Alkylative Reduction of Titanium(IV) Isopropoxide with EtMgBr: Convenient Method for the Generation of Subvalent Titanium Alkoxide Reagents and their Reactivity in Pinacol Coupling Reactions

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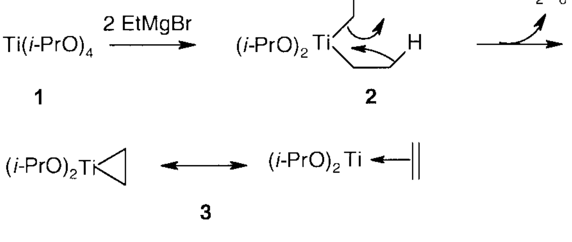
Abstract: The composition of the gaseous products from the reaction of Ti(IV) isopropoxide with ethylmagnesium bromide in diethyl ether evidences the formation of subvalent titanium isopropoxide species in various oxidation states depending on relative amounts of the reactants. Reaction of titanium(IV) isopropoxide with one equivalent of the Grignard reagent gives presumably titanium(III) isopropoxide. The latter is generated as a result of disproportionation of starting Ti(IV) species and titanium(II) isopropoxide–ethene complex which is formed as a result of ethane extrusion from diethyltitanium(IV) isopropoxide. Titanium(III) isopropoxide prepared by this way transforms the aldehydes and the aromatic ketones into the corresponding pinacols in good yields.

Key words: titanium compounds, reduction, Grignard reagents, carbonyl compounds, pinacol coupling

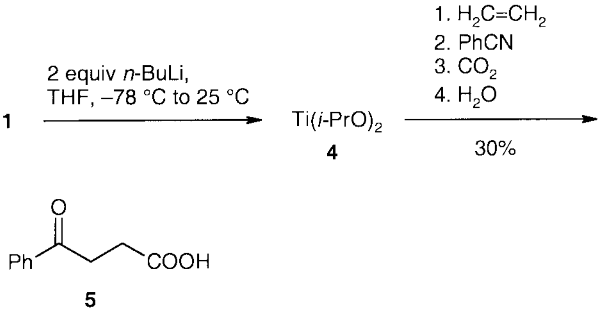
Some time ago we have found a convenient method for the cyclopropanation of carboxylic esters by titanium(IV) isopropoxide (**1**) catalyzed reaction with ethylmagnesium bromide.[1] Mechanistically, this transformation was rationalized by assuming the formation of thermally unstable diethyltitanium compound **2** which rapidly undergoes β-hydride elimination[1,2] to give ethane and titanacyclopropane (**3**) [titanium(II)-ethylene complex, Scheme 1]. The latter acts in situ as a 1,2-dicarbanion equivalent in reaction with carboxylic esters producing a 2-fold alkylation of the alkoxycarbonyl group, leading to cyclopropanols.[1,3] It also exhibits the properties of titanium(II) isopropoxide-olefin complex by involving an olefin ligand exchange reactions with styrene[4] and some other unsaturated compounds.[3]



Scheme 1[1,2]

All our attempts to generate titanacyclopropane (**3**) in the absence of either carboxylic esters or some other unsaturated substrates, and then to involve it in the carbon-carbon bond forming reactions with electrophiles met with failures.

Our results were in some inconsistency with the data recently reported by Eisch and co-workers on the generation and reactivity of titanium(II) isopropoxide **4**.[5] The latter was prepared by alkylative reduction of Ti(i-PrO)$_4$ with n-butyllithium in THF at –78 °C followed by removal of the solvent with warming under reduced pressure.The authors clearly demonstrated the ability of this titanium reagent **4** to involve olefins and acetylenes in the reactions where they act as 1,2-dicarbanion equivalents.[5a] Thus, for example, redissolving of black solid reagent **4** in THF, subsequent bubbling of ethylene into the obtained solution followed by addition of benzonitrile, passing CO$_2$ into the resulting reaction mixture and hydrolysis led to formation of 3-benzoylpropanoic acid (**5**) in 30% overall yield[5a] (Scheme 2).



Scheme 2[5a]

In this paper we report the data that evidence the generation of titanium(III) isopropoxide (**6**) under treatment of titanium(IV) isopropoxide (**1**) with one equivalent of ethylmagnesium bromide. This finding elucidates the reasons of our failed attempts to generate titanium 1,2-dicarbanionic equivalents in the absence of the tested substrates and opens a convenient and flexible way for the preparation of subvalent titanium alkoxide reductants.

When titanium(IV) isopropoxide (**1**) was treated with a 10-fold excess of ethylmagnesium bromide in diethyl ether at room temperature, the intensive gas evolution was only observed during addition of the first 5 equivalents of

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the Grignard reagent (Table 1, entry 1–5). Ethane and ethene were the main components of the gaseous products from the reaction together with the formation of about 10% of the C_4 hydrocarbons. In total a little bit less than 4 equivalents of gaseous hydrocarbons were evolved, which indicated nearly complete alkylative reduction[5a] of Ti(IV) isopropoxide into the Ti(0) species. After addition of the first equivalent of Grignard reagent to titanium(IV) isopropoxide (**1**), ethylene formation decreased drastically (Table 1, entry 2–6). This result evidences the total consumption of titanium(IV) isopropoxide (**1**) and its alkylative reduction to titanium(III) isopropoxide (**6**)[6] (Scheme 3). The reactivity of the latter towards ethylmagnesium bromide could be lower, in comparison with titanium(IV) isopropoxide (**1**), due to the formation of its homogenous binuclear complexes or mixed complexes with magnesium salts.[7] The observed distinct viscosity increase of a solution of **1** in diethyl ether after treatment with one equivalent of ethylmagnesium bromide was in agreement with this supposition.

Table 1 Yields and Ratios of the Gaseous Products Formed in the Reaction of Ethylmagnesium Bromide with Titanium(IV) Isopropoxide in Diethyl Ether

Entry	EtMgBr (equiv)[a]	Time (min)[b]	Gaseous products[c]		
			C_2+C_4 hydrocarbons (equiv)	Ethylene (%)	Ethane (%)
1	1	9	0.64	48	51
2	2	15	0.86	15	77
3	3	18	0.74	1	87
4	4	20	0.61	<1	88
5	5	33	0.54	4	85
6	6–10	60	0.18	8	84

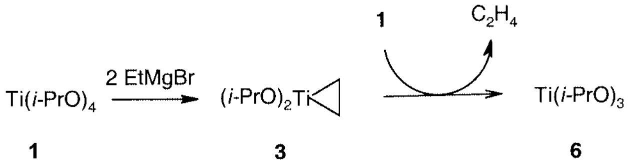
[a] Added to a solution of **1** (0.02 mol) in Et_2O (15 mL) at r.t.

[b] Time for the complete gas evolution after addition of EtMgBr.

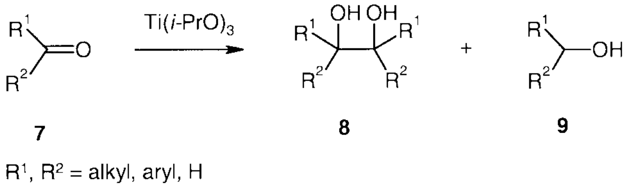
[c] Gaseous product ratio was determined by GC.

Taking into account the considerable amount of ethene in the gaseous products at this step of the alkylative reduction (Table 1, entry 1), we believe that **6** is formed by ethene displacement in titanacyclopropane (**3**) with titanium isopropoxide (**1**) (Scheme 3). Further alkylative reduction of titanium(III) isopropoxide (**6**) with excess of ethylmagnesium bromide proceeds possibly via homolytic cleavage of Ti-C bond in a low valent alkyltitanium species being formed and does not involve the formation of the corresponding subvalent titanacyclopropane intermediates.

The subvalent titanium species generated by alkylative reduction of titanium(IV) isopropoxide with ethylmagnesium bromide were tested for the pinacol coupling of carbonyl compounds.[8] As illustrated in Table 2, titanium(III) isopropoxide (**6**) readily reacted with aromatic aldehydes **7** (entries 1–6) to afford the corresponding hydrobenzoins **8** as the main products (Scheme 4). In these experiments the reagent **6** was preliminary prepared in 1.5–2 fold excess toward the carbonyl substrate[9] and used immediately to reduce the complications caused by its instability. When benzaldehyde was treated with **6** in diethyl ether the pinacol coupling product was formed in good yield and low *dl*-/*meso*-stereoselectivity after hydrolytic workup of the heterogeneous reaction mixture (entry 1). Small amounts of benzylic alcohol and 1-phenylpropanol were detected as byproducts. The reaction proceeded more smoothly and in homogeneous conditions when tetrahydrofuran was used as the solvent (entry 2). Formation of 1-phenylpropanol was not observed in this case, which indicates the total decomposition of organometallic impurities after a short reflux of **6** in THF. Aromatic aldehydes bearing acceptor halogen substituents (entries 3, 4) or donor dimethylamino group (entry 5) also gave the corresponding pinacols in good yields and low stereoselectivity. A similar result was obtained with hexanal, however larger amounts of the corresponding primary alcohol **9** were formed (entry 6).



Scheme 3



Scheme 4

Hydrogenation of the carbonyl group in dibutylketone and aldol self-condensation of cyclohexanone were dominant processes when these compounds were treated with reagent **6** (entries 7, 8). Aromatic ketones showed similar reactivity as aldehydes and the pinacol coupling products were formed in high yields (entries 9–11). It is interesting to compare these results with published data on the interaction of benzophenone with titanium(II) isopropoxide reagent **4**.[5a] The latter was prepared by reductive alkylation of Ti(*i*-PrO)$_4$ with two equivalents of *n*-butyllithium, and reduced benzophenone to benzhydrol in 95% yield. The authors suppose that the reduction proceeded via epimetallation of the carbonyl group to afford the corresponding oxatitanacyclopropane intermediate, which was further transformed into benzhydrol upon hydrolytic work-up. We found, in contrast, that pinacol coupling remained the dominant reaction pathway even when two equivalents of ethylmagnesium bromide were used for the alkylative reduction of titanium(IV) isopropoxide.

Table 2 Reaction of Carbonyl Compounds with Ti(i-PrO)$_3$

Entry	Substrate	Time (h)	Product[a]	Yield (%)[b]	DL-:*meso*-
1	C_6H_5CHO	2[c,d]	$(C_6H_5CHOH)_2$	75[e]	36:64
2	C_6H_5CHO	0.3[d]	$(C_6H_5CHOH)_2$	95[f]	61:39
3	p-BrC_6H_4CHO	12	(p-$BrC_6H_4CHOH)_2$	85[f]	47:53
4	p-ClC_6H_4CHO	12	(p-$ClC_6H_4CHOH)_2$	85[f]	47:53
5	p-$Me_2NC_6H_4CHO$	2	(p-$Me_2NC_6H_4CHOH)_2$	95[f]	33:67
6	$CH_3(CH_2)_4CHO$	10	$[CH_3(CH_2)_4CHOH]_2$	75[f]	60:40
7	$(CH_2)_5CO$	15	$[(CH_2)_5COH]_2$	11[g]	–
8	(n-$C_4H_9)_2CO$	15	[(n-$C_4H_9)_2CHOH)]_2$	<5[h]	–
9	$C_6H_5COCH_3$	0.2	$(C_6H_5CCH_3OH)_2$	75	80:20
10	$C_6H_5COCH_3$	0.5[i]	$(C_6H_5CCH_3OH)_2$	100	79:21
11	Ph_2CO	15	$(Ph_2COH)_2$	93	–

[a] Selected ^{1}H NMR data of the pinacol coupling products, see ref.[12]

[b] Was determined by ^{1}H NMR spectra.

[c] In Et_2O.

[d] 1.5 Equiv of Ti(O-i-Pr)$_3$ was used.

[e] Near 20% of 1-phenylpropanol was formed.

[f] The corresponding alcohol **9** was formed as byproduct.

[g] Isolated yield. The aldol self-condensation product (50%) and cyclohexanol (**9**) (35%) were isolated by column chromatography on silica gel.

[h] The starting compound (25%) and the corresponding alcohol **9** (55%) were detected by ^{1}H NMR.

[i] At reflux.

Remarkably, it was no matter whether the Ti(i-PrO)$_4$ and EtMgBr were mixed at room temperature[10] or at –78 °C,[11] with subsequent half an hour reflux in both cases. In other words, Ti(II) isopropoxide species **4** generated by the latter procedure, and prepared by Eisch's procedure[5a] completely differ in the reactivity towards benzophenone. The origin of this difference could be associated with unequal influence on the reaction pathway of magnesium and lithium alkoxides formed during the alkylative reduction of Ti(IV) with ethylmagnesium bromide or *n*-butyllithium,[5] respectively.

In conclusion, the simple procedure for the generation of putative titanium(III) isopropoxide (**6**) described in this work, as well as the alternative way to Ti(II) isopropoxide species (**4**) early reported by Eisch[5] and coworkers are flexible tools for the elaboration of synthetically useful titanium alkoxide reductive agents in variable valent state. Investigations on the use of these reagents for the reductive cleavage of carbon-halogen and nitrogen-oxygen covalent bonds in organic molecules are in progress in our laboratory.

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References

(1) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 2027. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234.

(2) Epstein, O. L.; Savchenko, A. I.; Kulinkovich, O. G. *Russ. Chem. Bull.* **2000**, 278.

(3) For reviews see: (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789.

(4) (a) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevsky, D. A. *Mendeleev Commun.* **1993**, 230. (b) Epstein, O. L.; Savchenko, A. I.; Kulinkovich, O. G. *Tetrahedron Lett.* **1999**, *40*, 5935.

(5) (a) Eisch, J. J.; Gitua, J. N.; Otieno, P. O.; Shi, X. *J. Organomet. Chem.* **2001**, *624*, 229. (b) Eisch, J. J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24.

(6) For physical and spectral data on monomeric (t-$Bu_3SiO)_3Ti$, see: Covert, K. J.; Wolchanski, P. T.; Hill, S. A.; Krusic, P. J. *Inorg. Chem.* **1992**, *31*, 66.

(7) For physical and spectral data on dimeric aryloxide derivative $[(2,6\text{-}Ph_2C_6H_3O)_2TiCl]_2$, see: (a) Thorn, M. G.; Hill, J. E.; Waratuke, S. A.; Johnson, E. S.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 8630. (b) Hill, J. E.; Fanwick, P. E.; Rothwell, I. P. *Polyhedron* **1990**, *9*, 1617.

(8) For a recent review, see: Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771; and references therein.

(9) **Procedure for Pinacol Coupling**: To a solution of Ti(*i*-PrO)$_4$ (2.05 g, 7.3 mmol) in THF (6 mL) under argon atmosphere, a solution of EtMgBr prepared from Mg (0.19 g, 7.9 mmol) and EtBr (0.9 g, 8.2 mmol) in THF (8 mL) was added for a 2 min. The initially colorless solution turned blue, green-brown and black-brown over the course of EtMgBr addition. The reaction mixture was stirred and refluxed for 30 min under argon, then a solution of carbonyl compound in THF (2 mL) was added in one portion at r.t. or at reflux. The reaction mixture was stirred for a denoted time (Table 2) and then diluted with 20 mL of Et_2O and quenched with 20 mL of 10% H_2SO_4 (in the case of the example in entry 5 the reaction mixture was quenched with aq NH_4CI and filtered). Organic layer was separated, washed with H_2O, aq $NaHCO_3$ and dried over $MgSO_4$. After removing of the solvent in vacuo the resulting reaction mixtures were analyzed by ^{1}H NMR and then crystallized from CCI_4 or EtOH.

(10) The treatment of benzophenone with 1 equiv of Ti(II) isopropoxide, prepared by alkylative reduction of Ti(IV) isopropoxide with EtMgBr in THF at r.t., led to 39% of pinacol **8**, 3% of benzhydrol **9**, and 47% of the starting compound was recovered.

(11) The treatment of benzophenone with 1 equiv of Ti(II) isopropoxide, prepared by alkylative reduction of Ti(IV) isopropoxide with EtMgBr in THF at –78 °C, led to 58% of pinacol **8**, 1% of benzhydrol **9**, and 21% of the starting compound was recovered.

(12) Selected NMR data for pinacol coupling products:
dl*- and *meso*-1,2-bis(4′-Chlorophenyl)ethane-1,2-diol**. ^{1}H NMR (lit.[13]) (400 MHz, $CDCI_3$), ***dl: δ = 2.93 (s, 2 H, OH), 4.61 (s, 2 H, CH), 7.00 (d, 4 H, $J = 8.6$ Hz), 7.20 (d, 4 H, $J = 8.6$ Hz); ***meso***: δ = 2.36 (s, 2 H, OH), 4.83 (s, 2 H, CH), 7.09 (d, 4 H, $J = 8.6$ Hz), 7.25 (d, 4 H, $J = 8.6$ Hz).
dl*- and *meso*-2,3-Diphenylbutane-2,3-diol**. ^{1}H NMR (lit.[14]) (400 MHz, $CDCI_3$), ***dl: δ = 1.50 (s, 6 H, CH_3), 2.59 (s, 2 H, OH), 7.17–7.26 (m, 10 H, Ph-H); ***meso***: δ = 1.58 (s, 6 H, CH_3), 2.29 (s, 2 H, OH), 7.17–7.26 (m, 10 H, Ph-H).
dl*- and *meso*-Dodecane-6,7-diol**.[15] ^{1}H NMR (400 MHz, $CDCI_3$), ***dl: δ = 0.85–0.93 (m, 6 H, CH_3), 1.21–1.54 (m, 16 H, CH_2), 1.92–2.05 (s, 2 H, OH), 3.37–3.41 (m, 2 H, CH); ***meso***: δ = 0.85–0.93 (m, 6 H, CH_3), 1.21–1.54 (m, 16 H, CH_2), 1.92–2.05 (s, 2 H, OH), 3.57–3.63 (m, 2 H, CH).

(13) Trahanovsky, W. S.; Gilmore, J. R.; Heaton, P. C. *J. Org. Chem.* **1973**, *38*, 760.

(14) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Fürstner, A.; Csuk, R.; Rohrer, Ch.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729.

(15) Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* **1956**, *599*, 6.