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Highly selective addition reaction of organotitaniums with Garner's aldehyde. Easy preparation of optically active allylic, allenylic, homoallylic and homopropargylic alcohols

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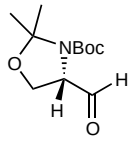
Abstract—Organotitanium complexes **3**–**5** prepared from a Ti(O-*i*-Pr)$_4$/2/*i*-PrMgX reagent (**2**) and the corresponding unsaturated compounds reacted with Garner's aldehyde (**1**) to provide *anti*-addition products highly predominantly, thus allowing an easy access to a variety of optically active *anti*-1,2-aminoalcohol derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

The addition of organometallic compounds to Garner's aldehyde **1** opens access to an optically active 2-amino-1,3-dihydroxypropyl structure motif which is widespread in natural and artificial biologically important compounds.[1] From the synthetic point of view, the greatest concerns in the community of organic chemists have been to realize high selectivity of the addition reaction and the availability of the organometallic complexes applied.



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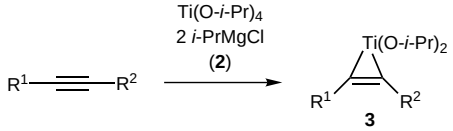
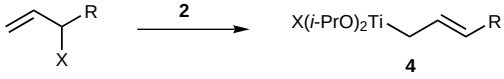
Recently, we have developed a method for synthesizing a variety of organotitanium complexes starting from a divalent titanium complex, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl (**2**), and unsaturated hydrocarbons.[2] Thus, the reaction of **2** with an alkyne affords (η^2-alkyne)Ti(O-*i*-Pr)$_2$ **3** which works as a vicinal vinylic dianion equivalent (Eq. (1)).[3] Meanwhile, allyltitaniums **4**[4] and allenyl/propargyltitaniums **5**[5] are readily prepared from **2** and allylic or propargylic derivatives, respectively, such as halides, carbonates or phosphates (Eqs. (2) and (3)). The easy and practical access to organotitaniums **3**, **4** and **5** from readily available starting material prompted us to carry out their reaction with **1**. In connection with the reaction of **1** with organotitanium complexes, only two reports using allyltitanium and alkynyltitanium complexes have been released. Hafner, Duthaler and coworkers reported that an allyltitanium complex having an optically active alkoxy ligand of the type CpTi(η^1-allyl)(OR*)$_2$ reacts with **1** with excellent diastereoselectivity; however, the reaction with a similar achiral allyltitanium complex proceeds with lower diastereoselectivity (ds) of 63%.[6] Alkynylation of **1** using a trimethylsilylethynyltitanium complex was reported by Herold which proceeded with 75% ds.[7]



(1)



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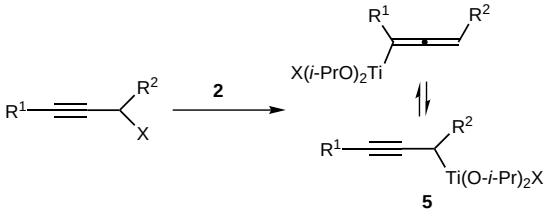

(3)

The results of the reaction of Garner's aldehyde (*S*)-**1**[8] with organotitanium complexes **3**–**5** are summarized in Table 1.

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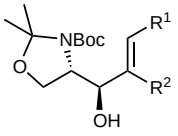
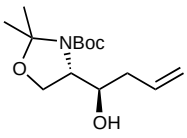
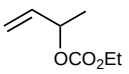
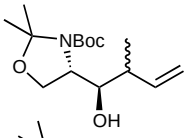
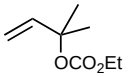
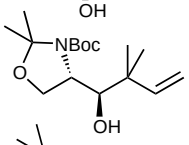
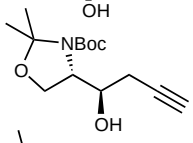
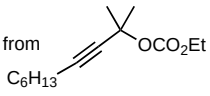
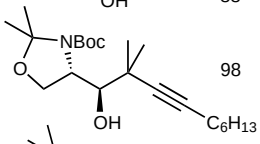
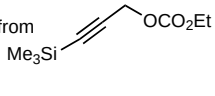
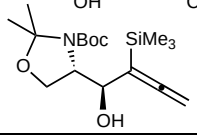
Table 1.

Entry	Organotitanium	Products[a] Major Diastereomer[b]	Ds, %[c]	Yield, %
	3 from R^1—≡—R^2			
1	$R^1=R^2=C_3H_7$		98	68
2	$R^1=SiMe_3$, $R^2=C_4H_9$		98	60
3	$R^1=SiMe_3$, $R^2=CH_2OTBS$		95	56
	4 from 			
4	X=Br		85	95
5	$X=OCO_2Et$		84	86
6	$X=OP(O)(OEt)_2$		84	93
7	**4** from 		75[d]	86
8	**4** from 		96	75
	5 from 			
9	X=Br		83	86
10	$X=OCO_2Et$		88	87
11	**5** from 		98	72
12	**5** from 		96	77

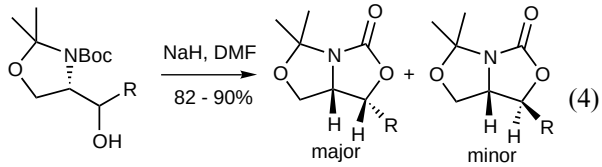
[a]For all cases no regio isomer was detected. [b]For the determination of the structure of the major diastereomer, see the text. [c]Established by NMR. [d]*Anti*-adduct consisted of two diastereomers in a ratio of 45:30.

The results of the reaction with **3** which are shown in entries 1–3 in Table 1 revealed the following characteristic features. As expected,[3] the reaction proceeded with exclusive regioselectivity with such unsymmetrical titanium–alkyne complexes shown in entries 2 and 3. To our satisfaction, excellent diastereoselectivity was attained to provide the *anti*-adduct highly predominantly. It is noted that the diastereoselectivity attained so far for the reaction of vinylic organometallic compounds was never up to 86%.[9]

Entries 4–8 in Table 1 show the results of the reaction of allyltitanium **4** with **1**. The reaction of **1** with an allyltitanium complex derived from **2** and 2-propenyl compounds such as bromide, carbonate or phosphate proceeded with 84–85% diastereoselectivity to afford the *anti*-addition product mainly (entries 4–6). The ds value observed here was not very high, but it is somewhat superior to that reached by using other achiral allylic organometallic reagents.[1] It can also be seen that the ds was not dependent so much on the nature of the starting allylic derivative used for the synthesis of the allyltitanium compound (entries 4–6). The reaction of crotyltitanium prepared from 3-buten-2-yl carbonate resulted in formation of a mixture of three adducts in a ratio of 45:30:25 in 86% total yield, where the ratio of *anti*:*syn* regarding the vicinal amino hydroxy moiety was found to be 75:25 (entry 7). Although the ds of the reaction with the crotyltitanium complex is not attractive from the synthetic viewpoint, as shown in entry 8 the reaction of the titanium compound derived from 2-methyl-3-buten-2-yl carbonate provided the *anti*-adduct in excellent ds of 96%.

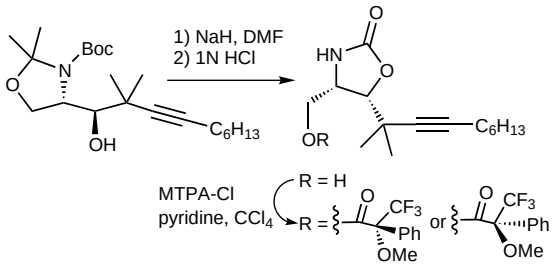
The results of the reaction of allenyl/propargyltitaniums **5** with **1** are summarized in entries 9–12. Even though the reaction of the titanium complex **5** prepared from the non-substituted propargyl derivatives did not proceed with very high level of diastereoselectivity (entries 9 and 10), to our satisfaction we found that the reactions of **5** prepared from 3-hexyl-1,1-dimethyl-2-propynylcarbonate (entry 11) and 3-trimethylsilyl-2-propynylcarbonate (entry 12) afforded highly predominantly homopropargylic and allenylic alcohols with *anti* stereochemistry, respectively. It is noteworthy that propargylation and allenylation of **1** have scarcely been reported despite the high synthetic potential of the corresponding products taking advantage of the reactivity of their propargyl or allenyl moiety.[10]

The stereochemistry of the products shown in entries 4–6 of Table 1 was confirmed by comparison of their spectroscopic data with those reported.[6] For other entries, except for entry 12, the adducts were respectively converted to the corresponding bicyclic oxazolidinones **6** by treatment with NaH (Eq. (4)) and their stereochemistries were confirmed. Thus, their coupling constants ($J=5.7$–8.4 Hz for the major isomers)[11] between two methine protons on the oxazolidinone ring and/or NOE experiments indicated *cis*-configuration of the major isomers of **6**, i.e. *anti*-stereochemistry of the major products shown in Table 1. Configuration of the product obtained in entry 12 was assigned from analogy with other entries.



(4)

It is well-known that aldehyde **1** is configurationally stable under neutral condition but is easily racemized under basic conditions.[1] Therefore, we checked the enantiomeric purity of the reaction product. The *anti*-addition product obtained in entry 11 was separated by column chromatography and converted to the corresponding 4-hydroxymethyloxazolidinone by sequential treatment with NaH in DMF and 1N HCl (Scheme 1). The ^1H NMR study of the MTPA-esters of the result-



Scheme 1.

ing alcohol indicated that no racemization occurred during the addition reaction.

In summary, the addition reaction of the organotitanium complexes **3**–**5** with Garner's aldehyde **1** proceeded with high to excellent diastereoselectivity to afford *anti*-addition products whatever the nature of the organotitanium reagent. The *anti* selectivity of the reaction may be explained by using the Felkin–Ahn transition structure shown below (Fig. 1),[1] where highly preferential attack of nucleophiles from the *re*-face of aldehyde (*S*)-**1** may be attributed to steric bulkiness of di(isopropoxy)organotitanium compounds.

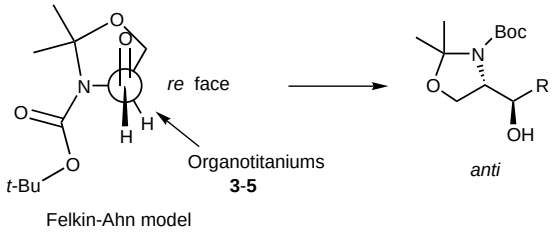


Figure 1.

Acknowledgements

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8. Either enantiomer of **1** was prepared from L- or D-serine according to the reported procedure (Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527) and the ee was determined by HPLC analyses with the use of a chiral column [Chiralcel OD-H, Daicel, 0.46 ϕ×25 cm, hexanes:*i*-PrOH = 10:1; 0.5 mL/min, R_t = 9.31 min for (*R*)-isomer, R_t = 9.81 min for (*S*)-isomer.] to be more than 98%. HPLC analyses were performed on a Shimadzu LC-VP system with a scanning diode array UV detector (190–370 nm, SPD-M10Avp). The λ_{max} of the aldehyde was 210 nm.
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