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Lewis Acid Promoted Reaction of Acetals with η^3-Crotyltitanium Reagents

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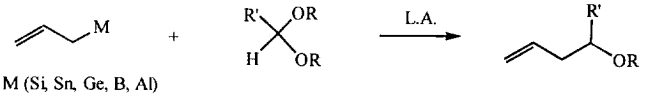
Abstract : In the presence of Lewis acids, η^3-crotyltitanocene reagents react with acetals to give homoallylic ethers in moderate to good yields. In all cases the reactions proceed with total γ-regioselectivity. The diastereoselectivity for aliphatic acetals is no longer observed in comparison with the total *anti* selectivity in the reaction involving benzaldehyde dimethyl acetal, as well as in the intramolecular addition to a tethered acetal. © 1999 Published by Elsevier Science Ltd. All rights reserved.

The addition of allylmetals to acetals under Lewis acid activation gives homoallylic ethers (eq 1) [1], which are useful substrates in a variety of synthetic transformations. This important reaction has been extensively studied for allylsilane reagents. The reactions employing allylic stannane, germanium, boron and aluminium reagents have also been reported [2]. The stereochemistry and mechanism have been investigated, demonstrating that even subtle changes in the allylmetal and acetal structures can significantly influence the course of these reactions [3].



M (Si, Sn, Ge, B, Al) (eq.1)

The allylmetals cited above are all η^1 species. Therefore, it seemed of interest to us to examine whether the η^3-allylmetal reagents can also add to acetals to afford homoallylic ethers. Besides the synthetic goal, the insight into the features of such reactions would provide new mechanistic information.

Among the nucleophilic η^3-allylmetal reagents, η^3-allyl(crotyl)titanocenes reveal considerable synthetic potential : (i) These complexes are readily available from the hydrotitanation of simple [4] or functionalized [5] dienes. (ii) Their addition to aldehydes and ketones occurs regiospecifically with a generally high *anti* diastereoselectivity [4, 5] [1]. (iii) Some other electrophiles have also been employed, such as imines, phenyl isocyanate and acetonitrile [6], carbon dioxide [7], acid chlorides [8], methyl chloroformate and dimethylcarbamoyl chloride [9]. The search for the new electrophiles appears as desirable to further extend the synthetic uses of η^3- allyltitanocene reagents.

The purpose of this Letter is to present our preliminary results on the addition of η^3- allyltitanocene reagents to acetals. They include examples of some representative acetals and ketals as well as Lewis acid promoters.

First, we focused on 1,1-dimethoxypropane **1** as a simple aliphatic acetal and $TiCl_4$ as a catalyst. The 1,2-dimethylallyl(tiglyl)titanium reagent **2** was prepared *in situ* at r.t. by reaction of Cp_2TiCl_2 with two moles of DIBALH and isoprene[2]. The reaction was carried out by adding **1** (1eq) at -40°C to a solution of the preformed

[1] The controlled reversal of *anti* to *syn* stereoselectivity has been recently achieved, see Szymoniak, J.; Thery, N.; Moïse, C. Synlett 1997: 1239-1240.

[2] To our knowledge, this is the first time that DIBALH is reported to prepare η^3- crotyltitanocenes instead of the usually used ^{i}PrMgCl. We noticed, that the successive crotyltitanations of aldehydes proceeded generally cleaner and with higher yields using this reagent.

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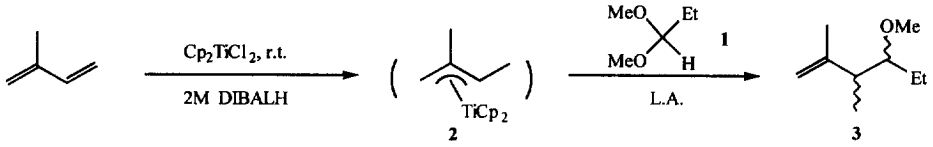
2 in THF, followed by $TiCl_4$ (1eq). The mixture was then stirred for 4h at -40°C. The conventional basic workup ($NaHCO_3$aq, then extraction with ether), followed by flash chromatography purification, afforded homoallylic ether **3** as a mixture of two diastereomers (*anti/syn*=50 :50) in 40% overall yield (Scheme 1). The use of $BF_3.Et_2O$ led to the slightly higher yield (65%) and stereoselectivity (*anti/syn*=55 :45).



L.A. (*anti/syn*, % yield) = $TiCl_4$(50:50, 40), $BF_3.Et_2O$(55:45, 65), TMSOTf(55:45, 80)

Scheme 1

The efficiency of the allylmetal additions to acetals often depend upon the Lewis acid employed, and in this respect trimethylsilyl triflate is shown to be quite appropriate [10]. We then performed above reaction using an equimolar quantity of TMSOTf [3]. The reaction carried out as above led to **3** (*anti/syn*=55 :45) in an overall 85% yield. Although the markedly increased yield was observed in this case the stereoselectivity remained modest.

Having demonstrated the feasibility of the addition of η^3-tiglyltitanocene to the acetal **1**, we next examined the effect of acetal structure on the course of the reaction. The aliphatic and aromatic acetals and ketals were used, i.e. dimethyl acetals of hexanal **4**, benzyloxyacetaldehyde **5**, benzaldehyde **6** as well as benzaldehyde dioxolane **7** and cyclohexanone dimethyl ketal **8**. The reactions employing substrates **4-8** and the reagent **2** were performed in the same way and conditions as above, using TMSOTf as inductor. These examples are given in Table 1 [4].

The crotylation of the compounds **4-8** afforded the expected homoallylic ethers **9-13**. In all cases, the addition occurred regiospecifically on the more substituted γ-carbon atom [5]. Similar to the reaction employing the acetal **1**, the lack of diastereoselectivity was observed in the reactions involving other aliphatic acetals. Thus, the stereoselectivity does not vary in a significant manner neither by extending the carbon chain nor by introducing the potentially chelating β-alkoxy group into the acetal (entries 1 and 2). On the contrary, the reaction of the reagent **2** with an aromatic acetal, i.e. benzaldehyde dimethyl acetal **6** proceeded in a totally *anti* selective mode (de higher than 98%) (entry 3). Surprisingly, the use of dioxolane benzaldehyde **7** instead of **6** led to a spectacular loss of stereoselectivity (entry 4). Finally, we noticed that the homoallylic ethers possessing a quaternary α-carbon atom can be easily prepared by the crotyltitanation of the corresponding ketals, as examplified by the reaction, entry 5.

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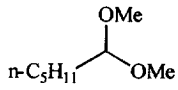
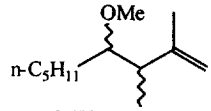
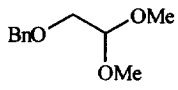
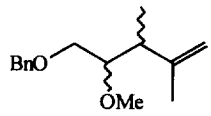
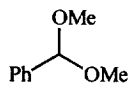
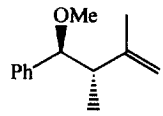
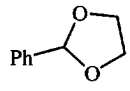
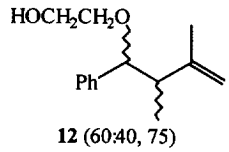
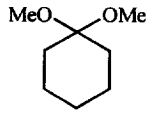
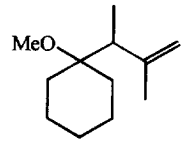
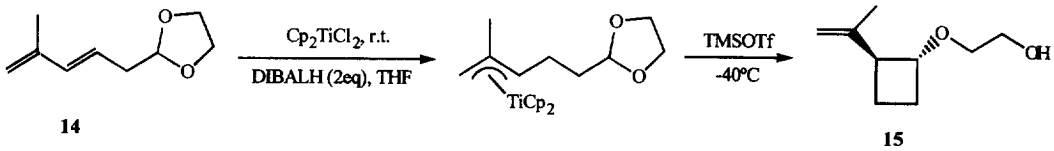
[3] Catalytic amount of TMSOTf as well as some other triflates or perchlorates were often used to perform Mukaiyama aldol and Sakurai-Hosomi allylation reactions. However, it has been demonstrated that these Lewis acids only serve as promoters to regenerate the real catalyst, namely «'Me_3Si^+' from the allyl- or enol-silane substrates : see [3]

[4] All new compounds gave satisfactory spectral data and elemental analysis.

[5] The same regioselection typically characterizes the reactions of crotyltitanocene reagents with aldehydes and other carbonyl bearing electrophiles : see [4, 5].

Table 1. Addition of tiglyltitanocene 2 to Acetals and Ketals **4-8** promoted by Trimethylsilyl Triflate.

entry	acetal (ketal)	product *anti/syn*, % yield
1	 **4**	 **9** (50:50, 64)
2	 **5**	 **10** (55:45, 72)
3	 **6**	 **11** (>98:2, 69)
4	 **7**	 **12** (60:40, 75)
5	 **8**	 **13** (60)



14 **15**

Scheme 2

To examine the scope of the title reaction we next tried to perform it in the intramolecular way. The dienyl-acetal **14** [11] structurally resembling isoprene was chosen as a substrate. The reaction carried out at -40°C in the presence of TMSOTf was particularly clean : it was high yielding (80%), regiospecific with respect both to the formation of the allyltitanium complex and to its γ-carbon reactivity, and totally stereoselective. As a result, the 1,2-disubstituted cyclobutane derivative **15** was formed with the unique *trans* configuration (Scheme 2). Easily available **15** appears as a useful intermediate for the preparation of some cyclobutane-derived natural products [12] [6].

The stereochemical outcome of the title reaction is different from that observed for the addition of η^1-allylic silanes and stannanes, generally proceeding in the *syn* fashion [7]. Furthermore, it is different from that characterizing the crotyltitanation of aldehydes (highly *anti* selective for the aliphatic aldehydes, and less selective for the aromatic ones) [4, 5]. The stereochemical trends that we observed, are possibly indicative of a mechanism other than the mechanisms postulated for the addition of η^1-allylmetals to acetals : a simple S_N2-like or S_N1 via an oxocarbenium ion [3]. On the other hand, this stereochemistry is also inconsistent with a conventional chair-form cyclic-transition state mechanism, analogous to that operating for aldehydes. Further study to clarify the reaction mechanism is now in progress. We also try to explore the promising synthetic potential of the intramolecular reaction.

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[6] Spectral data for **15**: ^{1}H NMR ($CDCl_3$) δ 4.89 (m, 1H), 4.81 (m, 1H), 4.16 (qd, J=6.4Hz, 1H) 3.69-3.61 (m, 2H), 3.47-3.41 (m, 2H), 3.08 (qd, J=6.4Hz, 1H), 2.11 (bs, 1H, D_2O exchangeable), 2.08-1.79 (m, 4H), 1.82 (s, 3H): ^{13}C NMR ($CDCl_3$) δ 144.6, 111.0, 76.1, 69.7, 61.8, 47.4, 27.8, 22.5, 19.3.

[7] The increased *anti* selectivity has been reported for the reaction involving an aromatic acetal **6** and Z-configured crotylsilane [3]. This stereochemical trend should not be associated, however, with the aforementioned total *anti* selectivity in the reaction involving **6** and η^3-crotyltitanocenes **2**. In fact, η^3-crotyltitanocenes appear to be configurationally stable equivalents of (E)-(and not Z)-η^1-crotylmetal reagents.