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Synthesis of Titanium Complexes Supported by Carbinolamide- and Amide-Containing Ligands Derived from $Ti(NMe_2)_4$-Mediated Selective Amidations of Carbonyl Groups

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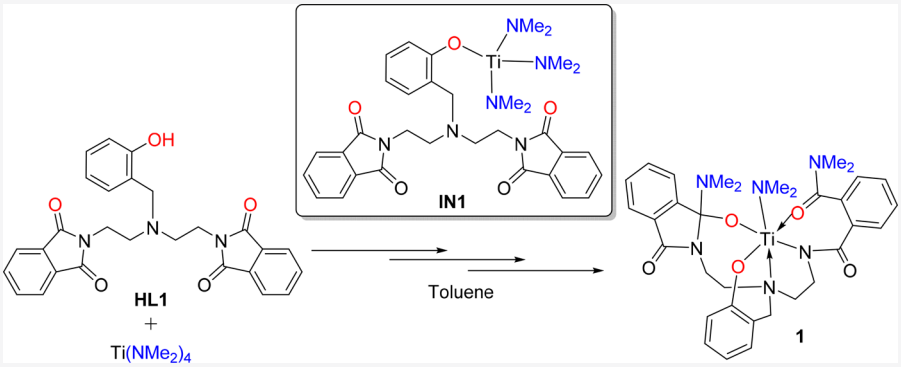

ABSTRACT: An efficient strategy for the syntheses of a series of titanium complexes has been developed. This protocol features the employment of $Ti(NMe_2)_4$ both as the metal center to trigger the deprotonation of the ligands and as an amine source to proceed the amidation reactions of carbonyl functionalities of the ligands. Treatment of $Ti(NMe_2)_4$ with a ligand HL1 (HL1 = 2,2′-(((2-hydroxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis(isoindoline-1,3-dione) results in the formation of $Ti(L1')(NMe_2)$ (**1**) (H_3L1' = N1-(2-((2-(1-(dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)(2-hydroxybenzyl)amino)ethyl)-N2,N2-dimethylphthalamide). One important feature regarding the synthesis of **1** is the occurrence of the *in situ* metal−ligand reaction between $Ti(NMe_2)_4$ and HL1, leading to the simultaneous formations of carbinolamide and amide scaffolds. Another prominent feature in terms of the preparation of **1** is the achievement of the selective ring-opening reaction of one of the two phthalimide units of the HL1 ligand, affording carbinolamide and amide functionalities within one ligand set. The developed methodology characterizes an ample substrate scope. The selective amidation reactions of the carbonyl groups have been realized for a series of analogous ligands HL2−HL7. Density functional theory calculations were employed to disclose the mechanisms for the formation of **1**−**7**, and the details for the selective ring-opening reactions of the phthalimide unit were uncovered.

INTRODUCTION

Titanium complexes continue to attract enormous interest from many groups around the world.[1−9] Such complexes have been employed as catalysts for a plethora of reactions including olefin polymerization,[10] Sharpless epoxidation,[11] hydroaminoalkylation,[12−15] aldol and allylic additions to carbonyl compounds,[16,17] carbonate formation from CO_2,[18] and multicomponent couplings.[19,20] Our recent studies revealed that $Ti(NMe_2)_4$ could mediate the *in situ* metal−ligand reactions,[21] affording the new nitrogen-containing compounds that could not be accessible via intuitive approaches.

Nitrogen-containing molecules are among the most important compounds possessing interesting physiological and biological activity. Most of pharmaceuticals contain nitrogen atoms.[22−26] As indicated in the "Top 200 pharmaceutical products by prescriptions in 2019",[27,28] most of pharmaceuticals are N-containing molecules. Thus, the researches for exploring versatile synthetic protocols for N-containing compounds continue to attract intense attention.[29−34]

Amide bond is a crucial functional group, which is ubiquitous in many important compounds, such as proteins, drugs, fertilizers, and plastics. Traditionally, amides are mainly prepared by amidation reactions of a range of starting materials including carboxylic acid derivatives,[35−41] aldehydes,[42−44] and alcohols.[45−50] Another two common methods for the synthesis of amides involve the hydrolysis of nitriles[51−54] and rearrange-

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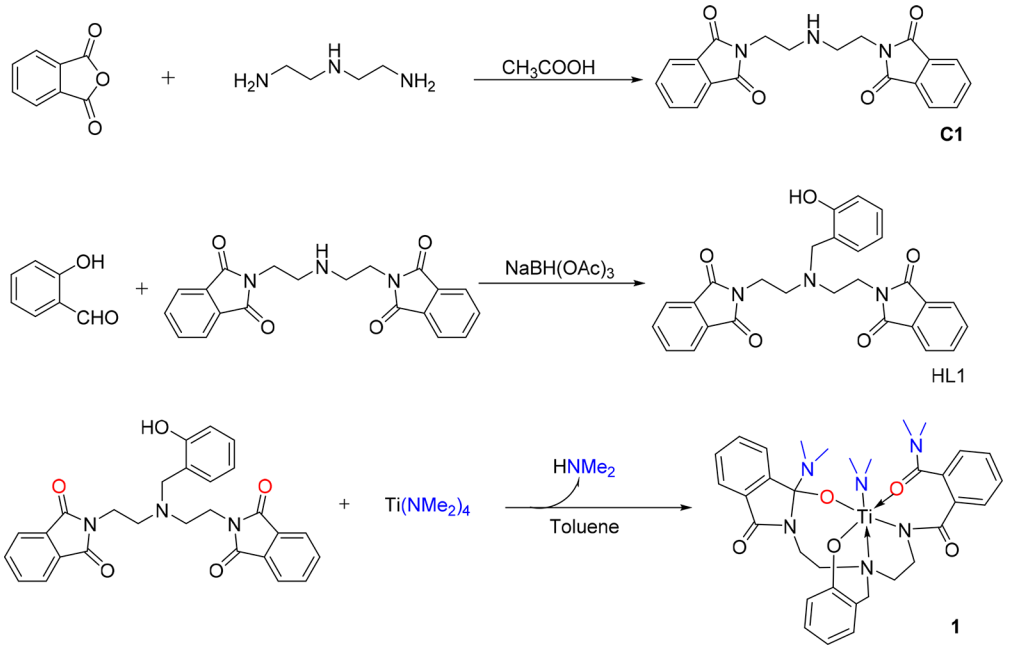
Scheme 1. Synthesis of Compound 1



ment of oxime.[55−57] Because of the broad applications of amides in both industrial and medicinal chemistry, the development of versatile methods for preparing amides is still an attractive research field.

Carbinolamide is the important structural motif present in small molecule natural products,[58−60] such as zampanolide[52,61] and ansamitocin.[62−64] Carbinolamide is conventionally prepared by the reaction of amide and aldehyde.[65−71] It plays vital roles in the activity of bicymycin.[72−75] Moreover, the unstable nature of carbinolamide renders it to be precursor for the preparation of more complicated N-containing compounds.[76]

Intrigued by the remarkable functionalities of amides and carbinolamides in various fields, we are interested in developing efficient protocols for preparing amides and carbinolamides. In this work, we demonstrate a new strategy that involving $Ti(NMe_2)_4$-mediated amidations of carbonyl groups (Scheme 1), achieving both amide and carbinolamide motifs in a one-pot reaction.

In our previous report, we disclosed that the $-NMe_2$ group of $Ti(NMe_2)_4$ could activate C−O bond.[21] We anticipate that the C═O bond and the C−N bond of an amide might be activated by the $-NMe_2$ group of $Ti(NMe_2)_4$ too. To examine this hypothesis, we selected a ligand 2,2′-(((2-hydroxybenzyl) azanediyl)bis(ethane-2,1-diyl))bis(isoindoline-1,3-dione) (HL1, Scheme 1) and conducted the reaction between $Ti(NMe_2)_4$ and HL1. Gratifyingly, activations of the C═O bond and the C−N bond of the amide proceeded smoothly, leading to the simultaneous formation of new amide and carbinolamide scaffolds (Scheme 1). The concept for the generation of the carbinolamide and the new amide scaffolds via $Ti(NMe_2)_4$-mediated amidations of carbonyl groups opens a new perspective for synthesizing bioactive molecules in a simple, efficient, and selective manner.

RESULTS AND DISCUSSION

Synthesis of 1. The chemistry of titanium complexes generated by the reactions between $Ti(NMe_2)_4$ and protonated ligands has been well developed.[2,77−80] It was found that $Ti(NMe_2)_4$ could mediate the C−N and C−C bond formation reactions.[21,81] Treatment of $Ti(NMe_2)_4$ with HL1 in toluene afforded (dimethylamido)titanium complex $Ti(L1')(NMe_2)$ (**1**) (Scheme 1, H_3L1' = N1-(2-((2-(1-(dimethyl amino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)(2-hydroxybenzyl)amino)-ethyl)-N2,N2-dimethylphthal-amide), which was isolated as a pure red solid after recrystallization in toluene.

Description of Crystal Structure of 1. Single-crystal X-ray diffraction studies reveal that complex **1** crystallizes in the triclinic $P\bar{1}$ space group (Table S1). The ORTEP representation of the structure of **1** is shown in Figure 1. The crystal structure of **1** exhibits several interesting features: (i) among four carbonyl groups (C10, C17, C22, and C25), only two carbonyl groups were involved in the reactions with $-NMe_2$ moiety; (ii) the ring-opening process only occurred in one five-

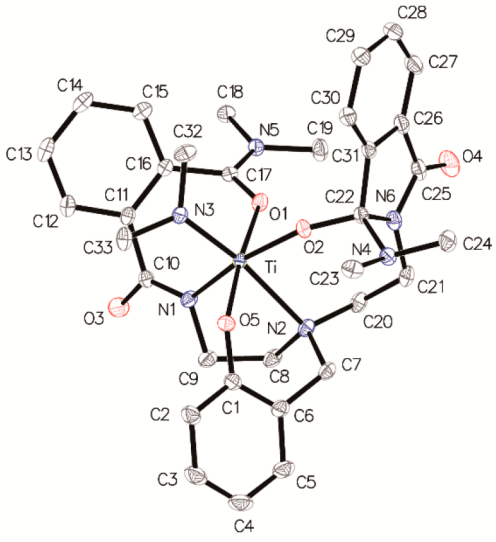


Figure 1. ORTEP representation of the structure of compound **1** (30% probability). Hydrogen atoms are omitted for clarity.

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Table 1. Selected Bond Lengths (Å) and Angles (deg) for Complexes 1−6

compound	1	2	3	4	5	6
Ti−O1	2.0736(11)	2.094(2)	2.108(3)	2.109(2)	2.1236(16)	2.089(4)
Ti−O2	1.8571(11)	1.836(2)	1.863(3)	1.855(2)	1.8584(15)	1.856(4)
Ti−O5	1.8844(11)	2.042(3)[a]	1.879(3)	1.883(2)	1.8721(16)	1.880(4)
Ti−N1	2.1152(13)	2.108(3)	2.108(3)	2.119(3)	2.1146(18)	2.109(4)
Ti−N2	2.4052(13)	2.369(3)	2.368(3)	2.379(3)	2.3717(18)	2.377(4)
O2−Ti−O1	85.95(5)	87.01(10)	84.20(11)	85.92(10)	86.32(6)	86.55(16)
O2−Ti−O5	97.64(5)	96.39(11)[b]	102.09(11)	100.29(11)	99.90(7)	99.39(18)
O5−Ti−O1	169.53(5)	163.38(11)[c]	166.54(11)	167.70(10)	167.53(6)	169.16(17)
O2−Ti−N1	160.22(5)	160.32(12)	158.33(12)	159.38(12)	159.53(7)	158.98(19)
O1−Ti−N1	81.74(5)	83.46(11)	80.92(11)	81.13(11)	81.25(7)	81.70(16)
O5−Ti−N1	92.03(5)	88.20(12)[d]	89.56(12)	89.81(11)	89.60(7)	89.83(18)

[a]Ti−N7. [b]O2−Ti−N7 [c]N7−Ti−O1. [d]N7−Ti−N1.

membered ring constructed by N1, C10, C11, C16, and C17, with the other five-membered ring being unaffected; (iii) the attack of one carbonyl (C17) group by $-NMe_2$ group led to the formation of a new amide, whereas the activation of another carbonyl (C22) motif initiated by $Ti(NMe_2)_4$ produced a carbinolamide moiety. Thus, the formations of two C−N bonds (C17−N5, C22−N4) and cleavage of a C−N bond (C17−N1) generated a new ligand $[L1']^{3-}$ as an unsymmetrical molecule. The metal center of **1** is hexacoordinated by three oxygen atoms and two nitrogen atoms from the $[L1']^{3-}$ ligand and one nitrogen atom from $-NMe_2$ group. The Ti^{IV} center displays distorted octahedron geometry. The bond length of Ti−O1 is 2.0736 Å, which is apparently longer than those of Ti−O2 (1.8571 Å) and Ti−O5 (1.8844 Å) bonds (Table 1).

Syntheses and Structures of 2−7. Motivated by the successful preparation of **1** which possesses intriguing structural features, we endeavored to expand the scope of the reaction. We next investigated the reactions of $Ti(NMe_2)_4$ with a series of ligands (HL2−HL7), with the results being summarized in Scheme 2. We introduced an electron-donating methoxy group at the ortho-, meta-, and para-positions of the hydroxyl group of phenol ring (HL3−HL5) and attached an electron-withdrawing chloride substituent at the meta- and para-positions (HL6 and HL7). It is interesting to find that the electronic natures of the substituents could not influence the ring-opening reactions and the formations of carbinolamides and amides, as characterized by X-ray diffraction studies. X-ray single-crystal diffraction analyses revealed that structures of **3**, **4**, **5**, and **6** are similar to that of **1** (Tables S1−S6). We failed to grow the crystal of **7**, whereas the characterization of **7** by NMR spectroscopy and elemental analysis indicated that it is isomorphous to **6**. To explore if the phenol moiety in the HL1 ligand could be replaced by other donors, 2,2′-(((1H-pyrrol-2-yl)methyl)azanediyl)bis(ethane-2,1-diyl)bis(isoindoline-1,3-dione (HL2) was synthesized. Transamination reaction between $Ti(NMe_2)_4$ and pyrrolyl motif of HL2 resulted in the formation of complex **2**. It was found that the selective activation of carbonyl groups and the ring-opening reaction occurred for the HL2 ligand as well, as confirmed by the X-ray crystal structure of **2** (Scheme 2).

Carbinolamides are important functionalities present in many bioactive molecules.[58−64] The broad scope of these transformations demonstrates the synthetic novelty of this work.

Hydrolysis Reaction. Intrigued by the discovery that carbinolamide and amide scaffolds were afforded in the preparation of **1**−**7**, we endeavored to isolate these *in situ* formed compounds via hydrolysis. As can be seen in Scheme 3, hydrolysis of **2** led to the production of compounds N1-(2-(((1H-pyrrol-2-yl)methyl)(2-(1-(dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)amino)ethyl)-N2,N2-dimethylphthalamide (**C2**) and N1-(2-(((1H-pyrrol-2-yl)methyl)(2-(1,3-dioxoisoindolin-2-yl)ethyl)amino)ethyl)-N2,N2-dimethylphthalamide (**C3**). The existences of **C2** and **C3** were confirmed by MS spectrometry and NMR spectroscopy of the mixture of **C2** and **C3**. However, they are hard to be separated by column chromatography due to the similar polarity of these two compounds.

Mechanistic Insights from DFT Calculations. Density functional theory (DFT) calculations[82] were carried out to better understand the experimental outcomes with the results given in Figures 2 and 3. It was proposed that the reaction should be initiated by deprotonation of the phenolic hydroxyl group in **HL1** with $Ti(NMe_2)_4$. In this process, the first formation of H-bonding complex **IN1** is endergonic by 18.0 kcal/mol. In **IN1** the proton is much closer to the N atom than to the O atom (N−H = 1.11 and O−H = 1.46 Å). The ligand displacement occurs via **TS1** with activation barrier of 21.3 kcal/mol from the starting materials. Alternatively, the direct addition of Ti-NMe_2 moiety to the carbonyl group in **HL1** would be much less favorable with a higher barrier of 26.8 kcal/mol (**TS1′**, given in the SI). From **TS1**, complex **IN2** and dimethylamine are formed exergonically by 10.6 kcal/mol (Figure 2). From **IN2**, the insertion of one carbonyl group of the phthalimide moiety into the Ti−N bond occurs via **TS2** with an activation barrier of 22.1 kcal/mol, affording the tetracoordinated complex **IN3** slightly endergonic. IRC calculations indicated that no pentacoordinated complex was formed prior to the insertion. From **IN3**, the C−N bond cleavage via **TS3** is very easy with a small barrier of 5.9 kcal/mol, opening the five-membered ring and forming hexacoordinated intermediate **IN4** exergonically. This could be transformed into **IN5** by an intramolecular ligand exchange prior to the incorporation of the other phthalimide moiety.[83] However, the second carbonyl insertion reaction via **TS4** would require a very high barrier of 39.8 kcal/mol from **IN4**, indicating the formation of a penta-coordinated intermediate **IN6** is impossible under the current conditions. Probably the high energy for this step originates from the steric effects, as the amino group has close interaction with both the phthalimide

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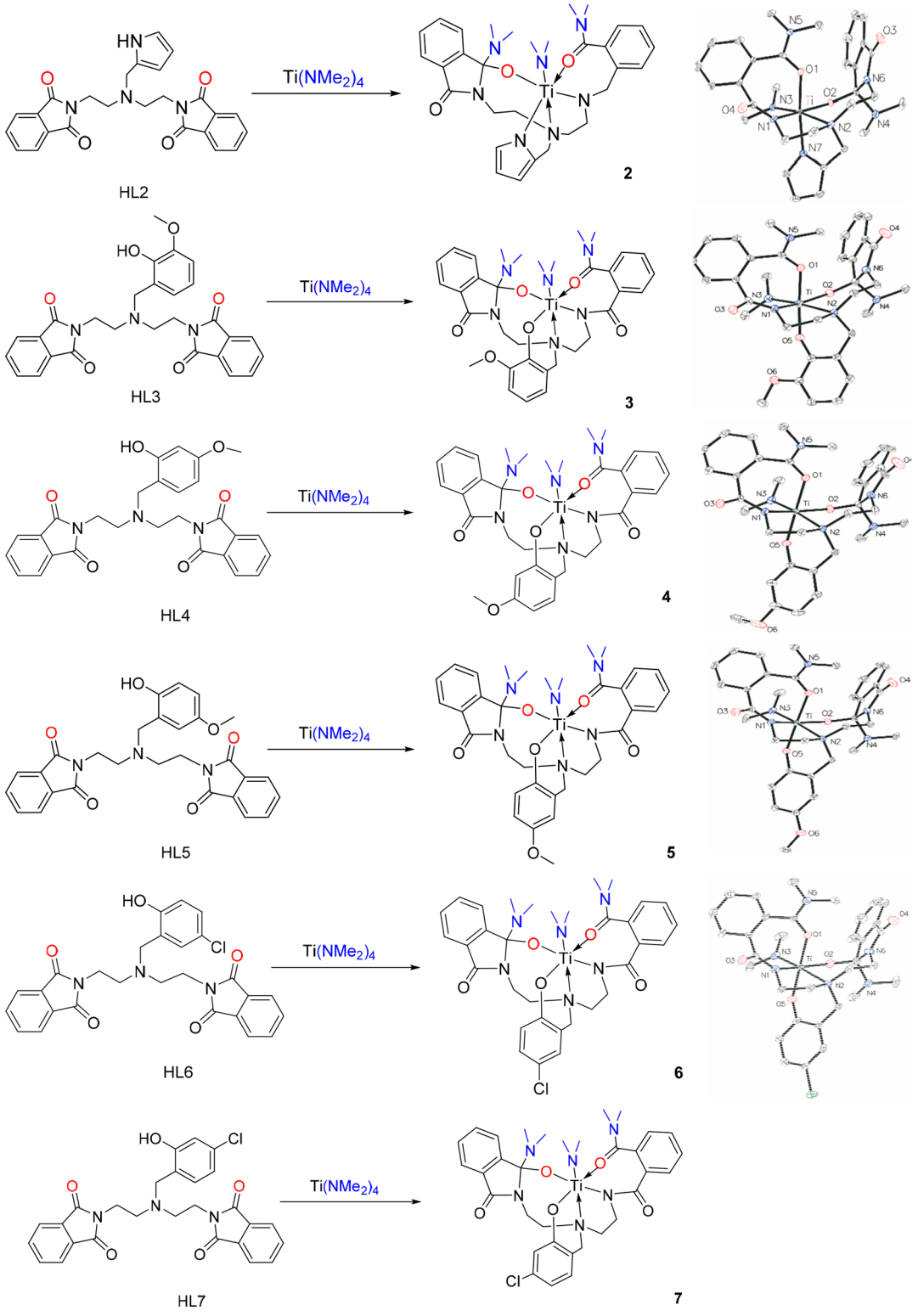
Scheme 2. Syntheses of Compounds 2−7



and benzamide moieties in **TS4**. Key structural parameters to show the steric effects in **TS4** are given in the SI.

According to the above energies, the transformation of **IN3** to **IN4** via **TS3** is very facile (5.9 kcal/mol) and exergonic, suggesting the complex **IN4** is first formed as a kinetic product. While further transformation of **IN4** via **TS4** is very difficult, its reversion to **IN3** via **TS2** is much easier with a barrier of 10.9 kcal/mol. We proposed that from **IN3**, the second carbonyl insertion could occur prior to the ring-opening process of the five-membered ring. As shown in Figure 3, from the hexa-coordinated intermediate **IN7**, which is slightly less stable than the tetra-coordinated **IN3**, the second carbonyl insertion via **TS5** is facile with a barrier of 10.1 kcal/mol from **IN3**. After the formation of penta-coordinated complex **IN8**, the ring-opening process of the five-membered ring via **TS6** requires a barrier of only 1.5 kcal/mol, leading to a highly

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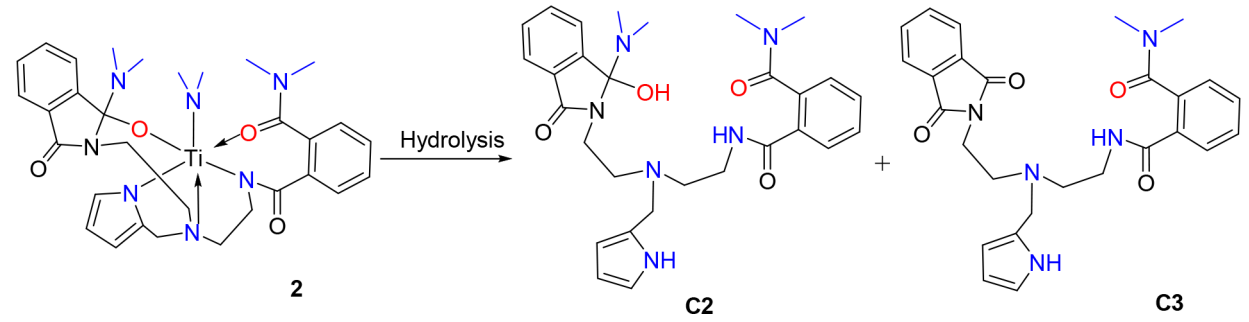
Scheme 3. Hydrolysis of 2



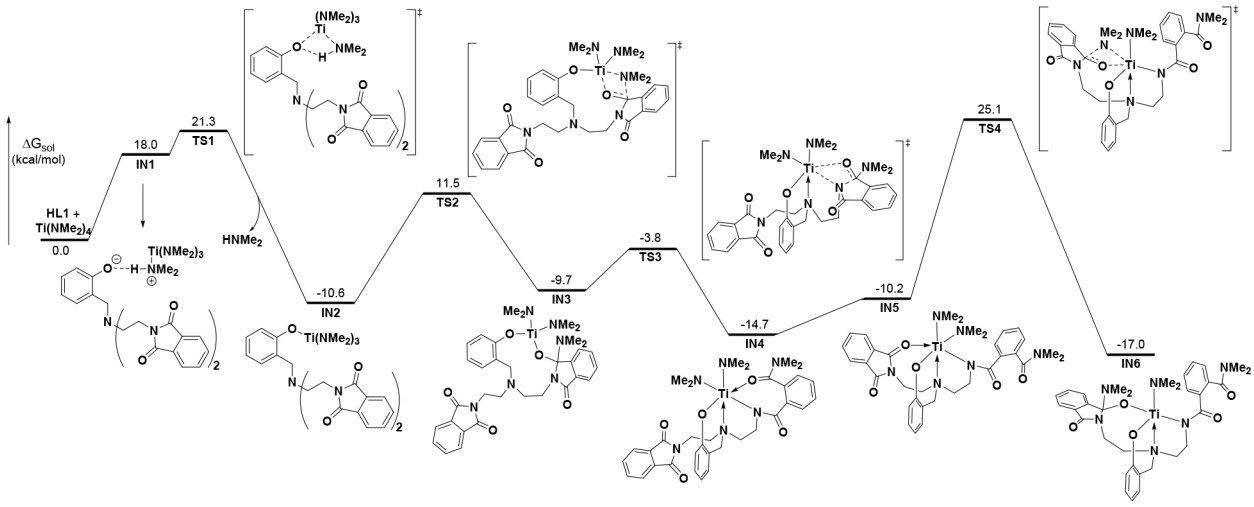


Figure 2. Possible formation of the penta-coordinated complex **IN6** by sequential carbonyl insertion, ring-opening C−N bond cleavage, and a second carbonyl insertion.[82]

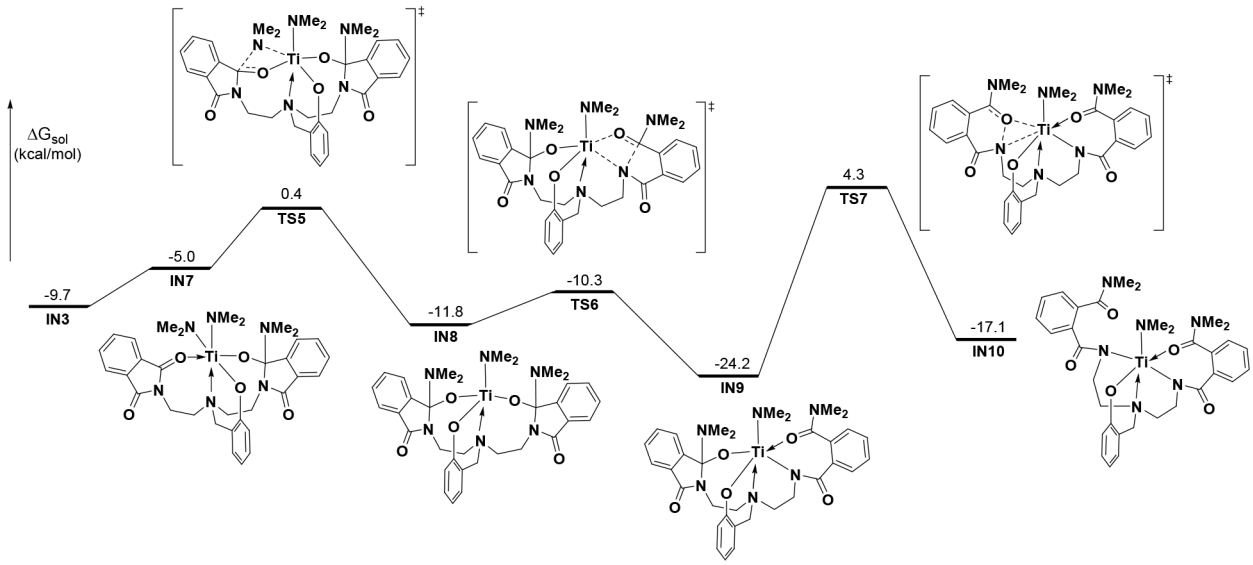


Figure 3. Energy profile explaining for the exclusive formation of compound **1** (**IN9**).[82]

exergonic hexa-coordinated complex **IN9**. The possible opening of the remaining five-membered ring in **IN9** was also evaluated, however, the energy for **TS7** is 28.5 kcal/mol above **IN9**, and the formed intermediate **IN10** is relatively unstable. While the high barrier for this process may result from the hepta-coordination nature of the Ti center in **TS7**, it is interesting to find that a slightly higher activation barrier is required for opening of the second ring (29.0 kcal/mol via **TS7′**, given in the SI) if dissociation of the carbonyl coordination in **IN9** occurs first. This could be attributed to a much closer interaction between the breaking C−N bond and Ti center in the latter case that causes more steric hindrance between the ligands, as revealed by detailed analysis of related geometries in the SI. Thus, the second carbinolamide

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moiety is retained in compound **1** (**IN9** in Figure 3), being in excellent agreement with the experimental observations.

CONCLUSION

In summary, the reactions of $Ti(NMe_2)_4$ with a series of monoanionic ligands HL1−HL7 bearing phthalimide scaffolds afforded titanium complexes **1**−**7**. The $Ti(NMe_2)_4$-mediated amidation reactions of carbonyl groups of the ligands occurred during the process for the formations of **1**−**7**, giving the new ligands $[L1']^{3-}$−$[L7']^{3-}$. The newly formed $[L1']^{3-}$−$[L7']^{3-}$ ligands bear the biologically active carbinolamide and amide moieties. The opening of one of two phthalimide units of HL1−HL7 is observed. The formation of **1** is ratified by DFT calculations. It is found that upon the insertion of the carbonyl group into the Ti−N bond, the ring-opening reaction of the first carbinolamide moiety is very facile. However, the ring-opening process for the second carbinolamide moiety is unfavorable in both thermodynamic and kinetic aspects.

EXPERIMENTAL SECTION

General Methods. All air- and moisture-sensitive reactions were carried out in an MBraun drybox under a dry nitrogen atmosphere. All solvents were dried over purple sodium benzophenone ketyl. $Ti(NMe_2)_4$ was purchased from Acros chemical and used as received. Elemental analyses for C, H, and N were carried out on a PerkinElmer 2400 analyzer. ^{1}H NMR spectra were recorded at the ambient temperature on Bruker Avance-III 400 and 600 MHz NMR spectrometer. ^{13}C NMR spectra were recorded at the ambient temperature on Bruker Avance-III 600 MHz NMR spectrometer.

Crystallographic Studies. The data collections of **1**−**6** were performed from a Bruker D8-Quest diffractometer equipped with a graphite monochromator utilizing Mo Kα radiation (λ = 0.7107 Å). A single crystal of suitable size was quickly wrapped with Paratone oil to prevent decomposition and was mounted on a glass fiber. The data were processed and reduced utilizing Bruker Apex III.[84] The crystal structures of **1**−**6** were solved by using the charge-flipping algorithm (program *SUPERFLIP*[85]) method and refined on F_0^2 using full-matrix least-squares method. All operations were done using the *OLEX2* interface.[86] For complex **2**, the crystals are very small, and the qualities of the crystals are not good. Thus, we cannot get satisfactory *R*(int) value for this compound. A small amount of spatially delocalized electron density could be found in the crystal lattice of compound **2**, but acceptable refinement results could not be obtained for this electron density. The *SQUEEZE* routine of *PLATON*[87] was used in the treatment of the solvent contribution, but the *R*(int) value is still high. Despite the difficulty in generating a lower *R*(int) value, the structure of complex **2** is unambiguous. All structures were examined using the Addsym subroutine of *PLATON*[88] to ensure that no additional symmetry could be applied to the models.

Syntheses of Ligands. *2,2′-(Azanediylbis(ethane-2,1-diyl))bis-(isoindoline-1,3-dione) (**C1**).* To a solution of phthalic anhydride (14.8 g, 0.1 mol) in acetic acid (80 mL) was added diethylenetriamine (5.2 g, 0.05 mol). The reaction mixture was heated to 135 °C for 2 h and then concentrated up to 10 mL. The concentrated solution was diluted by adding ethyl alcohol, and the resulting mixture was refluxed for 1.5 h to produce white precipitate. The white precipitate was collected by filtration and dried under vacuum.[89] Yield: 12.0 g (67%).

*2,2′-(((2-Hydroxybenzyl)azanediyl)bis(ethane-2,1-diyl))bis-(isoindoline-1,3-dione) (**HL1**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added salicylaldehyde (2.20 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced pressure to yield **HL1** as a white solid.[89] Yield: 6.92 g (82%).

*2,2′-(((1H-Pyrrol-2-yl)methyl)azanediyl)bis(ethane-2,1-diyl)bis-(isoindoline-1,3-dione) (**HL2**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added pyrrole-2-carboxaldehyde (1.71 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced pressure yielding **HL2** as a yellow solid. Yield: 6.21 g (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 8H, Ar^1-*H*, Ar^2-*H*), 6.15 (s, 1H, 2-C_4H_3N), 5.89 (s, 1H, 4-C_4H_3N), 5.85 (s, 1H, 3-C_4H_3N), 3.58 (t, 4H, $NCH_2CH_2NCH_2CH_2N$), 3.52 (s, 2H, $C_4H_3N-CH_2$), 2.67 (t, 4H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.48, 133.57, 132.26, 128.40, 122.96, 117.67, 107.99, 107.18, 52.64, 49.90, 35.96 ppm. Anal. calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.01; N, 12.66. Found: C, 67.48; H, 4.72; N, 12.56.

*2,2′-(((2-Hydroxy-3-methoxybenzyl)azanediyl))bis(ethane-2,1-diyl)bis(isoindoline-1,3-dione) (**HL3**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added 2-hydroxy-3-methoxybenzaldehyde (2.74 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced pressure yielding **HL3** as a white solid. Yield: 7.2 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, 4H, Ar^1-*H*, Ar^2-*H*), 7.69 (dd, 4H, Ar^1-*H*, Ar^2-*H*), 6.64 (d, 2H, 4,6-$C_6H_3(OCH_3)(OH)$), 6.57 (s, 1H, 5-$C_6H_3(OCH_3)(OH)$), 3.86 (d, 6H, $NCH_2CH_2NCH_2CH_2N$, $C_6H_3(OCH_3)(OH)$-CH_2), 3.60 (s, 3H, $C_6H_3(OCH_3)(OH)$), 2.93 (t, 4H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.13, 147.57, 146.00, 133.74, 132.13, 123.17, 122.12, 121.36, 119.11, 56.58, 55.76, 51.27, 34.90 ppm. Anal. calcd for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41. Found: C, 66.89; H, 4.68; N, 8.36.

*2,2′-(((2-Hydroxy-4-methoxybenzyl)azanediyl))bis(ethane-2,1-diyl)bis(isoindoline-1,3-dione) (**HL4**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added 2-hydroxy-4-methoxybenzaldehyde (2.74 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced pressure yielding **HL4** as a white solid. Yield: 6.54 g (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.75 (m, 4H, Ar^1-*H*, Ar^2-*H*), 7.71 (dd, 4H, Ar^1-*H*, Ar^2-*H*), 6.81 (d, 1H, 5-$C_6H_3(OCH_3)(OH)$), 6.29 (s, 1H, 3-$C_6H_3(OCH_3)(OH)$), 5.79 (s, 1H, 6-$C_6H_3(OCH_3)(OH)$), 3.87 (t, 4H, $NCH_2CH_2NCH_2CH_2N$), 3.80 (s, 2H, $C_6H_3(OCH_3)(OH)$-CH_2), 3.64 (d, 3H, $C_6H_3(OCH_3)(OH)$), 2.93 (t, 4H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.17, 160.49, 157.82, 133.78, 132.17, 129.56, 123.14, 113.66, 105.25, 101.67, 57.54, 55.05, 51.33, 34.82 ppm. Anal. calcd for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N 8.41. Found: C, 66.92; H, 4.73; N 8.40.

*2,2′-(((2-Hydroxy-5-methoxybenzyl)azanediyl))bis(ethane-2,1-diyl)bis(isoindoline-1,3-dione) (**HL5**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added 2-hydroxy-5-methoxybenzaldehyde (2.74 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced

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pressure yielding **HL5** as a white solid. Yield: 6.82 g (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, 4H, Ar^1-*H*, Ar^2-*H*), 7.71 (dd, 4H, Ar^1-*H*, Ar^2-*H*), 6.59 (s, 1H, 4-$C_6H_3(OCH_3)(OH)$), 6.51 (s, 1H, 6-$C_6H_3(OCH_3)(OH)$), 6.18 (s, 1H, 3-$C_6H_3(OCH_3)(OH)$), 3.88 (t, 4H, $NCH_2CH_2NCH_2CH_2N$), 3.83 (s, 2H, $C_6H_3(OCH_3)(OH)$-CH_2), 3.70 (s, 3H, $C_6H_3(OCH_3)(OH)$), 2.93 (t, 4H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.17, 152.63, 150.51, 133.78, 132.16, 123.15, 121.97, 116.47, 114.73, 113.99, 58.15, 55.64, 51.45, 34.79 ppm. Anal. calcd for $C_{28}H_{25}N_3O_6$: C, 67.33; H, 5.04; N, 8.41. Found: C, 66.97; H, 4.69; N, 8.38.

*2,2′-(((5-Chloro-2-hydroxybenzyl)azanediyl))bis(ethane-2,1-diyl)bis(isoindoline-1,3-dione) (**HL6**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added 5-chloro-2-hydroxybenzaldehyde (2.82 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced pressure yielding **HL6** as a white solid. Yield: 7.02 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86−7.63 (m, 8H, Ar^1-*H*, Ar^2-*H*), 6.98 (d, 1H, 6-C_6H_3(OH)Cl), 6.90 (s, 1H, 4-C_6H_3(OH)Cl), 6.19 (d, 1H, 3-C_6H_3(OH)Cl), 3.87 (dd, 6H, $NCH_2CH_2NCH_2CH_2N$, C_6H_3(OH)Cl−CH_2), 2.94 (t, 4H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.16, 155.44, 133.84, 132.10, 128.79, 128.66, 123.88, 123.17, 122.72, 117.26, 57.59, 51.47, 34.66 ppm. Anal. calcd for $C_{27}H_{22}ClN_3O_5$: C, 64.35; H, 4.40; N, 8.34. Found: C, 66.15; H, 4.06; N, 8.40.

*2,2′-(((4-Chloro-2-hydroxybenzyl)azanediyl))bis(ethane-2,1-diyl)bis(isoindoline-1,3-dione) (**HL7**).* To a solution of **C1** (6.53 g, 18 mmol) in 1,2-dichloroethane (200 mL) was added 4-chloro-2-hydroxybenzaldehyde (2.82 g, 18 mmol). The mixture was stirred for 10 min after which time $NaBH(OAc)_3$ (7.06 g, 0.032 mol) was slowly added. The resulting mixture was further stirred at room temperature for 24 h and was quenched by adding 80 mL of water. The organic components and water layer were separated, and the organic fraction was evaporated to afford a yellow oily product. The oil was extracted into methanol and filtered. The volatiles were removed under reduced pressure yielding **HL7** as a white solid. Yield: 6.91 g (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.71 (m, 8H, Ar^1-*H*, Ar^2-*H*), 6.71−6.63 (m, 2H, 3,5-C_6H_3(OH)Cl), 6.48 (dd, 1H, 6-C_6H_3(OH)Cl), 3.88 (dd, 6H, $NCH_2CH_2NCH_2CH_2N$, C_6H_3(OH)Cl-CH_2), 2.94 (t, 4H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.16, 157.52, 133.86, 132.10, 129.80, 123.18, 119.94, 119.57, 116.38, 57.50, 51.53, 34.74 ppm. Anal. calcd for $C_{27}H_{22}ClN_3O_5$: C, 64.35; H, 4.40; N, 8.34. Found: C, 66.11; H, 4.06; N, 8.38.

Synthesis of Compounds. *Ti(L1′)(NMe$_2$) (**1**) (H_3L1′ = N1-(2-((2-(1-(Dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)(2-hydroxybenzyl)amino)ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL1** (0.469 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.510 g (82%). Crystals suitable for X-ray crystallography were grown from a saturated toluene solution left standing at −35° in a vibration-free environment. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, 1H, 4-Ar^1-*H*), 7.73 (d, 1H, 2-Ar^2-*H*), 7.50−7.47 (m, 1H, 5-Ar^1-*H*), 7.31 (t, 1H, 3-Ar^1-*H*), 7.15 (t, 1H, 2-Ar^1-*H*), 7.12−7.07 (m, 3H, 3, 4, 5-Ar^2-*H*), 7.04 (d, 1H, 6-C_6H_4O), 6.80 (dd, 2H, 3,5-C_6H_4O), 6.70−6.67 (m, 1H, 4-C_6H_4O), 4.05 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.98 (dd, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.75 (t, 1H, NCH_2CH_2N CH_2CH_2N), 3.46 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.08 (s, 6H, NMe_2), 2.89−2.83 (m, 6H, $CONMe_2$), 2.75 (s, 2H, $C_6H_4O-CH_2$), 2.65−2.57 (m, 6H, $CONMe_2$), 2.21−2.19 (m, 1H, $NCH_2CH_2NCH_2CH_2N$), 2.13 (s, 2H, $NCH_2CH_2NCH_2CH_2N$), 1.80 (s, 1H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.13, 170.35, 166.88, 164.18, 163.19, 145.53, 141.33, 131.69, 131.14, 130.00, 129.82, 129.66, 129.50, 128.91, 128.52, 126.75, 125.09, 122.69, 120.42, 118.76, 106.00, 64.87, 62.35, 60.47, 50.12, 49.00, 47.94, 45.00, 41.25, 37.66, 37.01, 33.59 ppm. Anal. calcd for $C_{33}H_{40}N_6O_5Ti$: C, 61.11; H, 6.22; N, 12.96. Found: C, 60.77; H, 6.41; N 12.47.

*Ti(L2′)(NMe$_2$) (**2**) (H_3L2′ = N1-(2-(((1H-Pyrrol-2-yl)methyl)(2-(1-(dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)amino)-ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL2** (0.442 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.603 g (93%). Crystals suitable for X-ray crystallography were grown from a saturated THF solution left standing at −35° in a vibration-free environment. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (dd, 2H, 4-Ar^1-*H*, 2-Ar^2-*H*), 7.50 (s, 2H, 5-Ar^1-*H*, 5-Ar^2-*H*), 7.39 (d, 1H, 3-Ar^1-*H*), 7.20 (t, 1H, 2-Ar^1-*H*), 7.01 (s, 1H, 3-Ar^2-*H*), 6.86 (d, 1H, 4-Ar^2-*H*), 6.02 (s, 1H, 2-C_4H_3N), 5.80 (s, 1H, 4-C_4H_3N), 5.32 (d, 1H, 3-C_4H_3N), 4.26 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 4.13 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.85 (t, 1H, $NCH_2CH_2NCH_2$ CH_2N), 3.37 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.26 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.08 (s, 2H, $C_4H_3N-CH_2$), 2.88 (s, 6H, $CONMe_2$), 2.76−2.67 (m, 6H, $CONMe_2$), 2.51 (t, 1H, $NCH_2CH_2NCH_2$ CH_2N), 2.39 (t, 2H, $NCH_2CH_2NCH_2CH_2N$), 2.01 (s, 6H, NMe_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.53, 170.26, 166.95, 144.71, 142.10, 137.08, 131.58, 131.41, 131.17, 130.10, 128.82, 127.70, 127.10, 124.95, 124.59, 123.05, 122.29, 106.51, 106.10, 100.07, 66.76, 61.90, 55.87, 50.27, 45.54, 41.24, 37.31, 37.08, 34.28 ppm. Anal. calcd for $C_{31}H_{39}N_7O_4Ti$: C, 59.95; H, 6.32; N, 15.77. Found: C, 59.80; H, 5.81; N, 15.44.

*Ti(L3′)(NMe$_2$) (**3**) (H_3L3′ = N1-(2-((2-(1-(Dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)(2-hydroxy-3-methoxybenzyl)-amino)ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL3** (0.500 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.529 g (78%). Crystals suitable for X-ray crystallography were grown from a saturated THF solution left standing at −35° in a vibration-free environment. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, 1H, 4-Ar^1-*H*), 7.75 (d, 1H, 2-Ar^2-*H*), 7.50−7.48 (m, 1H, 5-Ar^1-*H*), 7.34 (t, 1H, 3-Ar^1-*H*), 7.24 (d, 1H, 2-Ar^1-*H*), 7.18−7.12 (m, 3H, 3, 4, 5-Ar^2-*H*), 6.85−6.82 (m, 1H, 6-$C_6H_3(OCH_3)O$), 6.79 (d, 1H, 5-$C_6H_3(OCH_3)O$), 6.70 (t, 1H, 4-$C_6H_3(OCH_3)O$), 4.06 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.98 (dd, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.88 (s, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.81−3.76 (m, 3H, $C_6H_3(OCH_3)O$), 3.49 (t, 1H, NCH_2CH_2N CH_2CH_2N), 3.12 (s, 6H, NMe_2), 2.96−2.89 (m, 6H, $CONMe_2$), 2.78 (s, 6H, $CONMe_2$), 2.35 (s, 2H, $C_6H_3(OCH_3)O-CH_2$), 2.13 (s, 2H, $NCH_2CH_2NCH_2CH_2N$), 1.86−1.84 (m, 1H, NCH_2CH_2 NCH_2CH_2N), 1.80 (s, 1H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.09, 170.22, 166.89, 154.28, 146.97, 145.64, 141.34, 131.68, 131.14, 129.95, 128.48, 126.70, 125.34, 125.23, 122.68, 121.78, 121.01, 120.12, 118.42, 113.10, 112.04, 106.05, 64.93, 62.23, 60.54, 60.12, 56.30, 55.93, 49.47, 48.69, 48.14, 44.94, 41.26, 37.78, 37.03, 33.62, 31.54, 22.60, 14.08 ppm. Anal. calcd for $C_{34}H_{42}N_6O_6Ti$: C, 60.18; H, 6.24; N, 12.38. Found: C, 60.82; H, 6.34; N, 12.09.

*Ti(L4′)(NMe$_2$) (**4**) (H_3L4′ = N1-(2-((2-(1-(Dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)(2-hydroxy-4-methoxybenzyl)-amino)ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL4** (0.500 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.536 g (79%). Crystals suitable for X-ray crystallography were grown from a saturated THF solution left standing at −35° in a vibration-free environment. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, 1H, 4-Ar^1-*H*), 7.74 (d, 1H, 2-Ar^2-*H*), 7.51−7.48 (m, 1H, 5-Ar^1-*H*), 7.33−7.31 (m, 1H, 3-Ar^1-*H*), 7.13−7.10 (m, 2H, 4, 5-Ar^2-*H*), 7.01 (d, 1H, 3-Ar^2-*H*), 6.93 (d, 1H, 2-Ar^1-*H*), 6.82 (d, 1H, 6-$C_6H_3(OCH_3)O$), 6.39−6.36 (m, 1H, 3-$C_6H_3(OCH_3)O$), 6.30−6.27 (m, 1H, 5-$C_6H_3(OCH_3)O$), 4.05 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 4.00−3.97 (dd, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.82 (s, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.76 (s, 3H, $C_6H_3(OCH_3)O$), 3.46 (t,

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1H, $NCH_2CH_2NCH_2CH_2N$), 3.08 (m, 6H, NMe_2), 2.92−2.87 (m, 6H, $CONMe_2$), 2.76 (s, 2H, $C_6H_3(OCH_3)O-CH_2$), 2.63−2.57 (m, 6H, $CONMe_2$), 2.40−2.38 (m, 1H, $NCH_2CH_2NCH_2CH_2N$), 2.15 (s, 2H, $NCH_2CH_2NCH_2CH_2N$), 1.81 (s, 1H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.15, 170.36, 166.88, 164.97, 163.96, 161.16, 145.50, 141.29, 131.70, 131.14, 130.00, 129.90, 129.68, 129.11, 128.98, 128.54, 128.44, 128.17, 126.79, 125.16, 122.70, 117.33, 105.97, 104.80, 101.60, 64.84, 62.25, 60.04, 55.25, 45.00, 41.26, 37.65, 37.03, 33.58, 31.54, 22.61, 14.08 ppm. Anal. calcd for $C_{34}H_{42}N_6O_6Ti$: C, 60.18; H, 6.24; N, 12.38. Found: C, 60.77; H, 5.92; N, 11.86.

*Ti(L5′)(NMe$_2$) (**5**) (H_3L5′ = N1-(2-((2-(1-(Dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)(2-hydroxy-5-methoxybenzyl)-amino)ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL5** (0.500 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.489 g (72%). Crystals suitable for X-ray crystallography were grown from a saturated THF solution left standing at −35° in a vibration-free environment. ^1H NMR (600 MHz, $CDCl_3$): δ 7.79 (dd, 1H, 4-Ar^1-*H*), 7.73 (d, 1H, 2-Ar^2-*H*), 7.47 (t, 1H, 5-Ar^1-*H*), 7.31 (t, 1H, 3-Ar^1-*H*), 7.13−7.08 (m, 3H, 3, 4, 5-Ar^2-*H*), 6.77−6.75 (m, 1H, 2-Ar^1-*H*), 6.73−6.70 (d, 2H, 3, 4-$C_6H_3(OCH_3)O$), 6.63−6.60 (m, 1H, 6-$C_6H_3(OCH_3)O$), 4.05 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 4.00−3.97 (m, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.75 (s, 3H, $C_6H_3(OCH_3)O$), 3.73−3.70 (m, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.46 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.09 (s, 6H, NMe_2), 2.93−2.89 (m, 6H, $CONMe_2$), 2.75 (t, 2H, $C_6H_3(OCH_3)O-CH_2$), 2.63−2.57 (m, 6H, $CONMe_2$), 2.32 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 2.13 (s, 2H, $NCH_2CH_2NCH_2CH_2N$), 1.79 (s, 1H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.12, 170.29, 166.88, 158.76, 157.72, 153.38, 131.67, 131.12, 129.97, 129.81, 128.97, 128.48, 128.16, 126.71, 125.68, 125.18, 122.67, 116.05, 115.84, 115.20, 113.41, 64.82, 62.41, 60.76, 60.32, 55.76, 50.04, 47.92, 44.91, 41.23, 37.66, 36.99, 33.58 ppm. Anal. calcd for $C_{34}H_{42}N_6O_6Ti$: C, 60.18; H, 6.24; N 12.38. Found: C, 59.88; H, 6.44; N, 11.85.

*Ti(L6′)(NMe$_2$) (**6**) (H_3L6′ = N1-(2-((5-Chloro-2-hydroxybenzyl)(2-(1-(dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)amino)-ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL6** (0.504 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.560 g (69%). Crystals suitable for X-ray crystallography were grown from a saturated THF solution left standing at −35° in a vibration-free environment. ^1H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, 1H, 4-Ar^1-*H*), 7.50−7.47 (m, 2H, 2-Ar^2-*H*, 5-Ar^1-*H*), 7.33 (t, 1H, 3-Ar^1-*H*), 7.21 (d, 1H, 2-Ar^1-*H*), 7.15−7.10 (m, 3H, 3, 4, 5-Ar^2-*H*), 7.03 (s, 1H, 6-C_6H_3ClO), 6.83 (d, 1H, 5-C_6H_3ClO), 6.59 (d, 1H, 3-C_6H_3ClO), 4.08 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 4.04 (dd, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.71 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.47 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.09 (s, 6H, NMe_2), 2.94−2.87 (m, 6H, $CONMe_2$), 2.77 (s, 2H, $C_6H_3OCl-CH_2$), 2.60−2.56 (m, 6H, $CONMe_2$), 2.33 (s, 1H, $NCH_2CH_2NCH_2CH_2N$), 2.13 (s, 2H, $NCH_2CH_2NCH_2CH_2N$), 1.82 (s, 1H, $NCH_2CH_2NCH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.14, 170.41, 166.87, 162.75, 145.37, 141.27, 131.63, 131.23, 130.09, 129.92, 129.57, 129.38, 129.21, 128.98, 128.62, 128.31, 128.17, 126.85, 126.51, 125.19, 122.79, 122.64, 117.38, 64.82, 62.33, 60.22, 47.94, 45.12, 41.30, 37.61, 37.06, 33.59, 21.42 ppm. Anal. calcd for $C_{33}H_{39}ClN_6O_5Ti$: C, 58.03; H, 5.76; N, 12.30. Found: C, 58.18; H, 5.78; N, 12.19.

*Ti(L7′)(NMe$_2$) (**7**) (H_3L7′ = N1-(2-((4-Chloro-2-hydroxybenzyl)(2-(1-(dimethylamino)-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)amino)-ethyl)-N2,N2-dimethylphthalamide).* To a solution of **HL7** (0.504 g, 1 mmol) in toluene was added a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in toluene (10 mL). After the solution was stirred for 24 h, the volatiles were removed under vacuum to give a red solid. Yield: 0.622 g (81%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.82 (dd, 1H, 4-Ar^1-*H*), 7.50−7.45 (m, 2H, 2-Ar^2-*H*, 5-Ar^1-*H*), 7.33 (t, 1H, 3-Ar^1-*H*), 7.13−7.09 (m, 2H, 4, 5-Ar^2-*H*), 7.03 (d, 1H, 3-Ar^2-*H*), 6.95 (d, 1H, 2-Ar^1-*H*), 6.82 (dd, 2H, 3, 4-C_6H_3ClO), 6.70−6.68 (m, 1H, 6-C_6H_3ClO), 4.06 (d, 1H, $NCH_2CH_2NCH_2CH_2N$), 4.00 (dd, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.72 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.45 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 3.08 (s, 6H, NMe_2), 2.90−2.84 (m, 6H, $CONMe_2$), 2.76 (s, 2H, $C_6H_3OCl-CH_2$), 2.64−2.56 (m, 6H, $CONMe_2$), 2.38 (t, 1H, $NCH_2CH_2NCH_2CH_2N$), 2.12 (s, 2H, $NCH_2CH_2NCH_2CH_2N$), 1.81 (s, 1H, $NCH_2CH_2N\ CH_2CH_2N$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.17, 170.47, 166.85, 164.53, 145.31, 141.22, 134.61, 131.23, 130.13−129.82 (m), 128.63, 126.88, 125.15, 123.59, 122.71, 118.33, 116.66, 106.02, 64.89, 62.30, 60.06, 59.61, 47.98, 45.13, 41.29, 37.59, 37.04, 33.56, 31.53, 22.60, 14.08 ppm. Anal. calcd for $C_{33}H_{39}ClN_6O_5Ti$: C, 58.03; H, 5.76; N, 12.30. Found: C, 58.60; H, 5.99; N 11.95.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c01831.

Text, tables, figure, and CIF files giving X-ray crystallographic details data, ^1H NMR spectrum, ^{13}C NMR spectrum for all and entry compounds and computational details and results (PDF)
(XYZ)

Accession Codes

CCDC 1978110−1978113, 1978116, and 2009683 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(83) No transition state was found for the direct transformation of **IN4** to **IN5**. Probably, the dissociation of the carbonyl ligand in **IN4** occurs first to form a pentacoordinated complex **IN4′** and then the coordination of the phthalamide to Ti forms **IN5**. The relative energy for **IN4′** is −13.4 kcal/mol, which is higher than **IN4** only by 1.3 kcal/mol.
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