Synthesis of allyltitanium compounds by intramolecular nucleophilic acyl substitution reaction of alka-3,5-dienyl carbonates and their unusual regioselectivity in reaction with aldehydes

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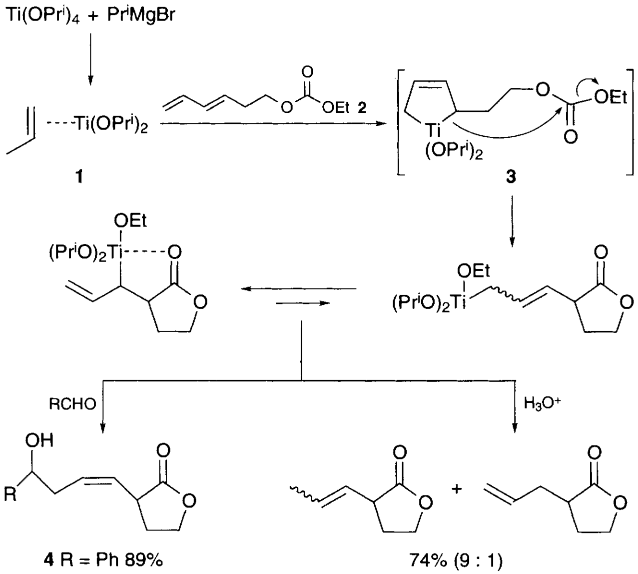
Treatment of carbonates of alka-3,5-dien-1-ols with (η^2-propene)Ti($\mathrm{OPr^i}$)$_2$ resulted in intramolecular nucleophilic acyl substitution (INAS) reaction to afford allyltitanium compounds containing lactone or ester moieties, which add regiospecifically to aldehydes.

Recently, we reported that treatment of 1 equiv. of Ti($\mathrm{OPr^i}$)$_4$ with 2 equiv. of $\mathrm{Pr^iMgX}$ (X = Cl, Br) provides a convenient procedure for *in situ* generation of (η^2-propene)Ti($\mathrm{OPr^i}$)$_2$ **1**.[1] This compound brings about facile intramolecular nucleophilic acyl substitution (INAS) reaction of carbonates of alk-3-ynyl or homoallyl alcohols to furnish alkenyl- or alkyl-titanium compounds having a lactone moiety, respectively.[2] With the intention of exploring the possibility of extending this $\mathrm{Ti^{II}}$-mediated INAS reaction to carbonates having a diene moiety, we examined the reaction of the ethyl carbonate of hexa-3,5-dien-1-ol **2** with **1**. The reaction proceeded smoothly to furnish the allyltitanium compound bearing a lactone moiety, presumably *via* the titanacyclopentene intermediate **3**,[3] thus providing a synthetically useful methodology for preparation of γ-butyrolactone derivatives as summarized in Scheme 1.[4] This result is noteworthy as the reaction of simple dienes such as 6-phenylhexa-1,3-diene with **1** was not synthetically useful and afforded a complex mixture of products after hydrolysis as a consequence of diene-diene and diene-propene (derived from **1**) coupling.[5] Therefore, the facile INAS reaction which prevents the coupling of the diene **2** with itself and propene seems to be essential for the success of the reaction shown in Scheme 1. We found that similar dienic carbonates bearing a methyl group at the 4 or 6 position such as ethyl carbonates of hepta-3,5-dien-1-ol and 4-methylhexa-3,5-dien-1-ol did not afford the corresponding INAS products and provided a complex mixture of products. This finding may be attributable to their slow INAS reaction compared to **2** due to steric factors.



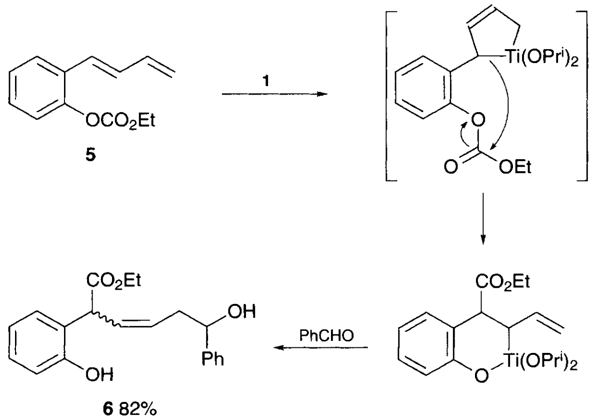
Scheme 1

Although hydrolysis of the allyltitanium compounds generated afforded a regioisomeric mixture of 2-allyl- and 2-(prop-1-enyl)-γ-butyrolactones as can be seen from Scheme 1, the reaction with aldehydes such as benzaldehyde and propanal occurred regiospecifically at the less substituted carbon of the allylic moiety to furnish the corresponding *cis*-2-(4-hydroxyalkenyl)-γ-butyrolactones **4**. This regiochemistry is in sharp contrast to the normal trend exhibited by allyltitanium compounds, which react with aldehydes exclusively at the more substituted allylic position.[6] Although the factors influencing the regioselectivity coupled with selective formation of the product having a *cis* double bond are not clear at this time, coordination of the lactone moiety to titanium, which might stabilize the internal allyltitanium intermediacy as shown in Scheme 1, may play an important role.[7]

The diene **5** also underwent facile INAS reaction and, on subsequent treatment with **1** and benzaldehyde, the hydroxy ester **6** was obtained in excellent yield as a mixture of *cis* and *trans* isomers as shown in Scheme 2. This result indicates that carbonates having an unsubstituted diene moiety are good substrates for the present INAS reaction. The formation of a product containing an ester (not lactone) fragment can be explained by a reaction pathway which includes the elimination of phenoxide rather than ethoxide, while the observed regioselectivity can be attributed to the generation of a six membered titanacycle.

The procedure reported herein should constitute a simple and valuable tool for the preparation of functionalized lactones and hydroxy esters, which are otherwise difficult to synthesize.[8][‡]

Further studies concerning the mechanism of the reaction described herein and its application to organic synthesis are currently underway.



Scheme 2

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Footnotes

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‡ A typical experimental procedure is as follows. To a solution of $Ti(OPr^i)_4$ (0.568 g, 2.00 mmol) and **2** (0.170 g, 1.00 mmol) in diethyl ether (10.0 cm^3) was added dropwise Pr^iMgCl (3.34 cm^3, 1.20 mol dm^{-3} in diethyl ether, 4.00 mmol) at −45 °C. The resulting solution was stirred at −40 to −45 °C for 1 h, then benzaldehyde (0.212 g, 2.00 mmol) was added. The reaction mixture was allowed to warm to room temperature for 2 h, quenched with 1 mol dm^{-3} HCl (10 cm^3) and extracted with diethyl ether. The organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to afford *cis*-2-(4-hydroxy-4-phenylbut-1-enyl)-4-butanolide (**4**, R = Ph) (0.206 g, 89% yield).

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