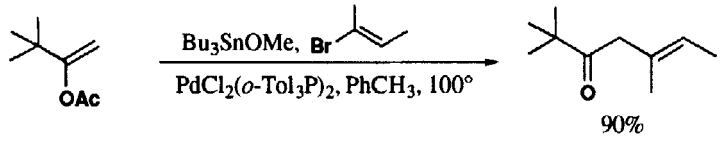
Aryl bromides react with tributyltin enolates, prepared from tributyltin methoxide and enol acetates *in situ*, in the presence of dichlorobis(tris-*o*-tolylphosphine) palladium.[12-14] αarylation proceeds in good yields with complete retention of the enol acetate regiochemistry (Eq. 4).



R = Me 83%
R = Et 67%
R = *i*-Pr 87%

(4)

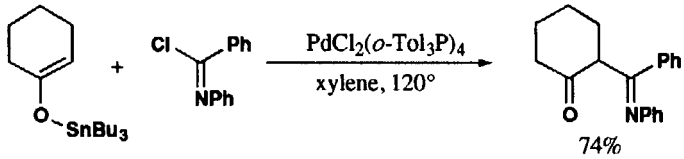
Vinyl halides can be also used as electrophiles, leading to allyl ketones,[15] the configuration of the vinyl bromide is retained completely (Eq. 5).



90%

(5)

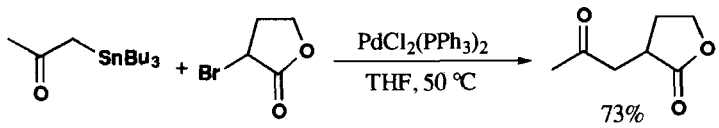
Imidoyl chlorides are good substrates to react with tin enolates to give ketimines in the presence of a palladium catalyst (Eq. 6).[16]



74%

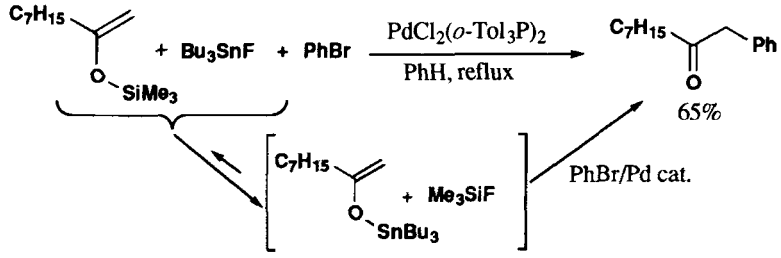
(6)

The coupling reaction of acetonyltin with α-bromo-γ-butyrolactone in the presence of Pd catalysts represents an effective procedure for the synthesis of α-acetonyl-γ-butyrolactone (Eq. 7).[17] The reaction of α-haloketones is described in Section III.



(7)

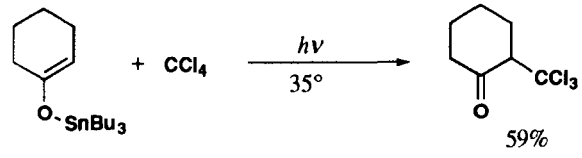
A one-pot arylation of easily available silyl enol ether to arylated ketones is accomplished in the presence of Bu_3SnF and a palladium catalyst (Eq. 8),[18] two sequential reactions are postulated: (1) *in situ* generation of an α-stannyl ketone *via* silyl/stannyl exchange and (2) its arylation with the aryl bromide. A variety of silyl enol ethers and aryl bromides can be employed with almost equal success. The mildness of the reaction conditions tolerates the presence of a ketone or an ester functionality in the substrate.



(8)

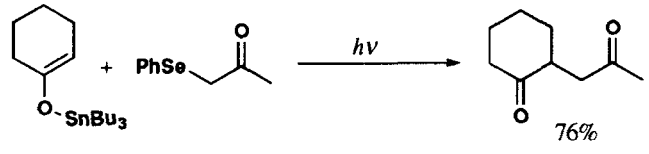
3. Free-Radical Reaction

Free-radical chain reaction of tin enolates is also carried out to furnish α-substituted ketones. For example, α-(trichloromethyl)cyclohexanone is prepared from tin enolate upon the photo-induced reactions with CCl_4 (Eq. 9)[19]



(9)

1,4-Dicarbonyl compounds are obtained on irradiation of tin enolate with α(phenylseleno)carbonyl compounds (Eq. 10).[20] The selenide is a better radical precursor than the sulfide, iodide and bromide.



(10)

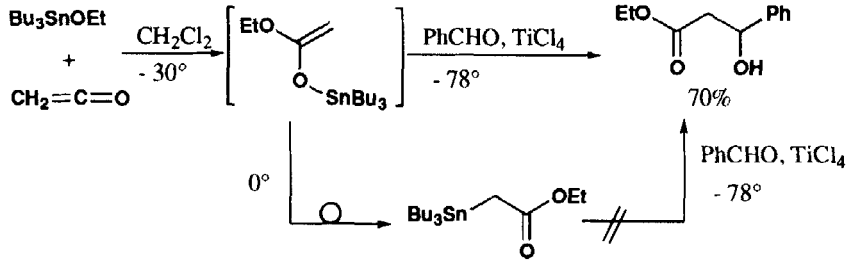
II. ADDITION TO ALDEHYDES

1. Reactivity of Organotin Enolates

Organotin enolates react with aldehydes to give β-hydroxy ketones in the absence of Lewis acids. For example, acetonyltriethyltin reacts with alkyl or aryl aldehydes exothermally.[21] *In situ*

generated tin enolates from silyl enol ethers have also been successfully used.[22] On the other hand, the aldol-type reaction of organotin ester enolates often requires accerelators such as $TiCl_4$,[23] BF_3OEt_2,[24] LDA,[25] Bu_3SnI,[24] and tetraalkylammonium halides.[24]

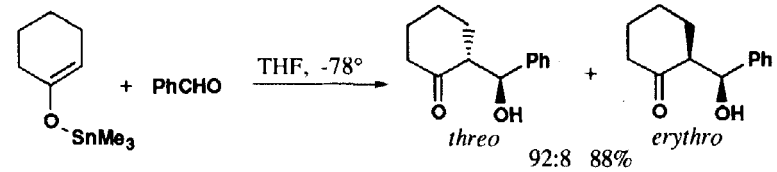
The difference in the reactivity between C-stannyl- and O-stannyl forms has been studied by using an organotin ester enolate produced by the addition of tin alkoxide to ketene (Eq. 11).[26] The β-hydroxyalkanoate is obtained in good yield when gaseous ketene is passed into a CH_2Cl_2 solution of Bu_3SnOEt at -30°, followed by the addition of benzaldehyde and $TiCl_4$ at -78°. However, the product is not obtained when the mixture of tin alkoxide and ketene is allowed to stand at 0° for several hours before the addition of benzaldehyde and $TiCl_4$ at -78°. The reaction is assumed to proceed, at low temperature, through an initial formation of active intermediate, the *enol* form, which in turn reacts with benzaldehyde to give β-hydroxyalkanoate, on the other hand, the *keto* form formed by the rearrangement of Bu_3Sn group at 0° is unreactive toward benzaldehyde.



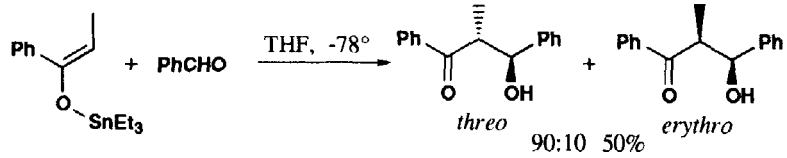
(11)

2. Diastereoselective Aldol Reaction

In the reaction of trialkyltin enolates of cyclohexanone and propiophenone with aldehydes, *threo*-aldol products are obtained efficiently at -78° (Eqs. 12 and 13).[27,28] Trimethyl- and triethyltin



(12)



(13)

enolates afford higher *threo*-selectivity than tributyltin enolates. The high *threo* selectivity under kinetic conditions classifies it as one of the few simple *threo*-selective reactions. The selectivity is explained in terms of a cyclic transition state **A** (Fig. 2).

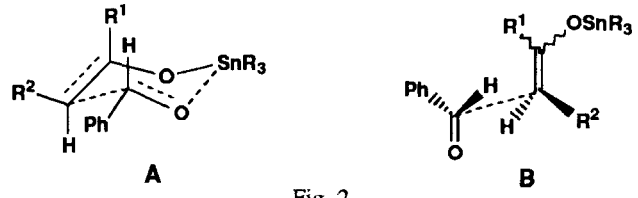
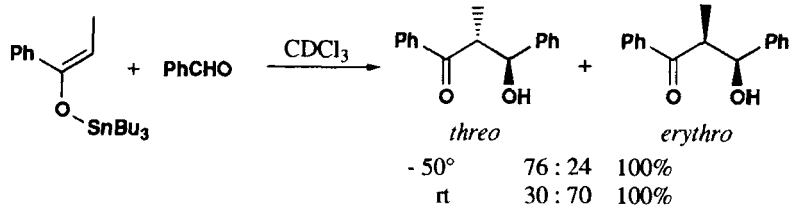


Fig. 2

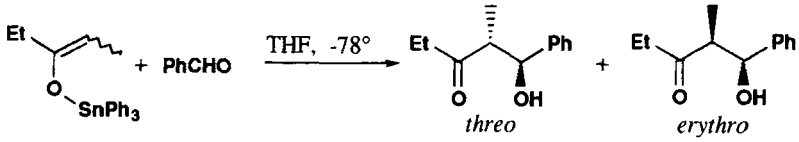
In the aldol reaction of tributyltin enolates, temperature-dependency of diastereoselectivity is observed (Eq. 14).[29] At -50°, tin enolate reacts with benzaldehyde rapidly to give *threo* adduct predominantly. The *threo* selectivity is interpreted by the cyclic transition state **A**. At r.t., the *erythro* product is formed with high selectivity, the *erythro* isomer is assumed to arise through the acyclic transition state **B**.



	threo	*erythro*
- 50°	76 : 24	100%
rt	30 : 70	100%

(14)

In contrast to the above trialkyltin enolates, triphenyltin enolates formed *in situ* from lithium enolates give predominantly the *erythro* product at -78° regardless of the geometry of the enolates used (Eq. 15).[30] An acyclic transition state **B** explains the *erythro* selectivity.

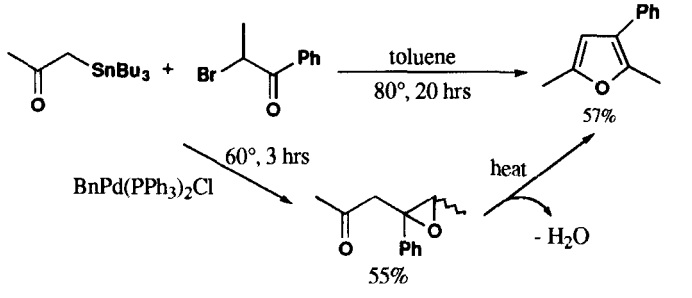


E : *Z* = 8 : 92	18 : 82	80%
86 : 14	26 : 74	80%

(15)

III. REACTION WITH α-HALOKETONES

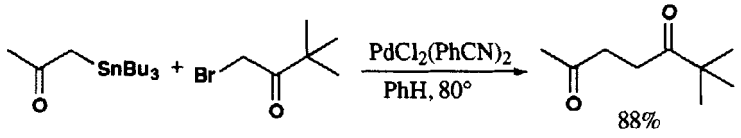
The reaction of tin enolates with α-bromoketones at 100° gives substituted furan derivatives.[31] The reaction is explained in terms of an initial addition of enolate to the carbonyl group of the α-bromo ketones, and the subsequent elimination of tributyltin bromide to produce the β,γ-epoxy ketones, which then undergoes cyclodehydration (Eq. 16). On the other hand, the selective



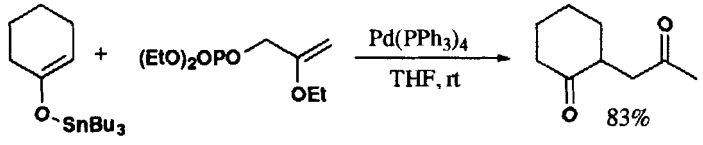
(16)

formation of β,γ-epoxy ketones can be accomplished in THF at reflux in the presence of $BnPd(PPh_3)_2Cl$.[32] On prolonged heating however, the β,γ-epoxy ketones formed undergo rearrangement with dehydration to yield the furans.

In contrast, the formation of unsymmetrical 1,4-diketones are reported in the $PdCl_2(PhCN)_2$ catalyzed reaction at the halide group of α-haloketones (Eq. 17),[33] the crosscoupling is successful only in the case of α-haloketones bearing bulky groups. However, the reaction of α-haloketones with tin enolates gives the furan derivatives either in the presence or absence of the palladium catalyst, showing that the addition of the enolates to the carbonyl group is faster than the coupling process with the halogen. For selective acetonylation, 2-ethoxy-2-propenyl diethyl phosphate is employed as a substrate in place of haloketone (Eq. 18),[34] to give 1,4-diketones regioselectively by the Pd-catalyzed reaction with various organotin enolates.

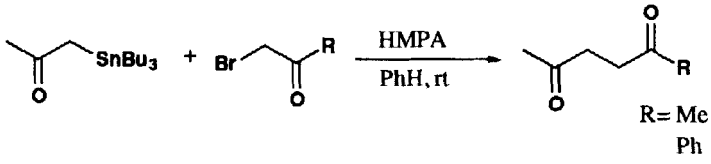


(17)



(18)

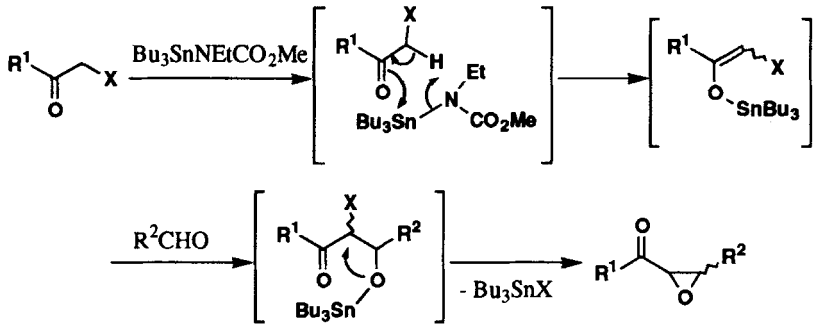
On the other hand, organotin enolates react with various α-haloketones to give 1,4diketones selectivity in the presence of HMPA (Eq. 19).[35,36] This chemoselective reaction proceeds even in the case of a haloketone. The coordination of HMPA to the tin center changes the nucleophilicity of the tin enolate, and promotes the chemoselective reaction.



(19)

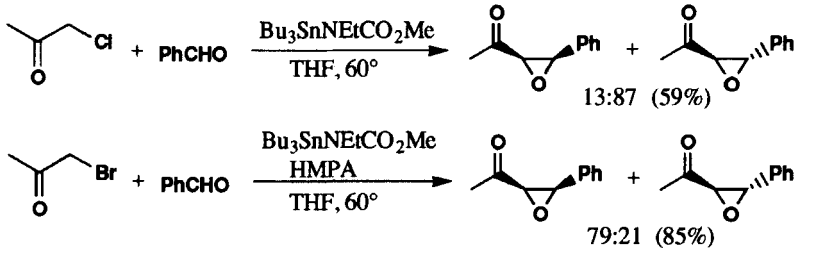
IV. NOVEL GENERATION METHOD OF ORGANOTIN ENOLATES

The generation of halo enolates from α-haloketones is generally limited because of serious problems such as nucleophilic reactions and α'-proton abstraction. In particular, haloacetones cannot be used. Tributylstannylcarbamate ($Bu_3SnNEtCO_2Me$) is effective as a generation reagent of halo enolates even in the case of haloacetones and has been used to perform Darzens reactions.[37,38] The halo enolates generated react with aldehydes to afford α,β-epoxy ketones with the elimination of tributyltin halide (Eq. 20). Furthermore, the method has also been extended to five- and six-membered cyclic ether derivatives by using ω-haloketones.



(20)

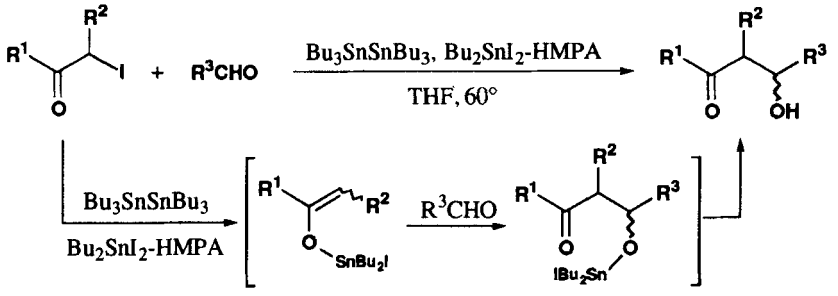
The stereoselectivity of the epoxy ketones is changed by the nature of the halogen and by additives. Thus, the reaction of chloroacetone with benzaldehyde gives *trans* epoxy ketones (Eq. 21), whereas bromoacetone in the presence of HMPA gives *cis* isomers predominantly (Eq. 22).



(21)

(22)

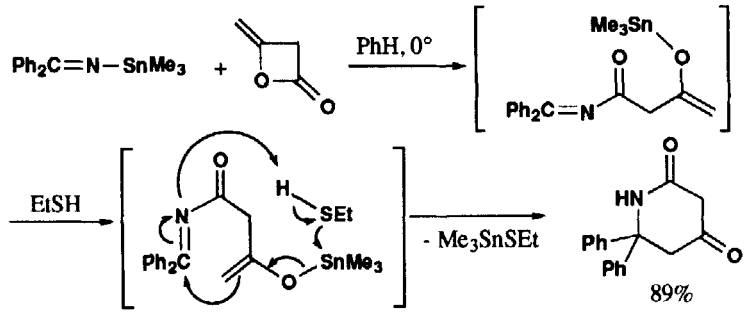
Iododibutyltin enolates can be formed from α-iodoketones in the presence of $Bu_3SnSnBu_3$, Bu_2SnI_2 and HMPA (Eq. 23).[39] Thus Reformatsky type reaction takes place. Aldol products are obtained in good yields from aromatic and aliphatic aldehydes.



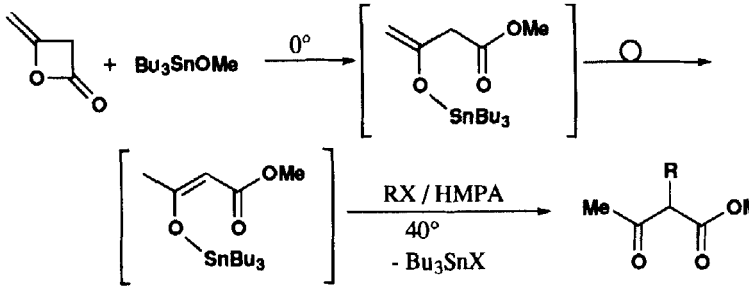
(23)

Tin compounds bearing Sn-O or Sn-N bond potentially cleavage β-lactone ring. Because diketene is a reactive β-lactone, the linear 1:1 adduct is obtained in the reaction with N-trimethylstannyl benzophenone imine (Eq. 24). Consecutive demetallation with ethanethiol gives a piperidine derivative.[40]

Bu_3SnOMe also cleaves diketene at the acyl-oxygen bond to give an organotin enolate. The resulting enolate reacts with various reactive halides to afford α-alkylated acetyl acetoacetates (Eq. 25).[41]

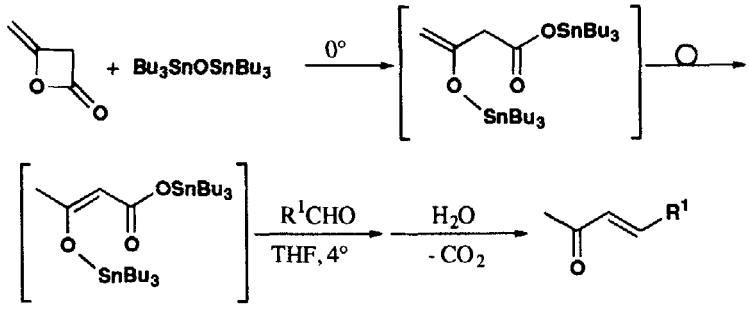


(24)



(25)

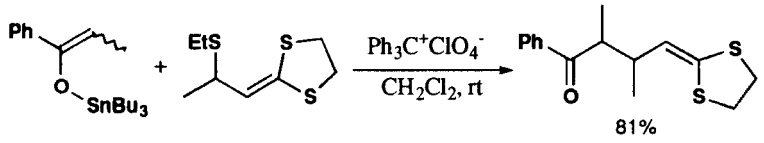
The ring cleavage with bis(tributyltin) oxide also affords the tin enolate bearing carbostannyloxy group at the terminal position. The enolate reacts with aldehydes *via* decarboxylations to produce α,β-unsaturated ketones effectively (Eq. 26).[42] Hence the tin enolate acts as an acetonylating agent of aldehydes. Similar types of decarboxylation of β-ketostannyl esters to form tin enolates are also reported.[43]



(26)

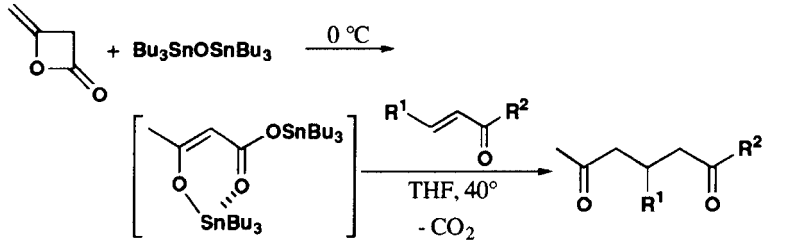
V. MICHAEL ADDITION

In general, it is difficult for organotin enolates to undergo Michael addition to α,β-unsaturated carbonyl compounds. Tin enolates react with 2-(2-ethylthioalkylidene)-1,3-dithiolane, a synthetic equivalent of α,β-unsaturated ester, to afford the corresponding Michael adducts in the presence of a catalytic amount of trityl salt (Eq. 27).[44] The highly thiophilic nature of trialkyltin cation plays an important role in the regeneration of trityl cation, the catalyst.



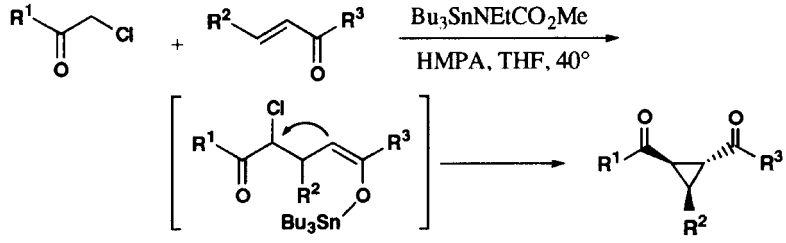
(27)

The tin enolate derived from the $(Bu_3Sn)_2O$ promoted cleavage of diketene is effective in Michael additions to produce 1,5-diketones (Eq. 28).[45] This unusual property of the tin enolate is interpreted by intramolecular coordination which affects the nucleophilicity of the tin enolate to give Michael adducts.



(28)

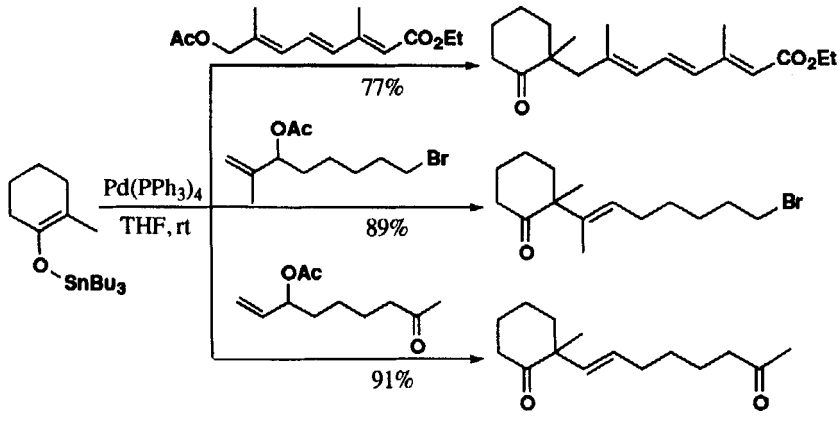
A similar type of Michael addition takes place in the reaction using the tin haloenolates generated by the stannylcarbamate. Thus, a one-pot formation of cyclopropane derivatives is accomplished *via* the intramolecular alkylation of the Michael adduct (Eq. 29).[46] The intramolecular coordination of chloro group to tin atom in the enolate also lead to the effective Michael addition.



(29)

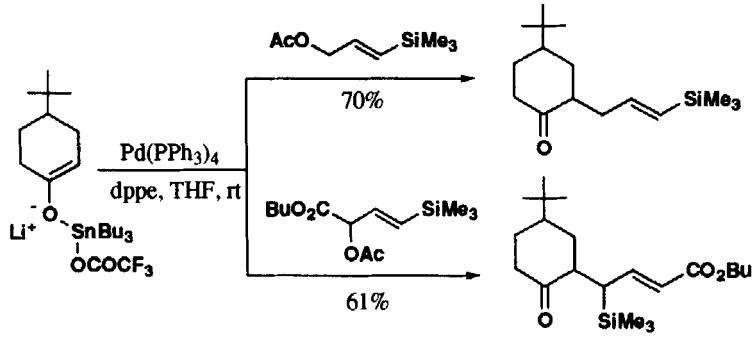
VI. MISCELLANEOUS REACTIONS

In the nucleophilic substitution of allylic acetates catalyzed by palladium, simple enolates such as lithium enolates give dialkylated products. Although the use of silyl enol ethers gives monoalkylated products, it cannot be extended to substituted allyl acetates. Switching to organotin enolates leads to a remarkably rapid and clean monoalkylation at room temperature (Eq. 30).[47] A high regioselectivity is observed for the alkylation at the less substituted end of the allyl moiety with the formation of E isomer. The chemoselectivity is high as demonstrated by the compatibility of functions like esters, alkyl bromides, and ketones.



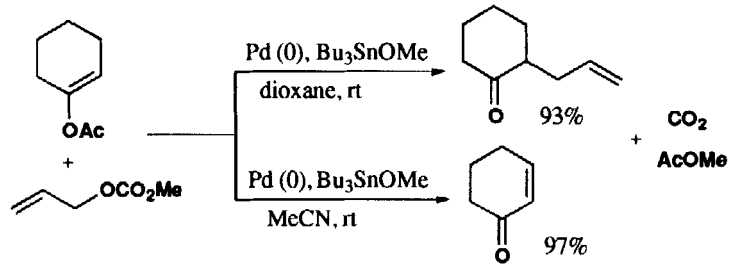
(30)

The complexes of tin enolates generated from lithium enolates and trialkyltin trifluoroacetates permit their use as regioselective nucleophiles in the reaction with 3-acetoxy-1(trimethylsilyl)-1-propene and butyl 2-acetoxy-4-(trimethylsilyl)-3-butenoate (Eq. 31).[48]



(31)

Bimetallic catalysts of palladium phosphine complex and tin methoxide allow the conversion of enol acetates to allyl ketones and α,β-unsaturated ketones, where a tin enolate is a key intermediate. When the reaction is carried out in MeCN, an α,β-unsaturated ketone is obtained,[49] whearas the use of dioxane as a solvent affords an α-allyl ketone (Eq. 32).[50] In these reactions, the *in situ* formation of tin enolate from enol acetates and Bu_3SnOMe occurs first (Fig. 3). Then the transmetallation of the tin enolate with π-allylpalladium complex, formed by the oxidative addition of allyl carbonate to Pd(0) complex, gives π-allylpalladium enolate. Finally, the enolate gives products and regeneration of the tin alkoxide makes the reaction catalytic.



(32)

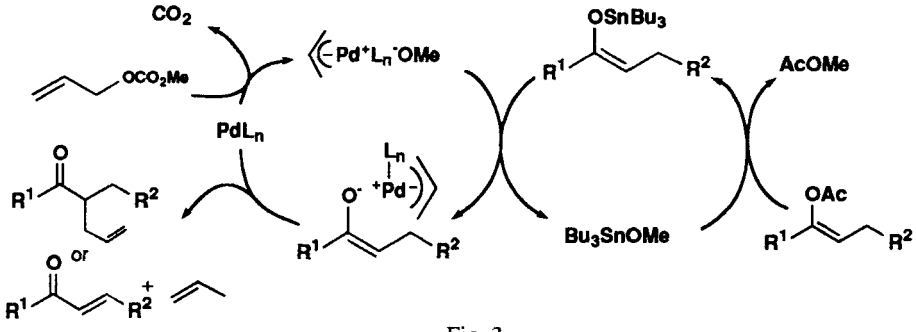
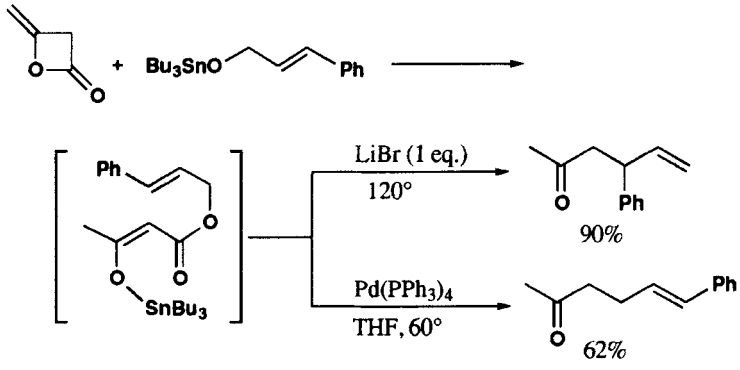


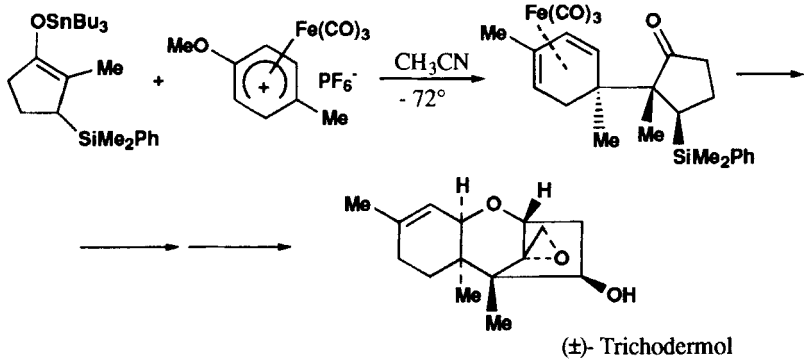
Fig. 3

Two types of Carroll rearrangement are performed from the tin enolate generated by the ring cleavage of diketene with allyloxytributyltin (Eq. 33).[41] A C-C bond formation occurs at the phenyl substituted site in the presence of LiBr, whereas, Pd catalyst promotes the reaction at the other site.



(33)

Tin enolates are more reactive than silyl ones and less basic than lithium ones. This property is suitable for the key step of total synthesis of the naturally occurring sesquiterpenes, trichothecenes, that show diverse biological activities.[51-53] First, a silyl enolate is convert to the corresponding tin enolate *via* the sequential treatment with methyllithium and tributyltin chloride. Next, reaction of the tin enolate formed in this way with cyclohexadienyliron complex proceeds in high yield to give addition to C5 of the complex with significant diastereoselectivity (Eq. 34). The formed adduct is converted to trichothecene such as (±)trichodermol.



(34)

(±)- Trichodermol

VII. CONCLUSION

Organotin enolates are becoming extremely important despite their recent history. Beside the present review, tin(II) enolates are reported to be versatile stereo-controlled tools.[5] Tin compounds are more reactive than the corresponding silicon compounds and promote a wide range of reactions such as radical reactions, transition metal-catalyzed reactions, Lewis acidmediated reactions, Lewis base-mediated reactions, and so on. Undoubtedly, broader awareness of organotin chemistry will lead to greater application to organic synthesis.

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