

Reactions of dicarbanion equivalents generated from complexation of 1,3-dienes on Ti(II) moiety

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Abstract—Conjugated dienes are able to react as 1,2- or 1,4-dicarbanions by coordination on Ti(II) moiety. These two possibilities are exemplified in this letter with isoprene, myrcene and several aldehydes to give 1,4- and 1,6-diols. When allowed to react with esters at room temperature, the titanium–diene complexes lead to cyclopentenol derivatives. Surprisingly, when this reaction is performed at lower temperature (−40 °C), allylic ketones are formed with high regio and diastereoselectivities.
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A wide variety of beautiful organic syntheses result from Kulinkovich's method.¹ It involves the generation of alkene–titanium reagents through an exchange of ligands of the in situ formed (η^2 -ethylene) or (η^2 -propene)Ti(O^{*i*}Pr)₂ complex, and their use as dicarbanion source with various electrophilic substrates. In this field, only few works are relevant to the employment of conjugated dienes. de Meijere and co-workers have observed that they behave as 1,2-dicarbanions due to the vinyltitanacyclopropane intermediates **A** and **C** whereas Sato and co-workers mentioned a titanacyclopentene **B** with 1,4-dicarbanionic properties (Fig. 1).^{2,3} Formation of the same five-membered intermediate was recently proposed by Goeke et al. when Ti(O^{*i*}Pr)₄ is treated with 2 equiv of butenylmagnesium chloride.⁴

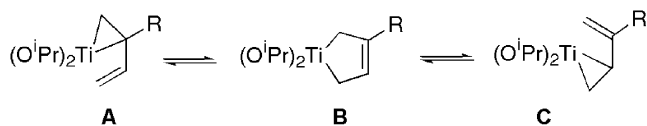


Figure 1. Conjugated diene–titanium complexes A–C.

As a continuation of our efforts on organic synthesis mediated by titanium derivatives,⁵ we have investigated

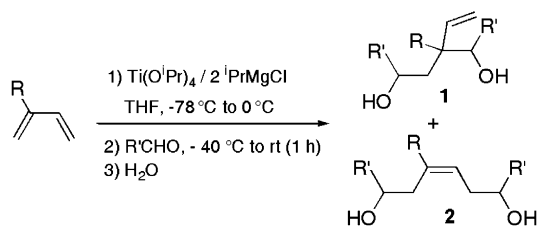
the reactivity of two dienes, isoprene and myrcene, towards aldehydes and esters according to the Kulinkovich methodology; we wish to report here our main results.

Benzaldehyde has been condensed first at low temperature (−40 °C) on the isoprene complex generated in situ by the ligand exchange method.⁶ After warming the solution to room temperature, the reaction mixture was stirred during 1 h and quenched with water. Usual treatment offered the two diols **1a** and **2a** in 1/2 ratio (Table 1, entry 1). Thus, while Goeke et al. reported that the butadiene complex leads exclusively to hex-3-ene-1,6-diol,⁴ the analogue isoprene complex behaves both as a 1,2- and 1,4-dicarbanion. This difference suggests that methyl substitution at the diene ligand gives rise to higher nucleophilicity of the substituted double bond allowing the diene to display its 1,2-dicarbanion properties. On the other hand, switching benzaldehyde to bulkier aldehydes such as isobutyraldehyde and pivalaldehyde led exclusively to 1,6-diols (**2b** and **2c**, Table 1, entries 2 and 3). We suggest that the absence of 1,2-condensation adduct in both the last cases may be due to steric factors. A similar regioselectivity was observed with myrcene. Thus, while the coupling with acetaldehyde and propanal led to a mixture of 1,4- and 1,6-diols, the reaction with isobutyraldehyde afforded exclusively the 1,6-diol **2f** (Table 1, entries 4 and 5 vs 6).

Remarkably, each diol has been isolated as a single diastereoisomer. Thus, this coupling which creates two

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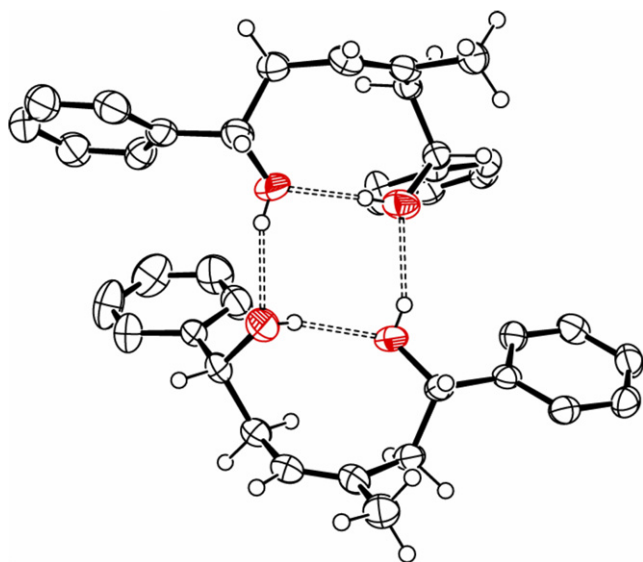
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Table 1. Synthesis of 1,4-diols **1** and 1,6-diols **2** from aldehydes and 1,3-dienes assisted with titanium complex

Entry	R	R'	1 Yield (%)	2 Yield (%)
1	Me	Ph	11 (1a) ^a	23 (2a) ^a
2	Me	^t Pr	—	38 (2b) ^a
3	Me	^t Bu	—	18 (2c) ^a
4	(CH ₂) ₂ CH=CM ₂	Me	17 (1d) ^a	51 (2d) ^a
5	(CH ₂) ₂ CH=CM ₂	Et	15 (1e) ^a	36 (2e) ^a
6	(CH ₂) ₂ CH=CM ₂	^t Pr	—	69 (2f) ^a

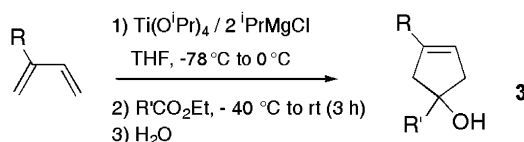
^a Product isolated as a single diastereoisomer.

or three chiral centres proceeds with a complete diastereoselectivity. Suitable crystals for X-ray diffraction have been obtained by slow evaporation of a CH₂Cl₂/pentane solution of **2a**.⁷ The ORTEP view represented in Figure 2 shows that both enantiomers of the pseudo-*meso* diastereoisomer **2a** crystallise in the unit cell with a square shape hydrogen bonds network. In addition, the geometry of the double bond can be attributed to be *Z* which is in accordance with the literature.⁴

**Figure 2.** ORTEP view of the racemate of the pseudo-*meso* diastereoisomer **2a**.

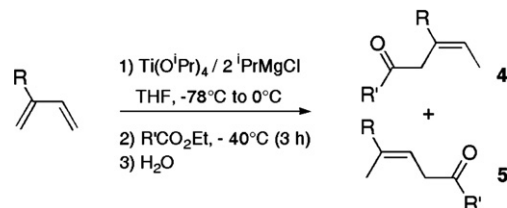
To extend the scope of this reaction, we applied the same procedure with esters. Thus, esters were added at $-40\text{ }^{\circ}\text{C}$ to the preformed titanium isoprene complex. Then, the solution was allowed to stir at room temperature during 3 h and quenched with water.⁸ Usual treatment afforded the cyclopentenol **3** in moderate to good yields (Table 2, entries 1–4).⁹ When employing myrcene instead of isoprene the reaction proceeds smoothly leading to the corresponding cyclopentenols in higher yields

(55–70% yields, Table 2, entries 5–8). It can be noticed that this reaction is only slightly affected by the bulkiness of the esters.

Table 2. Synthesis of cyclopentenols **3** from esters and 1,3-dienes assisted with titanium complex

Entry	R	R'	Yield (%)
1	Me	Me	30 (3a)
2	Me	Et	45 (3b)
3	Me	Ph	45 (3c)
4	Me	Bn	60 (3d)
5	(CH ₂) ₂ CH=CM ₂	Me	70 (3e)
6	(CH ₂) ₂ CH=CM ₂	Et	60 (3f)
7	(CH ₂) ₂ CH=CM ₂	^t Pr	65 (3g)
8	(CH ₂) ₂ CH=CM ₂	^t Bu	55 (3h)

At this point, it should be mentioned that cyclopentenols are always accompanied by a small amount of allylic ketones whose structures are represented in Table 3. Surprisingly, we noticed that when the temperature of the reaction mixture was carefully maintained below $-40\text{ }^{\circ}\text{C}$, the allylic ketones **4** and **5** can be formed selectively in moderate to good yields (Table 3).¹⁰ At this temperature, the ester insertion appears to be regio and stereoselective since the carbonyl products are obtained as a single isomer. Esters generally react with the most substituted double bond leading after hydrolytic workup to the head *cis*-allylic ketones (**4a–f**, Table 3, entries 1–6). The regioselectivity of this reaction can be reversed through the use of the bulky ethyl-2,2-dimethylpropionate (**5g**, Table 3, entry 7). Of significant importance is also the fact that no trace of 1,2-adduct (homoallylic ketones) or double insertion product

Table 3. Synthesis of allylic ketones **4** and **5** from esters and 1,3-dienes assisted with titanium complex

Entry	R	R'	4 Yield (%)	5 Yield (%)
1	Me	^t Pr	48 (4a)	—
2	(CH ₂) ₂ CH=CM ₂	H	22 (4b)	—
3	(CH ₂) ₂ CH=CM ₂	Me	54 (4c)	—
4	(CH ₂) ₂ CH=CM ₂	Et	57 (4d)	—
5	(CH ₂) ₂ CH=CM ₂	Bn	58 (4e)	—
6	(CH ₂) ₂ CH=CM ₂	^t Pr	35 (4f)	—
7	(CH ₂) ₂ CH=CM ₂	^t Bu	—	35 (5g)

(diketones) can be detected in these conditions. Finally, it is worth noting that an analogous synthesis of allylic ketones from dienes and carboxylic esters has been previously described by Rieke et al. with magnesium complexes.¹¹ Nevertheless they reported that this reaction does not proceed when unsymmetric dienes are used.

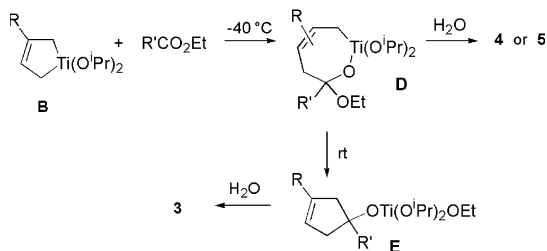


Figure 3. Possible reaction pathways for the syntheses of 3, 4 or 5.

In view of the above results, we can propose two different pathways conditioned upon the temperature (Fig. 3). First, the titanium diene complex reacts with esters to give the seven-membered oxatitanacycle D.¹² Below $-40\text{ }^{\circ}\text{C}$, these complexes are stable and lead to the allylic ketones 4 or 5 upon hydrolysis. When the temperature is allowed to warm to room temperature, the oxatitanacycle is rearranged to lead after hydrolytic cleavage to the cyclopentenol 3. The thermal instability of the metallacycle might be explained by the easy migration of the ethoxy group at the β -position onto the metal as previously reported in the zirconium series.¹³

In summary, the reactions of titanium complexes of isoprene or myrcene with aldehydes led to 1,4- or 1,6-diols with high stereoselectivity. The titanium–diene reagents were also found to react with esters with a remarkable chemoselectivity depending on the temperature reaction. At room temperature, cyclopentenols were formed in moderate to good yields, whereas at lower temperature ($-40\text{ }^{\circ}\text{C}$) allylic ketones were obtained with a complete regioselectivity. The titanium complex generally attacks the ester at the most substituted double bond of the ligated diene. This last being also the most congested, its reactivity is sometimes limited or precluded when a bulky electrophile is used. Further efforts to extend the scope of this reaction to functionalised dienes are underway.

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2000, 1483–1488; (d) Bareille, L.; Le Gendre, P.; Moïse, C. *Chem. Commun.* **2005**, 775–777.

- Typical procedure for the synthesis of diols: $i\text{-PrMgCl}$ (6 mL, 2 M in THF, 12 mmol) was added at $-78\text{ }^{\circ}\text{C}$ to a solution of $\text{Ti}(\text{O}^i\text{Pr})_4$ (1.8 mL, 6 mmol) and myrcene (1.8 mL, 9 mmol) in dry THF (30 mL). When the mixture was warmed to $0\text{ }^{\circ}\text{C}$, the colour of the solution slowly passed from yellow to green. Isobutyraldehyde (1.1 mL, 12 mmol) was then added at $-40\text{ }^{\circ}\text{C}$ and the mixture was allowed to stir at room temperature for 1 h. The solution was quenched by water and the salt was eliminated by filtration on celite. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel (pentane– $\text{Et}_2\text{O} = 2:1$). The product **2f** was obtained as a colourless oil (1.17 g, 69%); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 5.27 (1H, dd, $J = 5.8$ Hz, 10.3 Hz), 5.03 (1H, m), 3.40 (1H, ddd, $J = 2.0$ Hz, 5.2 Hz, 10.3 Hz), 3.28 (1H, ddd, $J = 2.2$ Hz, 5.4 Hz, 10.2 Hz), 2.63–3.13 (2H, m), 1.83–2.15 (8H, m), 1.56–1.68 (2H, m), 1.61 (3H, s), 1.53 (3H, s), 0.79–0.93 (12H, m); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 17.7, 17.8, 17.9, 25.7, 26.8, 32.4, 33.8, 34.0, 34.2, 36.7, 74.0, 76.2, 124.2, 124.9, 131.7, 139.8. Anal. Calcd (%) for $\text{C}_{18}\text{H}_{34}\text{O}_2$: C, 76.54; H, 12.13. Found (%): C, 76.67; H, 12.02.
- Crystal data and structure refinement for **2a**. Crystal data for **2a**: $\text{C}_{19}\text{H}_{22}\text{O}_2$, $M = 282.36$, colourless prism, crystal dimensions $0.25 \times 0.20 \times 0.13$ mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 12.1641(4)$ Å; $b = 14.6538(4)$ Å; $c = 18.0999(6)$ Å, $\beta = 91.716(1)^\circ$; $V = 3224.9(2)$ Å³, $Z = 8$, Mo–K α radiation ($\lambda = 0.71073$ Å), $D_{\text{calcd}} = 1.163$ g cm⁻³, $T = 110(2)$ K, $\mu = 0.074$ mm⁻¹, $F(0,0,0) = 1216$, Enraf-Nonius Kappa CCD diffractometer, $\sin \theta/\lambda_{\text{max}} = 0.55$ Å⁻¹, $h/k/l$: $-13 < h < 13$ / $-15 < k < 16$ / $-20 < l < 20$, 12071 measured reflections, 4567 unique reflections ($R(\text{int}) = 0.065$), 3102 observed reflections ($I > 2\sigma(I)$), 402 parameters refined against 4567 F^2 , $R1 = \Sigma(|F_o - F_c|)/\Sigma|F_o| = 0.051$ for the observed reflections and $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^2]^{1/2} = 0.119$ for all data, GOF = 1.04. The structure was solved by direct methods with the SIR-92 program. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 613423. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.jp].
- Typical procedure for the synthesis of cyclopentenols: To a solution of titanacyclopentene prepared as described above, was added ethyl acetate (1.8 mL, 18 mmol) at $-40\text{ }^{\circ}\text{C}$. The mixture was allowed to stir at room temperature for 3 h. Usual hydrolytic workup and chromatography on silica gel (pentane– $\text{Et}_2\text{O} = 2:1$) afforded **3e** as a colourless oil (0.75 g, 70%); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 5.30 (1H, m), 5.11 (1H, m), 2.35–2.45 (4H, m), 2.03–2.18 (4H, m), 1.69 (3H, s), 1.62 (3H, s), 1.58 (1H, br s), 1.42 (3H, s); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 17.8, 25.8, 26.3, 28.3, 31.6, 48.6, 51.0, 79.4, 121.4, 124.3, 131.7, 143.0. Anal. Calcd (%) for $\text{C}_{12}\text{H}_{20}\text{O}$: C, 79.94; H, 11.18. Found (%): C, 79.61; H, 11.11.
- The synthesis of cyclopentenol **3e** from myrcene and ethyl acetate together with $i\text{-PrMgCl}$ and $\text{Ti}(\text{O}^i\text{Pr})_4$ has been briefly reported previously: Laroche, C.; Bertus, P.; Szymoniak, J. *Chem. Commun.* **2005**, 3030–3032.
- Typical procedure for the synthesis of allylic ketones: The reaction was conducted in a manner similar to that described for **3e** except that the temperature was maintained at $-40\text{ }^{\circ}\text{C}$ for 3 h after the addition of ethyl acetate. The product **4c** was obtained as a colourless oil (0.58 g,

54%); ^1H NMR (500 MHz, CDCl_3): δ 5.47 (1H, q, $J = 6.8$ Hz), 5.05 (1H, m), 3.12 (2H, s), 2.11 (3H, s), 2.07–1.95 (4H, m), 1.65 (3H, s), 1.61 (3H, d, $J = 6.8$ Hz), 1.57 (3H, s); ^{13}C NMR (125 MHz, CDCl_3): δ 14.0, 17.9, 25.9, 26.8, 29.3, 38.1, 46.0, 123.0, 124.2, 131.0, 133.6, 207.1. Anal. Calcd (%) for $\text{C}_{12}\text{H}_{20}\text{O}$: C, 79.94; H, 11.18. Found (%): C, 79.43; H, 10.94.

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carboxylic esters cannot be completely ruled out. It would involve the attack of the titanium reagent at the 2-position of the diene and the formation of a titanium salt of a 2-vinyl cyclopropanol as key intermediate. However, the results obtained with the aldehydes clearly support an initial attack of the titanium complex on the carboxylic esters at one of the terminal positions of the diene.

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