# Regio- and Stereo-selective Reaction of 1,3-Dialkyl-substituted Allyl Anions with Aldehydes *via* $\eta^3$-Allyltitanium Compounds

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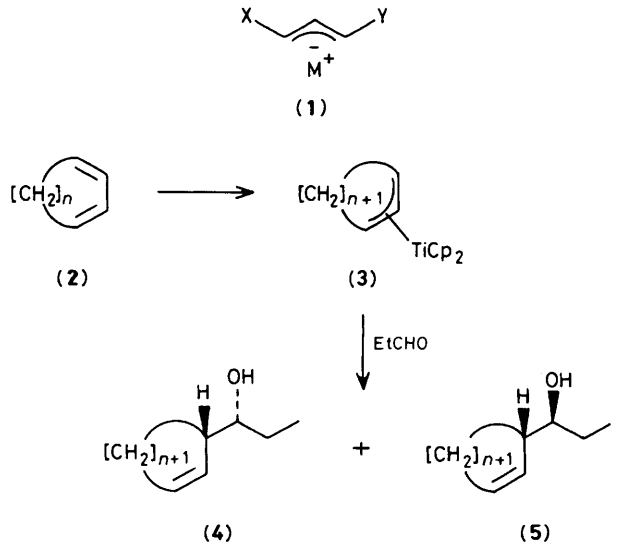
The regio- and stereo-chemistry in reactions of 1,3-dialkyl-substituted allyl anions with aldehydes is controlled *via* $\eta^3$-allyltitanium compounds, thus providing a simple method for preparation of cycloalkanes having a 1-hydroxyalkyl side chain.

Regio- and diastereo-selective reactions between allylic anions and aldehydes have received widespread attention recently in relation to the stereoselective synthesis of acyclic compounds containing multiple chiral centres. Control of the reactions of allylic anions (**1**) in which X is H and Y is Me or a heteroatom, or X is Me and Y is a heteroatom, is achieved in a number of ways.[1] Few investigations, however, have been done on the reaction of 1,3-dialkyl-substituted allyl anions,[2] *i.e.*, the compound (**1**) where both X and Y are alkyl groups, although such control appears to be desirable from a synthetic point of view.[3]

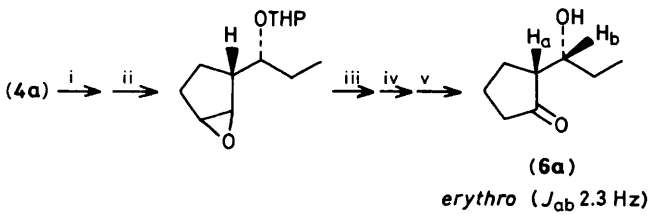
We have recently reported that the regio- and stereo-chemistry in addition reactions of an aldehyde to mono-substituted allyl anions such as but-2-enyl[4a] and 1-trimethylsilylallyl anions,[4b] or to 1,3-disubstituted allyl anions where at least one of the substituents is a heteroatom,[4c] can be controlled *via* the $\eta^3$-allyltitanium compound, $(\eta^5\text{-}C_5H_5)_2Ti(\eta^3\text{-allyl})$. Here we describe the applications of allyltitanium chemistry to the problem of regio- and/or stereo-chemical control of reactions of 1,3-dialkyl-substituted allyl anions with aldehydes.




**a**; $n = 1$
**b**; $n = 2$

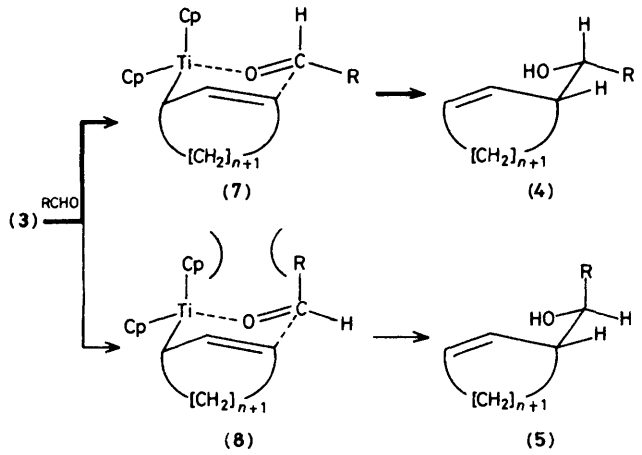
**Scheme 1.** Cp = $\eta^5$-$C_5H_5$.

First we examined the reactions of the $\eta^3$-allyltitanium compounds (**3**), where regiochemistry is not concerned. Compound $(\eta^5\text{-}C_5H_5)_2TiCl$ [formed *in situ* by the reaction of $(\eta^5\text{-}C_5H_5)_2TiCl_2$ with isobutylmagnesium chloride at room temperature in tetrahydrofuran (THF)] reacted with isobutylmagnesium chloride in the presence of cyclopentadiene (**2a**) in THF at −40 °C for 10 min to give (**3a**) *in situ*;[4c,5] all attempts to isolate (**3a**) have failed.[6] Reaction of (**3a**) with propionaldehyde (−40 °C, 30 min) proceeded stereoselectively to give the *erythro*-isomer (**4a**) exclusively, in 86% yield; the *threo*-isomer (**5a**) was not detected by $^1H$ and $^{13}C$ n.m.r. spectroscopy† (Scheme 1). The stereochemistry of (**4a**) was ascertained by converting (**4a**) into (**6a**) as shown in Scheme 2. The $^1H$ n.m.r. coupling constant between $H_a$ and $H_b$ of (**6a**) has the characteristic value (2.3 Hz) for an *erythro*-isomer.[7] Similarly, (**3a**) reacted with benzaldehyde to afford the *erythro*-isomer exclusively (79% yield). The $\eta^3$-allyltitanium



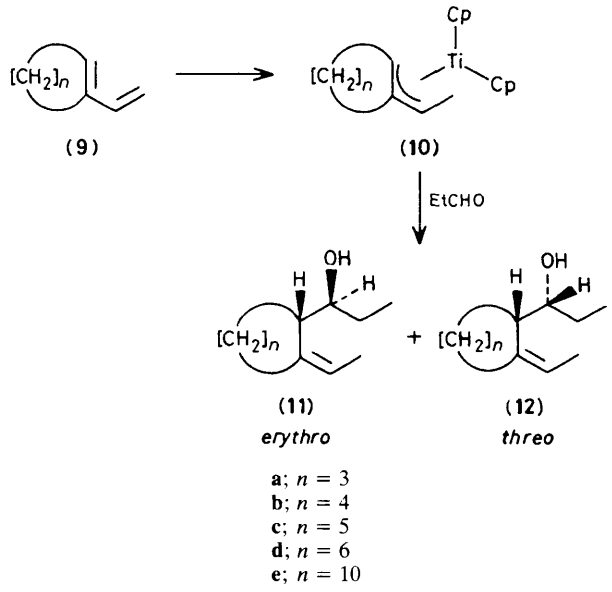

**Scheme 2.** THP = tetrahydropyranyl. *Reagents:* i, dihydropyran, $H^+$; ii, *m*-$ClC_6H_4CO_3H$, iii, $LiAlH_4$; iv, $CrO_3 \cdot HCl \cdot C_5H_5N$; v, *p*-$MeC_6H_4SO_3H \cdot C_5H_5N$.

† (**4a**): $^1H$ n.m.r. ($CDCl_3$) δ 0.99 (t, *J* 7 Hz, 3H, $CH_3$), 1.05—2.47 (m), 2.60—2.98 (m, 1H, CH), 3.46 (dt, *J* 7, 4.5 Hz, 1H, C*H*OH), 5.44—5.96 (m, 2H, HC=CH); $^{13}C$ n.m.r. ($CDCl_3$) δ 10.2, 23.3, 27.4, 32.3, 51.7, 75.3, 131.6, 133.3 p.p.m.



a; $n = 1$
b; $n = 2$

Scheme 3



a; $n = 3$
b; $n = 4$
c; $n = 5$
d; $n = 6$
e; $n = 10$

Scheme 4

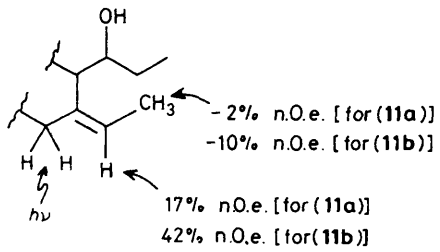
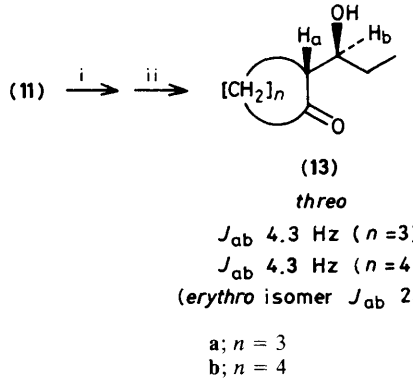


Figure 1

compound (**3b**), derived from (**2b**), also reacted with propionaldehyde to give the *erythro*-isomer (**4b**) predominantly. In this case, however, the ratio of (**4b**) to the *threo*-isomer (**5b**) was 8 : 2.

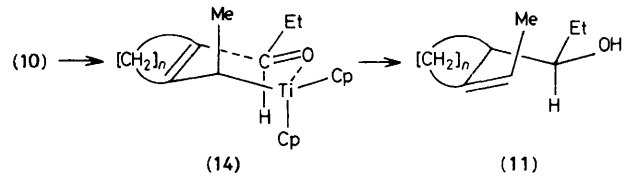
The exclusive or predominant formation of the *erythro*-isomer (**4**) in these reactions may be explained by assuming that the reaction proceeded *via* a cyclic six-membered transition state (**7**) rather than (**8**) which has pseudo 1,3-diaxial interaction between R and $\eta^5$-$C_5H_5$ (Scheme 3).



**(13)**
*threo*
$J_{ab}$ 4.3 Hz ($n = 3$)
$J_{ab}$ 4.3 Hz ($n = 4$)
(*erythro* isomer $J_{ab}$ 2.5 Hz)

a; $n = 3$
b; $n = 4$

Scheme 5. *Reagents:* i, $O_3$; ii, $Me_2S$.



Scheme 6

Next, we turned our attention to compound (**10**). Compound (**10a**) was formed by addition of isobutylmagnesium chloride to a solution of $(\eta^5\text{-}C_5H_5)_2TiCl$ and 1-vinylcyclopent-1-ene (**9a**) in THF at −20 °C with stirring for 20 min at this temperature. Compound (**10a**), thus prepared, reacted (−20 °C, 30 min) with propionaldehyde regiospecifically at the ring carbon atom rather than at the side-chain carbon atom to give (**11a**) exclusively (by $^1H$ and $^{13}C$ n.m.r. spectroscopy) in 86% yield (Scheme 4). The structure of (**11a**) was ascertained from its $^1H$ and $^{13}C$ n.m.r. spectra.‡ Nuclear Overhauser effect (n.O.e.) measurements indicate that compound (**11a**) has (*Z*)-olefin geometry. For example, (**11a**) showed a strong positive n.O.e. on the olefinic proton upon irradiation of the methylene protons next to the double bond (Figure 1). The *threo*-stereochemistry of (**11a**) was determined from the coupling constant between $H_a$ and $H_b$ of (**13a**) [obtained by ozonolysis of (**11a**), Scheme 5] and by comparison of this value with that of the *erythro*-isomer (**6a**) (*vide supra*).

Similarly, complex (**10b**), derived from 1-vinylcyclohex-1-ene (**9b**), reacted with propionaldehyde to afford (**11b**)§ exclusively. Complexes (**10c**), (**10d**), and (**10e**), prepared from (**9c**), (**9d**), and (**9e**), respectively, also reacted with propionaldehyde predominantly at the ring carbon atom. Regiochemistry, however, decreased with increase in the size of the ring. Thus, the selectivity was 90% for (**10c**), 75% for (**10d**), and 66% for (**10e**).

The specific formation of (**11a**) and (**11b**) may be rationalized by assuming that the allyl moieties of (**10a**) and (**10b**) had *anti*-geometries and that the reaction proceeded *via* a

‡ (**11a**): $^1H$ n.m.r. ($CDCl_3$) δ 1.01 (t, *J* 8 Hz, 3H, $CH_3$), 1.69 (d, *J* 7 Hz, 3H, $CH_3$), 1.05—2.60 (m), 2.66—2.83 (m, 1H, CH), 3.32 (dt, *J* 3, 8 Hz, 1H, C*H*OH), 5.55 (q, *J* 7 Hz, 1H, HC=C); $^{13}C$ n.m.r. ($CDCl_3$) δ 10.5, 15.3, 23.8, 27.0, 28.3, 33.2, 46.1, 75.0, 118.6, 144.4 p.p.m.

§ (**11b**): $^1H$ n.m.r. ($CDCl_3$) δ 1.02 (t, *J* 6 Hz, 3H, $CH_3$), 1.64 (dd, *J* 1, 7 Hz, 3H, $CH_3$), 1.20—1.96 (m), 2.01—2.33 (m, 2H, $CH_2$C=CH), 2.66 (d, *J* 10 Hz, 1H, CH), 3.78 (ddd, *J* 3, 7.5, 10.5 Hz, 1H, C*H*OH), 5.52 (q, *J* 7 Hz, 1H, HC=C); $^{13}C$ n.m.r. ($CDCl_3$) δ 9.6, 12.8, 21.7, 26.8, 28.1, 33.3, 41.8, 70.4, 121.2, 139.3 p.p.m.

six-membered transition state (**14**) with a chair conformation (Scheme 6).

In our opinion, the present simple and selective method for the introduction of 1′-hydroxyalkyl side chains into cycloalkanes has wide applicability in syntheses of natural products such as steroids and terpenoids.[8]

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