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1-Alkoxy-1-siloxycyclopropanes as homoenolate nucleophiles of esters

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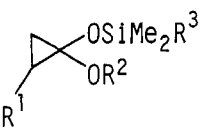
Abstract Under the influences of several metal halides, 1-alkoxy-1-siloxy-cyclopropanes undergo ring opening to yield the corresponding esters bearing metal moieties at their β-positions, namely metal homoenolates of ester, which can be used for several important carbon chain homologation processes as homoenolate nucleophiles.

INTRODUCTION

For a long period enolate anions have been used as one of the most important nucleophiles in organic synthesis, but carbonyl compounds **A** bearing nucleophilic centers at their β-positions, namely metal homoenolates (ref. 1), have not received due attention thus far. One of the major reasons is that their reactivities are critically dependent on the nature of metals; sufficiently reactive species undergo rapid cyclization to the corresponding cyclopropanol derivatives, whereas several isolable metallic species bearing [M = Sn(IV) and Hg(II)] are not reactive enough to couple with various electrophiles. Lack of general preparative method is another factor to prevent the studies on the homoenolate chemistry.

A

We have studied on the ring opening of 1-alkoxy-1-siloxycyclopropanes **1**, which are readily available from one of the following two procedures. The first method involves a reductive silylation of β-halo esters with metallic sodium or potassium-sodium alloy in the presence of chlorosilanes (ref. 2). This procedure has allowed a preparation of optically pure substrates, e.g. methyl substituted ones from commercially available R and S β-hydroxy isobutyrates via their chlorides. The second one is an application of Simmons-Smith methylenation with diiodometane and diethylzinc to ketene silyl acetals (ref. 3) and is also employable for the preparation of siloxycyclopropanes from enol silyl ethers.

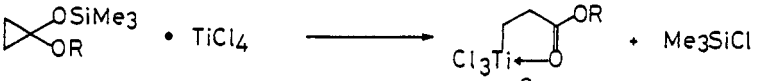


1a: R^1=H, R^2=*i*-Pr, R^3=Me
1b: R^1=H, R^2=Et, R^3=Me
1c: R^1=Me, R^2=Me, R^3=Me
1d: R^1=Ph, R^2=Et, R^3=Me
1e: R^1=Me, R^2=Me, R^3=*t*-Bu

PREPARATION OF METAL HOMOENOLATES OF ESTERS 2

In 1977, it was found in our laboratory that titanium tetrachloride effects an addition reaction of the siloxycyclopropane **1** toward aldehydes to give γ-butyrolactones (ref. 4). On this unique behavior of **1**, two mechanistic rationales were conceivable; one was based on an assumption that **1** might react in a similar manner with enol silyl ethers in the presence of Lewis acids, and the other involved an intermediary formation of titanium homoenolate species through a ring opening of the cyclopropane, which reacted with aldehydes. Based on the latter assumption, we attempted to isolate unprecedented organotitanium species **2**, and after several trial, we found treatment of titanium tetrachloride with **1** in hexane has allowed an isolation of the expected **2** as

a dark-purple needle-like crystal of extraordinary thermal stability (ref. 5). The titanium homoenolate **2** thus obtained reacted with aldehydes to afford butyrolactones or γ-chlorinated esters. Molecular weight measurement has supported it exists as a dimer possibly bridged by chlorine ligands.



1 **2**

Success in an isolation of **2** has attracted our attention on the possibility that what kind of metal halides might form similar homoenolates from the cyclopropane **1**. Accordingly, we have examined reactions of **1** with metal halides systematically, which led a finding that various metal halides have also induced similar ring opening of **1** to produce organometallics **2** bearing mono- or multi-homoenolates moiety as following: **Bu_3Sn-R, ClHg-R, Cl_3Sn-R, Cl_2Bi-R, Cl_3Ti-R, Cl_4Sb-R, ClCd-R, Cl_2Ga-R, $Zn(R)_2$, $Cl_2Sn(R)_2$, $ClBi(R)_2$, $Cl_2Te(R)_2$** (R represents $-CH_2CH_2CO_2$-i-Pr moiety)(ref. 6). Although several characteristic reactivities might be expected with other metal homoenolates, we focused attention to titanium and zinc species since they are rather familiar with organic chemists, and have attempted to develop synthetically useful reactions.

REACTIONS OF METAL HOMOENOLATES 2

(a) Titanium homoenolates

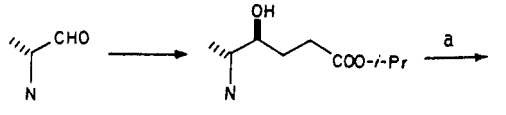
As described above, titanium homoenolate **2**(M = $TiCl_3$) reacts with several aldehydes, but its nucleophilic reactivity seems not to be sufficient for several synthetic purposes. To effect the addition to aldehydes, the reaction must be carried out at room temperature, and chlorinated products in stead of butyrolactones are formed from the reaction with aromatic or α,β-unsaturated aldehydes (Table 1)(ref. 7). Further, ketones can not be participated in this addition reaction. The observed low nucleophilic character may be attributable to the strongly electron-withdrawing chlorine ligands, which may decrease an electron density on the carbon bearing titanium. In order to enhance the reactivity of titanium homoenolates, we examined the ligand exchange of one of three chlorines into an alkoxy group. Reaction of **2** with lithium alkoxides failed to exchange the chlorine with the alkoxy group. (On such case, alkoxide appears to act as a base to decompose **2** to form low valent titanium species.)

However, it has been found that treatment of **2** (M = $TiCl_3$) with half an equivalent of $Ti(O\text{-}i\text{-}Pr)_4$ or $Ti(O\text{-}t\text{-}Bu)_4$ effected the ligand exchange smoothly to yield the alkoxytitanium homoenolates **2** (M = $Ti(O\text{-}i\text{-}Pr)Cl_2$ or $Ti(O\text{-}t\text{-}Bu)Cl_2$), whose formations were confirmed by spectroscopic analysis of the resulting solution.

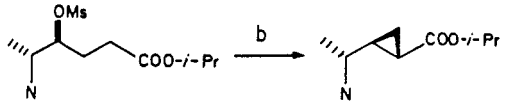
Use of such alkoxytitanium homoenolates, especially the latter t-butoxy one, has remarkably improved the reactivity as a nucleophile: it reacts with aldehydes at -20 or 0 °C to afford the adduct as γ-hydroxy esters. At room temperature, it also adds to ketone carbonyl to give the corresponding γ-butyrolactones in high yield (Table 2)(ref. 7).

In the reaction with 2-phenylpropanal, a moderate Cram-selectivity was observed (Table 2, entry 1).

The observed Cram-selectivity has allowed a stereoselective construction of several steroid side chains. Thus, the reaction of an aldehyde **3a** with the alkoxy-modified homoenolate gave the γ-hydroxy ester of C-22(S) configuration **4a** in 60% yield as a major diastereomer (>6:1), which can be converted to the precursor of demethylgorgosterol **6a** through **5a** (ref. 8).



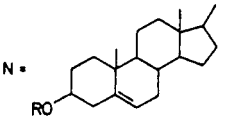
3a **4a**



5a **6a**

a: $MsCl/Et_3N$, CH_2Cl_2

b: t-BuOK, THF, room temp



(a) R=Ac, (b) R=H,

(c) $R=SiMe_2{}^tBu$

Table 1. The Reaction of Trichlorotitanium Homoenolate

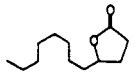
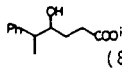
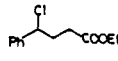
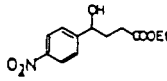
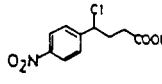
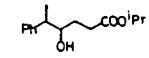
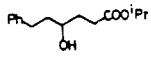
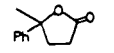
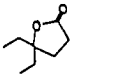
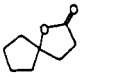
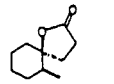
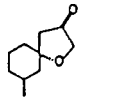
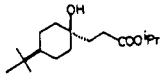
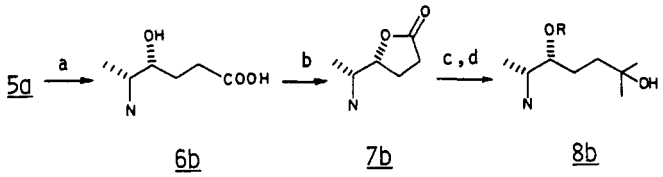
aldehyde	product	% yield
nonanal		81
2-methylbutanal		79
2-phenylpropanal		67 (85:15)
benzaldehyde		90
p-nitrobenzaldehyde		41
p-nitrobenzaldehyde		100
crotonaldehyde		83
acetophenone		31

Table 2. The Reaction of the *tert*-Butoxide-modified Homoenolate

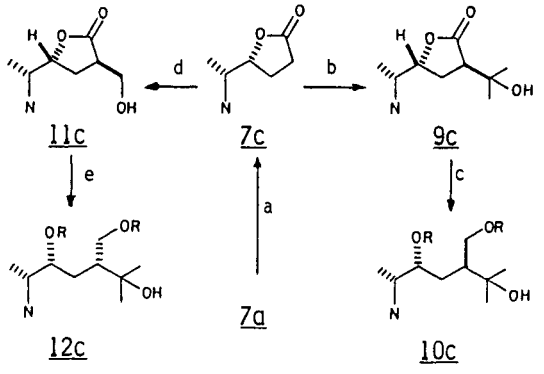
carbonyl compds	condns (°C),(h)	product	% yield
2-phenylpropanal	-20, 3		81(86:14)
3-phenylpropanal	25, 1.5		86
acetophenone	20, 1		93
3-pentanone	20, 18		82
cyclopentanone	20, 2		74
2-methylcyclohexanone	ca. 20, 25		81(84:16)
3-methylcyclohexanone	ca. 20, 1		91(88:12)
4-*tert*-butylcyclohexanone	-20, 3		50(91:9)

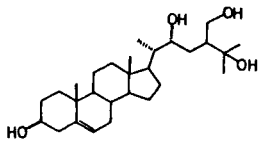
For construction of the ecdysone side chain **8b**, an inversion of the C(22) configuration was required, but it has easily been accomplished: mesylation of the hydroxy group of **4a** followed by alkaline hydrolysis of the terminal ester gave the γ-hydroxy carboxylic acid **6b**. Acid-catalyzed lactonization provided the (22R)-lactone **7b** as a sole product.



a: KOH, aq.MeOH, 50°C, aq.HCl
b: *p*-TsOH, $CHCl_3$
c: Ac_2O/Py, room temp
d: MeMgBr, Et_2O, room temp

Depresosterol **13** possesses one of the most highly oxygenated side-chain, but the stereochemistry of C(24) had not been determined. Using the (22R)-lactone **7c**, a short step synthesis of both C-24(R) and (S) steroids has been performed as shown in the following scheme, and the stereochemistry of depresosterol can be assigned as the 20(S),22(R),24(R) configuration (ref. 8).





a: *t*-$BuMe_2SiCl$/DMAP/Et_3N
b: LDA, THF, -78 to -10°C, acetone
c: $LiAlH_4$
d: LDA, -78 to -10°C, CH_2O
e: MeLi

(b) Zinc homoenolates

As described above, the reaction of **1** with zinc chloride or iodide produces the zinc homoenolates bearing two β-alkoxycarbonylethyl groups. On using as nucleophile, we at first encountered some difficulty to understand the behavior of this homoenolate which sometimes reacted with aldehydes but sometimes did not. Conclusive results were obtained by using preformed zinc homoenolate. As expected from the behavior of dialkylzinc, this reagent is essentially much less reactive toward carbonyl compounds, and does not add to aldehydes or ketones by itself in synthetically acceptable yield. It has been incidentally found that chlorotrimethylsilane has a remarkable effect to accelerate such addition reaction to afford the adduct as γ-siloxy esters. Finally, procedures for such purpose can be greatly simplified: Treatment of **1** with aldehydes in the presence of ca. 2 mol% of zinc iodide in methylene chloride at room temperature afforded the corresponding γ-siloxy ester in high yield (Table 3)(ref. 9). While a variety of aldehydes serve as electrophiles in this reaction, ketones except acetophenone usually give complex mixtures. Interestingly, benzaldehyde acetal also takes part in the reaction (entry 13). Similar coupling reactions with aldehydes can also be effected by 30-50 mol% of zinc chloride.

A chelation controlled 1,2-asymmetric induction has been observed in the reaction with a 2-alkoxyaldehyde (93% selectivity, entry 11), whereas the titanium homoenolate showed lower selectivity (79%).

Further, regiochemistry on a ring opening of **1** appears to be controlled efficiently by this zinc-catalyzed "homo-Reformatsky reaction". Thus, 2-methyl-substituted cyclopropane undergoes an addition on methylene site (entries 3 and 4), whereas the reaction takes place selectively on benzyl site on using a phenyl-substituted one (entry 5). On using 2-methyl substituted optically pure cyclopropane, its chirality has been almost completely transferred to the resulting 4-siloxy-2-methylcarboxylate during the present transformation (ref. 10). Such chirality transfer has also been realized in the other types of cross-coupling reactions using zinc homoenolates (ref. 11). The selectivity on a ring opening may be understood by a preferential formation of more stable organo-zinc species. On using titanium chloride, similar selectivities have been observed but their degrees were decreased to ca. 7:3 in the reactions of both cyclopropanes.

A mechanistic rationale based on various evidence is depicted in Fig 1. The fact that chlorotrimethylsilane greatly accelerates the reaction of zinc homoenolate with aldehydes supports this proposal which involves an activation of the carbonyl function by the chlorosilane. The higher Lewis acidity of iodotrimethylsilane (ref. 12), as compared with the chlorosilane, may account for the wider tolerance of the electrophiles in the zinc iodide catalyzed reaction.

Acylation of the zinc homoenolate is also useful for the preparation of γ-keto esters. However, sites of the acylation reaction is critically dependent on the choice of the reaction solvent. Surprisingly, the purified homoenolate in CH_2Cl_2 or $CDCl_3$ reacted with acyl chloride exclusively on oxygen to produce the corresponding 1-(acyloxy)-1-alkoxycyclopropane in good yield. In contrast, in ether containing HMPA, the reaction proceeded as fast as in the $CDCl_3$, but now gave only a C-acylated product. Under the optimized conditions with 2 equiv each of TMS-Cl and HMPA in ether, the corresponding γ-keto esters were obtained in good yield (Table 4)(ref. 10, 13). This reaction is also catalyzed by transition metals (ref. 14), e.g. $PdCl_2(Ph_3)_2P$ (5 mol%) or CuBr Me_2S (5 mol%) and HMPA (2 equiv).

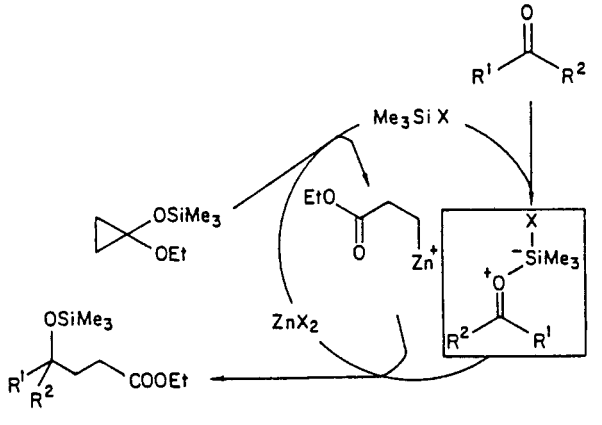


Fig. 1

Table 3. Catalytic Homo-Reformatsky Reaction

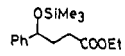
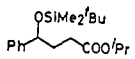
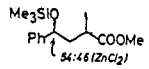
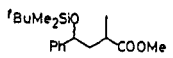
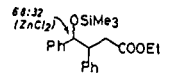
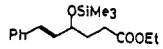
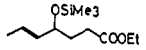
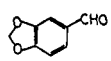
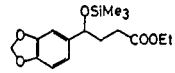
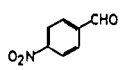
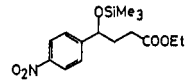
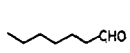
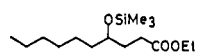
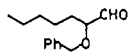
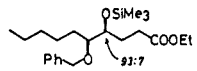
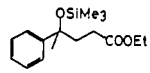
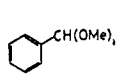
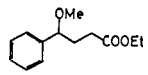
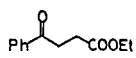
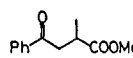
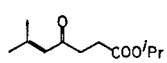
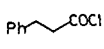
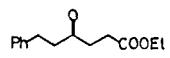
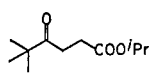
entry	carbonyl compd	cyclopropane	product	Catalyst, %yield $ZnCl_2$	ZnI_2
1	PhCHO	1b		84	89
2				0	86
3		1c		56	72
4		1e		88	0
5		1d		83	76
6		1b		94	84
7		1b		54 (77)	72
8		1b		91	95
9		1b		--	84
10		1b		51 (74)	44 (50)
11		1b		79	--
12		1b		0	77
13		1b		0	91

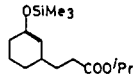
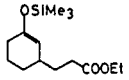
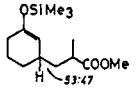
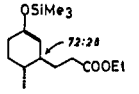
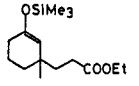
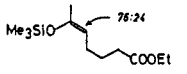
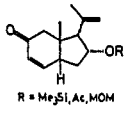
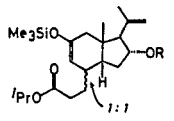
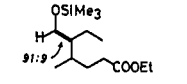
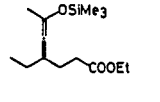
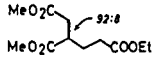
Table 4. C-Acylation Reaction

acid chloride	cyclopropane	product	catalyst	%yield
PhCOCl	1b		HMPA Pd Cu/HMPA	76 93 76
	1c		Pd	93
	1a		Pd	81
	1b		HMPA Pd Cu/HMPA	79 83 89
	1a		Pd	50

We were also attracted to develop a methodology for conjugate addition of homoenolate moiety to enones. As suggested by a facile transfer of an alkyl group from dialkylzinc to Cu(I) (ref. 15) and the behavior of the resulting Cu(I) species as a conjugate addition nucleophile, such transformation may be considered to achieve with the zinc homoenolate under the influence of Cu(I). However, several examinations led to disappointing results; purified zinc homoenolate gave the addition product in only very low yield even on using a variety of Cu(I). Even in the presence of several ligands whose effects for conjugate addition were demonstrated, the yields were not improved. So, we studied on the effects of various additives, and finally found a combination of chlorotrimethylsilane and HMPA remarkably enhance the rate of addition. The addition products were usually isolated as the enol silyl ethers in high yield by performing the reaction in the presence of the reagents mentioned above as well as a stoichiometric or preferably a catalytic amount of CuI in ether at 0°C (Table 5)(ref. 10, 13). Depending on the substrates which react slowly, the reaction can be performed at higher reaction temperature, e.g. ca. 35°C, at which most of usual organocopper reagents undergo decomposition. Thus, copper homoenolates also seem to be of exceptionally thermal stability according to a similar reason with titanium species.

Such procedure may be applicable for construction of B-ring of steroidal nucleus. However, we could not control the stereochemistry of conjugate addition by using the reagent system as above (entry 6). Instead, we employed a boron-copper homoenolate complex for such purpose, which undergo conjugate addition from α-face with high stereoselectivity (ref. 16).

Table 5. Conjugate Addition of Homoenolate

entry	enone	cyclopropane	product	%yield
1		1a		93 (100)
1a		1b		76
2		1c		91
3		1b		78
4		1b		92
5		1b		75
6		1a		85-95
7		1b		75
8		1b		73
9		1b		63

As a bonus, it has also been disclosed that an accelerating effect of the chlorosilane for conjugate addition is not limited to homoenolate species, but is generally effective with usual organocopper species (ref. 17). Both types of conjugate additions with dialkylcuprates as well as a Cu(I) catalyzed Grignard reagents (in the presence of HMPA) proceeded very cleanly at ambient reaction temperature.

In the presence of a catalytic amount of Cu(I), zinc homoenolates react with allylic halides in a S_N2' fashion (ref. 10, 11). On this occasion, the chlorosilane has little effect on both yield of the cross-coupling product and regioselectivity, but polar additives such as HMPA or DMF have exhibited a pronounced effect not only on the product yields, but also on the S_N2' selectivity. Thus, under the optimized conditions [HMPA(2 equiv) in THF or DMF/THF(1:4)], the reaction proceeded almost quantitatively with a high ratio of S_N2'/S_N2.

The allylation and conjugate addition proceed under essentially the same conditions except that the latter requires the chlorosilane. Due to their subtle difference, selective allylation can be performed in the presence of an enone function in the same molecule (Table 6, entry 7). In the presence of chlorotrimethylsilane, both reactions occurs competitively.

Table 6. S_N2' Allylation of Homoenolate

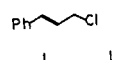
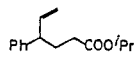
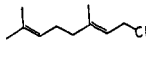
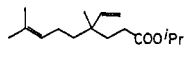
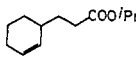
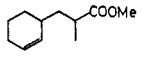
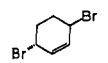
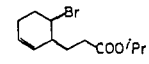
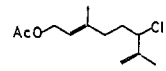
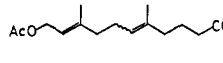
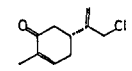
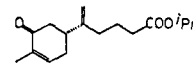
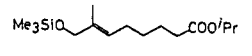
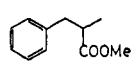
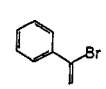
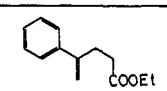
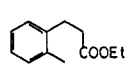
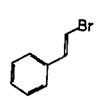
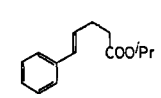
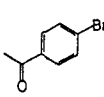
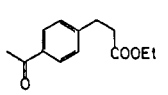
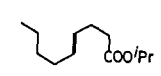
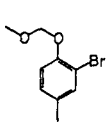
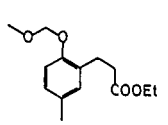
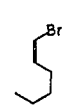
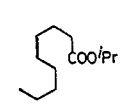
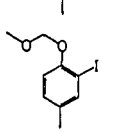
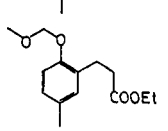
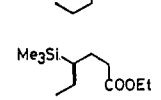
entry	electrophile	cyclopropane	S_N2'product	%yield ($S_N2':S_N2$)
1		1a		97 (96: 4)
2		1a		81 (88:12)
3		1a		93
4		1c		59
5		1a		79 (85:15)
6		1a		72 (100: 0)
7		1a		87
8		1a		48

Table 7. Arylation and Vinylation Reaction

electrophile	cyclopropane	product	%yield	electrophile	cyclopropane	product	%yield
	1c		79		1b		85
	1b		83		1b		76
	1b		49 (68)		1b		90
	1b		5		1b		76
	1b		73		1b		87

In contrast, a nickel-catalyzed cross-coupling with cinnamyl chloride takes place in S_N2 manner with high selectivity (ref. 10).

Similar with usual organocopper reagents, the homoenolate also reacts with acetals of α,β-unsaturated aldehydes (ref. 10). To effect this transformation, a catalytic amount of Cu(I) as well as chlorotrimethylsilane or boron trifluoride etherate are required and S_N2 product was obtained in ca. 95% selectivity.

In the Ni- or Pd-catalyzed cross-coupling reactions with aryl or vinyl halides, this zinc homoenolates is employable as a nucleophile (ref. 10, 14). To effect these reactions, $PdCl_2(o\text{-}Tol_3P)_2$ (usually 1-2 mol%) is much more preferable to the well recommended $PdCl_2(dppf)$ (ref. 18). In the nickel catalyzed reaction dppf is found superior to $o\text{-}Tol_3P$. This reaction proceeded in THF and required neither HMPA nor TMS-Cl, whose presence sometimes reduced the product yields. As usually observed, reactivities decrease in the order of I > Br > Cl, and the reaction with vinyl halides is stereospecific.

CONCLUSION

As described above, different from usual nucleophiles widely employed in organic synthesis, titanium and zinc homoenolates **2** generated from **1** are not so reactive enough to couple with a variety of electrophiles. In other words, their low reactivities seem to allow the formation or isolation of these unique organometallics. To effect synthetic transformation by using **2** as nucleophiles, either their own modification or activation of the reaction partners is sometimes required, but such feature has originated several selectivities depending on electrophiles. These studies have also disclosed a unique and important character of silyl halides to activate electrophiles with high chemoselectivity. Such feature is expected to play increasing roles for development of selective synthetic organic reactions.

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