A Silica-Supported Titanium Catalyst for Heterogeneous Hydroamination and Multicomponent Coupling Reactions

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A Silica-Supported Titanium Catalyst for Heterogeneous Hydroamination and Multicomponent Coupling Reactions

Kelly E. Aldrich and Aaron L. Odom*

Highly dehydrated silica gel , SiO_2^{700}, gave a material with a total surface hydroxyl density of 0.31 ± 0.05 mmol/g, 0.9 ± 0.1 Si–OH sites/nm^2. Treatment of this material with $Ti(NMe_2)_4$ gave $Ti(NMe_2)_3/SiO_2^{700}$, which is 1.46% ± 0.12 Ti, where the titanium is bound to the surface, on average, through a single O–Si–Ti linkage. This material was tested for its properties as a catalyst for C–N bond forming reactions and was found to be a competent alkyne hydroamination and iminoamination catalyst. For iminoamination, which is the 3-component coupling of an alkyne, primary amine, and isonitrile, this heterogeneous catalyst was able to carry out some catalyses faster than previously reported homogeneous catalysts with lower catalyst loadings. The material is also a catalyst for the addition of aniline to dicyclohexylcarbodiimide to form a substituted guanidine. In addition, a known quinoline with biological activity was prepared using the heterogeneous catalyst in a one-pot procedure using half the catalyst loading of the previously reported synthesis.

Introduction

Homogeneous transition metal complexes that catalyze C–N bond forming reactions are abundant and varied, and high oxidation state Group-4 transition metals have been extensively studied for this purpose.[1-3] In addition to simple C–N bond forming reactions like hydroamination, some of the same catalysts enable multicomponent coupling reactions.[4-13] For example, titanium complexes can catalyze the 3-component coupling (3CC) of an amine, alkyne, and isonitrile to yield tautomers of 1,3-diimines (Figure 1); the reaction is the formal addition of an iminyl group and an amine to an alkyne, iminoamination.[14, 15] A small selection of relevant Group-4 transition metal catalysts and precatalysts competent for C–N bond forming reactions is shown in Figure 1. Catalysts such as these have been thoroughly studied over the past few decades. These studies have provided a well-developed mechanistic understanding, illustrating the details of these C–N bond forming reactions.[16-19] This, in turn, supports targeted design of improved catalysts.

Many groups (Bergman, Doye, Mountford, Odom, Schafer, Tonks, and others) have demonstrated the versatility and practicality of such high oxidation state catalysts for complex organic transformations involving C–N bond formation.[1, 5, 6, 12, 13, 17, 18, 20-32] These transformations lead to heterocycles and other organic building blocks that are more difficult to access via other synthetic methodologies.[5, 7, 33] Recent efforts employing these catalysts often focus on improvements in rate, substrate scope, selectivity, or new reaction pathways, requiring new ancillary ligand designs.[34, 35] Despite these advancements, recent work in the field also demonstrates some of the fundamental limits of homogeneous catalysts. For example, often with these catalysts, the active species can dimerize or undergo other equilibrium processes that reduce the catalyst's activity or deactivate it altogether; noninnocence with ancillary ligands is also reported.[34, 36]

While a tremendous amount of work has gone into different ancillary ligands for hydroamination, there are relatively few studies on heterogeneous catalysts for the reaction. For hydroamination chemistry, and the related iminoamination reaction (Figure 1), this approach seemed promising and remains relatively unexplored, particularly with Group-4 metals. Hydroamination has been examined with a few different types of heterogeneous catalysts,[37-41] including a recent example by Copéret, which used a silica-supported Zn catalyst to produce indoles via an intramolecular hydroamination.[42] These examples primarily utilize late transition metals in low oxidation states. Additionally, multicomponent coupling of the sort shown in Figure 1 with heterogeneous catalysts is not common.[32]

Of course, there are disadvantages to this strategy, perhaps most significant of which is a loss of the detailed understanding associated with molecular catalysis. Thus, in targeting a heterogeneous system, we sought to retain a similar coordination environment at the metal to the homogeneous systems. With this goal in mind, the use of silica-supported titanium catalysts with 2 or more protolytically active sites on the metal (Figure 1) became an attractive option.[37, 43]

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In a recently published study,[32] we examined the catalytic activity of a silica-bound titanium species similar to one reported by Beaudoin and Scott.[44] In this study, the activity of the heterogeneous titanium precatalyst, $Ti(NMe_2)_2/SiO_2^{200}$, was explored for hydroamination and iminoamination activity. This catalyst was easily prepared and performed well as a high-yielding, highly regioselective catalyst for intermolecular hydroamination of a variety anilines and alkynes. However, the catalyst was intolerant of alkylamines and performed poorly as a catalyst for iminoamination. Steric protection of the aniline substrate at the 2 and/or 6 position was necessary to outcompete hydroamination, and the off-cycle formation of formamidine, in the multicomponent coupling.[14] While initial results were promising, we sought more active and selective heterogeneous catalysts.

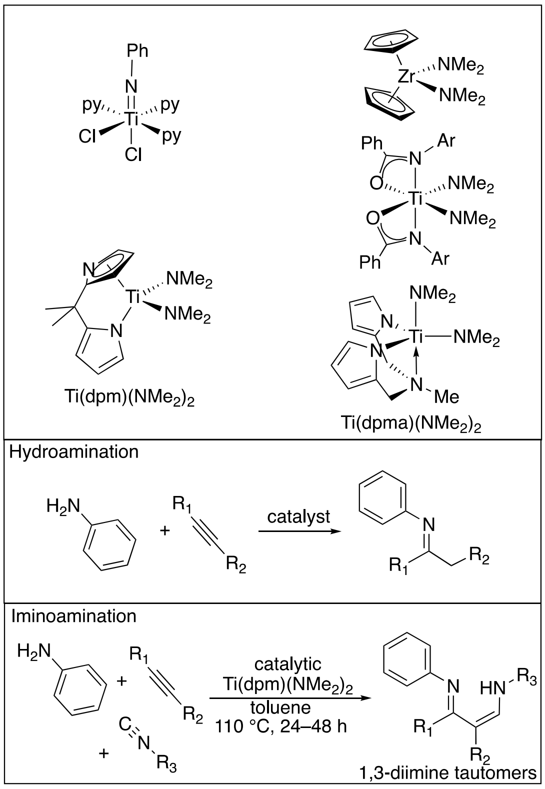


Figure 1. (top) A selection of *Group-4* transition metal catalyst competent for C–C and C–N bond formation reactions. (middle) The addition of a primary amine to an alkyne is catalyzed by all of the example catalysts shown, which provides imines as products. (bottom) Iminoamination effectively adds an iminyl group and an amine across the triple bond of the alkyne, which is catalyzed by $Ti(dpm)(NMe_2)_2$ and $Ti(dpma)(NMe_2)_2$. The products of the reaction are unsymmetrical tautomers of 1,3-diimines.

To alter the reactivity of our surface-supported $Ti(NMe_2)_2/SiO_2^{200}$ catalyst,[32] we turned to the well-explored silica gel preparation of Copéret and coworkers,[37] which often gives species bound to the surface by a single oxygen. A titanium species bound to a SiO_2 surface via a single Si–O–Ti linkage provides a few substantial differences, and possible advantages, compared to the previously studied $Ti(NMe_2)_2/SiO_2^{200}$ catalyst. First, reducing the number of bonds to the surface should provide a dramatically different steric profile around the active metal center. Second, one of the Ti–O bonds, effectively a siloxide ligand, is replaced by an additional dimethylamide, which will participate in protolytic substitution in the reaction mixture. This provides an electronic modification to the active Ti metal.[34] With the objective of producing a catalyst material with titanium bound through a single site to SiO_2, SiO_2^{700} was prepared using a slightly modified version of the Copéret procedure.[37] Onto the SiO_2^{700}, $Ti(NMe_2)_4$ was grafted, to provide the target material.

In this study, the preparation and characterization of the new $Ti(NMe_2)_3/SiO_2^{700}$ is presented, including NMR titration and ICP-OES analysis of titanium content in the as-prepared material. Reactivity of the material in both hydroamination and iminoamination reactions was explored. Activity for hydroamination was comparable to that of $Ti(NMe_2)_2/SiO_2^{200}$, while dramatic improvement in iminoamination catalysis was observed.

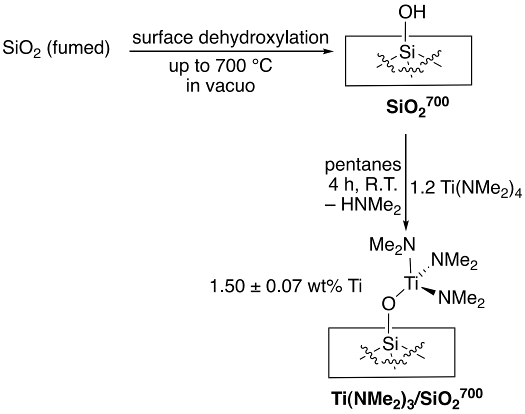
Results and Discussion

$Ti(NMe_2)_3/SiO_2^{700}$ Characterization and Properties

A highly dehydroxylated, high-surface area SiO_2 support material was prepared from slight modification of the literature reported method.[37] The production of SiO_2^{700} involves heating commercially available, high surface area, fumed silica for extended periods of time at several different temperatures. A detailed procedure is given in the Supplementary Information, but, since the procedure includes heating up to 700 °C, we are using the moniker SiO_2^{700}. Upon dehydroxylation, the surface density of hydroxyl sites was determined by NMR titration with $Ti(NEt_2)_4$. The release of $NHEt_2$ was monitored relative to the number of equivalents of $Ti(NEt_2)_4$ consumed vs. hexamethyldisiloxane as an internal standard. This gave a total surface hydroxyl density of 0.31 ± 0.05 mmol/g, or 0.9 ± 0.1 Si–OH sites/nm^2; additionally, this correlates with 0.98 ± 0.04 moles of $NHEt_2$ released per 1.0 mole of $Ti(NEt_2)_4$ consumed to saturate the acidic SiOH sites.

The amount of physisorbed or coordinated (Figure 2c) amine in the isolated catalyst was investigated by treatment with excess pyridine in the presence of an internal standard. This resulted in liberation of 9% $HNMe_2$ relative to the number of moles of titanium sites. This observation suggests that during the titration experiments described above, up to 1.07 ± 0.4 moles of amine may be released per titanium complex added to the silica surface. The stoichiometry determined by titration alone may then provide a slight underestimate of the amount of amine released due to amine interaction with the silica support itself. However, both measurements indicate values very close to 1 amine per titanium site and nearly within experimental error from triplicate measurement using the two techniques. The predicted weight percentage of the SiO_2^{700} upon saturation with $Ti(NMe_2)_4$ was calculated to be 1.46% ± 0.12. This value closely matches the experimentally determined wt% of 1.50% ± 0.07, established by ICP-OES measurements.

The $Ti(NMe_2)_3/SiO_2^{700}$ catalyst was examined by IR spectroscopy as well, which shows new resonances consistent with C–H bonds, which is expected with the proposed dimethylamide structure. No N–H resonance was observed, but, as indicated by the pyridine experiment above to release coordinated and physisorbed amine, the amine present is quite small in the catalyst material, even relative to the 1.5 wt% titanium. Consistent with the above, solid-state ^{13}C NMR resonances at 43 and 36 ppm are observed and tentatively assigned to the dimethylamide and dimethylamine in the sample, respectively.



Scheme 1. Synthesis of $Ti(NMe_2)_3/SiO_2^{700}$ from commercially available SiO_2 and $Ti(NMe_2)_4$.

These bulk material characterizations suggest that the average titanium species in the $Ti(NMe_2)_3/SiO_2^{700}$ material is bound via one Si–O–Ti linkage (Figure 2a). It is worth mentioning that the bulk properties reported here leave some room for variation at individual Ti sites. For example, there could be small numbers of titanium atoms bound by more than one Ti–O bond, as depicted in Figure 2b. There could also be small numbers of Ti species where HNR_2 remains datively bound to the Ti after protonation (Figure 2c). Our bulk characterization in no way rules out some statistical mixture of these site variations, but these potential site variations also don't preclude the material's use in the targeted catalysis. Naturally, this difficulty in determination of the *true* active species is not unique to heterogeneous catalysis and is a problem shared by those studying homogeneous catalysis as well.

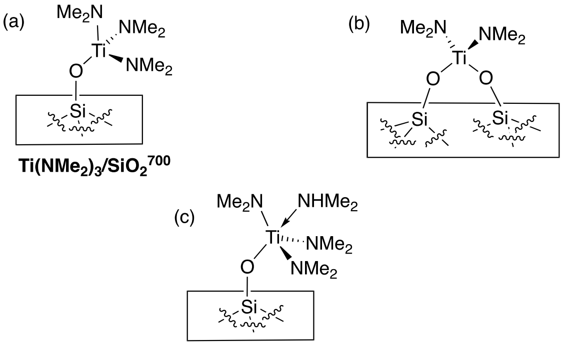
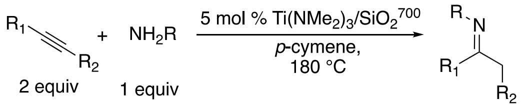
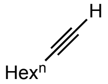
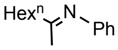
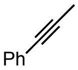
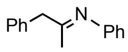
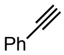
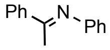
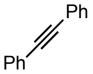
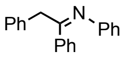
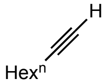
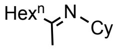
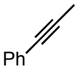
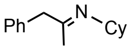
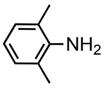
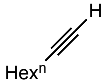
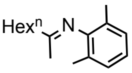
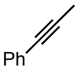
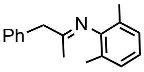
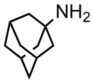
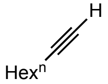
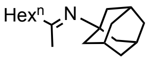
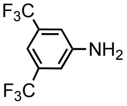
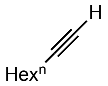
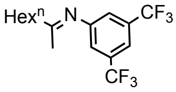
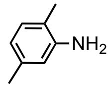
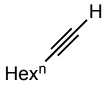
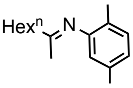
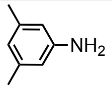
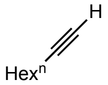
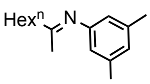
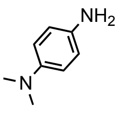
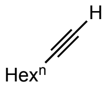
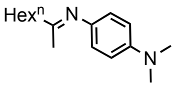
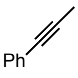
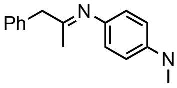


Figure 2. A selection of potential surface site variations in the $Ti(NMe_2)_3/SiO_2^{700}$ bulk material: (a) The stoichiometry calculated from NMR titrations and ICP-OES determination of Ti content; (b) Ti bound to SiO_2^{700} through two Ti–O bonds, similar to $Ti(NMe_2)_2/SiO_2^{200}$;[32] (c) Ti bound through one Ti–O bond, which retains an equivalent of datively bound amine.

Table 1. Substrate scope for intermolecular hydroamination using $Ti(NMe_2)_3/SiO_2^{700}$.[a]



	NH_2R	**Alkyne**	**Product (major)**	**Yield (%)[b] (Isomer ratio)**
1	H_2NPh			92 (>100:1)
2				92 (15:1)
3				33 (28:1)
4				92
5	H_2NCy[c]			11[d] (1:1)
6				34[d] (2.1:1)
7				85 (43:1)
8				91 (>100:1)
9				0
10				28[d] (>100:1)
11				69 (60:1)
12				59 (>100:1)
13				86 (>100:1)
14				80 (>100:1)

[a] Entries 1 and 2 were run for less than 1 h. Yields for all other entries were determined at 12 h. [b] Calibrated GC/FID yields with dodecane as the internal standard. The GC response was found by reducing the imine to the amine, isolating the amine, and calibrating amine derivative response versus dodecane. That calibration curve was used to get the GC yield for each related imine. [c] Cy = cyclohexyl. [d] Because of the low yield, the compound couldn't be isolated for GC calibration, and the calibration curve for a derivative with a close molecular formula was used. The correct regioisomer is unestablished in these cases and the isomer shown is simply one possibility.

Catalytic Activity of $Ti(NMe_2)_3/SiO_2^{700}$ for Hydroamination

The application of $Ti(NMe_2)_3/SiO_2^{700}$ as a catalyst for hydroamination (HA) was examined with a variety of substrates (Table 1), including aniline; substituted anilines; and a variety of alkynes, including terminal alkyl, terminal aromatic, internal aromatic, and diphenylacetylene.

Yields of hydroamination product are relatively high, overall, for hydroamination, however, there are a few substrates with which this catalyst does not perform well. These include HA with aniline and phenylacetylene (entry 3), as well as reactions with alkylamines (entries 5, 6, and 9), and an electron-withdrawing aniline derivative, 3,5-bis(trifluoromethyl)aniline (entry 10). While this catalyst material is slightly more tolerant of different amines than the previously studied $Ti(NMe_2)_2/SiO_2^{200}$, the yields obtained with some amines are still quite low.

The regioselectivities of substrates that this catalyst tolerates are high (entries 1, 2, 7, 8, and 11-14), giving results comparable to those obtained with homogeneous catalysts.[1, 5] This heterogeneous $Ti(NMe_2)_3/SiO_2^{700}$ offers some additional benefits over other available catalysts, including the ease with which the catalyst material can be separated from the organic reaction mixture, an advantage when organic compounds produced via this route are carried on in organic synthesis.[45, 46]

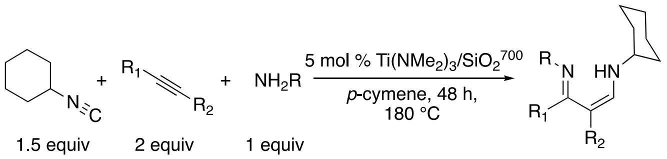
The catalyst material does not perform hydroamination of *N*-methylaniline. This is preliminary support that the catalyst may favor the Bergman-mechanism for hydroamination, where the active species is a titanium-imide that undergoes cycloaddition with the alkyne, as opposed to a Marks-mechanism where olefin insertion into a metal-amide bond is observed.[17, 18, 47] Additionally, it is worth noting that upon addition of a primary amine or aniline, the catalyst material goes from pale yellow to an intense red color, reminiscent of similar homogeneous titanium catalysts and $Ti(NMe_2)_2/SiO_2^{200}$.

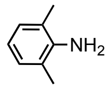
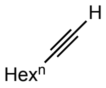
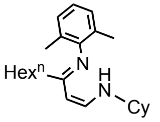
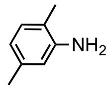
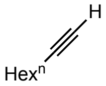
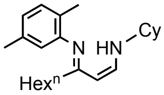
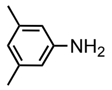
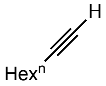
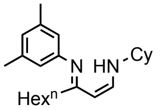
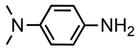
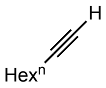
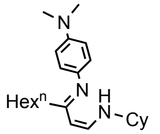
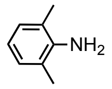
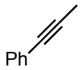
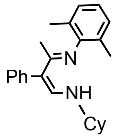
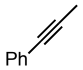
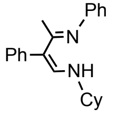
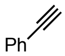
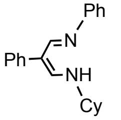
Iminoamination Catalysis with $Ti(NMe_2)_3/SiO_2^{700}$

$Ti(NMe_2)_3/SiO_2^{700}$ demonstrates marked improvement over previously-studied $Ti(NMe_2)_2/SiO_2^{200}$ both in terms of yield and substrate tolerance for iminoamination reactions.[32] First, considering the same substrate scope as was studied with $Ti(NMe_2)_2/SiO_2^{200}$ (entries 1-5, Table 2), the yields are higher and the amounts of formamidine and hydroamination side products noted in these reactions are much lower. In fact, with the most sterically protected aniline, 2,6-dimethylaniline (entry 1), the yield of the iminoamination product is 94% under the standard reaction conditions. Only trace amounts of hydroamination (HA) and formamidine (FA) are noted by GC analysis. The only substrate combination not significantly improved is that in entry 4, which is still quite low; the combination of coupling a terminal alkyne with the small but very electron rich aniline is not productive.

In addition, we noted one other vast improvement with $Ti(NMe_2)_3/SiO_2^{700}$—it can couple unsubstituted aniline with internal and terminal aromatic alkynes in iminoamination reactions (entries 6 and 7). These substrate combinations did not result in observable quantities of iminoamination product with $Ti(NMe_2)_2/SiO_2^{200}$.[32] This marks a dramatic improvement in the substrate tolerance of the $Ti(NMe_2)_3/SiO_2^{700}$ relative to $Ti(NMe_2)_2/SiO_2^{200}$. For those substrates in entries 1, 2, and 5-7, the simple $Ti(NMe_2)_3/SiO_2^{700}$ catalyst provides yields that could be isolated or easily carried on in additional reactions (vide infra).[4, 14] While these results indicate enhancement of catalytic activity over the previous effort, we are currently investigating ways to further improve the scope of the catalyst, such as iminoamination involving unsubstituted aniline and terminal alkynes with CyNC.

Table 2. Iminoamination Substrate scope examined with $Ti(NMe_2)_3/SiO_2^{700}$ as catalyst.



Entry	NH_2R	Alkyne	Product (major)	Yield (%)[b] (Isomer ratio)
1				94 (6.6:1) 6% HA[c,d]
2				71 (>100:1) [d]
3				33 (1.5:1)[d]
4				8[e] (>100:1) 16% HA[c]
5				61 (3.0:1) 5% HA[c]
6	H_2NPh			88[a] (10.3:1)
7	H_2NPh			52[a] (6.3:1)

[a] Yields given are after 18 h. [b] Yields are calculated from GC/FID standardized with internal dodecane, utilizing the authentic isolated products or a close derivative to calibrate the FID responses (See SI). [c] HA = hydroamination product. [d] A trace of formamidine due to coupling of the amine and isonitrile was detected. [e] The yield of the compound made isolation very difficult, and the calibration curve for a derivative with a similar formula was used to estimate the GC yield.

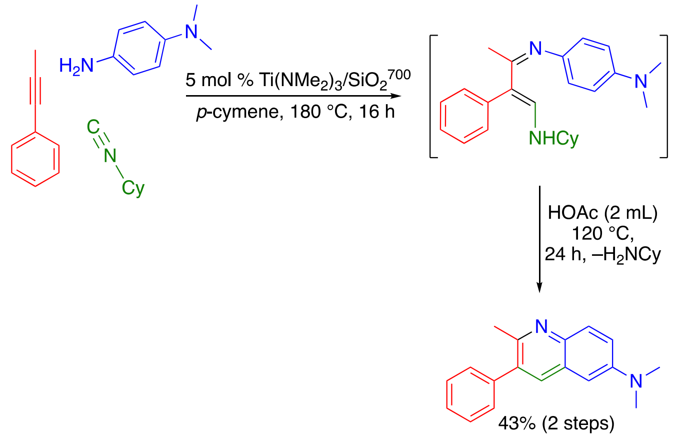
Application of $Ti(NMe_2)_3/SiO_2^{700}$ to Quinoline Synthesis

The one-pot, two-step synthesis of substituted quinoline derivatives has been previously reported by our group.[45]

Utilizing homogeneous titanium catalysts to perform iminoamination reactions, followed by acid-catalyzed heterocycle formation with glacial acetic acid, quinolines can be produced from simple starting materials. Further, these quinoline products are of interest in biological applications, as they have been shown to exhibit µM inhibition of the human proteasome, which bears relevance to several human diseases.[45]

As mentioned above, for several substrate combinations, $Ti(NMe_2)_3/SiO_2^{700}$ provides clean reactions with high enough yields to pursue functionalization of the 3CC product. We sought a direct comparison with the homogeneous titanium-catalyzed pathway to these substituted quinolines in order to assess the practicality of the heterogeneous catalyst.

The reaction shown in Scheme 2 was carried out to produce (*N*,*N*,2)-trimethyl-3-phenylquinolin-6-amine, which has a ~10 µM LC_{50} value for proteasome inhibition.[45] With 5 mol % $Ti(NMe_2)_3/SiO_2^{700}$, the iminoamination step was run for 16 h, followed by heating with glacial acetic acid for 20 h. A final isolated yield of 43% was obtained after column chromatography. The original report used 10 mol % $Ti(dpm)(NMe_2)_2$ for 24 h, and glacial acetic acid for 24 h, to achieve a final yield of 50%. The overall yield between the homogeneous and heterogeneous catalyzed reactions are very similar. With respect to both reaction time and amount of catalyst used, however, the heterogeneous catalyst outperforms the homogeneous catalyst, i.e., 36 h compared to 48 h with half the catalyst loading.



Scheme 2. One-pot, two-step quinoline synthesis utilizing $Ti(NMe_2)_3/SiO_2^{700}$ catalyst. The overall reaction yield is comparable to that achieved with homogeneous Ti catalysts, with half of the catalyst loading.

Recyclability of the $Ti(NMe_2)_3/SiO_2^{700}$ Material

Following a single use of the catalyst for either hydroamination or 3CC, subsequent reuse of the same catalyst material resulted in dramatically reduced activity. After hydroamination or iminoamination following the general procedure, the catalyst material was removed from the reaction mixture by filtration in the glovebox. The catalyst was then rinsed with toluene, followed by pentanes, and was then dried in vacuo. The dried material was added, as recovered, to a second reaction, for which the general procedure was followed for either HA or 3CC. After the second run of each batch of catalyst, with a variety of substrates in both HA and 3CC, only trace amounts of product (<5% yield) were observed, even after extended reaction times.

With previously reported $Ti(NMe_2)_2/SiO_2^{200}$, small amounts of titanium leaching were detected during catalysis.[32] To verify whether the same phenomenon was affecting $Ti(NMe_2)_3/SiO_2^{700}$, batches of the used catalyst from both HA and 3CC were examined by ICP-OES. The results of these analyses show very similar amounts of titanium before and after $Ti(NMe_2)_3/SiO_2^{700}$ use in catalysis (Table 3); consequently, it appears that the metal is not leaching from the surface during catalysis to any measurable extent.

Table 3. Ti content in the as-prepared $Ti(NMe_2)_3/SiO_2^{700}$ and used catalyst from both hydroamination and 3 component coupling reactions determined by ICP-OES.

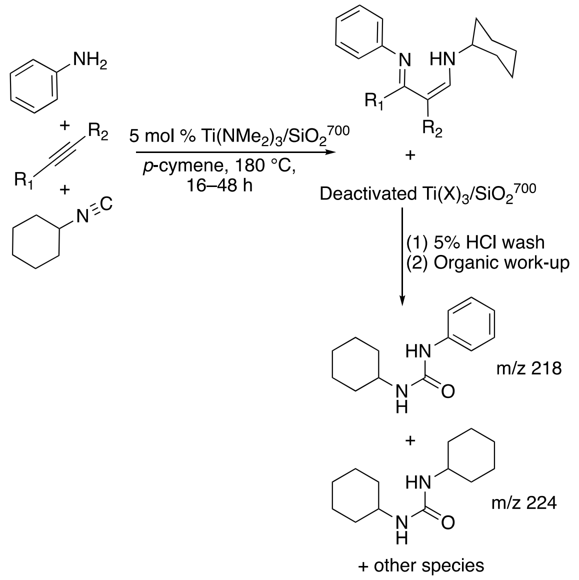
Sample Species	ICP-OES wt%	Predicted wt%[a]
$Ti(NMe_2)_3/SiO_2^{700}$	1.50 (0.07)	1.46 (0.12)
$Ti(NMe_2)_3/SiO_2^{700}$ (used for HA)	1.44 (0.03)	1.35-1.46 (0.10)[b]
$Ti(NMe_2)_3/SiO_2^{700}$ (used for 3CC)	1.48 (0.04)	

[a]Calculated from the surface density of Si–O–H sites determined by NMR titrations of SiO_2^{700}. [b]Variable weight % from Ti predicted because of differences that could occur in speciation of ligands on Ti after reactions are complete (e.g., dimethylamide ligands will be replaced by anilides or other protonated species in the catalytic mixture).

No experimental evidence has been found to date to suggest why HA catalysis deactivates $Ti(NMe_2)_3/SiO_2^{700}$. However, we have observed, via a post-reaction acid wash of the catalyst used in iminoamination, several organic residues not observed in the crude reaction solution. Several of these species show m/z ratios and fragmentation patterns that don't match any of the previously encountered products or side products in these catalysed reactions. Among these new organic residues are two interesting sets of m/z peaks that correspond to 1,3-dicyclohexylurea and 1-cyclohexyl-3-phenylurea.

These same organic residues are noted when the alkyne in the iminoamination reaction is changed, suggesting that the alkyne does not affect the formation of these organic residues (Scheme 3.) These observations suggest that, in the case of the 3CC reactions, side reactions between the silica-bound titanium sites, aniline, and excess isonitrile in the reaction solutions may contribute to the deactivation of the material. However, no specific products or reaction routes have been clearly identified.

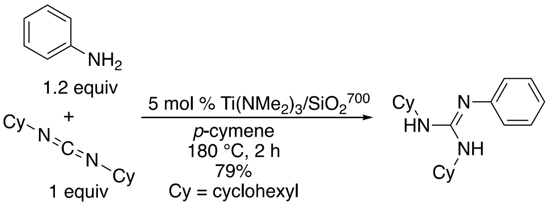
Surface-bound species with sufficient thermodynamic stability could certainly prevent re-entry into the active catalytic cycle. An example of this type of deactivation has been previously presented by Mountford in homogeneous systems.[48] In this instance, homogeneous titanium catalysts for hydroamination could undergo addition of 2 equivalents of alkyne to the active titanium-imide. This extra insertion forms an isolable complex with a 6-membered ring that includes the titanium and may inhibit this catalysis, even though double alkyne insertion is useful for other transformations.[24, 49, 50] Efforts to circumvent or reverse catalyst poisoning with the material are ongoing.



Scheme 3. Products observed by GCMS after mild acid treatment of the catalyst material post-iminoamination reaction. The two urea species shown were observed, in addition to several other masses.

Catalytic Guanidine Formation from 1,3-dicyclohexylcarbodiimide

Richeson and coworkers have previously demonstrated that a terminal titanium imide can react directly with carbodiimide, resulting in the formation of a guanidine.[51, 52] In these guanidine-forming reactions, the ancillary ligands are themselves often guanidines.



(1)

In the catalytic reaction examined here with $Ti(NMe_2)_3/SiO_2^{700}$, 5 mol % $Ti(NMe_2)_3/SiO_2^{700}$, 1,3-dicyclohexylcarbodiimide, and aniline produce *N,N'*-dicyclohexyl-*N''*-phenylguanidine in 79% isolated yield. The discovery of an additional catalytic C–N bond forming reaction for which $Ti(NMe_2)_3/SiO_2^{700}$ is competent is exciting and suggests further exploratory reactivity studies with the catalyst material may be fruitful. Additionally, this reaction in particular highlights one of the $Ti(NMe_2)_3/SiO_2^{700}$ catalyst's inherent advantages over a homogeneous system. The heterogeneous catalyst can successfully catalyse the formation of products which would exchange with ancillary ligands in homogeneous systems, irreversibly altering the homogeneous catalyst's reactivity.

Conclusions

The $Ti(NMe_2)_3/SiO_2^{700}$ material presented here has low titanium content by mass (1.50 wt%), yet demonstrates good catalytic activity for both hydroamination and multicomponent coupling chemistry. The catalyst performs the intermolecular hydroamination of anilines and alkynes in moderate to high yields (~30-90%) with high regioselectivities. The catalyst also demonstrates moderate to high yields of 1,3-diimine tautomers from the 3-component coupling of anilines, alkynes, and isonitriles, provided either the alkyne or the aniline derivative are sterically hindered (52-94%). Despite substrate scope limitations relative to some homogeneous catalysts active for the same reactions, the $Ti(NMe_2)_3/SiO_2^{700}$ material shows marked improvement over closely-related $Ti(NMe_2)_2/SiO_2^{200}$. In fact, $Ti(NMe_2)_3/SiO_2^{700}$ only falls short when trying to use small aniline derivatives in conjunction with terminal alkyl-substituted alkynes.

The usefulness of $Ti(NMe_2)_3/SiO_2^{700}$ was tested directly by functionalizing a 3CC product to form a quinoline. In this one-pot, two-step transformation $Ti(NMe_2)_3/SiO_2^{700}$ provides 43% isolated yield of *N,N*,2-trimethyl-3-phenylquinolin-6-amine in 36 h with 5 mol % catalyst. This result is competitive with homogeneous titanium-catalyzed reactions of this type, while using half the catalyst loading.

Additionally, other benefits noted with this catalyst over the typical homogeneous catalyst primarily include: (1) the ease with which it is separated from the complex organic reaction mixture (2) ease of preparation, and (3) the lower catalyst loadings relative to homogeneous systems.[45, 46] With some substrates, $Ti(NMe_2)_3/SiO_2^{700}$ (entries 1, 5, and 6 in Table 2) even outperforms the homogeneous systems by increasing yield, reducing side reactions, and approaching completion in shorter reaction times. These results demonstrate the promise of further investigation into silica-supported titanium catalysts as C–N bond formation catalysts.

Unfortunately, the material is not recyclable for either of the catalytic reactions investigated here. However, this lack of reusability is not due to loss of titanium from the silica. Alternative reaction conditions or post-reaction surface treatments may allow for catalyst reactivation in future studies, since the titanium remains on the surface.

For the iminoamination reaction in particular, this new titanium-supported silica gel is a superior catalyst to previous homogeneous catalysts for some substrate combinations, e.g., bulky anilines such as 2,6-dimethylaniline. Additionally, the supported catalyst can be further modified to tune reactivity, which is being explored for later reports.

Experimental

General Considerations

All syntheses and handling of materials were carried out under an inert N_2 atmosphere, either in an MBraun glovebox or by standard Schlenck techniques. Any handling of materials in air is specified. Generally, this was limited to column chromatography and preparation of ICP or iminoamination GC samples.

Fumed SiO_2 was purchased from Sigma Aldrich and used as received (200 ± 25 m^2/g, Lot # SLBT0198). The following solvents were purchased commercially and dried prior to use: *para-*

cymene was dried over CaH_2 and distilled in vacuo; pentanes and toluene were dried by passage over activated alumina and sparged with N_2; and tetrahydrofuran was dried over sodium and distilled under N_2. C_6D_6 was purchased from Sigma Aldrich, dried over CaH_2, and distilled under N_2. All dried solvents were stored in an N_2 glovebox after purification. Additionally, $CDCl_3$ used for routine organic product NMR samples was purchased from Cambridge Isotopes and used as received. On $Ti(NMe_2)_3/SiO_2^{700}$, solid-state CP-MAS ^{13}C NMR was carried out with a spin rate = 6 kHz, frequency = 100 MHz, mixing time = 1.8 ms, a recycle delay = 2 s, and an acquisition time = 5.12 ms. The spectra are in the Supplementary Information.

$Ti(NMe_2)_4$ and $Ti(NEt_2)_4$ were purchased from Gelest and used as received. Aniline, 2,6-dimethylaniline, 2,5-dimethylaniline, and 3,5-bis(trifluoromethyl)aniline were dried over an appropriate drying agent and distilled under vacuum. The 4-N,N-dimethylaniline was dried by azeotroping with benzene using a Dean-Stark trap for 48 h under N_2 prior to use. NH_2Cy was purchased from Strem and was dried over CaH_2 and distilled under N_2 before use; 1-NH_2Ad was dried under reduced pressure and recrystallized from dry solvents before use. The alkynes phenylacetylene, 1-phenylpropyne, 1-octyne, and 4-octyne were purchased from Alfa and dried over Na_2SO_4, then distilled under N_2 before use. Cyclohexylisonitrile was prepared according to literature procedures.[53]

SiO_2^{700} was prepared following slight modification of literature procedures,[37] to accommodate differences in equipment, etc. For a detailed procedure, see the supporting information.

Preparation of $Ti(NMe_2)_3/SiO_2^{700}$

From $Ti(NEt_2)_4$ titrations, the surface abundance of Si-OH sites was estimated (0.00031 mol/g). Based on this measurement, 1.2 equiv of $Ti(NMe_2)_4$ was added to 1 equiv of SiO_2^{700} stirred as a slurry in *n*-hexane. The SiO_2^{700} rapidly went from colorless to orangish-yellow. The mixture was stirred for 2 h at room temperature. The $Ti(NMe_2)_3/SiO_2^{700}$ was then collected by filtration, rinsed with 20 mL of hexane, and 20 mL of benzene. The $Ti(NMe_2)_3/SiO_2^{700}$ was dried *in vacuo*, yielding a powdery, pale yellow material. *ICP-OES:* 1.50 % Ti (± 0.07). (See associated supporting information for details of error analysis.)

General Hydroamination Procedure with $Ti(NMe_2)_3/SiO_2^{700}$

A 15 mL pressure tube was charged with $Ti(NMe_2)_3/SiO_2^{700}$ (163 mg, 5 mol %), a stir bar, and *p*-cymene (1.0 mL). Separately, a volumetrically prepared 1.0 mL solution of NH_2R (1 mmol) and alkyne (2 mmol) in p-cymene was prepared. This solution was added to the catalyst mixture in the pressure tube, with stirring. The pressure tube was sealed and transferred from the glovebox to a preheated 180 °C aluminum well plate. The reaction was heated with magnetic stirring for 40 min to 12 h depending on the substrates. The pressure tube was ambiently cooled to room temperature and centrifuged to compact the $Ti(NMe_2)_3/SiO_2^{700}$ into an orange pellet at the bottom of the tube. The pressure tube was transferred back to the glovebox, and the liquids decanted. The crude solution was utilized for GC analysis.

General 3CC Procedure with $Ti(NMe_2)_3/SiO_2^{700}$

A 15 mL pressure tube was charged with $Ti(NMe_2)_3/SiO_2^{700}$ (163 mg, 5 mol%), a stir bar, and *p*-cymene (1.0 mL). Separately, a volumetrically prepared 1.0 mL solution of NH_2R (1 mmol), CyNC (1.5 mmol), and alkyne (2 mmol) in *p*-cymene was prepared. This solution was added to the catalyst mixture in the pressure tube, with stirring. The pressure tube was sealed and transferred from the glovebox to a preheated 180 °C aluminum well plate. The reaction was heated with magnetic stirring for 18–48 h. The pressure tube was ambiently cooled to room temperature and centrifuged to compact the $Ti(NMe_2)_3/SiO_2^{700}$ into an orange pellet at the bottom of the tube. The pressure tube was transferred back to the glovebox, and the liquids decanted. The crude solution was utilized for GC analysis.

Synthesis of N,N,2-trimethyl-3-phenylquinolin-6-amine using 1-Pot-2-Step Procedure

In the glovebox, a 15 mL pressure tube was loaded with $Ti(NMe_2)_3/SiO_2^{700}$ (320 mg, 5 mol %), a stir bar, and *p*-cymene (1.0 mL). Separately, 2 mmol of each of the following reagents was massed: 1-phenypropyne (232 mg, 1 equiv), CyNC (218 mg, 1 equiv), and 4-*N,N*-dimethylaniline (272 mg, 1 equiv). These reagents were added to the stirred contents of the pressure tube with additional *p*-cymene (1.0 mL). The pressure tube was sealed and transferred from the glovebox to a 180 °C aluminum well plate and was heated with stirring for 16 h. The tube was removed from heat and allowed to cool to room temperature. Once cooled, the tube was opened in air, and 2 mL of glacial acetic acid was added. The tube was sealed and heated with stirring for an additional 20 h at 120 °C. The contents of the tube were transferred to a 100 mL beaker and neutralized to a pH of 7–8 with sodium bicarbonate solution. The neutralized mixture was extracted with Et_2O (3 x 50 mL) and concentrated by rotary evaporation to give a viscous reddish-brown solution. Note, the silica material becomes suspended in the aqueous layer, and is separated from the organics during extraction. The crude product was purified by column chromatography using neutral alumina and hexane with 1% triethylamine (v:v) with a gradient to 20% EtOAc as eluent. This provided the quinoline product as a red oil (43%, 224 mg). The properties of the isolated complex match those previously reported by ^1H and ^{13}C NMR, and GCMS fragmentation pattern and retention time.[46]

General Procedure: Recycling Experiments

The general procedure for HA or iminoamination was followed. Upon completion of the initial reaction (run 1), the pressure tube was cooled ambiently, centrifuged, and returned to the glovebox. The catalyst material was collected by filtration and thoroughly rinsed with 10 mL toluene followed by 10 mL hexane. The catalyst material was dried in vacuo and loaded into a pressure tube with a stir bar and *p*-cymene (1.0 mL). The reagent solution for a second reaction (run 2) was then loaded into the tube. The tube was sealed and heated at 180 °C in an aluminum well plate, and the process repeated as many times as needed.

Catalytic Formation of 1,2-dicyclohexyl-3-phenylguanidine

A pressure tube was charged with $Ti(NMe_2)_3/SiO_2^{700}$ (163 mg, 5 mol %), a stir bar, and *p*-cymene (1.0 mL). To this solution was added H_2NPh (112 mg, 1.2 equivalents) and 1,3-dicyclohexylcarbodiimide (208 mg, 1 equivalents). The tube was sealed and transferred to a 180 °C aluminum block. The reaction was heated with stirring for 2 h. The reaction was cooled to room temperature, and 5 mL of water was added. This caused the precipitation of a white solid. The crude reaction mixture was filtered using a fritted funnel resulting in the collection of the silica gel catalyst as well as the white precipitate. The solids were then extracted with DCM and re-filtered with a fritted funnel. The DCM filtrate was dried with a rotovap to give 1,2-dicyclohexyl-3-phenyl guanidine as a crystalline white residue (236 mg, 79%). The properties of the isolated complex match those previously reported by ^{1}H and ^{13}C NMR, and GCMS.[54]

Conflicts of Interest

There are no conflicts to declare.

Acknowledgements

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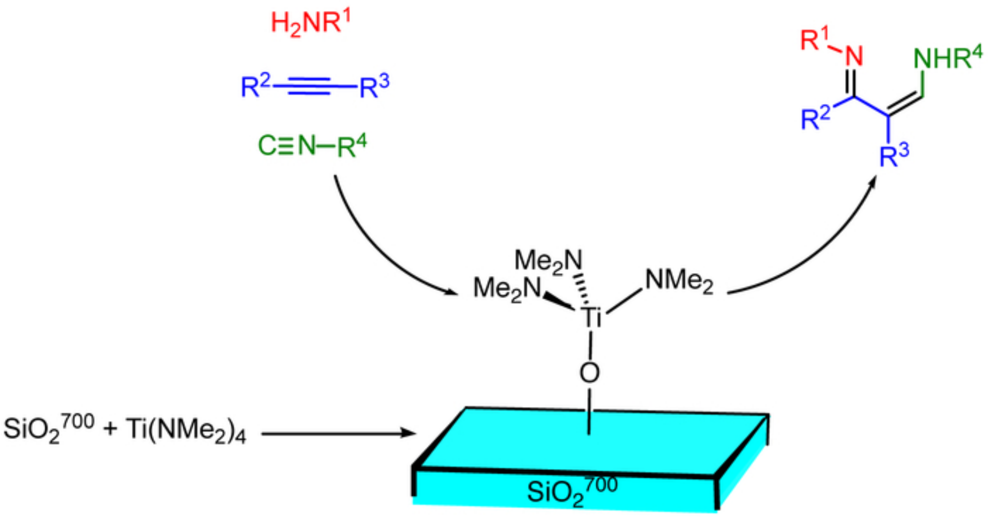

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