Communications

Titanium(IV)-Mediated Conversion of Carboxamides to Amidines and Implications for Catalytic Transamidation

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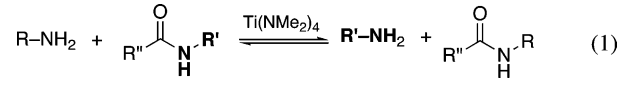
Summary: Cp-ligated imidotitanium(IV) complexes, Cp*TiCl(NR)(py)Cl (R = tBu (**5a**), $PhCH_2$ (**5b**), n-C_5H_{11} (**5c**), p-MeC_6H_4 (**5d**), p-$MeOC_6H_4$ (**5e**)), react with tertiary and secondary carboxamides to yield amidines, a result that is in contrast with previously reported titanium-catalyzed transamidation reactions. The tertiary amide dimethylacetamide reacts directly with the imidotitanium(IV) fragment, whereas the secondary amide phenylacetamide forms an amidate adduct, {(η^5-C_5Me_5)TiCl[OC(Me)NPh]$_2$} (**10**), which undergoes subsequent reaction with exogenous amine.*

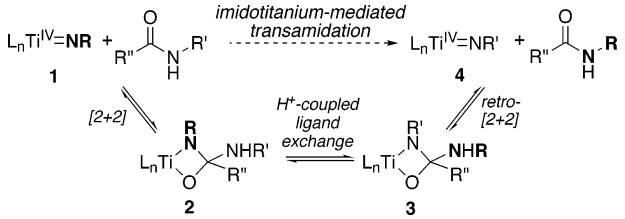
The carboxamide group is ubiquitous in chemistry and biology, and the development of facile amide exchange reactions will enable the selective manipulation of these molecules.[1] We recently reported a unique transamidation reaction that employs metal−amido complexes, such as $Ti(NMe_2)_4$, as catalysts (eq 1).[2] To



(1)

facilitate the development of improved catalysts for this reaction, we have begun probing the fundamental reactivity of amines and carboxamides with catalytically relevant metal centers. Primary amines react with $Ti(NMe_2)_4$ to form imido adducts,[3] and an imidotitanium-mediated pathway for transamidation can be envisioned (Scheme 1). Group 4 metal−imido complexes have received widespread attention in recent years because of their diverse reactivity with organic substrates and their role in catalysis;[4,5] however, reactions with secondary and tertiary carboxamides have not been explored.[6] Here we report that both types of substrates react with a well-defined imidotitanium(IV) complex, Cp*Ti(N*t*Bu)(py)Cl (**5a**), but neither yields transamidation products. Instead, the substrates undergo facile stepwise conversion to amidine products. These observations raise important mechanistic questions regarding Ti-mediated transamidation and have potential synthetic utility.

Scheme 1. Possible Mechanism for Imidotitanium-Mediated Transamidation



The readily accessible imidotitanium complex **5a**[7] was selected for study because Cp* serves as a robust and spectroscopically diagnostic ancillary ligand.[8] *N*,*N*-Dimethylacetamide reacts with an equimolar amount of **5a** to displace pyridine and form adduct **6a** in 74% isolated yield (Scheme 2). Crystallographic characterization of **6a** (Figure 1) reveals that the tertiary carboxamide ligand coordinates through the anti carbonyl lone pair. This orientation is probably sterically preferred over coordination of the more basic syn lone pair. Subsequent thermolysis of **6a** at 50 °C in toluene results in nearly quantitative conversion to the *tert*-butyl-*N*,*N*-dimethylamidine **7a** and the oxo-bridged titanium trimer **8** (Scheme 2). The C_s-symmetric structure of **8** was confirmed by crystallographic analysis.

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(8) Complex **5a** does serve as a catalyst for transamidation between benzylamine and *N*-phenylheptanamide under our previously reported conditions,[2] but it is less effective than $Ti(NMe_2)_4$ (~6 vs 20 turnovers after 20 h, respectively).

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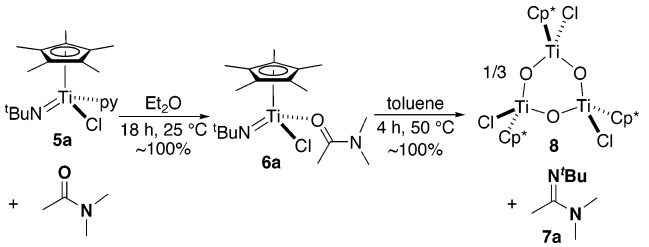
Scheme 2



The ability of the *tert*-butyl imido fragment to undergo exchange with primary amines enables the facile preparation of variously substituted amidines. Benzylamine reacts with **5a** at ambient temperature to form an imido-bridged, dimeric titanium complex, **9b**, which was characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Exchange between **5a** and *p*-$MeC_6H_4NH_2$, *p*-$MeOC_6H_4NH_2$, or *n*-$C_5H_{11}NH_2$ led to a mixture of species in solution; hence, no attempts were made to isolate the imidotitanium(IV) products. Removal of the volatiles, including *tert*-butylamine, from these exchange reactions, followed by dissolution in toluene, addition of *N,N*-dimethylacetamide, and thermolysis at 50 °C, led to nearly quantitative formation of the corresponding amidines and the oxotitanium trimer (Scheme 3).

Kinetic studies of the decomposition of **6a** in toluene-d_8 at 50 °C, monitored by ^{1}H NMR spectroscopy, revealed clean exponential decay of [**6a**] with a first-order rate constant of 4×10^{-4} s^{-1}.[9] The reaction rate is unaffected by the presence of free amine (3−5 equiv of *t*$BuNH_2$), and no evidence for transamidation is observed under the reaction conditions.

These data are consistent with a mechanism involving intramolecular [2 + 2] cycloaddition of the coordinated-carbonyl and Ti=N fragments. Retro [2 + 2] from the four-membered metallacyclic intermediate (cf. **2**; Scheme 1) yields amidine and the oxotitanium product. Group 4 metal−imido complexes undergo similar reactivity with aldehydes and ketones to yield imines;[10] however,

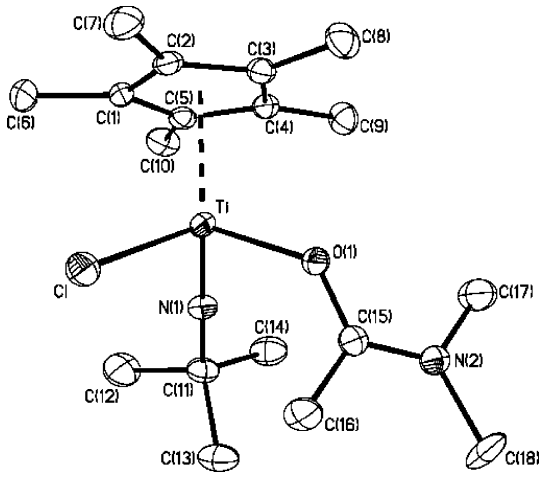
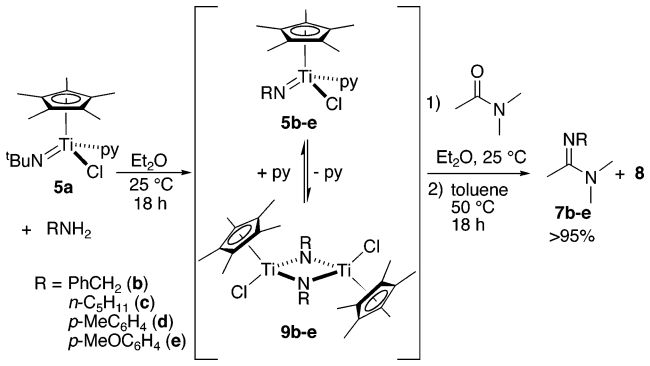
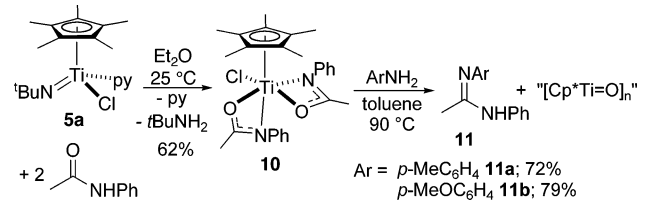


Figure 1. Molecular structure (50% thermal ellipsoids) of **6a** in the major conformation. Hydrogen atoms have been removed for the sake of clarity. Important bond distances (Å) and angles (deg): Ti−N(1) = 1.7056(16), Ti−O(1) = 2.004(7), Ti−Cl = 2.3697(6), N(1)−C(11) = 1.452(2), O(1)−C(15) = 1.268(4), N(2)−C(15) = 1.310(3); N(1)−Ti−O(1) = 102.2(7), N(1)−Ti−Cl = 103.76(6), O(1)−Ti−Cl = 98.8(2).

Scheme 3



Scheme 4



the present results are noteworthy because of the intrinsic differences in substrate reactivity. Aldehydes and ketones can form imines by simple condensation with primary amines under metal-free conditions, whereas carboxamides are kinetically inert under such conditions. Amidine synthesis from carboxamides generally requires preactivation with a highly reactive electrophile, such as triflic anhydride.[11,12]

Acetanilide reacts differently from *N,N*-dimethylacetamide. Two equivalents of the secondary amide react with **5a** by displacing pyridine and *t*$BuNH_2$ to form the bis(κ^2-amidate) **10**, which was isolated in 62% yield and characterized by X-ray crystallography (Scheme 4, Figure 2). This rare example of a well-defined amidate−titanium complex[13] exhibits a pseudo-octahedral geometry with the Cp* ligand and an amidate nitrogen occupying apical positions. The two amidate ligands are distinguished by their relative localization of π-electron density (Figure 2): the diequatorial amidate exhibits greater double-bond character for the C−O bond, whereas the equatorial/apical amidate exhibits a shorter C−N bond. Formation of the 2:1 adduct **10** appears to be highly favored over the 1:1 adduct. When only 1 equiv of acetanilide is added to a solution of **5a**, unreacted **5a** and **10** are the only products observed.

κ^2-Amidate adducts are reasonable intermediates in Ti(IV)-catalyzed transamidation reactions between aryl-

(9) See the Supporting Information for details.

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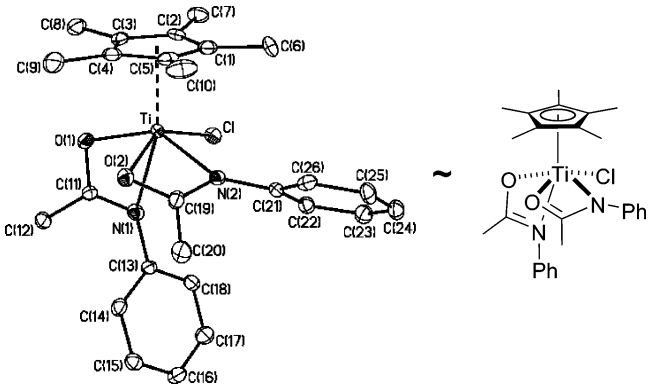

Figure 2. Molecular structure (50% thermal ellipsoids) of **10** and a line drawing reflecting the preferred resonance structures for the coordinated κ^2-amidates. Hydrogen atoms have been removed for the sake of clarity. Important bond distances (Å) and angles (deg): Ti−O(1) = 2.0232(11), Ti−O(2) = 2.1193(11), Ti−N(1) = 2.2406(14), Ti−N(2) = 2.1541(13), O(1)−C(11) = 1.317(2), O(2)−C(19) = 1.2875(19), N(1)−C(11) = 1.286(2), N(2)−C(19) = 1.310(2); O(2)−Ti−N(2) = 61.07(5), O(1)−Ti−N(1) = 61.05(5).

amides and arylamines (eq 1). However, when **10** is heated with 1 equiv of a para-substituted aniline in toluene, the secondary amidines **11a** and **11b** are formed (72% and 79% yields, respectively). No transamidation products are observed. The process is accompanied by the formation of small quantities of *N*-phenylacetanilide (<10%) and unidentified organometallic species believed to be aggregated oxotitanium fragments. The addition of 2 equiv of aniline instead of 1 equiv had no significant impact on the yield of amidines **11a** and **11b**. The conversion of **10** into **11b** was monitored by ^{1}H NMR spectroscopy under pseudo-first-order conditions (10 equiv of *p*-$MeOC_6H_4NH_2$). The formation of **11b** proceeds cleanly with a pseudo-first-order rate constant, k_{obs}, of 1.5×10^{-4} s^{-1} at 80 °C.[9] The lack of an observable intermediate in this process restricts our ability to establish the mechanism. Direct attack of the amine on a coordinated amidate seems unlikely on the basis of electrostatic considerations. No reaction occurs between amine and a neutral carboxamide under these conditions, and attack by amine on a formally anionic amidate fragment seems even less likely. Two alternatives seem more probable. Reversible reaction of amine with **10** could form an unobserved, but reactive, imidotitanium complex, which yields amidine via the [2 + 2] mechanism proposed for tertiary amides. Alternatively, an amidotitanium fragment could undergo nucleophilic attack on a coordinated carboxamide or amidate-ligated intermediate. These reaction pathways are the subject of ongoing studies.

This study highlights the ability of Ti(IV) to activate kinetically robust carboxamides to form amidines. A tertiary amide reacts directly with an imidotitanium(IV) fragment, whereas a secondary amide forms an amidate adduct that undergoes subsequent reaction with exogenous amine. In light of these observations, the success of Ti(IV)-catalyzed transamidation (eq 1) is rather surprising. In ongoing studies, we are investigating the origin of divergence between amidine formation and transamidation in Ti-promoted reactions between amines and carboxamides.

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Supporting Information Available: Text, figures, and tables providing details of the synthesis and characterization of compounds **5**−**11**, including crystallographic analysis of **6a**, **8**, and **10** and kinetic data for the decomposition of **6a** and **10**; crystallographic data are also given as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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