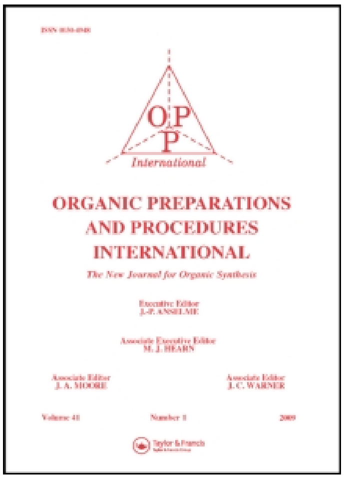

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HOMOENOLATES AND OTHER FUNCTIONALIZED ORGANOMETALLICS. A REVIEW

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HOMOENOLATES AND OTHER FUNCTIONALIZED ORGANOMETALLICS. A REVIEW

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INTRODUCTION

Metal homoenolates and other functionalized organometallics have become important reagents in organic synthesis in recent years. These reagents are characterized by the existence of a reactive organometallic species such as an organozinc or organotitanium species in the same molecule with an electrophilic functional group such as an ester or nitrile. The utility of these reagents may eventually surpass that of Grignard reagents and organolithium reagents since the less reactive metals which have been used allow the incorporation of many reactive and sensitive functional groups into the organometallic reagent. This review will outline recent developments in homoenolate equivalents, metal homoenolates derived from siloxycyclopropanes, direct coupling of siloxycyclopropanes to electrophiles, and the preparation and use of functionalized zinc reagents derived from halides. The review is organized according to the metal ion within each section. For example all reactions of zinc homoenolates are treated together within the same section. While the overview is not intended to be comprehensive, every attempt has been made to include the most important and useful reagents and some of their applications.

I. HOMOENOLATE EQUIVALENTS

Although true metal homoenolates, species containing a sigma bound metal ion in a β-position to a carbonyl group, have only recently been prepared and utilized, a large number of homoenolate equivalents have been investigated. An excellent review by Werstiuk on early homoenolate equivalents has appeared.[1] Only the most recent examples of internally stabilized metal homoenolate equivalents will be discussed here.

Kuwajima has reported a homoenolate equivalent in which the ketone carbonyl is protected as a silyl enol ether (Fig. 1).[2] The enol ether oxygen then serves to stabilize the allylic anion by chelation to the metal center. The homoenolate anion is obtained by a Brook-West rearrangement of an α-silyl alkoxide. Alkylations, Michael additions, additions to carbonyls and epoxide openings have been carried out with these anionic species.

Julia has reported the formation of ketone homoenolate equivalents from 1-alken-3-ols by formation of the dianions (Eq. 1).[3] These anions have been used in nucleophilic substitution reactions.

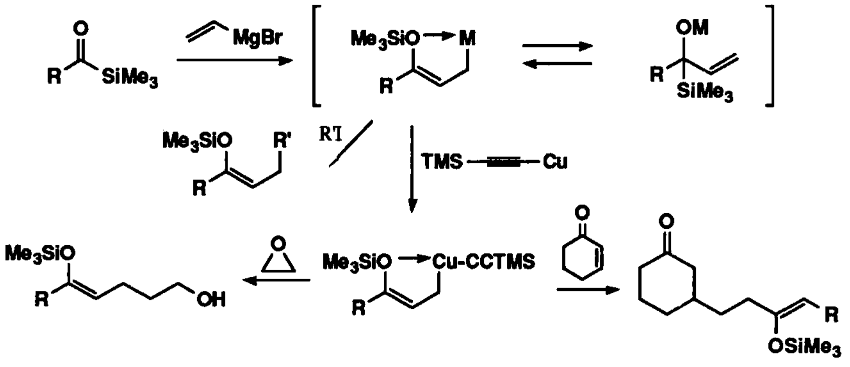
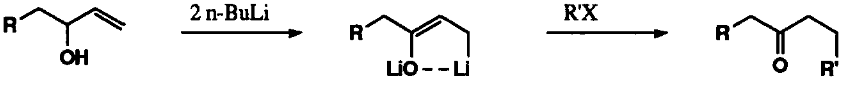


Fig. 1



(1)

$R = C_6H_{13}; C_{10}H_21; R' = -CH_3; CH_2{=}CH\text{-}CH_2\text{-}; (CH_3)_2CHCH_2\text{-}$

Hoppe has prepared lithiated and titanated O-allyl carbamates which add readily to aldehydes and ketones (Fig. 2).[4] The products can be easily converted to γ-lactones.

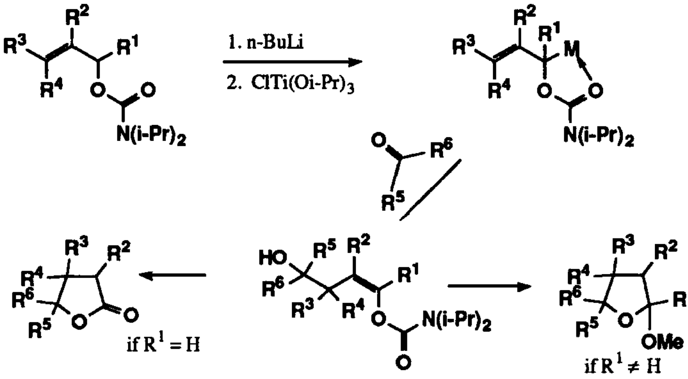
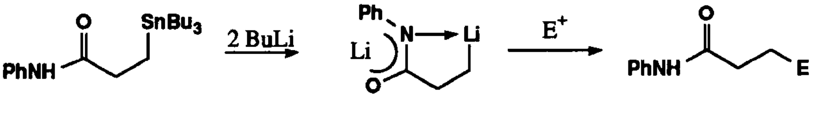


Fig. 2

Goswami reported the formation of the dianion of N-phenylpropionamide from N-phenyl 3-(tri-*n*-butylstannyl)-propionamide (Eq. 2).[5] The dianion constitutes a homoenolate equivalent and reacts with a variety of electrophiles.



(2)

$E = D, CH_2{=}CHCH_2Br, CH_3CH_2CH_2I, Me_3SiCl, Ph_2CO, CH_3CONMe_2$

Ghosez has described the γ-alkylation of metallated α-cyano enamines (Fig. 3).[6] These organolithium species also undergo 1,4 additions to α,β-unsaturated ketones with some competing 1,2-addition. The product α-cyano enamines can be hydrolyzed to carboxylic acids.

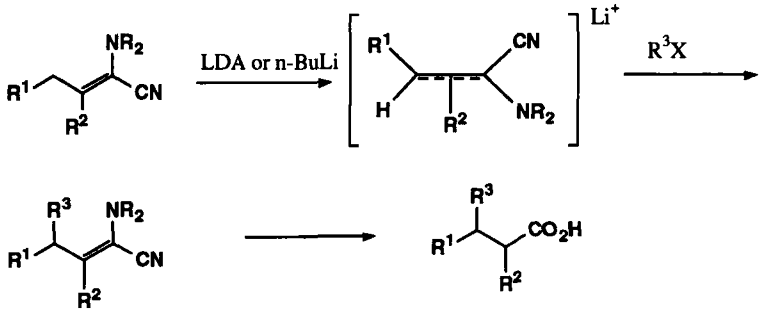
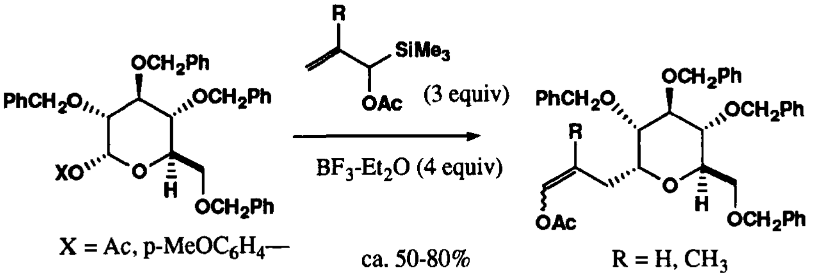


Fig. 3

Oxygenated allylic silanes have been used as homoenolate equivalents in the formation of C-glycosides by Panek (Eq. 3).[7] The enol acetate products have been transformed in a number of standard transformations to aldehydes, ketones or protected alcohols.



(3)

II. HOMOENOLATES FROM SILOXYCYCLOPROPANES

The difficulty with the preparation and use of metal homoenolates is that their stability and therefore their reactivity depends dramatically on the nature of the metal counterion. If the homoenolate is too reactive (M = Li, Na,...), cyclization to the corresponding cyclopropane derivative predominates (Fig. 4). If the reactivity is too low, reaction with the desired electrophile will not occur. Thus a

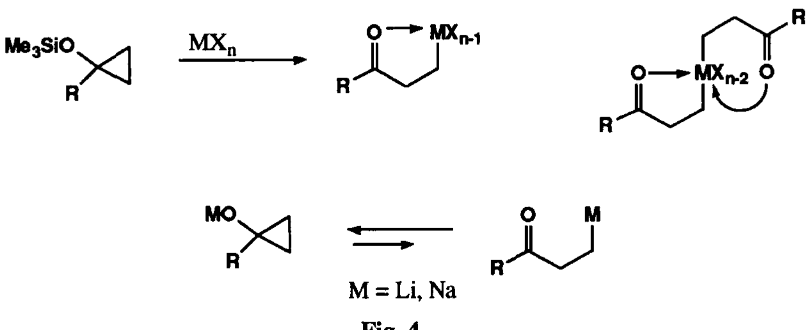


Fig. 4

careful balance between stability and reactivity must be achieved to find a useful homoenolate reagent. Examples of stable homoenolates which vary from unreactive to moderately reactive will be presented here.

Homoenolates can be prepared from appropriate silyloxycyclopropanes and the corresponding metal halides. The silyloxycyclopropanes may be obtained by reductive silylation of 3-haloesters (method A; Fig. 5)[8] or by the cyclopropanation (Simmons-Smith methylenation)[9] of ketone silylenol ethers (method B; Fig. 5). Method A can be used for the preparation of optically active homoenolate reagents.[10]

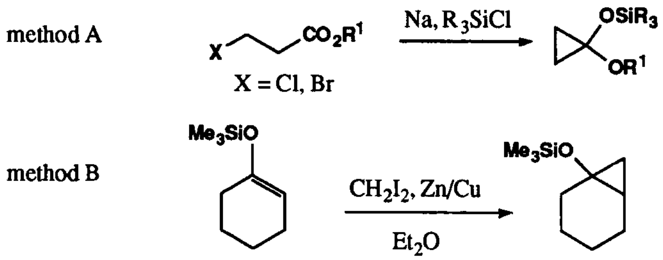
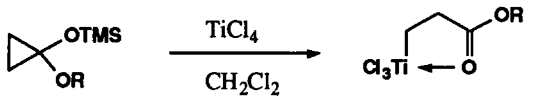


Fig. 5

a. Titanium Homoenolates

Treatment of the silyloxycyclopropanes 1a,b,c with $TiCl_4$ in CH_2Cl_2 results in the formation of the corresponding titanium homoenolates (Eq. 4). The homoenolate crystallizes from hexane and has been shown to contain only one homoenolate moiety per Ti center.[11] The addition of a second equivalent of the silyloxycycopropane does not incorporate a second homoenolate moiety per titanium. The structure is supported by ^1H and ^{13}C NMR which both showed two nonequivalent methylenes (not a cyclopropane derivative) and a very low field signal in the ^{13}C NMR which is characteristic of the C3 carbon bound to the metal center.[12] The IR spectrum shows a carbonyl stretch at about 1600 cm^{-1} which supports the proposed chelate structure. The titanium homoenolates are sensitive to oxygen and water, but are thermally stable due to the internal chelation of the ester to the metal center.



(4)

R =			
Me	1a		(70%)
Et	1b		(83%)
i-Pr	1c		(89%)

Two pathways [A] and [B] are possible for the formation of the homoenolate through cleavage of the cyclopropane (Fig. 6). Pathway [A] would not seem likely because common Lewis acids do not react. Pathway [B] is supported by the isolation of the titanium homoenolate and by the known σ coordination of cyclopropanes to heavy metals.[12]

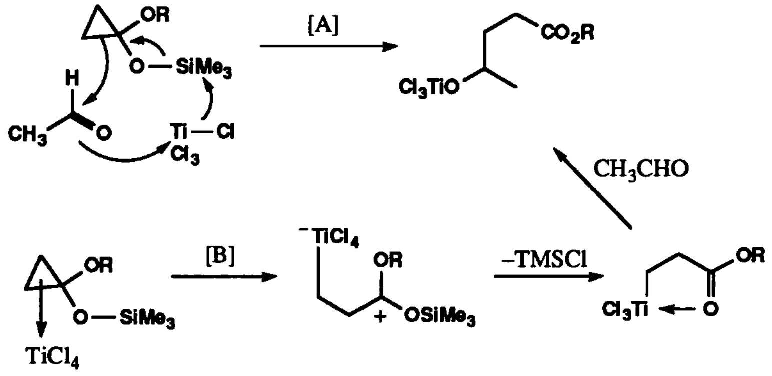


Fig 6

Titanium homoenolates react with a variety of aldehydes (Fig. 7, Table 1) to form the

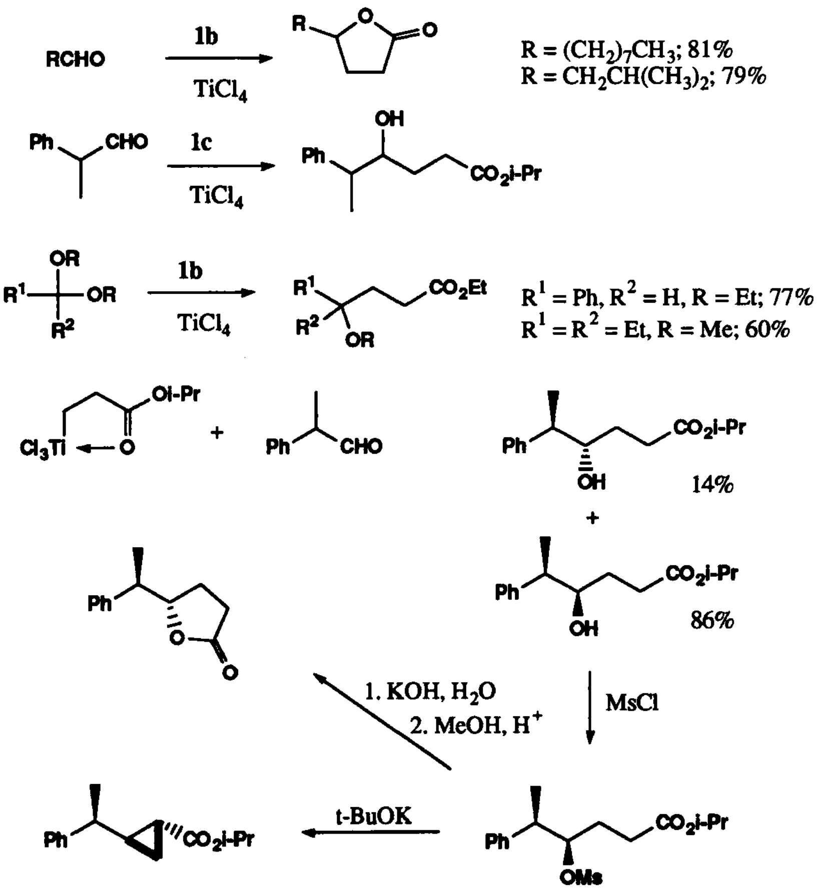
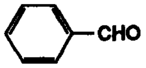
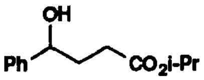
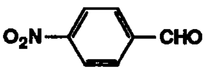
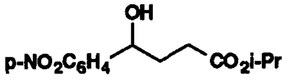
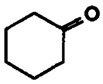
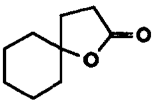
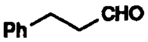
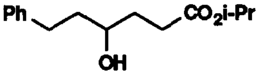
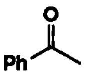
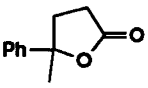
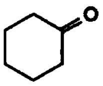
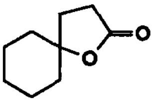
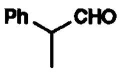
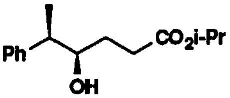
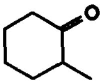
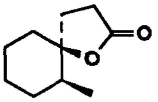
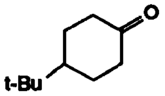
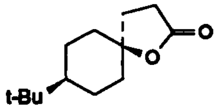
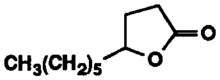
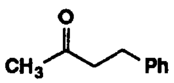
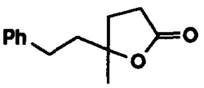
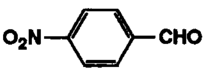
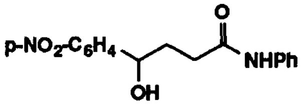


Fig. 7

TABLE 1. Addition of Titanium Homoenolates to Aldehydes

Entry	Carbonyl Compound	Product	Yield
1			90%[a]
2			97%[a]
3			62%[a]
4			86%[b]
5			93%[b]
6			91%[b]
7			81%[b] (86:14)
8			81%[b] (86:14)
9			94%[b] (88:12)
10	$CH_3(CH_2)_5CHO$		61%[c]
11			54%[c]
12			83%[c]

a). 0.5 equiv. Ti(Oi-Pr)$_4$ b) 0.5 equiv. Ti(Ot-Bu)$_4$ c) see ref 13

corresponding alcohols or butyrolactones.[12,13] They also react with acetals of ketones and aldehydes, but due to their limited nucleophilicity they do not ordinarily react with ketones. Acetophenone reacts in low yield and acyl chlorides do not normally react at all. Chlorination is often a problem when aromatic or unsaturated aldehydes are used. The limited nucleophilicity is due to the electron withdrawing effect of the chloride ligands on the titanium. The use of alkoxide ligands has improved both the yields and the range of reactivity of titanium homoenolates. The use of 0.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ or $Ti(O\text{-}t\text{-}Bu)_4$ as an additive illustrates this improvement: the yields on reaction with aldehydes are improved and ketones react in good yield. Good levels of diastereoselectivity are observed (ca. 86%) (see entries 7, 8 and 9; Table 1). The use of alkoxide modified titanium homoenolates allows the stereoselective preparation of γ-lactones and cyclopropane carboxylates.

The use of titanium homoenolates derived from tin homoenolates has also been described by Goswami (Fig. 8).[14] A direct transmetallation from tin to titanium as opposed to the intermediacy of a siloxycyclopropane is supported by deuterium labelling experiments.

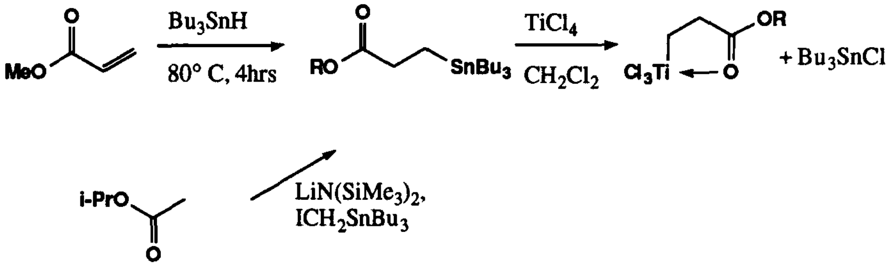
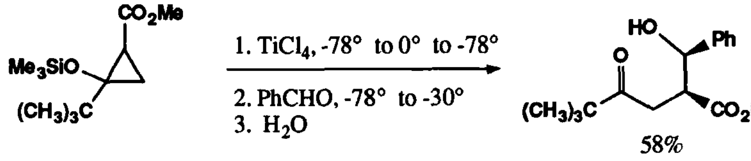


Fig. 8

Reaction of the siloxycyclopropane shown in Eq. 5 with titanium tetrachloride followed by benzaldehyde produced the aldol product with high diastereoselection in good yield.[15] This reaction could be viewed as an enolate and not a homoenolate reaction.



(5)

b. Tin Homoenolates

Treatment of the siloxycyclopropanes **1a,b,c** with 1 equivalent of $SnCl_4$ results in the formation of the tin homoenolate **3a,b,c** (Fig. 9).[16] The addition of a second equivalent of siloxycyclopropane leads to the formation of the homoenolate **4a,b** containing two homoenolate moieties per metal center. If Bu_3SnOTf is used instead of $SnCl_4$ the nonchelated homoenolate **5** is obtained. The chemical reactivity of **5** has not been investigated but is assumed to be limited.

Murai reported the preparation of tin homoenolates from ketones and aldehydes which can lead to unsaturated ketones and aldehydes after dehydrostannation in DMSO (Fig. 10);[17] a similar reaction is obtained with the tellurium homoenolates (obtained from $TeCl_4$).[18] No homoenolate formation has been reported with $GeCl_4$, $SiCl_4$, Me_3SiCl, Me_3SiOTf or $PbCl_2$. Metal homoenolates have been prepared from the action of $SbCl_5$ and $BiCl_3$ but their reactivity has not been demonstrated.[16]

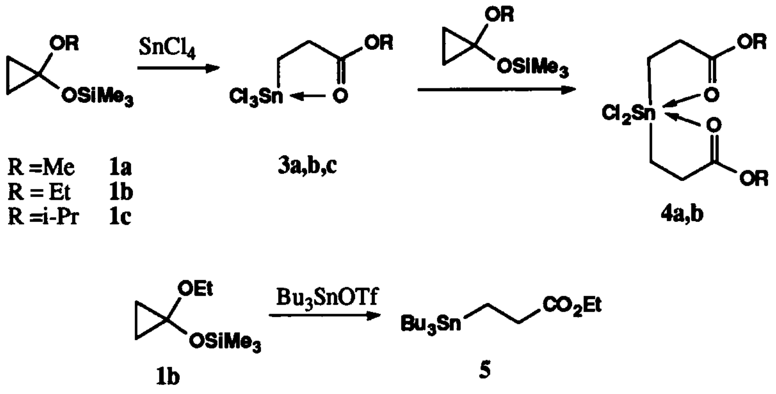


Fig. 9

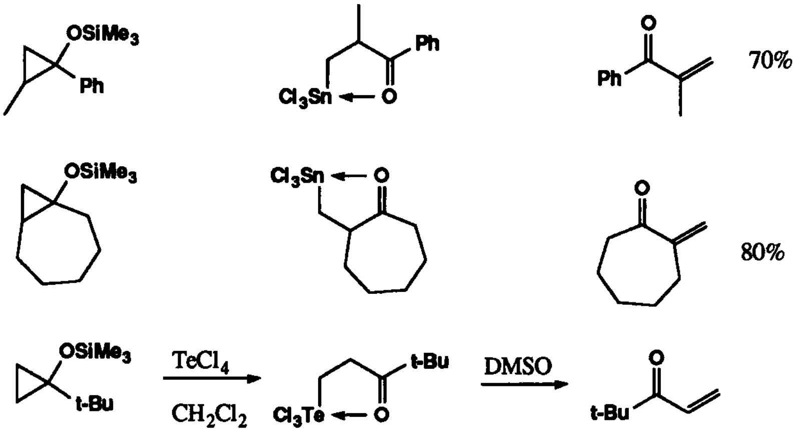
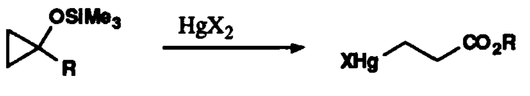


Fig. 10

c. Mercury Homoenolates

Mercury (II) is known to react with cyclopropanes and indeed mercury homoenolates of aldehydes, ketones and esters have been prepared form the corresponding siloxycyclopropanes (Eq. 6).[16,19-21]

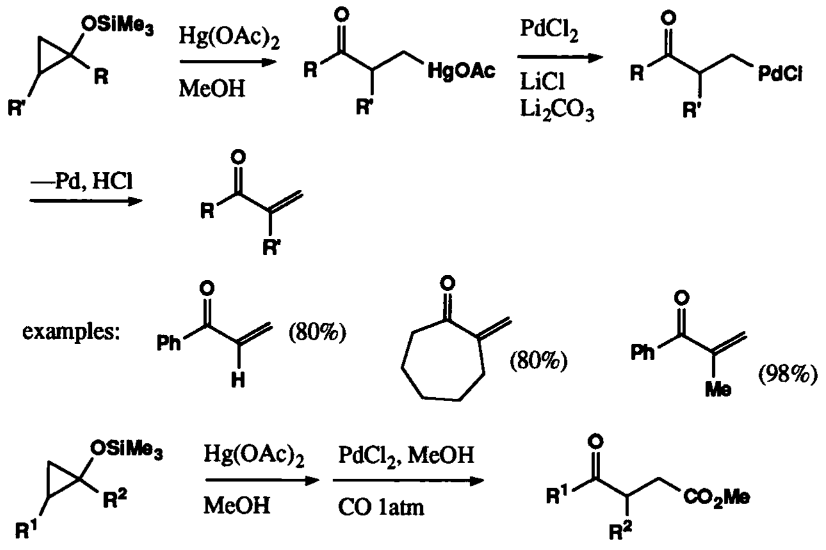


(6)

X = OAc, Cl, OCOCF$_3$
R = OEt, Oi-Pr, H, alkyl

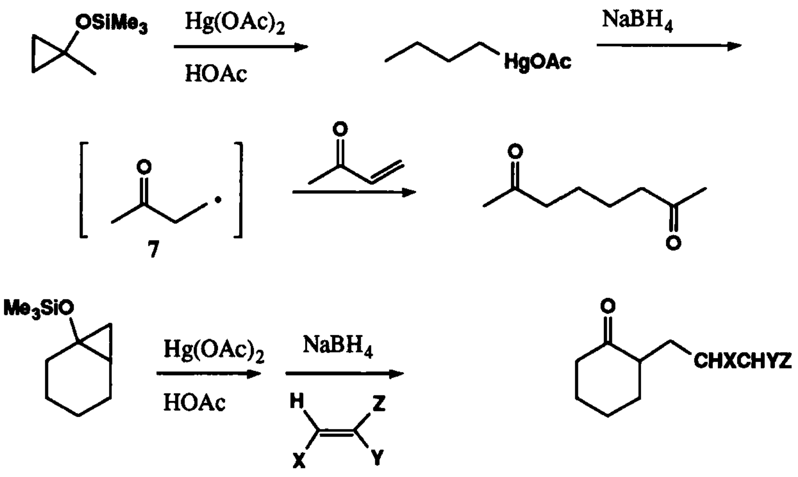
Murai and coworkers have performed dehydromercuration and carbonylative coupling on Hg homoenolates using either stoichiometric or catalytic PdCl$_2$ (Fig. 11).[19]

Giese reduced a Hg homoenolate to produce 1,4-ketoradical 7 which can then undergo additions to various functionalized alkenes (Fig. 12).[20,21] When the homoenolate is generated from a



R^1 = t-Bu, R^2 = H; 52%

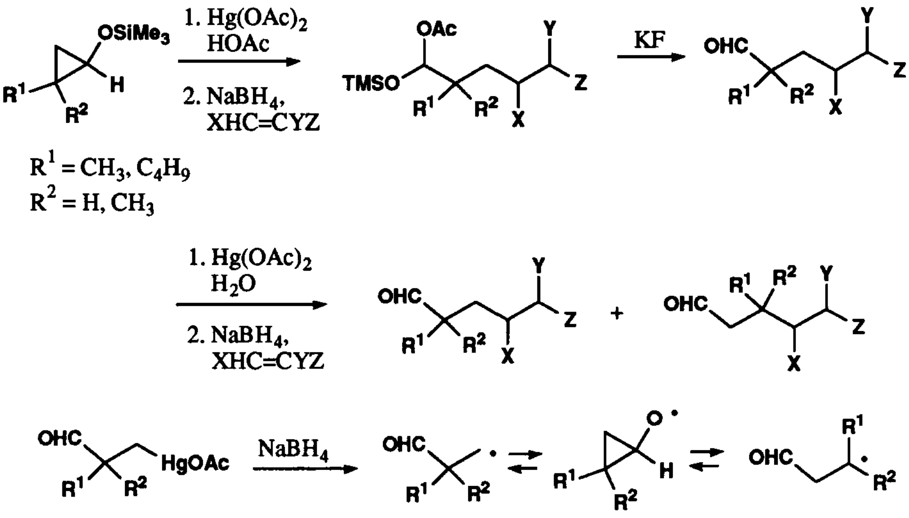
Fig. 11



X = H, CO_2Et; Y = H, Me, Cl; Z = CN, CO_2Me, CO_2Et

Fig. 12

substituted siloxycyclopropane, the position of the substituents can vary depending on the reaction conditions. This results from equilibration through the cyclopropyloxy radical species **8** (Fig. 13).

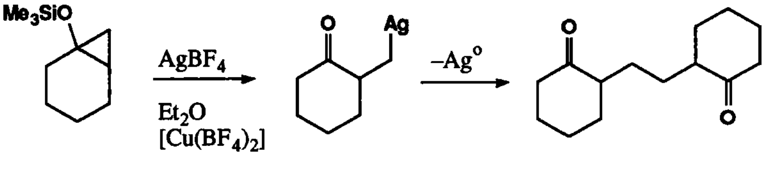


8

Fig. 13

d. Copper and Silver Homoenolates

Copper and silver homoenolates have been prepared by Murai, but have only been used in homocoupling reactions to produce 1,6-diketones (Eq. 7).[22] A silver homoenolate is a likely intermediate in the allylation of siloxycyclopropanes in the presence of silver fluoride as illustrated in Fig. 14.[23]



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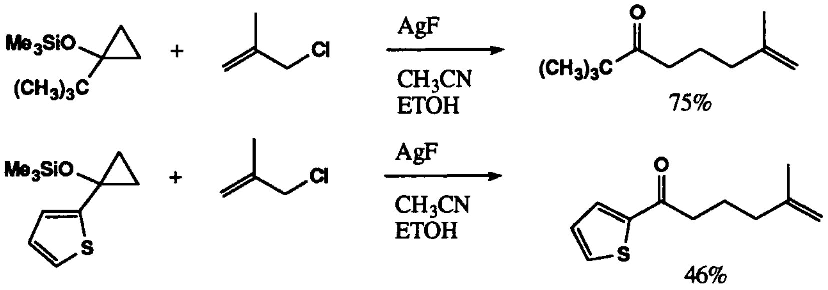
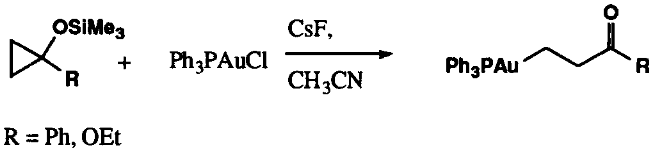


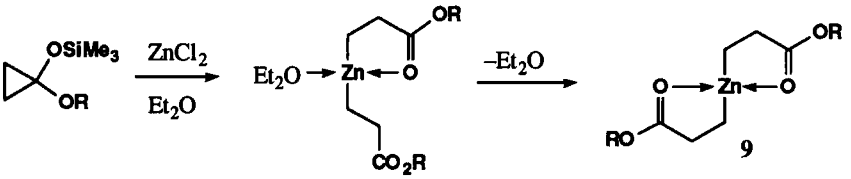
Fig. 14

Gold homoenolates have been prepared from siloxycyclopropanes by treatment with a gold halide in the presence of CsF (Eq. 8), however, they are not synthetically useful.[24,25]


(8)

e. Zinc Homoenolates

Zinc homoenolates are among the only stable and chemically reactive metal homoenolates. They have been extensively studied by Nakamura and Kuwajima. Treatment of siloxycyclopropanes **1a,b,c** with $ZnCl_2$ in ethyl ether results in the formation of a zinc homoenolate **9** containing two homoenolate moieties per metal center (Eq. 9).[26,27]


(9)

The copper catalyzed addition of zinc homoenolates to enones, unsaturated aldehydes and acetylenic esters and ketones proceeds in high yield to produce the silyl enol ethers of the adducts (Fig. 15, Table 2).[26-28] The presence of trimethylsilyl chloride and hexamethylphosphoramide (HMPA) are essential for the success of these reactions. The best conditions are as follows: 2.3 equiv of siloxycyclopropane, 2.4 equiv. of TMSCl, 0.12 equiv Cu(I), 2.4 equiv. of HMPA and 1 equiv of substrate in an ether-THF solvent mixture. While the zinc reagent contains two homoenolates bound to each zinc atom, only one of the homoenolates can be transferred; the second is unreactive.

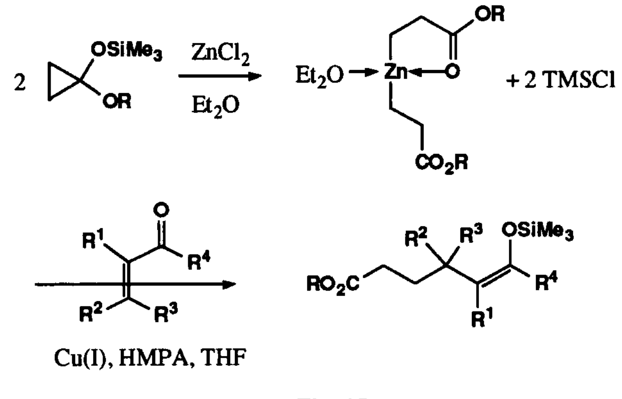
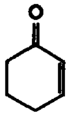
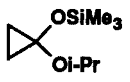
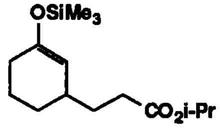
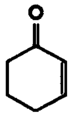
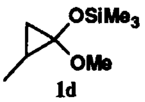
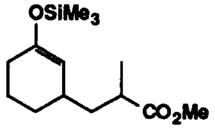
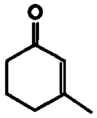
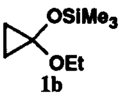
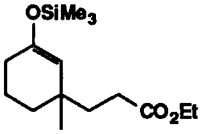
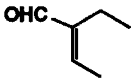
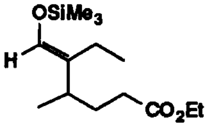
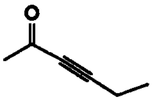
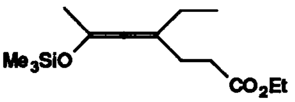
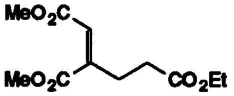


Fig. 15

The synthesis of highly substituted cyclopentenones has been developed in our laboratory by taking advantage of the conjugate addition of zinc homoenolates on acetylenic esters and amides followed by intramolecular capture of the resulting silyl allenolate (Fig. 16, Table 3).[29]

TABLE 2. Conjugate Addition of Zinc Homoenolates to Unsaturated Carbonyls

Entry	Enone/acetylenic ester	Cyclopropane	Product	Yield
1		 1c		93%
2		 1d		91%
3		 1b		92%
4		1b		75%
5		1b		73%
6	$MeO_2C-C\equiv C-CO_2Me$	1b		63%

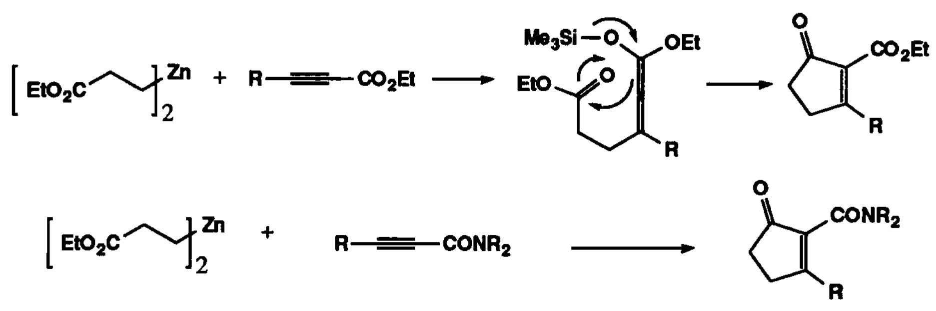
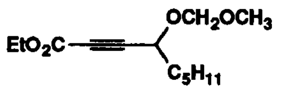
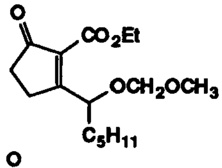
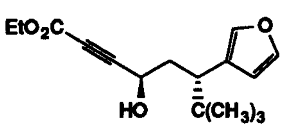
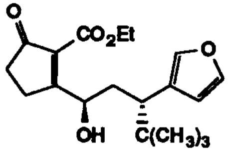
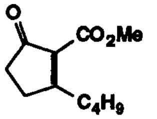


Fig. 16

Zinc homoenolates react rapidly with acyl chlorides in the presence of Cu or Pd catalysts, but C and O acylation compete (Table 4).[27,28] Acylation on carbon results when ether or THF in combination with HMPA is used as solvent while acylation on oxygen occurs in CH_2Cl_2 or $CHCl_3$.

TABLE 3. Addition-Cyclization of Zinc Homoenolates to Acetylenic Esters

Entry	Enone/acetylenic ester	Cyclopropane	Product	Yield
1		1b		71%
2		1b		83%
3	$MeO_2C-\equiv-C_4H_9$	1b		65%

Highly selective S_N2' reaction on allylic halides can be effected with zinc homoenolates in the presence of Cu(I) and cosolvents such as DMF or HMPA (Fig. 17).[27,28] Addition of TMSCl is not required and therefore selective allylation can be performed in the presence of unsaturated ketones. Direct nucleophilic substitution (S_N2) is generally not useful with zinc homoenolates.

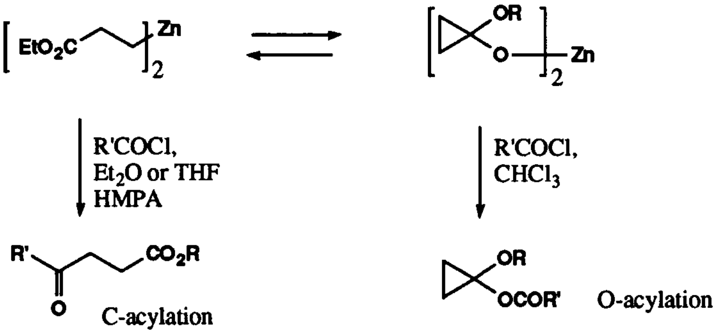
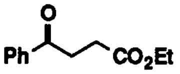
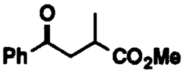
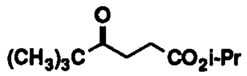
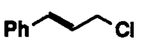
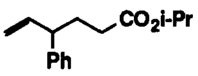
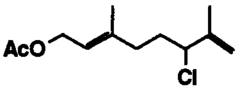
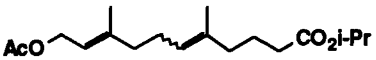
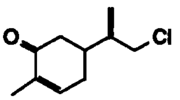
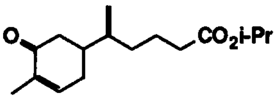
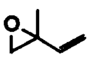
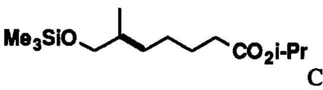
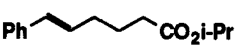
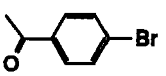
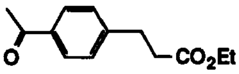
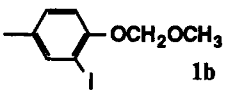
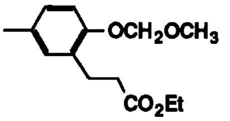
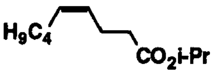
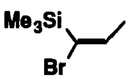
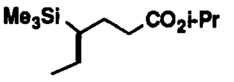


Fig. 17

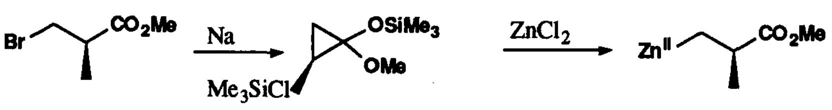
Coupling of zinc homoenolates to aryl, or vinyl halides can be readily accomplished with the use of Pd or Ni catalysts (Table 4).[27,28,30] Iodides are more reactive than the corresponding bromides and two homoenolate moieties can be transferred from the zinc reagent when it is coupled to iodobenzene. No reaction is obtained in the Pd or Ni catalyzed coupling of aryl triflates with zinc homoenolates, but the vinyl triflate derived from cyclohexanone reacts to give a 55% yield of the product derived from coupling with the homoenolate.

Chiral zinc honoenolates have been prepared from *S* and *R* β-bromoisobutyrates through conversion to the chiral siloxycyclopropanes 1e and 1f (Eq. 10).[31] No racemization occurs during the

TABLE 4. Coupling of Homoenolates to Acyl, Vinyl and Aryl Halides

Entry	Electrophile	Cyclopropane	Product	Catalyst	Yield
1	PhCOCl	1b		Cu^I, HMPA	76%
2	PhCOCl	1d		Pd	93%
3	$(CH_3)_3CCOCl$	1c		Pd	93%
4		1c		Cu^I, HMPA	97%
5		1c		Cu^I, HMPA	72%
6		1c		Cu^I, HMPA	87%
7		1c		Cu^I, HMPA	48%
8		1c		$NiCl_2$dppe TMSCl, HMPA	65%
9		1b		Pd	49%
10		1b		Pd	73%
11		1c		Pd	76%
12		1b		Pd	87%

preparation. These chiral homoenolates have been used to perform many of the reactions previously carried out with the simple zinc homoenolate (Table 5). Another method developed by Yoshida allows preparation of the homoenolate directly from the halide.[32]

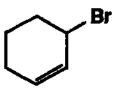
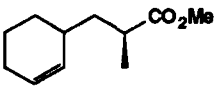
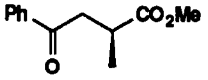
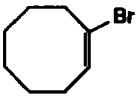
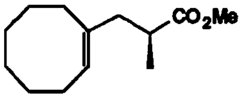
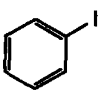
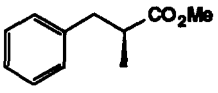


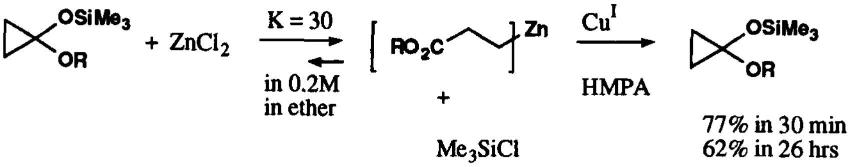
(10)

S *R* *S* 1e *R* 1f *S* 9f *R* 9f

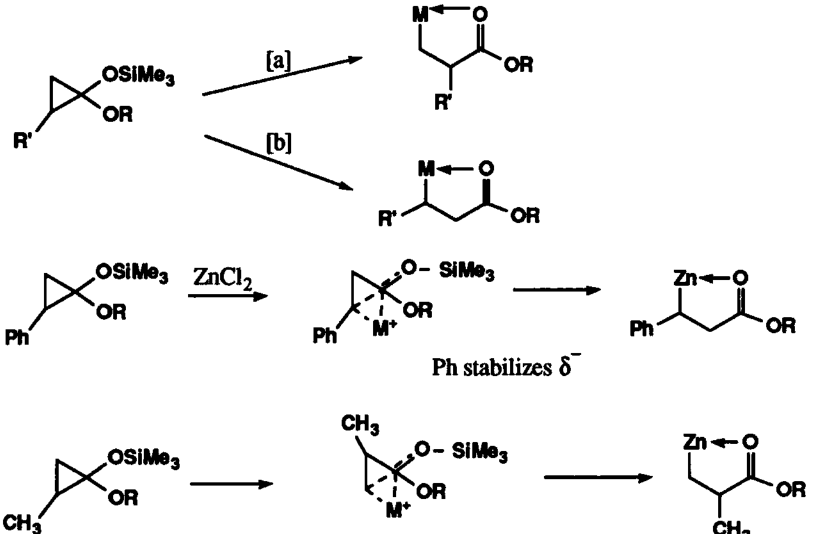
It is important to note that the formation of zinc homoenolates from siloxycyclopropanes is an equilibrium which can be shifted toward the siloxycyclopropane upon addition of Cu(I) and HMPA. When the siloxycyclopropane is substituted, the regiochemistry of the cleavage depends on the nature of the substituent. If R = phenyl the cleavage occurs at the most substituted position due to electronic stabilization.[27] If R = Me the cleavage occurs at the leastsubstituted position due to steric effects (Fig. 18). Treatment of substituted siloxycyclopropanes with $ZnCl_2$ or MeOLi results in >98% regioselectivity while cleavage with $Hg(OAc)_2$ or $TiCl_4$ is less selective.[12] The absence of racemization in the chiral zinc homoenolates mentioned above is due to the high regioselectivity in the cleavage of the siloxycyclopropane to the zinc homoenolate; k_b is very slow compared to k_a (Fig. 19).

TABLE 5. Coupling of Chiral Homoenolates to Halides

Entry	Electrophile	Product	yield (%e.e)
1			59% (96)
2	PhCOCl		55% (>91)
3			85% (>90)
4			79% (95)



(11)



Ph stabilizes δ^-

M^+ coordinates to least hindered σ bond

Fig. 18

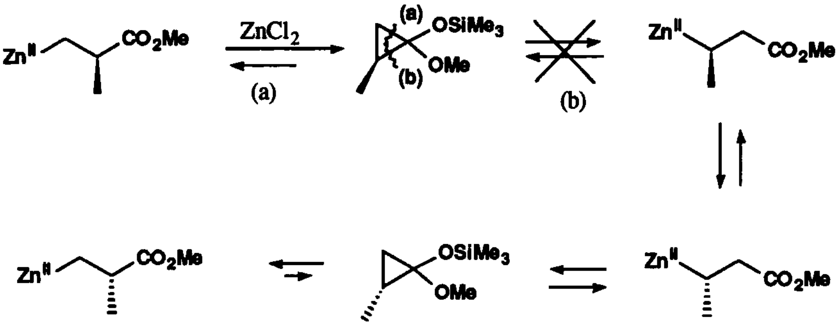


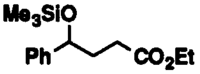
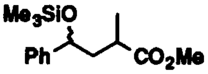
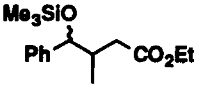
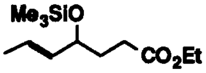
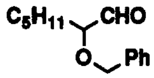
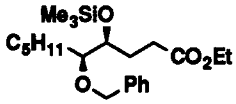
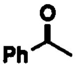
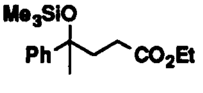
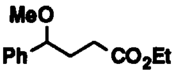
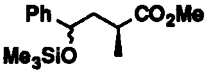
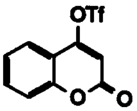
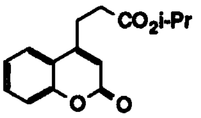
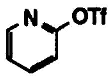
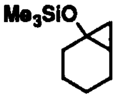
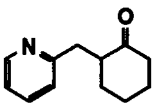
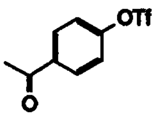
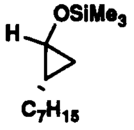
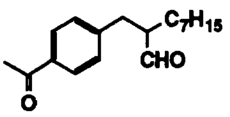
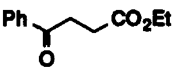
Fig. 19

III. DIRECT COUPLING OF SILYLOXYCYCLOPROPANES TO ELECTROPHILES

Homo-Reformatsky Reactions with ZnX_2 Catalysis

Zinc homoenolates are virtually unreactive to benzaldehyde and acetophenone in a variety of solvents even in the presence of HMPA, however, the presence of one equivalent of TMSCl allows the reaction to proceed in dichloromethane (no reaction in diethyl ether). The regeneration of $ZnCl_2$ when the reaction is mediated by TMSCl gives rise to a version of the reaction in which the siloxycyclopropane is directly coupled to the carbonyl compound.[27,28,33] Treatment of the siloxycyclopropane with aldehydes in the presence of 2 mole % ZnI_2 (or $ZnCl_2$) in CH_2Cl_2 at 25°C afford the corresponding γ-siloxyester in good yield. Ketones other than acetophenone are unreactive, but benzaldehyde dimethyl acetal also reacts under the same conditions.

TABLE 6. Direct Coupling of Siloxycyclopropanes to Electrophiles

Entry	Electrophile	Cyclopropane	Product	Catalyst	Yield
1	PhCHO	1b		ZnI_2	89%
2	PhCHO	1d		ZnI_2 $ZnCl_2$	72% 56%
3	PhCHO	1e		$ZnCl_2$	83%
4		1b		ZnI_2	72%
5		1b		$ZnCl_2$	79%
6		1b		ZnI_2 $ZnCl_2$	77% 0%
7	PhCH(OMe)$_2$	1b		ZnI_2 $ZnCl_2$	91% 0%
8	PhCHO	1d		ZnI_2	72%
9		1c		Pd	90%
10				Pd	50%
11				Pd	65%
12	PhCOCl	1b		Pd	86%

Chelation controlled 1,2 asymmetric induction is observed in the reaction with 2-alkoxyaldehydes (93% stereoselectivity). The previously discussed regioselectivity with methyl or phenyl substituted siloxycyclopropanes is also observed in the catalytic homo-Reformatsky reaction.[31] Optically pure siloxycyclopropanes result in nearly complete chirality transfer in the catalytic homo-Reformatsky reaction.

The catalytic cycle shown in Fig. 20 has been proposed to account for the accelerating effect of TMSX through activation of the carbonyl oxygen. The wider use of ZnI_2 is consistent with higher Lewis acidity of TMSI. Siloxycyclopropanes derived from esters ketones and aldehydes have been coupled to aryl triflates in the presence of 5 mole % $[PdCl(C_3H_5)]_2$ and PPh_3.[34] The reaction is presumably induced by the coordination of the cyclopropane to an electron deficient Pd-(ArOTf) complex. The reaction tolerates a variety of functional groups: CHO, ketones, COOR, NO_2. No reaction is observed with aryl halides.

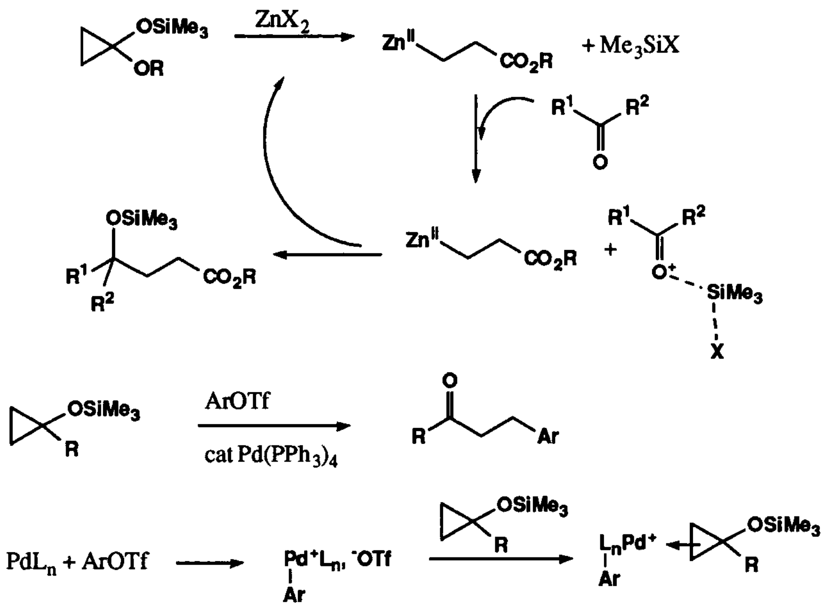
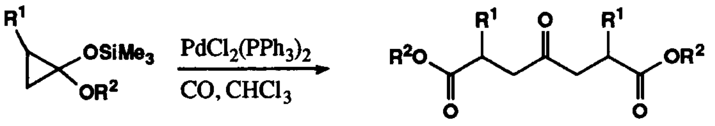


Fig. 20

Dimerization of homoenolates accompanied by CO insertion has been obtained in the presence of 5 mole % $PdCl_2(PPH_3)_2$ in chloroform (Eq. 12).[35] The reaction has been carried out with an optically pure siloxycyclopropane with no racemization.



(12)

The direct coupling of acyl chlorides to the siloxycyclopropanes which was not possible with catalytic ZnX_2 has been successfully executed with a Pd catalyst.[36] Carbonylative arylation of siloxycyclopropanes catalyzed by Pd° has also been recently achieved (Fig. 21).[37,38]

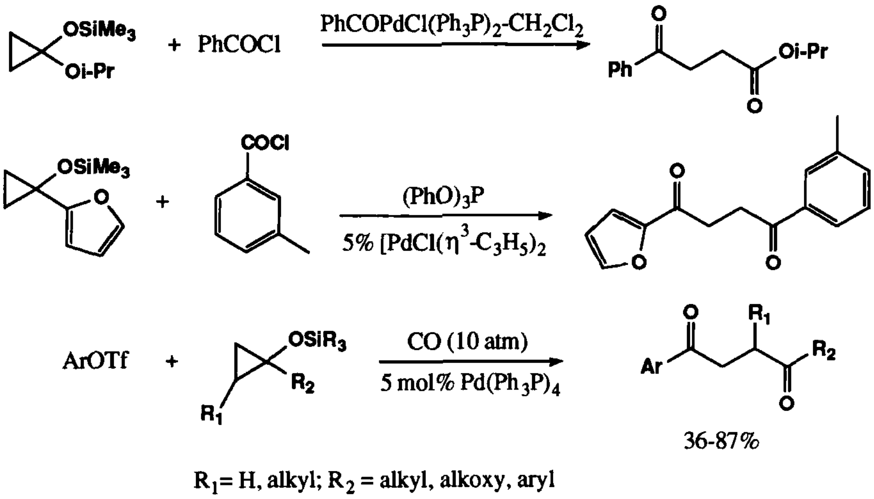


Fig. 21

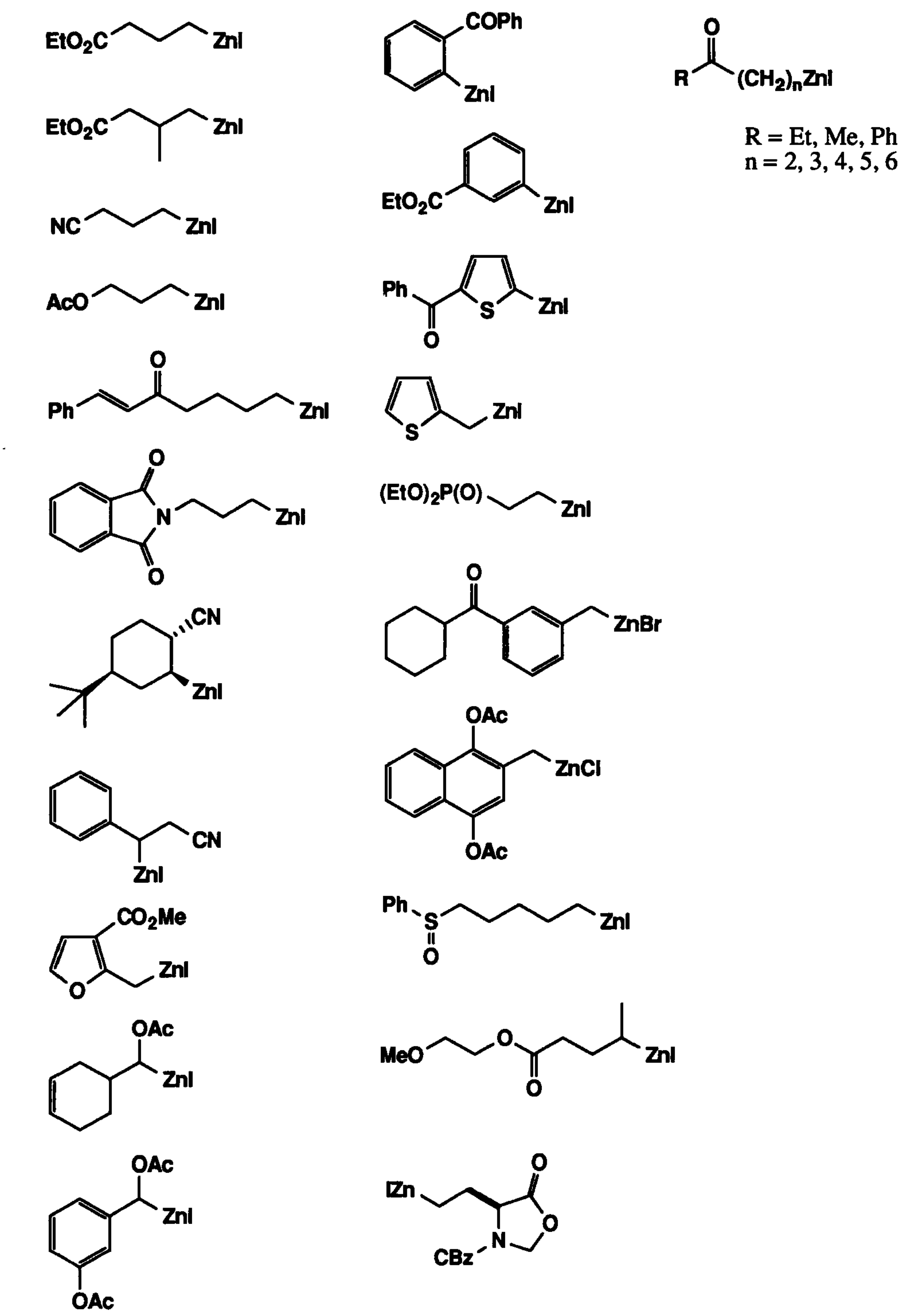
IV. FUNCTIONALIZED ORGANOZINC REAGENTS

Other methods for the preparation of homoenolates and various functionalized organometallics have been developed by Knochel, Yoshida, Riecke and Fukuzawa. The treatment of functionalized halides with activated zinc results in the formation of functionalized organozinc reagents. Several methods are known for the activation of zinc:[39] washing the zinc with HCl,[40] ultrasonic cleaning,[41] use of Zn/Cu couple,[32,42] use of Zn/Ag couple,[31] use of 1,2-dibromoethane[43] and TMSCl[44,45] as activating agents and preparation of highly activated zinc by the reduction of ZnX_2 with alkali metals.[46] These functionalized zinc reagents (see Table 7) have recently been shown by Knochel to be very weak bases in contrast to the corresponding Grignard or organolithium reagents.[47] They can be generated in the presence of benzyl amine, diethyl malonate and in some instances, *t*-butanol (Fig. 22). This is clearly one of the major advantages to these reagents allowing them to tolerate a wide variety of reactive or somewhat acidic functional groups. Even functionalized zinc reagents containing primary or secondary amides or acetylenic hydrogens have been prepared and further elaborated.[47]

a. Conjugate Addition

Most of the zinc reagents prepared by the methods mentioned above can be converted to the corresponding functionalized "organozinc cuprates" by treatment with a THF soluble CuCN-2LiCl salt.[45] These "organozinc cuprates" react with α,β-unsaturated ketones and aldehydes in the presence of TMSCl to give the corresponding β-substituted ketone or aldehyde (Table 8) (some substrates require the addition of HMPA to the reaction mixture).[45,48-51]

TABLE 7. Functionalized Organozinc Reagents



R = Et, Me, Ph
n = 2, 3, 4, 5, 6

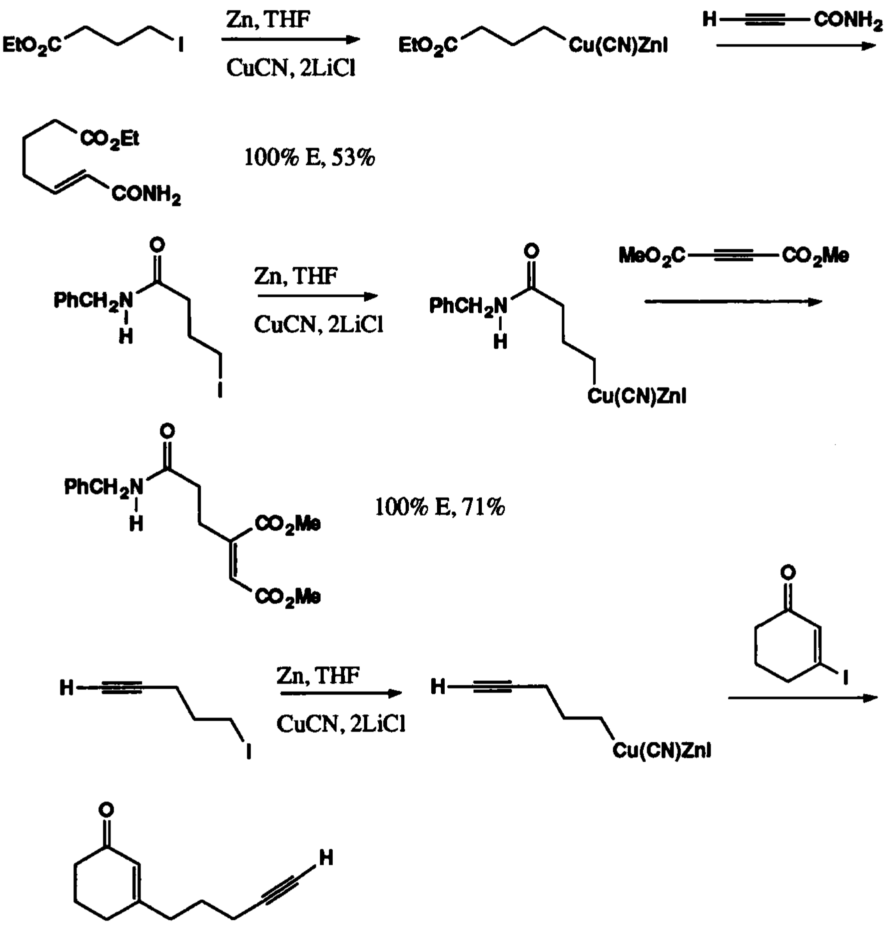


Fig. 22

Addition-elimination on β-haloenones results in the formation of β-substituted enones (Table 9).[48-50,52,53] Addition of "organozinc cuprates" to β-substituted enones does not readily occur without the use of $BF_3 \cdot Et_2O$ as a catalyst (Table 10). One example of intramolecular trapping of the enolate has been observed (Fig. 23).[54]

The conjugate addition of functionalized zinc-copper reagents to acetylenic esters in the the presence of TMSCl affords either the ethylenic esters, the C-silylated unsaturated esters or a mixture of both (HMPA is required in some examples, Table 11, Fig. 24).[50,51,55,56]

Conjugate additions to nitro olefins and unsaturated nitriles result in the corresponding functionalized nitro compounds or nitriles.[57,58] When the nitro compound is α-substituted a mixture of nitroalkane and the corresponding ketone (Nef reaction) is obtained; treatment of the mixture with aqueous acid leads to the ketone exclusively (Table 12).

TABLE 8. Conjugate Addition to Enones and Enals

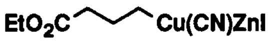
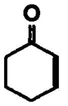
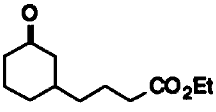
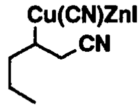
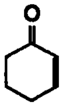
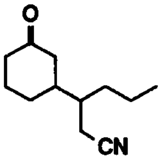
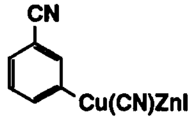
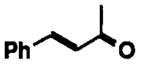
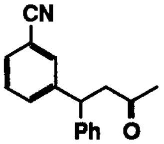
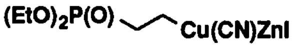
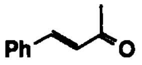
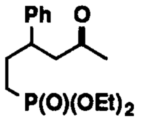
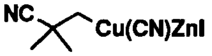
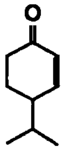
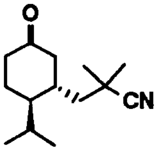
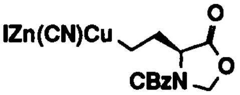
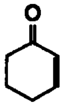
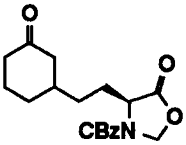
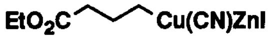
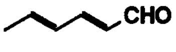
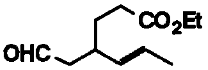
FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
			97%	44
			84%	47
			61%	48
			88%	49
			54%	50
			71%	50
			73%	50

TABLE 9. Conjugate Addition to β-Haloenones

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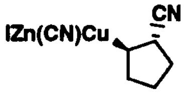
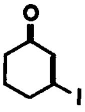
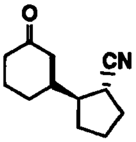
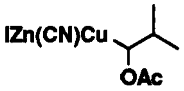
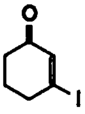
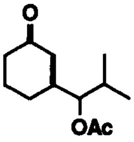
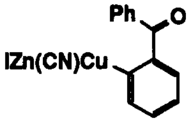
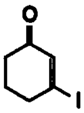
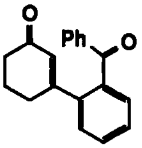
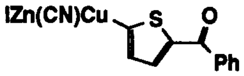
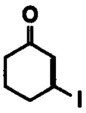
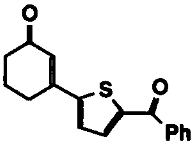
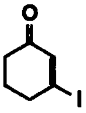
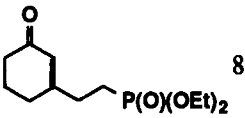
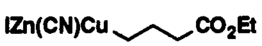
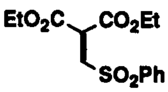
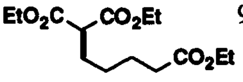
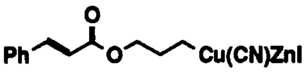
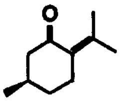
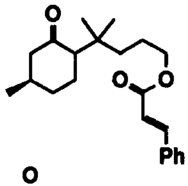
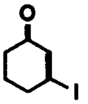
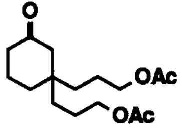
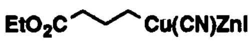
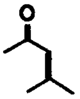
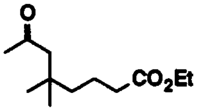
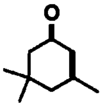
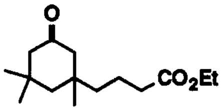
			80%	47
			97%	51
			71%	48
			88%	48
			86%	49
			90%	52

TABLE 10. Conjugate Addition to β,β-Disubstituted Enones

FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
			84%	53
			86%	53
			88%	53
			77%	50

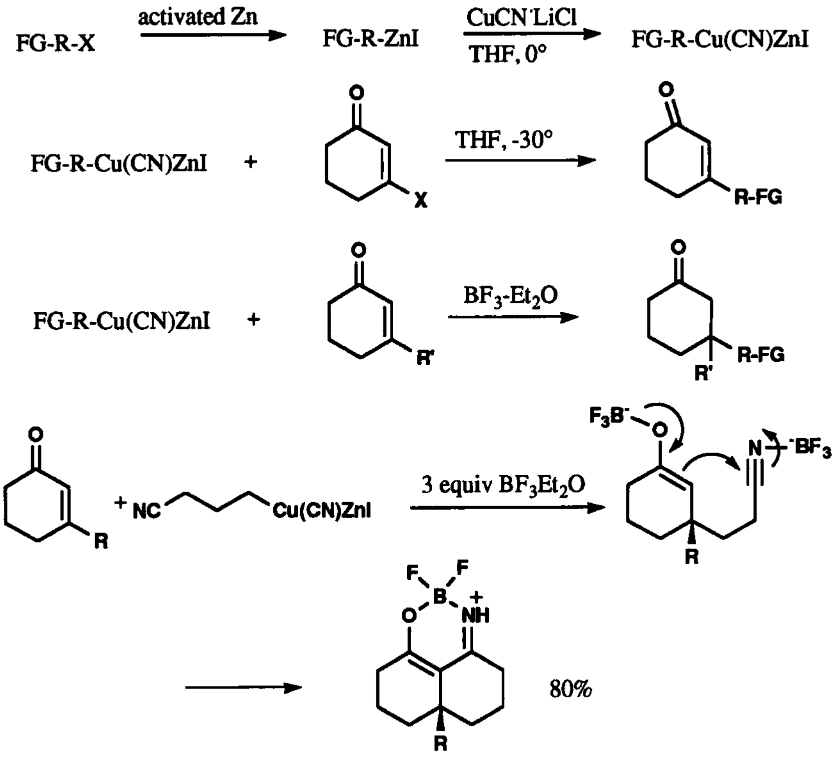


Fig. 23

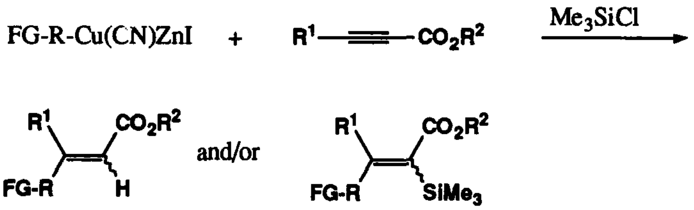
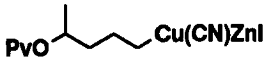
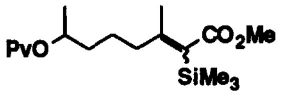
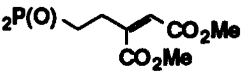
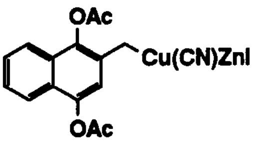
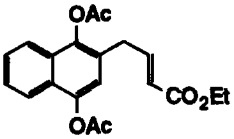
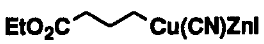
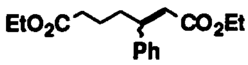


Fig. 24

TABLE 11. Conjugate Addition to Acetylenic Esters

FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
	$-\equiv-CO_2Me$		78%	54
	$MeO_2C-\equiv-CO_2Me$		91%	49
	$H-\equiv-CO_2Et$		79%	55
	$Ph-\equiv-CO_2Et$		70%	50

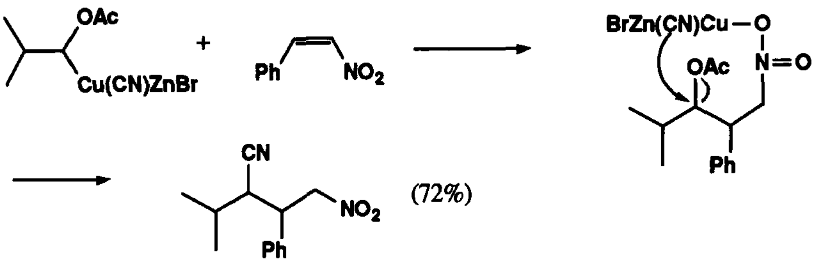
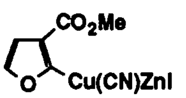
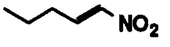
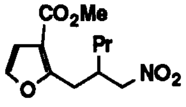
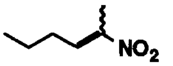
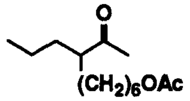
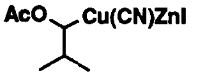
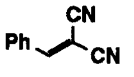
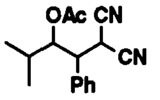


Fig. 25

TABLE 12. Conjugate Addition to Unsaturated Nitro Compounds

FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
			75%	56
$AcO(CH_2)_6Cu(CN)ZnI$			71%	56
			89%	57

b. 1,2 Addition

The 1,2 addition of functionalized organozinc reagents to acyl chlorides has been performed by Knochel using CuCN-2LiCl[45,46,48-52,56,58] to form the "organozinc cuprate" and also by Yoshida using a Pd(0) catalyst [usually $Pd(PPh_3)_4$].[32,59] Both methods result in the formation of the corresponding ketones in good yield (Table 13).

The functionalized organozinc reagents do not react with saturated aldehydes without the addition of $BF_3{\bullet}Et_2O$[60] or TMSCl.[61] However, the titanium reagents (obtained from the organozinc reagent by transmetallation) react readily to form the corresponding alcohols or lactones with fair disastereoselectivity where applicable.[58,62]

Ketones are unreactive with the organozinc reagents, but the titanium reagents can be used to prepare functionalized tertiary alcohols from ketones.[62]

c. S_N2' Reactions

Functionalized "organozinc cuprates" generally react with allylic halides to give S_N2' products. Very little direct S_N2 has been seen in the examples which have been studied. Allylic acetates and tosylates also undergo S_N2' displacement.[63,65] Several examples of double S_N2' reaction have been reported. Propargyl tosylates and bromides react to give the corresponding allenes.[65]

d. Coupling of Functionalized Organozinc Reagents with Vinyl and Aryl Halides.

Vinyl halides and triflates can be directly coupled to the functionalized organozinc reagents through the use of a Pd(0) catalyst.[46,59,67]

Arylation using Pd(0) catalysts or Ni catalysts have been reported by Yoshida and Riecke.[46,66]

TABLE 13. Coupling to Acyl Halides

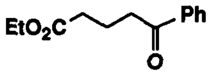
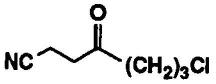
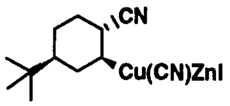
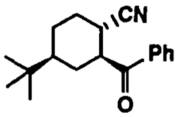
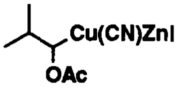
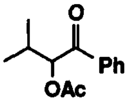
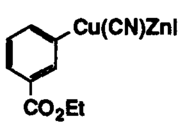
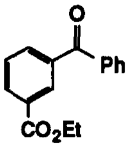
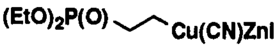
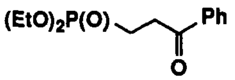
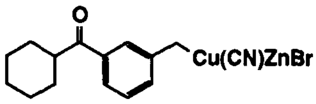
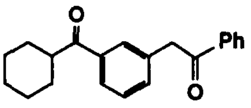
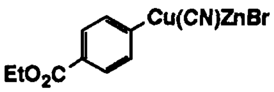
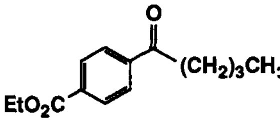
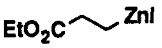
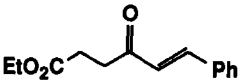
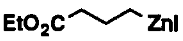
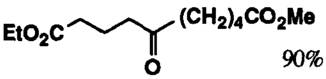
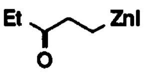
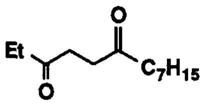
FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
	PhCOCl		87%	44
	Cl(CH$_2$)$_3$COCl		77%	57
	PhCOCl		67%	47
	PhCOCl		82%	51
	PhCOCl		67%	48
	PhCOCl		96%	49
	PhCOCl		90%	55
	CH$_3$(CH$_2$)$_3$COCl		80%	45
	PhCH=CHCOCl		92%	31
	MeO$_2$C(CH$_2$)$_4$COCl		90%	31
	C$_7$H$_{15}$COCl		62%	58

TABLE 14. Addition to Aldehydes and Ketones

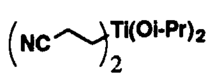
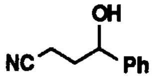
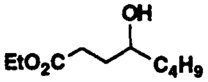
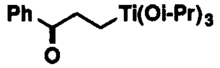
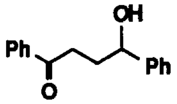
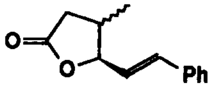
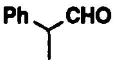
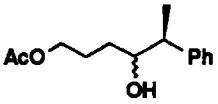
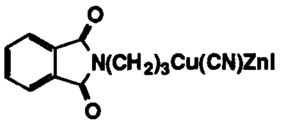
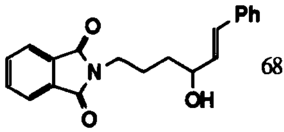
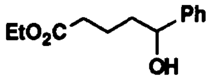
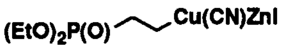
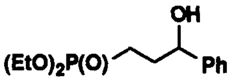
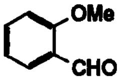
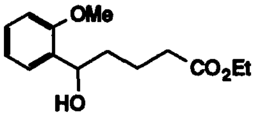
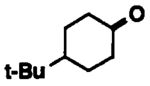
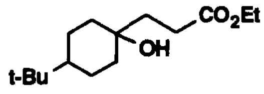
FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
	PhCHO		81%	57
	n-BuCHO		100%	61
	PhCHO		76%	61
	PhCH=CHCHO		95%	61
			77%	59
	PhCH=CHCHO		68%	59
	PhCHO		72%	59
	PhCHO		96%	49
			97%	60
			88%	61

TABLE 15. Allylic Substitution of Allyl Halides

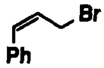
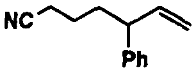
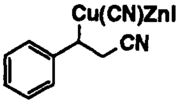
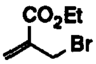
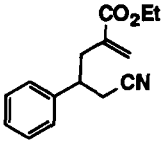
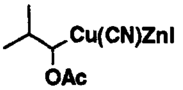
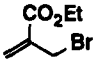
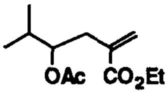
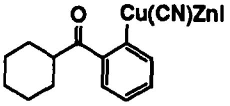
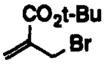
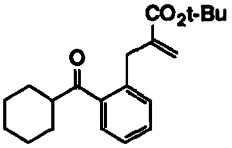
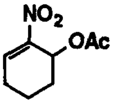
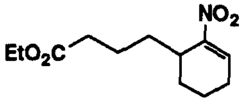
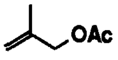
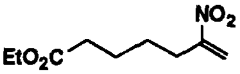
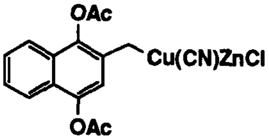
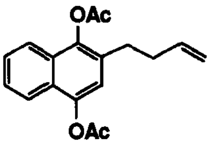
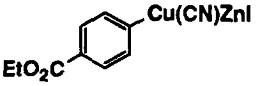
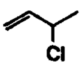
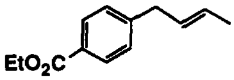
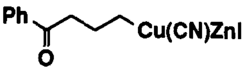
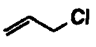
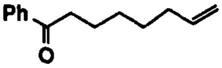
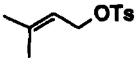
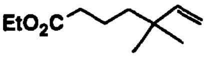
FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
			88%	57
			82%	47
			95%	51
			72%	48
			72%	56
			92%	56
			82%	55
			93%	45
			70%	58
			95%	62

TABLE 16. Substitution of Allyl and Propargyl Halides

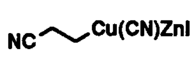
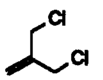
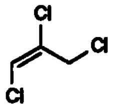
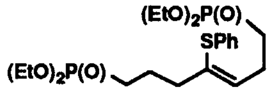
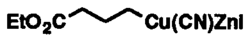
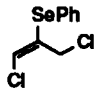
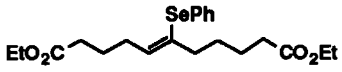
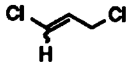
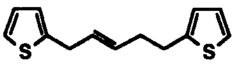
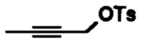
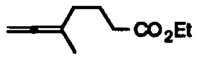
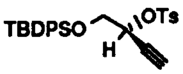
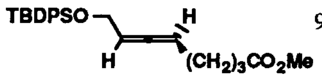
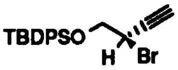
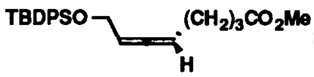
FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
			83%	57
			90%	63
			89%	63
			84%	63
			—%	62
			96%	64
			88%	64
			68%	57

TABLE 17. Coupling with Vinyl and Acetylenic Halides

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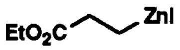
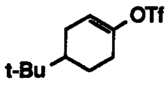
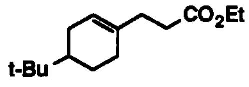
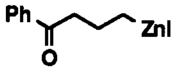
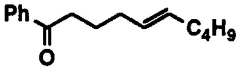
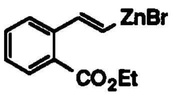
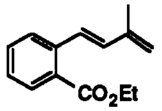
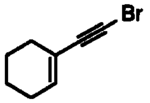
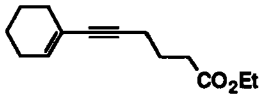
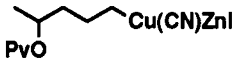
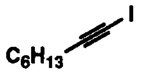
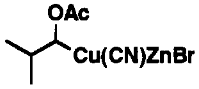
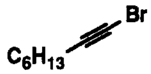
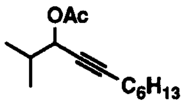
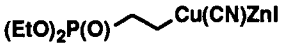
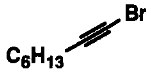
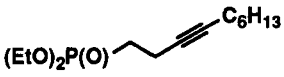
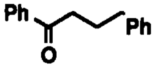
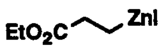
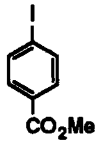
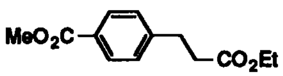
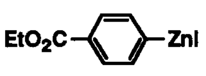
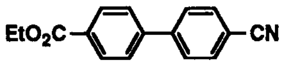
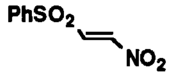
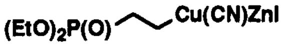
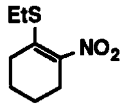
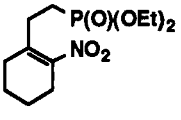
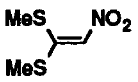
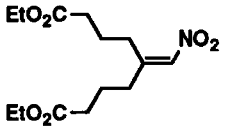
			74%	65
			89%	65
			77%	58
			93%	45
			74%	54
			75%	54
			76%	54
			89%	49

TABLE 18. Coupling with Aryl Halides and Vinyl Sulfides

FG-R-Cu(CN)ZnI	Electrophile	Product	Yield	Reference
	PhI		99%	58
			95%	65
	PhI		71%	65
			80%	45
			79%	66
			79%	66
			90%	66

A number of examples of the coupling of acetylenic halides and functionalized organozinc reagents without the aid of a transition metal catalyst have been noted by Knochel.

V. APPLICATIONS

Applications of homoenolate reagents in the total synthesis of natural products and other complex molecules has been somewhat limited to date, but these vertatile and powerful reagents should see increased use in the future due to their excellent functional group selectivity. Nakamura and Kuwajima have employed titanium ester homoenolates in two differnt ways in steroid synthesis (Fig. 26). The diastereoselective addition of a titanium homoenolate to a steroidal aldehyde served as a key step in the synthesis of depresosterol (Fig. 26).[68] Conjugate addition of a zinc ester homoenolate in the presence of BF_3 etherate produced a cortisone and andrenosterone intermediate with >97% diastereoselectivity while the TMSCl catalyzed addition gave only a 1:1 mixture (Eq. 13).[69] Paquette made use of the conjugate addition of a homoenolate in a synthetic approach to trixikingolides (Eq. 14).[70]

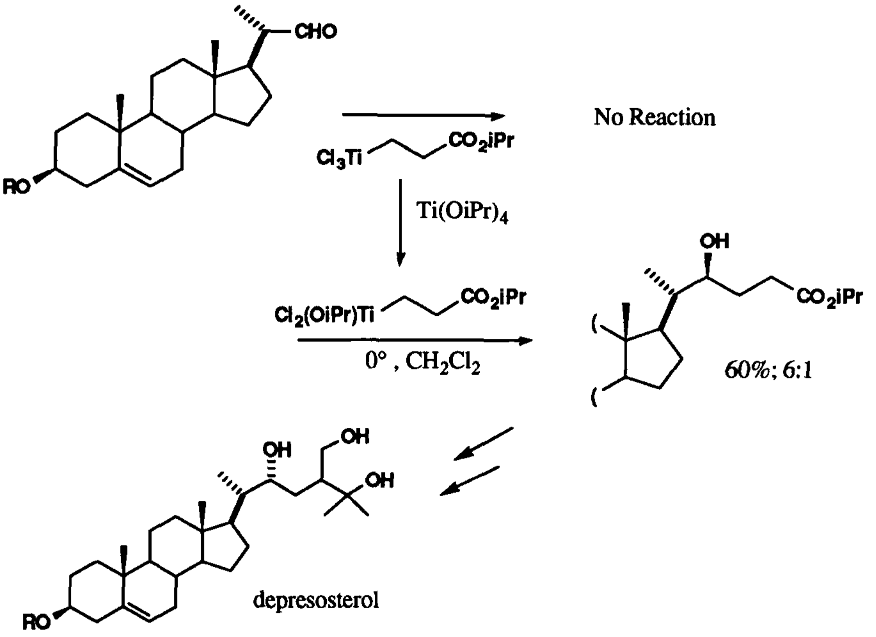
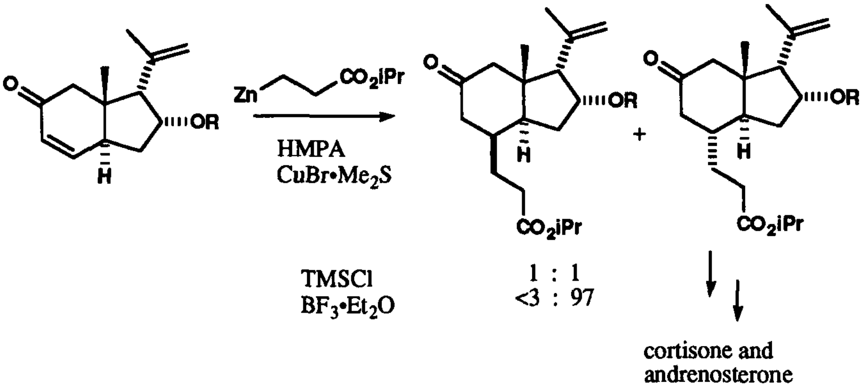
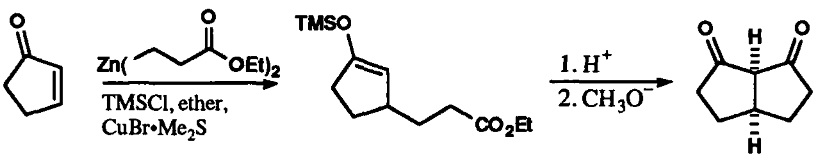


Fig. 26

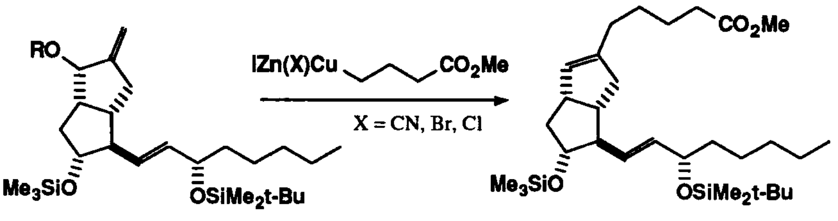


(13)



(14)

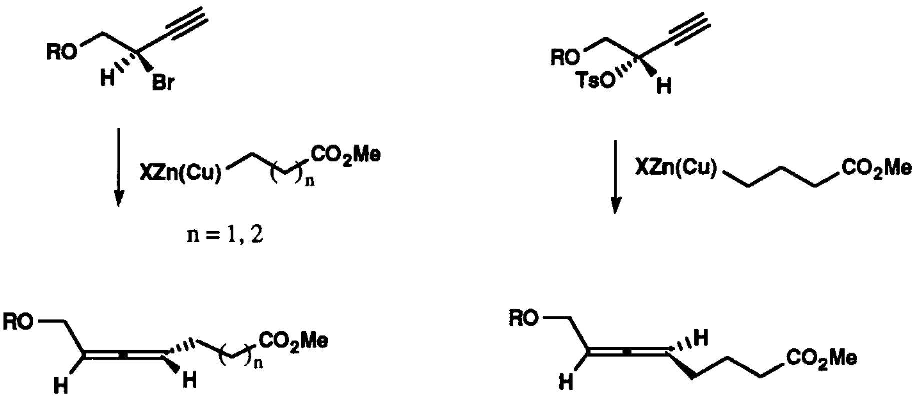
The synthesis of isocarbacyclin was accomplished by the S_N2' reaction of the zinc cuprate with an allylic phosphate in 95% yield to give the S_N2' product almost exclusively (>99%, Eq. 15).[71] The allylic tosylate displayed a lower selectivity for S_N2' reaction. An S_N2' reaction of a functionalized zinc copper reagent with an optically active propargyl bromide or tosylate was employed in the synthesis of the antifungal derivative from *Saponium japonicum*. The allenes which resulted retained very high enantiomeric purity (Fig. 27)[65]



(15)

R = $(EtO)_2PO$, $(PhO)_2PO$

95% yield, 99:1 regioselectivity



n = 1, 2

n = 1, 2; R = TBDPS, R(+)-MPT

R = TBDPS, R(+)- MPT

Fig. 27

Titanium homoenolates have been utilized by several groups in the preparation of hydroxyethylene isosteres of peptides.[72-74] Addition of the dichloro-monoisopropoxy titanium homoenalate displayed the best diastereoselectivity in additions to aminoacid derived aldehydes. Amino aldehydes which were protected as the N,N-dibenzyl amines were the most selective (Fig. 28).

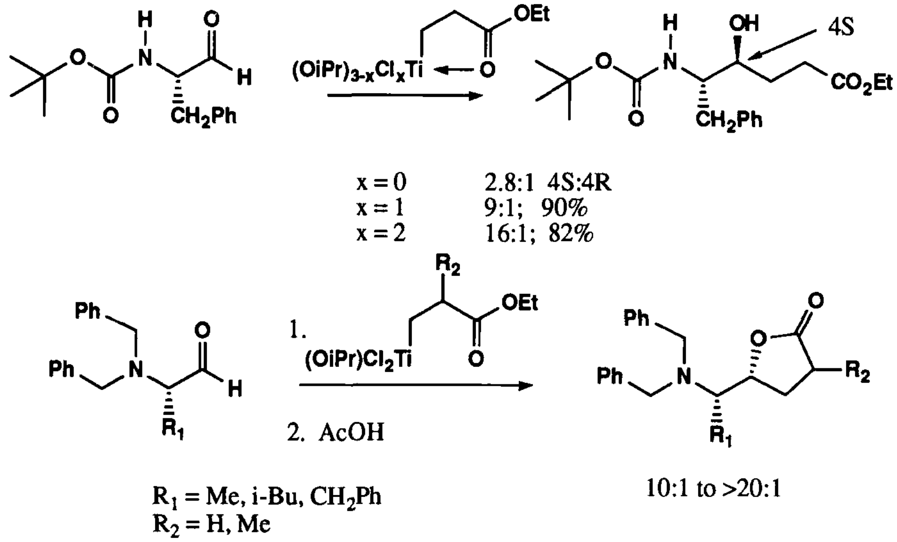


Fig. 28

The conjugate addition-cycloacylation of zinc homoenolates has been used to produce a wide variety of [2+2] photocycloaddition substrates. A typical example is the photoaddition of the cyclopentenone as a key step in a formal synthesis of bilobalide shown in Fig. 29.[75]

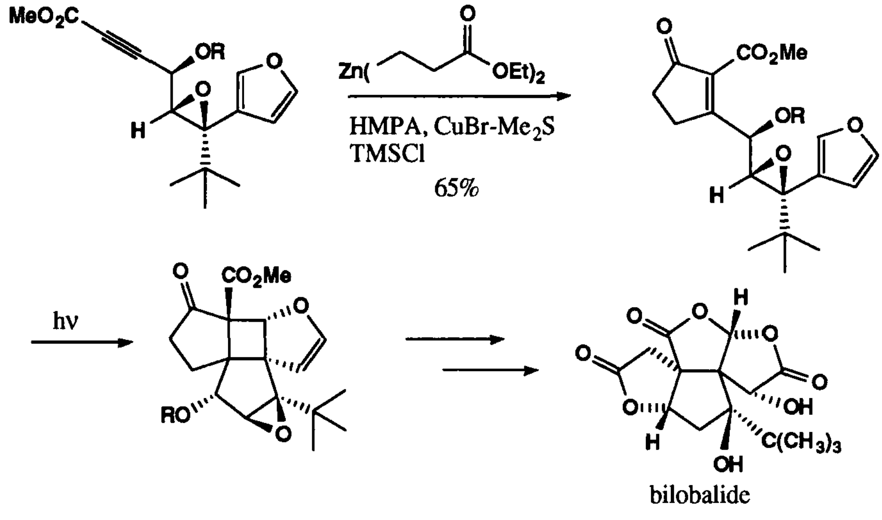


Fig. 29

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