

Simultaneous Coordination and Double Activation Phenomena of Carbonyl and Epoxy Oxygens by Bis-Titanium Reagent as a Bidentate Lewis Acid Catalyst

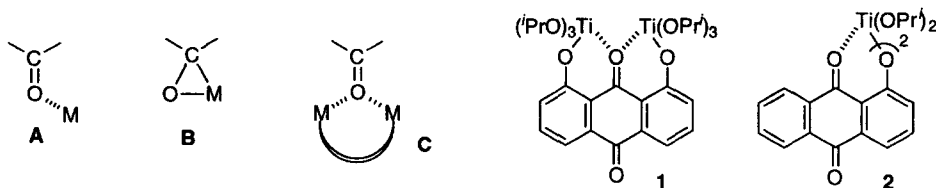
Naoki Asao, Satoshi Kii, Hideo Hanawa, and Keiji Maruoka*

*Department of Chemistry, Graduate School of Science, Hokkaido University
Sapporo 060-0810, Japan*

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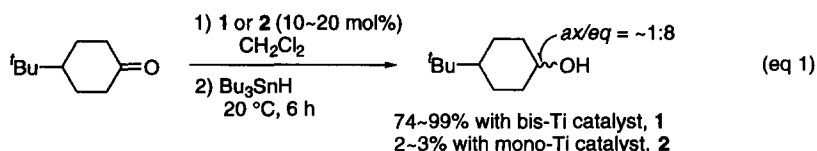
Abstract: The new bidentate Ti catalyst, (anthraquinone-1,8-dioxy)bis(triisopropoxy-titanium) (**1**) can be successfully designed and utilized for the simultaneous coordination to carbonyl substrates. The high double-activation ability of the bidentate Ti catalyst **1** toward carbonyls is emphasized using several synthetic examples in comparison with the corresponding monodentate Ti catalyst. The intermediary coordination complex formation of bidentate **1** with DMF or epoxycyclohexane as a carbonyl or epoxy substrate is characterized by ^{13}C NMR spectroscopy. © 1998 Elsevier Science Ltd. All rights reserved.

Addition of nucleophiles to carbonyl groups is undoubtedly one of the most fundamental yet important transformations in organic synthesis, and this reaction is dramatically accelerated by complexation of Lewis acids to the carbonyl oxygen.¹ The general modes of activation of carbonyls are the σ -complexation and π -complexation geometries, (A) and (B) with single-metal species.² Simultaneous coordination of carbonyls with bidentate Lewis acids possessing two sites of Lewis acidity, which forms the σ,σ -complexation geometry (C), was recently found to enhance both the reactivity and selectivity for the carbonyl substrates compared to the corresponding monodentate Lewis acids.^{3,4} Examples of these bridging types of double coordination are still rare despite its theoretical, mechanistic, and synthetic importance, and the nature of such double coordination phenomena remains elusive, particularly under the catalytic conditions.⁵ In view of the wide applicability and versatility of titanium-based Lewis acids in selective organic synthesis including asymmetric synthesis,⁶ we set out to design a new, bidentate bis-titanium catalyst of type **1** derived from a feeble Lewis acid, $\text{Ti}(\text{OPr}^i)_4$, and we here elucidate the double coordination phenomena toward carbonyl substrates by several synthetic examples.

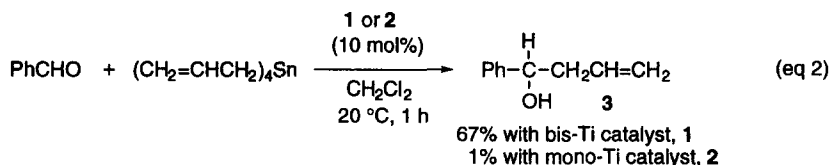


The requisite bis-titanium catalyst **1** can be readily prepared by mixing commercially available 1,8-dihydroxyanthraquinone with $\text{Ti}(\text{OPr}^i)_4$ (2 equiv) in CH_2Cl_2 at 25 °C.⁷ The simultaneous coordination of two titanium atoms to one anthraquinone carbonyl is verified by ^{13}C NMR analysis of the bis-titanium catalyst **1** [δ 207.38 and 183.89 (activated and non-activated C=O of **1**); cf. δ 184.03 and 182.60 (activated and non-activated C=O of **2**); δ 183.34 (C=O of anthraquinone)].^{8,9} Similarly, the corresponding mono-titanium catalyst **2** was obtained from 1-hydroxyanthraquinone and $\text{Ti}(\text{OPr}^i)_4$, though 2 equiv of 1-

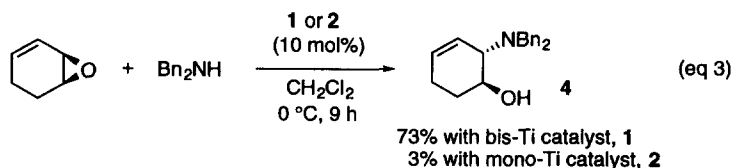
hydroxyanthraquinone is replaced by isopropoxy ligands in this particular case.¹⁰⁻¹³ Complexation of 4-*tert*-butylcyclohexanone with the *in situ* generated bis-titanium catalyst **1** (10~20 mol%) in CH₂Cl₂ and subsequent treatment of Bu₃SnH (1.1 equiv) at -20 °C for 5 min and at 20 °C for 6 h afforded 4-*tert*-butylcyclohexanol in 74~99% yield. The *i*-PrOH-free catalyst **1**, which was also prepared from 1,8-dihydroxyanthraquinone and Ti(OPr^{*i*})₄ (2 equiv) in CH₂Cl₂ by azeotropic removal of *i*-PrOH, gave similar results (97~99% with 20 mol% catalyst) in the reduction of 4-*tert*-butylcyclohexanone with Bu₃SnH. In marked contrast, however, reduction of 4-*tert*-butylcyclohexanone with mono-titanium catalyst **2** (10~20 mol%) under otherwise similar reduction conditions gave 4-*tert*-butylcyclohexanol in only 2~3% yield. Further, use of Ti(OPr^{*i*})₄ resulted in total recovery of the starting ketone. These results clearly demonstrate that the bidentate Ti catalyst **1** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of carbonyl moiety. It should be noted that attempted use of catalytic ClTi(OPr^{*i*})₃ and Cl₂Ti(OPr^{*i*})₂ (10 mol%) for this reduction afforded 4-*tert*-butylcyclohexanol (*ax/eq* = ~1:2) in low yields (10 and 16%, respectively, at 20 °C for 6 h).



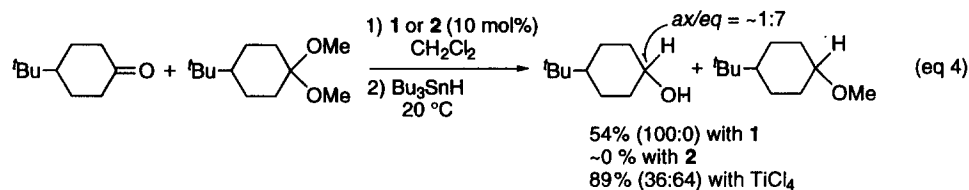
A similar difference of reactivity between bis-titanium **1** and mono-titanium **2** is observed in the allylation of aldehydes. Thus, reaction of benzaldehyde and tetraallyltin (1.1 equiv) with catalytic **1** (10 mol%) proceeded smoothly to furnish the corresponding homoallylic alcohol **3** in 67% yield, though its monodentate counterpart **2** yielded only 1% of the product under similar conditions.



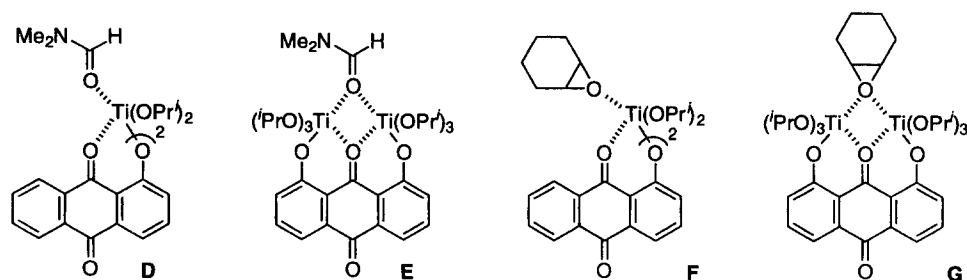
In addition to the double activation of carbonyl moiety, the synthetic application of bidentate Ti catalyst is further illustrated by the regio- and stereoselective ring-opening of epoxides with amine bases. For example, treatment of cyclohexadiene monoepoxide with dibenzylamine (1.1 equiv) in CH₂Cl₂ under the influence of catalytic bis-titanium **1** (10 mol%) at 0 °C gave amino alcohol **4** (73% yield)¹⁴ with rigorous regio- and stereoselectivity, while replacement of bis-titanium **1** by mono-titanium **2** under the otherwise identical reaction conditions afforded **4** in only 3% yield.



Noteworthy is the unique chemoselectivity in the selective addition of a nucleophile between a ketone and its acetal with the bidentate **1**, not observable in the ordinary Ti-catalyzed counterparts.



Although double coordination behavior of the bidentate **1**-carbonyl complex is consistent with the above experimental findings, more direct and convincing evidence was obtained by ^{13}C NMR spectroscopy using DMF and epoxycyclohexane as a carbonyl and an epoxy substrate, respectively. Thus, the 75 MHz ^{13}C NMR measurement of the 1:1 $\text{Ti}(\text{OPr}^i)_4$ -DMF complex and the 1:1 monodentate **2**-DMF complex (**D**) in CDCl_3 at $20\text{ }^\circ\text{C}$ showed that the original signal of DMF carbonyl at δ 162.61 shifted slightly to δ 162.44 and 162.41, respectively. These results imply the feeble Lewis acidity of $\text{Ti}(\text{OPr}^i)_4$ and **2**. In contrast, 1:1 bidentate **1**-DMF chelation complex under similar conditions undergoes a downfield shift for the DMF carbonyl (δ 165.43), implying the strong electrophilic activation of the DMF carbonyl by intervention of the double coordination complex (**E**).¹⁵ Here, both titaniums still coordinate to the anthraquinone carbonyl, the signal of which appears at δ 207.14 (*cf.* δ 207.38 for the activated $\text{C}=\text{O}$ of **1**). In a similar manner, the ^{13}C NMR study of the 1:1 $\text{Ti}(\text{OPr}^i)_4$ -epoxycyclohexane complex and the 1:1 monodentate **2**-epoxycyclohexane complex (**F**) in CDCl_3 confirmed that the original signal of epoxycyclohexane α -carbons at δ 52.04 shifted slightly to δ 51.91 and 51.76, respectively. In contrast, 1:1 bidentate **1**-epoxycyclohexane chelation complex under similar conditions undergoes a downfield shift for the epoxycyclohexane α -carbons (δ 53.14), suggesting the electrophilic activation of the epoxycyclohexane α -carbons by intervention of the double coordination complex (**G**). The ^1H NMR analysis also indicated the higher Lewis acidity of the bis-titanium catalyst **1**. The three peaks for aromatic protons of **1** (δ 7.86, 7.41, 7.10) were shifted to the higher magnetic field (δ 7.77, 7.36, 7.02) by addition of DMF. On the other hand, the signals of aromatic protons of **2** did not show any significant change and only one peak slightly shifted from δ 8.10 to 8.06. These results implied that DMF was tightly coordinated to the bis-titanium catalyst **1** compared to **2**.

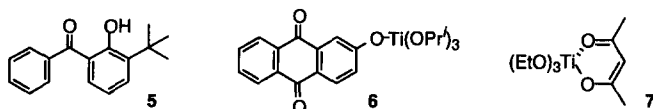


In conclusion, we successfully demonstrated that the feeble Lewis acidity of $\text{Ti}(\text{OPr}^i)_4$ can be dramatically enhanced by forming bidentate Ti reagent **1** with two Ti centers in an appropriate position using commercially available 1,8-dihydroxyanthraquinone as a desired spacer. Several of the synthetic examples disclosed herein are capable of transforming to the asymmetric versions by incorporation of certain chiral ligands, and hence this study implies the vast potential on the synthetic utility of bidentate Lewis acids in promising Ti chemistry.

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- In the early stage of this study, 2,7-dimethyl-1,8-biphenylenediol was utilized as a spacer for a new bis-titanium reagent based on our previous observation on a bidentate aluminum reagent (see ref 3d). However, the resulting (2,7-dimethyl-1,8-biphenylenedioxy)bis(triisopropoxytitanium) gave only disappointing results in the ketone reduction and allylation of aldehydes.
- A similar tendency in chemical shifts by ^{13}C NMR was also observed in the parent 1,8-dihydroxy- and 1-hydroxyanthraquinone: δ 193.19 and 181.74 (activated and non-activated C=O of 1,8-dihydroxyanthraquinone); δ 188.84 and 182.57 (activated and non-activated C=O of 1-hydroxyanthraquinone) compared to anthraquinone carbonyl (δ 183.34).
- The ^1H NMR measurement of the mixture of 1,8-dihydroxyanthraquinone (1 equiv) and $\text{Ti}(\text{OPr}^i)_4$ (2 equiv) in CDCl_3 at room temperature showed the only signal ascribed to isopropoxy methyne at δ 4.51. Furthermore, only three signals were detected in the aromatic range (δ 7.86, 7.41, and 7.10). These results indicate that the 1,8-dihydroxyanthraquinone/ $\text{Ti}(\text{OPr}^i)_4$ complex has a symmetric structure like 1.
- In the synthesis of mono-titanium reagents, 2 equiv of 1-hydroxyanthraquinone is incorporated, whether 0.5 or 1 equiv of $\text{Ti}(\text{OPr}^i)_4$ is present, to furnish fully-coordinated 2 as a sole product, which still has a coordination ability toward carbonyl and epoxy substrates by ligand exchange as ascertained by ^{13}C NMR analysis (see text).
- In order to form the monodenate Ti catalyst composed of $\text{Ti}(\text{OPr}^i)_4$ and the ligand in 1:1 ratio, we prepared 5 with a bulky substituent at the 2-position for preventing the formation of 1:2 complex. However, the resulting complex also consisted of $\text{Ti}(\text{OPr}^i)_4$ and the ligand 5 in 1:2 ratio like complex 2.



- We also prepared mono-substituted Ti reagent 6 from $\text{Ti}(\text{OPr}^i)_4$ and 2-hydroxyanthraquinone in case hexa-coordinated 2 might have the low reactivity toward carbonyl substrates. The tetracoordinate 6 showed similar low reactivity (~6%) to 2 in the reduction of 4-tert-butylcyclohexanone with Bu_3SnH . Moreover, the known penta-coordinated Ti complex 7 also exhibited the low reactivity (<1%) in the same reaction (See ref 13).
- For the penta-coordinated Ti complex formation from $\text{Ti}(\text{OR})_4$ with acetylacetone or ethyl acetoacetate, see: Yamamoto, A.; Kambara, S. *J. Am. Chem. Soc.* **1957**, *79*, 4344.
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- The simultaneous coordination of 1 toward DMF was also confirmed by the following two NMR experiments; The ^{13}C NMR measurement of 1-DMF complex showed six signals ascribed to aromatic ring (δ 162.84, 131.46, 130.82, 128.32, 121.10, 117.32), and the ^{49}Ti NMR measurement using TiCl_4 as an external standard gave only one signal (δ -848.64). These results suggest that the 1-DMF complex has a structure like E.