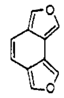
tert-butoxide in THF (room temperature, 8 h) dehydrohalogenated **8** to the novel and potentially useful tetraene **18** in excellent yield.

The cycloadditions described in Table I may proceed in a stepwise manner via two discrete isobenzofuran intermediates or they may proceed via intermediate **2**. That the intermediate, whatever it is, is extremely reactive is illustrated by entries 5, 10, and 11, in which the dienophiles are simple acyclic or cyclic alkenes. The mass spectral results (which show that the bis-retro-Diels–Alder reaction of 1–adducts predominates strongly over the mono-retro-Diels–Alder), preliminary calculations[17] (which show that **2** lies only about 30 kcal/mol above its known angular isomer **19**[8]), and the recent isolation of diradical **20**[18] (which is related to a more general class **21** to which **2** may belong) all encourage us to attempt to isolate and/or trap **2** and analogues. These experiments are actively being pursued.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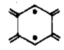
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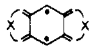
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Acknowledgment. We are indebted to the National Science Foundation (Grant CHE-87-12118) and the National Aeronautics and Space Administration (Grant NAG-3-670) for financial support of this research.

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[17] Carried out in collaboration with Professor James F. Harrison.

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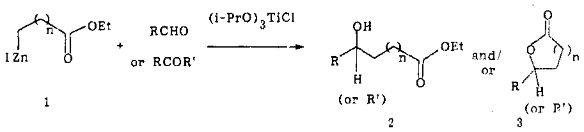
Titanium(IV)-Mediated Aldol-Type Condensation of Zinc Esters and Zinc Ketones with Carbonyl Electrophiles

Summary: Chlorotriisopropoxytitanium-mediated condensation of β-, γ-, δ-, and ϵ-zinc esters with aldehydes or ketones and γ- and ζ-zinc ketones with aldehydes provides the hydroxy esters and/or lactones and the hydroxy ketones, respectively, in good to excellent yields.

Sir: Metalloketones and metalloesters attract much attention not only because of the structural interest but also because of their potential applicability to the effective C–C bond formation at the arbitrary position remote from the carbonyl carbon. As for their generation, although metal halide promoted cyclopropane ring-opening reactions have been reported, this strategy is confined to β-metalloesters.[1,2]

In contrast, we succeeded in the versatile preparation of zinc esters[3] and zinc ketones[4] (β-, γ-, δ-, ϵ-, etc.) by the direct metalation of the iodocarbonyl compounds with Zn–Cu couple. We also demonstrated the transition-metal-catalyzed highly selective reactions of them.

The problem with our method was, however, the low reactivity of the zinc carbonyl reagents toward carbonyl electrophiles. Chlorotrimethylsilane-mediated condensation of zinc esters with aldehydes met with limited success: only aromatic aldehydes provided the addition products in moderate yields.[3d] To realize the successful condensation of metallocarbonyls, the nature of the carbon–metal bond is of crucial importance. Several attempts and a survey of the literature suggested that titanium should be the metal of choice.[5] Here we report a new titanium(IV)-mediated condensation of zinc esters and zinc ketones with carbonyl electrophiles, which discloses the feasibility of the zinc carbonyls as a practical synthetic reagent.



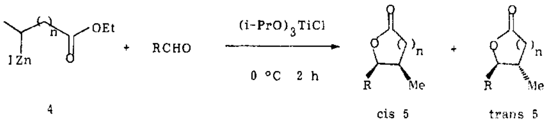
(1)

Zinc ester **1** was successively treated with chlorotriisopropoxytitanium and an aldehyde or a ketone to provide a hydroxy ester **2** and/or a lactone **3**[6] (eq 1). The results are summarized in Table I. The Ti(IV)-mediated reactions of β- (n = 1), γ- (n = 2), and ϵ-zinc ester **1** (n = 4) with (aromatic and aliphatic) aldehydes proceeded quite smoothly (runs 1–3 and 5). On the other hand, the similar reaction of δ-zinc ester **1** (n = 3) resulted in low conversion of the aldehyde (run 4). A small amount of cyclopentanone was detected in the reaction mixture. An intramolecular proton abstraction to form the enolate is the conceivable major reaction in this case.

The Ti(IV)-mediated condensation of **1** with ketones was sluggish at 0 °C, but it proceeded at slightly higher temperature during a longer period of stirring (run 6 vs 7).

Although the reaction profile revealed in the table as well as the spectral data[7] suggests the formation of (carbethoxyalkyl)triisopropoxytitanium, we could not isolate the complex or get conclusive spectral evidence of a C–Ti bond, because of the thermal instability of organotitanium compounds.[5]

1,2-Asymmetric induction was realized with secondary β-zinc ester **4** (n = 1) (eq 2). Excellent cis selectivity was observed in the reaction with benzaldehyde.



(2)

n = 1 R = Ph (conv 95%, yield 94%) cis/trans = > 99 : 1
n = 1 R = PhCH=CH (conv 76%, yield 95%) cis/trans = 83 : 17

The most outstanding advantage of the present method is exemplified by the selective reactions of zinc ketones **6** with aldehydes. Ti(IV)-mediated condensation of γ- (n

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[1] (a) Nakamura, E.; Shimada, J.; Kuwajima, I. *Organometallics* 1985, *4*, 641. (b) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* 1986, *108*, 3745.

[2] β-Metalloketones are also prepared by a similar method. However, their application to organic synthesis is limited: (a) Ryu, I.; Matsumoto, K.; Ando, M.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* 1980, *21*, 4283. (b) Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* 1982, *23*, 931. (c) Ryu, I.; Ando, M.; Ogawa, A.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* 1983, *105*, 7192. (d) Ryu, I.; Murai, S.; Sonoda, N. *J. Org. Chem.* 1986, *51*, 2389.

[3] (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* 1985, *26*, 5559. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* 1986, *27*, 955. (c) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* 1987, *52*, 4418. (d) Tamaru, Y.; Nakamura, T.; Sakaguchi, M.; Ochiai, H.; Yoshida, Z., to be submitted.

[4] Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem.*, in press.

[5] Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Tokyo, 1986.

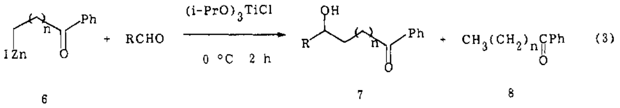
[6] All the products were properly characterized by spectral data (IR, ^{1}H NMR, ^{13}C NMR, high-resolution MS) and elemental analyses.

Table I. Ti(IV)-Mediated Condensation of 1 with Aldehydes or Ketones[a]

run	organozinc	electrophile	conditions	conv,[b] %	product (yield, %)[b]
1	**1** ($n = 1$)	PhCHO	0 °C, 2 h	>95	**3** (95)
2	**1** ($n = 1$)	*n*-BuCHO	0 °C, 2 h	>95	**3** (100)
3	**1** ($n = 2$)	PhCHO	0 °C, 2 h	85	**2** (52) + **3** (26)
4	**1** ($n = 3$)	PhCHO	0 °C, 8 h	30	**2** (80)
5	**1** ($n = 4$)	PhCHO	0 °C, 2 h	64	**2** (95)
6	**1** ($n = 1$)	4-*tert*-butylcyclohexanone	0 °C, 2 h	18	**3** (82)
7	**1** ($n = 1$)	4-*tert*-butylcyclohexanone	0–20 °C, 16 h[c]	68	**3** (88)
8	**1** ($n = 1$)	$I(CH_2)_4COPh$	0–20 °C, 19 h[c]	42	**3** (95)

[a] The reaction of **1** ($n = 1$) with benzaldehyde (run 1) is representative: to 780 mg (3 mmol) of (i-PrO)$_3$TiCl in 4 mL of dry dichloromethane was added at −30 °C a benzene–*N*,*N*-dimethylacetamide (or THF) solution of 3 mmol of **1** ($n = 1$),[3a] prepurified by filtration under nitrogen. After 10 min of stirring, 212 mg (2 mmol) of benzaldehyde was added. The whole mixture was warmed to 0 °C and kept at that temperature for 2 h. The reaction mixture was extracted with ether, washed with 1 N hydrochloric acid, and purified by means of column chromatography on silica gel. [b] Conversion and yield based on electrophile consumed. [c] After being kept at 0 °C for 2 h, the mixture was allowed to reach 20 °C overnight.

= 2) and ζ-zinc ketone **6** ($n = 5$) with aldehydes proceeded smoothly to provide the hydroxy ketones **7** ($n = 2$ or 5) in respectable yields (eq 3).[8]



		% yield (conv) of 7
n = 2	R = Ph	76 (55)
n = 5	R = n-Bu	75 (95)

Although the zinc ketones used for the reaction are confined to those of limited structural variety at present,[9] the preliminary result described here furnishes the first example of the aldol-type condensation of a metalloketone. Elucidation of the active intermediates as well as the Ti(IV)-mediated enantioselective reactions of zinc carbonyls is currently under investigation.

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[7] The carbonyl stretchings of β-zinc ester **1** ($n = 1$) (1680 and 1740 cm^{-1}, THF, 0.6 M) changed to 1630 and 1740 cm^{-1} (THF–CH_2Cl_2, 0.33 M) by treatment with (i-PrO)$_3$TiCl. The ^1H NMR spectrum (THF–CH_2Cl_2–$CDCl_3$) of this mixture showed a signal at 2.53 ppm (t, $J = 7.3$ Hz): see ref 1b. No signals were observed around 0.33 ppm, where β-zinc ester (C_6H_6–*N*,*N*-dimethylacetamide–$CDCl_3$) has a signal (t, $J = 7.3$ Hz).

[8] A benzene–HMPA solution of **6** (3 mmol) was treated, in the same way as **1**, with (i-PrO)$_3$TiCl (3 mmol) and an aldehyde (2–3 mmol) in dichloromethane. The excess titanium reagents were hydrolyzed to yield **8**. For the generation of **6**, see ref 4.

[9] An attempted Ti(IV)-mediated selective condensation of β- ($n = 1$) and δ-zinc ketone **6** ($n = 3$) with aldehydes is not successful yet. These organozincs, respectively, provided cyclopropanol and cyclopentanol as major products.