

34. Selectivities in the Reactions of Alkyl-, Aryl- and Heterosubstituted Organotitanium Compounds

Preliminary Communication

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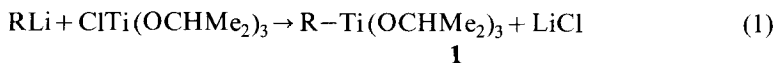
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Summary

Solutions of the title compounds $R-Ti(OR')_3$ (**1**) are generally available from organolithium (or magnesium) derivatives according to equation 1. It is shown (*Table 1*) that some heterosubstituted organotitanium compounds are more stable thermally than their lithium counterparts. The reagents **1** are highly selective carbonylphiles (*Tables 1* and *2*), their reactivity can be modified by variation of the $R'O$ -group (*Table 3*) and with the chiral (*S*)-2-methyl-1-butoxy group an enantioselective addition can be achieved [equ. 2].

In the preceding issue of this journal we reported the highly selective reactions of methyl-triisopropoxy-titanium [*1*]. The communication of closely related, independent work by another group [*2*] prompts us to describe here some further results of our continuing studies in this area. Apart from the selectivities of reactions of organotitanium derivatives, their thermal stabilities as compared with the lithium and magnesium analogues are of prime interest to us at the present stage of the investigation.

The general reaction [*3*] of equation 1 was used for the preparation of solutions of organotitanium compounds **1** in ether or tetrahydrofuran (THF)²⁾. The reagents of type **1** shown in *Table 1* are stable enough to undergo additions to



aldehydes and ketones at temperatures up to +25°. This is not surprising in the case of the phenyltitanium compound (**1**, $R = C_6H_5$ [*11*]), an isolable colorless solid, which

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²⁾ *In situ* preparation of **1** and even of the precursor chloro-titanium derivative $[0.75 (RO)_4Ti + 0.25 TiCl_4 \rightarrow (RO)_3TiCl]$ [*4*] is possible. - Instead of Li-derivatives, Mg- and Al-compounds can be employed [*3*].

Table 1. *Reactions of organotitanium derivatives with carbonyl compounds.* Compound **1** (R = C₄H₉, entry 1 to 3) was generated and allowed to react in diethyl ether, all other derivatives **1** in THF. Newly formed bonds are emphasized by heavy lines in the product *formulae*. The new products gave correct elemental analyses and spectra in accordance with the structures shown; the properties of the known products agree with literature data. In the references given in the second column, the preparations of those lithium derivatives, which are employed according to equation 1, are described. An especially mild, neutral work-up of the reactions of organotitanium reagents is the quenching with saturated aqueous KF-solution [5]. The yields given are those of products isolated from ≥ 5 mmolar batches.

Entry No.	R in 1	Electrophile	Reaction time [h]/ temperature [°]	Product	Yield [%]
1	Butyl	<i>p</i> -Cyano-benzaldehyde	15/– 10° to r.t.	$p\text{-CN-C}_6\text{H}_4\text{-CH(OH)-C}_4\text{H}_9$	97
2	Butyl	<i>p</i> -Iodo-benzaldehyde	15/– 10° to r.t.	 a)	82
3	Butyl	<i>o</i> -Bromo-benzaldehyde	12/– 20°		92
4	Phenyl	Benzaldehyde	0.2/0°	$\text{C}_6\text{H}_5\text{-CH(OH)-C}_6\text{H}_5$	> 95
5	Phenyl	<i>p</i> -Nitro-benzaldehyde	0.5/– 15°	$p\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH(OH)-C}_6\text{H}_5$	94
6	Phenyl	4- <i>t</i> -Butyl-cyclohexanon	15/r.t.		95
7	2-Fluorophenyl [6] [7]	2,4-Dinitro-benzaldehyde	1/r.t.	 b)	98
8	1,3-Dithian-2-yl [8]	Benzaldehyde	16/r.t.		90 ^{d)}
9	2-Methyl-1,3-dithian-2-yl [8]	Benzaldehyde	48/r.t.		90 ^{d)}
10	Tris(methylthio)-methyl [9a]	Acetaldehyde	40/– 25° 40/– 40° to r.t.	$\text{CH}_3\text{-CH(OH)-C(SCH}_3)_3$	50 ^{d)} 60 ^{d)}
11	LiS–CH=CH–CH ₂ [10]	Benzaldehyde then iodomethane	12/– 78° to r.t. 3/r.t.	$\text{C}_6\text{H}_5\text{-CH(OH)-CH}_2\text{-CH=CH-SCH}_3$ (<i>E/Z</i>)-mixture)	45

a) M.p. 41–43°. b) See typical procedure at the end of this communication. c) While $\text{LiC}(\text{SCH}_3)_3$ decomposes rapidly at -20° [9], solutions of the Ti-derivative can be stored at this temperature for at least 12 h. d) Yields determined by NMR.-spectroscopy.

can be stored for weeks in a refrigerator. On the other hand, inspection of *Table 1* reveals that reductive elimination, β -elimination, and α -elimination, which could have been expected to occur with butyl³⁾ or methyldithianyl (entries 1–3, 9), the *o*-fluorotitanobenzene (entry 7), and the sulfur substituted derivatives (entries 8, 9, 10), respectively, do not interfere with the desired transformations. In fact, the *o*-fluorobenzene- and the dithiane-derivatives (entries 7–9 of *Table 1*) are clearly more stable than the Li- and Mg-counterparts [6–8]. Compounds **1a** and **1b** have even been isolated⁴⁾.

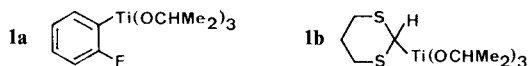


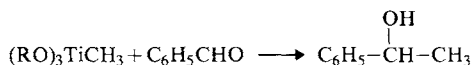
Table 2. Comparison of the selectivities of addition of organolithium and organotitanium reagents *RM* to benzaldehyde/acetophenone. The competition experiments were carried out by adding the solutions of the organometallic compound (1 mol-equiv.) to a 1:1 mixture of 1 mol-equiv. each of the two carbonyl derivatives. For conditions for complete reaction see *Table 1*. The ratios were determined by GC. and/or NMR. integrations. In the presence of tert. amines such as tetramethylethylenediamine (TMEDA) or diaza-bicyclo[2.2.2]-octane (DABCO) the organotitanium compounds led to increased chalcone formation, i.e. aldol condensation between the two carbonyl derivatives. In all cases, the titanium derivatives were generated and used *in situ*, i.e. in the presence of LiCl (*cf.* *Table 3*).

R	M	Conditions	Ratio		Remarks
			$\frac{\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{R}}{\text{C}_6\text{H}_5\text{C}(\text{OH})\text{CH}_3\text{R}}$		
C ₄ H ₉	Ti(OCHMe ₂) ₃	Hexane/TMEDA – 70° to r.t.; 16 h	> 99:1		Chalcone formation
C ₆ H ₅	Li	THF, 0°, 10 min	2:3		Chalcone and non-identified products are also formed Only traces of unreacted C ₆ H ₅ CHO and of ketone adduct
	Ti(OCHMe ₂) ₃	THF, 0°, 10 min	> 98:2		
C ₆ H ₅ SCH ₂	Li [9b]	THF/DABCO, 6 h, – 50° to r.t.	2:1		Incomplete reaction, chalcone formation
	Ti(OCHMe ₂) ₃	THF/DABCO, 16 h, – 60° to r.t.	> 98:2		
	Li	THF, – 70°, 2 h	2:1		Incomplete reaction
	Ti(OCHMe ₂) ₃	THF, – 70° to + 10°, 16 h	> 98:2		
	Li	THF, – 70°, 2 h	2:1		Incomplete reaction
	Ti(OCHMe ₂) ₃	THF, – 70° to r.t., 2 days	> 98:1		
(C ₆ H ₅ S) ₃ C	Li [9c]	THF, – 70°, 4 h	> 98:1		Incomplete reaction
	Ti(OCHMe ₂) ₃	THF, – 70° to r.t., 16 h	> 98:1		

³⁾ The *t*-butyl-derivative **1** (R = *t*-C₄H₉) does not appear to be stable under conditions required for addition to benzaldehyde.

⁴⁾ This is done in the following way: evaporation of the THF-solution [see equ. (1)], dissolving **1** in hexane to remove LiCl, and again evaporation. Compound **1a** crystallizes from hexane at dry ice temperature as colorless solid, **1b** is a glassy, red material at 0°.

Table 3. Comparison of the reactivities of different methyl-trialkoxo-titanium derivatives towards benzaldehyde



Reaction conditions: 16 mmol benzaldehyde, 20 mmol MeTi, 30 ml ether, -50° , argon atmosphere. **Sampling and analysis:** 0.03 ml probes were withdrawn and quickly (1 s) quenched with aq. HCl-solution/ether; ratio $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}_3/\text{C}_6\text{H}_5\text{CHO}$ by GC., with FID.-integration. **Preparation of $(\text{RO})_3\text{TiCH}_3$:** entries 1, 2, 4, 5 *in situ* from $(\text{RO})_4\text{Ti}$, Cl_4Ti and CH_3Li [see equation 1 and footnote 2]. For entry 3, pure, distilled and LiCl free material was employed. **Result:** the more bulky groups R accelerate (*cf.* entries 1/2, 2/4), LiCl from *in situ* preparation slows down (*cf.* entries 2/3).

Entry No.	R	Percent of phenylethanol after x minutes of reaction time at -50°				
		x = 1	5	15	30	60
1	Propyl	1	3	6	10	20
2	<i>i</i> -Propyl	5	20	50	75	90
3	<i>i</i> -Propyl (distilled reagent)	10	45	85	98	100
4	(<i>R,S</i>)- <i>sec</i> -Butyl	40	80	90	99	100
5	(<i>S</i>)-2-Methyl-butyl [<i>cf.</i> eq. 2]		≥ 95			

Another advantageous effect observed with the dianion-titanium derivative of entry 11 in Table 1 is that the reaction with benzaldehyde leads to the isolation of the γ -adduct only, while with lithium and magnesium, mixtures or the α -adduct alone are obtained [10].

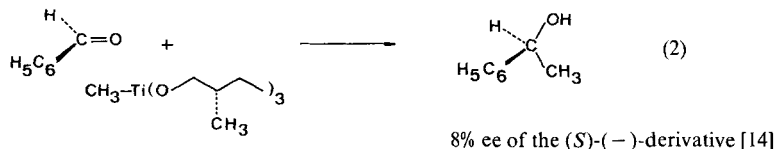
Just like the methyl-titanium derivative **1** ($\text{R}=\text{CH}_3$ [1]), the other organo-titanium reagents **1** can be considered as tamed analogues of the much more reactive, and hence less selective, lithium and magnesium compounds. The preference of addition to aldehyde *versus* ketone carbonyl groups is evident from Table 2. As an example, 2-lithio-1,3-dithiane adds to benzaldehyde/acetophenone with a selectivity of 2:1 at dry ice temperature within a few minutes. In comparison, the titano-dithiane **1b** requires a reaction time of 16 hours at ambient temperatures to combine with benzaldehyde selectively. Likewise, other functional groups, such as cyano, nitro, and iodo, do not disturb the carbonyl additions of the titanium reagents (see Table 1, entries 1, 2, 5 and 7). In contrast, the product of entry 2 cannot be detected by gas chromatography in the crude reaction mixture from *p*-iodo-benzaldehyde and butyllithium⁵⁾.

The rates of additions of the organotitanium reagents **1** to benzaldehyde decrease from phenyl⁶⁾ to methyl to butyl to dithianyl. The reactivities can be modified by varying the RO-groups on titanium (see the methyltrialkoxo-titanium-derivatives in Table 3).

⁵⁾ The I/Li-exchange, which is even faster than Br/Li-exchange [12], is the major process; the NMR. spectrum of the crude product indicates that diaryl and alkyl-aryl methanols are present in a *ca.* 1:1 ratio.

⁶⁾ The *o*-fluorophenyl-titanium derivative **1a** is much slower reacting than the simple phenyl derivative.

A first example of an *asymmetric induction* with a chiral, monodentate RO-group on titanium is the enantioselective methylation outlined in equation (2)⁷⁾. In view of the large distance (1.6!) between the reagent's centres of chirality, which carries such similar groups as methyl and ethyl, and the newly formed asymmetric C-atom, the observed enantiomeric excess is promising.



Typical procedure for the in situ generation of a reagent of type 1: 2,4-Dinitro-2'-fluoro-benzhydrol from 2,4-dinitro-benzaldehyde and 1-bromo-2-fluorobenzene. A solution of 1.08 ml (10 mmol) of the dihalobenzene derivative in 20 ml THF is combined with an equimolar amount of butyllithium (1.6M in hexane) at -100° . After 10 min the calculated amount of a 2M $\text{ClTi}(\text{OCHMe}_2)_3$ in hexane is added, the cooling bath is removed, and 8 mmol of the aldehyde (in 5 ml THF) is introduced at room temperature. The reaction mixture is stirred for 1 h and poured into 2N aqueous HCl (50 ml)/ether (100 ml). Yield of benzhydrol: 2.3 g (98%), m.p. $94-95^{\circ}$ (from ether/pentane) (product formula see Table 1, entry 7).

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⁷⁾ The commercially available (S)-(-)-2-methyl-1-butanol (fermentation amyl alcohol, $[\alpha]_D = -5.5^{\circ}$ ($c=10$, EtOH)) and TiCl_4 gave tetrakis(amyloxy)titanium [13] of $[\alpha]_D = +16.4^{\circ}$ ($c=6.5$, C_6H_6); this was converted into the methyl derivative shown in equ. 2, see footnote 2) and equ. 1.