

Pentadienyltitaniums as Versatile Intermediates: Regio- and Stereoselectivities

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Abstract: The adduct obtained upon consecutive treatment of 1,4-dienes with butyllithium in the presence of potassium *tert*-butoxide, chlorotri(isopropoxy)titanium and a carbonyl compound contains the α -hydroxyalkyl group invariably and exclusively linked to the 3-position of the former diene. When chlorotri(isopropoxy)titanium is replaced by the Duthaler-Hafner reagent [(4*R*,5*R*)-chloro(cyclopentadienyl)(2,2-dimethyl- α,α,α' , α' -tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O,O'*)(titanium)] the reaction does not only occur regioselectively but also with appreciably high enantioselectivity.

Key words: superbase, metal effects, regioselectivity of electrophilic attack, stereoselectivity of carbon-carbon bond formation, natural product synthesis

Crotyl type and prenyl type 2-alkenylpotassiums react with most electrophiles mainly, if not exclusively at the unsubstituted terminal position. Typical 1-/3-substitution ratios are > 100:1 with chlorotrimethylsilane, 20:1–50:1 with fluorodimethoxyborane, 5:1–10:1 with alkylating reagents, 1:1–5:1 with oxiranes and aldehydes and 10:1–20:1 with carbon dioxide.¹ In contrast, the corresponding magnesium derivatives afford preferentially the branched products resulting from electrophilic attack at the internal end of the allylic unit, typical 3-/1-substitution ratios being 4:1–10:1 for borylation, 2:1–3:1 for alkylation and \geq 50:1 for the addition to oxiranes, aldehydes and carbon dioxide. The regioselectivity becomes total when carbonyl compounds are combined with allylic boron^{2,3} or titanium⁴ derivatives. At the same time, these reagents exhibit high diastereoselectivities.

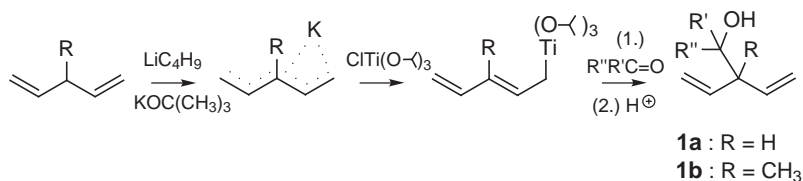
An extension of the area of delocalization makes the outcome of trapping reactions with alkali or alkali-earth metal compounds less predictable. Both, 2,4-pentadienylpotassium⁵ and 2,4-pentadienylmagnesium halide^{6,7} give rise to regioisomeric mixtures when treated with alkyl halides or aldehydes. On the other hand, two boronates, (2*Z*,4*E*)- and (2*E*,4*Z*)-2,4-hexadienyl(dimethoxy)borane, were found to combine with propanal under allylic transposition to give *threo*⁸-(*E*)-4-vinyl-5-hepten-3-ol and, respectively, *erythro*⁸-(*Z*)-4-vinyl-5-hepten-3-ol

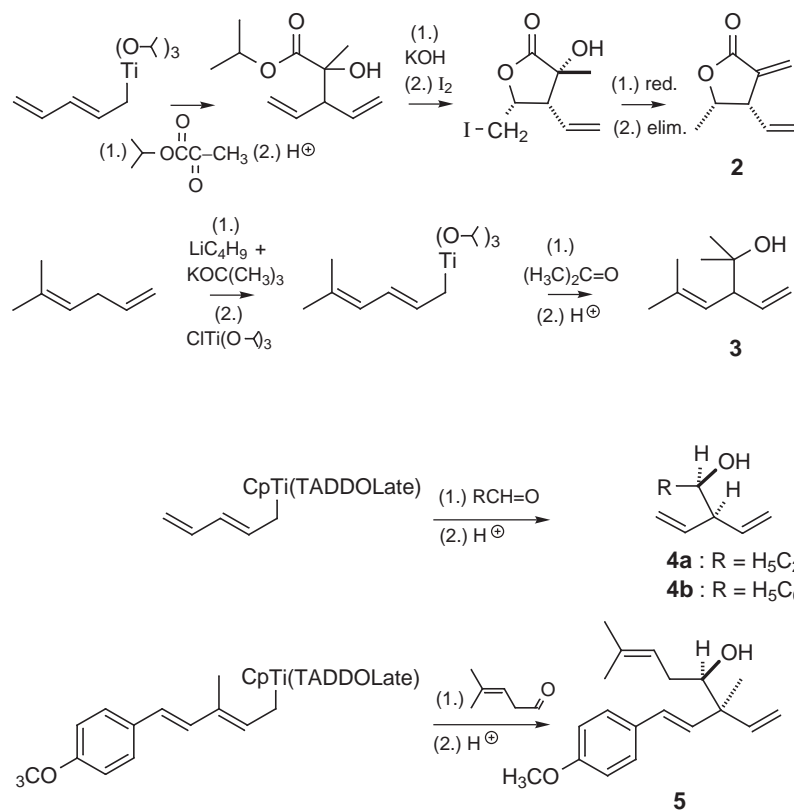
as the sole characterized products.⁹ With this as a background we wanted to find out how dienyl type organotitanium reagents behave in this respect.

The latter species were readily prepared by treatment of the analogous lithium or potassium compounds with chlorotri(isopropoxy)titanium. The intermediate thus generated was allowed to react with 9 aliphatic or aromatic aldehydes and 3 ketones (cyclohexanone, methyl pyruvate and methyl acetoacetate) to afford the adducts **1a** derived from electrophilic attack at the 3-position of the pentadienyl entity as the sole detectable products.⁵ In the same way, 3-methyl-1,4-pentadiene was converted into the doubly vinyl-branched adducts **1b** by addition of the tri(isopropoxy)titanium compound to 7 aliphatic, saturated or unsaturated aldehydes and to a ketone (acetone), the average yield amounting to 63% in both series.⁵

To demonstrate its practical utility, the method was applied to the synthesis of the *cis*-substituted α -methylene-lactone **2** starting with the metalation of 5-methyl-1,4-pentadiene and involving the addition of the resulting intermediate to isopropyl pyruvate and the subsequent iodination-cyclization as key steps. Furthermore, racemic santolina alcohol^{10–12} **3** was prepared in the same way.

Organotitanium chemistry offers still a major stereochemical bonus. The metal seeking high and tight coordination can be placed in a “chiral atmosphere” by employing an enantiomerically pure alcoholate as a ligand. Judging from previous work of R.O.Duthaler, A.Hafner et al.,¹³ the simultaneous complexation of titanium with (*R,R*)-TADDOL¹⁴-diolate and cyclopentadienyl is an efficacious means for promoting asymmetric α -hydroxy-alkylations of organometallic allyl and crotyl derivatives. We have now successfully extended this option to the accordingly modified 2,4-pentadienyl reagent which gave with *trans*-2-butanal and benzaldehyde the products **4a** and **4b** in 62% and 66% yield and 72% and 92% ee, respectively. Analogously, the 5-(4-anisyl)-3-methyl-2,4-pentadienyl CpTi(TADDOL) compound reacted with 4-methyl-3-pentenal to form the Bakuchiol congener **5** in





38% yield and 78% ee. The configuration at the quaternary carbon atom is presumably (*S*); the aldehyde should always be approached on the *Si*-face.¹³

Products and Protocols

Metalation, transmetalation and addition to carbonyls: At 0 °C, the 1,4-diene (25 mmol) and butyllithium (25 mmol) in hexanes (15 mL) were added to a suspension of potassium *tert*-butoxide (2.8 g, 25 mmol) in hexanes (25 mL). After 30 min of vigorous stirring, the solvent was evaporated under reduced pressure and the residue dissolved at -75 °C in precooled tetrahydrofuran (125 mL). The color of the red solution intensified when chlorotri(isopropoxy)titanium (6.5 g, 25 mmol) in tetrahydrofuran (25 mL) was added dropwise in the course of 60 min before the mixture was treated, still at -75 °C, with the aldehyde or ketone (25 mmol). The mixture was allowed to warm to 25 °C and was then poured into a saturated aqueous solution of ammonium chloride (0.10 L). After extraction with diethyl ether (3 × 50 mL), the product was purified by distillation or column chromatography (silica gel; diethyl ether/hexanes 1:4). Examples: **1-(1-Vinyl-2-propenyl)-1-cyclohexanol**¹⁵ (**1a**: R = H, R'⁺R'' = -(CH₂)₅-) from cyclohexanone (2.6 mL, 2.5 g, 25 mmol); colorless liquid; bp 94–96 °C/8 mmHg; n_D²⁰ 1.4895 (lit.¹⁵ n_D²⁰ 1.4903); 3.0 g (71%). **Isopropyl 2-hydroxy-2-methyl-3-vinyl-4-pentenoate**¹⁵ from 1,4-pentadiene and methyl pyruvate (2.3 mL, 2.6 g, 25 mmol); colorless liquid; bp 56–58 °C/1 mmHg; n_D²⁰ 1.4440; 3.0 g (60%).

Lactones: **4,5-Dihydro-*r*-3-hydroxy-5,*c*-iodomethyl-3-methyl-4,*c*-vinyl-2(3*H*)furanone**¹⁵ From the latter ester (0.20 mol) by saponification to the acid¹⁵ (colorless needles, mp 57–58 °C; 92%) followed by simultaneous treatment with iodine (0.10 mol) and a saturated aqueous solution (0.30 L) of sodium hydrogen carbonate;

colorless platelets; mp 111–112 °C; 19 g (67%). Configuration assignment based on ¹H,¹H-NOESY. ***cis*-4,5-Dihydro-3-methylene-5-methyl-4-vinyl-2(3*H*)furanone (2)**¹⁵ by deiodination of the preceding lactone (14 g, 50 mmol) with tributyltin hydride (0.10 mol) in the presence of azoisobutyronitrile (0.1 g, 0.5 mmol) in toluene (0.30 L) followed by conversion into the xanthogenate and thermolysis (refluxing toluene); colorless liquid; bp 68–69 °C/12 mmHg; n_D²⁰ 1.4713; 3.5 g (51%).

***Santolina* alcohol**: **1,1,4-Trimethyl-2-vinyl-3-penten-1-ol (3)**¹⁵ from 5-methyl-1,4-hexadiene¹⁶ (25 mmol) and acetone (25 mmol); colorless liquid; bp 70–72 °C/12 mmHg; n_D²⁰ 1.4632 (lit.¹² n_D²⁰ 1.4640); 2.6 g (67%).

Enantioselective reactions: The ee-values of (*E*)-**3-vinyl-1,5-heptadien-4-ol**¹⁵ (**4a**; bp 72–74 °C/12 mmHg; n_D²⁰ 1.4730; 62%, 72% ee), **1-phenyl-2-vinyl-3-buten-1-ol**¹⁷ (**4b**; 66%, 92% ee) and **(3*S*,4*R*,*E*)-1-(4-anisyl)-3,7-dimethyl-3-vinyl-1,7-octadien-4-ol**¹⁵ (**5**; viscous colorless liquid; mp -21 °C to -19 °C; bp 146–148 °C/0.1 mmHg; n_D²⁰ 1.4771; 38% yield, 78% ee; diastereomeric ratio ≥ 95:5) were determined after esterification with Mosher's reagent¹⁸ by ¹⁹F-nmr. Compound **5** was prepared by consecutive treatment of (*E*)-5-(4-anisyl)-3-methyl-1,3-pentadiene (10 mmol; from 4-anisylmagnesium bromide and 3-methyl-2,4-pentadienyl acetate in the presence of the dilithiotetrachlorocuprate catalyst in tetrahydrofuran at -30 °C¹⁹) with butyllithium in the presence of potassium *tert*-butoxide, the Duthaler-Hafner complex¹³ and 4-methyl-3-pentenal.²⁰

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