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 [(4R,5R)-chloro(cyclopentadienyl)(2,2-dimethyl-5,5'-tetraphenyl-1,3-dioxolane-4,5-dimethoxy)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

Crottyl 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 alkylation 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 ≥ 50:1 for the addition to oxiranes, aldehydes and carbon dioxide.2 In the corresponding transition state, the intermediate thus generated 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 ≥ 50:1 for the addition to oxiranes, aldehydes and carbon dioxide. The regioselectivity becomes total when carbonoyl compounds are combined with allylic boron3,4 or titanium5 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-pentadienylpotassium3 and 2,4-pentadienylmagnesium halide6,7 give rise to regioisomeric mixtures when treated with alkyl halides or aldehydes. On the other hand, two boronates, (Z,4E)- and (2E,4Z)-2,4-hexadienyl(dimethoxy)borane, were found to combine with propanol under allylic transposition to give threo-(E)-4-vinyl-5-hepten-3-ol and, respectively, erythro-(Z)-4-vinyl-5-hepten-3-ol as the sole characterized products.8 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.3 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 alcohol10-12 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 alkoholate 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-hydroxylalkylations 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 (0.30 L). After extraction with diethyl ether (3 mL, 2.5 g, 25 mmol); colorless liquid; bp 94 °C/c45 1/8 mmHg; nD 19 1.4440; 3.0 g (67%).

**3-(Isopropylhydroxy)-2-hydroxy-2,4-pentadienyltitaniums as Versatile Intermediates**

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References and Notes

(15) Correct elementary analysis, 1H and 13C NMR and mass spectra: ref. 5.

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