The Head-to-Head Reductive Coupling of Homoallylic Alcohols Promoted by Titanium(II)-Olefin Complexes

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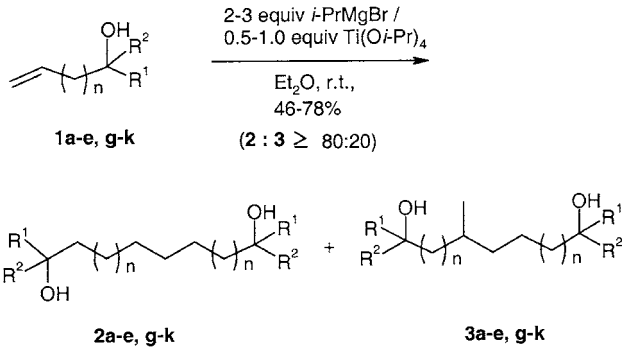
Abstract: Reaction of homoallylic alcohols **1a**–**e** with *i*-PrMgBr in the presence of Ti(*i*-PrO)$_4$ leads to the unbranched saturated diols **2a**–**e** as the main products in moderate to good yields. The head-to-head regioselectivity in reductive coupling of 4-penten-1-ol and 5-hexen-2-ol was also observed. Coupling of 2-methyl-5-hexen-2-ol, as well as unsaturated alcohols in which vinyl and hydroxyl groups are more distant from one another, proceeded with head-to-tail or tail-to-tail regioselectivity. It is supposed, that the unusual head-to-head regioselectivity in reductive coupling of homoallylic alcohols **1a**–**e** is due to the formation of the key titanacyclopentane intermediates **F** and **G** having two fused oxatitanacyclopentane rings.

Key words: titanium alkoxides, Grignard reagents, homoallylic alcohols, reductive coupling

Carboxylic esters react with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide to afford 1-substituted cyclopropanols.[1] It was supposed, that the reaction proceeds via disproportionation of diethyltitanium(IV) isopropoxide to give diisopropoxytitanacyclopropane as a key 1,2-dicarbanionic equivalent. This putative species exhibits also the properties of an titanium(II)-ethylene complex, and the first example of its involvement in a ligand exchange reaction was ethylene displacement by styrene with the formation of the titanium(II)-styrene complex (1,1-diisopropoxy-2-phenyltitanacyclopropane).[2] Interaction of Ti(*i*-PrO)$_4$ with higher alkylmagnesium halides containing β-H atoms also resulted in the generation of the corresponding 2-substituted titanacyclopropanes,[3] and some of them were more effectively involved in the olefin ligand exchange reaction with alkenes than the parent diisopropoxytitanacyclopropane.[4–7] The use of the ligand exchange approach to the 2-substituted titanacyclopropane reagents, in combination with their in situ reaction with carboxylic esters, represents a versatile way to synthetically useful 1,2-disubstituted cyclopropanols.[8] From our experience, sterically unhindered β- and γ- vinylic alcohols,[6,9] as well as β,γ-unsaturated acetals[10] are most effectively involved in the titanium-mediated hydroxycyclopropanation reaction, and this appears to be due to coordination of the oxygen atom of the substrate with the oxophilic titanium atom of the reagent. Thus, for example, dialkoxytitanacyclopropanes promote a smooth hydroxycyclopropanation of the homoallylic alcohols with the carboxylic esters.[9,11] In this paper we report that, in the absence of an ester, the dialkoxytitananacyclopropane reagents effectively induced reductive coupling of homoallylic alcohols affording linear diols as main products with unusual head-to-head regioselectivity[12].

Treatment of homoallylic alcohols **1a**–**e** with 2 equivalents *i*-PrMgBr in the presence of 0.5 equivalents Ti(*i*-PrO)$_4$ or 3 equivalents *i*-PrMgBr in the presence of 1 equivalents Ti(*i*-PrO)$_4$, followed by quenching of the reaction mixture with water, led to the formation of diols **2a**–**e** and **3a**–**e** (Scheme 1).[13] For example, 3-buten-1-ol (**1a**) was converted into 1,8-octanediol (**2a**) and the branched 1,7-heptanediol (**3a**) in 4:1 ratio under the action of 2 equivalents *i*-PrMgBr/0.5 equivalents Ti(*i*-PrO)$_4$ in diethyl ether at room temperature.



$R^1 = R^2 = H$, n = 1 (a); R^1 = Me, R^2 = H, n = 1 (b); $R^1 = R^2$ = Me, n = 1 (c);
$R^1 + R^2 = (CH_2)_4$, n = 1 (d); R^1 = *trans*-MeCH=CH, R^2 = H, n = 1 (e);
$R^1 = R^2 = H$, n = 2 (g); R^1 = Me, R^2 = H, n = 2 (h);
$R^1 = R^2$ = Me, n=2 (i); $R^1 = R^2 = H$, n = 3 (j); $R^1 = R^2 = H$, n = 8 (k)

Scheme 1

As illustrated in the Table 1, the linear reductive coupling products **2a**–**e** were formed in this reaction in moderate to good yields (entries 1–6). Diene alcohol **1e** having an allylic double bond gave the products **2e** and **3e** in lower yields (entry 6), probably due to side reactions of allylic substitution of hydroxyl group under treatment with titanacyclopropane reagents.[14] A moderate yield of the reductive coupling products was also observed for 2-methyl-1-phenyl-3-buten-1-ol (**1f**), bearing a sterically more hindered vinyl group, however the regioselectivity of the head-to-head reductive coupling remained high (entry 7). At the same time, in the case of unsaturated alcohols, in which the vinyl and hydroxyl groups are more

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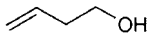
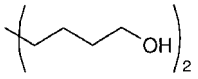
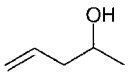
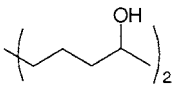
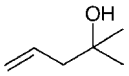
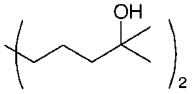
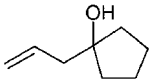
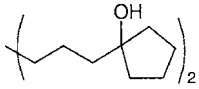
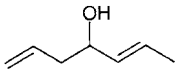
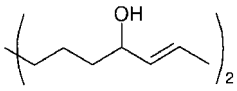
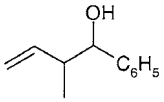
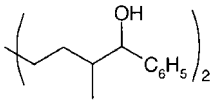
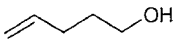
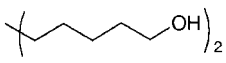
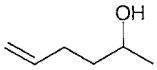
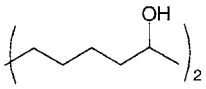
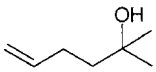
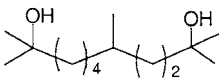
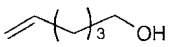
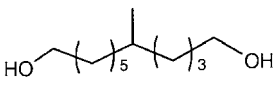
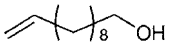
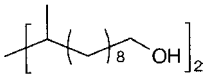
distant from each other, the regularity of preferable formation of head-to-head coupling products **2** was not observed. Whereas, 4-penten-1-ol (**1g**) and 5-hexen-2-ol (**1h**) under treatment with *i*-PrMgBr in the presence of Ti(*i*-PrO)$_4$ undergo the above mentioned the head-to-head reductive coupling to afford the corresponding linear diols **2g** and **2h** as main products (entries 8 and 9), 2-methyl-5-hexen-2-ol (**1i**) and 5-hexen-1-ol (**1j**) gave preferably the corresponding head-to-tail coupling products **3i** and **3j**, respectively (entries 10 and 11). Finally, under the same

Table 1 Yields of Reductive Coupling Products in the Reaction of Unsaturated Alcohols with *i*-PrMgBr in the Presence of Ti(*i*-PrO)$_4$

Entry	Substrate	Equiv Ti(*i*-PrO)$_4$	Main product[a]	**2:3**	Yield (%)[b]
1	 **1a**	0.5	 **2a**	80:20	68
2	 **1b**	0.5	 **2b**	90:10	70
3	 **1c**	0.5	 **2c**	80:20	69
4		1.0[c]		95:5	77
5	 **1d**	1.0[c]	 **2d**	95:5	78
6	 **1e**	0.5	 **2e**	90:10	46
7	 **1f**	0.5	 **2f**	85:15	54
8	 **1g**	0.5	 **2g**	83:17	62
9	 **1h**	0.5	 **2h**	90:10	72
10	 **1i**	1.0[c]	 **3i**	30:45[d]	70
11	 **1j**	0.5	 **3j**	0:60[e]	49
12	 **1k**	0.5		15:30[f]	62

[a] Selected NMR data of the reductive coupling products, see ref.[15]
[b] Isolated yield of mixture of the regioisomeric diols.
[c] 3 equiv of *i*-PrMgBr was used.
[d] Near 25% (GC-MS) of tail-to-tail reductive coupling product was formed.
[e] Near 40% (NMR) of tail-to-tail reductive coupling product was formed.
[f] Near 55% (NMR) of tail-to-tail reductive coupling product was formed.

conditions, 10-undecen-1-ol (**1k**) was mainly converted into the tail-to-tail coupling product (entry 12). When increased amounts of *i*-PrMgBr and Ti(*i*-PrO)$_4$ were used to promote reductive coupling of compounds **1c**, an improvement in the yields and in the regioselectivity were observed (entry 4).

The unusual head-to-head regioselectivity of the reductive coupling of vinylic alcohols is the most noteworthy observation in this work. In contrast to alcohol **1b**, its tetrahydropyranyl ether gave under the same reaction conditions mainly the corresponding tail-to-tail and head to-tail coupling products in low yields.[16] A possible mechanism for the transformation of homoallylic alcohols **1a**–**e** into the head-to-head reductive coupling products **2a**–**e** is presented in Scheme 2. Exchange of alkoxide groups between magnesium alcoholate **A** and Ti(*i*-PrO)$_4$ leads to the formation of titanium alcoholate **B**, which is further alkylated with the Grignard reagent to form dialkyltitanium derivative **C**. The latter is transformed into titanacyclopropane intermediate **D** by β-elimination of propane.[17] Displacement of propylene in the intermediate **D** by alcoholate **B** gives titanacyclopropane-olefin complex **E**. Earlier we supposed,[18] that the formation of a carbon-carbon bond in titanacyclopropane-olefin complexes is initiated by alkylation of the titanium atom with the organomagnesium reagent. In this case, titanacyclopropane-olefin complex **E**, which may be considered as an 18e$^-$ organometallic species, under the action of *i*-PrMgBr should be transformed into the corresponding 18e$^-$ titanacyclopentane ate-complex **F**. The organomagnesium compound can further be liberated from the ate complex **F** by ligand exchange to form titanacyclopentane alcoholate **G**, whose hydrolysis gives diols **2a**–**e**.

The titanacyclopentane intermediates, in which the metallacycle is fused to oxatitanacyclopentane or oxatitanacyclohexane rings, are probably more stable than the corresponding titanacyclopentane intermediates fused to larger oxatitanacycloalkane rings, or bearing noncyclic substituents. This is probably the main reason of the observed head-to-head regioselectivity of the reductive coupling of unsaturated alcohols. The stability of tricyclic intermediates, in which the titanacyclopentane fragment is fused to oxatitanacyclopentane rings (**F** and **G)**, is probably less sensitive to steric hindrance than that of the corresponding intermediates with fused oxatitanacyclohexane rings. Indeed, although the reductive coupling of primary and secondary γ-vinylic alcohols led to preferable formation of the head-to-head products (entries 8 and 9), tertiary γ-vinylic alcohol gave mainly the head-to-tail coupling product (entry 10). When the vinyl and hydroxyl groups are more distant from one another, monocyclic organotitanium intermediates bearing the substituents at less sterically crowded β-carbon atoms of the metallacycle are formed as the predominant intermediates, and the reductive coupling of such compounds proceeds with the generally observed head-to-tail or tail-to-tail regioselectivity (entries 11 and 12).

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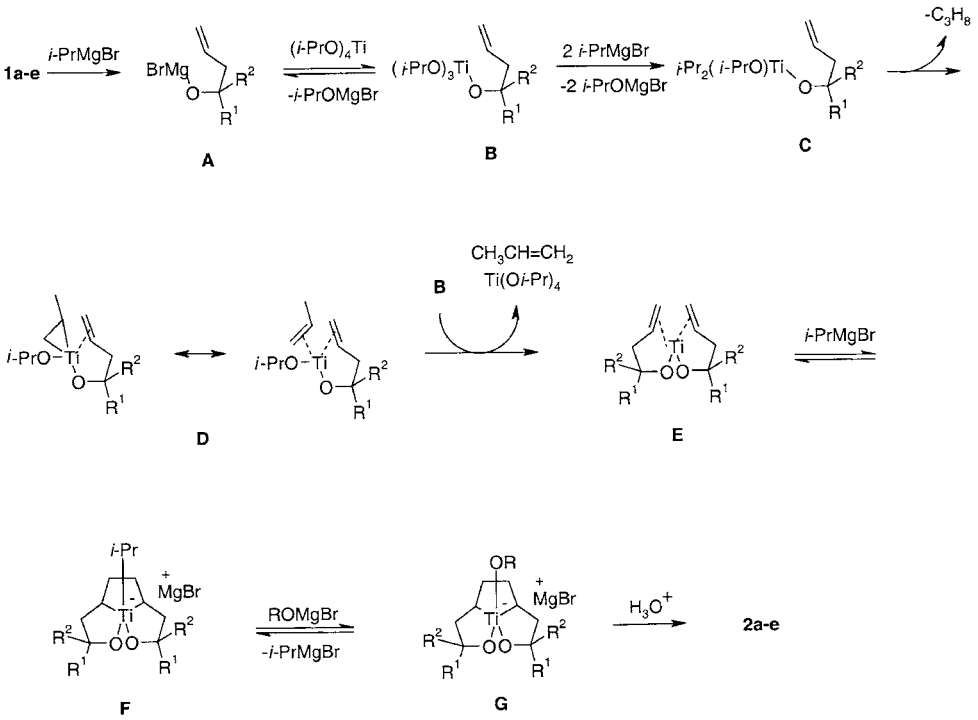

Scheme 2

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(13) **Typical procedure:** To a solution of homoallylic alcohol **1b** (0.86 g, 10 mmol) in Et_2O (15 mL) Ti(*i*-PrO)$_4$ (1.5 mL, 5 mmol) and *i*-PrMgBr (20 mmol of 1.2-1.5 M solution in Et_2O) were added consequently dropwise in 30 min at room temperature, and the mixture was stirred for an additional 30 min. After acidic work up (20 mL of 10% aq. H_2SO_4) and extraction with ethyl acetate, organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. 2,9-Decanediol **2b** (containing near 10% of 4-methyl-2,8-nonanediol **3b** by NMR and GC-MS-analysis) (0.61 g, 70%) was isolated by column chromatography on silica gel (eluent: cyclohexane–ethyl acetate). After two crystallisations (petroleum ether–benzene) 0.38 g of crystalline 2,9-decanediol **2b** was obtained: mp 32–33 °C. (lit. [19] mp 33 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, 6 H, *J* = 6.4 Hz), 1.20–1.48 (m, 12 H), 2.07 (br s, 2 H), 3.68–3.78 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.33, 25.57, 29.48, 39.18, 67.89; MS (70 eV) 29, 45 (100%), 55, 69, 81, 96, 112, 123, 141, 155; IR (CCl_4, cm^{-1}) 3600.

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(15) Selected NMR data of the reductive coupling products: **1-[6-(1-Hydroxycyclopentyl)hexyl]-1-cyclopentanol (2d):** ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.79, 24.59, 30.18, 39.64, 41.47, 82.51. **(2*E*, 12*E*)-2,12-Tetradecadiene-4,11-diol (2e):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.38 (m, 8 H), 1.38–1.56 (m, 4 H), 1.67 (d, 6 H, *J* = 6.4 Hz), 1.72 (br s, 2 H), 3.98 (q, 2 H, *J* = 6.6 Hz), 5.40–5.48 (m, 2 H), 5.56–5.68 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.56, 25.32, 29.42, 37.20, 73.00, 126.52, 134.38. **2,9-Dimethyl-2,9-decanediol (2c):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.20 (m, 12 H), 1.24–1.36 (m, 4 H), 1.36–1.46 (m, 4 H), 1.50 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.22, 29.14, 30.09, 43.89, 70.90. **1,10-Decanediol (2g):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.44 (m, 12 H), 1.48–1.64 (m, 4 H), 2.05 (br s, 2 H), 3.61 (t, 4 H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.66, 29.31, 29.43, 32.67, 62.85. **2,11-Dodecanediol (2h):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, 6 H, *J* = 6.4 Hz), 1.24–1.50 (m, 16 H), 1.94 (br s, 2 H), 3.71–3.84 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.34, 25.65, 29.44, 29.53, 39.25, 67.95.

(16) After acidic hydrolysis of the reaction products, diols **3b** and 4,5-dimethyl-2,7-octanediol were obtained in 29% yield as an nearly equimolar mixture (GC-MS).

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