Pergamon

Tetrahedron Letters, Vol. 35, No. 41, pp. 7553-7556, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01620-8

Correlation of the Structure of Chiral *o,o'*-Bisphenol-Ti(IV) Complexes with Ligand Electronic Effects. A Relationship Between Lewis Acidity and Angle Strain

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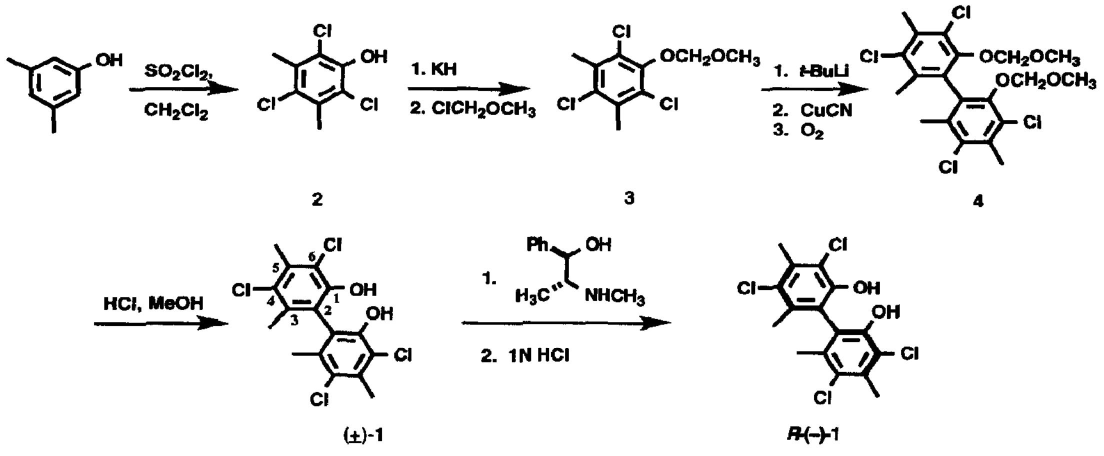
Summary: *The electron deficiency of Ti(IV) in complexes with chiral o,o'-bisphenols influences the C_{Ar}–O–Ti angle which, in turn determines the topology of the most stable (or easily formed) cyclic complex.*

Although chiral Lewis Acids derived from *o,o'*-bisphenols and Ti or Al have been applied as catalysts for a number of useful enantioselective reactions, e.g. ene,[1] Diels-Alder,[2] and carbonyl allylation[3] processes, in no case is the structure of the catalytic species known.[4,5] Two important questions with regard to titanium are (1) whether structures of the type  $Ar_2{<}^{O}_{O}{>}Ti{<}^{Cl}_{Cl}$, or their μ-bridged dimers, which are expected to be powerful Lewis acids, can be generated by the usual direct preparative methods, e.g. from $Ar_2(OH)_2$ and $TiCl_4$, and (2) if not, why not. The formation of such structures has in the past been taken for granted, without supporting evidence,[1,6] for the catalyst from $TiCl_4$ and 1,1'-bis-2-naphthol (BINOL). Reported herein are structural studies on three Ti(IV) derivatives of 3,3',5,5'-tetramethyl-4,4',6,6'-tetrachloro-2,2'-bisphenol (**1**), a ligand which was selected on the basis of elevated acidity (which translates into enhanced Lewis acidity for metal derivatives) and synthetic availability. These new data clearly reveal important electronic and geometrical factors which operate to determine the favored three-dimensional structure of cyclic Lewis acid-Ti(IV) complexes.

The synthesis of **1** was completed in three steps from 3,5-dimethylphenol in an overall yield of 54%. Trichlorination of 3,5-dimethylphenol (sulfuryl chloride, dichloromethane–diethyl ether, 23 °C, 1 h) gave the trichloride **2**[7] as colorless needles (mp 155-165 °C, subl.) in 96% yield.[8] Protection of the phenol (KH, chloromethylmethyl ether, THF, 23 °C, 1 h) proceeded to give the methoxymethyl ether **3**[9] (100%) as a colorless solid (mp 46-48 °C). *Ortho*-lithiation of **3** (*t*-butyllithium, -78 °C, THF) followed by formation of the cyanocuprate (CuCN, 0 °C, THF)[10] and coupling with oxygen provided the biaryl **4**. Upon treatment with HCl in methanol the racemic bis-phenol (±)-**1**[11] was obtained as a colorless solid (mp 196.0-197.5 °C) in 58% yield from **3** after silica gel chromatography.

Enantiomerically pure *R*-(–)-**1** (mp 179.5-180.5 °C, $[\alpha]_D^{23} = -21.8°$ (c=7.1, $CHCl_3$) was obtained after salt formation with (1*R*, 2*R*)-pseudoephedrine in hot toluene. Two recrystallizations of the salt from dichloroethane gave *R*-(–)-**1** in 53% yield and >99.5% enantiomeric excess as determined by chiral HPLC analysis of the bis-acetate.[12] The chiral bis-phenol was obtained from the salt by treatment with aqueous HCl and extraction into dichloromethane (pseudoephedrine was efficiently recovered). Reaction of **1** with titanium(IV) chloride (1 equiv) in dichloromethane at -78 °C afforded after warming to 23 °C and removal of the solvent, a red solid that was shown to be homogeneous by ^1H NMR analysis (two CH_3 singlets at 2.03 and 2.60 ppm). Recrystallization from dichloromethane at -20 °C gave red-orange, air-sensitive prisms.[13] A single crystal (0.40 mm x 0.40 mm x 0.40 mm) was subjected to X-ray analysis under nitrogen at -80 °C and yielded the structure (and absolute



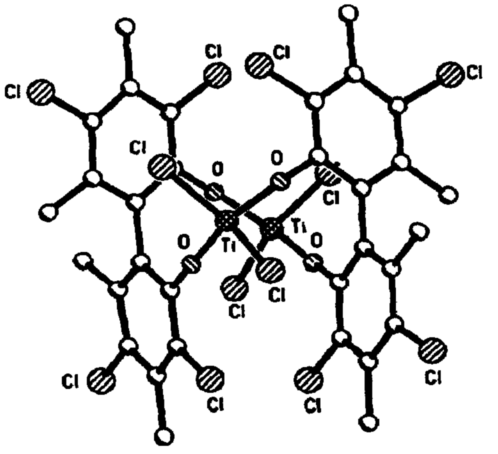
configuration) depicted by 5,[14] which contains a 14-membered ring with two titanium and four oxygen members. An important feature of this structure is that the Ar–O–Ti angle is nearly linear (168° and 169°), indicating strong *n* → *d* electron donation from O to Ti. It is clear that with two electronegative chlorines attached to tetracoordinate Ti(IV), the electron deficiency of the metal is so great that electron density is transferred from the oxygen ligands with a large increase in C_{Ar}–O–Ti angle. It is this factor which accounts for the non-formation (and probable relative instability) of the 7-membered structure $\mathrm{Ar_2}\begin{smallmatrix}\mathrm{O}\\ \mathrm{O}\end{smallmatrix}\mathrm{Ti}\begin{smallmatrix}\mathrm{Cl}\\ \mathrm{Cl}\end{smallmatrix}$ or even its μ-bridged dimer.

When the reaction of *R*-(−)-1 and $TiCl_4$ was conducted in toluene (at -78 °C for 1 h and 23 °C for 12 h) a new orange compound (6) was obtained in addition to 5 (ratio of 6 : 5 = 7 : 1 if 1 : $TiCl_4$ = 1.5 : 1). Recrystallization from 2 : 1 CH_2Cl_2–$CHCl_3$ at 0 °C afforded X-ray quality orange crystals of pure 6; ^1H NMR (400 MHz) 1.88 (s, 12H), 2.40 (s, 12H); ^{13}C NMR (100 MHz) 18.1, 18.9, 122.5, 125.1, 129.8, 134.7, 135.0, 158.5. The structure of 6 was determined by X-ray analysis.[14a,15] Structure 6 consists of two bridgehead ClTi fragments bridged by three bis-phenol ligands with Ti–O–C_{Ar} angles of 152°, again indicating substantial *n* → *d* electron delocalization from O to Ti.

Reaction of *S*-(+)-1 with 1 equiv of $Ti(Oi\text{-}Pr)_4$ in toluene at 23 °C for 1 h afforded a crystalline product (yellow prisms from CH_2Cl_2 at -20 °C) the structure of which was shown to be 7 by X-ray crystallography.[14a,16] Formula 7 corresponds to the μ-oxobridged dimer of the 7-membered titanacycle corresponding to $\mathrm{Ar_2}\begin{smallmatrix}\mathrm{O}\\ \mathrm{O}\end{smallmatrix}\mathrm{Ti(Oi\text{-}Pr)_2}$. This type of dimeric structure, which has been observed previously,[17] represents another way of stabilizing the monomeric unit $\mathrm{Ar_2}\begin{smallmatrix}\mathrm{O}\\ \mathrm{O}\end{smallmatrix}\mathrm{Ti(Oi\text{-}Pr)_2}$ which is coordinatively unsaturated. Evidently this monomeric unit is relatively stable with minimal enlargement of the C_{Ar}–O–Ti angle by *n* → *d* electron donation due to the two Oi–Pr donor groups on Ti which greatly diminish this effect relative to the Cl substituents in 5 and 6. Interestingly, reaction of 7 with a solution of BCl_3 in CH_2Cl_2 produced a mixture of 5 and 6, demonstrating the relative instability of $\mathrm{Ar_2}\begin{smallmatrix}\mathrm{O}\\ \mathrm{O}\end{smallmatrix}\mathrm{Ti}\begin{smallmatrix}\mathrm{Cl}\\ \mathrm{Cl}\end{smallmatrix}$.

The ^1H NMR spectra of Ti(IV) compounds 5, 6, and 7 in CD_2Cl_2 solution at 23 °C are consistent with the structures determined by X-ray for the solid state. In the case of compound 7, the ^1H NMR spectrum at -200 K indicated the presence of two diastereomeric forms, 7 and 7' which interconvert slowly on the NMR timescale at -200 K and rapidly at 296 K.

In summary, the present work shows clearly why the formation of 5-, 6- and 7-membered cyclic compounds of the type $\mathrm{R}\langle{}^{\mathrm{O}}_{\mathrm{O}}\rangle\mathrm{Ti}{}^{\mathrm{Cl}}_{\mathrm{Cl}}$ (or their dimers) is so unfavorable. *More broadly, our results suggest that, as a general rule, 5-, 6- and 7-membered cyclic Lewis acids of structure* $\mathrm{R}\langle{}^{\mathrm{O}}_{\mathrm{O}}\rangle\mathrm{MX_n}$ *will be destabilized by angle strain in proportion to the electron deficiency of the metal in the MX_n subunit.* Although this angle strain effect complicates the synthesis (and perhaps even the discrete existence) of such compounds, it also should increase their Lewis-acid catalytic activity since angle strain is relieved upon coordination.[18,19]



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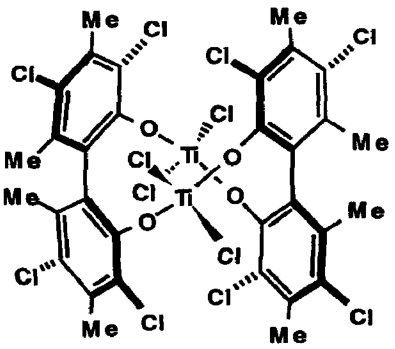

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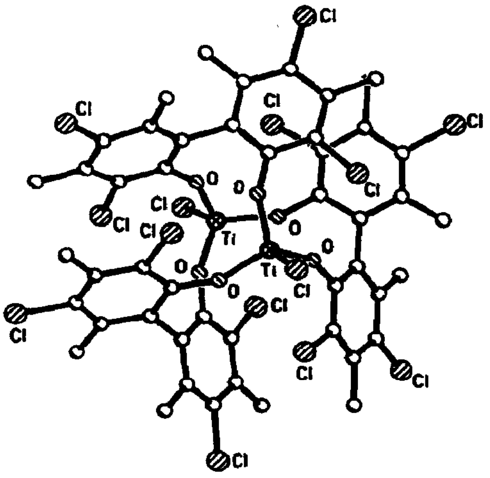

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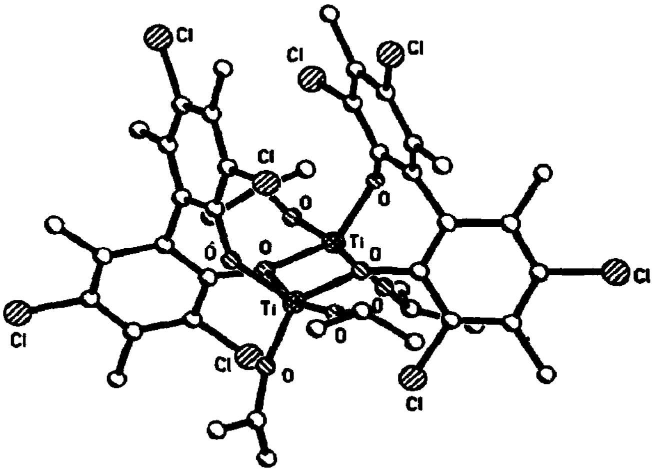

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5. The reaction of (*S*)-(–)-1,1'-bi-2-naphthol (BINOL) with monobromoborane produced a borate ester in which two borons occupy bridgeheads and three BINOLs serve as connecting six-atom bridges; see Kaufmann, D.; Boese, R. *Angew. Chem. Int. Engl.* **1990**, *29*, 545.
6. Evidence of structure is also lacking for aluminum derivatives of *o,o'*-bisphenols. In consequence, the mechanistic basis of enantioselectivity using such catalysts is unknown.[2]
7. Physical data for **2**: mp (EtOAc) 155-165 °C (subl.); $R_f = 0.47$ (1:9 ethyl acetate–hexanes); ^{1}H NMR (CDCl$_3$) (400 MHz) 2.47 (s, 6H), 6.45 (s, 1H); ^{13}C NMR (100 MHz) 18.4, 119.4, 126.8, 133.4, 146.3; FTIR (neat) 1206, 1268, 1397, 3517 cm^{-1}; HRMS *m/z* 223.9574 (calcd for $C_8H_7Cl_3O$ 223.9563).
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9. Physical data for **3**: mp (hexanes) 46-48 °C; $R_f = 0.57$ (1 : 9 ethyl acetate–hexanes); ^{1}H NMR (CDCl$_3$) (500 MHz) 2.49 (s, 6H), 3.70 (s, 3H), 5.15 (s, 2H); ^{13}C NMR (125 MHz) 18.7, 58.3, 99.4, 127.6, 131.3, 134.1, 148.2; FTIR (neat) 912, 1100, 1379, 2930 cm^{-1}; HRMS *m/z* 267.9837 (calcd for $C_{10}H_{11}Cl_3O_2$ 267.9825).
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11. Preparation of **1**: To a THF solution of **4** (911 mg) at -78 °C was added 2 equiv of *t*-BuLi. After 40 min this solution was added to a THF suspension of CuCN (150.0 mg, 1.68 mmol) also at -78 °C. The mixture was warmed to 0 °C and then cooled to -78 °C prior to the addition of tetramethylethylenediamine (1 mL). After 10 min, O_2 was bubbled through the solution for 20 min at -78 °C and the solution was warmed to 23 °C. The product was isolated by extractive workup and purified by chromatography on silica gel using 5% ethyl acetate in hexanes as eluent to give **1** (372.6 mg, 58%), mp 196.0-197.5 °C; ^{1}H NMR (CDCl$_3$) (400 MHz) 2.05 (s, 6H), 2.55 (s, 6H), 5.44 (s, 2H); ^{13}C NMR (100 MHz) 17.8, 18.7, 119.0, 121.5, 127.2, 134.6, 135.1, 147.2; FTIR (neat) 1207, 1394, 3516 cm^{-1}; HRMS *m/z* 377.9738 (calcd. 377.9748).
12. The bis-acetate of **1** was analyzed by HPLC using a Daicel AD column (0.5% 2-propanol in hexane, 1 mL/min), R_f=7.3 and 8.7 min.
13. Procedure for the preparation of **5**: A solution of **1** (0.36 g, 0.95 mmol) in 15 mL of CH_2Cl_2 was cooled to -78 °C and treated with $TiCl_4$ (0.1 mL, 0.95 mmol). The solution was stirred at -78 °C for 10 min, warmed to 23 °C and concentrated *in vacuo* . The solid was dissolved in CH_2Cl_2 (5 mL) and cooled to -20 °C to give orange crystals. ^{1}H NMR (CDCl$_3$) (500 MHz) 2.03 (s, 12H), 2.60 (s, 12H); ^{13}C NMR (125 MHz) 18.79, 18.84, 123.8, 125.3, 132.3, 135.2, 136.4, 159.9.
14. (a) Detailed X-ray crystallographic data are obtainable from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U. K. (b) Empirical formula $C_{32}H_{24}Cl_{12}O_4Ti_2$; tetragonal, space group $P4_12_12$; *a,b* = 14.103 (2) Å, *c* = 21.827 (4) Å, V = 4341.1 (13); Z = 4, d = 1.650; Mo-K_α radiation (-80 °C); reflections collected 7757, unique reflections 3826, observed reflections 2815 ($F > 4.0\,\sigma(F_o)$), R_w 0.0397, GOF = 1.05, absolute stereochemistry determined by refinement of Rogers' η parameter: $\eta = 1.18$.
15. Empirical Formula of **6**, $C_{48}H_{36}O_6Cl_{14}Ti_2$; trigonal, space group $P3_221$; ***a,b*** = 15.587(3) Å, *c* = 26.802(14) Å, V = 5639(5) Å^3; Z = 3, d = 1.660; Mo–K_α radiation (-80 °C); reflections collected 7665, unique reflections 6326, observed reflections 5077 ($F_o > 4.0\,\sigma\,(F_o)$), R_w 0.0911, GOF = 1.66, absolute configuration determined by refinement of Rogers' η parameter: $\eta = 1.05\ (17)$.
16. Empirical formula of **7**, $C_{44}H_{52}Cl_8O_8Ti_2$; monoclinic space group C_2, *a* = 21.745(13) Å, *b* = 12.180(6) Å, *c* = 24.495(9) Å, β = 116.040 (10)°, V = 5830(6) Å,^{3} Z = 4, d = 1.337; Mo–K_α radiation (-80 °C); reflections collected 11063, unique reflections 5870, observed reflections 4767 ($F_o > 4.0\,\sigma\,(F_o)$), R-index 0.0655, GOF = 5.15. ^{1}H NMR (CDCl$_3$) (400 MHz) 0.99 (d, *J*= 6, 6H), 1.05 (d, *J*= 6, 6H), 2.03 (s, 6H), 2.51 (s, 6H), 4.66 (dq, *J*= 6, 6, 2H). ^{13}C NMR (CDCl$_3$) (100 MHz) 18.7, 18.9, 25.0, 25.3, 82.4, 123.1, 125.5, 128.0, 133.5, 134.3, 155.8.
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18. See ref. 1b and also Bachand, B.; Wuest, J. D. *Organometallics* **1991**, *10*, 2015 and Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 256 for interesting discussions.
19. This research was assisted financially by the National Science Foundation and the National Institutes of Health.

(*Received in USA* 8 *July* 1994; *revised* 12 *August* 1994; *accepted* 18 *August* 1994)