Enantioselective Grignard-Type Addition of Allyltitanium Reagents Having the Center of Chirality at Titanium

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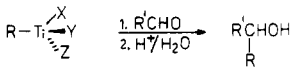
Addition of allylmagnesium chloride to the chiral and racemic titanium(IV) compound $CpCp'Ti(C_6F_5)Cl$, in which Cp = η^5-C_5H_5 and Cp′ = η^5-$C_5H_4C(CH_3)_3$, yields $CpCp'Ti(C_6F_5)C_3H_5$. The latter reacts diastereoselectively with aldehydes to afford adducts of the type $CpCp'Ti(C_6F_5)OCHRC_3H_5$, diastereomeric excess (de) being 12–40%. Optically active (+)-$CpCp'Ti(C_6F_5)Cl$ was also treated with allylmagnesium chloride, benzaldehyde added, and the adduct hydrolyzed in a one-pot reaction to provide the Grignard-type adduct. Enantiomeric excess (ee) amounts to 11%. Since the de value in the racemic series is 20%, loss of chiral information is occurring, possibly during the addition of allylmagnesium chloride to (+)-$CpCp'Ti(C_6F_5)Cl$.

Introduction

Organotitanium reagents of the type $RTiX_3$ (X = Cl, OR′, NR'_2) generally show high degrees of chemo- and diastereoselectivity in reactions with such electrophiles as S_N1-active alkyl halides[1] or carbonyl compounds.[2,3] In contrast, attempts to observe pronounced *enantioselectivity* have not been rewarding to date. For example, the ee value of Grignard-type additions of methyltitanium reagents having chiral alkoxy ligands are meager (ee = 5–60%).[3] A different approach is to use optically active titanium reagents **1** in which the metal itself represents the center of chirality.[4] This would put the chiral in-



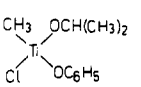
1 **2**

formation in the closest vicinity to the carbonyl function during the process of addition. We wish to report the results of exploratory studies directed toward this goal. The basic problem is to find ligands X, Y, and Z that impart configurational stability upon the tetrahedral titanium but also ensure enough reactivity in reactions with aldehydes. Unfortunately, these two factors oppose each other. For example, racemic **3** adds to benzaldehyde in ether at room temperature within 30 min to form ~95% of the addition product 1-phenylethanol, but the reagent is not configurationally stable.[5] Its ^1H NMR spectrum displays only one doublet for the formally diastereotopic methyl groups of the isopropoxy ligand. Cooling to −30 °C simply leads to line broadening of *all* signals, which speaks for aggregation phenomena.[5] The configurational stability of chiral organotitanium compounds such as **4** having one η^5-cyclopentadienyl ligand is higher, but separation of enantiomers is still not feasible.[5] At 0 °C the 100-MHz ^1H NMR spectrum (in toluene-d_8) shows sharp singlets for the methyl group at titanium and the Cp ligand, two resolved doublets for the diastereotopic methyl groups, and a heptet due to the lone hydrogen of the isopropoxy moiety. At higher temperature dynamic effects are observed; i.e., the two doublets coalesce to one doublet. $\Delta G^{\ddagger}$ for enantiomerization amounts to ~19.2 kcal/mol.[5]

Table I. Diastereoselective Reaction of **7** with Aldehydes RCHO To Form **8**

R	diastereo ratio in **8**	de, %
C_6H_5	60:40	20
CH_3	70:30	40
CH_3CH_2	64:36	28
$(CH_3)_2CH$	56:44	12

The reason for enantiomeric interconversion is presently not entirely clear but may well have to do with rapid intermolecular exchange of alkoxy ligands. Ti–O bonds are thermodynamically strong[6] but many appear to be kinetically labile.[7] In contrast to **3** and **4**, compound **5** is configurationally stable, but the reagent fails to add to benzaldehyde (22 °C/7 days).[5] Bis(η^5-cyclopentadienyl)-titanium compounds related to **5** have been previously prepared and isolated in optically active (+) and (−) forms by Tirouflet,[8] but potential reactions with aldehydes were not studied and are not likely to occur.[5] Since allyltitanium reagents are considerably more reactive than the alkyl analogues,[3a] we decided to prepare and test chiral allylbis(cyclopentadienyl)titanium compounds.



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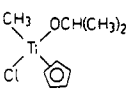

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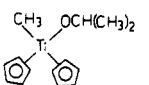

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Results and Discussion

The addition of allylmagnesium chloride to racemic **6**[8] afforded **7**, a sensitive compound[5] which was reacted in situ with various aldehydes in hope of obtaining diastereomeric

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(2) (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1011–1012. (b) Weidmann, B.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2451–2454. (c) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833–4835. (d) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989–990; *Angew. Chem. Suppl.* **1983**, 1511–1526.

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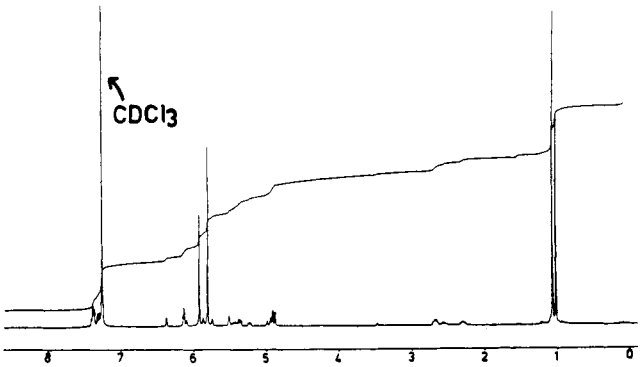
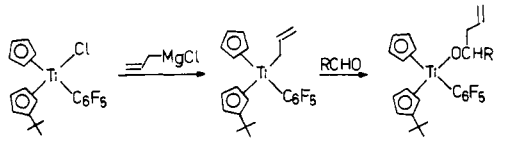


Figure 1. 400-MHz ^1H NMR spectrum ($CDCl_3$) of **8** with R = C_6H_5.

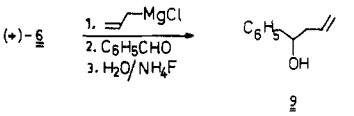
addition products **8**. Indeed, conversion at −78 °C to room temperature turned out to be ≥85%. Compounds **8** can be isolated by flash chromatography or TLC, which means that hydrolysis leading to the Grignard-type adducts (homoallyl alcohols) is very slow. However, the latter can



6 **7** **8**

easily be obtained by cleavage using a saturated aqueous NH_4F solution. Figure 1 shows a typical ^1H NMR spectrum of a chromatographed addition product, in this case the benzaldehyde adduct. Integration of the sharp signals due to the *tert*-butyl or the unsubstituted Cp groups allows the determination of the diastereomeric excess (de). No attempt was made to separate the diastereomers. Interestingly, the degree of diastereoselectivity *increases* with *decreasing* steric bulk of the aldehyde (Table I); however, the optimum de does not exceed 40%.

The relative low degree of stereoselection shows that the two Cp ligands are not sufficiently different in steric or electronic nature. Theoretically, the de value in the racemic series corresponds to the *maximum* ee value of the reactions in the optically active series leading to the alcohols.[9] Identical de and ee values would mean that displacement of chloride in the optically active form of **6** by an allyl group via allylmagnesium chloride proceeds stereospecifically with complete retention or inversion of configuration and that no enantiomerization occurs during the Grignard-type addition to aldehydes. In order to test this, we reacted configurationally stable (+)-**6**[8] with allylmagnesium chloride, added benzaldehyde, and cleaved the adduct with NH_4F in a one-pot reaction. The final product **9** turned out to have the *S* configuration, the ee value being 11%.[4] *This is the first and presently only example of an enantioselective Grignard-type addition in which the metal is the chiral center.*[10] Since the de value in the racemic series is 20%, loss of chiral information must be occurring. Partial racemization during allylmagnesium chloride addition to (+)-**6** is plausible. Control experiments involving the treatment of (+)-**6** with $MgCl_2$ under the same conditions show that such a process is not due to a potential salt-mediated exchange reaction. Thus, the trouble appears to lie in the actual substitution reaction.[11]



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The present study allows for two important conclusions. In order to achieve higher ee values, ligands must be chosen that are sterically very much different from one another. Second, care must be taken so that the carbon nucleophile transfers onto titanium stereospecifically. If this is not possible, one of the ligands itself should be chiral and optically active. This means that the diastereomers, each having chirality centers at titanium and in the ligand, would have to be separated prior to reaction with aldehydes. We are currently testing this strategy using compounds having only one Cp ligand in combination with bidentate ligands.

Experimental Section

Reagents and General Techniques. Racemic and optically active **6** were prepared according to the procedure of Tirouflet.[8a] All reactions using this reagent were performed under an N_2 atmosphere in a dry 100-mL three- necked flask equipped with a nitrogen inlet and a serum cap. Tetrahydrofuran was dried by distillation from CaH_2 followed by a second distillation over NaH under N_2.

General Procedure for the Preparation of Allyl Adducts 8. A solution of 0.22 g (0.5 mmol) of racemic **6**[8a] in 10 mL of THF was cooled to −78 °C and treated with 0.5 mmol of allylmagnesium chloride (0.31 mL of a 1.6 M solution). After addition, the solution was stirred for 1 h, during which the color changed from red to dark brown. The equivalent amount of aldehyde was added and the mixture stirred for 2 h at −78 °C and then allowed to come to room temperature. The solvent was stripped off, the residue treated with 15 mL of ether, and the $MgCl_2$ filtered off. Upon removal of the ether, the oily residue was examined with a 400-MHz ^1H NMR spectrometer. In all cases the crude product showed ≥85% conversion and diastereomeric ratios not exceeding 70:30 (Table I). The assignment of the structures was corroborated by treating the adducts with 5 mL of a saturated aqueous NH_4F solution at room temperature for 1 h and identifying the Grignard-type adducts by VPC using authentic samples.

Enantioselective Addition of (+)-6 to Benzaldehyde. The above procedure was employed by using optically active (+)-**6**.[8a] The benzaldehyde adduct was hydrolyzed with a saturated aqueous NH_4F solution, the Grignard-type adduct **9** (4-phenylbut-3-en-1-ol) extracted with ether, and a portion isolated by VPC. Its $[\alpha]^{22}_D$ value was −5.4° (*c* 6.7, benzene), compared to −48.7° (*c* 6.7, benzene) of an authentic optically pure sample having the *S* configuration.[12] This means an ee value of 11%.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Registry No. **6**, 57431-23-9; (+)-**6**, 57458-10-3; **7**, 91389-09-2; (*R**,*S**)-**8** (R = C_6H_5), 91389-10-5; (*R**,*R**)-**8** (R = C_6H_5), 91463-83-1; (*R**,*S**)-**8** (R = CH_3), 91389-11-6; (*R**,*R**)-**8** (R = CH_3), 91463-84-2; (*R**,*S**)-**8** (R = CH_3CH_2), 91389-12-7; (*R**,*R**)-**8** (R = CH_3CH_2), 91463-85-3; (*R**,*S**)-**8** (R = $(CH_3)_2CH$), 91389-13-8; (*R**,*R**)-**8** (R = $(CH_3)_2CH$), 91463-86-4; **9**, 77118-87-7; C_6H_5CHO, 100-52-7; CH_3CHO, 75-07-0; CH_3CH_2CHO, 123-38-6; $(CH_3)_2CHCHO$, 78-84-2; allylmagnesium chloride, 2622-05-1.

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(10) Recent attempts to induce addition of optically active allylmethylnaphthylphenylsilane to aldehydes in the presence of Lewis acids failed, in contrast to substitution reactions of acetals (ee = 3.9–5.5%): Hathaway, S. J.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 3351–3353.

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