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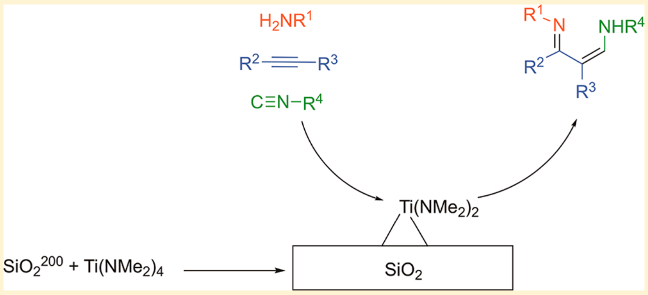
Titanium-Catalyzed Hydroamination and Multicomponent Coupling with a Simple Silica-Supported Catalyst

Kelly E. Aldrich and Aaron L. Odom*

Department of Chemistry, Michigan State University, 578 South Shaw Lane, East Lansing, Michigan 48823, United States

Supporting Information

ABSTRACT: Hydroamination and multicomponent coupling reactions catalyzed by homogeneous Ti(IV) complexes can produce valuable imines, amines, and other nitrogen-containing organic building blocks. Typically catalysts for this transformation are very sensitive to ancillary ligand design and often suffer from catalyst deactivation, necessitating use in a single reaction. Here, we have attempted to address these issues by moving toward a solid-supported Ti catalyst active for these reaction types. We present initial results to synthesize and probe the catalytic reactivity of silica-supported titanium amide precatalysts. With minimal treatment of commercially available fumed silica, $Ti(NMe_2)_2/SiO_2^{200}$ can be isolated upon addition of $Ti(NMe_2)_4$. This species gives high yields and high regioselectivity for hydroamination of a variety of alkynes with anilines. The solid-supported species is also an active catalyst for the formation of tautomers of unsymmetrical 1,3-diimines via three-component coupling of bulky anilines, alkynes, and isonitriles. Reusability and possible catalyst deactivation pathways are also discussed.



INTRODUCTION

Titanium- and zirconium-catalyzed hydroaminations (HA) are well-established reactions that have been studied for several decades.[1−9] HA allows for the formation of new C−N bonds across different types of C−C multiple bonds. This reaction pathway also can be modified to generate multicomponent coupling products by addition of a third reactant, which can result in additional C−C or C−N bond formation.[10−15]

An example of a titanium-catalyzed multicomponent coupling (Figure 1), iminoamination, involves the coupling of an amine, alkyne, and isonitrile to form tautomers of 1,3-diimines (3CC).[10] These reactions are carried out with a homogeneous catalyst, such as $Ti(NMe_2)_2dpm$, where dpm = 5,5-dimethyldipyrrolylmethane. A selection of titanium catalysts active for hydroamination or related multicomponent coupling reactions, such as Tonks and co-workers' azo-based reactions[22] which use Mountford's $Ti(NPh)Cl_2(py)_3$,[23,24] are also shown in Figure 1.

Some of the known homogeneous titanium HA catalyses are fast; for example, $Ti(NMe)_2dpm$ catalyzes the HA of 1-hexyne with aniline in ∼5 min, starting at room temperature, with 5 mol% loading.[8] However, the catalysts can suffer from dimerization processes and other deactivation pathways.[25] These issues are frequently addressed using bulky ancillary ligands and chelates to minimize loss of the active species (Figure 1). Even with these common design principles, prevention of these deactivation pathways and undesired reactivity can still be challenging.

We recently reported a detailed analysis of ligand design issues with regard to titanium HA catalysis.[25] In this study, the rates of many different titanium precatalysts were measured as a function of donor ability and steric profile of the ancillary ligands. The correlation demonstrated that electron-deficient and small ancillary ligands enhance the rate of the catalyst, quantitatively confirming previous qualitative observations.[25,26] However, it was also observed in this study that, in making sufficiently electron deficient or small ligands to enhance the rate of these catalysts beyond the fastest known derivative, pathways to side reactions or catalyst decomposition may be introduced or amplified.[25] Additionally, even with stable precatalyst variants that perform HA and 3CC cleanly, the catalyst would be difficult to recover from the crude reaction mixture.

One possible method to circumvent some decomposition pathways and allow catalyst recovery is to move towards a solid-supported catalyst. Further, supported catalyst systems would also be advantageous for incorporation of the chemistry into flow systems.[27,28] Solid-supported hydroamination and related reactions have been demonstrated with other metals capable of this transformation.[25] For example, Basset et al. have demonstrated that tantalum bound to silica, bearing dimethylamide ligands, can perform hydroaminoalkylation of alkenes through a proposed tantalaziridine species.[29,30] Intramolecular hydroamination was also demonstrated by Le Roux and co-workers using mesoporous silica-supported lanthanum

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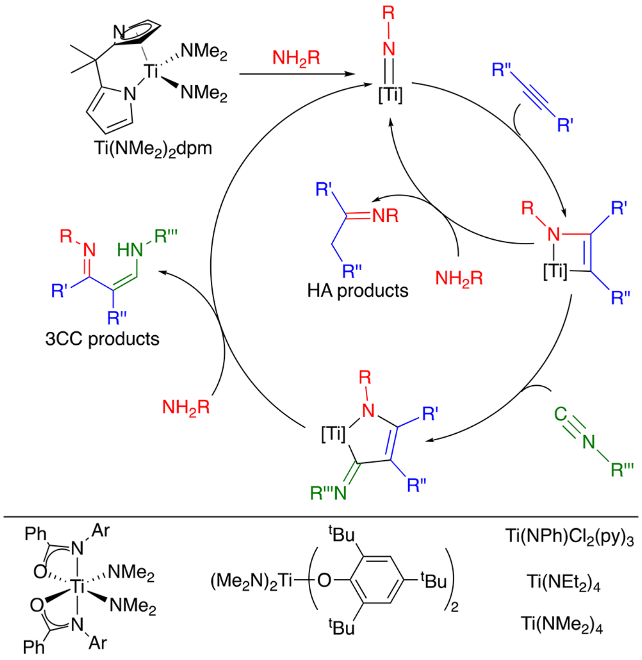


Figure 1. (top) Proposed catalytic cycle for homogeneous hydroamination of alkynes based on the Bergman mechanism and a three-component coupling reaction, iminoamination. The reactions are demonstrated with the known precatalyst Ti(NMe$_2$)$_2$dpm. (bottom) Sampling of known Ti precatalysts for hydroamination and related reactions.[5,9,16−22]

silylamides (Y, La, and Nd) under mild conditions.[30,31] Additionally, hydroamination by heterogeneous catalysts has been demonstrated by a few others, with a number of new reports in the past few years, including late-metal nanoparticles and gel-supported catalysts.[32−35]

There is precedence for the use of titanium bound to a solid support material as an active catalytic species. For example, solid-supported silica catalysts with surface-bound titanium have been shown to be active catalysts for olefin epoxidation or olefin polymerization (with cocatalysts) by Scott and coworkers.[36,37]

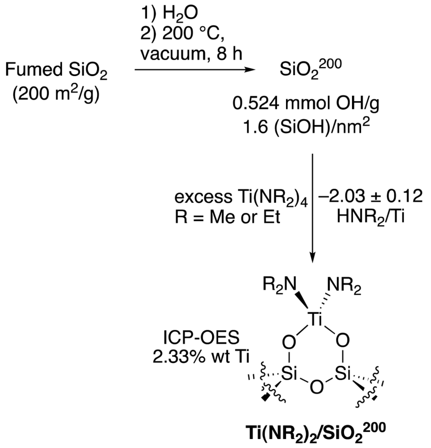
In a separate report by Scott, they demonstrated that Ti(NR$_2$)$_4$ (R = Me, Et) can bind to silica by protolytic replacement of the amide ligands, yielding Ti(NR$_2$)$_2$/SiO$_2$^{200}.[38] This binding motif at the silica surface bears a strong electronic resemblance to known homogeneous systems capable of HA and 3CC chemistry. It was also observed that, under mild conditions, titanium imide species can be formed from titanium amides.[38]

Surface-bound titanium amides and imides on silica would seem ideal species with which to translate titanium-catalyzed HA and 3CC reactions to heterogeneous catalysis. This prospect is especially attractive for the titanium systems because of the thorough mechanistic work that has been done to establish the interactions between substrate and metal in the homogeneous systems. In addition to the mechanistic foundation, there is also a precedence for recycling solid-supported catalysts, which can easily be recovered from catalytic reaction mixtures and reactivated with minimal manipulation.[39] Here, we present initial investigations into solid-supported titanium species that can catalyze HA and 3CC related to our homogeneous systems, exploration of the substrate scope accessible to the heterogeneous catalyst, and catalyst reusability.

■ RESULTS AND DISCUSSION

Fumed silica was treated much as Beaudoin and Scott described.[38,40] The silica was partially dehydrogenated under vacuum at 200 °C for 8 h to give SiO$_2$^{200}. They reported that treatment with Ti(NMe$_2$)$_4$ gave a solid with 1.93 ± 0.4 wt % Ti with "0.49 Ti per hydroxyl (average of 12 experiments.) The amount of HNMe$_2$ liberated during grafting corresponds to 1.99 ± 0.04 per Ti."[38] Similarly, we measured 2.33 ± 0.12 wt % Ti with our sample and 2.03 ± 0.12 HNR$_2$ per Ti(NR$_2$)$_4$ added (Scheme 1), suggesting a very similar material.

Scheme 1. Preparation and Some Properties of Ti(NR$_2$)$_2$/SiO$_2$^{200} (R = Et, Me)

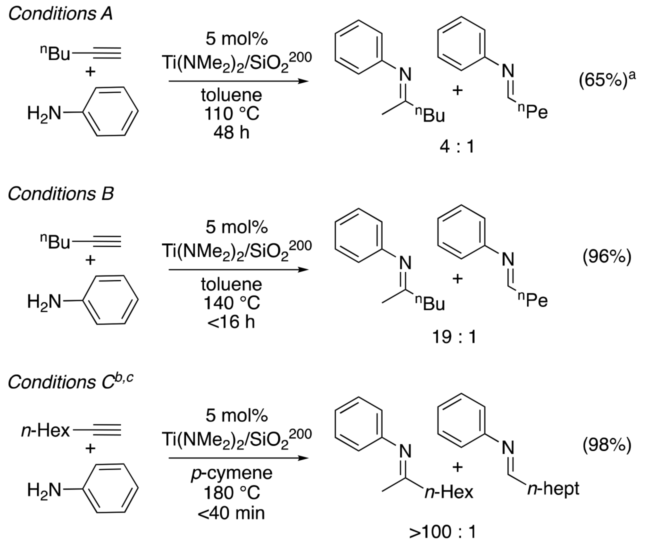


The Ti(NEt$_2$)$_4$-based material Ti(NEt$_2$)$_2$/SiO$_2$^{200} was prepared for ease of NMR titration of the HNEt$_2$ byproduct and determination of the number of hydroxyl sites added to the metal center (Scheme 1). For the catalyses discussed below, Ti(NMe$_2$)$_2$/SiO$_2$^{200} was used.

Hydroamination Activity of Ti(NMe$_2$)$_2$/SiO$_2$^{200}. Upon addition of a primary amine to the Ti(NMe$_2$)$_2$/SiO$_2$^{200} material, a color change is observed in the material, transitioning from pale yellow to deep reddish orange. This is similar to the color change observed for homogeneous precatalysts upon addition of a primary amine. Initially, 5 mol % of the precatalyst at 110 °C in toluene was used; however, hydroamination of 1-hexyne with aniline was incomplete after 48 h (Scheme 2, Conditions A), and the regioselectivity was low at 4:1. At 140 °C (Conditions B), the same reaction was complete in ~16 h and, interestingly, gave a significantly *higher* regioselectivity of 19:1. To investigate the effect of increasing the temperature further, the solvent was changed to *p*-cymene, and the reaction was run at 180 °C (Conditions C). Under these conditions, the hydroamination of 1-octyne, which replaced the lower-boiling 1-hexyne for this experiment, with aniline is complete in <40 min and showed perfect regioselectivity to the limit of our GC detector (>100:1).

In addition to HA reactions with terminal alkyl-substituted alkynes, Conditions C (Scheme 2) provided the best outcomes for HA of internal alkynes, as well. For example, HA of aniline and diphenylacetylene takes more than 64 h to reach completion with Ti(NMe$_2$)$_2$/SiO$_2$^{200} at 140 °C (Conditions B). At 180 °C, the reaction is complete in under 14 h. A similar increase in both the regioselectivity and rate of HA was also

Scheme 2. Reaction Conditions Screened for $Ti(NMe_2)_2/SiO_2^{200}$-Catalyzed Hydroamination and Resulting Product Distributions



[a] Yields and isomer ratios determined by GC/FID. [b] Due to high reaction temperatures in conditions C, 1-hexyne was substituted with 1-octyne. [c] Conditions C are the same as the General Hydroamination Procedure in the Experimental Section.

noted with 1-phenylpropyne at these different reaction temperatures. Conditions C generally provided the highest regioselectivity, shortest reaction times, and comparable if not improved yields relative to the milder temperatures examined. Thus, Conditions C were applied to the screening of a variety of substrates.

The substrate screening experiments indicate that the catalyst is efficient for hydroamination of a variety of alkynes. However, $Ti(NMe_2)_2/SiO_2^{200}$ has demonstrated poor activity with primary alkyl amines and electron-withdrawing anilines. Additionally, with terminal alkynes, at these high reaction temperatures, significant amounts of the alkyne trimerization products can be observed by GC. Despite these inadequacies, the catalyst seems to perform the hydroamination of most anilines, including relatively bulky derivatives such as 2,6-dimethylaniline. Again, this is accomplished with a variety of alkynes in relatively short reaction times and high yields. Overall, these reactions also demonstrate high regioselectivity, comparable with that of many homogeneous catalysts (Table 1).[8]

Observing successful hydroamination with a surface-bound titanium species was an important step toward the goal of catalyzing the three-component coupling (3CC) iminoamination reaction with a surface-supported Ti catalyst. Namely, this reactivity suggests that the surface-bound titanium can form an imide and carry out [2 + 2]-cycloadditions with alkynes if the same mechanism is operative.

Iminoamination Activity of $Ti(NMe_2)_2/SiO_2^{200}$. Despite these promising HA results, the first attempts at 3CC with the $Ti(NMe_2)_2/SiO_2^{200}$ catalyst were largely unsuccessful. The 3CC of aniline, 1-octyne, and cyclohexylisonitrile resulted in large amounts of HA product and formamidine (FA) (Figure 2), observed in roughly equivalent quantities by GC. Only a trace amount of 3CC was observed. One can hypothesize that the 1,1-insertion into the amide is much faster than insertion into the Ti−C bond of the azatitanacyclobutene intermediate with these substrates and reaction conditions.

We attempted to manipulate these relative rates, to favor 3CC, by changing the electronics and sterics of the substrates. Increasing the size of the isonitrile could potentially impede the rate of formamidine formation. Unfortunately, many of the large tertiary and aromatically substituted isonitriles examined were unstable at these reaction temperatures, with masses for isonitrile oligomers and HA product observed from these reaction mixtures. We also examined the effects of using smaller isonitriles; when *n*-octyl isonitrile was used, a result similar to the that for the CyNC experiments was observed with considerable amounts of both HA and FA products, but essentially no 3CC product was observed.

Without evidence of improvement from manipulation of the isonitrile, focus was shifted to the amine substrate. By substantially increasing the size of the primary amine to 2,6-dimethylaniline (**1**), the iminoamination reaction yielded 51% of the 3CC product. HA and formamidine products (10−15% each) were still observed by GC analysis of the reaction mixture, but the distribution favored the desired product.

To further probe the steric effect of the primary amine, the series of reactions in Table 2 was examined. The amine was altered by two successive decreases in size near the nitrogen with the amine substrates 2,5-dimethylaniline (**2**) and 3,5-dimethylaniline (**3**), each used with 1-octyne and cyclohexyl isonitrile in the iminoamination reaction. The results demonstrated a marked difference in yield and product distribution. Amine **2** gave the 3CC product as the most abundant species generated in moderate overall yield (50% yield); this is comparable to the 3CC yield obtained with **1**. In addition, similar to **1**, iminoamination employing **2** shows about 15% HA product and a similar amount of formamidine. This accounts for roughly 85% of the starting primary amine in the crude reaction mixture after 48 h for both **1** and **2**.

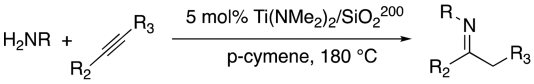
Using 3,5-dimethylaniline (**3**), however, gave just 7% yield for the 3CC product, close to stoichiometric. While HA and formamidine products are observed by GC, the combination of these products does not account for most of the initial mass of the aniline added to the reaction, and many unknown masses were observed by GC/MS, none in high abundance. In terms of favoring the 3CC product, it appears that with $Ti(NMe_2)_2/SiO_2^{200}$ as the catalyst, substitution of the 2-position of the aniline substrate, at a minimum, is required for a productive iminoamination rate relative to side reactions.

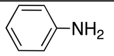
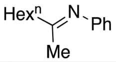
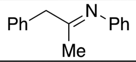
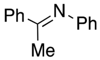
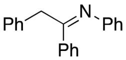
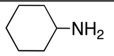
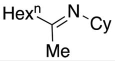
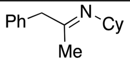
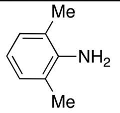
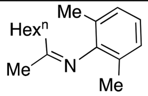
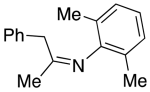
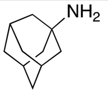
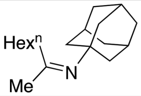
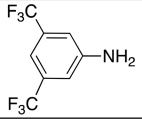
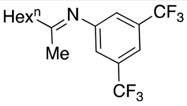
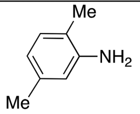
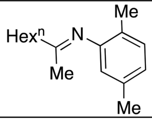
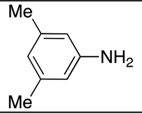
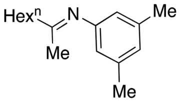
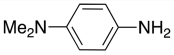
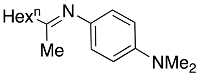
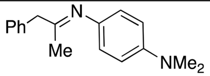
Switching from a terminal to an internal alkyne, 1-phenylpropyne, leads to results comparable with those for **1** and **2**. The reaction shows a reduced propensity toward side reactions (HA and FA) and a moderate yield of the 3CC product (36%) in 48 h. The reaction proceeds quite slowly, however, and there is a substantial amount of unreacted amine observed after 48 h.

These results demonstrate that multicomponent coupling reactions, such as iminoamination, are possible with a simple silica-supported titanium catalyst. The easily prepared $Ti(NMe_2)_2/SiO_2^{200}$ catalyst required steric blocking on the amine to inhibit side reactions observed in three-component coupling but still provided the 3CC products in moderate yield.

Reusability Studies on $Ti(NMe_2)_2/SiO_2^{200}$. It was discovered early in the catalytic activity studies that $Ti(NMe_2)_2/SiO_2^{200}$ can be recovered and reused in subsequent catalytic reactions by simply filtering the catalyst material from

Table 1. Hydroamination Reactions Examined with $Ti(NMe_2)_2/SiO_2^{200}$ [a]



Entry	H_2NR	Alkyne	Product (major isomer)	Isomer Ratio	Yields (%)[b]
1		Hex^n—≡—H		>100:1	98
2		Ph—≡—Me		8.7:1	92
3		Ph—≡		6.7:1	67
4		Ph—≡—Ph		NA	92
5		Hex^n—≡—H		24:1	24[c]
6		Ph—≡—Me		–	trace[c]
7		Hex^n—≡—H		>100:1	99
8		Ph—≡—Me		17:1	99
9		Hex^n—≡—H		3:1	7[c]
10		Hex^n—≡—H		–	trace[c]
11		Hex^n—≡—H		>100:1	92
12		Hex^n—≡—H		48:1	91
13		Hex^n—≡—H		>100:1	92
14		Ph—≡—Me		5.2:1	99

[a] Reaction Conditions C (Scheme 1): 5 mol % Ti as $Ti(NMe_2)_2/SiO_2^{200}$, 180 °C, 40 min (entry 1) or 14 h (entries 2–14). [b] Yields reported are calibrated GC/FID yields relative to the isolated amine derivative or a close derivative; see the Supporting Information for more details. Reactions went to full conversion, except entries 5, 6, 9, and 10. [c] These products were not isolated to determine regioselectivity because of their poor yields; the likely Markovnikov product is shown. See the Supporting Information for more details.

the reaction mixture, washing it with organic solvent, and removing residual volatiles under vacuum. Following this simple processing step, the used $Ti(NMe_2)_2/SiO_2^{200}$ was directly employed in subsequent reactions. The activity in the second and third catalytic runs was comparable to the initial use in terms of product yield after the same reaction time. An experiment to examine the limits of catalyst recycling was conducted in which a sample of $Ti(NMe_2)_2/SiO_2^{200}$ was used five times to perform the reaction shown in entry 1 of Table 1. The yields from each trial are shown in Table 3.

As is obvious from these results, the catalyst is in fact undergoing deactivation in subsequent runs. In the first three reactions, there is little deviation in yield; however, reactions 4 and 5 indicate a severe reduction in product formation under identical conditions. While some of this may be attributed to mass loss of the catalyst itself over the course of the five reactions due to handling, it seemed likely that something else is more detrimental to catalyst recycling.

Examination of the used $Ti(NMe_2)_2/SiO_2^{200}$ catalyst by ICP-OES shows that titanium is lost from the surface of the

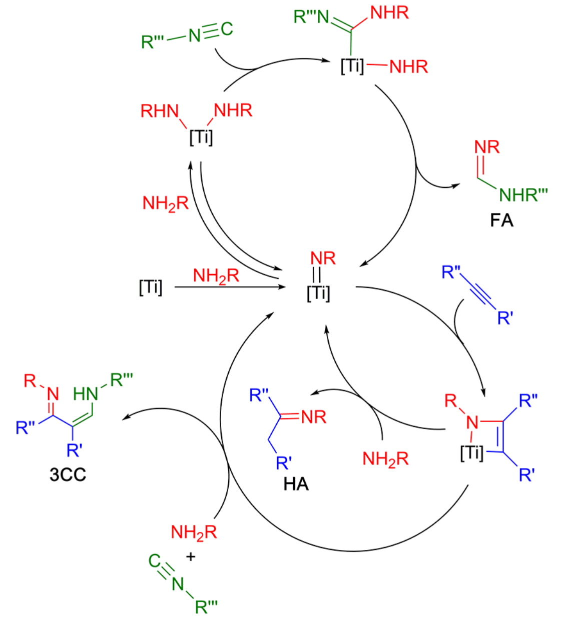


Figure 2. Possible pathways for the three predominant reactions during iminoamination: formation of formamidine (FA), hydroamination (HA), and iminoamination (3CC). The products from the three reactions are labeled by their reaction of production.

Table 3. Reusability of $Ti(NMe_2)_2/SiO_2^{200}$ for HA of 1-Octyne with Aniline

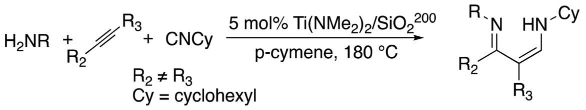
trial no.	yield (%)[a]	regioselectivity ratio
1	98	>100:1
2	96	32:1
3	90	14:1
4	44	10:1
5	23	10:1
6[b]	71	7.3:1

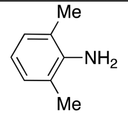
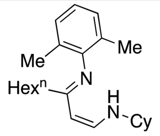
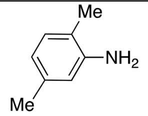
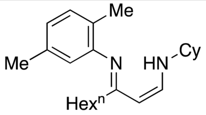
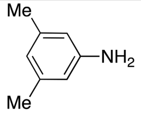
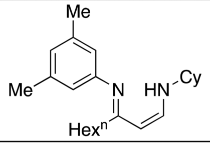
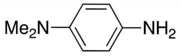
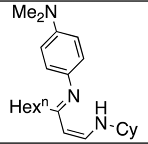
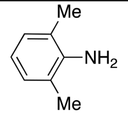
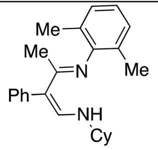
[a] Yields are from GC-FID of the crude reaction mixture, using a calibrated internal standard. [b] Material was treated with $Ti(NMe_2)_4$ to reactivate.

catalyst during hydroamination. A series of control reactions were run to determine what reagent or other factor is primarily responsible for leaching the titanium from the surface of the silica support (Table 4). Simply heating $Ti(NMe_2)_2/SiO_2^{200}$ in *p*-cymene at 180 °C for 16 h has no effect on the mass of titanium in $Ti(NMe_2)_2/SiO_2^{200}$. Similarly, heating to 180 °C with 20 equiv of NH_2Ph has no effect on titanium concentration on the silica surface.

Somewhat surprisingly, heating $Ti(NMe_2)_2/SiO_2^{200}$ to 180 °C in the presence of 1-octyne (40 equiv) for 16 h resulted in a loss of 11% of the titanium from $Ti(NMe_2)_2/SiO_2^{200}$. On the

Table 2. Three-Component Coupling Reactions Examined with $Ti(NMe_2)_2/SiO_2^{200}$ [a]



Entry	H2NR	Alkyne	Product (major isomer)	Yield (%)[b]	Regioisomer Ratio	Side Products Observed[c]
1		$Hex^n—\equiv—H$		51	5.2:1	14% HA 10% FA
2		$Hex^n—\equiv—H$		50	>100:1	16% HA 10% FA
3		$Hex^n—\equiv—H$		7	>100:1	13% HA 10% FA
4		$Hex^n—\equiv—H$		12	3.3:1	31% HA 10% FA
5		Ph—≡—Me		36	6.8:1	8% HA 6% FA

[a] Reaction conditions: 5 mol % Ti as $Ti(NMe_2)_2/SiO_2^{200}$, 1.5 equiv of cyclohexyl isonitrile, *p*-cymene, 180 °C, 48 h. [b] Yields reported are calibrated GC-FID yields relative to an isolated isomer of 3CC1. For more details, see the Supporting Information. [c] Side products due to two-component reactions: HA, hydroamination product; FA, formamidine product.

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Table 4. Results of ICP-OES Analysis of $Ti(NMe_2)_2(SiO_2)^{200}$ Samples after Different Treatments

treatment of $Ti(NMe_2)_2(SiO_2)^{200}$	Ti found by ICP (±) (wt %)	Ti retained after treatment (%)
none	2.33 ± 0.12	100
HA (entry 1, Table 1)	1.94 ± 0.11	83
180 °C in *p*-cymene	2.35 ± 0.14	~100
180 °C, 20 equiv NH_2Ph	2.38 ± 0.14	~100
180 °C, 40 equiv 1-octyne	2.05 ± 0.11	88

basis of these results, it seems that the loss of titanium from the catalyst is related to reaction with the alkyne.

Interestingly, upon treatment of this deactivated $Ti(NMe_2)_2/SiO_2^{200}$ with a slight excess of $Ti(NMe_2)_4$ and thorough washing and drying the material under vacuum, a substantial amount of the catalytic reactivity is regained. This "regenerated" material gives a total HA yield of 71% under the same conditions as the reactions given in Table 3.

Perhaps more interesting than the yields are the regioselectivities in Table 3. The regioselectivity drops consistently with use, which suggests that the catalytic species in the system are changing with repeated use. Even with the "regenerated" material, entry 6, the regioselectivity continues to drop even as some of the yield was restored. Perhaps more important than a practical application of this approach to regenerate the catalyst material, this experiment suggests that, in addition to some titanium leaching from the catalyst material by substrates, the surface of the catalyst material may be undergoing changes that lead to alterations in the titanium environment. The ramifications of these changes can be observed directly in the effects borne out in the catalysis.

Several control experiments were carried out to assess which component of the $Ti(NMe_2)_2/SiO_2^{200}$ catalyst system is responsible for the catalytic activity observed: the bound titanium, the free titanium leached into solution, or the solid support itself. If the leached titanium is responsible for the catalysis, the regioselectivity and activity should be similar to those of $Ti(NMe_2)_4$, where all of the ligands are protolytically labile.[25] Thus, HA and 3CC reactions were screened with 5 mol% of $Ti(NMe_2)_4$ and with SiO_2^{200} without titanium ligated to the surface. While $Ti(NMe_2)_4$ is a catalyst for HA under these reaction conditions, the regioselectivities for its products versus those of the products when $Ti(NMe_2)_2/SiO_2^{200}$ is employed are very different. For example, hydroamination of 1-phenylpropyne with aniline using $Ti(NMe_2)_4$ and $Ti(NMe_2)_2/SiO_2^{200}$ gave products with regioselectivities of >100:1 and 8.7:1, respectively. Additionally, $Ti(NMe_2)_4$ demonstrates only a small amount of 3CC product formation (Table 2, entry 1) under the same 3CC conditions (17%) as for $Ti(NMe_2)_2/SiO_2^{200}$ (52%), again with different regioselectivity (see the Supporting Information for additional details).

Another set of experiments was conducted to verify that the catalytic activity is in fact from $Ti(NMe_2)_2/SiO_2^{200}$. Two catalytic reactions were run side by side following entry 2, Table 1. These reactions were prepared by following the general procedure but were then heated for only 20 min. After 20 min of heating, the reaction mixtures were cooled to room temperature, centrifuged, and transferred back into a glovebox. GC-FID analysis of the crude reaction solutions showed 74% and 67% conversion to HA2, with the same regioisomer distributions of 8.6:1 and 8.8:1, respectively (Figure 3). Next, the solid catalyst was removed from the latter reaction by filtration. The other reaction mixture was simply resealed after sampling, with no further manipulation.

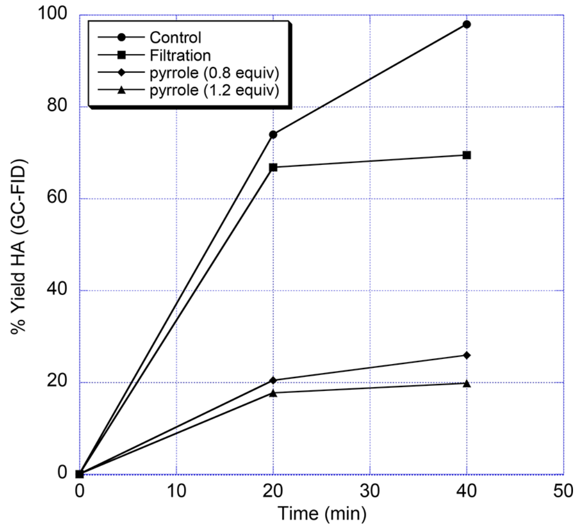

Figure 3. Yield of hydroamination product vs time using the conditions and substrates in entry 2 of Table 1. The "control" experiment (solid circles) is as in entry 2 of Table 1. The "filtration" experiment (solid squares) had the solid catalyst removed by filtration at 20 min. The reactions indicated by diamonds and triangles have 0.8 and 1.2 equiv of pyrrole added as a catalyst poison, respectively. See the text for more details.

Both reaction mixtures were then heated for an additional 20 min. After heating was carried out a second time, another GC-FID analysis was performed. The reaction from which the catalyst was filtered showed no change in product concentration within experimental error, ±2%. The control experiment, which still contained the solid catalyst, went to 100% conversion after the second round of heating (Figure 3). These observations are consistent with a heterogeneous catalyst being responsible for the reactivity observed.

To further explore the nature of the catalytically active species relative to known homogeneous systems, we explored catalyst poisoning experiments. One specific aspect of $Ti(NMe_2)_2/SiO_2^{200}$ that we wanted to scrutinize further was the local Ti environment on the SiO_2^{200} surface (Scheme 1) and its mechanistic similarity to homogeneous species. Characterization of the material suggests that two protolytically cleavable sites remain on the titanium in the form of two dimethylamide ligands. Two protolytically cleavable sites are required for imide formation and catalytic activity through the pathways in Scheme 1. Two experiments were conducted, in which two different concentrations of pyrrole were added to the $Ti(NMe_2)_2/SiO_2^{200}$. The first experiment was conducted with a substoichiometric amount of pyrrole (0.8 equiv) relative to titanium, and the second experiment used a slight excess (1.2 equiv). The results of these studies are shown in Figure 3.

In both catalyst poisoning experiments, a substantial decrease in catalytic activity was noted, relative to the control reaction. The pyrrole-containing reactions appear <30% as active as $Ti(NMe_2)_2/SiO_2^{200}$ itself. In both pyrrole-containing reactions, it was noted that similar regioisomer ratios were observed versus the reaction without pyrrole (~9:1), suggesting the same active species is facilitating the catalytic transformation.

Secondary amines appear to be inactive for hydroamination, also consistent with imido formation being necessary. Attempted hydroamination of 1-octyne and 1-phenylpropyne with *N*-methylaniline using $Ti(NMe_2)_2/SiO_2^{200}$ as catalyst resulted in no product formation that was detectible by GC-MS.

Overall, the control experiments strongly suggest that the reactivity observed with the $Ti(NMe_2)_2/SiO_2^{200}$ is due to the bound titanium species, not the titanium that is leached from the surface during the catalysis. The SiO_2^{200} demonstrates no catalytic activity for either HA or 3CC products, which also supports the assignment of catalytic activity to bound titanium species. Additionally, the severe reduction in catalytic activity noted when pyrrole is included as a poison in reaction mixtures, as well as the lack of reactivity with secondary amine, is consistent with a hydroamination mechanism involving a titanium imido species, although it is certainly not conclusive proof of such a pathway.

On the basis of these results, $Ti(NMe_2)_2/SiO_2^{200}$ is readily recoverable and reusable two to three times with yields comparable to that of freshly prepared catalyst. Additional reuse results in a precipitous decline in performance.

CONCLUSIONS

In this study, we have demonstrated that titanium bound to silica can perform some of the same hydroamination and multicomponent coupling reactions catalyzed by homogeneous titanium complexes. The catalyst itself is reusable several times for hydroamination but eventually succumbs to surface leaching of titanium that appears to be due to side reactions with the alkyne.

Aside from actual loss of the catalyst from the surface, additional interactions with substrate and the silica surface could be deactivating the catalyst. For example, in a manner similar to that for homogeneous analogues, it could be possible that some stable intermediate is achieved through side reactions, involving irreversible binding of substrates to the titanium itself. An example of this was presented by Mountford and co-workers, whereby their titanium catalyst forms a stable six-membered ring upon a second insertion of alkyne into the azatitanacyclobutene.[41] While the solid support inherently aids in the prevention of pathways such as dimerization, deactivation via substrate side reactions is obviously still possible. Deactivation pathways such as these bear further investigation as improvements to catalyst design are pursued.

The heterogeneous catalyst $Ti(NMe_2)_2/SiO_2^{200}$ was found to be readily synthesized, allowed very fast to moderate catalysis at 5 mol % loading with good stability at the temperatures investigated (up to 180 °C), and was very inexpensive to prepare. Thus, the catalytic activity of $Ti(NMe_2)_2/SiO_2^{200}$ shows promise for silica-based titanium HA and multicomponent coupling reactions. As-prepared $Ti(NMe_2)_2/SiO_2^{200}$ catalyzes HA, in some cases, with excellent regioselectivity and high yield. The biggest drawback of $Ti(NMe_2)_2/SiO_2^{200}$ as an HA catalyst is the lack of tolerance to alkyl amines and the undesired formation of alkyne trimers noted with terminal alkynes.

The catalyst's ability to successfully produce modest yields of the 3CC products is significant. While there does appear to be a steric demand that limits the choice of amine to ortho-substituted anilines, this catalyst still provides a route to a versatile organic building block.[10−13,42−46] These results suggest that further examination of surface-bound titanium species may provide the substrate scope, tolerance, and surface stability needed to achieve a reusable and selective titanium catalyst for multicomponent couplings.

EXPERIMENTAL SECTION

General Procedures. All manipulations were carried out using standard Schlenk techniques or in a glovebox with a purified nitrogen atmosphere, unless otherwise specified. Anilines, amines, and alkynes were purchased from commercial sources and distilled under N_2 prior to use. Cyclohexyl isonitrile was prepared according to literature methods.[47] $Ti(NMe_2)_4$ and $Ti(NEt_2)_4$ were purchased from Gelest and used as received. Toluene and pentane(s) were sparged with N_2 and dried by passing over a column of activated alumina prior to use. *p*-Cymene was dried over CaH_2 and distilled under reduced pressure prior to use. Tetrahydrofuran was dried over sodium and distilled under dinitrogen prior to use. NMR solvents were purchased from Cambridge Isotope Laboratories and distilled before use. Sodium cyanoborohydride and *p*-toluenesulfonic acid were purchased commercially and used as received.

Preparation of SiO_2^{200}. Fumed silica (Sigma-Aldrich, 200 ± 25 m^2/g, lot no. SLBT0198) was treated similarly to the published preparation by Scott and co-workers.[38] Silica (20 g) was placed in a 1 L beaker and mixed with deionized water to form a slurry. This slurry was air-dried at room temperature for 48 h and dried further in a 100 °C glassware oven for 48 h. The dried silica was finely divided using a mortar and pestle until the material was free-flowing and had an even appearance. The silica was transferred to a 200 mL beaker and dried for 8 h in a vacuum oven at 200 °C. This silica was transferred to an inert-atmosphere glovebox, where it was stored in a sealed container until use. This resulted in silica (SiO_2^{200}) with a surface hydroxyl group density of 0.52 ± 0.03 mmol/g (1.58 ± 0.2 sites/$Å^3$) by ^1H NMR titration of the silica with $Ti(NEt_2)_4$ as judged by released $HNEt_2$.

Preparation of $Ti(NMe_2)_2/SiO_2^{200}$. In an inert-atmosphere glovebox, a 125 mL Erlenmeyer flask was charged with SiO_2^{200} (4 g, 2.08 mmol OH, 1 equiv) and 30 mL of pentanes. The slurry was stirred, and $Ti(NMe_2)_4$ (800 mg, 1.2 equiv, 2.50 mmol) was added dropwise. The mixture was stirred for 4 h at room temperature, during which time the silica turned pale yellow. The solids were collected by filtration, rinsed with 20 mL of benzene, and briefly dried in vacuo. The material was stored in the glovebox. A separate experiment with $Ti(NEt_2)_4$, which was used because of easier quantitation of $HNEt_2$ relative to gaseous $HNMe_2$, liberated 2.03 (±0.12) molecules of $HNEt_2$ per molecule of $Ti(NEt_2)_4$ consumed, which correlates to 2.32 ± 0.14 wt % Ti (see the Supporting Information for additional details on this $Ti(NEt_2)_4$ experiment). These results agree with a doubly bound titanium motif at the SiO_2^{200} surface as reported by Scott.[38] ICP analysis for titanium in the $Ti(NMe_2)_2/SiO_2^{200}$ material agrees with the NMR titrations, giving a matching 2.33 ± 0.12 wt % for titanium. Obviously, the above gives an average of two attachment sites for the silica to titanium, but there could be a distribution of singly, doubly, and triply attached species along with other minor variations, such as metal centers with HNR_2 as a dative ligand. However, the data are consistent with the doubly bound titanium on silica variant as the major species on the surface. Additionally, in light of the reactivity studies (vide infra), the presence of, on average, two protolytically cleavable sites is a predominant feature of the catalyst material. Again, this does not preclude the presence of a mixture of bound products.

General Hydroamination Procedure. A pressure tube (15 mL) was charged with 5 mol % of $Ti(NMe_2)_2/SiO_2^{200}$ (100 mg, 0.05 mmol of Ti) and a Teflon stir bar. A solution containing NH_2R (1 mmol) and alkyne (1−2 mmol) in *p*-cymene was prepared in a 1 mL volumetric flask. This solution was then placed in the pressure tube, which was sealed and transferred from the glovebox to a preheated aluminum well plate (180 °C). For terminal alkynes, an excess of the alkyne was needed for the reactions to go to completion, as judged by amine conversion in GC-FID; thus, 2 mmol was used in these cases. For terminal alkynes, a larger amount of alkyne trimerization product was observed. The pressure tube was heated for 14 h with magnetic stirring. The pressure tube was ambiently cooled and then centrifuged, compacting the $Ti(NMe_2)_2/SiO_2^{200}$ into an intensely colored orange to brown pellet at the bottom of the tube. This left a transparent yellow to orange solution. See the Supporting Information for characterization details of the organic products.

General Iminoamination Procedure. A pressure tube (15 mL) was charged with 5 mol % of $Ti(NMe_2)_2/SiO_2^{200}$ (100 mg, 0.05 mmol of Ti) and a Teflon stir bar. A solution of NH_2R (1 mmol), alkyne (1−2 mmol), and CyNC (1.5 mmol) was prepared in a 1.5 mL volumetric flask, diluted to this volume with *p*-cymene. This solution was then placed in the pressure tube, which was sealed and transferred from the glovebox to a preheated (180 °C) aluminum well plate. The pressure tube was heated for 48 h with magnetic stirring. The pressure tube was cooled to ambient temperature and was centrifuged, compacting the $Ti(NMe_2)_2/SiO_2^{200}$ into a dark brown pellet at the bottom of the tube. This left a dark orange to opaque brown solution. See the Supporting Information for characterization details of the organic products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00313.

Additional experimental and synthetic details and spectral data for isolated products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for A.L.O.: odom@chemistry.msu.edu.

ORCID

Aaron L. Odom: 0000-0001-8530-4561

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. Generation, alkyne cycloaddition, arene carbon-hydrogen activation, nitrogen-hydrogen activation and dative ligand trapping reactions of the first monomeric imidozirconocene (Cp2Zr:NR) complexes. *J. Am. Chem. Soc.* **1988**, *110*, 8729−8731.

(2) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. Stoichiometric and catalytic hydroamination of alkynes and allene by zirconium bisamides Cp2Zr(NHR)2. *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719.

(3) Johnson, J. S.; Bergman, R. G. Imidotitanium Complexes as Hydroamination Catalysts: Substantially Enhanced Reactivity from an Unexpected Cyclopentadienide/Amide Ligand Exchange. *J. Am. Chem. Soc.* **2001**, *123*, 2923−2924.

(4) Pohlki, F.; Doye, S. The Mechanism of the [Cp2TiMe2]-Catalyzed Intermolecular Hydroamination of Alkynes. *Angew. Chem., Int. Ed.* **2001**, *40*, 2305−2308.

(5) Khedkar, V.; Tillack, A.; Beller, M. A Dramatic Effect of Aryloxo Ligands on the Titanium-Catalyzed Hydroamination of Alkynes. *Org. Lett.* **2003**, *5*, 4767−4770.

(6) Thomson, R. K.; Bexrud, J. A.; Schafer, L. L. A Pentagonal Pyramidal Zirconium Imido Complex for Catalytic Hydroamination of Unactivated Alkenes. *Organometallics* **2006**, *25*, 4069−4071.

(7) Bhattacharjee, J.; Das, S.; Kottalanka, R. K.; Panda, T. K. Hydroamination of carbodiimides, isocyanates, and isothiocyanates by a bis(phosphinoselenoic amide) supported titanium(iv) complex. *Dalton Transactions* **2016**, *45*, 17824−17832.

(8) Odom, A. L. New C-N and C-C bond forming reactions catalyzed by titanium complexes. *Dalton Transactions* **2005**, 225−233.

(9) Severin, R.; Doye, S. The catalytic hydroamination of alkynes. *Chem. Soc. Rev.* **2007**, *36*, 1407−1420.

(10) Cao, C.; Shi, Y.; Odom, A. L. A Titanium-Catalyzed Three-Component Coupling To Generate *α*,*β*-Unsaturated *β*-Iminoamines. *J. Am. Chem. Soc.* **2003**, *125*, 2880−2881.

(11) Majumder, S.; Odom, A. L. Titanium catalyzed one-pot multicomponent coupling reactions for direct access to substituted pyrimidines. *Tetrahedron* **2010**, *66*, 3152−3158.

(12) Odom, A. L.; McDaniel, T. J. Titanium-Catalyzed Multicomponent Couplings: Efficient One-Pot Syntheses of Nitrogen Heterocycles. *Acc. Chem. Res.* **2015**, *48*, 2822−2833.

(13) Majumder, S.; Gipson, K. R.; Staples, R. J.; Odom, A. L. Pyrazole Synthesis Using a Titanium-Catalyzed Multicomponent Coupling Reaction and Synthesis of Withasomnine. *Adv. Synth. Catal.* **2009**, *351*, 2013−2023.

(14) Vujkovic, N.; Fillol, J. L.; Ward, B. D.; Wadepohl, H.; Mountford, P.; Gade, L. H. Insertions into Azatitanacyclobutenes: New Insights into Three-Component Coupling Reactions Involving Imidotitanium Intermediates. *Organometallics* **2008**, *27*, 2518−2528.

(15) Straub, B. F.; Bergman, R. G. The Mechanism of Hydroamination of Allenes, Alkynes, and Alkenes Catalyzed by Cyclopentadienyltitanium−Imido Complexes: A Density Functional Study. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632−4635.

(16) Yim, J. C. H.; Bexrud, J. A.; Ayinla, R. O.; Leitch, D. C.; Schafer, L. L. Bis(amidate)bis(amido) Titanium Complex: A Regioselective Intermolecular Alkyne Hydroamination Catalyst. *J. Org. Chem.* **2014**, *79*, 2015−2028.

(17) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. Titanium dipyrrolylmethane derivatives: rapid intermolecular alkyne hydroamination. *Chem. Commun.* **2003**, 586−587.

(18) Ackermann, L. TiCl4-Catalyzed Intermolecular Hydroamination Reactions. *Organometallics* **2003**, *22*, 4367−4368.

(19) Ackermann, L.; Born, R. TiCl4/t-BuNH2 as the sole catalyst for a hydroamination-based Fischer indole synthesis. *Tetrahedron Lett.* **2004**, *45*, 9541−9544.

(20) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. Intramolecular Hydroamination of Unactived Olefins with Ti(NMe2)4 as a Precatalyst. *Org. Lett.* **2005**, *7*, 1959−1962.

(21) Li, C.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. Amidate complexes of titanium and zirconium: a new class of tunable precatalysts for the hydroamination of alkynes. *Chem. Commun.* **2003**, 2462−2463.

(22) Gilbert, Z. W.; Hue, R. J.; Tonks, I. A. Catalytic formal [2 + 2+1] synthesis of pyrroles from alkynes and diazenes via TiII/TiIV redox catalysis. *Nat. Chem.* **2016**, *8*, 63.

(23) Blake, A. J.; Collier, P. E.; Dunn, S. C.; Li, W. S.; Mountford, P.; Shishkin, O. V. Synthesis and imido-group exchange reactions of tert-butylimidotitanium complexes. *J. Chem. Soc., Dalton Trans.* **1997**, 1549−1558.

(24) Mountford, P. New titanium imido chemistry. *Chem. Commun.* **1997**, 2127−2134.

(25) Billow, B. S.; McDaniel, T. J.; Odom, A. L. Quantifying ligand effects in high-oxidation-state metal catalysis. *Nat. Chem.* **2017**, *9*, 837.

(26) Swartz, D. L.; Odom, A. L. Synthesis, Structure, and Hydroamination Kinetics of (2,2′-Diaryldipyrrolylmethane)- and Bis(2-arylpyrrolyl)titanium Complexes. *Organometallics* **2006**, *25*, 6125−6133.

(27) Britton, J.; Jamison, T. F. The Assembly and Use of Continuous Flow Systems for Chemical Synthesis. *Nat. Protoc.* **2017**, *12*, 2423−2446.

(28) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892−4928.

(29) Hamzaoui, B.; Pelletier, J. D. A.; Abou-Hamad, E.; Chen, Y.; Eter, M. E.; Chermak, E.; Cavallo, L.; Basset, J. M. Solid-State NMR and DFT Studies on the Formation of Well-Defined Silica-Supported Tantallaaziridines: From Synthesis to Catalytic Application. *Chem. - Eur. J.* **2016**, *22*, 3000−3008.

(30) Copéret, C.; Comas-Vives, A.; Conley, M. P.; Estes, D. P.; Fedorov, A.; Mougel, V.; Nagae, H.; Núñez-Zarur, F.; Zhizhko, P. A. Surface Organometallic and Coordination Chemistry toward Single-Site Heterogeneous Catalysts: Strategies, Methods, Structures, and Activities. *Chem. Rev.* **2016**, *116*, 323−421.

(31) Le Roux, E.; Liang, Y.; Storz, M. P.; Anwander, R. Intramolecular Hydroamination/Cyclization of Aminoalkenes Catalyzed by Ln[N(SiMe3)2]3 Grafted onto Periodic Mesoporous Silicas. *J. Am. Chem. Soc.* **2010**, *132*, 16368−16371.

(32) Ng, E.-P.; Law, S.-P.; Mukti, R. R.; Juan, J.-C.; Adam, F. Hydroamination of cyclohexene enhanced by ZnCl2 nanoparticles supported on chiral mesoporous silica. *Chem. Eng. J.* **2014**, *243*, 99−107.

(33) Davaasuren, B.; Emwas, A.-H.; Rothenberger, A. MAu2GeS4-Chalcogel (M = Co, Ni): Heterogeneous Intra- and Intermolecular Hydroamination Catalysts. *Inorg. Chem.* **2017**, *56*, 9609−9616.

(34) Sengupta, M.; Bag, A.; Das, S.; Shukla, A.; Konathala, L. N. S.; Naidu, C. A.; Bordoloi, A. Reaction and Mechanistic Studies of Heterogeneous Hydroamination over Support-Stabilized Gold Nanoparticles. *ChemCatChem* **2016**, *8*, 3121−3130.

(35) Cook, A. K.; Copéret, C. Alkyne Hydroamination Catalyzed by Silica-Supported Isolated Zn(II) Sites. *Organometallics* **2018**, *37*, 1342.

(36) Sensarma, S.; Bouh, A. O.; Scott, S. L.; Alper, H. Olefin epoxidation catalyzed by an air stable-supported titanium catalyst. *J. Mol. Catal. A: Chem.* **2003**, *203*, 145−152.

(37) Scott, S. L.; Church, T. L.; Nguyen, D. H.; Mader, E. A.; Moran, J. An investigation of catalyst/cocatalyst/support interactions in silica-supported olefin polymerization catalysts based on Cp*TiMe3*. *Top. Catal.* **2005**, *34*, 109−120.

(38) Beaudoin, M.; Scott, S. L. Spontaneous Evolution of Silica-Supported Ti Amide Fragments to Imine and Imido Complexes. *Organometallics* **2001**, *20*, 237−239.

(39) Eedugurala, N.; Wang, Z.; Chaudhary, U.; Nelson, N.; Kandel, K.; Kobayashi, T.; Slowing, I. I.; Pruski, M.; Sadow, A. D. Mesoporous Silica-Supported Amidozirconium-Catalyzed Carbonyl Hydroboration. *ACS Catal.* **2015**, *5*, 7399−7414.

(40) Bouh, A. O.; Rice, G. L.; Scott, S. L. Mono- and Dinuclear Silica-Supported Titanium(IV) Complexes and the Effect of TiOTi Connectivity on Reactivity. *J. Am. Chem. Soc.* **1999**, *121*, 7201−7210.

(41) Vujkovic, N.; Ward, B. D.; Maisse-François, A.; Wadepohl, H.; Mountford, P.; Gade, L. H. Imido-Alkyne Coupling in Titanium Complexes: New Insights into the Alkyne Hydroamination Reaction. *Organometallics* **2007**, *26*, 5522−5534.

(42) Pasko, C. M.; Dissanayake, A. A.; Billow, B. S.; Odom, A. L. One-pot synthesis of pyrroles using a titanium-catalyzed multicomponent coupling procedure. *Tetrahedron* **2016**, *72*, 1168−1176.

(43) Dissanayake, A. A.; Staples, R. J.; Odom, A. L. Titanium-Catalyzed, One-Pot Synthesis of 2-Amino-3-cyano- pyridines. *Adv. Synth. Catal.* **2014**, *356*, 1811−1822.

(44) Dissanayake, A. A.; Odom, A. L. Regioselective conversion of alkynes to 4-substituted and 3,4-disubstituted isoxazoles using titanium-catalyzed multicomponent coupling reactions. *Tetrahedron* **2012**, *68*, 807−812.

(45) Barnea, E.; Majumder, S.; Staples, R. J.; Odom, A. L. One-Step Route to 2,3-Diaminopyrroles Using a Titanium-Catalyzed Four-Component Coupling. *Organometallics* **2009**, *28*, 3876−3881.

(46) Majumder, S.; Gipson, K. R.; Odom, A. L. A Multicomponent Coupling Sequence for Direct Access to Substituted Quinolines. *Org. Lett.* **2009**, *11*, 4720−4723.

(47) Ugi, I.; Meyer, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. Cyclohexyl Isocyanide. *Org. Synth.* **1961**, *41*, 13.