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Characterization of the Chiral Titanium Reagent Prepared from the Tartrate-derived Chiral Diol and Titanium Dichloride Diisopropoxide

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The chiral titanium reagent prepared from the tartrate-derived chiral 1,4-diol and titanium dichloride diisopropoxide was characterized based on the NMR and experimental analyses.

In the previous papers, we reported highly enantioselective Diels-Alder reaction,$^{1)}$ intramolecular ene reaction,$^{2)}$ [2+2] cycloaddition reaction$^{3)}$ and hydrocyanation reaction,$^{4)}$ using a chiral titanium reagent prepared in situ from titanium dichloride diisopropoxide ($TiCl_2(O^iPr)_2$) and the tartrate-derived chiral 1,4-diol. Especially noteworthy is the fact that in the Diels-Alder and [2+2] cycloaddition reactions, high enantioselectivity is realized by using only a catalytic amount of the chiral titanium reagent in the presence of Molecular Sieves (MS) 4A. In this paper, we would like to report our study concerning the nature of the chiral titanium reagent.

In the first place, 500 MHz ^1H NMR analysis of the chiral titanium reagent was carried out. In Figure 1 are shown the NMR spectra of the chiral diol $\underline{1}$ itself and the chiral titanium reagent prepared by mixing an equimolar amount of the chiral diol $\underline{1}$ and $TiCl_2(O^iPr)_2$ in toluene-d_8. The spectrum of the chiral titanium reagent clearly indicates two sets of the signals corresponding to the chiral diol $\underline{1}$ in the ratio of 87:13 (determined by the integration of the methine proton), and the minor signals completely coincide with those of the chiral diol $\underline{1}$ itself. The other set of the signals is thought to belong to the chiral titanium alkoxide $\underline{2}$, which is produced by the alkoxy exchange reaction. The existence of the chiral diol $\underline{1}$ itself in the mixture indicates that the exchange reaction of isopropoxy groups with $\underline{1}$ does not proceed completely, and the presence of non-complexed chiral diol means the existence of unchanged $TiCl_2(O^iPr)_2$ which is thought to have comparable Lewis acid activity to the chiral titanium alkoxide $\underline{2}$. This result seems incompatible with the high enantioselecivity achieved in the asymmetric Diels-Alder, ene, and [2+2] cycloaddition reactions.$^{1-3)}$

At this point, it is assumed that the presence of liberated isopropyl alcohol must play some role in this reaction and the rate of the Diels-Alder reaction between the fumaric acid derivative $\underline{3}$ and isoprene was examined using three kinds of titanium reagents, and the results are summarized in Table 1. As expected, $TiCl_2(O^iPr)_2$ alone is the most active, and the Lewis acid activity of the chiral

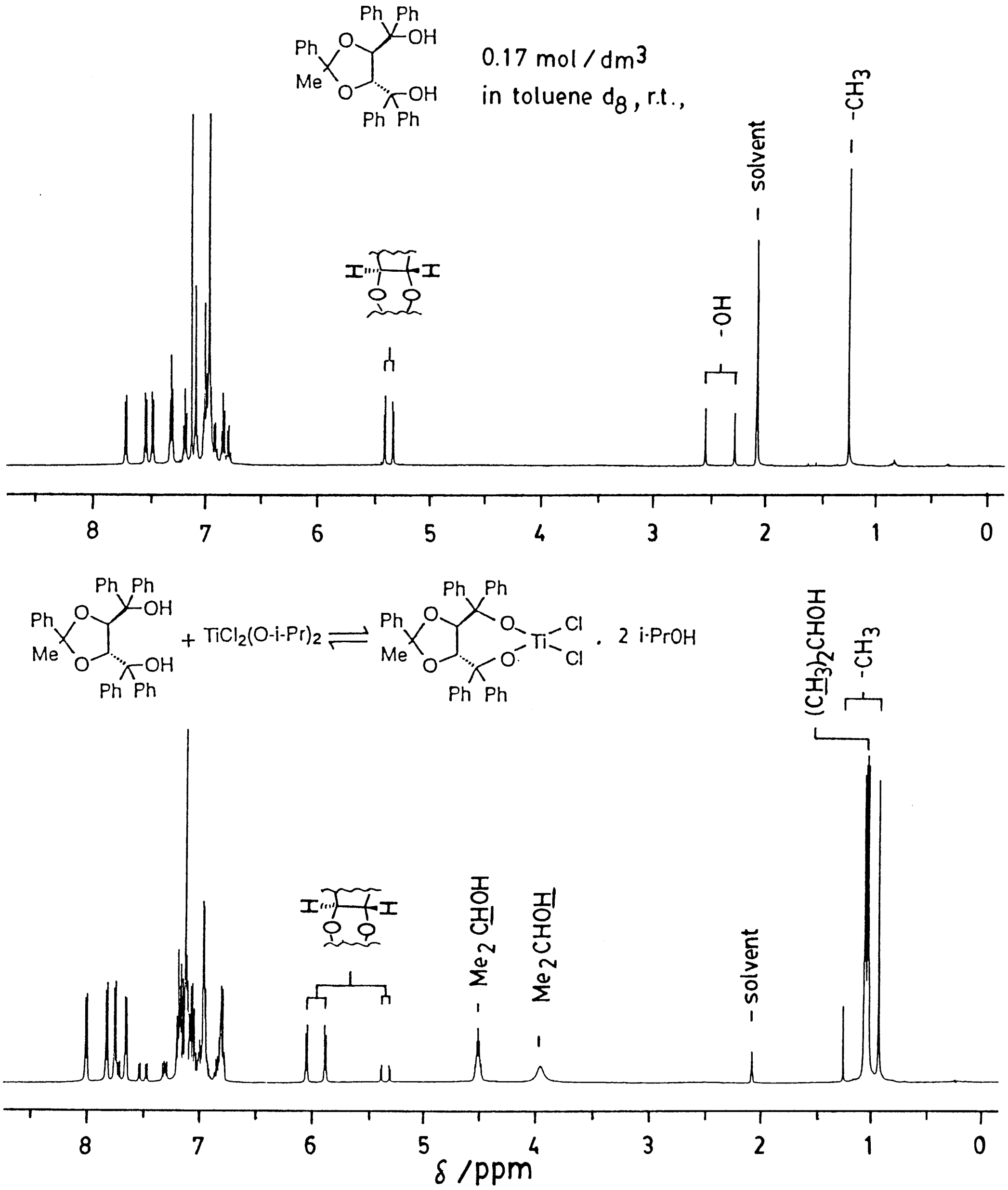

Fig. 1. 500 MHz ^{1}H NMR spectra of the chiral diol 1 and the chiral titanium reagent.

titanium reagent prepared from 1 and $TiCl_2(O^iPr)_2$ slightly decreased probably due to the bulkiness of the chiral diol moiety. Moreover, the addition of isopropyl alcohol to $TiCl_2(O^iPr)_2$ almost completely suppressed the activity of the titanium. The particular deactivation of $TiCl_2(O^iPr)_2$ by the addition of isopropyl alcohol is presumably ascribed to the complexation of isopropyl alcohol with $TiCl_2(O^iPr)_2$ to cause aggregation of titanium species.

We further measured the NMR spectra of the mixture of the different ratios of $TiCl_2(O^iPr)_2$ and isopropyl alcohol. In every case, only one set of the signals corresponding to isopropyl group were observed. And when a small amount of

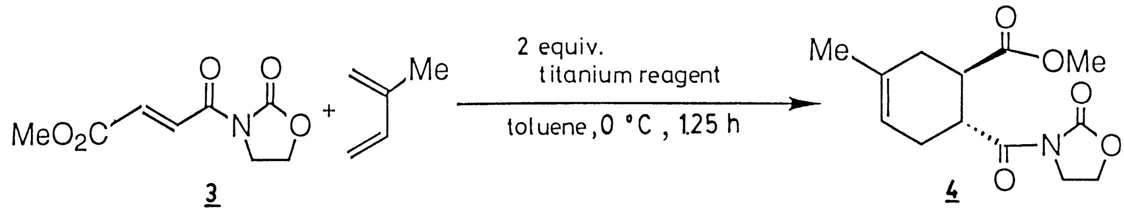

Table 1. The Reactivity of Titanium Reagents

Titanium reagent	$\underline{3}$: $\underline{4}^{a)}$
$TiCl_2(O^iPr)_2$	9 : 91
$TiCl_2(O^iPr)_2$-$\underline{1}$	26 : 74
$TiCl_2(O^iPr)_2$-^iPrOH	100 : 0

a) The ratio was determined by the NMR analysis of the crude product.

isopropyl alcohol is added to $TiCl_2(O^iPr)_2$, there is a specific downfield shift of the methine proton,[5)] which supports the assumption that the addition of isopropyl alcohol causes aggregation of $TiCl_2(O^iPr)_2$.

Then, the NMR spectrum of the chiral titanium reagent in the presence of MS 4A was next examined. The spectrum shows that the ratio of the chiral titanium alkoxide $\underline{2}$ to the non-complexed chiral diol $\underline{1}$ increased to 94:6 by the addition of MS 4A(about 150 mg per 0.1 mmol titanium reagent in 0.6 dm^3 toluene-d_8).(without MS 4A; 87:13) This result indicates that the equilibrium of the mixture of the chiral diol and $TiCl_2(O^iPr)_2$ shifted to the side of the formation of the chiral titanium alkoxide $\underline{2}$ by the addition of MS 4A.

In the asymmetric Diels-Alder reaction using a catalytic amount of the chiral titanium reagent, it is essential to carry out the reaction in the presence of MS 4A.[6)] Otherwise, the optical purity of the cycloadduct decreased. Thus, in the absence of MS 4A, it is supposed that the concentration of the liberated isopropyl alcohol is not sufficient to suppress the Lewis acidity of $TiCl_2(O^iPr)_2$ in the high dilution conditions of the catalytic reaction (about 0.01 mol/dm^{-3}). On the other hand, the presence of MS 4A shifted the equilibrium to the side of the formation of the chiral titanium complex, and the reaction catalyzed by the uncomplexed $TiCl_2(O^iPr)_2$ does not take place.

There have been some reports concerning the structure of the Sharpless epoxidation catalyst. Sharpless reported the X-ray analysis of the tartaric acid amide-titanium tetraisopropoxide complex suggesting a dimeric, tricyclic, and unsymmetrical structure,[7,8)] while Potvin suggested a dimeric, symmetrical ten-membered cyclic structure based on the NMR spectra.[9)]

From the NMR spectrum of the mixture of the chiral diol $\underline{1}$ and $TiCl_2(O^iPr)_2$ which is shown in Fig. 1, there seemed to be formed a single symmetric species. The symmetric nature of the titanium species did not change between 220 K and 340 K. However, it is not clear whether this chiral titanium reagent is monomeric or dimeric only from this spectrum. In order to clarify these points, we next carried out the Diels-Alder reaction between 3 and isoprene using the titanium reagent prepared from $TiCl_2(O^iPr)_2$ and a partially optically active diol. When a partially optically active diol (25% e.e.) was added to $TiCl_2(O^iPr)_2$, formation of white precipitates was observed, and the stoichiometric use of this mixture afforded the cycloadduct 4 in 83% e.e. Isolation of the intermediate precipitates, followed by acid hydrolysis afforded the diol 1 in a completely racemic form. This result indicates that the precipitated titanium species is at least dimeric and is composed of the (R)- and (S)-diols in 1:1 ratio.10)

When 3-cinnamoyl-1,3-oxazolidin-2-one was added to the chiral titanium reagent prepared in the usual manner, precipitations occurred within several minutes. Isolation followed by acid hydrolysis of the complex afforded the chiral diol 1 and 3-cinnamoyl-1,3-oxazolidin-2-one in 1:1 ratio. The reaction of this isolated complex with cyclopentadiene in toluene proceeded to give the corresponding cycloadduct in 75% optical yield.11) Thus, it was confirmed that the chiral titanium reagent and 3-acyl-1,3-oxazolidin-2-one form 1:1 complex in the reaction medium.

References

1) K. Narasaka, M. Inoue, and N. Okada, Chem. Lett., 1986, 1109; K. Narasaka, M. Inoue, and T. Yamada, ibid., 1986, 1967; K. Narasaka, M. Inoue, T. Yamada, J. Sugimori, and N. Iwasawa, ibid., 1987, 2409.
2) K. Narasaka, Y. Hayashi, and S. Shimada, Chem. Lett., 1988, 1609.
3) Y. Hayashi and K. Narasaka, Chem. Lett., 1989, 793.
4) K. Narasaka, T. Yamada, and H. Minamikawa, Chem. Lett., 1987, 2073; H. Minamikawa, S. Hayakawa, T. Yamada, N. Iwasawa, and K. Narasaka, Bull. Chem. Soc. Jpn., 61, 4379 (1988).
5) The chemical shifts of the methine proton of isopropyl group are as follows; isopropyl alcohol: δ 3.89, isopropyl alcohol-$TiCl_2(O^iPr)_2$ (0.7:1): δ 4.95, $TiCl_2(O^iPr)_2$: δ 4.47.
6) Sharpless first reported that high enantioselectivity can be achieved by carrying out the reaction in the presence of MS 4A in the catalytic asymmetric epoxidation reaction using diisopropyl tartrate and titanium tetraisopropoxide,7,12) and recently Yamamoto13) and Nakai14) reported related phenomena in their asymmetric ene reactions.
7) M. G. Finn and K. B. Sharpless, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1985), Vol. 5, Chap. 8.
8) I. D. Williams, S. F. Pedersen, K. B. Sharpless, and S. J. Lippard, J. Am. Chem. Soc., 106, 6430 (1984); S. F. Pedersen, J. C. Dewan, R. R. Eckman, and K. B. Sharpless, ibid., 109, 1279 (1987).
9) P. G. Potvin, P. C. C. Kwong, and M. A. Brook, J. Chem. Soc., Chem. Commun., 1988, 773.
10) There still exists the possibility that the chiral titanium species is a monomer in solution. In particular, the NMR spectrum shown in Scheme I supports this possibility because only a single species is observed in this spectrum. If the chiral titanium species is a dimer, it is probable that two diastereomers which are discernable by NMR would be produced.
11) Under the standard conditions using a stoichiometric amount of the titanium reagent,1) the corresponding cycloadduct was obtained in 81% e.e.
12) R. M. Hanson and K. B. Sharpless, J. Org. Chem., 51, 1922 (1986); Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, J. Am. Chem. Soc., 109, 5765 (1987).
13) K. Maruoka, Y. Hoshino, T. Shirasaka, and H. Yamamoto, Tetrahedron Lett., 29, 3967 (1988).
14) K. Mikami, M. Terada, and T. Nakai, J. Am. Chem. Soc., 111, 1940 (1989).

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