144. Alkyl-, Aryl-, Vinyl-, and Heterosubstituted Organozirconium Compounds. – Selective Nucleophiles of Low Basicity

Preliminary Communication

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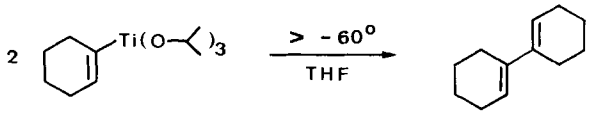
Summary

Solutions of the title compounds are accessible from organolithium reagents and trialkoxyzirconium chloride (equation 2). In contrast to their titanium analogues, vinylzirconium reagents are stable enough to be employed. Generally, organozirconium reagents are highly selective aldehyde and ketone carbonylophiles of exceedingly low basicity (*Tables 1, 2, 3* and typical procedure).

We [1–3] and others [4] have recently shown that the reactivity of lithium and magnesium reagents can be strongly modified by replacement of the main group metals by titanium. Although the substituent R in reagents of type R-Ti(OR')$_3$ can be varied greatly [2], there are certain undesirable transition metal-like properties of titanium or too high a basicity of these reagents, which restrict their usage.

Thus, we have so far been unable to add non-heterosubstituted vinyltitanium reagents to carbonyl compounds: We have observed upon warming a solution of cyclohexenyl-triisopropoxytitanium, above $-60°$ that an oxidative coupling [5] occurs according to equation 1. Also, we have not succeeded in employing secondary or tertiary alkyltitanium compounds [2] – probably because of reductive elimination.



(1)

These limitations led us to investigate zirconium derivatives, since it was to be expected, that zirconium, being a second-row transition metal, would be less prone to reduction.

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Table 1. *Comparison of the selectivity in the reaction of organolithium and organozirconium reagents with equimolar mixtures of benzaldehyde and acetophenone.* For full experimental details see the procedure herein and our previous related publications [1] [2].

R	M	Conditions	Ratio PhCH(OH)R/ PhC(OH)MeR	Remarks
CH_3	Li	Ether, 0°, 5 min	2:3	Benzyl alcohol and chalcone formation
CH_3	$Zr(OBu)_3$	Ether, −30°, 5 h	15:1	
CH_3	$Zr(OBu)_3$	THF, −30°, 5 h	>50:1	Incomplete reaction
CH_3	$Zr(OBu)_3$	THF, RT., 12 h	20:1	
t-C_4H_9	Li	THF, −80 to +20°	~1:1	
t-C_4H_9	$Zr(OBu)_3$	THF, −20 to +20°	>50:1	Benzyl alcohol formation (see text)
	Li	Ether, −100°, 5′	~2:1	
	$Zr(OBu)_3$	Ether, −100 to +20°	>50:1	Benzyl alcohol formation *(cf. Table 2)*
	$Zr(OBu)_3$	THF, −80 to +20°	8:1	Chalcone formation *(cf. Table 2)*

We prepared solutions of organozirconium reagents according to equation 2[3]) and found that they exhibit a similar preference for addition to aldehydes as opposed to ketones, although their selectivity was not as pronounced, as that shown by the titanium analogues [1] [2] *(Table 1)*.

$$\underset{\mathbf{1}}{Cl\text{-}Zr(OBu)_3} + RLi \rightarrow R\text{-}Zr(OBu)_3 + LiCl \qquad (2)$$

The information given and the examples listed in *Table 2* demonstrate the *similar* stability towards chlorinated solvents, diastereoselectivity (entries 1–6, 9, and 11), and preferential reactivity towards aldehydes and ketones, with respect to other functional groups (entries 6–9, 12, 18), shown by titanium and zirconium derived reagents[4]).

Further investigations have highlighted the following remarkably *different* behaviour of some titanium and zirconium reagents (Tables 1, 2 *and 3*):

1) The reaction outlined in equation 2 for the preparation of zirconium reagents takes place much more slowly than with the titanium analogues. Thus, displacement of chloride from $ClZr(OBu)_3$ by butyllithium in tetrahydrofuran (THF) takes six hours to complete[5]) at −80°, in ether warming to 0° for 30 minutes is recommended;

[3]) A stock solution of tributoxyzirconium chloride in ether was obtained by a method analogous to that used to prepare the triisopropoxytitanium chloride [2]: $3\ Zr(OBu)_4 + ZrCl_4 \rightarrow 4\ ClZr(OBu)_3$ (see procedure *a*).

[4]) The zirconium-addition of entries 8 and 9 in *Table 2* could not be achieved in good yields using triisopropoxy-methyltitanium, which indicates the incompatibility of aliphatic – but not aromatic! – nitro groups with titanium reagents [1] [2].

[5]) Samples were quenched at regular intervals with 1,2-dibromoethane (R-Li only) and iodine (total R-metal) [6].

Table 2. *Products of reactions of organozirconium reagents R-Zr(OC$_4$H$_9$)$_3$* (**1**) *with carbonyl derivatives.* If not stated otherwise, **1** was generated *in situ* from the corresponding Li-compound under argon in ether (*cf.* equ. 2), **1** was usually employed in an excess of 1.1–1.5 mol-equiv. In the reactions of entries 5–7, 9, 11–13, and 17 the ketones were added as solutions in CH_2Cl_2. Newly formed bonds are emphasized with heavy lines. B.p. indicated are air bath temperature/Torr. The physical properties of the known products described are in accord with those in the literature.

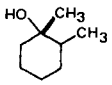
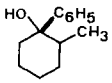
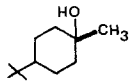
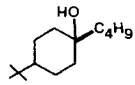
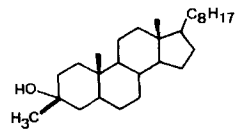
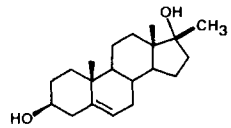
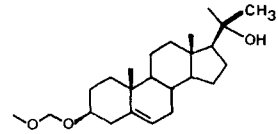
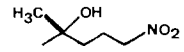
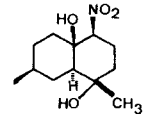
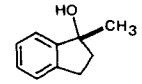
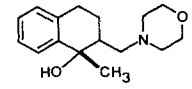
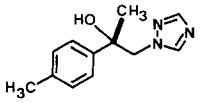
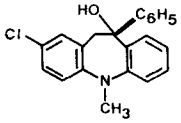
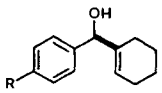
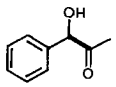
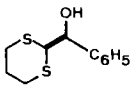
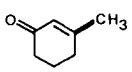
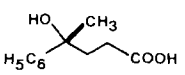
1)		*1,2-Dimethylcyclohexanol:* from **1** (R = CH_3) and 2-methylcyclohexanone; 15 h; −20 to +20°; 70%. Mixture of diastereomers.
2)		*2-Methyl-1-phenylcyclohexanol:* from **1** (R = C_6H_5) and 2-methylcyclohexanone; 15 h; −20 to +20°; 90%. One diastereomer (by ^{1}H-NMR.); b.p. 110°/0.001.
3)		*4-t-Butyl-1-methylcyclohexanol:* from **1** (R = CH_3) and 4-*t*-butylcyclohexanone; 15 h, 20°; 95%. *Cis/trans* ratio 4:1 (by GC.)
4)		*1-Butyl-4-t-butylcyclohexanol:* from **1** (R = C_4H_9) and 4-*t*-butylcyclohexanone; 8 h, −80 to +20°; 78%. *Cis/trans* ratio 86:14 (by ^{1}H-NMR.).
5)		*3-Methyl-3-cholestanol:* from **1** (R = CH_3) and 3-cholestanone; −20 to +20°, overnight; 80%. β-Methyl/α-methyl ratio 2.5:1; m.p. of β-methyl: 124–125°, m.p. of α-methyl: 146–147.
6)		*17α-Methyl-5-androstene-3β,17β-diol:* from **1** (R = CH_3) and 3β-acetoxy-5-androsten-17-one with subsequent alkaline ester hydrolysis; −20 to +20°, overnight; 80%. One diastereomer, m.p. 201–202°.
7)		*3-O-Methoxymethyl-20-methyl-5-pregnene-3β,20-diol:* from **1** (R = CH_3) and 3-*O*-methoxymethyl-5-pregnen-3β-ol-20-one; −20 to +20°, 15 h; 95%, m.p. 130–131°.
8)		*2-Methyl-5-nitro-2-pentanol:* from **1** (R = CH_3) and 5-nitro-2-pentanone; 2 h, 0°, 72%, b.p. 100°/0.5.
9)		*5,8-Dimethyl-2-nitro-bicyclo[4.4.0]decan-1,5-diol:* from **1** (R = CH_3) and 1-hydroxy-8-methyl-2-nitro-bicyclo[4.4.0]-decan-5-one [9] (see procedure).
10)		*1-Methylindan-1-ol:* from **1** (R = CH_3) and 1-indanone; 5 h, 10°; 84%; b.p. 90°/0.01.
11)		*1-Methyl-2-(morpholinomethyl)-1,2,3,4-tetrahydro-1-naphthol:* from **1** (R = CH_3) and the corresponding tetralone; 15 h, 20°; 80%. Diastereomeric ratio 9:1 (by ^{1}H-NMR.).

Table 2 (continued)

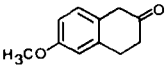
12)		*2-(4-Tolyl)-1-(1,2,4-triazol-1-yl)-2-propanol:* from **1** (R = CH_3) and 4-tolyl 1,2,4-triazol-1-yl ketone; 2 d, 20°; 60% (by ^{1}H-NMR.).
13)		*8-Chloro-5-methyl-11-phenyl-11-hydroxy-10,11-dihydro-5H dibenz[b,f]azepin:* from **1** (R = C_6H_5) and the suitable dibenzo-azepinone; 2 h, 0°; 78% (by ^{1}H-NMR.).
14)		R = H: *1-Cyclohexenyl-phenyl-methanol:* from **1** (R = cyclohexenyl) and benzaldehyde; 6 h, – 80 to + 20°; 80% (by ^{1}H-NMR., mixture with 20% benzyl alcohol). R = NO_2: *1-Cyclohexenyl-(4-nitrophenyl)-methanol:* from **1** (R = cyclohexenyl) and *p*-nitrobenzaldehyde; 6 h, – 80 to + 20°; 50% (by ^{1}H-NMR., 1:1-mixture with 4-nitro-benzyl-alcohol).
15)		*1-Phenyl-1-hydroxy-2-propanone:* from **1** (R = CH_2=C(OCH_3) and benzaldehyde, with subsequent acidic work-up; – 60 to + 20°, overnight; 30% [the reaction was carried out in THF; the lithium derivative CH_2=C(Li)(OCH_3) gives better results than the titanium and the zirconium analogues].
16)		*(1,3-Dithian-2-yl)-phenyl-methanol:* from **1** (R = 1,3-dithian-2-yl) and benzaldehyde; THF, – 80 to + 20°, overnight; 85% (by ^{1}H-NMR.).
17)		*3-Methyl-2-cyclohexenone:* from **1** (R = CH_3) and 3-ethoxy-2-cyclohexenone; – 20 to + 20°, overnight; 70% (by ^{1}H-NMR.).
18)		*4-Hydroxy-4-phenylpentanoic acid:* from **1** (R = CH_3) and 4-oxo-4-phenylbutanoic acid; 15 h, – 20 to + 20°; 72%.

2) In contrast to its titanium analogue (equation 1), the vinylzirconium compound **1** (R = cyclohexenyl) is much more stable, and can be temporarily warmed to room temperature without oxidative coupling occurring. Addition to an aldehyde is however accompanied by the formation of reduction products (*Table 2*, entry 14)[6];

3) Although organotitanium derivatives are certainly less basic than lithium or *Grignard*-reagents, they did not turn out to be sufficiently nucleophilic towards the carbonyl function of readily enolizable ketones. As is evident from *Table 2* (entries 6, 10–13) and from *Table 3*, the zirconium compounds in contrast show

[6]) The reduction product benzyl alcohol was also obtained from the reaction of **1** (R = *t*-C_4H_9) with benzaldehyde *(Table 1)* in a *ca.* 1:1 ratio with the desired alcohol. *t*-Butyl-triisopropoxytitanium and benzaldehyde afforded almost exclusively benzyl alcohol and benzaldehyde pinacols.

Table 3. *Comparison of the reactivity of titanium and zirconium derivatives with readily enolizable ketones.* In a general procedure, the ketone was added dropwise to a *ca.* 1M solution of the reagent, and stirred at room temperature for one day. The degree of conversion to the alcohol was determined by NMR. spectroscopy. The total recovery of starting material and product was better than 90%.

Ketone	Reagent	Solvent	Alcohol/starting material ratio
	$MeTi(OCHMe_2)_3$	Ether	50:50
	$MeZr(OBu)_3$	Ether	90:10
	$PhTi(OCHMe_2)_3$	THF	25:75
	$PhZr(OBu)_3$	THF	90:10
	$MeTi(OCHMe_2)_3$	Ether	< 5:95
(Androstenone, see *Table 2*, entry 6)	$MeZr(OBu)_3$	Ether	> 80:20

a pronounced affinity for carbonyl groups of such substrates and are distinctly less basic. Also, basic N-atoms in the substrate molecules (entries 11 and 12 of *Table 2*) do not influence the apparent basicity of the zirconium reagents as much as they do with the lithium, *Grignard*, or titanium derivatives [2] [7].

The surprisingly high reaction *type-*, *site-* and *stereo*-selectivity [8] – or should we say enzyme-like selectivity?! –, which the simple and cheap[7]) organozirconium reagents **1** can exhibit, is evident from the example (see *Table 2*, entry 9) described in the following typical procedure.

5,8-Dimethyl-2-nitro-bicyclo[4.4.0]decan-1,5-diol. – a) *Preparation of the stock solution of* $ClZr(OBu)_3$. To a solution of 288 g (0.75 mol) tetrabutoxyzirconium in 600 ml ether stirred at 0° under argon is slowly added 58.5 g (0.25 mol) $ZrCl_4$. A brown, slightly pale solution results after stirring overnight. Concentration to a volume of 500 ml by partial evaporation of the solvent furnishes a 2M solution which can be stored at room temperature.

b) *Generation of* **1** ($R = CH_3$) *and addition to 1-hydroxy-8-methyl-2-nitrobicyclo[4.4.0]decan-5-one* (see entry 9 of *Table 2*). To a mixture of 6 ml ether and 1.55 ml (3.1 mmol) $ClZr(OBu)_3$ stock solution stirred at –10° under argon is added 2 ml of 1.5M CH_3Li (3.0 mmol) in ether. After 1 h at 0°, a solution of 223 mg (1.0 mmol) of the title ketone [9] in 2 ml CH_2Cl_2 is added, and stirring is continued with warming to room temperature overnight. The reaction mixture was worked up by pouring into ether/20% aq. KF-solution[8]). The ether phase was dried over $MgSO_4$, and the solvents removed. The crude product (208 mg) contained 8% of starting material (by ^{1}H-NMR.), which was

[7]) The price of 1 kg of $Zr(OBu)_4$ when purchased in 50 kg quantities is *ca.* $10.–. The *ca.* 70%-solution in butanol, supplied by the *Dynamit-Nobel* Co., was distilled in a Kugelrohr apparatus *(Aldrich)* to give the zirconate, b.p. 200–250°/10^{-3} Torr.

[8]) The solution was brought to pH 6–7 with conc. HCl-solution. Non-acid sensitive compounds were worked up with 1N HCl.

separated by layer chromatography (SiO_2, CH_2Cl_2/EtOAc 10:1) to give 178 mg (74%) of a single pure diastereomer. – ^{13}C-NMR. ($CDCl_3$): 92.7 (*d*), 72.3 (*s*), 70.9 (*s*), 48.7 (*d*), 38.6 (*t*), 35.4 (*t*), 32.0 (*d*), 29.0 (*t*), 28.8 (*t*), 27.3 (*qa*), 23.0 (*t*), 22.2 (*qa*).

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