The reactions of α-amino acids and α-amino acid esters with high valent transition metal halides: synthesis of coordination complexes, activation processes and stabilization of α-ammonium acylochloride cations†

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Titanium tetrachloride smoothly reacted with a selection of α-amino acids (aaH) in CH₂Cl₂ affording yellow to orange solid coordination compounds, 1a−d, in 70−78% yields. The salts [NHEt₃][TiCl₄(aa)], 2a−b, were obtained from TiCl₄/aaH/NEt₃ (aa = L-phenylalanine, N,N-dimethylphenylalanine), in 60−65% yields. The complex Nb₂Cl₆[μ-κ₂O₂K₂₂N-(CH₂CH₂CH(NH₂)CO₂Me)]₃, 3, was isolated from the reaction of L-proline with NbCl₅/NEt₃ in CH₂Cl₂ at room temperature. The X-ray structure of 3 features a bridging (E)-1,2-bis(3,4-dihydropyridyl-5-y1)ethene-1,2-diolate ligand, resulting from the unprecedented C−C coupling between two proline units. Unusually stable α-ammonium acyl chlorides were prepared by the reactions of PCl₅/MCl₅ (MCl₅ = NbCl₅, WCl₆) with L-proline, N,N-dimethylphenylalanine, sarcosine and L-methionine. MX₅ (M = Nb, Ta; X = F, Cl) reacted with L-leucine methylester and L-proline ethylester to give ionic coordination compounds, [MX₅L₂]MX₄ (M = Nb, L = Me₂CHCH₂CH(NH₂)CO₂Me, X = F, 9; Cl, 11a; M = Nb, X = Cl, L = HIVCH₂CH₂CH₂CO₂Et, 11c; Ta, 11d), in moderate to good yields. [Nb₂Cl₆(Me₂CHCH₂CHNH₂CO₂Me)][NbCl₅], 12, was isolated as a co-product of the reaction of NbCl₅ with L-leucine isopropylester, and crystallographically characterized. The reaction of NbCl₅ with L-serine isopropylester afforded NbCl₅(OCH₂CH₂CH₂CO₂Pr), 13, in 66% yield. The activation of the ester O−R bond was observed in the reactions of L-leucine methyl ester with NbF₅ and L-proline ethyl ester with MB₃ (M = Nb, Ta), these reactions proceeding with the release of EiF and EiBr, respectively. All the metal products were characterized by analytical and spectroscopic methods, while DFT calculations were carried out in order to provide insight into the structural and mechanistic aspects.

Introduction

α-Amino acids constitute a class of organic compounds arousing great interest in synthetic chemistry, in view of their easy availability and low toxicity,¹ the typical presence of a stereogenic centre (making them suitable substrates for asymmetric catalysis)² and the possibility of firmly coordinating metal ions.³ The esterification of the carboxylic acid moiety is one of the most viable modifications of the α-amino acid skeleton, and indeed a good number of α-amino acid esters have been synthesized and employed with reference to several application fields.⁴ Metal complexes containing α-amino acid esters as ligands are especially relevant to bio-inorganic chemistry, being useful to the synthesis of peptides,⁵ as biological models,⁶ and as scaffolds for the development of new drugs.⁷ Furthermore, α-amino acids and α-amino acid ester metal complexes, being possible chiral sources,⁸ have found increasing attention as privileged, potential catalysts for environmentally friendly asymmetric syntheses.⁹⁺¹⁰

It is noteworthy that the large majority of these studies refer to middle to late transition metals, whereas very little is known about the parallel chemistry with early transition metal compounds. In particular, the homoleptic halides of high valent
elements (oxidation state ≥ 4) belonging to groups 4, 5 and 6, HVTMH, are strongly oxophilic species, usually very air sensitive and incompatible with water. This characteristic has probably discouraged the linking with an “opposite world”, i.e. the exploration of the reactivity with amino acids, which in turn exhibit high water affinity, and their simple derivatives such as amino acid esters.

As a matter of fact, the coordination chemistry of HVTMH with amino acid esters still remains an unexplored field of research, with the exception of a former synthetic study regarding MoCl$_5$. Similarly, the only information available up to 2014 on the interaction of HVTMH with amino acids, in the absence of further reactants, is a note dealing with the reactivity of TiCl$_4$ with glycine. In all of the cases, the structural characterization of the products relied on limited data.

Recently, in the framework of our interest in the chemistry of HVTMH with naturally occurring compounds, we have found that MoCl$_5$ and WCl$_6$ behave as chlorinating agents towards natural amino acids, affording fairly stable ammonium acetylchloride salts.

On the other hand, the interaction of MX$_5$ (M = Nb, Ta; X = Cl, Br) with amino acids leads to dinuclear complexes containing bridging amino acidato ligands via HX release. Subsequent activation of the coordinated amino acidato moiety has been observed in mild conditions in some specific cases, leading to iminium salts.

Herein, we will present an extension of our study on the reactivity between amino acids and HVTMH, including the synthesis of TiCl$_4$ derivatives, the unprecedented metal mediated C–C dimerization of a amino acid (L-proline) and the stabilization of otherwise reactive ammonium acetylchloride cations.

The carboxylato group. In general, the wavenumber difference ($\Delta\nu_{C=O} = \nu_C - \nu_O$) is considered as a useful parameter to discriminate between monodentate, chelating, and bridging bidentate carboxylato ligands. If the IR data available for 1a–d, i.e. $\Delta\nu_{C=O}$ varies between 103 (1a) and 135 (1d) cm$^{-1}$, and the DFT results (vide infra), we propose a bridging bidentate-coordination fashion. This implies that the amino acid ligand should be coordinated to titanium as a zwitterion. Accordingly, a broad IR absorption is observed at 3091 cm$^{-1}$ in the IR spectrum of 1d, assigned to ammonium N–H stretching vibration.

The geometry proposed on the basis of spectroscopic data was supported by DFT calculations on the possible isomers of 1b. The dinuclear structure [TiCl$_4$(H$_2$O)$_2$O$_2$CCH(CH$_2$Ph)NH$_2$]$_2$, depicted in Fig. 1, resulted meaningfully more stable than mononuclear structures (see Fig. S1 given as ESI†).

Compounds 1a–d display low solubility in common organic solvents. The NMR spectra were recorded in CD$_3$CN, displaying single sets of resonances. The $^1$H NMR spectra exhibit broad

**Results and discussion**

**Reactivity of MCl$_5$ with amino acids**

**Titanium tetrachloride.** Titanium tetrachloride smoothly reacted with a series of amino acids in dichloromethane affording moisture sensitive, yellow to orange solid materials 1a–d, in 70 to 78% yields (Scheme 1). Compounds 1 are coordination adducts: in this respect, the reactivity of TiCl$_4$ with amino acids differs from that of MCl$_5$ (M = Nb, Ta), featured by HCl release, and from those of MoCl$_5$ and WCl$_6$, leading to Cl/O interchange products (see Introduction).

Compounds 1a–d were characterized by analytical and spectroscopic methods. The IR spectra (solid state) contain one medium and one strong intensity absorption in the range 1600–1400 cm$^{-1}$. These two absorptions are due, respectively, to the asymmetric ($\nu_s$) and the symmetric ($\nu_s$) stretching vibrations of the carboxylato group. In general, the wavenumber difference ($\Delta\nu_{C=O} = \nu_C - \nu_O$) is considered as a useful parameter to discriminate between monodentate, chelating, and bridging bidentate carboxylato ligands. If the IR data available for 1a–d, i.e. $\Delta\nu_{C=O}$ varies between 103 (1a) and 135 (1d) cm$^{-1}$, and the DFT results (vide infra), we propose a bridging bidentate-coordination fashion. This implies that the amino acid ligand should be coordinated to titanium as a zwitterion. Accordingly, a broad IR absorption is observed at 3091 cm$^{-1}$ in the IR spectrum of 1d, assigned to ammonium N–H stretching vibration.

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**Fig. 1** DFT-optimized geometry of the most stable isomer of 1b (C-PCM/ M06 calculations). Selected computed bond lengths (Å): Ti1–O 2.020, 2.081; Ti2–O 1.990, 2.080; Ti1–Cl (trans O) 2.295, 2.232; Ti2–Cl (trans O) 2.232, 2.304; Ti1–Cl (cis O) 2.266, 2.392; Ti2–Cl (cis O) 2.291, 2.394; C–O 1.244, 1.261, 1.251, 1.252; N–H 1.025, 1.028, 1.038, 1.027, 1.028, 1.037. Selected computed angles (°): O–Ti1–O 86.1, O–Ti2–O 84.6; Ti1–O–C 149.8, 151.4; Ti2–O–C 139.2, 151.3; O–C–O 124.9, 126.4.
resonances in the 7.7–7.0 ppm range, related to the uncoordinated ammonium group. The 13C-NMR spectra of the more soluble 1a–b show the resonance of the carboxylate carbon at 176.1 and 170.0 ppm, respectively. These values are similar to those reported for O,N-coordinated α-amino acids in NbCl5 derivatives.23

The coordination of organic species to high valent transition metal chlorides represents, in a number of cases, the preliminary step of some activation process.13–19 The activation is favoured by the strong Lewis acidity of the metal centre, and may be triggered by the addition of a Brønsted base. For instance, Peryshkov and coworkers recently described a C–H bond activation reaction of nitriles by means of NEt3 upon coordination to TaCl5.20

Thus, the reaction of 1b with NEt3 proceeded with selective deprotonation of the ammonium group; analogous result was achieved by treatment of a TiCl4/L-N,N-dimethylphenylalanine mixture with NEt3 (Scheme 2).22 The reactions of 1a,c,d with NEt3 were not straightforward, leading to non identified compounds; the solid isolated from 1a/NEt3 revealed to be paramagnetic.

The CH2Cl2 soluble compounds 2a–b (Scheme 2) were isolated by addition of hexane to the respective reaction mixtures.22 The 1H NMR spectra of 2a–b display a low field resonance accounting for the triethylammonium proton (e.g. at 9.09 ppm in the case of 2a); the resonances of the N-bound protons within the anion undergo significant upfield shift on going from the amino acid unit in 1b to the amino acidate one in 2b (Δδ > 3 ppm). The IR spectra of 2a–b exhibit a strong absorption around 1700 cm−1; this evidence suggests O,N-coordination of the aminoacidate moiety, leaving a uncoordinated C=O bond. The geometries of the 2a,b anions were DFT optimized, considering either mononuclear and dinuclear structures as starting points (Fig. S2†). Thus, mononuclear compounds bearing N,O-chelating α-aminoacids (Fig. 2) resulted much more stable than dinuclear homologues (see ES1† for more details).

Niobium pentachloride. We reported that the 2 : 1 reactions of NbX5 (X = Cl, Br) with a variety of α-amino acids afforded dinuclear α-aminoacidate complexes via HCl release. The addition of a further equivalent of organic reactant resulted in the decarboxylation of one amino acidate moiety, with consequent formation of iminium salts and Nb-formate species (see Scheme 3, showing the specific case of N,N-dimethylphenylalanine).15

With the aim of exploring the possibility of further activation pathways, we investigated the reactions of Nb2Cl6(α-aminoacidate) complexes with NEt3. In general, the amino acidate moiety did not undergo activation under these conditions, with an exception provided by the Nb2Cl6(L-prolinate)/NEt3 system. This latter evolved into a complicated mixture of products, including minor amounts of NbCl4[κ-O,N-(κ’-H-Ch2·Ch2·Ch2·C(n)(O))L], 3. The use of NH4Pr3 in the place of NEt3 allowed to isolate red crystals of 3 (12% yield), and also yellow crystals of [NH4][Pr3][NbCl6], 4 (40% yield), Scheme 4.
Table 1  Selected bond lengths (Å) and angles (°) for 3

<table>
<thead>
<tr>
<th></th>
<th>Bond Lengths (Å)</th>
<th>Bond Angles (°)</th>
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<tr>
<td>Nb(1)-Cl(1)</td>
<td>2.3319(13)</td>
<td>Nb(1)-Cl(2)</td>
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<tr>
<td>Nb(1)-Cl(3)</td>
<td>2.3454(12)</td>
<td>Nb(1)-Cl(4)</td>
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<td>Nb(1)-O(1)</td>
<td>1.927(3)</td>
<td>Nb(1)-N(1)</td>
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<td>C(1)-O(1)</td>
<td>1.357(6)</td>
<td>C(1)-Cl(1)</td>
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<td>C(1)-C(2)</td>
<td>1.471(7)</td>
<td>C(2)-Cl(3)</td>
</tr>
<tr>
<td>C(1)-C(4)</td>
<td>1.530(6)</td>
<td>C(4)-Cl(5)</td>
</tr>
<tr>
<td>N(1)-C(2)</td>
<td>1.276(6)</td>
<td>N(1)-Cl(5)</td>
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<tr>
<td>Cl(1)-Nb(1)-O(1)</td>
<td>158.18(10)</td>
<td>Cl(2)-Nb(1)-N(1)</td>
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<td>Cl(3)-Nb(1)-Cl(4)</td>
<td>170.32(5)</td>
<td>O(1)-Nb(1)-N(1)</td>
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<td>Nb(1)-O(1)-C(1)</td>
<td>122.9(3)</td>
<td>Nb(1)-N(1)-C(2)</td>
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<td>Nb(1)-N(1)-C(5)</td>
<td>132.0(3)</td>
<td>C(2)-N(1)-C(5)</td>
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<td>N(1)-C(2)-C(3)</td>
<td>115.8(4)</td>
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<td>C(1)-C(2)-C(3)</td>
<td>133.5(4)</td>
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<td>C(1)-C(4)-C(5)</td>
<td>105.8(4)</td>
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<tr>
<td>O(1)-C(1)-C(2)</td>
<td>116.4(6)</td>
<td>O(1)-C(1)-C(1_1)</td>
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<tr>
<td>C(2)-C(1)-C(1_1)</td>
<td>125.2(6)</td>
<td></td>
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* Symmetry transformation used to generate C(1_1): −x + 1, −y, −z + 1.

The X-ray structure of 3 is shown in Fig. 3, with relevant bonding parameters listed in Table 1; the X-ray structure of 4 is given as ESI (Fig. S3; Tables S1 and S1†).

Complex 3 displays crystallographic (C2) symmetry with the inversion centre located on the middle of the C(1)–C(1) bond. The complex is composed of an unprecedented anionic \( \left\{\text{C}1_1\text{H}_3\text{C}1\text{H}_3\text{C}1\text{(NH}2\text{)}\text{O}_2\text{Cl}\right\}^- \) ligand \((\text{E}^-\text{1,2-bis(3,4-dihydro-2H-pyrrol-5-yl)ethene-1,2-diolate})\) that is \( \mu^2\text{O}_2\text{N}^2 \)-coordinated over two \([\text{NbCl}_4]^\text{−}\) cationic fragments. Such anionic ligand is almost perfectly planar (mean deviation from the least squares plane 0.0387 Å), being the two Nb atoms respectively 0.1879 Å above and below this plane. C(1), C(2) and N(1) [sum angles 360.0(9), 360.0(7) and 360.0(6)°, respectively] show a perfect sp² hybridization, and the C(1)–C(1) [1.357(6) Å] and C(2)–N(1) [1.276(6) Å] distances are typical for double bonds.²²

The \{C_2O_2\} core of the \((\text{E})^-\text{1,2-bis(3,4-dihydro-2H-pyrrol-5-yl)ethene}-1,2\text{-diolate}\) ligand in 3 is a fully deprotonated 1,2-enediol. In general, 1,2-enediols are quite unstable species,²⁴ whose stabilization may be supplied by hydrogen-bonded protons,²⁵ or by chelating (N,O) coordination to transition metals.²⁶

Fig. 3  ORTEP drawing of 3. Displacement ellipsoids are at the 50% probability level.

Basic ally, the process leading to 3 is a C–C bond forming condensation of two proline units (Scheme 5A). Differently, typical \( \alpha \)-amino acid condensation generates a peptide bond (Scheme 5B).²⁷

In order to gain some insight into the mechanism of the low yield formation of 3, a DFT study was undertaken (see Scheme S1 in the ESIF). It seems plausible that the C–C bond forming step consists in the coupling of two acetylene units, accompanied by the release of HCl and assisted by the amine (see Scheme S1, † E → F → G). Indeed the side reactions NH\(_2\)\(\text{PF}_3 + \text{HCl} \rightarrow \text{NH}_2\text{PF}_3\text{Cl} \) and \([\text{NH}_2\text{PF}_3]\text{Cl} + \text{NbCl}_5 \rightarrow 4\) should contribute to decrease the \(\Delta G\) variation of the process leading to 3.

The crystals of 3 exhibited insufficient solubility in suitable deuterated solvents, thus preventing the NMR characterization.

MCL\(_5\)/phosphorous pentachloride (MCL\(_5 = \text{NbCl}_5\), WCl\(_6\)). The carbonylic acid to acyl chloride conversion is an important preliminary step for the subsequent functionalization of \( \alpha \)-amino acids.²⁸ PCl\(_3\) has been traditionally employed as Cl source in order to obtain the relevant \( \alpha \)-ammonium acylchloride salts (Fischer procedure); the counterion is Cl⁻ or [PCl\(_6\)]⁻ depending on the employed PCl\(_3/\alpha\)-aminoacid molar ratio.²⁹ \( \alpha \)-Ammonium acylchloride species stable at room temperature have been obtained only with primary ammonium groups and in the absence of donor atoms within the side chain. On the other hand, in the case of the \( \alpha \)-proline derivative (secondary N), both Cl⁻ and [PCl\(_6\)]⁻ salts undergo quick degradation at room temperature, due to HCl release and subsequent condensation reactions.²⁹ Furthermore, the reactions of PCl\(_5\) with \( \alpha \)-N,N-dimethylphenylalanine (tertiary N), sarcosine (secondary N) and \( \alpha \)-methionine (thioether group), in \( \text{CH}_2\text{Cl}_2\), proceed with the formation of complicated mixtures of products (¹H and ³¹P NMR spectroscopy). Thus, the \( \alpha \)-N,N-dimethylphenylalanine and \( \alpha \)-methionine acylchloride derivatives have not been known heretofore, while the highly moisture sensitive [\(\text{NH}(\text{Me})\text{CH}_2\text{COCl}\)][WO\(_2\)Cl\(_5\)] has been recently obtained by ourselves from sarcosine/WCl\(_6\).³⁰

Some of us recently reported¹³b,²⁹ a straightforward and clean route to unusually stable salts of the acylchloride derivative of \( \alpha \)-proline, by combination of the traditional PCl\(_3\)-chlorinating reaction with the considerable stability imparted by the [MCl\(_5\)]⁻ (M = Nb, Ta) anions, Scheme 6.¹³b,²⁸,²⁹,³⁰

We reckoned that the easily available [NbCl\(_5\)]⁻ anion could provide stability also to other unstable/unknown \( \alpha \)-ammonium acylchloride cations (see above). Therefore, we tried to optimize
and generalize the synthetic procedure shown in Scheme 6. When a dichloromethane 1 : 1 molar mixture of PCl₅ and NbCl₅ was treated with L-N,N-dimethylphenylalanine or sarcosine, the subsequent ³¹P NMR analysis on the reaction solution evidenced the presence of POCl₃ as prevalent phosphorous species [singlet at 6.2 ppm (from PCl₅/NbCl₅/L-N,N-dimethylphenylalanine) and 5.6 ppm (from PCl₅/NbCl₅/sarcosine), respectively]. The corresponding [NbCl₆]⁻ cation, which has never been reported heretofore. The bonding parameters of the cation are comparable to those previously reported for other N₃-ammonium acylchloride salts, 5a-b, which were isolated at room temperature in 40–50% yields (Scheme 7). The presence of [NbCl₆]⁻ in 5a-b was unambiguously detected by a typical ⁹³Nb NMR resonance around 0 ppm. The structure of 5a was determined by X-ray diffraction (Fig. 4, Table 2). It contains the [PhCH₂CH(NHMe₂)⁺ COCl₂]⁻ cation, which has never been reported heretofore. Within crystals of 5a, some intermolecular N-H...Cl hydrogen bonds are present involving the ammonium group of the cation as donor and the chloride ligands of the anion as an acceptor. The bonding parameters of the cation are comparable to those previously reported for other N₃-ammonium acylchloride salts. Thus, the C(1)-O(1) distance [1.178(5) Å] corresponds to an almost pure double bond, whereas all the other contacts are typical for single bonds. The C(2) atoms displays an absolute S configuration with refined Flack parameter 0.03(2).

The iminium salt [PhCH₂=NMe₂][NbCl₆] (see Scheme 3) and the adduct NbCl₅(O=PCl₅), 6, identified by comparison of the crystal cell data with those reported in the literature, were obtained as minor products from NbCl₅/L-N,N-dimethylphenylalanine and NbCl₅/sarcosine, respectively.

The synthetic approach leading to 5a-b exploits the M-Cl (M = P, Nb) bond energy scale, making PCl₅ a preferential chlorinating agent respect to NbCl₅ and the stability of the [NbCl₆]⁻ anion. Similar considerations led us to test the PCl₅/WCl₆ mixture; it should be noted that anionic simple derivatives of WCl₆ (i.e., WCl₆, WOCl₅) have recently proposed as effective partners for the stabilization of otherwise reactive cations.

Hence, the reactions of PCl₅/WCl₆ (1 : 1 mixture) with L-proline, L-N,N-dimethylphenylalanine, sarcosine and L-methionine proceeded with PCl₅ to POCl₃ conversion (³¹P NMR), and straightforwardly afforded the respective N₃-ammonium acylchloride cations (Scheme 7). According to elemental analyses and magnetic measurements, the cations were isolated in good yields as [WCl₆]⁻ salts, 7a-b, respectively from PCl₅/WCl₆/ L-proline and PCl₅/WCl₆/L-N,N-dimethylphenylalanine. Otherwise, different anions were presumably associated with sarcosine and methionine derivatives, including [WOCl₅]⁻ (few crystals of [MeNH₂CH₂CH(Cl)=O][WOCl₅] were isolated and X-ray characterized) and W[n] species.

The characterization of the 1 : 1 mixture WCl₆/PCl₅ suggested that both chlorides remained intact when mixed together (see Experimental for details). This implies that the WCl₆ to WCl₅⁻ reduction, as clearly observed in 7a-b, is promoted by the α-amino acid. Analogous WCl₅ reduction has

Scheme 6 Stable pyrrolidinium-2-carbonylchloride salts from L-proline and MC₅ (M = Nb, Ta).

Scheme 7 Formation of otherwise unstable α-ammonium acylchloride cations from α-amino acids and niobium and tungsten chlorides.

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**Table 2** Selected bond lengths (Å) and angles (°) for 5a

| Bond/Angle | Nb(1)-Cl(1) | Nb(1)-Cl(2) | Nb(1)-Cl(3) | Nb(1)-Cl(4) | Nb(1)-Cl(5) | Nb(1)-Cl(6) | C(1)-O(1) | C(1)-C(2) | C(1)-N(1) | N(1)-C(2) | N(1)-C(3) | N(1)-C(4) | Cl(1)-Nb(1)-Cl(4) | Cl(1)-Cl(2)-Cl(5) | Cl(1)-Cl(3)-Cl(6) | O(1)-C(1)-Cl(7) | C(1)-C(2)-N(1) | C(2)-N(1)-C(4) | C(2)-N(1)-C(5) |
|------------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-----------|-----------|-----------|-----------|-----------|----------------|------------------|----------------|----------------|--------------|--------------|--------------|--------------|
| Nb(1)-Cl(1) | 2.3305(11)  | 2.3344(11)  | 2.3475(11)  | 2.4206(11)  | 1.728(5)    | 1.553(6)    | 1.500(6)   | 1.506(5)  | 1.499(5)  | 1.516(5)  | 1.516(5)  | 1.516(5)  | 174.23(5)       | 120.64(4)         | 111.4(3)        | 111.4(4)       | 111.4(4)     | 111.4(4)     | 111.4(4)     | 111.4(4)     |
been previously observed in a number of cases by interaction with organic compounds.\textsuperscript{38,39}

All the $\alpha$-ammonium acylchloride cations produced from PCl$_5$/NbCl$_5$ and PCl$_5$/WCl$_6$ were fully characterized by IR and NMR spectroscopy, and those cations derived from $\alpha$-N,N-dimethylphenylalanine and $\alpha$-methionine are reported here for the first time. The chloro-acyl moiety manifests itself by a strong IR absorption in the region 1765–1783 cm$^{-1}$, other than the $^{13}$C NMR resonance in the range 169.0–171.7 ppm.

**Reactivity of MCl$_n$ with $\alpha$-amino acid esters**

**Preparation of $\alpha$-amino acid ester hydrochlorides and $\alpha$-amino acid esters.** The $\alpha$-amino acid ester derivatives, 8, were prepared from the corresponding hydrochlorides, 8-HCl, which were in general isolated (Scheme 8). Although most of the compounds 8 and 8-HCl have been already appeared in the literature,\textsuperscript{40} we decided to collect their preparations and IR and NMR data in this paper, in view of possible modifications to the reported procedures or additional spectroscopic data.

**Reactions with niobium and tantalum pentahalides.** The reactions of $\alpha$-amino acid esters with NbF$_5$ are often non-selective, affording in most cases mixtures of products where the only recognizable compounds are the scarcely soluble ammonium ester salts [RCH(NH$_3$)COOR]'[NbF$_6$]. These might be formed as a consequence of some activation reaction or the adventitious presence of water.\textsuperscript{41} We were able to isolate satisfactory yields of well defined coordination compounds only in two cases (Scheme 9).

Compound 9 can be viewed as a coordination compound resulting from the unsymmetrical rupture of the structure of NbF$_5$ (a tetramer in the solid state\textsuperscript{17a,42} The IR spectrum shows a strong absorption at 1648 cm$^{-1}$, attributed to the stretching vibration of the C=O bond belonging to the ester function. The ca. 100 cm$^{-1}$ shift to lower wavenumbers is in agreement with the coordination of the carbonyl moiety to niobium. The shift of the absorptions due to the stretching of the amino group from 3380 cm$^{-1}$ (in 8k) to 3232 cm$^{-1}$ (in 9) suggests that also the nitrogen atom is involved in the coordination to the metal centre. Accordingly, two low field $^1$H NMR resonances have been found for the NH$_2$ group in 9 ($\delta$ = 8.6 and 7.0 ppm, CDCl$_3$ solution). On the other hand, the same group
gives rise to a singlet at 1.65 ppm in the ¹H NMR spectrum of 8k.

In addition, the ¹F and ⁹³Nb NMR spectra (deacet at 103 ppm and septet at -1553 ppm, respectively) are unequivocal fingerprints for the presence of the [NbF₆]⁻ anion in solution.¹³e,⁴²,⁴³

In conclusion, on considering the tendency of NbF₅ to the unsymmetrical breaking of the Nb–F bridges, with formation of [NbF₄]⁺ cations and [NbF₆]⁻ anions,⁴² analytical and spectroscopic data suggest that 9 is a salt containing an octacoordinate [NbF₅(Me₂CHCH₂CH₄NH₂CO₂Me)]²⁺ cation, comprising two O,N-ligated α-amino acid esters, and a [NbF₆]⁻ anion. The coordination number of the cation was confirmed by DFT calculations, being six-coordinate geometries less stable by more than 30 kcal mol⁻¹. The optimized geometry is shown in Fig. 5. DFT calculations with dichloromethane as implicit solvent also indicated that the [NbF₅(Me₂CHCH₂CH₄NH₂CO₂Me)]²⁺[NbF₆]⁻ salt is slightly more stable compared to its neutral isomer [NbF₅(Me₂CHCH₂CH₄NH₂CO₂Me)]. The metal centre in this last species should be eight-coordinated, the α-amino acid ester behaving as N,O-donor chelating ligand (Fig. S4†).

It worth noting that the majority of coordination complexes containing α-amino acid ester ligands are based on late transition metals (Ru, Os, Co, Rh, Pt, Zn).⁴⁴ Only few examples are known with group 6 elements⁴⁵ and also derivatives of group 4 and group 5 metals are very rare.

The reaction of NbF₅ with L-proline ethyl ester, 8b, revealed a different outcome, and 10 was obtained under the same conditions employed for NbF₅/8k. The use of Nb/8b molar ratio = 2 afforded 10 with the best yield (Scheme 9). Ethyl fluoride was NMR identified as a co-product of the reaction performed in CD₂Cl₂ in a closed tube, while L-proline was recovered after hydrolysis of the reaction mixture. These experimental facts support the presence in 10 of a carboxylato moiety originated from the cleavage of the ester function.

Compound 10 is a colourless solid whose salient spectroscopic features are two IR bands at 3381 cm⁻¹ (N–H) and 1636 cm⁻¹ (C=O), and ¹H and ¹⁹F NMR resonances at 11.77 ppm (NH) and 100.9 ppm ([NbF₄]⁻), respectively. These data suggest a bidentate N,O-coordination of the α-amino carboxylate ligand. Dinuclear geometries with the α-amino acidate as bridging ligand were ruled out by DFT calculations. The optimized geometry of the cation of 10 is depicted in Fig. 6 (see also Fig. S5 given as ESI†).

We extended the present study to the interaction of α-amino acid esters with the heavier niobium pentachlorides. These reactions led to complicated mixtures of metal products, with presumable activation of the organic substrates. Only in a few cases, all involving the metal pentachlorides, a clean reaction pathway was observed (Scheme 10).

All the identified products, 11a-d and 12, are colourless to pale yellow solids, being scarcely soluble in organic solvents. Spectroscopic considerations discussed for 10 are valid also for 11a-d, thus suggesting the bidentate N,O coordination of two α-amino acid ester ligands to the same metal centre within a cation. The presence of the [NbCl₆]⁻ anion in 11a-c is the consequence of unsymmetrical cleavage of the dinuclear NbCl₅ structure,¹³e,¹⁵,⁴⁶ and was unambiguously evidenced by a sharp ⁹³Nb NMR resonance occurring in the interval 4–13 ppm.¹³e,²¹

DFT calculations were carried out on the cation of 11a, considering either one or two α-amino acid esters in the niobium sphere. The coordination of another equivalent of the α-amino acid ester to [NbCl₅(Me₂CHCH₂CH₄NH₂CO₂Me)]⁻ resulted a favourable process, being the associated ΔG variation

Fig. 5 DFT-optimized geometry of the cation of 9 (C-PCM/M06 calculations). Selected computed bond lengths (Å): Nb–O 2.273, 2.273; Nb–N 2.364, 2.364; Nb–F 1.900, 1.900, 1.900, 1.900; C–O(Nb) 1.234, 1.234; C–O(Me) 1.303, 1.303; N–H 1.019, 1.019, 1.019, 1.020. Selected computed angles (°): O–Nb–N 68.3, 68.3; O–Nb–O 135.0; N–Nb–N 132.3; C–O–Nb 123.3, 123.3.

Fig. 6 DFT-optimized geometry of the cation of 10 (C-PCM/M06 calculations). Selected computed bond lengths (Å): Nb–O 1.902; Nb–N 2.243; Nb–F 1.833, 1.835, 1.857; C–O 1.365; C–O(Nb) 1.234; C–O(Me) 1.303, 1.303; N–H 1.019; N–H 1.022. Selected computed angles (°): O–Nb–N 73.5; O–Nb–F 97.7, 97.7, 147.3; C–O–Nb 131.0.

Scheme 10 Synthesis of niobium pentachloride derivatives of α-amino acid esters.
around −25 kcal mol⁻¹. The DFT-optimized geometry of [NbCl₄(Me₂CHCH₂CHNH₂CO₂Me)]⁺ cations and [NbCl₆]⁻ anions is reported in Table S2A. A crop of X-ray quality crystals of 12 was obtained directly from the reaction mixture after separation from 11a.

Compound 12 consists of an ionic packing of [NbCl₅(CH₃)₂CHCH₂CHNH₃CO₂Me)]⁺ cations and [NbCl₆]⁻ anions. The cation is represented in Fig. 8, and the related bonding parameters are reported in Table 3. A view of the structure of the anion is given in Fig. S6,† the relevant bonding parameters being collected in Table S2A.† H-bonds between the NH₃-group of the cation and the chlorides of [NbCl₆]⁻ are present within the crystals (see Table S2B† for details). Compound 12 crystallizes in the chiral space group P2₁, and the C(2) atom of the α-amino acid ester ligand displays S absolute configuration.

The source of protonation leading to 12 is not clear, being possibly the result of some activation of the organic reactant promoted by the strongly acidic niobium chloride. Nevertheless, the occurrence of fortuitous hydrolysis might play some role and should not be ruled out.

12 represents the second crystallographically characterized example where a cationic α-amino acid ester is coordinated to any metal centre, and the first one where the coordination occurs via oxygen. In fact, previous to this work, only the structure of a Ru(II) complex containing a η⁶-bonded 1-phenylalaninum methyl ester was reported. More commonly, α-amino acid esters act as ligands in the neutral form RCHNH₂·CO₂R’, via the N-atom or both N and O. More recently, a cationic α-amino acid ester bearing a peripheral OH group and potentially acting as a pincer ligand, 8h, i.e. a α-amino acid ester bearing a peripheral OH group and potentially acting as a pincer ligand. The 1 : 1 reaction of NbCl₅ and 8h in refluxing chloroform led to the formation of NbCl₄(OCHCH₂NHCOOiPr), 13, as a colourless precipitate. The ν(C=O) stretching band in 13 (1732 cm⁻¹) is only slightly shifted respect to 8h (1728 cm⁻¹), thus indicating that the ester group is not involved in coordination.

### Table 3

<table>
<thead>
<tr>
<th>Bond Distances (Å)</th>
<th>N(2)-Cl(7)</th>
<th>N(2)-Cl(8)</th>
<th>N(2)-Cl(9)</th>
<th>N(2)-Cl(10)</th>
<th>N(2)-Cl(11)</th>
<th>N(2)-Cl(12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3555(9)</td>
<td>2.3264(10)</td>
<td>2.3318(10)</td>
<td>2.2918(9)</td>
<td>2.3250(10)</td>
<td>2.2612(10)</td>
<td>2.2641(10)</td>
</tr>
</tbody>
</table>

The data relative to the [NbCl₆]⁻ anion are reported in Tables S2A and S2B.

Fig. 7 DFT-optimized geometry of the cation of 11a (C-PCM/M06 calculations). Selected computed bond lengths (Å): Nb–O 2.251, 2.266; Nb–N 2.377, 2.381; Nb–Cl 2.390, 2.382, 2.413, 2.414; C–O(Nb) 1.236, 1.237; C–O(Me) 1.294, 1.294; N–H 1.020, 1.021, 1.020, 1.021. Selected computed angles (°): O–Nb–N 68.4, 68.4; O–Nb–O 136.2; N–Nb–N 132.9; C–O–Nb 123.7, 123.8.

Fig. 8 ORTEP drawing of the [NbCl₄(CH₃)₂CHCH₂CHNH₂CO₂Me)]⁺ cation in 12. The [NbCl₄]⁻ anion is reported in Fig. S6.† Displacement ellipsoids are at the 50% probability level.

Fig. 9 DFT-optimized geometry of 13 (C-PCM/M06 calculations). Selected computed bond lengths (Å): Nb–O 1.873; Nb–N 1.943; Nb–Cl 2.359, 2.368, 2.389; N–H 1.019. Selected computed angles (°): O–Nb–N 76.0; O–Nb–N 93.3, 96.7, 157.8; N–Nb–Cl 82.0, 109.3, 110.0.
Compound 13 showed a single set of signals in $^1$H and $^{13}$C NMR spectra (in CD$_3$CN); $^1$H resonances are shifted to higher ppm values with respect to 8h [most notably $\delta$(NH) from 2.6 ppm in 8h to 7.0 ppm in 13], while $^{13}$C resonances are shifted to lower ppm values [e.g., $\delta$(CO) from 175 ppm in 8h to 167 ppm in 13].

At variance to the other $\alpha$-amino acid ester complexes of niobium in this work, compound 13 is a neutral species in solution with a single $^{93}$Nb resonance at $-493$ ppm. DFT calculations suggest a mononuclear structure (Fig. 9) as the most probable geometry. A positive Gibbs energy variation (about 3.5 kcal mol$^{-1}$) is accompanied to the dimerization of this species to the dinuclear form (see Fig. S7 and S8 for more details).

We could not cleanly isolate metal products from MBr$_5$/$\alpha$-amino acid ester (M = Nb, Ta). However, NMR investigations outlined the release of ethyl bromide from $\lambda$-proline ethylester, in the presence of MBr$_5$ (see Experimental for details).

**Conclusions**

The reactions of TiCl$_4$ with a series of $\alpha$-amino acids do not proceed with HCl release, in spite of the Lewis acidic character of the metal centre, and afford dinuclear coordination compounds containing zwitterionic ligands. Deprotonation of the ammonium function may be easily promoted by the addition of triethylamine, resulting in a modification of the coordination fashion of the $\alpha$-amino acic acid frame. On the other hand, the interaction of $\lambda$-proline with NbCl$_5$/NH$_2$Et$_2$ has provided the first example of C–C bond forming self-condensation of a $\alpha$-amino acid, although in modest yield. The overall transformation may be regarded as a Lewis acid-mediated intramolecular redox reaction, in which the carboxylate ion is reduced and the pyrrolidine ring is oxidized. The overall transformation may be regarded as a Lewis acid induced intramolecular redox reaction, in which the carboxylate ion is reduced and the pyrrolidine ring is oxidized. The overall transformation may be regarded as a Lewis acid induced intramolecular redox reaction, in which the carboxylate ion is reduced and the pyrrolidine ring is oxidized.

Solvents (Sigma-Aldrich) were distilled before use from appropriate drying agents. Chromatographic purification of organic products was carried out on columns of deactivated alumina (4% w/w water). Infrared spectra were recorded at 298 K on a FT IR-Perkin Elmer Spectrometer, equipped with a UATR sampling accessory. NMR spectra were recorded at 293 K on a Bruker Avance II DRX400 instrument equipped with a BBFO broadband probe. The chemical shifts for $^1$H and $^{13}$C were referenced to the non-deuterated aliquot of the solvent; the chemical shifts for $^{93}$Nb were referenced to external [NEt$_4$][NbCl$_6$]; the chemical shifts for $^{19}$F were referenced to external CFCl$_3$. Conductivity measurements were carried out using an Eutech Con 700 instrument (cell constant = 1.0 cm$^{-1}$). Magnetic susceptibilities (reported per W atom) were measured on solid samples at 298 K with a Magway MSB Mk1 magnetic susceptibility balance (Sherwood Scientific Ltd). Diamagnetic corrections were introduced according to König. Carbon, hydrogen and nitrogen analyses were performed on a Carlo Erba mod. 1106 instrument. The chloride/bromide content was determined by the Mohr method on solutions prepared by dissolution of the solids in aqueous KOH and heated at boiling temperature for 72 hours, followed by cooling to room temperature and addition of HNO$_3$ up to neutralization.

Titanium, niobium and tantalum were analyzed, respectively, as TiO$_2$ and M$_2$O$_3$ (M = Nb, Ta), obtained by hydrolysis of the samples followed by calcination in a platinum crucible.

**Experimental**

**General**

**Warning:** all the metal products reported in this paper are highly moisture-sensitive, thus rigorously anhydrous conditions were required for the reaction and crystallization procedures. The reaction vessels were oven dried at 140 °C prior to use, evacuated (10$^{-2}$ mmHg) and then filled with argon. TiCl$_4$, NbX$_5$ (X = F, Cl), PCl$_3$ and WCl$_6$ were purchased from Strem (>98% purity) and stored in sealed tubes under argon atmosphere. NbBr$_3$ and TaBr$_3$ were prepared according to literature procedures and stored under argon atmosphere. Once isolated, the metal products were conserved in sealed glass tubes under argon. The organic reactants were commercial products (Sigma-Aldrich) stored under argon atmosphere as received.

Reactions of TiCl$_4$ with $\alpha$-amino acids: synthesis of TiCl$_4$(aa)$\quad$ (aa = $\lambda$-proline, 1a; $\lambda$-phenylalanine, 1b; sarcosine, 1c; N,N-dimethylglycine, 1d)

**General procedure.** A suspension of the appropriate $\alpha$-amino acid (1.50 mmol) in CH$_3$Cl$_2$ (ca. 15 mL) was treated with a solution (100 mg mL$^{-1}$) of TiCl$_4$ (1.50 mmol) in heptane. The mixture was stirred at room temperature overnight, then hexane (ca. 30 mL) was added. The precipitate was separated and dried in vacuo.

TiCl$_4$(a-proline), 1a. Yellow solid, yield 321 mg (70%). Anal. calcd for C$_5$H$_9$ClNO$_2$Ti: C, 19.70; H, 2.98; N, 4.60; Cl, 46.52; Ti, 15.70. Found: C, 19.39; H, 3.09; N, 4.52; Cl, 45.88; Ti, 15.89. IR (solid state): $\nu = 3219$ mw, 2962 w, 1570 m, 1544 vs, 1441 vs, 1367 m, 1331 ms, 1260 m, 1081 m, 1031 ms, 798 s cm$^{-1}$. $^1$H NMR (CD$_3$CN): $\delta = 7.46, 7.15$ (br, 2H, NH$_2$); 4.53 (br, 1H, NCH); 3.54, 3.45, 2.42, 2.20, 2.06 (br, 6H, CH$_2$) ppm. $^{13}$C NMR (CD$_3$CN): $\delta = 176.1$ (OCO); 61.6 (CH); 47.6, 28.6, 23.7 (CH$_3$) ppm.

TiCl$_4$(a-phenylalanine), 1b. Light orange solid, yield 388 mg (73%). Anal. calcd for C$_8$H$_{11}$ClNO$_2$Ti: C, 30.46; H, 3.12; N, 3.95; Cl, 39.96; Ti, 13.49. Found: C, 30.60; H, 3.02; N, 4.13; Cl, 39.40; Ti, 13.28. IR (solid state): $\nu = 3030$ m-br, 1600 m, 1558 vs, 1445 vs-br, 1336 m, 1047 w, 744 m, 698 ms cm$^{-1}$. $^1$H NMR (CD$_3$CN): $\delta = 7.39-7.50$, 6.98 (8H, Ph + NH$_2$); 4.46 (m, 1H, CH); 3.28 (m, 2H, CH$_2$) ppm. $^{13}$C NMR (CD$_3$CN): $\delta = 170.0$ (OCO); 134.1 (ipso-H); 129.8, 129.2. Anal. calcd for C$_9$H$_{13}$ClNO$_2$Ti: C, 30.46; H, 3.12; N, 3.95; Cl, 39.96; Ti, 13.49. Found: C, 30.60; H, 3.02; N, 4.13; Cl, 39.40; Ti, 13.28. IR (solid state): $\nu = 3030$ m-br, 1600 m, 1558 vs, 1445 vs-br, 1336 m, 1047 w, 744 m, 698 ms cm$^{-1}$. $^1$H NMR (CD$_3$CN): $\delta = 7.39-7.50$, 6.98 (8H, Ph + NH$_2$); 4.46 (m, 1H, CH); 3.28 (m, 2H, CH$_2$) ppm. $^{13}$C NMR (CD$_3$CN): $\delta = 170.0$ (OCO); 134.1 (ipso-H); 129.8, 129.2; 127.9 (C$_6$H$_5$); 61.8 (CH); 35.3 (CH$_2$) ppm.

TiCl$_4$(sarcosine), 1c. Yellow solid, yield 448 mg (78%). Anal. calcd for C$_7$H$_{15}$ClNO$_2$Ti: C, 39.86; H, 2.53; N, 5.02; Cl, 50.87; Ti, 17.17. Found: C, 39.86; H, 2.43; N, 4.98; Cl, 36.23; Ti, 12.80. IR (solid state): $\nu = 3185$ m, 2930 vw, 2810 vw, 1757 ms, 1561 vs.
Reactions of TiCl₄ with α-amino acid/NEt₃: synthesis of [NHEt₃][TiCl₄(aa)] (aa = 1-phenylalanine, 2a; N,N-dimethylphenylalanine, 2b)

General procedure. A suspension of the appropriate α-amino acid (1.00 mmol) in CH₂Cl₂ (ca. 10 mL) was treated with a solution (100 mg mL⁻¹) of TiCl₄ (1.00 mmol) in heptane. The mixture was stirred at room temperature overnight, then hexane (ca. 30 mL) was added. The liquors were filtered off in order to remove a minor amount of solid, layered with hexane and settled at −30 °C. Red crystals of 2 were recovered after 48 h. Yield 56 mg, 12%. Anal. calc. for C₁₅H₂₆Cl₄N₂O₂Ti: C, 39.50; H, 5.87; N, 4.91; Cl, 48.26; Ti, 16.35. Found: C, 39.33; H, 5.87; N, 4.91; Cl, 48.43; Ti, 16.57. IR (solid state): ν = 3306 w, 3240 w (br, NH₂); 3138 m-s (br, CH₂); 2963 w-br, 2923 w-br, 2857 w, 2734 m-w, 2456 m-w, 2358 w, 1766 vs (OCO); 1702 s, 1660 vs, 1581 vs, 1454 vs, 1260 m, 1012 s, 937 w (CH); 4.13, 3.62 (br, 2H, NH₂); 3.26 (m, 6H, NCH₂); 3.40, 3.17 (dd, 4H, NCH₂); 2.81 (t, 2H, CH₂); 1.40 (t, 3H, NMe₂); 129.4, 129.2, 128.6, 126.6 (Ph); 75.6 (CH); 50.9, 47.6 (NMe₂); 47.5 (NCH₂); 30.8 (CH₂); 9.0 (SMe₂); 8.1 (NMe₂) ppm.

Reactions of NbCl₅ with 1-proline/NEt₃: synthesis and isolation of [NbCl₅(CH₂CH₂CONHR)] (R = Me, 3a; and [NbCl₅(CH₂CH₂CONHR)] (R = Ph, 3b)

Reaction of NbCl₅ with 1-proline/NEt₃: synthesis and isolation of [NbCl₅(CH₂CH₂CONHR)] (R = Me, 3a; and [NbCl₅(CH₂CH₂CONHR)] (R = Ph, 3b)

NbCl₅ (0.385 g, 1.42 mmol) and 1-proline (0.163 g, 1.42 mmol) were allowed to react in CH₂Cl₂ (20 mL). The solution was subsequently purged with nitrogen gas in order to remove released HCl. After six hours, the yellowish mixture was treated with NH₄Pr₂ (0.203 mL, 1.45 mmol), then the stirring was prolonged for additional 20 min. The final dark-red mixture was filtered off in order to remove a minor amount of solid, layered with hexane and settled at −30 °C. Red crystals of 3 were recovered after 48 h. Yield 56 mg, 12%. Anal. calc. for C₁₀H₁₂Cl₄N₂O₂Nb: 2.0, 2.2, 16.1; HCl, 0.41; Ti, 9.72. IR (solid state): ν = 3341 w, 2963 w, 2934 w (br, NH₂); 3138 m-s (br, CH₂); 2998 w-br, 2894 w-br, 2765 w-br, 2488 w-br, 1691 vs, 1652 vs, 1568 s, 1454 s, 1228 m, 1099 m-s, 1070 m-s, 749 vs, 702 s cm⁻¹. ¹H NMR (CD₃CN): δ = 7.76 (br, 1H, NH); 4.09 (br, 2H, CH₂); 3.01 (br, 6H, CH₂) ppm. ¹³C NMR (CD₃CN): δ = 6.30 (br, 1H, NH); 3.48 (m, 2H, CH₂); 1.31 (m, 12H, Me) ppm. ¹⁷O NMR (CD₃CN): δ = 47.7 (CH); 18.2 (Me) ppm. ¹⁷N NMR (CD₃CN): δ = −0.2 (Δν₃² = 95 Hz) ppm.

Reactions of α-amino acids with PCl₅/NbCl₅: synthesis of [(R)[MeNHCH₂C(O)Cl][NbCl₆]], [(R')[Me₂NHCH(CH₂Ph)C(O)Cl][NbCl₆]] (R = Me, 5a; R' = R = H, 5b)

General procedure. A suspension of PCl₅ (169 mg, 0.81 mmol) and NbCl₅ (220 mg, 0.81 mmol) in CH₂Cl₂ (10 mL) was stirred at room temperature for 2–3 h. Then the appropriate α-amino acid (0.81 mmol) was added. The resulting mixture was stirred at room temperature overnight, then hexane (ca. 30 mL) was added. The liquors were filtered off in order to remove a minor amount of solid, layered with hexane and stored in the freezer (−30 °C) for one week. A crop of crystalline material was collected and then stored at −30 °C. By slow evaporation of the crystallization solutions under inert atmosphere, few crystals of [PhCH₄CH₂NMe₂][NbCl₆] and NbCl₅(O-PCl₅), 6, were obtained from PCl₅/NbCl₅/CH₂Cl₂, respectively.

[Me₂NHCH₂C(O)Cl][NbCl₆] and NbCl₅(O-PCl₅), 6, were obtained from PCl₅/NbCl₅/CH₂Cl₂, respectively.
Reactions of \( \alpha \)-amino acids with PCl\(_5/WCl_6\): synthesis of [NH\(_2\)(CH\(_2\))\(_2\)CH(C=O)Cl][WCl\(_6\)], 7a, [Me\(_2\)NHCH(CH\(_2\))Ph(C=O)Cl][WCl\(_6\)], 7b, and [\( \{\{NH2\}CH(R)C(=O)Cl\}^\cdot\) (R = Me, R' = H; R = H, R' = CH\(_2\)CH\(_2\)SMe)

**General procedure.** A suspension of PCl\(_5\) (163 mg, 0.78 mmol) and WCl\(_6\) (310 mg, 0.78 mmol) in CD\(_2\)Cl\(_2\) (4 mL) was stirred at room temperature overnight. Then the appropriate \( \alpha \)-amino acid (0.78 mmol) was added. The resulting mixture was stirred at room temperature for 3 h. Thus, \(^{31}\)P NMR analyses revealed the presence of POCI\(_3\) as unique phosphorous species. In addition, \(^1\)H and \(^{13}\)C NMR analyses on PCl\(_5/WCl_6/\alpha\)-N,N-dimethylphenylalanine and PCl\(_5/WCl_6\)/sarcosine solutions pointed out the clean formation of 7a and [MeNH\(_2\)CH\(_2\)C(O)Cl][WCl\(_6\)]

These solutions were layered with hexane and stored at ~30 °C for a few days, thus resulting in the isolation of 7a and a mixture of [MeNH\(_2\)CH\(_2\)C(O)Cl][WCl\(_6\)] salts. In the cases of PCl\(_5/WCl_6/\alpha\)-methionine and PCl\(_5/WCl_6/\alpha\)-proline, dark solid materials precipitated, which were isolated from the respective yellow solutions and dried in vacuo.

In a different experiment, a 1 : 1 PCl\(_5/WCl_6\) mixture obtained in CD\(_2\)Cl\(_2\) (3 mL) was analyzed. \( \Delta M \) (CD\(_2\)Cl\(_2\)) = 0.3 S cm\(^{-1}\) mol\(^{-1}\).

\(^{31}\)P NMR (CD\(_2\)Cl\(_2\)): \( \delta = 81.1\) ppm (PCL\(_3\)) ppm. CI analysis was carried out on the solid residue obtained by removal of the volatiles in vacuo.

**Magnetic measurement:** diamagnetic.

\[\text{[NH}_2\text{(CH}_2\text{)}\text{2CH(C=O)Cl}][\text{WCl}_6]\], 7a. Green solid, yield 302 mg (73%) from PCl\(_5/WCl_6\)-proline. Anal. calc'd for C\(_{12}\)H\(_7\)Cl\(_2\)N\(_2\)O\(_2\): C, 50.66; H, 3.65; N, 16.10.

**In vacuo**

\[\text{Me}_2\text{NHC(H}_2\text{)CH(=O)Cl}}][\text{WCl}_6\text{], 7b. Dark yellow - brown solid, yield 280 mg (65%) from PCl\(_5/WCl_6/\alpha\)-N,N-dimethylphenylalanine. Anal. calc'd for C\(_{14}\)H\(_{13}\)Cl\(_2\)N\(_2\)O\(_2\): C, 50.0; H, 4.11; N, 16.55. CI, 46.72. Found: C, 50.10; H, 4.20; N, 16.41.**

**Solid state:**

\[\{\{NH}_2\}CH(R)C(=O)Cl\}^\cdot\] (R = Me, R' = H; R = H, R' = CH\(_2\)CH\(_2\)SMe). Brown solid, from PCl\(_5/WCl_6/\alpha\)-methionine. IR (solid state): \( \nu = 3350\) w-m (\( \nu = 3293\) m), 3008 w, 2921 w, 1779 s (\( \nu = 1677\) m), 1569 w, 1480 w, 1449 m-w, 1415 m, 1367 w-m, 1309 w, 1263 w, 1176 w, 1144 w, 1094 w, 1025 m, 964 vs, 897 s, 759 s, 733 m, 699 w, 661 w cm\(^{-1}\). Magnetic measurement: \( \chi_M = 7.08 \times 10^{-5}\) cm\(^3\) g\(^{-1}\).

**Synthesis of \( \alpha \)-amino acid ester hydrochlorides**

These compounds were obtained by a slight modification of the literature procedures.

**Procedure A (compounds 8a-d-HCl).** A 250 mL flask was charged with the appropriate alcohol (120 mL)/\( \alpha \)-amino acid (ca. 35 mmol) combination. SOC\(_2\) (12 mL, 170 mmol) was slowly added (3 h) to the suspension under vigorous stirring at room temperature. After 24 h stirring, volatiles were removed in vacuo at room temperature. The residue was suspended in Et\(_2\)O (50 mL) for 4 h. The suspension was filtered and the resulting solid was dried in vacuo at 40 °C.

**Procedure B (compounds 8e-i-HCl).** SOC\(_2\) (10 mL, 138 mmol) was slowly added (30 minutes) at 0 °C to the alcohol (80 mL) in a 500 mL Schlenk tube. The solution was then allowed to reach room temperature and the \( \alpha \)-amino acid (24 mmol) was introduced. The mixture was refluxed for 8 h and a pale yellow solution was obtained. Afterwards, the volatiles were removed in vacuo and the residue was suspended in Et\(_2\)O (50 mL) for 2 h. The suspension was filtered and the resulting solid was dried in vacuo at 40 °C.

\( \nu \)-Proline methylester hydrochloride, \( \nu \)-HCl. Colourless solid, yield 97%. IR (liquid film): \( \nu = 3115\) w (\( \nu = 3055\) m), 2925 w (\( \nu = 2850\) m), 1755 m, 1564 m, 1442 m, 1391 m-s, 1089 m, 1015 m cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \( \delta = 10.68\) (br, 2H, NH\(_2\)), 4.51 (m, 2H, CH\(_2\)NCH\(_2\)), 2.48, 2.20, 2.10 (m, 4H, CH\(_2\)P), 1.1H (C=O)] NMR (CDCl\(_3\)): \( \delta = 169.3\) (C=O); 59.2 (CH); 53.6 (OCH\(_2\)), 46.0 (NCH\(_2\)), 28.7, 23.6 (CH\(_2\)P) ppm.

\( \nu \)-Proline ethylester hydrochloride, \( 8b \)-HCl. Colourless solid, yield 79%. \(^1\)H NMR (CDCl\(_3\)): \( \delta = 10.37\) (br, 2H, NH\(_2\)), 4.42 (1.1H, 1H, CH\(_2\)), 3.42 (d, 3H, OMe), 3.31, 3.19 (s, 6H, NMe\(_2\)), 1.83 (t, 8H, OHCH\(_2\)), 1.57 (C=O)] NMR (CDCl\(_3\)): \( \delta = 168.7\) (C=O); 62.9 (OCH\(_2\)), 59.2 (CH); 45.9 (NCH\(_2\)), 28.7, 23.6 (CH\(_2\)P).

\( \nu \)-Proline isopropylester hydrochloride, \( 8c \)-HCl. Colourless solid, yield 97%. \(^1\)H NMR (CDCl\(_3\)): \( \delta = 10.70\) (br, 2H, NH\(_2\)), 5.11 (sept, 3H, J = 6.2 Hz, 1H, OCH\(_2\)), 4.44 (m, 1H, CH\(_2\)NCH\(_2\)), 3.57 (m, 2H, NCH\(_2\)), 1.24 (br, 2H, NH\(_2\)), 1.19 (t, 8H, J = 6.2 Hz, 3H, OCH\(_2\)P), 1.07 (C=O)] NMR (CDCl\(_3\)): \( \delta = 168.3\) (C=O); 71.2 (OCH\(_2\)), 59.3 (CH); 46.1 (NCH\(_2\)), 29.0, 23.6 (CH\(_2\)P).

\( \nu \)-Phenylalanine methylester hydrochloride, \( 8d \)-HCl. Colourless crystalline solid, yield 83%. IR (solid state): \( \nu = 3091\) m-br (\( \nu = 2944\) m), 2944 w-sh, 2906 w, 2825 w, 2725 m, 1743 w, 1532 w, 1378 m, 1291 w, 1238 w, 1214 vs, 1146 m, 1119 m, 1084 s, 1061 m, 1033 w, 990 m, 934 m, 865 w, 760 n, 741 vs, 701 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \( \delta = 8.7\) (3H, NH\(_2\)), 7.31, 7.28 (m, 5H, Ph), 4.38

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10168 | RSC Adv., 2017, 7, 10158–10174
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(br, 1H, CH); 3.72 (s, 3H, OMe); 3.42 (m-br, 2H, CH2) ppm. $^{13}$C

$^1$H NMR (CDCl$_3$): $\delta = 169.2$ (C=O); 133.9 (ipso-Ph); 129.6, 129.0, 127.7 (Ph); 54.4 (CH); 53.0 (OMe); 36.3 (CH$_2$) ppm.

- L-Leucine ethyl ester hydrochloride, $8e$.$^{10}$H Colourless solid, yield 80%. $^1$H NMR (CDCl$_3$): $\delta = 8.5$ (br, 3H, NH$_3$); 4.26 (m, 2H, OCH$_2$); 4.07 (m, 1H, CH); 1.92 (m, 1H, CHMe$_2$); 1.83 (m, 2H, CH$_2$); 1.31 (m, 6H, CHMe$_2$); 1.23 (t, $^3$J$_{HH} = 6.85$ Hz, 3H, OCH$_2$CH$_2$) ppm. $^{13}$C$^1$H NMR (CDCl$_3$): $\delta = 169.9$ (C=O); 62.6 (OCH$_3$); 51.9 (CH); 39.5 (CH$_2$); 24.5 (CHMe$_2$); 22.2, 22.1 (CH$_2$Me) ppm. 14.0 (OCH$_2$CH$_2$) ppm.

- L-Leucine isopropyl ester hydrochloride, $8f$.$^{14}$H Colourless solid, yield 97%. $^1$H NMR (CDCl$_3$): $\delta = 8.50$ (br, 3H, NH$_3$); 5.10 (sept, $^3$J$_{HH} = 6.1$ Hz, 1H, OCH$_3$); 3.96 (q, $^3$J$_{HH} = 4.2$ Hz, 2H, CH$_2$); 1.26 (d, $^3$J$_{HH} = 6.1$ Hz, 6H, CHMe$_3$) ppm.

- L-Leucine ethyl ester hydrochloride, $8g$.$^{10}$H Colourless solid, yield 98%. $^1$H NMR (DMSO-d$_6$): $\delta = 8.51$ (br, 3H, NH$_3$); 5.71–5.52 (m, 1H, OH); 5.05–4.94 (m, 1H, CHMe$_2$); 4.04–3.98 (m, 1H, CH$_2$); 3.83–3.78 (s, 2H, CH$_2$OH + CHN); 1.26–1.21 (m, 6H, CHMe$_3$) ppm. $^{13}$C$^1$H NMR (DMSO-d$_6$): $\delta = 167.6$ (CO); 69.6 (CHMe$_2$); 59.5 (CH$_3$); 54.4 (CH$_3$); 21.5 and 21.4 (CH$_3$Me) ppm.

- Tyrosine isopropyl ester hydrochloride, $8h$.$^{10}$H Colourless solid, yield 71%. $^1$H NMR (DMSO-d$_6$): $\delta = 8.49$ (s, 1H, OH); 8.49 (br, 3H, NH$_3$); 7.01 (d, $^3$J$_{HH} = 8.2$ Hz, 2H, Ar); 6.71 (d, $^3$J$_{HH} = 8.2$ Hz, 2H, Ar); 4.88 (sept, $^3$J$_{HH} = 5.9$ Hz, 1H, OCH$_3$); 4.07 (t, $^3$J$_{HH} = 6.6$ Hz, 1H, CH$_2$); 3.00–2.83 (m, 2H, CH$_2$); 1.16 (d, $^3$J$_{HH} = 6.2$ Hz, 3H) and 1.06 (d, $^3$J$_{HH} = 6.2$ Hz, 3H, CHMe$_3$) ppm.

**Synthesis of $\alpha$-amino acid esters.** Three different procedures were adopted. Compounds $8a$–$g$ were prepared by treating the appropriate $\alpha$-amino acid ester hydrochloride with $\text{NH}_4\text{aq}$ as described in detail for $8a$. Compounds $8h$–$n$ were prepared by treating the appropriate $\alpha$-amino acid ester hydrochloride with $\text{NaOH}_{aq}$ as described in detail for $8h$. Compounds $8k$–$l$ were obtained directly from the appropriate alcohol/$\text{CH}_2\text{Cl}_2$ (2 × 20 mL) after filtration and the solvent was removed by distillation at 40 °C and p = 700 mbar. The product was obtained as a colourless viscous liquid, 1.11 g, yield 87%. IR (liquid film): $\nu = 3500–3100$ br, 3362 w, 3308 w, 2981 w, 2938 w, 2879 w, 1728 s (P(C=O)), 1595 w, 1468 w, 1455 w, 1384 w-sh, 1375 m, 1326 w, 1209 n, 1179 m, 1145 m, 1105 s, 1039 m, 933 m, 903 w, 849 w, 822 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta = 5.07$ (sept, $^3$J$_{HH} = 6.2$ Hz, 1H, OCH$_3$); 3.85 (dd, $^3$J$_{HH} = 10.2$ Hz, $^3$J$_{HH} = 2.5$ Hz, 1H, CH$_2$); 3.71 (dd, $^3$J$_{HH} = 10.7$ Hz, $^3$J$_{HH} = 5.8$ Hz, 1H, CH$_2$); 3.66–3.60 (m, 1H, CH$_2$); 2.59 (br, 3H, NH$_3$ + OH); 1.29–1.25 (m, 6H, CHMe$_3$) ppm. $^{13}$C$^1$H NMR (CDCl$_3$): $\delta = 173.3$ (CO); 68.8 (OCH$_3$); 63.9 (CH$_3$); 56.1 (CH$_2$); 21.7 (Me$_3$) ppm.

$^1$H NMR (CD$_3$CN): $\delta = 4.97$ (sept, $^3$J$_{HH} = 6.3$ Hz, 1H, OCH$_3$); 3.62–3.58 (m, 2H, CH$_2$); 3.38 (t, $^3$J$_{HH} = 4.8$ Hz, 1H, CH$_2$); 2.19 (br, 3H, NH$_3$ + OH); 1.23–1.20 (m, 6H, Me$_2$) ppm. $^{13}$C$^1$H NMR (CD$_3$CN): $\delta = 174.6$ (CO); 68.9 (OCH$_3$); 65.1 (CH$_2$); 57.3 (CH$_3$); 22.0 and 21.9 (Me$_3$) ppm. The compound was dissolved in CDCl$_3$ and stored in a graduated Schlenk tube under nitrogen. The

**Scheme 1**

- $\text{NaOH}_{aq}$ as described in detail for $8a$.
Reactions of NbF5 with x-amino acid esters

Synthesis and isolation of [NbCl₅(Me₆CHCH₂CHNH₂CO₂-)
Me₂] [NbCl₅], 11a, and [NbCl₅(Me₆CHCH₂CHNH₂CO₂-)
Me₂] [NbCl₅], 12. A suspension of NbCl₅ (199 mg, 0.736 mmol) in CH₂Cl₂ (15 mL) was treated with 8k (97 mg, 0.74 mmol). After 24 h stirring at room temperature, a pale orange solution was obtained. By addition of hexane, 11a was obtained as a colourless solid. Yield 130 mg (44% based on Nb). Anal. calc. for C₁₆H₂₁Cl₁₂N₂O₁₃Nb: C, 20.05; H, 3.08; N, 3.37; Cl, 42.68; Nb, 22.37. Found: C, 19.77; H, 3.18; N, 3.27; Cl, 42.36; Nb, 23.13.

Hydrolysis of a CD₃CN solution (0.6 mL) of 11a resulted in the formation of an abundant precipitate; a solution was separated whose ¹³C NMR analysis evidenced the presence of proline only.

In a different experiment, the reaction solution was set aside at ca. −30 °C for two weeks. Thus pale yellow crystals of 12 were collected. Yield 65 mg (25% based on Nb). Anal. calc. for C₁₇H₁₆Cl₁₁N₂O₂Nb₂: C, 23.33; H, 3.32; N, 3.73; Cl, 43.31; Nb, 25.74. Found: C, 23.06; H, 3.18; N, 3.69; Cl, 43.25; Nb, 25.74.

Synthesis of [NbCl₅(Me₆CHCH₂CHNH₂CO₂-)
Me₂] [NbCl₅], 11b, and [NbCl₅(Me₆CHCH₂CHNH₂CO₂-)
Me₂] [NbCl₅], 11c. These products were prepared by a procedure analogous to that described for 11a, from the appropriate niobium pentahalide (ca. 0.70 mmol)/x-amino acid ester combination.

11b. Colourless viscous solid, yield 73%. Anal. calc. for C₁₆H₂₃Cl₁₂N₂O₁₄Nb: C, 22.28; H, 3.99; N, 3.26; Cl, 41.28; Nb, 21.64. Found: C, 22.25; H, 4.06; N, 3.16; Cl, 41.70; Nb, 21.29.

¹³C NMR (CDCl₃): δ = 170.2 (C₁₄O), 165.4 (C₁₃O), 159.3 (CH₃); 148.9 (CH₂); 137.2 (CH₂); 130.4 (CH₂); 126.8 (CH₂); 103.8 (CH₃); 74.1 (CH₃); 73.6 (CH₃); 65.7 (OMe); 61.3 (NH₂); 51.1 (C₂H₅); 40.8 (C₂H₅); 38.6 (C₂H₅); 36.1 (C₂H₅); 34.0 (C₂H₅). ¹⁹F NMR (CDCl₃): δ = −280.9 (q, J= 66.5 Hz, NbF₅).

11c. Colourless solid, yield 70%. Anal. calc. for C₁₄H₂₄Cl₁₆N₂O₁₄Nb: C, 20.34; H, 3.17; N, 3.39; Cl, 42.88; Nb, 22.48. Found: C, 20.78; H, 3.15; N, 3.37; Cl, 42.78; Nb, 22.45.

Reactions of NbF₅ with x-amino acid esters

Synthesis of [NbF₅(Me₆CHCH₂CHNH₂CO₂-)
Me₂] [NbF₅], 8k. A suspension of NbF₅ (167 mg, 1.15 mmol) in CH₂Cl₂ (15 mL) was treated with 8k (167 mg, 1.15 mmol). After 24 h stirring at room temperature, a colourless solution was obtained. By addition of hexane (10 mL), 9 was obtained as a colourless solid, which was recovered by filtration and dried in vacuo at room temperature. Yield 185 mg (48%). Anal. calc. for C₁₇H₂₅F₆O₁₄Nb: C, 33.27; H, 4.54; N, 4.20; Nb, 27.89. Found: C, 33.17; H, 4.57; N, 4.18; Nb, 27.91.

IR (solid state): ν = 3332 w-br (ν₃C=O), 3241 w, 2959 w-m, 1641 m (ν₁C=O); 1572 s (ν₁C=N); 1473 m (ν₂C=N); 1392 m (ν₁C=O); 1383 m (ν₂C=O); 1315 m (ν₂C=O); 1285 m (ν₂C=O); 1267 m (ν₂C=O); 1163 m (ν₂C=O); 1127 m (ν₂C=O); 1093 s (ν₃C=O); 1035 m (ν₂C=O); 1017 m (ν₂C=O); 985 s (ν₃C=O); 927 w (ν₂C=O); 883 w (ν₂C=O); 841 w (ν₂C=O); 763 m (ν₂C=O).
The reactions of MBr₅ (M = Nb, Ta) mediated formation of EtBr from L-proline ethylester

C₃H₁₂Cl₂N₂Nb₂O₂

661.64

100(2)

Monoclinic

P2₁/c

6.7734(9)

18.4927

18.104(4)

103.854(2)

1515.1(10)

2.074

1.878

1.073

1.023

2.092/−1.392

0.769/−0.891

Synthesis of NbCl₅(OCH₂CHNHCO₂Me)

13. A suspension of NbCl₅ (258 mg, 0.954 mmol) and 8b (1.32 mL of a 0.72 M solution in CdCl₃, 0.95 mol) in CHCl₃ (8 mL) was refluxed for 3 h. Then, the mixture was allowed to cool to room temperature and the colourless solution was separated from the colourless precipitate. The solid was washed with CH₂Cl₂ (2 × 5 mL) and dried in vacuo. Yield 239 mg (66% based on Nb). Anal. calcd for C₆H₁₁Cl₃NNbO₃: Cl, 30.9. Found: Cl, 30.8.

X-ray crystallographic studies

Crystal data and collection details for 3, 4, 5a and 12 are reported in Table 4. The diffraction experiments were carried out on a Bruker APEX II diffractometer equipped with a CCD detector and using Mo-Kα radiation (λ = 0.71073 Å). Data were corrected for Lorentz polarization and absorption effects (empirical absorption correction SADABS). Structures were solved by direct methods and refined by full-matrix least-squares based on all data using F₃. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were fixed at calculated positions and refined by a riding model, except hydrogens bonded to N(1) in 4, 5a and 12 which were located in the Fourier map and refined isotropically using the 1.2 fold for 4 and 5a and 1.5 fold for 12. Uiso value of the parent N-atom. The N(1)–H distances were restrained to 0.93 Å (s.u. 0.02).

Computational studies

The computational geometry optimizations were carried out without symmetry constrains using the hybrid-GGA EDF2 functional, in combination with the 6-31G** basis set (ECP-based LANL2DZ basis set for elements beyond Kr). The "restricted" formalism was applied in all cases. The software used was Spartan 08. Further computational geometry optimizations were carried out without symmetry constrains, using the hyper-GGA functional M06, in combination with a polarized basis set composed by the 6-31G(d,p) set on the light atoms.
and the ECP-based LANL2TZ(f) on the metal centre.64 The CPCM implicit solvation model $\{\varepsilon = 9.08\}$ was added to M06 calculations.65 Gaussian '09 was used as software.66 All the stationary points were characterized by IR simulations (harmonic approximation), from which zero-point vibrational energies and thermal corrections ($T = 298.15$ K) were obtained.67 Vibrational simulation supported the interpretation of experimental IR data. Cartesian coordinates of the optimized geometries are collected in a separated $\text{xyz}$ file.

### Acknowledgements

The University of Pisa is gratefully acknowledged for financial support.

### Notes and references


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21 The combination of TiCl$_4$ with aromatic amines affords a mixture of two products, that could not be unambiguously characterized.

22 The reaction of the TiCl$_4$ - L-proline adduct affords a deep green, paramagnetic compound probably formed via activation reactions involving the amino acid ligand.


31 The analogous reaction PCl$_5$/NbCl$_5$/L-methionine proceeded with clean formation of POCl$_3$, and led to the isolation of a brown, solid product containing [NbCl$_6$]$,^-$, which could not be clearly identified.


53 The addition of water to the reaction mixtures facilitates the release of the organic material from the highly oxophilic metal species, and allows the spectroscopic identification of the former. This strategy has been successfully adopted by ourselves in previous works, having proved that H₂O is generally inert towards ligand activation reactions.¹⁸

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