Nonorganometallic Pathway of the Passerini Reaction Assisted by Titanium Tetrachloride†

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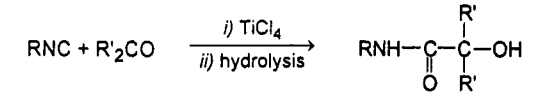
Received January 25, 1993

The Passerini reaction assisted by $TiCl_4$ is a three component reaction (RNC, R'_2CO, $TiCl_4$) leading to C—C bond formation between the carbonyl and the isonitrile groups, and the formation of α-hydroxy amides. In order to clarify the mechanism of the reaction, we have isolated $TiCl_4$–RNC and $TiCl_4$–R_2CO adducts, $\{2,6\text{-}Me_2C_6H_3NC)TiCl_3]_2(\mu\text{-}Cl)_2\}_2$, **2**, $[TiCl_4\{\mu_2\text{-}CO{=}C(OEt)CH_2NC\}]_2$, **3**, $[TiCl_4\{\mu_2\text{-}O{=}P(OEt)_2CH_2NC\}]_2$, **4**, and $[TiCl_4\{PhC(O)—C(O)Ph\}]$, **5**. Spectroscopic and X-ray analysis on **2** and **3** ruled out any insertion of the isocyanide into Ti—Cl bonds, as required by the accepted mechanism of this reaction. The reaction on the ketone– or isocyanide–$TiCl_4$ adducts with the third component of the Passerini reaction led us to the isolation and full characterization of [*mer*-$TiCl_3(\eta^3\text{-}OC(Mes)(H)C(Cl){=}NCH_2C(OEt){=}O]$, **6**, [*mer*-$TiCl_3(\eta^3\text{-}OC(Ph)(Me)C(Cl){=}NCH_2C(OEt){=}O]$, **7**, [*mer*-$TiCl_3(\eta^3\text{-}OC(Ph)(Me)C(Cl){=}NCH_2P(OEt)_2{=}O]$, **10**, and [*mer*-$TiCl_3(\eta^3\text{-}OC(Ph)(OCPh)C(Cl){=}NCH_2C(OEt){=}O]$, **12**, derived from the reaction of MesCHO and PhCOMe with $EtOOCCH_2NC$, of $PhCOCH_3$ with $O{=}P(OEt)_2CH_2NC$, and PhCOCOPh with $EtOOCH_2NC$, respectively. These are high yield reactions and form, as imposed by the planar assembled ligand, the *mer*-isomer only. The hydrolysis of **6**, **7**, **10**, and **12** gave the expected α-hydroxy amide derivatives, **8**, **9**, **11**, and **13**, respectively. The overall mechanism of the $TiCl_4$-assisted Passerini reaction can be described as the electrophilic activation of a carbonyl group by $TiCl_4$ followed by the nucleophilic attack on the carbonylic carbon by the RNC nucleophile. Crystallographic details: **2** is monoclinic, space group $P2_1/n$, a = 13.943(1) Å, b = 8.045(1) Å, c = 12.141(1) Å, $\alpha = \gamma = 90°$, β = 104.76(1)°, Z = 2, R = 0.048; **4** is monoclinic, space group $P2_1/c$, a = 12.961(1) Å, b = 11.770(1) Å, c = 10.917(1) Å, $\alpha = \gamma = 90°$, β = 114.13(1)°, Z = 2, R = 0.049; **5** is triclinic, space group $P\bar{1}$, a = 10.549(1) Å, b = 10.668(1) Å, c = 9.533(1) Å, α = 115.08(1)°, β = 115.47(1)°, γ = 95.01(1)°, Z = 2, R = 0.035; **7** is triclinic, space group $P\bar{1}$, a = 9.731(2) Å, b = 10.552(3) Å, c = 8.978(2) Å, α = 96.66(2)°, β = 101.86(2)°, γ = 95.30(2)°, Z = 2, R = 0.042; **10** is monoclinic, space group $P2_1/c$, a = 11.503(2) Å, b = 14.095(2) Å, c = 15.110(2) Å, $\alpha = \gamma = 90°$, β = 96.79(2)°, Z = 4, R = 0.116; **12** is triclinic, space group $P\bar{1}$, a = 9.272(4) Å, b = 9.965(4) Å, c = 15.029(6) Å, α = 101.84(3)°, β = 104.12(3)°, γ = 99.53(3)°, Z = 2, R = 0.092.

Introduction

The Passerini reaction is a classic method for C–C bond formation between a ketone and an isocyanide.[1] This acid-assisted reaction leads to the formation of an α-hydroxy acid ester.[2]

A variation of the Passerini method involves the use of a protic mineral acid or a Lewis acid such as $TiCl_4$ as promoter.[3] In the latter case, the reaction produces upon hydrolysis an α-hydroxy amide.



A number of mechanisms have been proposed for this reaction, and these vary with the acid catalyst and the reaction conditions used. Except for the Saegusa mechanism,[4] which involves the intermediate formation of an imino oxirane, all the others, *i.e.* Ugi,[5] Baker,[6] and Passerini himself,[1] proposed an electrophilic activation of the

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† Dedicated to Professor Gian Paolo Chiusoli on the occasion of his 70th birthday.

(1) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181, 250; **1922**, *52*, 432; **1923**, *53*, 410; **1924**, *54*, 672; **1925**, *55*, 721; **1926**, *56*, 365, 826.

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(6) Baker, R. H.; Stanonis, D. *J. Am. Chem. Soc.* **1951**, *73*, 699. See also: Baker, R. H.; Schlesinger, A. *Ibid.* **1945**, *67*, 1499. Baker, R. H.; Linn, L. E. *Ibid.* **1948**, *70*, 3721.

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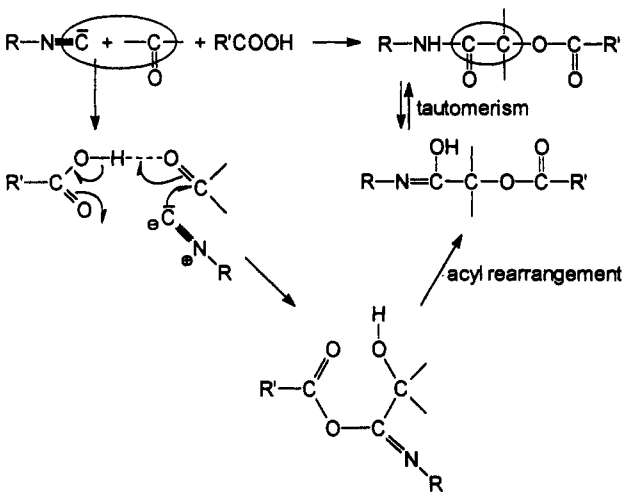
Scheme I



carbonyl group, followed by the nucleophilic attack of the isocyanide (see Scheme I).

In the case of the $TiCl_4$-assisted reaction, a typical organometallic pathway was proposed (*vide infra*) based on previous investigations of $TiCl_4$–isocyanide chemistry.[7] An important feature of this mechanism is the supposed insertion of RNC into a Ti–Cl bond.

We were particularly interested in the formation of an organometallic species from nonorganometallic precursors, so we went back to examine $TiCl_4$. Preliminary results have been briefly communicated.[8,9] This investigation led us to conclude the following: (*i*) the $TiCl_4$–RNC interaction never leads to organometallic species *via* an insertion reaction; (*ii*) as proposed by Passerini and others, the acid, *i.e.* $TiCl_4$, serves to enhance the electrophilicity of the carbonyl group; (*iii*) the preliminary interaction between $TiCl_4$ and an isocyanide has a deactivating rather than an activating effect on the reaction; (*iv*) titanium in $TiCl_4$ acts as a template Lewis acid assembling around itself the two components of the reaction.

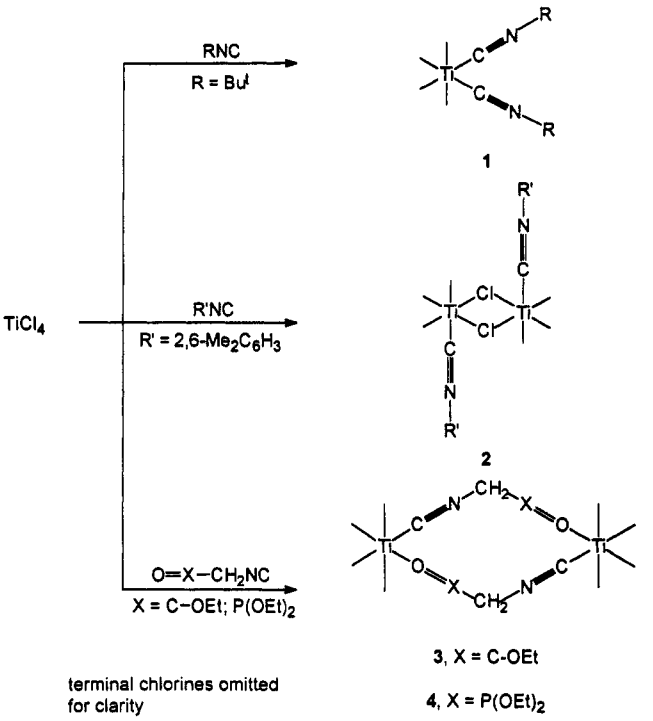
Our investigations have resulted in the isolation of a reactive intermediate which not only clarifies the role of $TiCl_4$ in the Passerini reaction but also allows us to make suggestions for designing template Lewis acids for use in organic synthesis.

Results and Discussion

In order to understand the basis for the three component reaction taking place in the $TiCl_4$-assisted Passerini reaction, we needed to first explore the reactivity of $TiCl_4$ separately with isocyanides and ketones.

(i) Reaction of $TiCl_4$ with Isocyanides. $TiCl_4$ reacts in CH_2Cl_2 or toluene solutions with isocyanides to form exclusively the corresponding $TiCl_4$–CNR adducts.[8,10] Two factors which are crucial for a positive outcome are (i) a short reaction time and (ii) the absence of any trace of water. The neglect of these conditions has in the past contributed to the misinterpretation of the identities of the $TiCl_4$–isocyanide reaction products[7] (*vide infra*).

Scheme II



Isocyanides form adducts with $TiCl_4$ in either 1:1 or 1:2 molar ratios, depending on the nature of the R group of the isocyanide which can have an influence due to steric factors or the presence of donor atoms in its skeleton. This is summarized in Scheme II.

Three classes of compounds have been identified, and they are exemplified by complexes **1**–**4**. These have been characterized by analytical and spectroscopic data including an X-ray analysis of **1**,[8] **2** (*vide infra*), and **4** (*vide infra*). Some common features are the hexacoordination of titanium(IV) and an increase in the C–N stretching vibration frequency compared with the uncoordinated isocyanide, which is as expected for coordination to an electron deficient metal. The two ligands in the $TiCl_4$ adducts **1**, **3**, and **4** are *cis* to each other.

Complex **2** has the structure shown in Figure 1. A selection of bond distances and angles are listed in Table VIII. The structure consists of centrosymmetric dimers. Each titanium atom is surrounded by four chlorine atoms and an isonitrile ligand, and the octahedron is completed by dimerization through symmetric chlorine bridges. The Ti–C9–N1–C1 fragment is linear and nearly perpendicular to the Ti_2Cl_2 plane, the dihedral angle between the two being 11.3(1)°.

The structure of complex **4** is shown in Figure 2, and a selected list of bond distances and angles is given in Table IX. The most interesting feature is the existence of a centrosymmetric twelve-membered dimetallacycle where two $TiCl_4$ molecules are doubly bridged by two isocyanide ligands through the O1 oxygen atom and the C5 carbon atoms of the isocyanide moieties. The linear Ti′–C5–Ni–C6 skeleton does not allow the functionalized isocyanide to chelate to the same metal. The dimetallacycle assumes a "bed" conformation with P1 and O1 being 1.337(1) and 1.083(3) Å out of the mean plane running to the ring.

(7) (a) Crociani, B.; Nicolini, M.; Richards, R. L. *J. Organomet. Chem.* **1975**, *101*, C1. (b) *Ibid.* **1979**, *181*, 69. (c) Crociani, B.; Richards, R. L. *J. Chem. Soc., Chem. Commun.* **1973**, 127. (d) Dahkordy, B.; Crociani, B.; Richards, R. L. *J. Chem. Soc., Dalton Trans.* **1977**, 2015. (e) Crociani, B. "Reactions of Coordinated Isocyanides." In *Reactions of Coordinated Ligands*; Braterman, P. S., Ed.; Plenum: New York, 1986; p 553.

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(10) Insertion of RNC into a V–Cl bond[7] has been proved to be incorrect: Silverman, L. D.; Dewan, J. C.; Giandomenico, C. M.; Lippard, S. J. *Inorg. Chem.* **1980**, *19*, 3379.

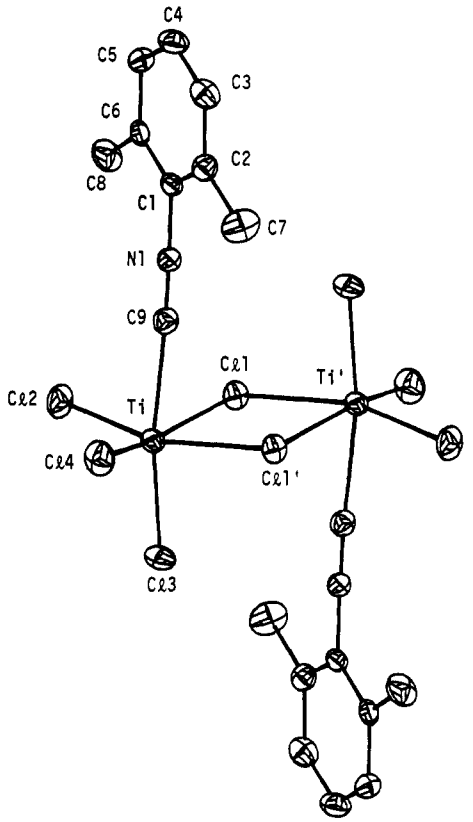

Figure 1. ORTEP drawing for complex **2** (30% probability ellipsoids). The prime indicates a transformation of $-x, -y, -z$.

Obviously, the centrosymmetric atoms P1′ and O1′ are out of the plane at the opposite side. Bond distances and angles (Table IX) are in good agreement with those found in complex **2**, and a significant Cl···H–C contact [Cl2···C6, 3.470(6) Å, Cl2–C62, 2.87 Å, Cl2···H62–C6, 124°] suggests a hydrogen bonding interaction. The Ti–C distances are significantly longer [Ti–C1, 2.240(8) Å; Ti–C6, 2.256(6) Å] than those reported for the few bis(cyclopentadienyl)-titanium isocyanide complexes so far structurally studied, i.e. $[(\eta^5\text{-}C_5Me_5)_2Ti(Bu^tNC)\text{-}\eta^2\text{-}Bu^tN{=}CCH_2CH_2COR e_2\text{-}(CO)_9]$ [2.17(2) Å],[11a] $[(cp)_2Ti\{\eta^2\text{-}C(Me)NBu^t\}(CNBu^t)]\text{-}BPh_4\cdot MeCN$ [2.192(6) Å],[9b] and $[(cp)_2Ti(CO)(CNBu^t)]$ [2.112(9) Å].[9c]

The results we found for $TiCl_4$–RNC chemistry are not surprising but are nevertheless in strong disagreement with the literature results used to support the mechanism of the $TiCl_4$-assisted Passerini reaction.[7,3] The reaction of $TiCl_4$ with isocyanides has been reported to give rise to the "insertion" of an isocyanide group into a Ti–Cl bond as shown in eq 1.[7] Reaction 1 has to be considered rather unusual, because of the formation of a Ti–C bond from a nonorganometallic precursor.

$$TiCl_4 + 2\ Bu^tNC \longrightarrow (Bu^tNC)Cl_3Ti{-}C(NR)Cl \quad (1)$$

A

The structure A previously proposed for complex **2** was essentially based on a band seen at around 1600–1700 cm^{-1} in the IR spectrum.[3,7] However this band is not due to an imino group but to the hydrolysis of the compound in air which gives rise to formamide $[Bu^tNHC(O)H]$, to which the band belongs.[8,9] A further explanation of the band at 1600–1700 cm^{-1} may be the presence in the solid formed from the reaction in Scheme I of an adventitious amount of the dimer of the isocyanide.[12,13] We found that $TiCl_4$, under the conditions reported in the literature[7] (see Experimental Section) promotes the formation of a small amount of the same dimer containing an imino group RC(CN)=NR which has also been observed in the reaction with Et_2OBF_3 (see Experimental Section).[13]

(ii) Reaction of $TiCl_4$ with Carbonyl Compounds. The reaction of $TiCl_4$ with the other component of the Passerini reaction, the ketone or the aldehyde, is well-known and leads to the corresponding adduct. Mono or bis adducts may be formed depending on the molar ratio used and on the substituents at the carbonyl group.[14,15] These adducts have been studied mainly in solution,[14] but recently we undertook an analysis of some solid state structures.[16] These structures belong to the two classes exemplified by the isocyanide adducts **1** and **2**. The metal is hexacoordinate both in solution and in the solid state.

We report here the adduct of $TiCl_4$ with the dibenzoyl only:

$$TiCl_4 \xrightarrow{PhCOCOPh} \mathbf{5} \quad (2)$$

5

Dibenzoyl was used in this study since it can fill all the coordination sites in $TiCl_4$, thus preventing, in the case of the Passerini reaction, any precoordination of the isocyanide. This strategy enabled us to understand whether a $TiCl_4$–RNC interaction is a prerequisite for the Passerini reaction. The structure of **5** is shown in Figure 3, and significant structural parameters are listed in Table X. Complex **5** is monomeric and the α,α'-diketone chelates through both oxygens, resulting in a pseudooctahedral coordination geometry around the metal.

(iii) Reaction of $TiCl_4$ with Ketones and Isocyanides. The accepted mechanism of the $TiCl_4$-assisted Passerini reaction between ketones and isocyanides is shown in Scheme III.[2,3]

This mechanism is based on a number of findings we were unable to confirm, starting with the important insertion of the isocyanide into a Ti–Cl bond. In none of the reactions between $TiCl_4$ and isocyanides did we observe the formation of iminochloroacyl A. This is not surprising given, firstly, the oxophilicity of Ti(IV) which would favor attack by R′R″CO over RNC as the first step in Scheme III, and secondly, the tendency of Ti(IV) to form hexacoordinate complexes.

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Table I. Experimental Data for the X-ray Diffraction Studies on Crystalline Complexes 2, 4, 5, 7, 10, and 12

complex	2	4	5	7	10	12
cryst habit	prisms	prisms	irregularly shaped crystals	prisms	unshaped fragments	twinned unshaped fragments
formula	$C_{18}H_{18}Cl_8N_2Ti_2$	$C_{12}H_{24}Cl_8O_6N_2P_2Ti_2$	$C_{14}H_{10}Cl_4O_2Ti$	$C_{13}H_{15}Cl_4O_3NTi$	$C_{14}H_{20}Cl_4O_4NPTi\cdot C_7H_8$	$C_{19}H_{17}Cl_4O_4NTi\cdot CH_2Cl_2$
cryst syst	monoclinic	monoclinic	triclinic	triclinic	monoclinic	triclinic
space group	$P2_1/n$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
cell param at 295 K[a]						
a, Å	13.943(1)	12.961(1)	10.594(1)	9.731(2)	11.503(2)	9.272(4)
b, Å	8.045(1)	11.770(1)	10.668(1)	10.552(3)	14.095(2)	9.965(4)
c, Å	12.141(1)	10.917(1)	9.533(1)	8.978(2)	15.110(2)	15.029(6)
α, deg	90	90	115.08(1)	96.66(2)	90	101.84(3)
β, deg	104.76(1)	114.13(1)	115.47(1)	101.86(2)	96.79(2)	104.12(3)
γ, deg	90	90	95.01(1)	95.30(2)	90	99.53(3)
V, Å^3	1316.9(2)	1519.9(3)	831.7(2)	889.7(4)	2432.7(6)	1283.6(10)
Z	2	2	2	2	4	2
D_{calcd}, g cm^{-3}	1.618	1.603	1.597	1.579	1.581	1.547
mol wt	641.8	733.7	399.9	423.0	579.1	598.0
cryst dimens, mm	0.28 × 0.32 × 0.41	0.45 × 0.56 × 0.60	0.27 × 0.53 × 0.64	0.39 × 0.41 × 0.55	0.06 × 0.19 × 0.40	0.10 × 0.15 × 0.30
linear abs coeff, cm^{-1}	129.8	13.62	11.56	10.90	8.84	9.86
transm factor range	0.852–1.000	0.900–1.000	0.847–1.000	0.968–1.000	0.6085–1.000	0.569–1.000
diffractometer	Siemens A.E.D.	Philips PW 1100	Philips PW 1100	Philips PW 1100	Rigaku AFC6S	Rigaku AFC6S
diffraction geometry	equatorial	equatorial	equatorial	equatorial	equatorial	equatorial
radiation	*b*	*c*	*c*	*c*	*c*	*c*
2θ range, deg	6–130	6–50	6–50	6–60	5–50	5–60
scan type	θ–2θ	ω–2θ	ω–2θ	ω–2θ	ω–2θ	ω–2θ
scan speed, deg min^{-1}	4–12	4–12	6–12	4–12	8	4
scan width, deg	1.20 + 0.015 tan θ	1.20 + 0.35 tan θ	1.20 + 0.35 tan θ	1.20 + 0.35 tan θ	1.68 + 0.35 tan θ	1.78 + 0.35 tan θ
reflcns measd	$\pm h,k,l$	$\pm h,k,l$	$\pm h,\pm k,l$	$\pm h,\pm k,l$	$\pm h,k,l$	$\pm h,\pm k,l$
no. of unique total data	2381	2674	2939	5221	3241	5651
criterion for observn	2	2	2	2	2	2
no. of unique obsd data	1591	1936	2043	3200	2356	2596
no. of variables	136	148	190	199	210	266
overdetermination ratio	11.7	13.1	10.8	16.1	11.2	9.7
max Δ/σ on last cycle	0.001	0.3	0.1	0.7	0.2[d]	0.1[e]
$R = \sum\|\Delta F\|/\sum\|F_o\|$	0.048	0.049	0.035	0.042	0.116	0.092
$R_w = \sum[w\|\Delta F\|]^{1/2}/\sum[w\|F_o\|]^{1/2}$	0.050	0.057	0.038	0.052	0.119	0.098
GOF = $[\sum w\|\Delta F\|^2/(NO - NV)]^{1/2}$	0.73	1.12	1.13	0.26	1.28	0.89

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 25–30 carefully centered reflections from diverse regions of reciprocal space. [b] Ni filtered Cu Kα (λ = 1.54 178 Å). [c] Graphite monochromatized Mo Kα (λ = 0.710 688 Å). [d] 1.0 for the disordered atoms. [e] 0.5 for the disordered atoms.

Table II. Atomic Coordinates (×10^4) for Complex 2

atom	*x/a*	*y/b*	*z/c*	U_{eq}, Å^2
Ti	805.2(6)	1607.3(12)	994.3(8)	325(3)
Cl1	875(1)	−1286(2)	303(1)	367(4)
Cl2	2197(1)	1135(2)	2290(1)	541(6)
Cl3	1397(1)	2637(2)	−391(1)	551(6)
Cl4	314(1)	3920(2)	1663(1)	586(6)
N1	−298(3)	−383(5)	2797(4)	350(15)
C1	−707(3)	−1186(6)	3602(4)	309(17)
C2	−1700(4)	−855(7)	3564(5)	377(20)
C3	−2077(4)	−1632(7)	4380(6)	460(20)
C4	−1489(4)	−2638(7)	5179(5)	480(23)
C5	−513(4)	−2940(7)	5194(5)	454(22)
C6	−97(3)	−2218(6)	4384(4)	323(17)
C7	−2325(5)	231(9)	2666(6)	646(29)
C8	959(4)	−2570(8)	4351(6)	579(26)
C9	55(4)	282(7)	2162(5)	380(20)

Table III. Atomic Coordinates (×10^4) for Complex 4[a]

atom	*x/a*	*y/b*	*z/c*	U_{eq}, Å^2
Ti	1930.7(6)	481.2(7)	3732.8(6)	536(4)
Cl1	3258(1)	−523(1)	3402(2)	853(7)
Cl2	495(1)	−839(1)	2731(2)	857(7)
Cl3	1389(2)	1552(2)	1907(2)	1159(10)
Cl4	3044(1)	1845(1)	5082(2)	996(9)
P1	2368(1)	−1362(1)	6304(1)	586(6)
O1	2178(3)	−325(3)	5469(3)	614(15)
O2	3305(3)	−2165(3)	6284(4)	780(18)
O3	2614(3)	−1076(3)	7763(4)	856(19)
N1	218(3)	−1776(3)	5775(4)	554(18)
C1	4500(5)	−1848(7)	6816(8)	1096(35)
C2	5057(6)	−2721(9)	6426(10)	1400(53)
C3	2532(5)	59(6)	8287(6)	926(33)
C4A	2616(16)	3(15)	9668(17)	
C4B	3271(29)	−27(30)	9852(32)	
C4C	2120(19)	−116(19)	9388(23)	
C5	−528(4)	−1344(4)	5879(5)	555(20)
C6	1172(4)	−2329(4)	5702(5)	613(23)

[a] The site occupation factors for C4A, C4B, and C4C are 0.5, 0.2, and 0.3, respectively.

In the original mechanism proposed by Passerini[1] the acid served to enhance the electrophilicity of the carbonyl, so as to facilitate attack by the RNC nucleophile. Conversely, $TiCl_4$ can have a deactivating effect on the isocyanide by decreasing its nucleophilicity. This implies that when the reaction is carried out by adding the carbonyl to the $TiCl_4$–RNC adduct, as is often the case, the carbonyl must first displace the isocyanide.

Scheme IV represents what we believe to be the correct mechanism for the $TiCl_4$-assisted Passerini reaction. The initial step is the coordination of R′R″CO, giving the adduct A. The subsequent addition of the nucleophilic "carbene" RNC across Cl and C, B, is a well-known mode of reactivity.[17] An alternate possibility is the addition of the isocyanide to the activated >C=O bond to form an imino oxirane intermediate, subsequently opened by the Cl$^-$ nucleophile. The latter mechanism was proposed for the Passerini reaction assisted by BF_3.[4] Both routes lead to

(17) See for example: Walborsky, H. M.; Periasamy, M. P. In *The Chemistry of Functional Groups, Supplement C*; Patai, S., Rappaport, Z., Eds.; J. Wiley: New York, 1983; p 835.

Table IV. Atomic Coordinates (×10⁴) for Complex 5

atom	x/a	y/b	z/c	U_{eq}, Å²
Ti	1443.6(8)	−2720.6(8)	−699.8(10)	418(4)
Cl1	1097(1)	−3074(1)	−3301(1)	584(6)
Cl2	3824(1)	−2731(2)	507(2)	674(7)
Cl3	−644(1)	−2098(1)	−1007(2)	591(7)
Cl4	472(2)	−4970(1)	−1439(2)	634(8)
O1	2527(3)	−413(3)	607(3)	469(17)
O2	1968(3)	−1677(3)	2102(4)	454(16)
C1	4236(4)	1779(4)	3292(5)	424(21)
C2	4486(5)	2398(5)	2364(5)	517(25)
C3	5645(5)	3668(5)	3293(6)	598(31)
C4	6591(5)	4317(5)	5136(7)	640(28)
C5	6377(5)	3702(5)	6077(6)	582(27)
C6	5191(4)	2446(5)	5168(5)	482(25)
C7	3066(4)	398(4)	2259(5)	397(22)
C8	2430(4)	−332(4)	3029(5)	398(23)
C9	2316(4)	460(4)	4614(5)	420(23)
C10	2113(5)	−279(5)	5460(6)	507(26)
C11	1926(5)	453(5)	6915(6)	601(31)
C12	1905(5)	1868(6)	7493(6)	611(30)
C13	2076(5)	2584(5)	6637(6)	590(29)
C14	2286(5)	1887(5)	5205(6)	489(26)

Table V. Atomic Coordinates (×10⁴) for Complex 7

atom	x/a	y/b	z/c	U_{eq}, Å²
Ti	2132.2(5)	2897.0(5)	2391.7(5)	319(2)
Cl1	1437(1)	1369(1)	3737(1)	510(3)
Cl2	4429(1)	3237(1)	3823(1)	502(2)
Cl3	−196(1)	3221(1)	1346(1)	557(3)
C14	3334(1)	4804(1)	−1605(1)	561(3)
O1	2438(2)	1991(2)	718(2)	373(7)
O2	2050(2)	4723(2)	3642(2)	408(7)
O3	2210(2)	6847(2)	3716(3)	454(7)
N1	2747(2)	4338(2)	1032(2)	330(7)
C1	4006(3)	1920(3)	−1048(3)	372(9)
C2	4096(4)	1604(3)	−2565(4)	492(10)
C3	5324(4)	1130(4)	−2874(4)	612(14)
C4	6419(4)	972(3)	−1705(5)	583(14)
C5	6317(4)	1293(3)	−216(4)	520(12)
C6	5114(3)	1772(3)	131(4)	447(10)
C7	2683(3)	2424(3)	−667(3)	382(9)
C8	2907(3)	3886(3)	−267(3)	365(9)
C9	1330(4)	2006(4)	−1939(4)	599(13)
C10	2819(3)	5678(3)	1622(3)	403(9)
C11	2329(3)	5712(3)	3102(3)	352(8)
C12	1763(4)	7001(3)	5199(4)	473(10)
C13	2060(4)	8370(4)	5797(4)	577(13)

Table VI. Atomic Coordinates (×10⁴) for Complex 10[a]

atom	x/a	y/b	z/c	U_{eq}, Å²
Ti	2900.5(18)	1633.3(15)	2897.9(12)	505(7)
Cl1	2006(3)	1013(3)	1626(2)	843(15)
C12	3157(3)	3112(2)	2248(2)	777(12)
Cl3	2391(3)	338(2)	3765(2)	761(14)
C14A	5622(30)	2109(32)	5311(25)	789(76)
C14B	5897(33)	1917(33)	5270(27)	687(80)
P1	1765(3)	2870(3)	4311(2)	706(13)
O1	4377(6)	1252(6)	2888(5)	567(27)
O2	1608(7)	2302(6)	3474(5)	626(30)
O3	882(11)	2628(9)	4949(7)	1124(56)
O4	1617(10)	3964(8)	4183(8)	1105(47)
N1	3843(9)	2153(7)	4165(6)	579(36)
C1A	6325(13)	1978(12)	3272(10)	
C2A	7459(13)	1620(12)	3291(10)	
C3A	8320(13)	2157(12)	2948(10)	
C4A	8048(13)	3052(12)	2586(10)	
C5A	6915(13)	3409(12)	2567(10)	
C6A	6053(13)	2872(12)	2910(10)	
C1B	6440(15)	1547(14)	3259(12)	
C2B	7528(15)	1103(14)	3422(12)	
C3B	8509(15)	1513(14)	3115(12)	
C4B	8402(15)	2367(14)	2646(12)	
C5B	7313(15)	2811(14)	2484(12)	
C6B	6332(15)	2401(14)	2790(12)	
C7A	5328(25)	1432(23)	3569(18)	
C7B	5303(22)	1109(23)	3605(16)	
C8	4869(11)	1858(9)	4321(7)	612(47)
C9	5558(13)	241(12)	3902(10)	895(66)
C10	3253(11)	2727(10)	4801(7)	685(51)
C11	688(19)	1746(18)	5228(15)	
C12A	−471(25)	1752(28)	5643(25)	
C12B	217(81)	1344(60)	6065(38)	
C13	660(25)	4474(23)	3738(20)	
C14A	651(56)	4842(45)	2778(25)	
C14B	1049(67)	5470(32)	4079(51)	
C1S	2530(50)	−1122(44)	82(41)	
C2S	3623(14)	−634(16)	18(18)	
C3S	4336(14)	−274(16)	752(18)	
C4S	5385(14)	177(16)	633(18)	
C5S	5722(14)	269(16)	−220(18)	
C6S	5009(14)	−91(16)	−954(18)	
C7S	3959(14)	−543(16)	−835(18)	

[a] The site occupation factors are as follows: 0.55 and 0.45 for the A and B positions of Cl4, C1–C6, and C7, respectively; 0.6 and 0.4 for the A and B positions of C12 and C14 respectively; 0.5 for C1S–C7S.

the transfer of the chlorine atom to the carbon of the isocyanide and formation of the same intermediate C, in the second step of the reaction.

The transfer of the chlorine from titanium to carbon frees up a coordination site in C which is subsequently filled by the nitrogen atom, D, so that the organic fragment chelates titanium. In order to isolate D it would be desirable to have an organic fragment that could act as a tridentate ligand, filling the empty coordination site. This could also help to stabilize D by replacing the weakly coordinated ligand L. With this in mind, we used isocyanides having R substituents containing an oxygen donor atom. The reactions were carried out by adding either the isocyanide to the $TiCl_4$–ketone adduct or the ketone to the $TiCl_4$–RNC adduct. The reaction of mesitylaldehyde or acetophenone with $EtOOCCH_2NC$ in the presence of $TiCl_4$ gave high yields of **6** and **7** which have been isolated in crystalline form.

Complexes **6** and **7** undergo hydrolysis to the corresponding α-hydroxy amides, **8** and **9**, respectively (see Experimental Section). These are the expected intermediates (D) seen in Scheme IV. Their structures have been determined by analytical and spectroscopic methods, including an X-ray analysis of **7** (Figure 4). We expected the *fac*-isomer, since the donor atom on R should replace the ligand L in D. However, the *mer*-isomers of **6** and **7** were obtained exclusively, even though their formation requires a rather complex rearrangement of the coordination sphere. The formation of the *mer*-isomer is dictated by the sp^2-trigonal hybridization of the imino nitrogen, forcing the three donor atoms to be in a plane.

Following one of the procedures used for **6** and **7** we added acetophenone to complex **4**, as shown in Scheme VI.

Complex **10** formed in high yield, and an X-ray analysis confirmed it to be the *mer*-isomer (Figure 5). Its spectroscopic and chemical properties are very close to those of **7**. The hydrolysis led to **11**.

In order to provide further evidence for the reaction sequence sketched in Schemes IV–VI, we reacted **5** with $EtOOCCH_2NC$. In this case the reaction should proceed via the external attack of the isocyanide on the ketone (Scheme VII).

Complex **12** was obtained as a yellow crystalline solid and was fully characterized including by X-ray analysis (Figure 6) which shows that the *mer*-isomer is again exclusively formed. Complex **12** was hydrolized under the usual conditions employed in the $TiCl_4$-assisted Passerini reaction, leading to the corresponding α-hydroxy-

Table VII. Atomic Coordinates (×10⁴) for Complex 12[a]

atom	x/a	y/b	z/c	U_{eq}, Å²
Ti	3062.9(19)	3357.6(17)	1549.6(11)	413(6)
Cl1	1983(3)	4168(3)	2667(2)	671(12)
Cl2	1705(3)	1050(3)	1215(2)	631(10)
Cl3	4121(3)	5569(3)	1427(2)	678(13)
Cl4	6387(3)	1632(3)	24(2)	507(10)
O1	4850(7)	3083(6)	2176(4)	410(24)
O2	1525(7)	3288(8)	243(5)	528(28)
O3	705(7)	2457(7)	-1313(5)	531(27)
O4	7722(10)	4617(8)	1493(6)	730(35)
N1	4082(8)	2551(7)	442(5)	365(28)
C1	6716(6)	1638(5)	2187(4)	403(30)
C2	8248(6)	1612(5)	2294(4)	487(38)
C3	8851(6)	587(5)	2670(4)	655(47)
C4	7922(6)	-412(5)	2938(4)	706(55)
C5	6390(6)	-385(5)	2831(4)	653(53)
C6	5787(6)	640(5)	2455(4)	527(42)
C7	7904(8)	4952(6)	3121(4)	490(36)
C8	7419(8)	4527(6)	3849(4)	666(49)
C9	8060(8)	5331(6)	4785(4)	843(59)
C10	9186(8)	6559(6)	4993(4)	975(64)
C11	9670(8)	6984(6)	4265(4)	892(61)
C12	9029(8)	6180(6)	3329(4)	714(50)
C13	7309(11)	4178(10)	2097(6)	471(34)
C14	6071(9)	2797(8)	1811(6)	351(27)
C15	5392(9)	2362(8)	740(6)	341(30)
C16	3140(10)	2250(10)	-543(6)	462(37)
C17	1706(9)	2699(9)	-512(6)	373(32)
C18	-774(11)	2878(12)	-1337(9)	621(46)
C19	-1898(12)	2055(12)	-2239(10)	682(53)
C1S	5731(49)	7895(44)	5527(28)	
Cl1A	6904(58)	8684(57)	5984(33)	
Cl1B	7360(14)	9393(13)	5414(8)	
Cl1C	6664(36)	9536(32)	5529(21)	
C12A	4903(24)	7059(22)	4206(15)	
Cl2B	4690(24)	7115(23)	4516(14)	
C12C	4021(37)	7782(34)	4667(22)	

[a] The site occupation factors for Cl1A, Cl1C, Cl2A, and Cl2C are 0.25; those for Cl1B and Cl2B are 0.5.

Table VIII. Selected Bond Distances (Å) and Angles (deg) for Complex 2[a]

Ti–Cl1	2.485(2)	Ti–Cl4	2.208(2)
Ti–Cl1′	2.481(2)	Ti–C9	2.235(6)
Ti–Cl2	2.198(1)	N1–C1	1.408(7)
Ti–Cl3	2.214(2)	N1–C9	1.147(8)
Cl4–Ti–C9	86.0(2)	Cl1–Ti–C9	80.3(2)
Cl3–Ti–C9	170.2(2)	Cl1–Ti–Cl4	163.0(1)
Cl3–Ti–Cl4	100.1(1)	Cl1–Ti–Cl3	92.3(1)
Cl2–Ti–C9	86.2(2)	Cl1–Ti–Cl2	88.7(1)
Cl2–Ti–Cl4	100.5(1)	Cl1–Ti–Cl1′	78.5(0)
Cl2–Ti–Cl3	100.2(1)	Ti–Cl1–Ti′	101.5(1)
Cl1′–Ti–C9	80.5(2)	C1–N1–C9	178.3(5)
Cl1′–Ti–Cl4	89.4(1)	N1–C1–C6	117.8(4)
Cl1′–Ti–Cl3	91.8(0)	Ti–C9–N1	177.3(5)
Cl1′–Ti–Cl2	162.8(1)		

[a] The prime indicates a transformation of $-x, -y, -z$.

β-keto amide, **13**, which proves that the Passerini reaction[3] also works well with α-diketones.

The structures of the intermediates **7**, **10**, and **12** are shown in Figures 4–6, respectively, while relevant structural parameters are given in Tables XI–XIII. The complexes consist of discrete monomeric molecules containing a $TiCl_3$ unit pseudooctahedrally bonded to an approximately planar tridentate ligand. The main features common to the three complexes are as follows.

(i) The tridentate ligands are nearly planar and give rise to the *mer*-isomers. The planarity is imposed by the sp^2 hybridization state of the nitrogen atom, the double bond being localized on N1–C8 for complexes **7** and **10** [1.254(3) and 1.247(16) Å, respectively] and N1–C15 for complex **12** [1.248(11) Å]. In the case of complex **12** there

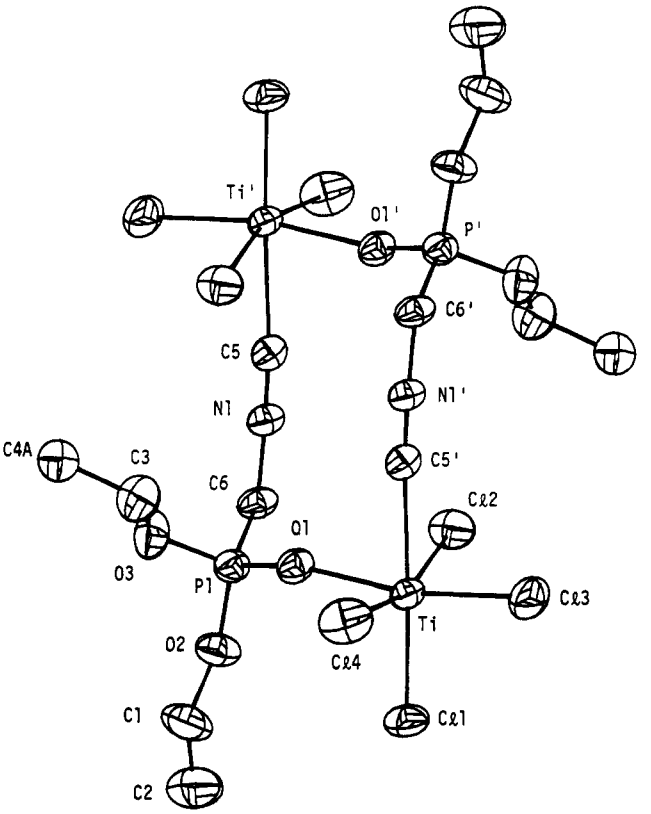


Figure 2. ORTEP drawing for complex **4** (30% probability ellipsoids). The prime indicates a transformation of $-x, -y, 1-z$.

Table IX. Selected Bond Distances (Å) and Angles (deg) for Complex 4[a]

Ti–Cl1	2.235(2)	P1–O1	1.483(4)
Ti–Cl2	2.326(2)	P1–O2	1.546(4)
Ti–Cl3	2.216(2)	P1–O3	1.529(4)
Ti–Cl4	2.256(2)	P1–C6	1.816(5)
Ti–O1	2.024(4)	N1–C5	1.138(7)
Ti–C5′	2.269(6)	N1–C6	1.428(7)
O1–Ti–C5′	82.4(2)	Cl1–Ti–Cl2	95.3(1)
Cl4–Ti–C5′	84.7(1)	O3–P1–C6	107.4(2)
Cl4–Ti–O1	84.7(1)	O2–P1–C6	99.8(2)
Cl3–Ti–C5′	86.0(2)	O2–P1–O3	108.6(2)
Cl3–Ti–O1	168.3(2)	O1–P1–C6	113.0(2)
Cl3–Ti–Cl4	93.8(1)	O1–P1–O3	111.8(2)
Cl2–Ti–C5′	80.7(2)	O1–P1–O2	115.4(2)
Cl2–Ti–O1	85.3(1)	Ti–O1–P1	152.2(2)
Cl2–Ti–Cl4	163.2(1)	P1–O2–C1	123.3(4)
Cl2–Ti–Cl3	93.3(1)	P1–O3–C3	125.9(4)
Cl1–Ti–C5′	174.6(1)	C5–N1–C6	177.6(5)
Cl1–Ti–O1	93.8(1)	Ti–C5′–N1′	175.4(4)
Cl1–Ti–Cl4	98.8(1)	P1–C6–N1	108.9(3)
Cl1–Ti–Cl3	97.9(1)		

[a] The prime indicates a transformation of $-x, -y, 1-z$.

are two ways for $TiCl_3$ to bind to the fragment arising from the isocyanide–α-diketone coupling reaction. This may result in the formation of either a *fac*-isomer with the two oxygens from the diketone moiety remaining bonded to the metal or a *mer*-isomer where only a single oxygen remains bonded, as is the case for complex **12**.

(ii) The near coplanarity of the two metallacycles is indicated by the maximum distortions from the mean plane running through them: 0.115(3) for C7, 0.120(12) for C8, 0.120 Å for C14 in complexes **7**, **10**, and **12**, respectively.

(iii) The geometry of the coordination polyhedra is quite similar in all complexes (Table XI–XIII for **7**, **10**, and **12**, respectively), the Ti–Cl, Ti–N, and Ti–O bond distances

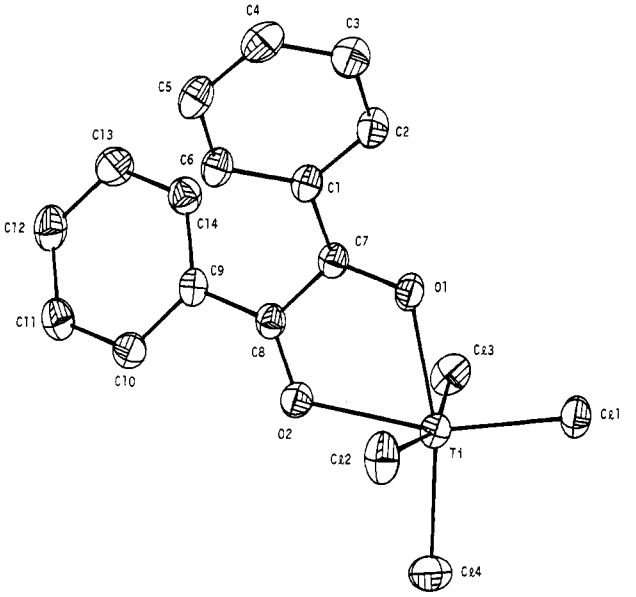
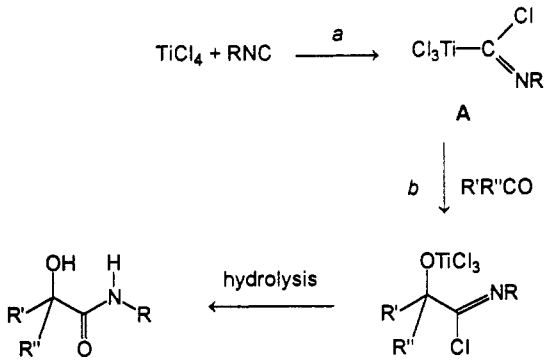


Figure 3. ORTEP drawing for complex **5** (30% probability ellipsoids).

Table X. Selected Bond Distances (Å) and Angles (deg) for Complex 5

Ti–Cl1	2.197(2)	Ti–Cl4	2.197(2)
Ti–Cl2	2.281(2)	Ti–O1	2.146(3)
Ti–Cl3	2.299(2)	Ti–O2	2.186(3)
O1–Ti–O2	71.6(1)	Cl1–Ti–O2	162.6(1)
Cl4–Ti–O2	96.1(1)	Cl1–Ti–O1	91.4(1)
Cl4–Ti–O1	167.5(1)	Cl1–Ti–Cl4	101.1(1)
Cl3–Ti–O2	79.6(1)	Cl1–Ti–Cl3	95.9(1)
Cl3–Ti–O1	85.1(1)	Cl1–Ti–Cl2	97.4(1)
Cl3–Ti–Cl4	94.7(1)	Ti–O1–C7	120.6(3)
Cl2–Ti–O2	84.1(1)	Ti–O2–C8	118.9(3)
Cl2–Ti–O1	82.4(1)	O1–C7–C8	111.7(4)
Cl2–Ti–Cl4	94.7(1)	O2–C8–C7	112.6(4)
Cl2–Ti–Cl3	161.9(1)		

Scheme III



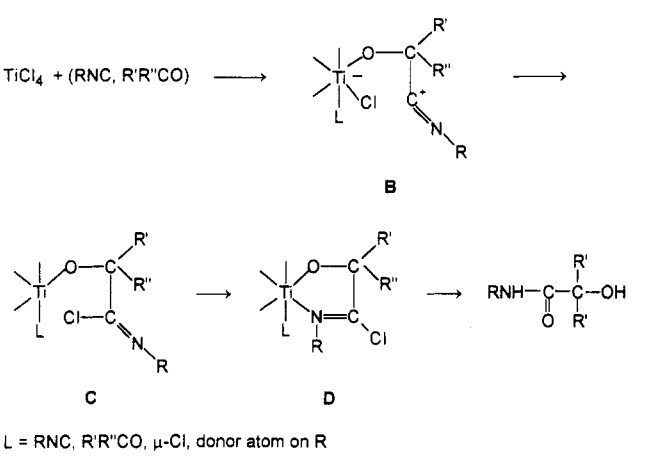
falling in the usual ranges. The Ti–O1 bond distances involving the O⁻ oxygen are much shorter than the Ti–O2 ones [Ti–O1, 1.779(2), 1.784(8), 1.794(7) for **7**, **10**, and **12**, respectively].

Conclusions

Our investigation of the mechanism of the $TiCl_4$-assisted Passerini reaction has allowed us to develop some understanding of the role of Lewis acids in promoting organic reactions. We can conclude the following.

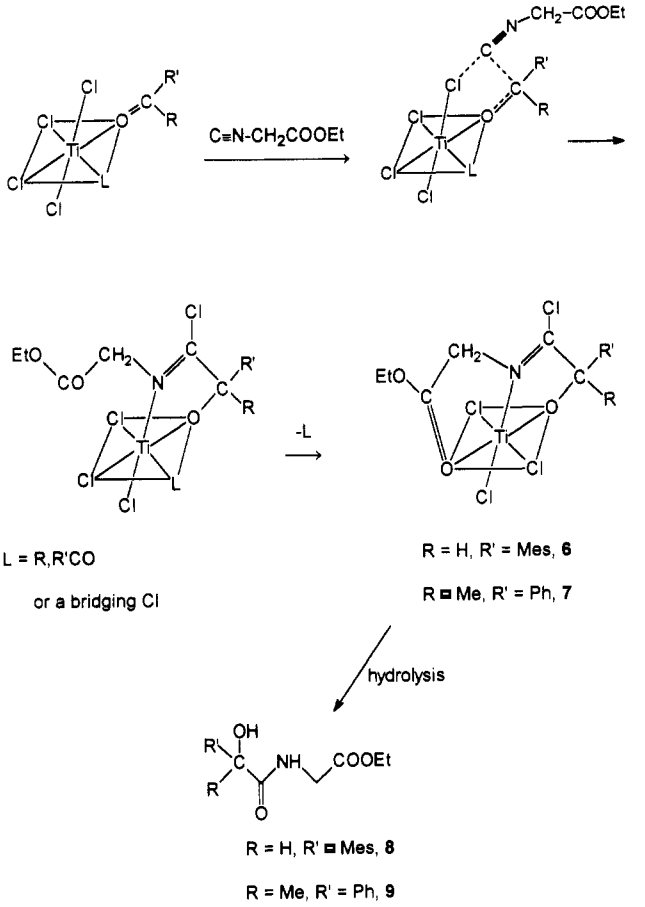
(i) A major difference in the use of a metallic acid rather than a protic one lies in the assembling properties around the metal. The Lewis acid $TiCl_4$ acts as a template agent

Scheme IV



L = RNC, R'R''CO, μ-Cl, donor atom on R

Scheme V



using three coordination sites. This should allow us to control and predict the stereochemistry of the reaction.

(ii) The assembled organic ligand around $TiCl_3$ contains a reactive C–Cl bond which can be used for transferring the organic fragment to organic or organometallic substrates.

Experimental Section

General Procedure. All reactions were carried out under an atmosphere of purified nitrogen. Solvents were dried and distilled before use by standard methods. Infrared spectra were recorded with a Perkin-Elmer 883 spectrophotometer; ^1H NMR spectra were measured on a 200-AC Brucker instrument. The synthesis of **1** has been carried out as reported.[8]

Synthesis of $[TiCl_4(2,6\text{-}Me_2C_6H_3NC)]_2$ (2). $TiCl_4$ (1.45 g, 7.6 mmol) was added to a CH_2Cl_2 solution (100 mL) of

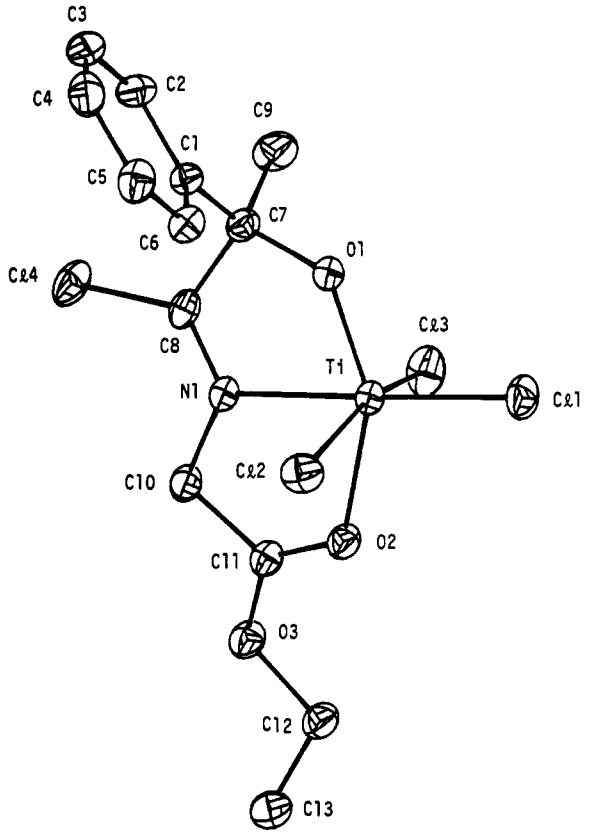


Figure 4. ORTEP drawing for complex 7 (30% probability ellipsoids).

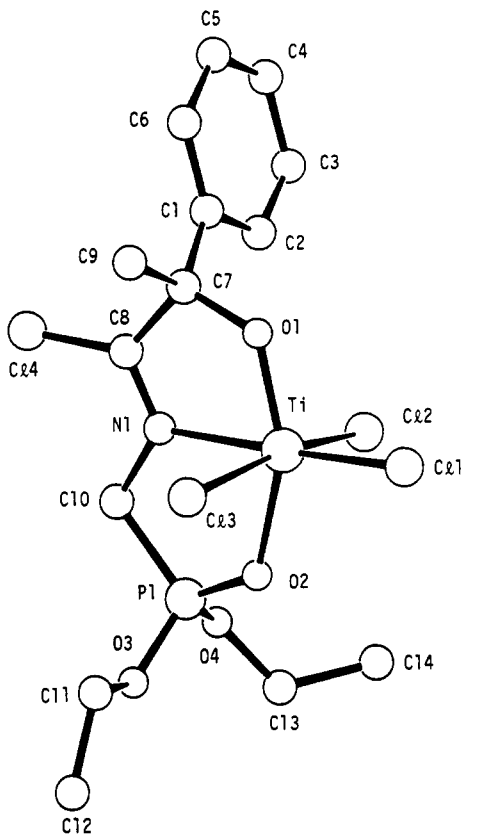
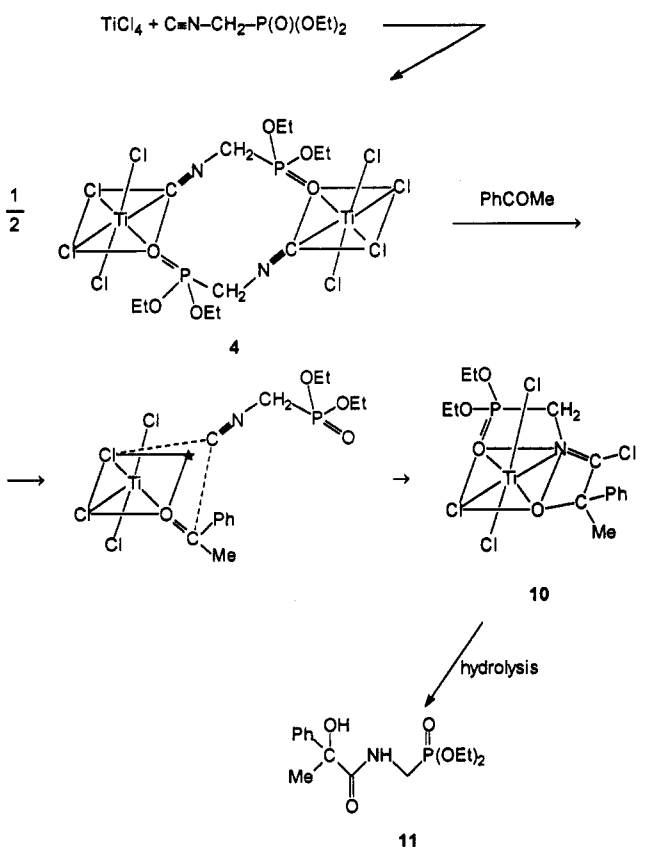


Figure 5. SCHAKAL drawing for complex 10. Disordered atoms with highest site occupation factors have been included.

Scheme VI



2,6-$Me_2C_6H_3NC$ (1.0 g, 7.6 mmol). A yellow solid crystallized in a few minutes, then the solvent was evaporated to half-volume, and the mixture was stored overnight at −30 °C. The solid was filtered off, washed with *n*-hexane (100 mL), and dried under vacuum (82%). The 1:1 adduct forms independently of the Ti:RNC ratio used. Anal. Calcd for $C_9H_9Cl_4Ti$: C, 33.56; H, 2.76; N, 4.30. Found: C, 33.60; H, 2.83; N, 4.36. ^1H NMR (δ, CD_2Cl_2): 7.25–7.10 (m, 3 H), 2.25 (s, 6 H). IR (cm^{-1}): ν_{CN} 2210 (Nujol); 2200 (CD_2Cl_2). ν_{CN} for free isocyanide 2123 (Nujol).

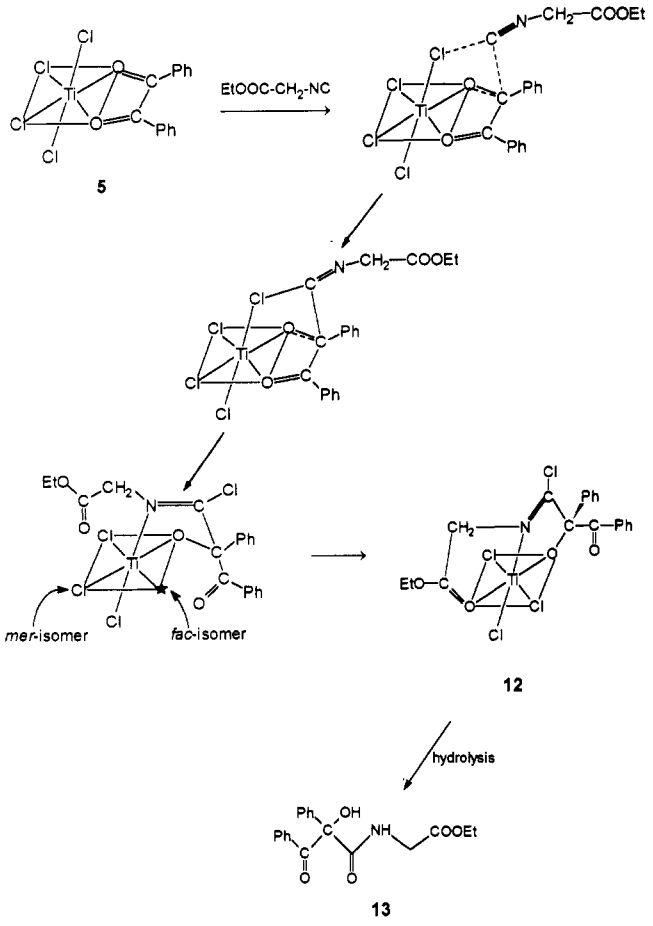
Synthesis of $[(TiCl_4)_2(\mu_2\text{-}O{=}C(OEt)CH_2NC)_2]$ (3). The slow addition of $TiCl_4$ (2.0 mL, 3.47 g, 18.3 mmol) to a CH_2Cl_2 (100 mL) solution of $CNCH_2COOEt$ (2.0 mL, 2.07 g, 18.3 mmol) gave a yellow solid which was filtered, washed with hexane (20 mL × 2), and dried under vacuum (5.2 g, 93%). Anal. Calcd for $C_5H_7Cl_4NO_2Ti$: C, 19.83; H, 2.33; N, 4.63. Found: C, 20.25; H, 2.69; N, 4.43. ^1H NMR (δ, CD_2Cl_2): 4.64 (s, 2 H, CH_2), 4.33 (q, 2 H, Et, J = 6.84 Hz), 1.33 (t, 3 H, Et, J = 6.84 Hz). IR (cm^{-1}) (Nujol): $\nu_{C\equiv N}$ 2254 [$\nu_{C\equiv N}$ for free isocyanide 2165 (Nujol)].

Synthesis of $[TiCl_4(CNCH_2P(O)(OEt)_2)]_2$ (4). $TiCl_4$ (1.18 g, 6.2 mmol) was added to a CH_2Cl_2 solution (50 mL) of $CNCH_2P(O)(OEt)_2$ (1.10 g, 6.2 mmol). A deep yellow solution was obtained, which was evaporated to half-volume and stored at −30 °C over 3 days. A yellow crystalline solid was obtained (83%). Anal. Calcd for $C_6H_{12}Cl_4NPO_3Ti$: C, 19.52; H, 3.21; N, 3.77. Found: C, 19.64; H, 3.30; N, 3.82. IR (cm^{-1}): $\nu_{C\equiv N}$ 2245 (Nujol); $\nu_{C\equiv N}$ for free isocyanide 2153 (Nujol). ^1H NMR (δ, CD_2Cl_2): 4.70–4.40 (m, 6 H), 1.50 (t, 6 H, J = 6.6 Hz). IR (cm^{-1}) (Nujol): $\nu_{C\equiv N}$ 2254 [$\nu_{C\equiv N}$ for free isocyanide 2165 (Nujol)].

Synthesis of Bu^{t}NC Dimer.[13a] Bu^{t}NC (2.0 g, 24.1 mmol) in hexane (20 mL) at 0 °C was treated with 48% $BF_3{\cdot}OEt_2$ in Et_2O (0.5 mL, 3.5 mmol) and stirred for 5 days at room temperature. The solution became gradually purple-red. It was poured into a saturated solution of $NaHCO_3$ and extracted with diethyl ether (40 mL). The solvent was distilled off and the dimer distilled under vacuum (bp 48 °C, 10 mmHg) (74%). GC–MS: m/z 166.15 (M^+).

Reaction between $TiCl_4$ and Bu^{t}NC According to Reference 7a. Bu^{t}NC (2.0 mL, 1.47 g, 17.7 mmol) was added to a solution of $TiCl_4$ (2.0 g, 10.5 mmol) in CH_2Cl_2 (4.0 mL). A very exothermic reaction took place, causing the almost complete evaporation of the solvent. Thus, 4 mL of CH_2Cl_2 was added. A yellow precipitate was formed which turned dark purple after

Scheme VII



1 day. After the mixture was stirred for 3 days at 20 °C, it was filtered and the dark-purple solid was washed with CH_2Cl_2 (3 × 5 mL) and dried (50%). When this solid was washed with hexane (3 × 10 mL), it turned yellow and was identified as 1. The mother purple solution was hydrolyzed with a saturated solution of $NaHCO_3$ and extracted with diethyl ether (10 mL). The organic phase was analyzed by GC–MS. It contained mainly the dimer of Bu^tNC (see above) together with traces of the trimer and the tetramer.

Synthesis of 5. Addition of $TiCl_4$ (3.46 g, 18.2 mmol) to a toluene solution (100 mL) of dibenzoyl (3.83 g, 18.2 mmol) caused immediate precipitation of an orange solid which dissolved on heating. From the solution at room temperature, an orange crystalline solid formed, which was filtered off, washed with *n*-hexane, and dried (90%). Anal. Calcd for $C_{14}H_{10}Cl_4O_2Ti$: C, 42.04; H, 2.53. Found: C, 42.44; H, 2.53. ^1H NMR (δ, CD_2Cl_2): 8.0 (m, 3 H, Ph), 7.62 (m, 6 H, Ph). IR (cm^{-1}): $\nu_{C=O}$ 1662 (Nujol).

Synthesis of 6. Method A. $CNCH_2COOEt$ (2.7 g, 18.3 mmol) and $TiCl_4$ (3.47 g, 18.3 mmol) were mixed at room temperature in CH_2Cl_2 (120 mL). A yellow solution was obtained, from which in a few minutes a light yellow solid precipitated. After 15 min. MesCHO (2.71 g, 18.3 mmol) was added under stirring and a red solution immediately formed. After 6 h the solvent was distilled off and the orange solid obtained was carefully washed with *n*-hexane (97%). Anal. Calcd for $C_{15}H_{19}Cl_4NO_3Ti$: C, 39.95; H, 4.25; N, 3.11. Found: C, 40.22; H, 4.51; N, 3.15. ^1H NMR (δ, CD_2Cl_2): 7.49 (t, 1 H, J = 2.9 Hz), 7.07 (s, 2 H), 4.89 (d, 2 H, J = 2.9 Hz), 4.76 (q, 2 H, J = 7.2 Hz), 2.44 (s, 6 H), 2.32 (s, 3 H), 1.48 (t, 3 H, J = 7.2 Hz). IR (cm^{-1}) (Nujol): ν_{Ti-O} 992, $\nu_{C=O}$ 1671 ($\nu_{C=O}$ in free isocyanide, 1759), $\nu_{C=N}$ 1635.

Synthesis of 6. Method B. To a toluene (75 mL) suspension of 5 (1.55 g, 3.19 mmol) was added $CNCH_2COOEt$ (0.36 g, 3.2 mmol). In a few minutes a red solution was obtained. The solvent was evaporated to dryness and the solid washed with *n*-hexane (90%). Comparison of spectral data confirmed that this product was the same as the one obtained from method A.

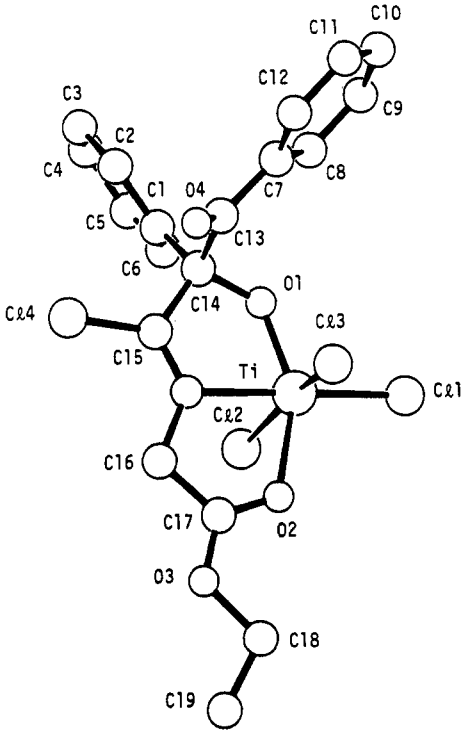


Figure 6. SCHAKAL drawing for complex 12.

Table XI. Selected Bond Distances (Å) and Angles (deg) for Complex 7

Ti–Cl1	2.258(1)	O1–C7	1.430(4)
Ti–Cl2	2.311(1)	O2–C11	1.232(4)
Ti–Cl3	2.340(1)	N1–C8	1.254(3)
Ti–O1	1.779(2)	N1–C10	1.441(4)
Ti–O2	2.131(2)	C7–C8	1.528(4)
Ti–N1	2.174(2)	C10–C11	1.499(4)
O2–Ti–N1	73.3(1)	Cl1–Ti–O1	103.2(1)
O1–Ti–N1	75.6(1)	Cl1–Ti–Cl3	92.8(1)
O1–Ti–O2	148.9(1)	Cl1–Ti–Cl2	94.1(1)
Cl3–Ti–N1	85.8(1)	Ti–O1–C7	129.1(2)
Cl3–Ti–O2	80.0(1)	Ti–O2–C11	119.8(2)
Cl3–Ti–O1	96.7(1)	Ti–N1–C10	118.9(2)
Cl2–Ti–N1	87.6(1)	Ti–N1–C8	114.2(2)
Cl2–Ti–O2	81.5(1)	C8–N1–C10	126.6(2)
Cl2–Ti–O1	98.4(1)	O1–C7–C8	103.5(2)
Cl2–Ti–Cl3	161.4(1)	N1–C8–C7	116.8(2)
Cl1–Ti–N1	178.1(1)	N1–C10–C11	106.0(2)
Cl1–Ti–O2	107.8(1)	O2–C11–C10	121.8(3)

Hydrolysis of 6, Synthesis of *rac*-*N*-[hydroxy(2,3,5-trimethylphenyl)acetyl]glycine Ethyl Ester, 8. In a flask containing CH_2Cl_2 (50 mL) and H_2O (50 mL), 6 (1.49 g) was introduced and the mixture stirred for 20 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The two organic portions were combined, washed with a saturated solution of $NaHCO_3$ (50 mL) and NaCl (50 mL), dried, and concentrated under reduced pressure to give a yellow oil which was purified by flash chromatography (Et_2O:hexane, 4:1) (633 mg). ^1H NMR (δ, CD_2Cl_2): 6.87 (s, 2 H), 6.40–6.30 (br, 1 H), 5.49 (s, 1 H), 4.17 (q, 2 H, J = 7.2 Hz), 4.02 (d, 2 H, J = 5.6 Hz), 2.36 (s, 6 H), 2.28 (s, 3 H), 1.29 (t, 3 H, J = 7.2 Hz). IR (cm^{-1}) ($CHCl_3$): $\nu_{C=O}$ 1747, 1679.

Synthesis of 7. Acetophenone (0.45 mL, 0.46 g, 3.9 mmol) was added to a toluene (50 mL) suspension of 4 (1.17 g, 1.93 mmol). The resulting deep yellow solution gave on standing a light yellow crystalline solid. Suitable crystals for X-ray analysis were obtained by crystallization from hot toluene. The synthesis of 9 can be carried out equally well by adding the isocyanide to a CH_2Cl_2 solution containing $TiCl_4$ and acetophenone. Anal. Calcd for $C_{13}H_{15}Cl_4NO_3Ti$: C, 36.92; H, 3.57; N, 3.31. Found: C, 37.16; H, 3.59; N, 3.34. ^1H NMR (δ, CD_2Cl_2): 7.80 (m, 2 H, Ph), 7.45 (m, 3 H, Ph), 4.77 (s, 2 H, CH_2), 4.73 (q, 2 H, Et, J =

Table XII. Selected Bond Distances (Å) and Angles (deg) for Complex 10

Ti–Cl1	2.247(4)	P1–C10	1.794(12)
Ti–Cl2	2.338(3)	O1–C7A	1.433(27)
Ti–Cl3	2.360(3)	O1–C7B	1.441(24)
Ti–O1	1.784(8)	N1–C8	1.247(16)
Ti–O2	2.040(9)	N1–C10	1.481(16)
Ti–N1	2.211(9)	C7A–C8	1.440(32)
P1–O2	1.490(8)	C7B–C8	1.631(31)
O2–Ti–N1	77.6(3)	Cl1–Ti–Cl2	93.2(1)
O1–Ti–N1	74.7(4)	O2–P1–C10	107.7(6)
O1–Ti–O2	152.3(3)	Ti–O1–C7B	131.0(11)
Cl3–Ti–N1	84.5(2)	Ti–O1–C7A	126.0(12)
Cl3–Ti–O2	83.1(2)	Ti–O2–P1	126.1(5)
Cl3–Ti–O1	94.1(3)	Ti–N1–C10	121.8(7)
Cl2–Ti–N1	89.7(3)	Ti–N1–C8	114.2(8)
Cl2–Ti–O2	84.4(3)	C8–N1–C10	123.8(10)
Cl2–Ti–O1	95.6(3)	O1–C7A–C8	108.7(19)
Cl2–Ti–Cl3	167.1(1)	O1–C7B–C8	98.7(15)
Cl1–Ti–N1	176.2(3)	N1–C8–C7B	116.6(13)
Cl1–Ti–O2	105.2(3)	N1–C8–C7A	114.7(15)
Cl1–Ti–O1	102.5(3)	P1–C10–N1	106.4(8)
Cl1–Ti–Cl3	93.2(1)		

Table XIII. Selected Bond Distances (Å) and Angles (deg) for Complex 12

Ti–Cl1	2.249(4)	O1–C14	1.418(12)
Ti–Cl2	2.322(4)	O2–C17	1.230(12)
Ti–Cl3	2.316(4)	N1–C15	1.247(11)
Ti–O1	1.794(6)	N1–C16	1.464(10)
Ti–O2	2.096(7)	C14–C15	1.518(12)
Ti–N1	2.175(8)	C16–C17	1.479(14)
O2–Ti–N1	73.7(3)	Cl1–Ti–O1	105.0(2)
O1–Ti–N1	75.4(3)	Cl1–Ti–Cl3	94.9(2)
O1–Ti–O2	149.1(3)	Cl1–Ti–Cl2	93.9(2)
Cl3–Ti–N1	85.8(2)	Ti–O1–C14	127.3(5)
Cl3–Ti–O2	82.9(2)	Ti–O2–C17	120.6(6)
Cl3–Ti–O1	94.2(3)	Ti–N1–C16	116.7(6)
Cl2–Ti–N1	85.4(2)	Ti–N1–C15	115.0(6)
Cl2–Ti–O2	82.3(2)	C15–N1–C16	128.2(8)
Cl2–Ti–O1	96.0(2)	O1–C14–C15	105.2(7)
Cl2–Ti–Cl3	164.4(1)	N1–C15–C14	115.4(8)
Cl1–Ti–N1	179.3(3)	N1–C16–C17	106.8(7)
Cl1–Ti–O2	105.9(2)	O2–C17–C16	121.1(8)

8.0 Hz), 2.24 (s, 3 H, Me), 1.51 (t, 3 H, Et, J = 8.0 Hz). IR (cm^{-1}) (Nujol): ν_{Ti-O} 940, $\nu_{C=O}$ 1655 (free isocyanide, 1759), $\nu_{C=N}$ 1654.

Hydrolysis of 7, Synthesis of *rac*-*N*-(2-hydroxy-2-phenylpropionyl)glycine Ethyl Ester, 9.[3b] In a flask containing CH_2Cl_2 (50 mL) and H_2O (50 mL), **7** (1.69 g) was hydrolyzed under stirring. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The two organic portions were combined, washed with saturated solutions of $NaHCO_3$ and NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give an orange oil which was purified by flash chromatography (Et_2O:hexane, 7:3) to afford a white solid (67%) recrystallized from Et_2O/hexane. ^1H NMR (δ, CD_2Cl_2): 7.62–7.60 (m, 2 H), 7.40–7.30 (m, 3 H), 7.12 (br, 1 H), 4.23 (q, 2 H, J = 7.2 Hz), 4.00 (dd, 2 H, J = 5.4 Hz, J = 2.8 Hz), 3.30 (br, 1 H), 1.85 (s, 3 H), 1.29 (t, 3 H, J = 7.2 Hz). IR (cm^{-1}): $\nu_{C=O}$ 1729, 1655. Mp: 86 °C.

Synthesis of 10. $TiCl_4$ (1.17 g, 6.24 mmol) was added to a toluene solution (100 mL) of $CNCH_2P(O)(OEt)_2$ (1.1 g, 6.24 mmol), resulting in a yellow oil. After 5 min, acetophenone (0.75 g, 6.24 mmol) was added dropwise with stirring. The oil slowly disappeared, and a light yellow microcrystalline solid precipitated, which redissolved by gently heating. After standing, a yellow crystalline solid formed (76%). Anal. Calcd for $C_{14}H_{20}Cl_4NPTi$: C, 34.50; H, 4.10; N, 2.86. Found: C, 34.70; H, 4.28; N, 2.82. ^1H NMR (δ, CD_2Cl_2): 7.86–7.84 (m, 2 H), 7.47–7.41 (m, 3 H), 4.62–4.51 (m, 4 H), 4.23 (dd, 2 H, J = 2.0 Hz, J = 12.2 Hz), 2.23 (s, 3 H), 1.52–1.43 (m, 6 H). IR (cm^{-1}) (Nujol): $\nu_{C=N}$ 1651.

Hydrolysis of 10, Synthesis of *rac*-*N*-[[(2-hydroxy-2-phenylpropionyl)amino]methyl]phosphonic Acid Diethyl Ester, 11. Into a flask containing CH_2Cl_2 (50 mL) and H_2O (50 mL) was introduced **10** (1.10 g), and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The two organic portions were combined, washed with saturated solutions of $NaHCO_3$ and NaCl, dried, and concentrated under reduced pressure to give a pale yellow oil which was purified by flash chromatography (CH_2Cl_2:CH_3OH, 9:1) (56%). ^1H NMR (δ, CD_2Cl_2): 7.70–7.50 (m, 2 H), 7.40–7.20 (m, 3 H), 4.10–3.30 (m, 7 H), 1.81 (s, 3 H), 1.19 (t, 3 H, J = 7.2 Hz), 1.08 (t, 3 H, J = 7.2 Hz). IR (cm^{-1}) ($CHCl_3$): $\nu_{C=O}$ 1679.

Synthesis of 12. To a toluene solution (300 mL) of **7** (2.30 g, 5.75 mmol) was added $CNCH_2COOEt$ (0.65 g, 5.75 mmol). A yellow solution was obtained which was kept at room temperature. A yellow crystalline solid formed, which was filtered off, washed with *n*-hexane, and dried (83%). Crystals suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2. Anal. Calcd for $C_{19}H_{17}Cl_4O_4Ti\cdot(C_7H_8)_{0.5}$: C, 48.33; H, 3.79; N, 2.51. Found: C, 48.33; H, 3.80; N, 2.33. ^1H NMR (δ, CD_2Cl_2): 7.87–7.39 (m, 10 H), 4.87 (d, 2 H, J = 2.1 Hz), 4.76 (q, 2 H, J = 7.2 Hz), 1.51 (t, 3 H, J = 7.2 Hz). IR (cm^{-1}) (Nujol): ν_{Ti-O} 965; $\nu_{C=O}$ 1823, 1695; $\nu_{C=N}$ 1671.

Hydrolysis of 12, Synthesis of *rac*-*N*-(2-hydroxy-3-oxo-2,3-diphenylpropionyl)glycine Ethyl Ester, 13. Into a flask containing CH_2Cl_2 (50 mL) and H_2O (50 mL) was introduced **12** (1.47 g), and the mixture was stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The two organic portions were combined, washed with saturated solutions of $NaHCO_3$ and NaCl, dried, and concentrated under reduced pressure to give a white oil which was purified by flash chromatography (hexane:Et_2O, 3:7) to afford a white solid (56%) recrystallized from hexane:Et_2O. ^1H NMR (δ, CD_2Cl_2): 7.86–8.02 (m, 2 H), 7.70–7.85 (br, 1 H), 7.34–7.51 (m, 8 H), 5.92 (s, 1 H), 4.25 (q, 2 H, J = 7.2 Hz), 4.12 (AM part of AMX, J = 5.4 Hz, J = 8.4 Hz), 1.28 (t, 3 H, J = 7.2 Hz). IR (cm^{-1}): $\nu_{C=O}$ 1750, 1699, 1658.

X-ray Crystallography. The crystals selected for study were mounted in glass capillaries and sealed under nitrogen. Crystal data and details associated with data collection are given in Table I. The reduced cells quoted were obtained using TRACER.[18] Data were collected at room temperature (295 K) on a single-crystal four circle diffractometer. For intensities and background, individual reflection profiles were analyzed.[19] The structure amplitudes were obtained after the usual Lorentz and polarization corrections,[20] and the absolute scale was established by the Wilson method.[21] The crystal quality was tested by ψ scans, showing that crystal absorption effects could not be neglected for complexes **4** and **5**. Data for complexes **2** and **7** were corrected for absorption using ABSORB[22] and, for complexes **10** and **12**, using a semiempirical method.[23] The function minimized during the full-matrix least-squares refinement was $\sum w|\Delta F|^2$. Weights were applied according to the scheme $w = k/[\sigma^2(F_o) + |g|F_o)^2]$. Scattering factors for neutral atoms were taken from ref 24a for non-hydrogen atoms and from ref 25 for H. Anomalous scattering corrections were included in all structure factor calculations.[24b] Among the low-angle reflections no correction for secondary extinction was deemed necessary.

Solution and refinement were based on the observed reflections. The structures were solved by the heavy-atom method starting

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(19) Lehmann, M. S.; Larsen, F. K. *Acta Crystallogr., Sect. A: Cryst. Phys. Diffr. Theor. Gen. Crystallogr.* **1974**, *A30*, 580–584.
(20) Data reduction, structure solution, and refinement were carried out on a GOULD 32/77 computer using: Sheldrick, G. SHELX-76. System of Crystallographic Computer Programs; University of Cambridge: Cambridge, England, 1976.
(21) Wilson, A. J. C. *Nature* **1942**, *150*, 151.
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(23) Ugozzoli, F. ABSORB. A program for F_o absorption correction. *Comput. Chem.* **1987**, *11*, 109.
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(25) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

from a three-dimensional Patterson map. Refinement was first done isotropically and then anisotropically for all the non-H atoms excepting those affected by disorder. The structures of complexes **2**, **4**, and **5** were refined straightforwardly. For **4** a methyl carbon (C4) was found to be disordered over three positions (A, B, C) and was isotropically refined with the site occupation factors given in Table III. Some troubles were encountered in the refinement of complex **10** owing to the severe disorder affecting both the complex molecule and the toluene solvent molecule of crystallization which was found to be disordered about a center of symmetry. The disorder involving the complex was solved by considering the C7 carbon atom, the Ph ring, and the Cl4 chlorine atom as statistically distributed over two positions (A and B) symmetrically displaced with respect to the C8,N1,Ti1,O1 chelation plane. The C12 and C14 methyl carbons were also split in two positions (A and B). Refinement was then carried out anisotropically only for the Ti, Cl, P, O, and N atoms and for the C8, C9, and C10 carbon atoms. The remaining ones were refined isotropically with the site occupation factors given in Table VI. The final difference map showed no unusual feature with a residual peak of 1.0 e A^{-3} close to the disordered Cl4 chlorine atom.

In complex **12** refinement was performed anisotropically except for the CH_2Cl_2 solvent molecule which was found to be completely spread around a central atom called C1S. The six most intense peaks around C1S on a difference map were interpreted as "partial" chlorine atoms and isotropically refined with the site occupation factors reported in Table VII. The final difference map showed no unusual feature with no significant peak above the general background. During the refinement of complexes **10** and **12** the phenyl rings were constrained to be regular hexagons (C–C = 1.395 Å).

All the hydrogen atoms but those associated with the disordered atoms were introduced in calculations as fixed contributors with isotropic U's fixed at 0.08 $Å^2$ (0.09 $Å^2$ for complex **10**). Hydrogen atoms were located from difference maps for complexes **2**, **4**, **5**, and **7** and put in geometrically calculated positions for complexes **10** and **12**.

Final atomic coordinates are listed in Tables II–VII for non-H atoms and in Tables SI–SVI (supplementary material) for hydrogens. Thermal parameters are given in Tables SVII–SXII; selected bond distances and angles, in Tables VIII–XIII.[26]

Acknowledgment. We would like to thank the "Fonds National Suisse de la Recherche Scientifique" (Grant. No. 20-33420-92) and Ciba-Geigy Co. (Basel) for financial support.

Supplementary Material Available: Listings of unrefined hydrogen coordinates (Tables SI-SVI), thermal parameters (Tables SVII-SXII), and nonessential bond distances and angles (Table SXIII-SXVIII) for complexes **2**, **4**, **5**, **7**, **10**, and **12** (17 pages). Ordering information is given on any current masthead page.

OM930042E

(26) See paragraph at the end regarding supplementary material.