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Ti^{IV}-Mediated Reactions between Primary Amines and Secondary Carboxamides: Amidine Formation Versus Transamidation

Denis A. Kissounko, Justin M. Hoerter, Ilia A. Guzei, Qiang Cui,*
Samuel H. Gellman,* and Shannon S. Stahl*

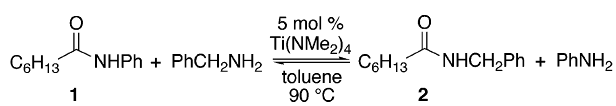
Contribution from the Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706

Received July 14, 2006; E-mail: cui@chem.wisc.edu; gellman@chem.wisc.edu; stahl@chem.wisc.edu

Abstract: Titanium(IV)-mediated reactions between primary amines and secondary carboxamides exhibit different outcomes, amidine formation versus transamidation, depending on the identity of the Ti^{IV} complex used and the reaction conditions employed. The present study probes the origin of this divergent behavior. We find that *stoichiometric* Ti^{IV}, either Cp^*Ti^{IV} complexes or $Ti(NMe_2)_4$, promotes formation of amidine and oxotitanium products. Under *catalytic* conditions, however, the outcome depends on the identity of the Ti^{IV} complex. Competitive amidine formation and transamidation are observed with Cp^*Ti^{IV} complexes, generally favoring amidine formation. In contrast, the use of catalytic $Ti(NMe_2)_4$ ($\leq$20 mol %) results in highly selective transamidation. The ability of Ti^{IV} to avoid irreversible formation of oxotitanium products under the latter conditions has important implications for the use of Ti^{IV} in catalytic reactions.

Introduction

Methods for facile, equilibrium-controlled exchange of covalent bonds have gained widespread attention in recent years because they enable product formation under thermodynamic, rather than kinetic, control.[1] Prominent functional groups compatible with these transformations include esters, disulfides, imines, acetals, and alkenes.[2] Carboxamides are ubiquitous in chemistry and biology, and numerous methods have been developed to prepare carboxamides under kinetic control via the condensation of amines with carboxylic acids, esters, or acid halides;[3] however, thermodynamically controlled exchange reactions involving carboxamides, including transamidation and amide metathesis, have very little precedent.[4,5] In our initial studies focused on this type of reactivity, we discovered that homoleptic metal−amido complexes, $Ti(NMe_2)_4$ and $Al_2(NMe_2)_6$, promote equilibration of simple primary amine/secondary carboxamide pairs under moderate conditions (e.g., eq 1).[6] In order to develop improved catalysts, we have been investigating the mechanism of these reactions.[7]



(1)

Primary amines are known to react with $Ti(NMe_2)_4$ to form imido ligands,[8,9] and we recently postulated that imidotitanium

(1) Equilibrium-controlled manipulation of other functional groups is the subject of significant current interest. For reviews, see: (a) Lehn, J.-M. *Chem.—Eur. J.* **1999**, *5*, 2455−2463. (b) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898−952.

(2) For selected recent examples of DCC, see (a) Brady, P. A.; Bonar-Law, R. P.; Rowan, S. J.; Suckling, C. J.; Sanders, J. K. M. *Chem. Commun.* **1996**, 319−320. (b) Oh, K.; Jeong, K.-S.; Moore, J. S. *Nature* **2001**, *414*, 889−893. (c) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Science* **2002**, *297*, 590−593. (d) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281−3285. (e) Vignon, S. A.; Jarrosson, T.; Iijima, T.; Tseng, H.-R.; Sanders, J. K. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 9884−9885. (f) Cantrill, S. J.; Grubbs, R. H.; Lanari, D.; Leung, K. C.-F.; Nelson, A.; Poulin-Kerstien, K. G.; Smidt, S. P.; Stoddart, J. F.; Tirrell, D. A. *Org. Lett.* **2005**, *7*, 4213−4216. (g) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2005**, *127*, 13666−13671.

(3) Beckwith, A. L. J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, 1970; p 73−185.

(4) Most precedents consist of intramolecular reactions. See, for example: (a) Çalimsiz, S.; Lipton, M. A. *J. Org. Chem.* **2005**, *70*, 6218−6221. (b) Álajarín, M.; Vidal, A.; Tovar, F. *Tetrahedron* **2005**, *61*, 1531−1537. (c) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533. (d) Lasri, J.; González-Rosende, M. E.; Sepúlveda-Arques, J. *Org. Lett.* **2003**, *5*, 3851−3853. (e) Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 9531−9533. (f) Gotor, V.; Brieva, R.; González, C.; Rebolledo, F. *Tetrahedron* **1991**, *47*, 9207−9214. (g) Zaragoza-Dörwald, F.; von Kiedrowski, G. *Synthesis* **1988**, *11*, 917−918. (h) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5151−5154. (i) Martin, R. B.; Parcell, A.; Hedrick, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 2406−2413.

(5) For intermolecular precedents, see: (a) Beste, L. F.; Houtz, R. C. *J. Polym. Sci.* **1952**, *8*, 395−407. (b) Ogata, N. *Makromol. Chem.* **1959**, *30*, 212−224. (c) Miller, I. K. *J. Polym. Sci., Part A: Polym. Chem.* **1976**, *14*, 1403−1417. (d) McKinney, R. J. U.S. Patent 5,302,756, 1994. (e) McKinney, R. J. U.S. Patent 5,395,974, 1995. (f) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035−4036.

(6) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422−3423.

(7) (a) Kissounko, D. A.; Guzei, I. A.; Gellman, S. H.; Stahl, S. S. *Organometallics* **2005**, *24*, 5208−5210. (b) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 5177−5183.

(8) (a) Bradley, D. C.; Torrible, E. G. *Can. J. Chem.* **1963**, *41*, 134−138. (b) Nugent, W. A.; Harlow, R. L. *Inorg. Chem.* **1979**, *18*, 2030−2032. (c) Thorn, D. L.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 357−363.

(9) $Ti(NMe_2)_4$ catalyzes the hydroamination of alkynes and alkenes, reactions that probably proceed via imidotitanium intermediates. For leading references, see: (a) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967−3969. (b) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956−11963. (c) Lorber, C.; Choukroun, R.; Vendier, L. *Organometallics* **2004**, *23*, 1845−1850. (d) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959−1962.

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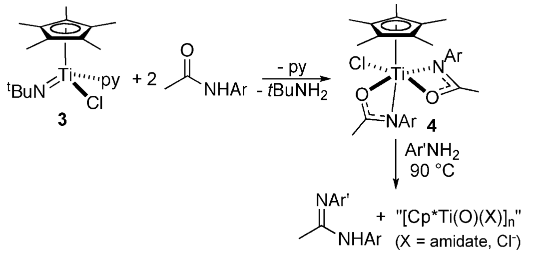
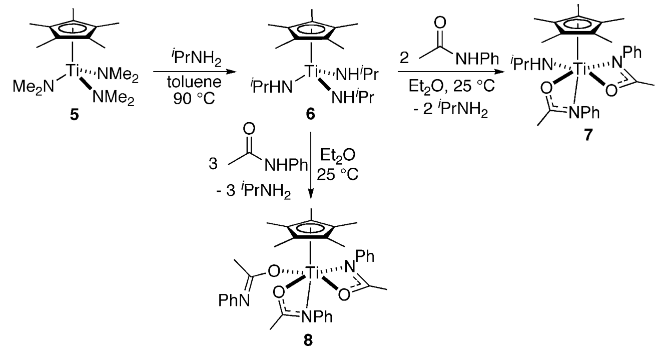
Scheme 1. Reactions of an Imido-Ti^{IV} Species with Secondary Carboxamides



Scheme 2. Preparation of Bis- and Trisamidate Complexes of Ti^{IV}



intermediates might participate in the transamidation reaction.[7a] To test this hypothesis, we investigated the reactivity of a well-defined imido-Ti^{IV} complex, Cp*Ti(N*t*Bu)(py)Cl (**3**, Cp* = η^5-C_5Me_5),[10] with secondary carboxamides; however, no transamidation was observed. Secondary amides react with complex **3** at room temperature by displacing pyridine and *tert*-butylamine together with the formation of bis(κ^2-amidate)Ti^{IV} complex **4** (Scheme 1). Subsequent treatment of **4** with aniline derivatives at elevated temperatures (90 °C) results in formation of 1 equiv of *N,N′*-diarylamidine and unidentified Ti byproducts.[11]

This previous study highlighted the ability of Ti^{IV} to activate intrinsically unreactive carboxamides toward a reaction with simple primary amines; however, the formation of amidines in these reactions raises fundamental questions concerning the ability of Ti^{IV} to promote transamidation under catalytic conditions. How do amido-, imido-, and/or amidatotitanium adducts, which seem certain to exist under catalytic conditions, avoid generating amidines and inert oxo-Ti products? What factors dictate whether amines and carboxamides will undergo transamidation or form amidines in the presence of Ti^{IV}?

In our consideration of these questions, we noted at least two significant differences between the catalytic transamidation reactions (eq 1) and the stoichiometric reactions of Ti^{IV} complexes (Scheme 1). First, the ligands coordinated to Ti^{IV} differ between the two classes of reactions. In the catalytic reactions initiated by $Ti(NMe_2)_4$, only amine and carboxamide substrates are available as ligands, whereas the stoichiometric reactions feature Ti^{IV} bearing ancillary Cp* and chloride ligands. Another important difference is the substrate/Ti ratio. Under catalytic conditions, both the amine and carboxamide substrates are present in a 20:1 ratio relative to Ti, whereas the mechanistic studies feature a substrate/Ti ratio of approximately 1:1.[12]

The present study seeks to address whether either of these differences underlies the divergence between transamidation and amidine formation in Ti-promoted reactions between primary amines and secondary carboxamides. We describe reactions of Ti^{IV}−amidate complexes in which the ancillary chloride ligand in **4** (Scheme 1) has been replaced by catalytically more relevant amido or amidate ligands. In addition, we probe the effect of substrate/Ti loading under catalytic conditions. The results reveal that amidine formation is relatively insenstitive to the ancillary ligand environment and is the major reaction pathway when the substrate/Ti ratio approaches 1:1. In contrast, transamidation can be achieved only with a relatively high substrate/Ti ratio and proceeds most effectively when the Ti^{IV} lacks the electron-donating and sterically bulky Cp* ligand. The results of this study potentially have general implications for avoiding the formation of inert oxotitanium complexes in catalytic reactions.

Results and Discussion

Synthesis of Ti-Amidate Complexes. To probe the effect of the Ti^{IV} coordination sphere on the outcome of Ti-mediated reactions between primary amines and secondary carboxamides, we sought an analogue of Cp*Ti(κ^2-amidate)$_2$Cl (**4**) in which the chloride is replaced by an amido or a third amidate ligand. The known Cp*Ti$(NMe_2)_3$ (**5**) complex[13] reacts cleanly in the presence of a 10-fold excess of *i*PrNH_2 to provide the trisisopropylamido derivative **6** (Scheme 2). The amido ligands in **6** undergo facile exchange with secondary carboxamides. Addition of 2 equiv of acetanilide to **6** in diethylether at ambient temperature yields the bis(amidate)monoamidoTi^{IV} complex, **7**. Three equiv of acetanilide react with **6** to form the tris(amidate)-Ti^{IV} complex **8**. Attempts to form the monoamidate complex, however, were unsuccessful. The reaction of **6** with 1 equiv of acetanilide provides **7** in reduced yield together with unreacted **6**. These observations indicate a strong (albeit, not surprising) preference of Ti^{IV} for amidate rather than amido ligands. This preference can be explained, in part, by the ability of the amidates to serve as chelating ligands; however, the facile formation of **8** from **6** shows that even monodentate amidates are favored over amido ligands. The oxophilicity of Ti^{IV} together with the significantly higher acidity of amides relative to amines undoubtedly contributes to these results. Comparable observations have been made recently in our study of amine and carboxamide reactions with Al^{III}.[7b]

Complexes **6**−**8** were characterized by infrared, ^1H, and $^{13}C\{^1H\}$ NMR spectroscopy and elemental analysis. The ^1H NMR signal of the amido N−*H* in **7** is shifted significantly downfield relative to that in **6** (9.24 and 5.18 ppm, respectively; C_6D_6). This shift presumably reflects the enhanced electrophilicity of the Ti center in **7** relative to **6**. We cannot exclude the possibility of intramolecular hydrogen bonding in **7** between the N−H and the oxygen of an amidate ligand; however, no evidence for such

(10) Dunn, S. C. Mountford, P.; Robson, D. A. *J. Chem. Soc., Dalton Trans.* **1997**, 293−304.
(11) In light of these results, it is noteworthy that Schafer and co-workers recently reported the first example of Ti and Zr imido complexes bearing ancillary amidate ligands. The lack of amidine formation from these complexes, even at elevated temperatures (up to 140 °C), presumably reflects the presence of the extremely bulky 2,6-diisopropylphenyl substituents on the amidate nitrogen atoms. See: Thomson, R. K.; Bexrud, J. A.; Schafer, L. L. *Organometallics* **2006**, *25*, 4069−4071.
(12) As noted by a reviewer, we observed catalyst-dependent chemoselectivity in our initial discovery of transamidation (ref 6)—namely, *alkylamide* substrates are more reactive with Al catalysts, whereas *arylamides* are more reactive with Ti complexes. The present study focuses exclusively on Ti chemistry and, therefore, does not address the origin of transamidation chemoselectivity. The latter issue will be the focus of future work.
(13) Martín, A.; Mena, M.; Yélamos, C.; Serrano, R.; Raithby, P. R. *J. Organomet. Chem.* **1994**, *467*, 79−84.

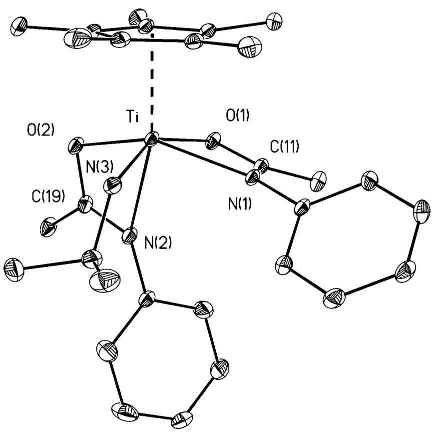


Figure 1. Molecular structure of **7** (30% thermal ellipsoids). All hydrogen atoms have been removed for clarity.

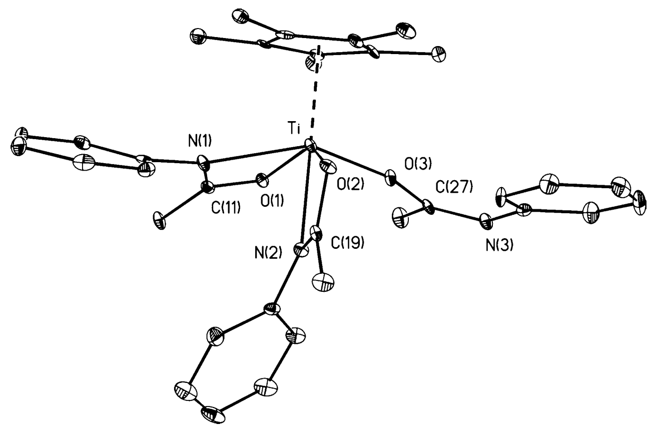


Figure 2. Molecular structure of **8** (30% thermal ellipsoids). All hydrogen atoms have been removed for clarity.

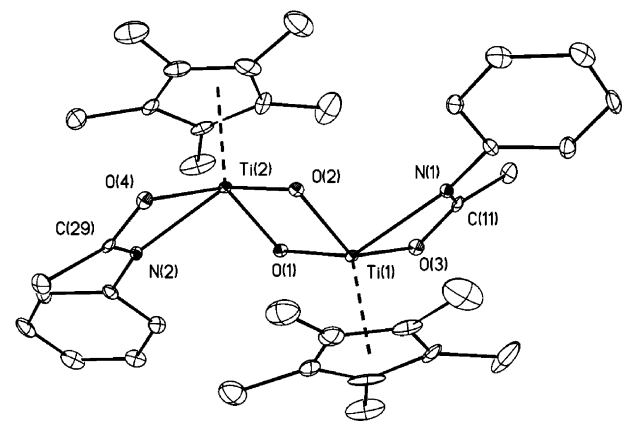


Figure 3. Molecular structure of compound **10** (30% thermal ellipsoids). All hydrogen atoms have been removed for clarity.

an interaction is provided by the IR spectroscopic or X-ray crystallographic data (see later).

Structural Analysis of Ti-Amidate Complexes. Only a few examples of titanium amidate complexes have been reported in the literature.[7a,14] A particularly interesting class of compounds has been described by Schafer and co-workers, who have prepared and structurally characterized pseudo-octahedral $Ti^{IV}(\kappa^2$-amidate$)_2(NEt_2)_2$ complexes for use as catalysts in the hydroamination of alkynes.[14b−d] Although the hydroamination reactions are performed in the presence of excess primary amine, no reaction of the ancillary κ^2-amidate ligands (e.g., transamidation or amidine formation) has been noted. The relative inertness of the amidate ligands in these reactions, which are performed in benzene at 65 °C, probably has a steric origin. The amidate ligands have large substituents on nitrogen (e.g., *tert*-butyl and 2,6-diisopropylphenyl) and an aryl group bonded to the central carbon atom that orients perpendicular to the amidate π-system.

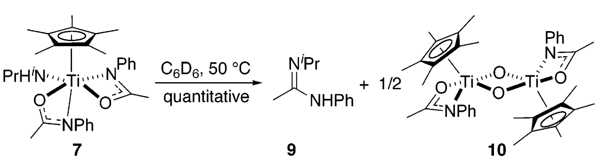
X-ray crystal structures of **7** and **8** were obtained. As shown in Figure 1, complex **7** exhibits a pseudo-octahedral geometry with the Cp* ligand and an amidate nitrogen atom occupying the apical positions. The two amidate ligands are distinguished by different relative C−O and C−N bond lengths: the bond lengths for the diequatorial amidate implicates more double-bond character for the C−O bond [C(11)−O(1), 1.2848(19); C(11)−N(1), 1.311(2) Å] relative to the equatorial/apical amidate, in which the C−O and C−N bond lengths are identical [C(19)−O(2), 1.300(2); C(19)−N(2), 1.300(2) Å]. Corresponding differences are evident in the Ti-amidate bond lengths. For the diequatorial amidate, the Ti−N bond is shorter than the Ti−O bond [Ti−N(1), 2.1570(13); Ti−O(1), 2.2037(12) Å], whereas for the equatorial/apical amidate, the Ti−O bond is shorter than the Ti−N bond [Ti(1)−O(2), 2.0664(12); Ti(1)−N(2), 2.2985(14) Å].

The structure of trisamidate complex **8** is similar to that of **7**, but an *O*-bound κ^1-amidate occupies the position of the isopropylamido ligand in **7** (Figure 2). More detailed analysis of the structure of **8** reveals that bonding distinctions between the diequatorial and equatorial/apical κ^2-amidate ligands in **8** are negligible, and for both ligands, the Ti−O bonds are shorter than the Ti−N bonds [*Diequatorial*: C(11)−O(1), 1.298(5); C(11)−N(1), 1.307(6); Ti−O(1), 2.070(3); Ti−N(1) 2.225(4) Å. *Equatorial/apical*: C(19)−O(2), 1.316(5); C(19)−N(2), 1.299(5); Ti−O(2), 2.052(3); Ti−N(2) 2.231(4) Å]. The third amidate in **8** coordinates in a monodentate fashion through the oxygen atom, and the Ti−O bond [1.907(3) Å] is significantly shorter than that of the κ^2-amidate ligands. Furthermore, the C−O and C−N bond lengths of this ligand [C(27)−N(3), 1.281(6); C(27)−O(3), 1.319(5) Å] are consistent with the C═N and C−O formulation in Scheme 2.[15] Other structural parameters are available in the Supporting Information.

Reactivity of Ti-Amidate Complexes. We previously demonstrated that exogenous amine reacts with the bis(amidate)-Ti^{IV} complex **4** to yield an amidine product (Scheme 1).[7a] Preparation of the bis(amidate)monoamidoTi^{IV} complex **7** enabled us to test whether an amido ligand present *within* the coordination sphere of Ti would undergo transamidation or form an amidine product. Thermolysis of complex **7** at 50 °C in C_6D_6 resulted in exclusive formation of a 2:1 mixture of the secondary amidine, MeC(═N*i*Pr)NHPh (**9**), and the bis(μ-oxo)Ti dimer, {Cp*Ti(μ-O)[κ^2-OC(Me)NPh]}$_2$ (**10**) (eq 2). The structure of **10** was confirmed by NMR spectroscopy and X-ray crystal-

(14) (a) Giesbrecht, G. R.; Shafir, A.; Arnold, J. *Inorg. Chem.* **2001**, *40*, 6069−6072. (b) Zhang, Z.; Schafer, L. L. *Org. Lett.* **2003**, *5*, 4733−4736. (c) Li, C. Y.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun.* **2003**, 2462−2463. (d) Thomson, R. K.; Zahariev, F. E.; Zhang, Z.; Patrick, B. O.; Wang, Y. A.; Schafer, L. L. *Inorg. Chem.* **2005**, *44*, 8680−8689.

(15) For similar structural parameters observed in κ^1-amidate structures of aluminum and lithium, see (a) Peng, Y.; Bai, G.; Fan, H.; Vidovic, D.; Roesky, H. W.; Magull, J. *Inorg. Chem.* **2004**, *43*, 1217−1219. (b) Davidson, M. G.; Davies, R. P.; Raithby, P. R.; Snaith, R. *Chem. Commun.* **1996**, 1695−1696.



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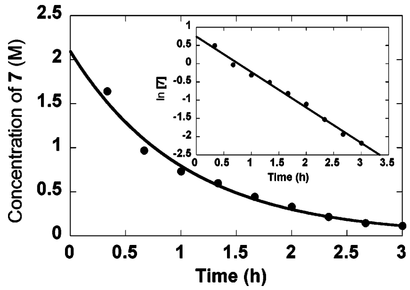
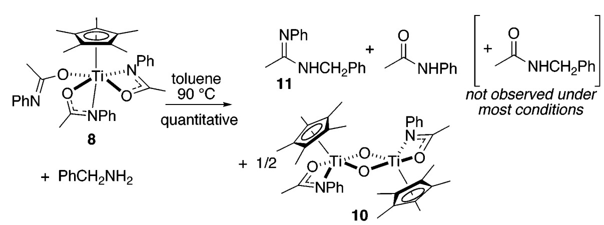


Figure 4. Kinetic data for the thermolysis of **7** at 50 °C in C_6D_6, which yields amidine **9** and the bis(*m*-oxo)Ti dimer **10**, [**7**] = 0.11 M.



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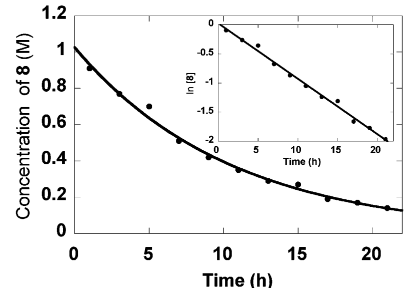


Figure 5. Kinetic data for the reaction of **8** with benzyl amine (10 equiv) at 70 °C in C_6D_6, [**8**] = 0.46 M.

lography (Figure 3). No evidence for transamidation was obtained in this reaction.

Kinetic studies of the conversion of **7** into **9** and **10** were performed by monitoring the reaction by ^{1}H NMR spectroscopy. Clean exponential decay of **7** ($k = 2.97(3) \times 10^{-4}$ s^{-1}) (Figure 4) together with the fact that free amine (3−5 equiv *i*PrNH$_2$) does not affect the rate suggests that the reaction proceeds by an intramolecular pathway. Thermolysis of the deuterated analogue of **7**, Cp*Ti(ND*i*Pr)[κ^2-OC(Me)NPh]$_2$ (**7**-d_1), revealed that the reaction does not exhibit a kinetic isotope effect ($k_H/k_D = 1.0(\pm 0.1)$).

The reactivity of trisamidate complex **8** in the presence of exogenous benzyl amine was examined (Figure 5). At elevated temperatures, **8** reacts with 1 equiv of benzyl amine ($PhCH_2$-NH_2) to afford the amidine MeC(=NPh)NHCH$_2$Ph (**11**), the bis(μ-oxo)Ti dimer **10**, and acetanilide in 2:1:2 ratio, respectively (eq 3). The same products are observed when the reaction is performed in the presence of a 10- and 20-fold excess of benzyl amine, and the rate approximately doubles when the benzyl amine concentration is increased from 10 to 20 equiv (pseudo-first-order rate constants = $1.6(3) \times 10^{-4}$ and $3.4(3) \times 10^{-4}$ s^{-1}, respectively, at 70 °C). No significant kinetic isotope effect is observed when the reaction is performed with $PhCH_2ND_2$ ($k_H/k_D = 1.1(\pm 0.1)$). As for thermolysis of **7**, the reaction of **8** with benzyl amine provides no evidence for transamidation (e.g., formation of *N*-benzylacetamide or -amidate products).

Whereas transamidation was not observed under the conditions of eqs 2 and 3, we previously reported that 5 mol % Cp*Ti-(N*t*Bu)(py)Cl (**3**) catalyzes transamidation between carboxamide **1** and benzyl amine (six turnovers after 20 h; cf. eq 1).[7a] This evidence that Cp*-ligated Ti complexes can promote transamidation (albeit not as effectively as Ti(NMe$_2$)$_4$) prompted us to test the possibility that transamidation could be observed with complex **8** under alternate reaction conditions (Table 1). The first three entries in Table 1 denote the results described above wherein 1, 10, and 20 equiv of benzyl amine react with **8** in toluene at 90 °C to produce the amidine **11** in nearly quantitative yield. Addition of exogenous acetanilide to the reaction of **8** with 1 equiv of benzyl amine does not alter the outcome (entries 4 and 5). The only conditions identified that lead to transamidation with **8** feature the use of excess benzyl amine *and* acetanilide (i.e., conditions simulating catalytic conditions with

Table 1. Composition of a Product Mixture from the Reaction between **8** and Benzyl Amine in the Presence of Acetanilide at 70 °C and in C_6D_6 for 24 h

entry	[**8**] (M)	$PhCH_2NH_2$ (equiv)	acetanilide (equiv)	transamidation yield (%)[a,b]	amidine yield[a] (%)
1	0.26	1	0	0	≥97
2	0.26	10	0	0	≥97
3	0.26	20	0	0	≥97
4	0.26	1	1	0	≥97
5	0.26	1	10	0	≥97
6	0.26	10	10	8	89
7	0.26	25	10	24	75
8	0.02	10	10	0	≥97

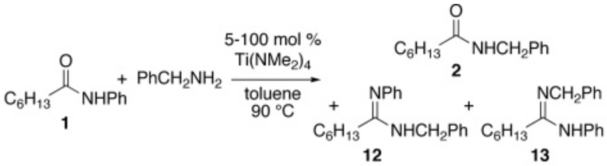
[a] Transamidation product = *N*-benzylacetamide. [b] Yields of *N*-benzylacetamide and amidine **11** reported relative to the initial concentration of complex **8**.

a substrate/Ti ratio ≥ 10).[16] Even in these cases, however (entries 6 and 7), the transamidation yield is substoichiometric with respect to **8**. Furthermore, the transamidation reactivity disappears when the substrate and Ti concentration is reduced (entry 8). Under the reaction conditions employed in this final entry, exclusive transamidation is observed if **8** is replaced by Ti(NMe$_2$)$_4$ (see later).

These results with Cp*-ligated Ti complexes reveal that the Cp* ligand significantly reduces or eliminates the ability of Ti^{IV} to promote transamidation. In nearly every case tested, the formation of amidines and oxotitanium products is favored over transamidation. For transamidation to be observed, a large excess of amine and carboxamide substrate relative to Ti and a high Ti concentration appear to be essential. These conclusions provided a basis for further investigation of the origin of the divergence between amidine formation and transamidation.

Reactivity of Primary Amine/Carboxamide Mixtures in the Presence of Ti(NMe$_2$)$_4$. The transamidation reaction between benzyl amine and *N*-phenylheptanamide (**1**), which forms aniline and *N*-benzylheptanamide (**2**), is catalyzed ef-

(16) After these reactions were complete, a small amount of water was added to quench the Ti catalyst, and the organic layer was analyzed by gas chromatography. No evidence for the presence of free Cp*H ligand was found. We conclude from this result that a [Cp*Ti]-based complex accounts for the observed transamidation, not a small amount of a Cp*-free Ti complex that forms under the reaction conditions.



(4)

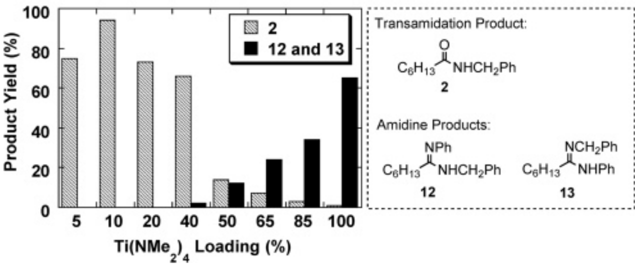
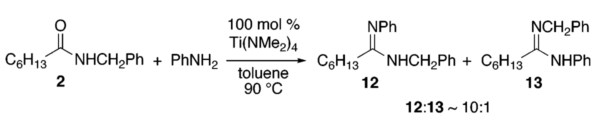


Figure 6. Dependence of the product distribution on the $Ti(NMe_2)_4$ loading in the reaction between benzyl amine and the *N*-phenylheptanamide. Reaction conditions: **1** (0.39 mmol), $PhCH_2NH_2$ (0.39 mmol), $Ti(NMe_2)_4$ (0.020−0.39 mmol), toluene (2 mL), 90 °C, 18 h.

fectively by $Ti(NMe_2)_4$ (5 mol %) (eq 1).[6] On the basis of the results with Cp*-ligated Ti complexes, we investigated the effect of varying the $Ti(NMe_2)_4$ loading on the outcome of the reaction between **1** and benzyl amine (eq 4, Figure 6).

When ≤20 mol % $Ti(NMe_2)_4$ is used, the only product obtained from the reaction is **2**, resulting from the transamidation of **1**. As the titanium loading is increased, however, the reaction yields a mixture of **2** and amidine isomers, **12** and **13**. With 50 mol % $Ti(NMe_2)_4$, both transamidation and amidine products form; however, neither forms in good yield. When a *stoichiometric* quantity of $Ti(NMe_2)_4$ is present, amidine products form almost exclusively in a ratio of ∼2:1 favoring **13**. No dibenzylamidine (i.e., the amidine arising from reaction of amide **2** and benzyl amine) is observed under any of these conditions. The reaction progress under these stoichiometric conditions was monitored to ascertain whether enhanced levels of transamidation are evident at short reaction times (i.e., whether transamidation is kinetically favored, but amidine formation thermodynamically favored); however, only trace amounts of the transamidation product are observed throughout the course of the reaction.

The amidine product ratio appears to be under kinetic control. A different product ratio (**12**/**13**−10:1) is observed in the reaction between *N*-benzylamide **2** and aniline in the presence of 100 mol % $Ti(NMe_2)_4$ (eq 5), indicating that amidines **12** and **13** do not equilibrate, at least not rapidly, under the reaction conditions. None of the transamidation product **1** is observed under the conditions of eq 5. We note that the amidine product that is favored in eqs 4 and 5 incorporates the amine substrate into the "imine" site of the product. These observations are consistent with a mechanism in which the primary amine reacts to form an imido ligand prior to reaction with the carbonyl of the amide substrate (see later).



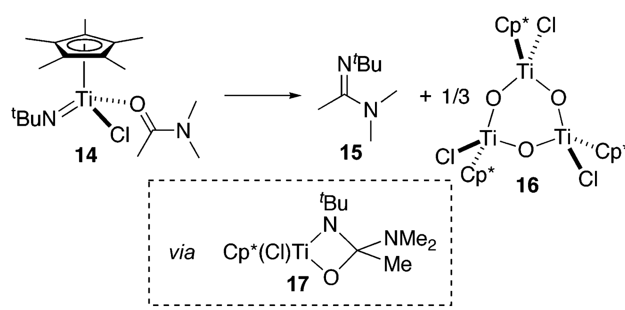
(5)

These collective results indicate that the divergence between transamidation and amidine formation can be dictated by varying the substrate/Ti ratio and is not necessarily a function of the identity of the titanium complex. Nevertheless, the ancillary ligands play an important role because Cp*-ligated Ti complexes are poor transamidation catalysts and promote amidine formation even under conditions that lead to transamidation with $Ti(NMe_2)_4$ as the catalyst. The size as well as the electron-rich character of the Cp* ligand could contribute to diminished transamidation activity of Cp^*Ti^{IV}-based complexes.

Mechanistic Considerations Relevant to the Divergence between Amidine Formation and Transamidation. The results of this study reveal that primary amines react with carboxamides to form amidines if a stoichiometric quantity of Ti^{IV} is present. With a catalytic quantity of Ti^{IV}, either transamidation or amidine formation can occur, depending on the identity of the Ti complex.

Thermolysis of the $Cp^*Ti(\kappa^2\text{-amidate})_2$(amido) complex **7** (eq 2) is perhaps the simplest reaction among those investigated in this study. The kinetics data reveal that the reaction proceeds intramolecularly. The negligible kinetic isotope effect indicates that proton transfer is not rate-limiting; however, pre-equilibrium proton transfer cannot be excluded, particularly if the proton is transferred between two atoms whose bonds to hydrogen have similar force constants. In this context, a plausible reaction sequence for amidine formation (Scheme 3) consists of (i) pre-equilibrium proton transfer from the amido ligand to the κ^2-amidate ligand to produce a neutral *O*-bound carboxamide and an imido ligand (**B**), (ii) [2+2]-cycloaddition to form metallacycle **C**, (iii) retro-[2+2]-cycloaddition to produce a Ti complex bearing a coordinated amidine and an oxo ligand (**D**), and (iv) dissociation of the amidine together with aggregation of the oxotitanium species.

The [2+2]-cycloaddition of group 4 imidometal fragments with organic carbonyl groups has precedent with ketone and aldehyde substrates,[17] and we recently reported a similar reaction involving a tertiary carboxamide (eq 6).[7a] *N,N*-Dimethylacetamide adduct **14**, which resembles intermediate **B** in Scheme 3, reacts intramolecularly to produce amidine **15** and the oxotitanium trimer **16**. The metallacyclic species **17** (cf. **C**, Scheme 3) is a probable intermediate in the reaction shown in eq 6, and the formation of strong Ti−O bonds provides a thermodynamic driving force for this process.



(6)

In principle, transamidation, too, could proceed via a four-membered metallacycle (i.e., **C**, Scheme 3). Such a transamidation pathway would require that the uncoordinated amine fragment in **C** exchange with the amido ligand (**C** → **C′**, Scheme 4) followed by retro-[2+2] cycloaddition to regenerate an imido-

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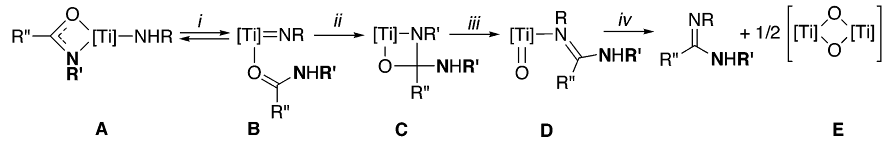
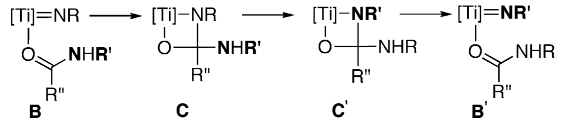
Scheme 3. Proposed Mechanism for Amidine Formation from the Bis(amidate)amidoTi Complex **7**



Scheme 4. Hypothetical Mechanism for Transamidation Proceding via Metallacyclic Intermediates



rather than an oxotitanium species (**C′** → **B′**, Scheme 4). The retrocycloaddition of **C′** to form **B′** seems unlikely, however, and preliminary density-functional theory (DFT) calculations confirm this suspicion. The energy profile in Figure 7 reveals that [2+2]-retrocycloaddition from **C1** (a methyl-substituted analogue of intermediate **C**) to form an oxotitanium fragment with a coordinated amidine (**D1)** is both kinetically and thermodynamically favored over formation of an imidotitanium fragment and a coordinated carboxamide (**B1**). These results imply that transamidation does not proceed via the metallacyclic structure **C** because such a metallacycle should instead lead to amidine formation.

We do not yet fully understand the mechanistic origin of transamidation activity; however, several of our observations establish important constraints for any mechanistic hypothesis. Transamidation requires a high substrate/Ti ratio (cf. Table 1 and Figure 6). In addition, secondary carboxamides exchange readily with amido and imido ligands at Ti^{IV} to form Ti^{IV}-amidate species, and the amidate ligands may coordinate in a κ^1 or κ^2 manner (cf. Schemes 1 and 2). These observations suggest that $Ti(NMe_2)_4$ will form a tetrakis(amidate)Ti^{IV} species in the presence of ≥4 equiv of carboxamide (e.g., under catalytic conditions). A similar conclusion was reached in our recent study of Al^{III}-catalyzed transamidation, which revealed the formation of tris(amidate)Al^{III} species when $Al_2(NMe_2)_6$ is combined with ≥3 equiv of secondary carboxamide per Al center.[7b,18] In the Ti-mediated reactions, we propose that the presence of excess carboxamide substrate under catalytic conditions serves to prevent formation of imidotitanium species (**B**, Scheme 4) and, thereby, inhibits the production of amidines.

In light of these considerations, we suggest two possible mechanisms to explain the origin of transamidation activity. In

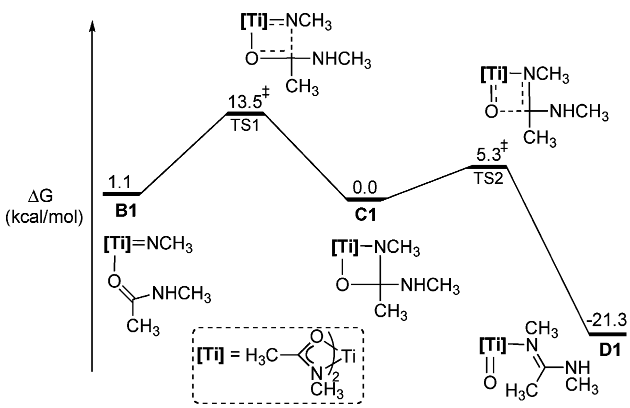
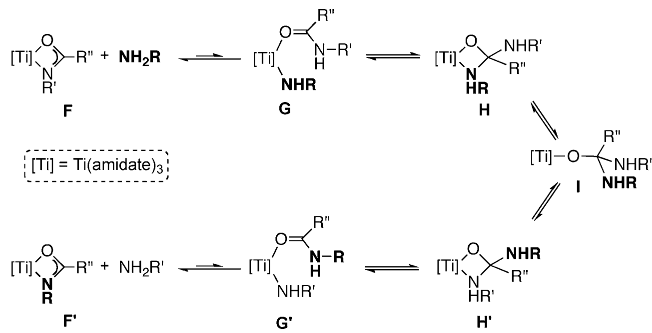
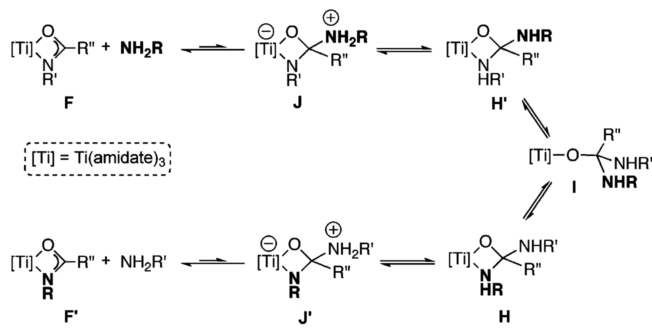


Figure 7. Free energy profile for retrocycloaddition from a model metallacycle **C1** at 90 °C derived from DFT calculations optimized with a double ζ basis set. See Experimental Section for details.

Scheme 5. Proposed Mechanism for Ti^{IV}-Mediated Transamidation Involving Intramolecular Nucleophilic Attack of an Amido Ligand on a Coordinated Neutral Carboxamide Ligand



Scheme 6. Proposed Mechanism for Ti^{IV}-Mediated Transamidation Involving Nucleophilic Attack of an External Amine on a Coordinated Amidate Ligand



the first pathway (Scheme 5), a primary amine reacts with a tetrakis(amidate)Ti^{IV} species **F** to form an amidotitanium species **G**, which possesses a neutral, oxygen-bound carboxamide ligand. Intramolecular nucleophilic attack of the amido ligand on the carboxamide forms metallacycle **H**, which can undergo dissociation of the amino fragment to yield the symmetrical tetrahedral intermediate **I**. The latter species can revert to starting materials or proceed to the transamidation product **F′**. The second hypothetical mechanism (Scheme 6) is related to Scheme 5 but features a different C−N bond-forming step. An external amine undergoes nucleophilic attack on a coordinated amidate ligand to produce zwitterionic intermediate **J**, and intramolecular proton transfer generates metallacycle **H′**, which appears also in Scheme 5.

Both of these mechanisms avoid formation of metallacycle **C** (Scheme 4, Figure 7), which appears to lead to amidine formation. Although intermediates **H** and **H′** resemble **C**, we hypothesize that the presence of a proton on the coordinated nitrogen atom of the metallacycles in **H** and **H′** will weaken the Ti−N bond, thereby facilitating exchange of the amino fragments and enabling transamidation. Because amidines also

(18) Further support for (amidate)titanium species under catalytic conditions is obtained from kinetic studies. Both Ti- and Al-catalyzed transamidation reactions exhibit a zero-order rate dependence on [carboxamide], consistent with the proposal that the amide substrate is complexed to the catalytic metal center prior to the rate-determining step (ref. 7b for detailed discussion).

can potentially form via intermediates **H**/**H′** and **I**, further studies will be needed test these proposals. Extensive DFT studies have been initiated to probe the mechanisms in Schemes 5 and 6 in an effort to identify the preferred C−N bond forming pathway and to evaluate whether the intermediates in these mechanisms face higher barriers for amidine formation relative to transamidation.

Conclusion

The data reported here significantly advance our understanding of Ti-mediated exchange processes involving carboxamides and amines, particularly with respect to the ability of Ti^{IV} to promote either transamidation or amidine formation depending on the reaction conditions. We find that Ti^{IV}, when present in approximately stoichiometric quantity with respect to the substrates, promotes amidine formation rather than transamidation. This result is attributed to the formation of a four-membered metallacycle that can undergo retrocycloaddition to form amidine and a thermodynamically stable oxotitanium product. The ability of Ti^{IV} to avoid irreversible formation of oxotitanium products and promote transamidation under the catalytic conditions is quite remarkable. Insights from the present study suggest that exogenous substrates (both amine and carboxamide) present under catalytic conditions prevent formation of a four-membered metallacycle, as in **C**, that leads to amidine formation and Ti inactivation via formation of an oxo complex. Avoidance of metallacycle **C** under catalytic reaction conditions enables transamidation to occur. Substoichiometric transamidation is observed in the presence of the Cp^*Ti^{IV}-(amidate)$_3$ complex **8**; however, the electron-donating and sterically bulky Cp* ligand renders Ti^{IV} ineffective as a transamidation catalyst. Thus, we find that the ability of Ti^{IV} to promote transamidation depends upon both the substrate/Ti ratio and the ancillary ligands coordinated to Ti^{IV}. Although further work will be necessary to elucidate the mechanistic origin of transamidation activity, the results of this study highlight an unexpected dichotomy in the reactivity of Ti^{IV} with carboxamides and amines.

Experimental Section

General Procedures. All manipulations were carried out under an atmosphere of nitrogen using standard Schlenk or glove box techniques. All solvents (diethyl ether, dichloromethane, toluene, and pentane) were dried by passing over a column of activated alumina followed by a column of Q-5 scavenger. Complex **5**,[13] $PhCH_2ND_2$, and *i*PrND_2[19] were synthesized according to literature procedures. All other reagents were purchased from commercial sources and used as supplied.

Benzene-d_6 and CD_2Cl_2 were dried over Na−K alloy/benzophenone and CaH_2, respectively, for 24 h and vacuum transferred prior to use. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on Bruker AC-300 spectrometers at 300 and 75 MHz, respectively. Elemental analyses were performed by Midwest Microlab laboratory.

Cp*Ti(NH*i*Pr)$_3$ (6). To a solution of **5** (0.372 g, 1.18 mmol) in 10 mL of toluene, isopropyl amine (1.0 mL, 11.80 mmol) was added at ambient temperature. The reaction was brought to reflux in a sealed Schlenk tube at 110 °C overnight, whereupon all the volatiles were removed under vacuum, and the residue was extracted with 10 mL of pentane, filtered through Celite and evaporated to dryness. The residue was crystallized from ca. 7 mL of pentane at −30 °C to afford the product **6** as yellow crystals (0.219 g, 52.5%). ^{1}H NMR (300 MHz, benzene-d_6): δ 1.11 (d, 18 H, J = 7.2 Hz, CHMe_2), 1.87 (s, 15 H, C_5Me_5), 4.27 (sept, 3 H, J = 7.2 Hz, CHMe$_2$), 5.18 (br s, 3 H, NH). ^{13}C{^{1}H} NMR (75 MHz, benzene-d_6): δ 11.7 (C_5Me_5), 27.8 (CHMe_2), 54.8 (CHMe$_2$), 116.8 (C_5Me$_5$). IR (CH_2Cl_2): ν_{max} 2956 s, 2912 s, 2859 s (NH) cm^{-1}. Anal. Calcd for $C_{34}H_{39}N_3O_3Ti$: C, 63.83; H, 11.02; N, 11.76. Found: C, 63.62; H, 10.95, N, 11.73.

Cp*Ti(ND*i*Pr)$_3$ (6-d_1). This complex was prepared in a similar way as **6** from **5** (0.372 g, 1.18 mmol) and *i*PrND_2 (0.56 g, 11.80 mmol) to afford the product **6**-d_1 as yellow crystals (0.201 g, 49.2%). ^{1}H NMR (300 MHz, benzene-d_6): δ 1.11 (d, 21 H, J = 7.2 Hz, CHMe_2), 1.88 (s, 15 H, C_5Me_5), 4.28 (sept, 3 H, J = 7.2 Hz, CHMe$_2$).

Cp*Ti(NH*i*Pr)[κ^2-OC(Me)NPh]$_2$ (7). To a solution of **6** (0.047 g, 0.13 mmol) in 10 mL of Et_2O, acetanilide (0.025 g, 0.19 mmol) was added at ambient temperature. The reaction was stirred overnight, whereupon all the volatiles were removed under vacuum, and the residue was extracted with pentane, filtered through Celite, and evaporated to dryness. The residue was crystallized from ca. 3 mL of pentane at −30 °C to afford the product **7** as yellow crystals (0.032 g, 47.8%). ^{1}H NMR (300 MHz, benzene-d_6): δ 0.91 (d, 6 H, J = 6.6 Hz, CHMe_2), 2.80 (s, 3 H, CMe[OC(Me)NPh]), 2.08 (s, 15 H, C_5Me_5), 4.86 (sept, 1 H, J = 6.6 Hz, CHMe$_2$), 6.94−7.21 (m, 10 H, Ph), 8.64 (br s, 1 H, NH). ^{13}C{^{1}H} NMR (75 MHz, benzene-d_6): δ 14.2 (C_5Me_5), 21.7 (CMe[OC(Me)NPh]), 28.7 (CHMe_2), 57.6 (CHMe$_2$), 125.3 (C_5Me$_5$), 125.9, 128.2, 131.4, 150.8 (Ph), 178.6 (CMe[OC(Me)NPh]). IR (CH_2Cl_2): ν_{max} 3044 m (NH) cm^{-1}; 1588 s, 1546 m (sh) (amidate) cm^{-1}. Anal. Calcd for $C_{29}H_{39}N_3O_2Ti$: C, 68.36; H, 7.73; N, 8.25. Found: C, 68.66; H, 7.90, N, 8.22.

Cp*Ti(ND*i*Pr)[κ^2-OC(Me)NPh]$_2$ (7-*d*). This complex was prepared in a similar way as **7**-d_1 from **6**-d_1 (0.047 g, 0.13 mmol) and acetanilide (0.026 g, 0.19 mmol) to afford the product **7**-d_1 as yellow crystals (0.034 g, 51.2%). ^{1}H NMR (300 MHz, benzene-d_6): δ 0.87 (d, 6 H, J = 6.6 Hz, CHMe_2), 1.75 (s, 3 H, CMe[OC(Me)NPh]), 2.02 (s, 15 H, C_5Me_5), 4.80 (sept, 1 H, J = 6.6 Hz, CHMe$_2$), 6.90−7.15 (m, 10 H, Ph).

Cp*Ti[κ^1-OC(Me)NPh][κ^2-OC(Me)NPh]$_2$ (8). To a solution of **6** (0.094 g, 0.26 mmol) in 15 mL of Et_2O, acetanilide (0.107 g, 0.78 mmol) was added at ambient temperature. The reaction was stirred overnight, whereupon all the volatiles were removed under vacuum, the residue was extracted three times with 4 mL of 6:1 pentane/toluene solvent mixture, filtered through Celite, and evaporated to dryness. The residue was crystallized from ca. 5 mL of 6:1 pentane/toluene solvent mixture at −30 °C to afford the product **8** as red crystals (0.107 g, 70.0%). ^{1}H NMR (300 MHz, benzene-d_6): δ 1.66 (s, 3 H, CMe[κ^1-OC(Me)NPh]), 2,12 (s, 6 H, CMe[κ^2-OC(Me)NPh]), 1.92, 1.93 (s, 15 H, C_5Me_5), 6.99−7.53 (m, 15 H, Ph). ^{13}C{^{1}H} NMR (75 MHz, benzene-d_6): δ 11.8, 12.0 (C_5Me_5), 19.1 (CMe[κ^1-OC(Me)NPh]), 24.3 (CMe[κ^2-OC(Me)NPh]), 123.3, 124.2 (C_5Me$_5$), 121.6, 124.6, 128.6, 129.0, 129.9, 146.4, 147.3, 150.8 (Ph), 174.8 (CMe[κ^1-OC(Me)NPh]), 175.3 (CMe-[κ^2-OC(Me)NPh]). IR (CH_2Cl_2): ν_{max} 1604 m (sh), 1596 s, 1561 m (sh) (amidate) cm^{-1}. Anal. Calcd for $C_{34}H_{39}N_3O_3Ti$: C, 69.73; H, 6.73; N, 7.18. Found: C, 69.65; H, 6.85, N, 7.63.

Thermolysis of 7 Leading to MeC(═N^{i}Pr)NHPh (9) and Cp*Ti(μ-O)[κ^2-OC(Me)NPh]}$_2$ (10). A solution of **7** (0.058 g, 0.11 mmol) in 1 mL of C_6D_6 was heated at 50 °C for 3 h, whereupon ^{1}H NMR spectrum showed ∼100% conversion of the starting material into amidine **9** and complex **10**. Then all the volatiles were removed under vacuum, the residue was dissolved in 1 mL of CH_2Cl_2, layered with 5 mL of pentane, and stored at −30 °C for 2 days. The supernatant, decanted from yellow crystals of **10** (0.042 g, 87.4%), which contained **9** and residual **10** was evaporated to dryness; the residue extracted with ca. 3 mL of 2:1 pentane/Et_2O solvent mixture, filtered through Celite, and crystallized at −30 °C to afford the amidine **9** as white crystals (0.014 g, 69.5%).

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9: ^{1}H NMR (300 MHz, benzene-d_6): δ 1.19 (d, 6 H, J = 6.6 Hz, CH*Me*$_2$), 3.54 (br s, 1 H, NH), 4.51 (sept, 1 H, J = 6.6 Hz, *CH*Me$_2$), 7.08−7.45 (m, 5 H, Ph). MS (EI) *m/z*: 176 (100, M^+).

10: ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.83 (s, 30 H, C_5Me_5), 2.25 (s, 6 H, C*Me*[OC(Me)NPh]), 7.09−7.36 (m, 10 H, Ph). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_2Cl_2): δ 11.5 (C_5*Me*$_5$), 19.5 (C*Me*[OC(Me)NPh]), 123.3 (*C*$_5$Me$_5$), 123.8, 124.2, 128.5, 144.9 (Ph), 175.7 (*C*Me[OC(Me)NPh]). Anal. Calcd for $C_{36.125}H_{46.28}Cl_{0.25}N_2O_4Ti_2$ (contains $^{1}/_{8}$ CH_2Cl_2 solvent molecule): C, 64.07; H, 6.90; N, 4.14. Found: C, 63.95; H, 6.97, N, 4.37.

Kinetic Studies of the Reaction between Trisamidate Complex 8 and Benzyl Amine. A solution of **8** (0.270 g, 0.46 mmol), benzyl amine (0.5 mL, 4.60 mmol), and 1,3,5-trimethoxybenzene (internal standard) in 0.5 mL of C_6D_6 was heated at 70 °C for 24 h, whereupon the ^{1}H NMR spectrum revealed ∼100% conversion of the starting material into amidine **11** and complex **10**.

Studies of the Thermal Reaction between Trisamidate Complex 8, Acetanilide, and Benzyl Amine. (a) A solution of **8** (0.077 g, 0.13 mmol), appropriate amounts of benzyl amine and acetanilide, and 1,3,5-trimethoxybenzene (internal standard) in 0.5 mL of C_6D_6 was heated at 70 °C for 24 h, whereupon the ^{1}H NMR spectrum revealed ∼100% conversion of the starting material into complex **10**, amidine **11**, and benzylacetamide (transamidated carboxiamide). After that, water (100 μL) was added to the reaction mixture to hydrolyze Ti-based species. The solution was dried over Na_2SO_4 and analyzed by GC.

(b) A solution of acetanilide (0.080 g, 0.39 mmol), **8** (0.022 g, 0.039 mmol) in 2 mL of toluene, benzyl amine (42 μL, 0.39 mmol), and Ph_3CH (3 mg, internal standard) was brought to 90 °C in a sealed tube and heated for 18 h, whereupon it was cooled to ambient temperature. Water (100 μL) was added to the reaction mixture to hydrolyze Ti-based species. The toluene solution was dried over Na_2SO_4 and analyzed by GC.

Reaction between *N*-Phenyl Heptanamide (1) and Benzyl Amine in the Presence of $Ti(NMe_2)_4$. To a solution of **1** (0.080 g, 0.39 mmol) and Ph_3CH (3 mg, internal standard) in 2 mL of toluene, benzyl amine (42 μL, 0.39 mmol) was added at ambient temperature followed by the appropriate amount of $Ti(NMe_2)_4$ (0.02−0.39 mmol). The reaction mixture was stirred for 5 min, whereupon it was stripped to dryness to remove any $HNMe_2$. Then the residue was redissolved in 2 mL of toluene and brought to 90 °C in a sealed vial and heated for 18 h, whereupon it was cooled to ambient temperature. Water (100 μL) was added to the reaction mixture to hydrolyze Ti-based species. The toluene solution was dried over Na_2SO_4 and analyzed by GC.

Computational Methods. The geometries for all critical species (reactants, intermediates, transition states, and products) were optimized in the gas phase using the hybrid density-functional theory, B3LYP.[20] To simplify calculations, the amide was replaced with acetamide. The effective core potential (ECP) of Hay and Wadt[21] and the corresponding basis set (augmented by an *f* function[22]) were used for Ti; the 6-31G(d,p) basis[23] was used for all other main group elements during geometry optimizations and frequency calculations. Vibrational frequency calculations were subsequently carried out to verify the character of the optimized structures and to obtain zero-point energy corrections to barrier heights. Single-point total energies were calculated for all atoms with the all electron 6-311+G(d,p) basis set,[24] and the thermal corrections from the optimized structure was added to generate the free energies. All calculations were performed with the Gaussian 03 program.[25]

Acknowledgment. We are grateful to the NSF Collaborative Research in Chemistry program (Grant CHE-0404704) for financial support of this work. We thank Prof. L. L. Schafer for sharing ref 11 with us prior to publication.

Supporting Information Available: Complete ref 25, crystallographic data for **7**, **8**, and **10** (PDF, CIF), and computed geometries for structures in Figure 7 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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