ORGANOMETALLICS

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Rapid Access to Substituted Piperazines via $Ti(NMe_2)_4$-Mediated C−C Bond-Making Reactions

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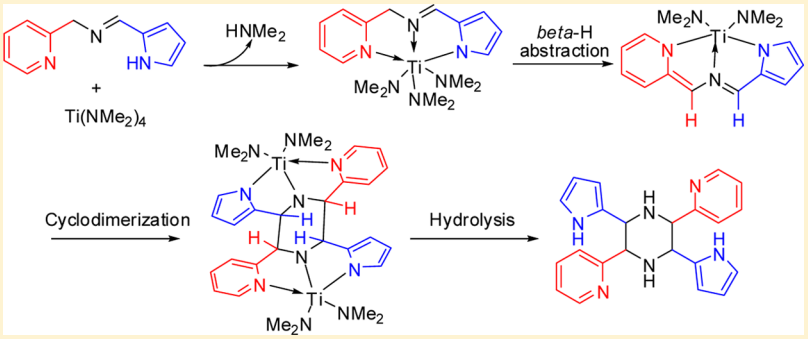
Supporting Information



ABSTRACT: An efficient $Ti(NMe_2)_4$-mediated C−C bond-forming methodology toward substituted piperazines, the basic skeleton of several biologically active natural products, has been developed. In reactions of tridentate monoanionic ligands bearing a $[-HCNCH_2-]$ linkage with $Ti(NMe_2)_4$, unusual [3 + 3] dimerized complexes through C−C coupling of the putative titanium aza-allyl complex intermediate could be obtained. These complexes contain substituted piperazine backbones and could give rise efficiently to substituted piperazine derivatives via hydrolysis. Treatment of $Ti(NMe_2)_4$ with a series of tridentate dianionic and bidentate monoanionic ligands bearing the $[-HCNCH_2-]$ moiety only generated chelated titanium complexes from ligand exchange reactions. Mechanistic studies using DFT/M06 calculations revealed that the methylene in the $[-HCNCH_2-]$ moiety of titanium complexes bearing tridentate monoanionic ligands could be deprotonated intramolecularly by dimethylamide anion with an activation energy of about 22 kcal/mol. The resulting titanium aza-allyl complexes from this β-H abstraction step then undergo a consecutive stepwise [3 + 2] cycloaddition/ring expansion reaction facilely to form the dimerized complex. However, β-H abstractions for Ti complexes bearing tridentate dianionic and bidentate monoanionic ligands were energetically demanding, as the negative charges could not be stabilized by the adjacent groups in the possible intermediates, explaining the experimental outcomes that no C−C coupled products were formed.

INTRODUCTION

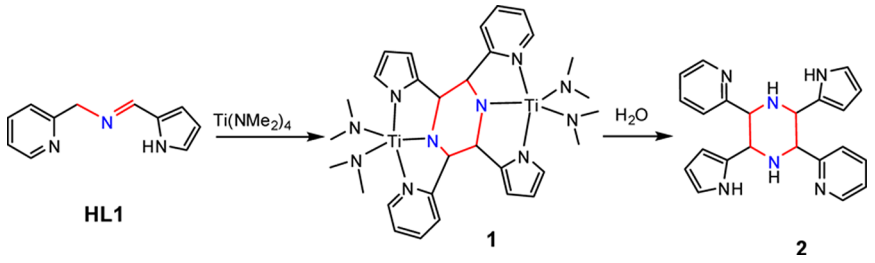
Carbon−carbon bond-making reactions mediated by transition metals are some of the most important transformations in organic and organometallic chemistry.[1] This process is of great academic and industrial significance for increasing molecular complexity and constructing natural products and extended polymeric structures from small organic compounds.[2] It has been documented that most stoichiometric and catalytic C−C bond-forming reactions mediated by middle and late transition metals typically follow oxidative addition, transmetalation and reductive elimination pathways that involve metal−carbon bonds,[3] whereas reactions mediated by group 4 metals occur mainly through σ-bond metathesis and migratory insertion, without requiring redox changes at the metal center.[4] Very few examples of redox reactions mediated by group 4 metals have been reported so far.[5]

Piperazine is the basic skeleton of a broad class of organic compounds,[6] which display a wide variety of biological activities, including antitumor,[7] antiviral,[8] antifungal,[9] and antibacterial.[10] In addition, a large number of piperazine compounds have been found to have anthelmintic action.[11] However, the piperazine is only obtained as a coproduct in the ammoniation of 1,2-dichloroethane or ethanolamine in industrial production.[12] The efficient synthesis of substituted piperazine often requires lengthy sequential synthesis, making the developments of diverse and efficient synthetic approaches highly desirable.

Received: January 12, 2012
Published: August 15, 2012

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

Scheme 1. Syntheses of Compounds 1 and 2



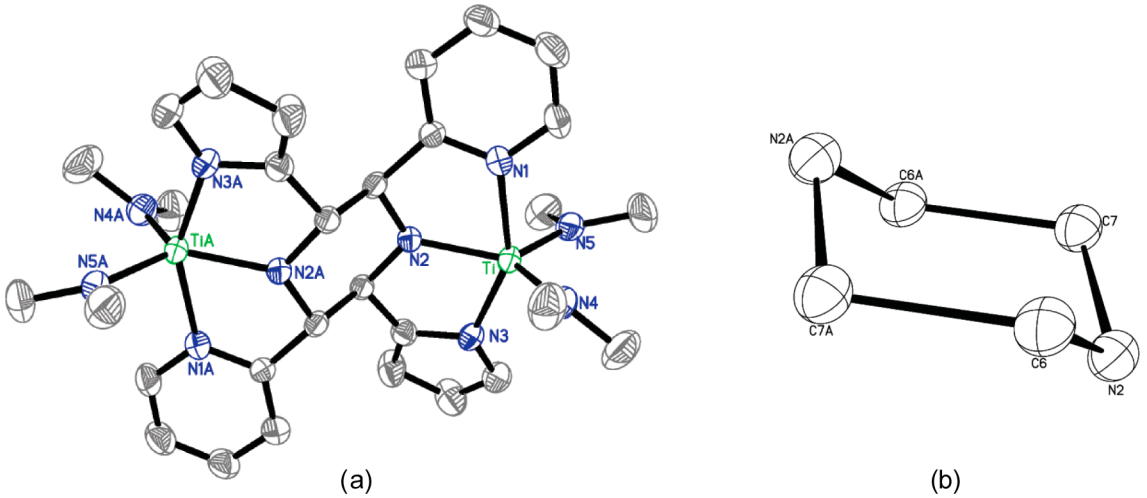


Figure 1. (a) ORTEP representation of the structure of $1{\cdot}2C_7H_8$ from X-ray diffraction (30% probability). Hydrogen atoms and solvate molecules are omitted for clarity. (b) Side view of the piperazine skeleton in $1{\cdot}2C_7H_8$, showing its chair configuration.

Recently Gibson et al. reported the syntheses of a series of group 4 metal complexes bearing Schiff base ligands and suggested that a C−C bond could be constructed from coupling of the $[-HCNCH-]^-$ moiety of the ligand without changing the oxidation state of Ti(IV).[13] This reaction leads to a dinuclear complex that is connected by a central piperazine ring. Despite a number of advantages of this protocol, the scope of the ligand is only limited to phenoxy(benzimidazolyl)imine, and the occurrence of the C−C bond-forming reaction is somewhat random. We proposed that the discovery of Gibson et al. could be employed as an efficient methodology for preparing substituted piperazines by using suitable tridentate monoanionic ligands. Thus, aiming at expanding the scope of the ligand, from which the titanium-mediated C−C bond-making reaction would occur, we have recently developed a method for the syntheses of substituted piperazines. By employing a series of rationally designed ligands containing the $[-HCNCH_2-]$ backbone, we have synthesized two substituted piperazines and a series of titanium complexes.

As a continuation of our ongoing efforts on group 4 metal mediated C−N and C−C bond construction,[14] in the current paper we describe the synthetic application, limitations, and DFT mechanistic study of the reactions between $Ti(NMe_2)_4$ and a series of tridentate and bidentate ligands with the $[-HCNCH_2-]$ linkage. This study provides an efficient method for the synthesis of substituted piperazines and discloses the factors that may control the reactivity of different proligands from both experimental and theoretical analysis.

RESULTS AND DISCUSSION

Synthesis of Substituted Piperazine from Proligand HL1. The chemistry of titanium complexes supported by pyrrolyl ligands has been well developed, and these complexes have been proven to be especially useful in mediating C−C and C−N bond formation.[15] The reaction of the pyrrolyl Schiff base ligand **HL1** (**HL1** = *N*-((1*H*-pyrrol-2-yl)methylene)-1-(pyridin-2-yl)-methanamine),[16] which contains the $[-HCNCH_2-]$ backbone, with $Ti(NMe_2)_4$ was explored. Treatment of $Ti(NMe_2)_4$ with 1 equiv of **HL1** in THF generated the unexpected dinuclear bis-(dimethylamido) titanium complex $(NMe_2)_2Ti(NC(C_4H_3N)$-$HC(C_5H_4N)HNC(C_4H_3N)HC(C_5H_4N)H)Ti(NMe_2)_2$ (**1**) (Scheme 1), which was isolated as a pure red solid after recrystallization in toluene.

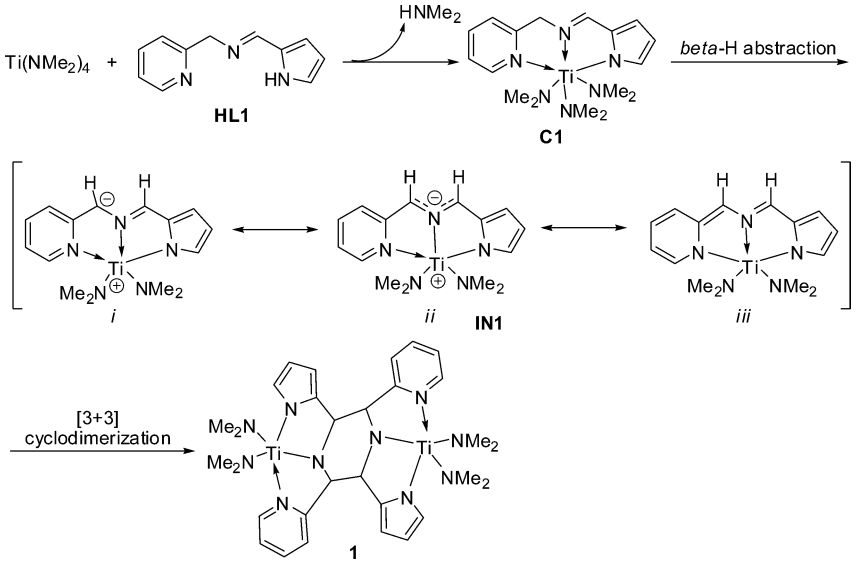
The crystal structure of $1{\cdot}2C_7H_8$ was determined by X-ray analysis, with an ORTEP representation of the structure of $1{\cdot}2C_7H_8$ being shown in Figure 1a and selected bond lengths and angles being summarized in Table 1. This complex exhibits approximate C_i symmetry and consists of two titanium(IV) ions,

Table 1. Selected Bond Distances (Å) and Angles (deg) from the X-ray Diffraction Study on $1{\cdot}2C_7H_8$

Ti−N(1)	2.181(4)	Ti−N(2)	1.964(4)
Ti−N(4)	1.879(5)	Ti−N(3)	2.036(4)
Ti−N(5)	1.896(5)	C(6)−C(7)#1	1.576(6)
N(2)−C(6)	1.452(6)	N(2)−C(7)	1.460(6)
N(4)−Ti−N(5)	109.8(2)	N(2)−Ti−N(1)	74.14(16)
N(4)−Ti−N(2)	123.6(2)	N(3)−Ti−N(1)	152.99(16)
N(5)−Ti−N(2)	125.6(2)	C(1)−N(1)−Ti	122.8(4)
N(4)−Ti−N(3)	105.5(2)	N(2)−Ti−N(3)	78.86(16)
N(5)−Ti−N(3)	97.6(2)	N(4)−Ti−N(1)	90.0(2)
N(5)−Ti−N(1)	97.68(18)		

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

Scheme 2. Plausible Mechanism



four dimethylamido groups, one bridging doubly deprotonated piperazine ring, and two solvated toluene molecules. The geometry around each titanium atom can be described as a distorted trigonal bipyramid, with the pyridyl and pyrrolyl nitrogens axial and the amido and piperazine nitrogens equatorial. As expected, the donor pyridine has the longest Ti−N(pyridine) bond of 2.186 Å in comparison with the bond lengths of Ti−N(pyrrolyl) and Ti−N(piperazine) and falls in the range of the previously reported Ti−N(pyridine) bond containing compounds (minimum 2.126 Å, maximum 2.450 Å for 317 examples in the CSD). The Ti−N(pyrrolyl) bond distance is 0.08 Å longer than the Ti−N(piperazine) bond.

The doubly deprotonated piperazine ring adopts a chair configuration (Figure 1b), with the newly formed C−C bond distance being about 1.58 Å (C6A−C7 = 1.576(6) Å) and a C−N bond length of 1.46 Å (C7−N2 = 1.460(6) Å), indicating that the C−C and C−N bonds in **1** are typical single bonds. The four atoms C6, C7A, C6A, and C7 are strictly coplanar.

It was found that complex **1** retained its structure in $CDCl_3$ solution. The ^{1}H NMR spectrum of **1** showed two doublets in the region of 4.18−4.22 and 4.38−4.40 ppm, which are assigned to the two groups of hydrogen atoms of the piperazine ring. A signal for the hydrogen of the R(*H*)C═NR fragment in $\mathbf{L1}^-$ was not observed, indicating the absence of a C═N bond in the complex.

Hydrolysis of **1** followed by filtering away the precipitate, drying the filtrates, and recrystallizing the resulting solid in ethanol gave the substituted piperazine 2,5-bis(pyridin-2-yl)-3,6-bis(1*H*-pyrrol-2-yl)piperazine (**2**) (Scheme 1). Compound **2** was characterized by NMR spectroscopic techniques and elemental analysis.

We propose that the dimerized complex **1** is formed via the plausible mechanism shown in Scheme 2. The hexacoordinated complex **C1** should be first formed from $Ti(NMe_2)_4$ and **HL1**. Then a β-H abstraction from the methylene moiety will generate **IN1**, which could be described as a titanium aza-allyl complex of mesomeric form *ii* or a structure of mesomeric form *iii* with a dearomatized pyridine moiety. Finally a [3 + 3] cyclodimerization of intermediate **IN1** forms complex **1**. Similar β-H abstractions were reported in the preparation of late-transition-metal aza-allyl complexes by Wolczanski and co-workers,[17] but no dimerization reactions were observed.

Reactions of $Ti(NMe_2)_4$ with Other Tridentate Dianionic and Bidentate Monoanionic Ligands. To expand the generality of the C−C coupling process, we next attempted the possible reactions of $Ti(NMe_2)_4$ with a variety of ligands containing phenol, benzenyl, furan, and tetrahydrofuran moieties, respectively, with the results being summarized in Scheme 3. It is interesting to find that no piperazine derivatives from Ti-mediated C−C coupling could be observed under these conditions, and only the complexes from ligand exchange reactions were obtained, as characterized by X-ray diffraction.

Treatment of $Ti(NMe_2)_4$ with 1 equiv of $\mathbf{H_2L2}$ ($\mathbf{H_2L2}$ = 2-(((1*H*-pyrrol-2-yl)methylimino)methyl)phenol) resulted in complex $Ti(\mathbf{L2})_2$ (**C-L2**), which contains one bis-ligated titanium center. This complex exhibits pseudo-octahedral geometry with one oxygen atom and one pyrrolyl nitrogen atom of the *mer*-$\mathbf{L2}^{2-}$ ligand trans. No deprotonation of the methylene moieties of tridentate dianionic ligands was observed.

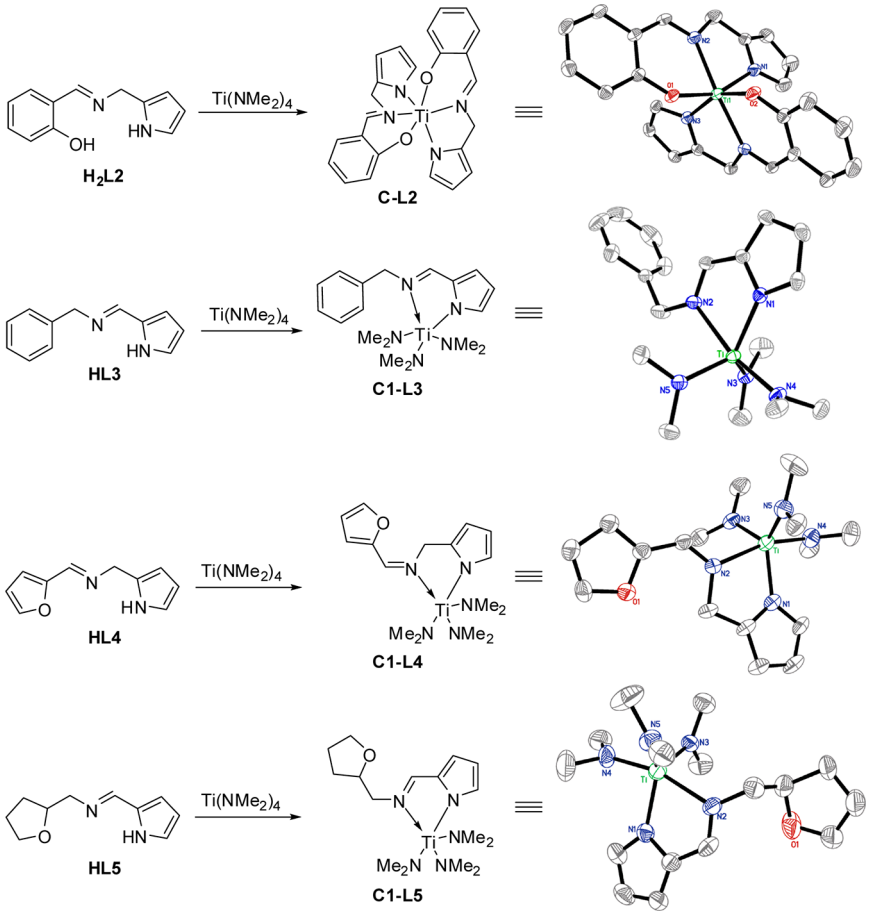
The reaction of the bidentate monoanionic ligand **HL3** (**HL3** = *N*-((1*H*-pyrrol-2-yl)methylene)-1-phenylmethanamine),[18] in which the pyridine donor of **HL1** was replaced by a phenyl group, with $Ti(NMe_2)_4$ gave $Ti(\mathbf{L3})(NMe_2)_3$ (**C1-L3**), which is a five-coordinate tris-amido complex with trigonal-bipyramidal geometry.

To explore if the pyridine in proligand **HL1** could be replaced by other donors, **HL4** (**HL4** = *N*-(furan-2-ylmethylene)-1-(1*H*-pyrrol-2-yl)methanamine) and **HL5** (**HL5** = (*S*,*E*)-*N*-((1*H*-pyrrol-2-yl)methylene)-1-(tetrahydrofuran-2-yl)methanamine) were synthesized. It was found that the furan and tetrahydrofuran moieties in these ligands did not coordinate to the titanium centers in the formed complexes $Ti(\mathbf{L4})(NMe_2)_3$ (**C1-L4**) and $Ti(\mathbf{L5})(NMe_2)_3$ (**C1-L5**). The trigonal-bipyramidal geometries show that one dimethylamido nitrogen atom and the imine nitrogen atom occupy the axial sites. Thus, both **HL4** and **HL5** serve as bidentate proligands similar to **HL3**. These suggest that the β-H abstraction step (Scheme 2) should be more favorable in the presence of tridentate monoanionic ligands.

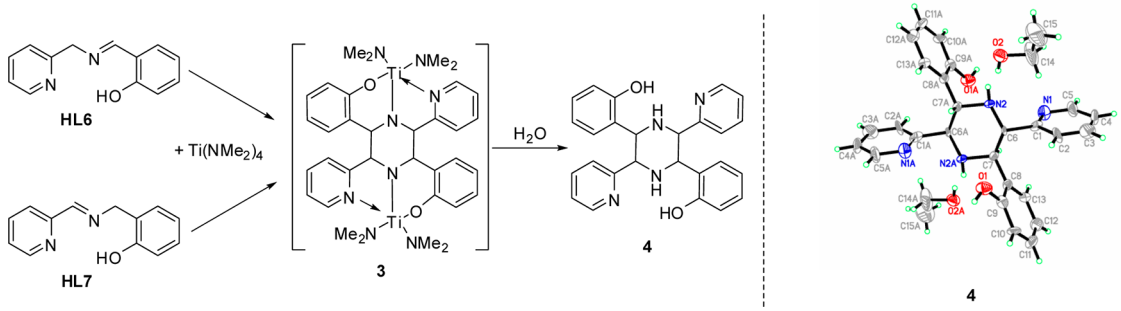
Synthesis and Structure of 2,2′-(3,6-Bis(pyridin-2-yl)piperazine-2,5-diyl)diphenol (4). The above results show that no β-H abstraction occurred for titanium complexes

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

Scheme 3. Syntheses of Complexes C-L2, C1-L3, C1-L4, C1-L5 and Their Structures from X-ray Diffraction



Scheme 4. Synthesis of 4



bearing tridentate dianionic and tridentate monoanionic ligands, and the only tridentate monoanionic ligand with a [−HCNCH$_2$−] backbone is reactive toward the formation of a piperazine skeleton. To test this, proligands **HL6** (**HL6** = 2-((pyridin-2-ylmethylimino)methyl)phenol)[19] and **HL7** (**HL7** = 2-((pyridin-2-ylmethyleneamino)methyl) phenol) were synthesized and subjected to the standard conditions. These compounds form tridentate monoanionic ligands by deprotonation of the phenol moiety.

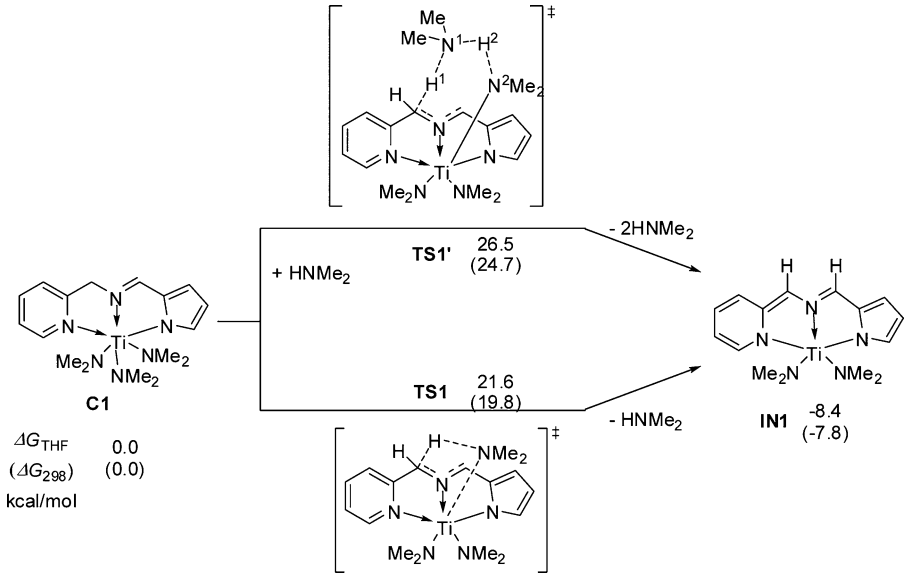
Treatment of Ti(NMe$_2$)$_4$ with 1 equiv of **HL6** (or **HL7**) generated a mixture of several indeterminable titanium complexes. Gratifyingly, both reactions generated the same substituted piperazine, 2,2′-(3,6-bis(pyridin-2-yl)piperazine-2,5-diyl)-diphenol (**4**), after hydrolysis (Scheme 4). This indicates that the same dinuclear titanium aza-allyl complex **3** was formed in both reactions of proligands **HL6** and **HL7**. The solid-state structure of product **4**·2EtOH (Scheme 4) revealed that the central piperazine ring has a chair conformation with the four carbon atoms perfectly coplanar.

Mechanistic Insights from DFT Calculations. DFT calculations[20] at the M06/6-31+G* (LANL2DZ for Ti) level[21] were carried out to better understand the experimental outcomes. This section will address the mechanistic problems of (1) how the β-H abstraction and [3 + 3] cyclodimerization occur, (2) the regiochemistry of the cyclodimerization process, and (3) why no similar piperazine derivatives were formed in the reactions of Ti(NMe$_2$)$_4$ with the bidentate monoanionic and tridentate dianionic ligands.

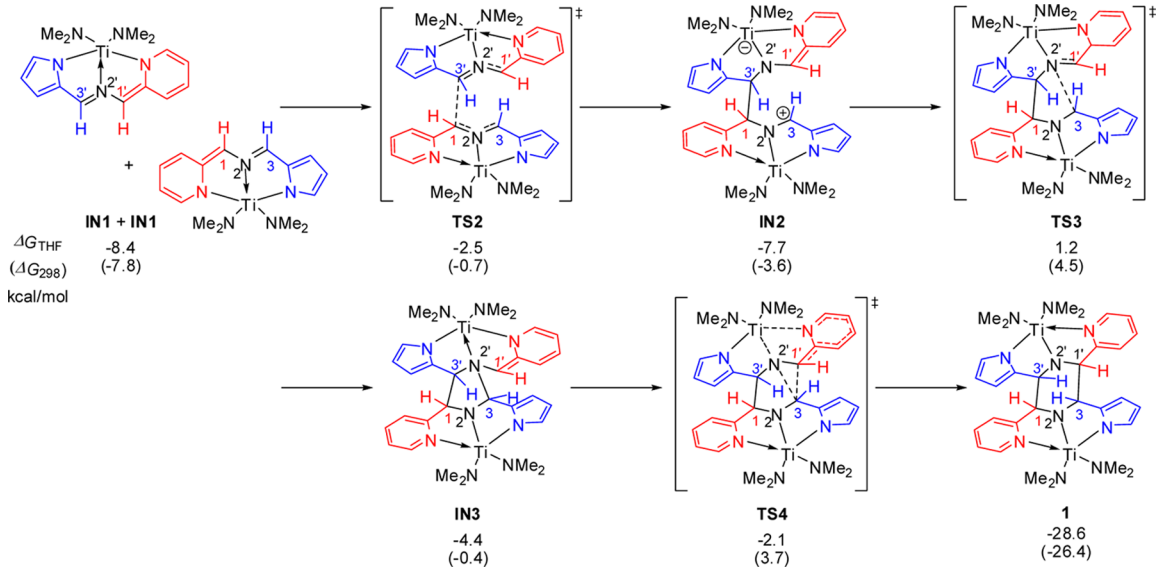
According to the plausible mechanism in Scheme 2, we first present the detailed mechanism for the reaction of **HL1** with Ti(NMe$_2$)$_4$. Theoretically, the β-H abstraction of **C1** could be completed via both inter- and intramolecular processes.

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

Scheme 5. Energies for Possible β-H Abstraction Pathways



Scheme 6. Mechanism for the Cyclodimerization of IN1



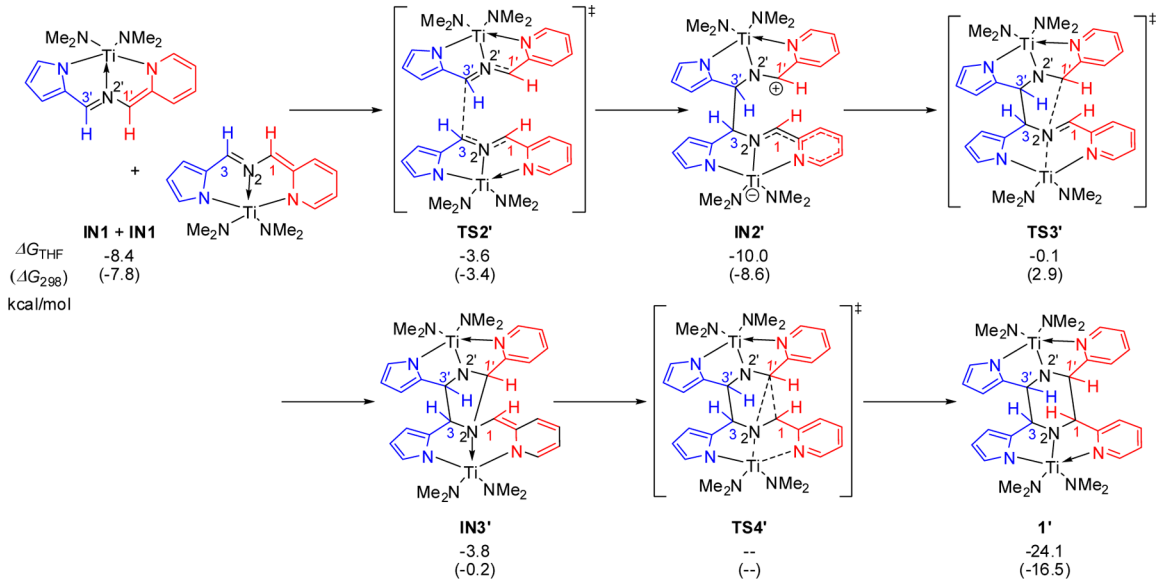
The results in Scheme 5 indicate that intramolecular H abstraction by one of the dimethylamino anions via **TS1** requires an activation barrier of 21.6 kcal/mol, while intermolecular H abstraction by one $HNMe_2$ molecule in the reaction media via **TS1′** has an activation barrier of about 5 kcal/mol higher. The geometry of **TS1′** indicates that a hydrogen bond is formed between the $HNMe_2$ molecule and the nitrogen atom of one dimethylamino anion. The formation of the titanium aza-allyl complex **IN1** is exergonic by 8.4 kcal/mol, indicating that the H-abstraction step is thermodynamically favorable. The geometric structure shows that **IN1** is closer to mesomeric form *iii* (Scheme 2) with a dearomatized pyridine ring, as the N(pyridine)−Ti distance (2.074 Å) is quite close to the N(pyrrole)−Ti distance (2.065 Å), while both are much shorter than the N(imine)−Ti distance (2.176 Å).

For reasons of orbital symmetry, no concerted or stepwise [3 + 3] cycloaddition between two **IN1** complexes could be found to generate complex **1**. Instead, the results in Scheme 6 indicate that the cyclodimerization of **IN1** follows a consecutive stepwise [3 + 2] cycloaddition/ring expansion pathway. In the first step, the coupling between C1 and C3′ is realized via **TS2**, which is only 5.9 kcal/mol higher in energy than two **IN1** complexes, leading to **IN2** being slightly endergonic by 0.7 kcal/mol. **IN2** could undergo a C3−N2′ formation reaction via **TS3** to generate the [3 + 2] cycloaddition intermediate **IN3**, which would undergo a facile ring-expansion reaction via **TS4** to generate the dimerized complex **1**. This last step is driven forward by the thermodynamic instability of **IN3**, and the formed intermediate **1** is 28.6 kcal/mol lower in energy than the starting complex **C1**. From **IN2**, the possible N2−C1′ coupling was also calculated, but a much higher activation energy is required.

The above results show that, after the β-H abstraction step, **IN1** could be transformed into the cross-coupled complex **1** very easily through C1−C3′ and C3−C1′ couplings. We wonder if it is possible to form a homocoupled complex from the C1−C1 and C3−C3′ couplings. To understand the observed regiochemistry of the cyclodimerization, the results for the possible homocoupling pathway are shown in Scheme 7, which shows that the

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

Scheme 7. Results Accounting for the Regioselectivity of the Cyclodimerization



relative energies for the transition states in reactions initiated by C3−C3′ coupling are relatively lower than those in Scheme 6, although we failed to locate **TS4′** for connecting **IN3′** and **1′**. **IN2′** would be formed more easily via **TS2′** than the formation of **IN2** via **TS2**, and **TS3′** is lower in energy than **TS3**. These indicate the homocoupling pathway is more kinetically favorable. However, **1′** is less stable relative to **1**, with the latter being 9.9 and 4.5 kcal/mol lower in energy in the gas phase and in THF solution, respectively, suggesting the homocoupling pathway is less favorable than the cross-coupling pathway for thermodynamic reasons.

While the tridentate monoanionic proligands **HL1**, **HL6**, and **HL7** could be efficiently transformed into substituted piperazines, it is interesting to find that the proligands **H_2L2**, **HL3**, **HL4**, and **HL5** only form ligand-exchanged complexes with $Ti(NMe_2)_4$, and no reactions from the β-H abstraction and [3 + 3] cyclodimerization occurred. The energies in Scheme 8 show that the possible β-H abstractions for the Ti complexes formed from **H_2L2**, **HL3**, and **HL4** and $Ti(NMe_2)_4$ are energetically demanding, being consistent with the experimental outcomes.

As **H_2L2** is a tridentate dianionic ligand, the pentacoordinated complex **C1-L2** will be first formed in the reaction with $Ti(NMe_2)_4$ (Scheme 8a). The intramolecular β-H abstraction from **C1-L2** requires a barrier of 44.6 kcal/mol. We proposed that the barrier may be lowered by incorporation of one neutral $HNMe_2$ ligand into **C1-L2** to form the hexacoordinated complex **C1′-L2**; however, the activation energy is still as high as 36.8 kcal/mol.

Scheme 8b shows that the intramolecular β-H abstraction of the monoanionic bidentate ligand from **HL3** is difficult, with an activation free energy of 33.9 kcal/mol. Similarly, β-H abstraction of the pentacoordinated complex **C1-L4** from **HL4** is also difficult, with an activation free energy of 39.7 kcal/mol. Notably, the results in Scheme 8c show that the hexacoordinated complex **C1′-L4** is 13.6 kcal/mol higher in energy than **C1-L4**, explaining why the furan oxygen is not coordinated with the metal in this reaction. This suggests that the coordination of the tridentate monoanionic ligand with titanium is sensitive to subtle electronic and steric factors. Similar results should be expected for the reaction of **HL5**. Notably, the negative charges in the formed intermediates in Scheme 8 could be not stabilized by the adjacent groups, suggesting the importance of pyridine dearomatization for facilitating the β-H abstraction step.[22]

CONCLUSIONS

An efficient method was developed for the synthesis of substituted piperazine derivatives based on $Ti(NMe_2)_4$-mediated C−C bond coupling reactions, and a better understanding of the experimental results was achieved by DFT calculations. It was found that the methylene on the [−HC═NCH$_2$−] linkage of the tridentate monoanionic ligand could be deprotonated intramolecularly via β-H abstraction to form a titanium aza-allyl complex, which undergoes consecutive [3 + 2] cycloaddition and ring-expansion reactions facilely to generate a dinuclear complex with a piperazine skeleton. No such reaction could be observed for titanium complexes bearing tridentate dianionic and bidentate monoanionic ligands, as calculations revealed the β-H abstractions in these systems are energetically demanding.

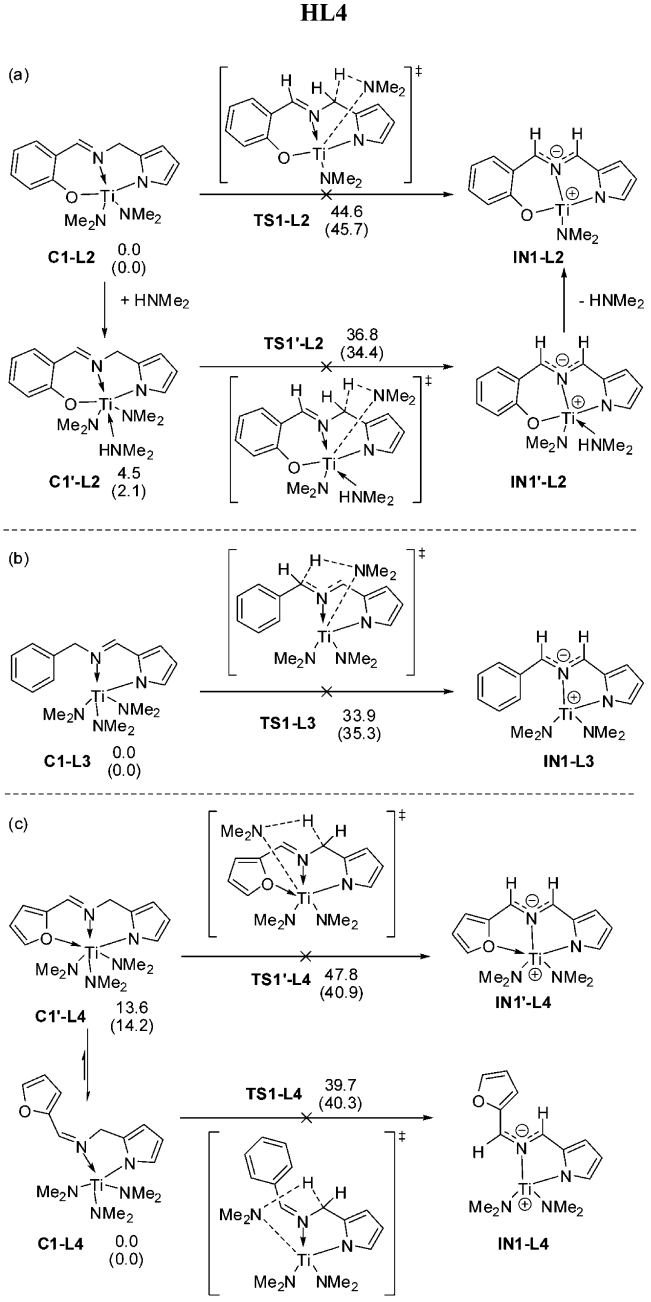
EXPERIMENTAL SECTION

General Methods. All manipulations of air-sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. THF was purchased from commercial suppliers and dried over purple sodium benzophenone ketyl. $Ti(NMe_2)_4$ was purchased from commercial sources. Elemental analyses (C, H, N) were performed with a Carlo-Erba EA 1110 CHNO-S microanalyzer. Crystal determination was performed with a Bruker SMART APEX II CCDC diffractometer equipped with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). ^{1}H and ^{13}C spectra were recorded on a Varian Inova-300 or VXR-500 spectrometer. HRMS spectra were obtained by TOF-MS.

Computational Details. All calculations were carried out with the Gaussian 09 suite of computational programs.[20] All stationary points along the reaction coordinate were fully optimized at the DFT level using the M06 hybrid functional.[21] The 6-31+G* basis set[23] was applied for all the atoms except Ti, which was described by the LANL2DZ basis set.[24] Frequencies were analytically computed at the same level of theory to obtain the gas-phase free energies and to confirm whether the structures are minima (no imaginary frequency) or transition states (only one imaginary frequency). Intrinsic reaction coordinate (IRC) calculations were carried out to conform that all transition-state

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

Scheme 8. Prediction for the Possible β-H Abstraction of the Ti Complexes from H_2L2, HL3, and HL4



structures connect the proposed reactants and products.[25] The solvation effect was examined by performing single-point self-consistent reaction field (SCRF) calculations based on the polarizable continuum model (CPCM) for gas-phase optimized structures.[26] Tetrahydrofuran (THF, ε = 7.4) was used as the solvent, corresponding to the experimental conditions. Solvation free energies (ΔG_{THF}) were calculated by adding the solvation energies to the computed gas-phase relative free energies (ΔG_{298}).

X-ray Diffraction. Crystals grown from concentrated solutions at room temperature were quickly selected and mounted on glass fibers in wax. The data collections were carried out on a Bruker AXS three-circle goniometer with a CCD detector equipped with graphite-monochromated Mo Kα radiation by using the ϕ/ω scan technique at room temperature. The structures were solved by direct methods with SHELXS-97.[27] The hydrogen atoms were assigned common isotropic displacement factors and included in the final refinement by use of geometrical restraints. A full-matrix least-squares refinement on F^2 was carried out using SHELXL-97.[27]

Syntheses of the Ligands and the Complexes. *Preparation of N-((1H-Pyrrol-2-yl)methylene)-1-(pyridin-2-yl)methanamine (**HL1**).* To a solution of 2-pyrrolaldehyde (0.951 g, 10 mmol) in water (10 mL) was added 2-aminomethylpyridine (1.081 g, 10 mmol) and 1 drop of acetic acid. After the mixture was stirred at room temperature overnight, a pale yellow solid precipitated, which was collected by filtration and dried in vacuo. Yield: 1.700 g (92%). ^{1}H NMR (300 MHz, DMSO): δ 11.50 (s, 1H, NH), 8.50 (d, 1H, CH═N), 8.24 (s, 1H, 2-C_5H_4N), 7.73 (t, 1H, 4-C_5H_4N), 7.38 (d, 1H, 5-C_5H_4N), 7.23 (t, 1H, 3-C_5H_4N), 6.90 (s, 1H, 2-C_4H_3N), 6.51 (s, 1H, 4-C_4H_3N), 6.13 (s, 1H, 3-C_4H_3N), 4.75 (s, 2H, CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO): δ 160.2 (CH═N), 154.2, 149.6, 137.3, 130.7, 123.1 (C_5H_4N), 122.9, 122.7, 114.7, 109.7 (C_4H_3N), 66.3 (CH_2N) ppm. Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.51; H, 5.96; N, 22.51.

*Preparation of 2-(((1H-Pyrrol-2-yl)methylimino)methyl)phenol (**H_2L2**).* To a solution of 2-aminomethylpyrrole (0.961 g, 10 mmol) in water (30 mL) was added salicylaldehyde (1.221 g, 10 mmol) and 1 drop of acetic acid. After the mixture was stirred at room temperature for 2 h, a yellow solid precipitated, which was collected by filtration and dried in vacuo. Yield: 1.802 g (90%). ^{1}H NMR (300 MHz, DMSO): δ 13.43 (s, 1H, OH), 10.86 (s, 1H, NH), 8.54 (s, 1H, CH═N), 7.40 (d, 1H, 3-C_6H_5O), 7.30 (t, 1H, 6-C_6H_5O), 6.89−6.83 (2H, 4,5-C_6H_5O), 6.68 (s, 1H, 2-C_4H_3N), 5.94 (s, 2H, 3,4-C_4H_3N), 4.68 (s, 2H, CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO): δ 166.5 (CH═N), 161.3, 133.0, 132.4, 128.6, 119.4, 119.2 (C_6H_5O), 118.5, 117.1, 108.1, 107.3 (C_4H_3N), 55.5 (CH_2N) ppm. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.82; H, 6.09; N, 14.09.

*Preparation of N-((1H-Pyrrol-2-yl)methylene)-1-phenylmethanamine (**HL3**).* To a solution of 2-pyrrolaldehyde (0.951 g, 10 mmol) in water (30 mL) was added benzylamine (1.072 g, 10 mmol) and 1 drop of acetic acid. After the mixture was stirred overnight, a white solid precipitated, which was collected by filtration and dried in vacuo. Yield: 1.438 g (78%). ^{1}H NMR (300 MHz, DMSO): δ 8.20 (d, 1H, CH═N), 7.30 (4H, 2,3,5,6-C_6H_5), 7.23 (t, 1H, 4-C_6H_5), 6.88 (s, 1H, 2-C_4H_3N), 6.49 (s, 1H, 4-C_4H_3N), 6.12 (s, 1H, 3-C_4H_3N), 4.64 (s, 2H, CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO): δ 153.2 (CH═N), 140.8, 130.6 (2,5-C_4H_3N), 128.9, 128.8, 127.3, 122.9 (Ph), 114.5, 109.6 (3,4-C_4H_3N), 64.4 (CH_2N) ppm. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.36; H, 6.53; N, 15.08.

*Preparation of N-(Furan-2-ylmethylene)-1-(1H-pyrrol-2-yl)-methanamine (**HL4**).* To a solution of 2-aminomethylpyrrole (0.961 g, 10 mmol) in water (30 mL) was added furfural (0.961 g, 10 mmol) and 1 drop of acetic acid. After the mixture was stirred at room temperature for 2 h, a pale brown product precipitated, which was collected by filtration and dried in vacuo. Yield: 1.481 g (85%). ^{1}H NMR (300 MHz, DMSO): δ 10.76 (s, 1H, NH), 8.14 (s, 1H, CH═N), 7.82 (s, 1H, 2-C_4H_3O), 6.92 (d, 1H, 2-C_4H_3N), 6.66 (d, 1H, 4-C_4H_3O), 6.61 (d, 1H, 3-C_4H_3O), 5.93 (d, 1H, 4-C_4H_3N), 5.90 (s, 1H, 3-C_4H_3N), 4.62 (s, 2H, CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO): δ 151.6 (CH═N), 150.0 (5-C_4H_3O), 145.2 (2-C_4H_3O), 128.6 (5-C_4H_3N), 117.4 (2-C_4H_3N), 114.0 (4-C_4H_3O), 111.9 (3-C_4H_3O), 107.3 (4-C_6H_5N), 106.5 (3-C_6H_5N), 56.6 (CH_2N) ppm. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.80; H, 5.81; N, 16.17.

*Preparation of (S,E)-N-((1H-Pyrrol-2-yl)methylene)-1-(tetrahydrofuran-2-yl)methanamine (**HL5**).* To a solution of 2-pyrrolaldehyde (0.951 g, 10 mmol) in water (10 mL) was added tetrahydrofurfurylamine (1.011 g, 10 mmol). After the mixture was stirred overnight, a white solid precipitated. The solid was collected by filtration and dried in vacuo. Yield: 1.301 g (73%). ^{1}H NMR (300 MHz, DMSO): δ 11.39 (s, 1H, NH), 8.04 (s, 1H, CH═N), 6.86 (s, 1H, 2-C_4H_3N), 6.44 (d, 1H, 4-C_4H_3N), 6.10 (t, 1H, 3-C_4H_3N), 4.03 (t, 1H, 5-C_4H_7O), 3.77−3.56 (2H, 2-C_4H_7O), 4.51 (t, 2H, CH_2N), 1.97−1.56 (4H, 3,4-C_4H_7O) ppm. ^{13}C NMR (75 MHz, DMSO): δ 152.2 (CH═N), 129.4 (5-C_4H_3N), 121.4 (2-C_4H_3N), 112.8 (4-C_4H_3N), 109.1 (3-C_4H_3N), 77.5 (CH_2N), 66.5 (5-C_4H_7O), 64.3 (2-C_4H_7O), 28.2 (4-C_4H_7O), 24.6 (3-C_4H_7O) ppm. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.52; H, 7.97; N, 15.44.

dx.doi.org/10.1021/om300022u | *Organometallics* 2012, 31, 6005−6013

*Preparation of 2-((Pyridin-2-ylmethyleneamino)methyl)phenol (**HL7**).* To a solution of 2-pyridinecarboxaldehyde (1.071 g, 10 mmol) in water (10 mL) was added Na_2CO_3 (1.060 g, 10 mmol). Then 2-hydroxybenzylamine acetate (1.831 g, 10 mmol) in water (40 mL) was added slowly with stirring. After the mixture was stirred overnight, a pale yellow solid precipitated, which was collected by filtration and dried in vacuo. Yield: 1.676 g (79%). ^{1}H NMR (300 MHz, DMSO): δ 9.55 (br s, 1H, OH), 8.61 (s, 1H, CH═N), 8.37 (s, 1H, 6-C_5H_4N), 7.95 (d, 1H, 4-C_5H_4N), 7.85 (t, 1H, 3-C_5H_4N), 7.43 (s, 1H, 5-C_5H_4N), 7.08−7.15 (2H, 3,6-C_7H_7O), 6.80 (2H, 4,5-C_6H_5O), 4.76 (s, 2H, CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO): δ 163.1 (CH═N), 155.9, 150.0, 137.6, 130.3, 128.8 (C_5H_4N), 125.8, 125.5, 121.1, 119.6, 115.7 (C_6H_5O), 59.2 (CH_2N) ppm. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.71; H, 5.66; N, 13.15.

*Preparation of $(NMe_2)_2Ti(NC(C_4H_3N)HC(C_5H_4N)HNC(C_4H_3N)CH-(C_5H_4N)H)Ti(NMe_2)_2$ (**1**).* To a solution of $Ti(NMe_2)_4$ (0.448 g, 2 mmol) in THF (5 mL) was added **HL1** (0.370 g, 2 mmol) in THF (5 mL) dropwise. After the mixture was stirred at room temperature for 3 days or at 60 °C for 16 h, the solution was evaporated to dryness to give a red solid. The red solid was washed with *n*-hexane and dried under reduced pressure to yield 0.549 g (86%) of product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (m, 2H, 5-C_5H_5N), 7.60 (m, 2H, 4-C_5H_5N), 7.38 (m, 2H, 3-C_5H_5N), 7.20 (m, 2H, 2-C_5H_5N), 7.16 (m, 1H, 5-C_4H_3N), 7.06 (m, 1H, 5-C_4H_3N), 6.19 (m, 2H, 4-C_4H_3N), 5.58 (m, 2H, 3-C_4H_3N), 4.39 (d, 2H, −CH−), 4.18 (d, 2H, −CH−), 3.36 (s, 12H, $N(CH_3)_2$), 2.98 (s, 12H, $N(CH_3)_2$) ppm. Anal. Calcd for $C_{30}H_{42}N_{10}Ti_2$: C, 56.44; H, 6.63; N, 21.94. Found: C, 55.97; H, 6.45; N, 21.96.

*Preparation of 2,5-Bis(pyridin-2-yl)-3,6-bis(1H-pyrrol-2-yl)-piperazine (**2**).* To a solution of **1** in THF was added several drops of water. After the mixture was stirred at room temperature for 6 h, the resulting precipitate was filtered. The filtrates were washed with CH_2Cl_2 and dried in vacuo to give a crude product. The pure red product was afforded by recrystallizing or washing the crude product with a mixture of ethanol and water. Yield: 0.288 g (78%). ^{1}H NMR (300 MHz, DMSO): δ 10.69 (s, 2H, NH), 8.44 (d, 2H, 6-C_5H_4N), 7.57 (t, 2H, 4-C_5H_4N), 7.17 (t, 2H, 3-C_5H_4N), 7.10 (d, 2H, 5-C_5H_4N), 6.50 (s, 2H, 5-C_4H_3N), 5.73 (s, 2H, 3-C_4H_3N), 5.67 (s, 2H, 4-C_4H_3N), 4.12 (t, 2H, CH), 4.21 (t, 2H, CH) ppm. ^{13}C NMR (75 MHz, DMSO): δ 159.8, 148.3, 135.8, 122.9, 122.0, 116.3, 106.5, 105.2 (Ar), 65.1 (CH), 57.6 (CH) ppm. HRMS: *m*/*z* 371.1978 (M + 1). Anal. Calcd for $C_{22}H_{22}N_6$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.41; H, 6.06; N, 22.44.

*Preparation of Ti(**L2**)$_2$ (**C-L2**).* To a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in THF (2 mL) was added **H$_2$L2** (0.200 g, 1 mmol) in THF (3 mL). After the mixture was stirred at room temperature for 2 days, the solution was evaporated to dryness to give a red solid. The red solid was washed with *n*-hexane and dried under reduced pressure to yield 0.167 g (75%) of product. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.92 (s, 1H, CH═N), 7.72 (d, 2H, 3-C_6H_4O), 7.56 (t, 2H, 6-C_6H_4O), 7.09 (t, 2H, 4-C_6H_4O), 6.72 (d, 2H, 5-C_6H_4O), 6.40 (s, 2H, 5-C_4H_3N), 5.84 (s, 2H, 4-C_4H_3N), 5.74 (s, 2H, 3-C_4H_3N), 5.53−5.19 (4H, CH_2) ppm. Anal. Calcd for $C_{24}H_{20}N_4O_2Ti$: C, 64.88; H, 4.54; N, 12.61. Found: C, 64.64; H, 4.63; N, 12.42.

*Preparation of Ti(**L3**)$(NMe_2)_3$ (**C1-L3**).* To a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in THF (2 mL) was added **HL3** (0.184 g, 1 mmol) in THF (3 mL). After the mixture was stirred at room temperature overnight, the solution was evaporated to dryness to yield 0.334 g (92%) of product. ^{1}H NMR (300 MHz, C_6D_6): δ 7.29 (s, 1H, CH═N), 7.87(s, 2H, $-C_6H_5$), 6.77 (d, 2H, $-C_6H_5$), 6.66 (s, 2H, 5-C_4H_3N, $-C_6H_5$), 6.37 (s, 1H, 3-C_4H_3N), 6.14 (s, 1H, 4-C_4H_3N), 3.89 (s, 2H, $-CH_2-$), 2.80 (d, 18H, $-N(CH_3)_2$). ^{13}C NMR (75 MHz, C_6D_6): δ 158.6 (CH═N), 139.2, 137.7, 136.4, 129.1, 128.1, 127.1, 115.6, 111.3 (C_4H_3N, Ph), 60.1 (CH_2), 45.1 ($N(CH_3)_2$) ppm. Anal. Calcd for $C_{18}H_{29}N_5Ti$: C, 59.50; H, 8.05; N, 19.28. Found: C, 58.88; H, 7.68; N, 19.85.

*Preparation of Ti(**L4**)$(NMe_2)_3$ (**C1-L4**).* To a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in THF (2 mL) was added **HL4** (0.174 g, 1 mmol) in THF (3 mL). After the mixture was stirred at room temperature for 1 day, the solution was evaporated to dryness to give a red powder. Yield: 0.265 g (75%). ^{1}H NMR (300 MHz, C_6D_6): δ 7.81 (s, 1H, CH═N), 7.04 (s, 1H, 5-C_4H_3O), 6.83 (s, 1H, 5-C_4H_3N), 6.57 (s, 1H, 3-C_4H_3O), 6.32 (s, 1H, 3-C_4H_3N), 6.20 (s, 1H, 3-C_4H_3O), 6.19 (s, 1H, 4-C_4H_3O), 5.91 (s, 1H, 4-C_4H_3N), 5.03 (s, 2H, CH_2), 3.13 (s, 18H, $N(CH_3)_2$) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ 150.6 (CH═N), 148.1 (1-C_4H_3O), 147.0 (5-C_4H_3O), 138.3 (5-C_4H_3N), 127.2 (3-C_4H_3O), 120.7 (2-C_4H_3N), 112.9 (4-C_4H_3O), 109.6 (3-C_4H_3N), 101.0 (4-C_4H_3N), 54.4 (CH_2), 46.2 ($N(CH_3)_2$) ppm. Anal. Calcd for $C_{16}H_{27}N_5OTi$: C, 54.40; H, 7.70; N, 19.82. Found: C, 53.91; H, 7.87; N, 19.51.

*Preparation of Ti(**L5**)$(NMe_2)_3$ (**C1-L5**).* To a solution of $Ti(NMe_2)_4$ (0.224 g, 1 mmol) in THF (2 mL) was added **HL5** (0.178 g, 1 mmol) in THF (3 mL). After the mixture was stirred at room temperature for 1 day, the solution was evaporated to dryness to give a red powder. Yield: 0.296 g (83%). ^{1}H NMR (300 MHz, C_6D_6): δ 7.85 (s, 1H, CH═N), 7.08 (s, 1H, 2-C_4H_3N), 6.63 (d, 1H, 4-C_4H_3N), 6.34 (d, 1H, 3-C_4H_3N), 3.68 (s, 1H, 2-C_4H_7O), 3.56−3.44 (2H, 5-C_4H_7O), 3.13 (s, 18H, NMe_2), 3.05 (s, 2H, CH_2N), 1.42 (br s, 4H, 3,4-C_4H_7O) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ 160.4 (CH═N), 139.7 (2-C_4H_3N), 136.2 (5-C_4H_3N), 115.5 (3-C_4H_3N), 111.3 (4-C_4H_3N), 77.2 (CH_2N), 67.4 (2-C_4H_7O), 60.7 (5-C_4H_7O), 45.6 (NMe_2), 29.7 (3-C_4H_7O), 25.6 (4-C_4H_7O) ppm. Anal. Calcd for $C_{16}H_{31}N_5OTi$: C, 53.78; H, 8.74; N, 19.60. Found: C, 53.01; H, 8.45; N, 19.13.

*Preparation of 2,2′-(3,6-Bis(pyridin-2-yl)piperazine-2,5-diyl)-diphenol (**4**).* To a solution of $Ti(NMe_2)_4$ (0.448 g, 2 mmol) in THF (5 mL) was added **HL6** (or **HL7**) (0.424 g, 2 mmol) in THF (5 mL). After the mixture was stirred at room temperature for 1 week, several drops of water were added. The resulting mixture was stirred for 6 h, and the precipitate was filtered away. The filtrates were washed with CH_2Cl_2 and dried under vacuum give a crude product. The pure yellow product was obtained by recrystallizing or washing the crude product with a mixture of ethanol and water. Yield: 0.255 g (60%, based on **HL6**); 0.225 g (53%, based on **HL7**). ^{1}H NMR (300 MHz, DMSO): δ 8.48 (d, 2H, 6-C_5H_4N), 7.55 (t, 2H, 4-C_5H_4N), 7.17 (t, 2H, 3-C_5H_4N), 6.98 (d, 2H, 5-C_5H_4N), 6.93 (d, 2H, 6-C_6H_5O), 6.68 (d, 2H, 4-C_6H_5O), 6.52 (br s, 2H, 3-C_6H_5O), 6.42 (t, 2H, 5-C_6H_5O), 4.31 (s, 4H, CH) ppm. HRMS (EI): *m*/*z* calcd for $C_{26}H_{24}N_4O_2$ 424.1899, found 425.1973 (M + H). Anal. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.21; H, 5.79; N, 13.05.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, figures, and CIF files giving X-ray crystallographic data, NMR spectroscopic data, and computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We appreciate the financial support of the Hundreds of Talents Program (2005012) of CAS, the Natural Science Foundation of China (20872105 and 21002073), the "Qinglan Project" of Jiangsu Province (Bu109805), and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions. Y.X. thanks the High Performance Computation Platform of Wenzhou University for providing the computation facility.

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