Electronic Supplementary Material (ESI) for Dalton Transactions.

Supporting Information

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

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Contents

General Considerations for Syntheses and Characterization

Solution phase NMR was utilized to perform the SiO_2^{700} surface titration experiments, as well as routine characterization of isolated products from catalytic reactions. Routine characterization spectra were obtained using an Agilent DDR2 500 MHz NMR spectrometer equipped with a 5 mm PFG OneProbe operating at 499.84 MHz (^1H) and 125.73 MHz (^{13}C). Calibrations of the SiO_2^{700} were performed using a Varian Inova 500 spectrometer equipped with a 5 mm pulse-field-gradient (PFG) switchable broadband probe operating at 499.84 MHz (^1H). ^1H NMR chemical shifts were referenced to residual $CHCl_3$ in $CDCl_3$ as 7.26 ppm, or residual C_6HD_5 in C_6D_6 as 7.16 ppm. ^{13}C NMR chemical shifts are reported relative to $^{13}CDCl_3$ as 77.16 ppm, or $(^{13}C)C_5D_6$ as 128.06 ppm.

ICP data was collected on a Varian 710es ICPOES spectrometer. A 1000 ppm Ti ICP standard in 2% HNO_3 was purchased from Sigma-Aldrich and used as received to prepare an external calibration curve. The $Ti(NMe_2)_3/SiO_2^{200}$ samples were then measured in triplicate and quantified from the external calibration allowing for the mass of Ti in each sample to be determined. Samples of $Ti(NMe_2)_3/SiO_2^{700}$ for ICP analysis were prepared according to previously published procedures.[1] Briefly, a known mass of $Ti(NMe_2)_3/SiO_2^{700}$ was measured in the glovebox and transferred, in a scintillation vial, to a fume hood. Concentrated HNO_3 (1-2 mL) was added to the sample, which typically elicited the release of colorless fumes and a color change from yellow to colorless. The sample was allowed to sit in the concentrated acid solution for several hours and was then carefully diluted with DI water (10 mL). The sample was transferred to a centrifuge tube (including solids), and centrifuged for 5-10 min, until the solids were compacted into a tight pellet. The liquid was decanted, and the solids were rinsed with another 10 mL of water. The two aqueous fractions were combined and further dilution to a known volume was carried out until the solution was within the calibration range of the instrument, of 0-6 ppm Ti.

GCMS data was collected on an Agilent 5973 MSD with a 6890N series GC. GCFID data was collected on a Hewlett Packard 6890 series GC system and standardized against dodecane as an internal standard. Hydroamination and iminoamination products were quantified *in situ* utilizing GCFID standardized calibration curves. For hydroamination products, the amine derivatives of the tautomerized imine products were used as calibration standards, with retention times confirmed by GCMS. The iminoamination products were compared to the closest isolated derivate in a similar fashion. This is described in more detail below.

Product Identification for Catalytic Hydroamination and Iminoamination Experiments

Many of the products of hydroamination and iminoamination presented in Tables 1 and 2 in the manuscript have been previously studied.[1, 2]

For the hydroamination compounds in Table 1, the reduced derivatives for Entries 1-3, 7-8, and 11-14 were prepared. The hydroamination products are imines, which are subject to hydrolysis and difficult to isolate by column chromatography. Consequently, authentic samples of the reduced compounds (by sodium cyanoborohydride) were prepared,[1] and their GC responses were found versus internal standard, assuming that the addition of the two hydrogens makes an inconsequential change to the GC response. Compounds that were prepared in miniscule quantities could not be isolated to set up calibration curves, and compounds with known calibration curves with similar formulas were used. This was done to estimate yields for the compounds for which the catalyst does not work well in the Table. These substitutions: Entry 5 uses the calibration curve for 1, Entry 6 uses the calibration curve for 2, and Entry 10 uses the calibration curve for 7. Obviously, in these cases, the yields may have substantial errors but were generally small regardless. Entry 9 has no product observed by GCMS or GCFID. Finally, the hydroamination product for Entry 4 is known and is a crystalline solid which could be isolated and purified by recrystallization from the crude catalytic reaction mixture. The isolated imine was used to generate a calibration curve for Entry 4.

Due to the possibility of regioisomers with unsymmetrical alkynes, the regioisomer(s) of these isolated amine derivatives were previously determined by NMR (^{1}H and ^{13}C).[1] With a combination of NMR, GCMS, and GCFID analysis for these isolated compounds, we were able to assess the identity of the regioisomers in the aforementioned reaction mixtures based on GC retention times (verified with m/z peaks by GCMS). For those compounds that were not isolated, due to poor yields, absolute regioselectivity cannot be determined, and rather the regioisomers shown are illustrative examples.

Similar analyses were applied to iminoamination derivatives examined in this study (Table 2). It was assumed that compounds with identical formulas have similar GCFID responses. Entry 1 has been isolated and fully characterized previously.[1] The known calibration curve for Entry 1 was used for Entries 1, 2, and 3, which are isomers. The yield of Entry 4 with this catalyst made the product very difficult to isolate; however, we wanted to still mention the compound and estimate the yield, which was done with the calibration curve of Entry 1; based on the leftover starting materials also observed in the crude reaction mixture the estimated yield calculated in this manner seems reasonable. Compound 5 was isolated in previous work and had a known calibration curve.[1] Compounds 6 and 7 were isolated in related work, and their GC response curves relative to dodecane internal standard were made from purified material.[3]

Synthesis of SiO_2^{700}

An OTF-1200X-S (MTI Corporation) high temperature furnace was utilized in the preparation of the SiO_2^{700}. The fumed SiO_2, purchased from Sigma-Aldrich, was poured into a 1 L beaker. To this was added DI water, and this mixture was stirred until it formed a homogenous slurry. This slurry was air-dried for 48 h, and then transferred to a 140 °C glassware oven for an additional 48 h. The resulting SiO_2 was compact and clumpy. The material was then ground with a mortar and pestle until a finely divided, free-flowing powder resulted. 15 g of this material could be loaded into a quartz tube closed at one end, and fitted with a gas-adapted ball-and-socket joint at one end (borosilicate glass).

Figure S1. Quartz tube utilized for tube furnace preparation of SiO_2^{700}, including heating to 700 °C under vacuum.

The loaded quartz tube was placed in the tube furnace, taking care to center the SiO_2 over the heating element. The heating and atmosphere protocol listed in Table S1 was then followed to de-hydroxylate the SiO_2.

Table S1. Dehydroxylation Protocol for Tube Furnace to Prepare SiO_2^{700}.

Temperature (°C)	**Ramp rate (°C/min)**	**Time (min)**	**Atmosphere**
20-500	5	96	Air
500	−	240	Air
500	−	720	Vacuum
500-700	1.33	150	Vacuum
700	−	480	Vacuum
700-20	≈4	180	Vacuum

After the tube was cooled to room temperature, it was sealed under vacuum and transferred to an N_2 atmosphere glovebox. The material was stored in sealed containers in the glovebox until further use.

Determination of the Composition of the Catalytic Sites

$Ti(NEt_2)_4$ titrations of the material following reported procedure provide a surface density Si-OH determination of 0.00031 ± 0.00005 mol/g SiO_2^{700} or 0.90 ± 0.11 Si–OH sites/nm^2. This correlates to a predicted Ti loading of 1.46 ± 0.12 wt %. 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 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.

Additionally, an experiment was done to determine if there is substantial amine physisorbed to the silica surface. A scintillation vial was charged with 157 mg of $Ti(NMe_2)_3/SiO_2^{700}$ catalyst material (4.9×10^{-5} mol Ti based on experimental wt%). To this vial was added a 2.0 mL solution containing pyridine (25 mg, 0.32 mmol, 6.5 equiv.), tetrakis(trimethylsilyl)silane (1.2 mg, 3.7×10^{-6} mol, internal standard), and C_6D_6 as solvent. The solution was stirred for 4 h at room temperature, after which the solution was decanted and examined by ^{1}H NMR spectroscopy. Relative to the internal standard 1.16 equiv of $HNMe_2$ were observed in the decanted solution. This equates to 4.3×10^{-6} mol of $HNMe_2$, or a molecular ratio of about 9% $HNMe_2$ vs Ti in the sample.

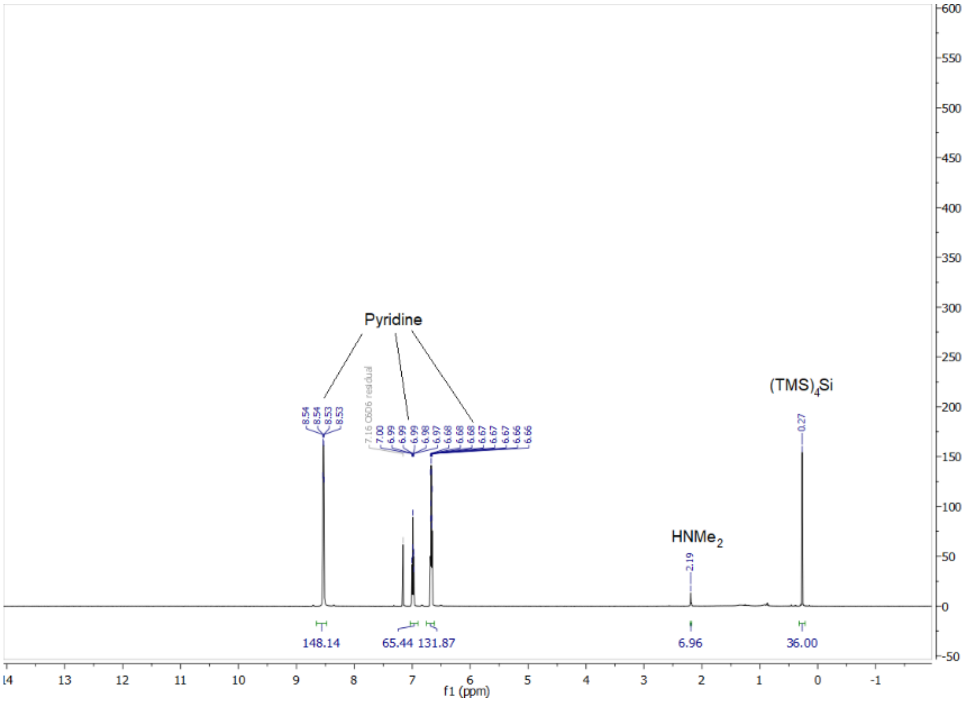


Figure S2. ^{1}H NMR of $Ti(NMe_2)_3/SiO_2^{700}$ in C_6D_6 with tetrakis(trimethylsilyl)silane as internal standard and excess pyridine. Liberated $HNMe_2$ is labeled, with a shift at 2.19 ppm.

Based on the results of this experiment, it would appear that a small amount of $HNMe_2$ remains datively bound to titanium or physisorbed to silica. In the presence of pyridine this $HNMe_2$ is liberated. These result suggest the ratio of $HNMe_2$ liberated on binding $Ti(NMe_2)_4$ to SiO_2^{700} is 1.07 ± 0.04, if we take into account the additional $HNMe_2$ liberated upon addition of excess base to the preformed catalyst material. This additional data supports the assessment of the average stoichiometry found in the material as $Ti(NMe_2)_3/SiO_2^{700}$ (i.e., >90%).

Notes on Error Propagation

The error for NMR titration measurements was assessed from triplicate (or more) NMR measurements for 3-5 separately prepared samples with each batch of SiO_2^{700} prepared. The triplicate NMR measurement provided a standard error due to integration error and other errors inherent to the measurement technique.

For each batch of material, 3-5 separately prepared samples were analyzed to provide a range of values from which the experimental error of mass and calculated concentration could be assessed. The standard error calculated from the triplicate NMR measurements of each sample was comparable in magnitude to the standard error calculated across multiple different samples, and thus both sources of error were fully propagated to the final averaged value following standard procedures.

In a similar manner, the error for ICP-OES measurements was analyzed from two sources. Each sample was measured in triplicate to assess error in the measurement technique. Additionally, multiple samples of each batch of material were measured to assess experimental errors in sample preparation, such as random errors in masses or dilutions. Error for both sources was propagated using standard error analysis into the final averaged wt% Ti.

IR Spectroscopy on $Ti(NMe_2)_3/SiO_2^{700}$

In the glovebox, the silica material was ground to a fine particulate with a mortar and pestle and was then mixed with Krytox Grease (Dupont) in a vial to provide a thick paste. This paste was spread in a thin layer onto a KBr plate. The loaded plate was pressed against a second plate to sandwich the thin layer of Krytox-coated silica material. The plates were loaded into a sample holder and were transferred to the IR instrument (Mattson Galaxy 3025) in a secondary container sealed in the box under nitrogen. The sample holder was transferred to the sample compartment in the instrument, which was flushed with a high flow rate of nitrogen gas prior to and during data collection.

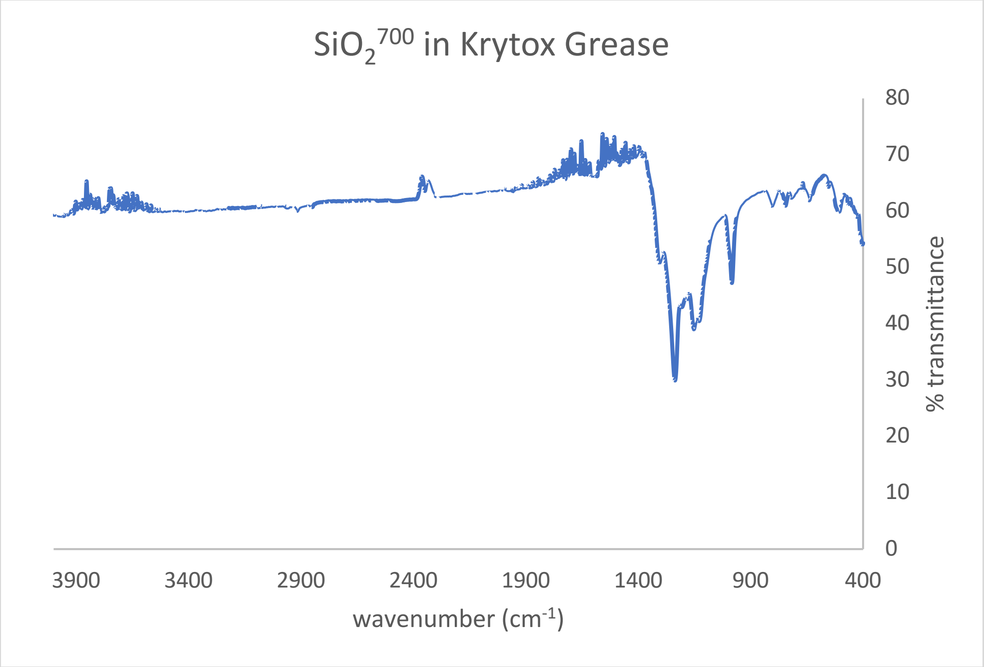


Figure S3. IR spectrum of SiO_2^{700} as a paste in krytox grease.

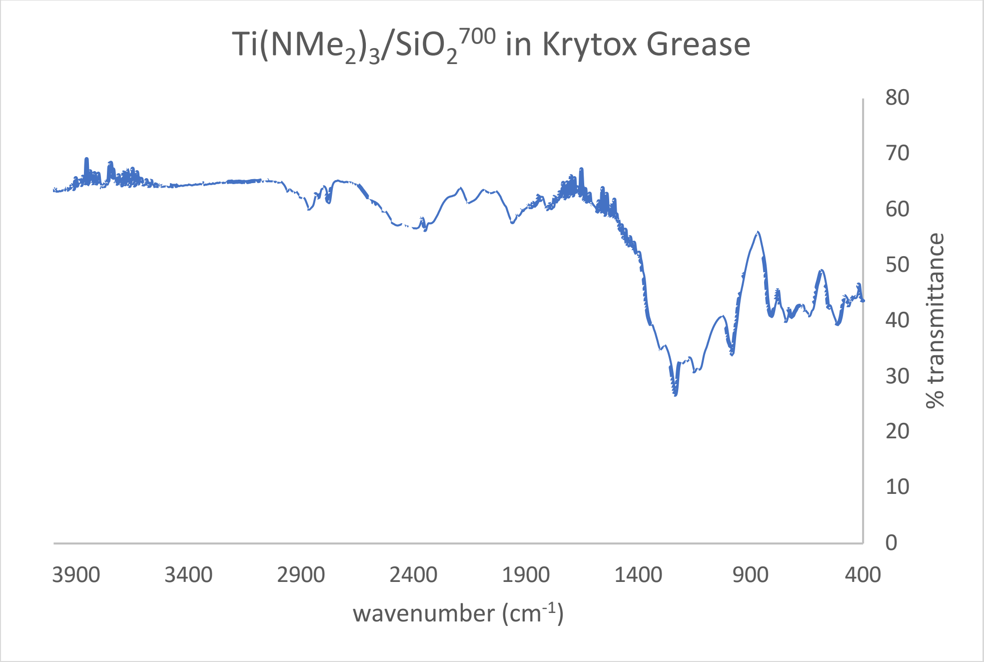


Figure S4. IR spectrum of $Ti(NMe_2)_3/SiO_2^{700}$ in Krytox grease. Note the appearance of new peaks in the C–H stretch region.

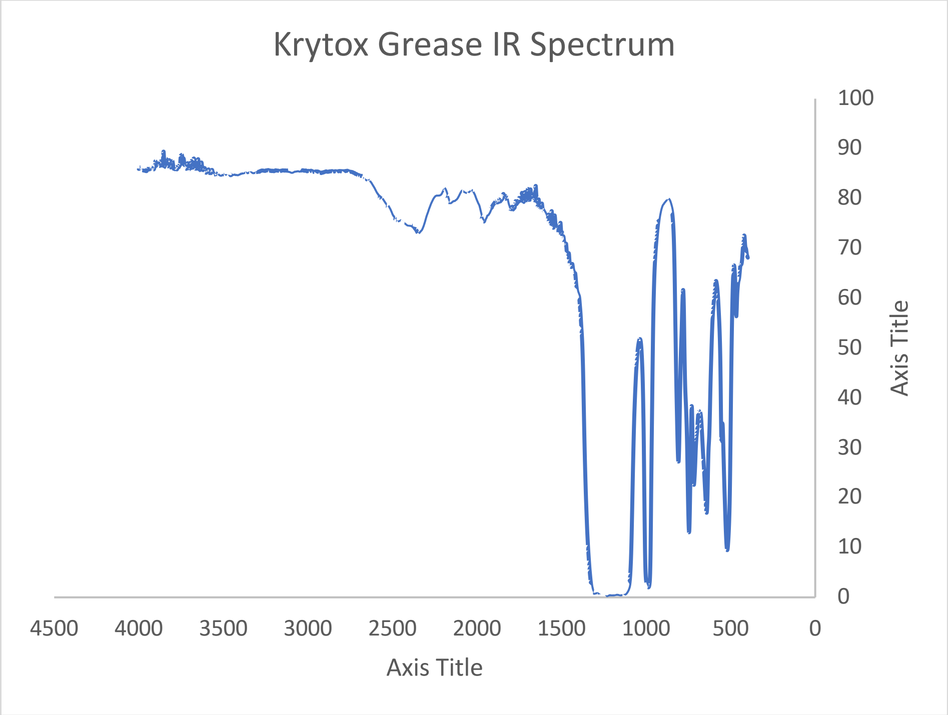


Figure S5. IR spectrum of Krytox grease.

^{13}C Solid-State NMR Spectroscopy on $Ti(NMe_2)_3/SiO_2^{700}$

The silica gel is adorned with a small amount of titanium (1-2%), and, as a result, the concentration on the surface is very low. Nevertheless, we were able to see ^{13}C NMR resonances for the titanium species on the surface as shown below. There are two resonances attributable to the sample at 43 and 36 ppm, which are assigned to the titanium amides and dimethylamine, respectively. The broad resonance centered around 170 ppm is apparently an artifact of our probe, which is generally not observed in samples but is observed here due to the long collection time and low concentration of carbon in the sample.

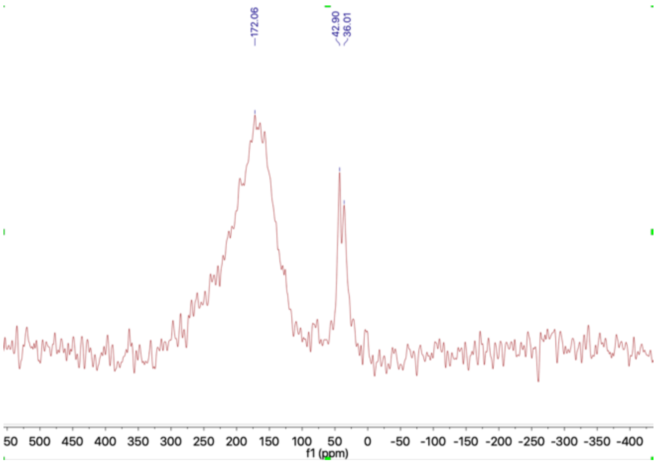


Figure S6. ss-^{13}C NMR of $Ti(NMe_2)_3/SiO_2^{700}$. Broad resonance at ~170 ppm is an artifact of the probe.

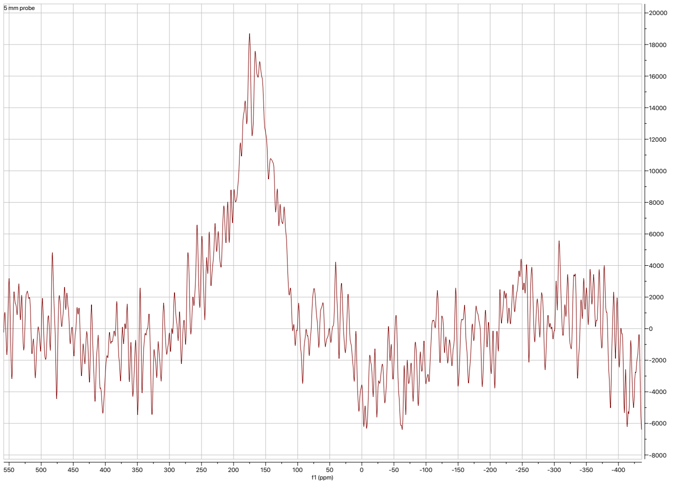


Figure S7. ss-^{13}C NMR of empty sample holder. Broad resonance at 170 ppm is an artifact of the probe.

Investigations into Catalyst Deactivation by HCl Wash

After running a 3CC reaction following the general procedure, the contents of the pressure tube were centrifuged to compact the catalyst material into a tight pellet at the bottom of the tube. In air, the organic phase was removed, and the catalyst material washed several times with hexanes (3 x 5 mL), vortexing and centrifuging with each wash. The catalyst material was air-dried and then washed with 3 mL of a dilute (10%) HCl solution. The HCl aliquot was then neutralized to pH 7-8 with sodium bicarbonate solution, and extracted with Et_2O, followed by EtOAc. The organic extracts were combined and examined by GCMS.

The GC results show several new compounds in the HCl wash not observed in the organic phase. While some compounds remain unidentified, two masses appear with m/z 218 and 224. In particular, the mass of 218 was determined to closely match that of 1-phenyl-3-cyclohexylurea. The urea was independently synthesized by literature procedures.[4] The synthesized urea and the peak observed with the same mass in the HCl wash display very similar retention times and fragmentation patterns. Thus, we believe this is likely the identity of the organic residue. Likewise, the m/z 224 peak has the same mass as 1,3-dicyclohexylurea. GC/MS fragmentation patterns are shown in Figures S6-8.

While other species are also found in the HCl wash of the deactivated catalyst material, from the identification of the urea species and the observation that both cyclohexyl and phenyl groups are involved, we strongly suspect that an off-cycle interaction between anilide and the cyclohexylisonitrile are leading to new and previously undetected reactivity. These species are not observed in the hexanes washes of the catalyst material. Only once an aqueous acid is added to the catalyst material do these species appear, which suggests that they are tightly bound to the surface. We postulate that the species bound to the deactivated catalyst may be a carbodiimide or urea species.

If urea is present on the surface before aqueous HCl addition, the only intentionally included source of oxygen to generate urea is from the silica gel. If dioxygen or water are the source of oxygen to make the urea and urea causes the deactivation, they must be present in every sample examined, as deactivation is always observed.

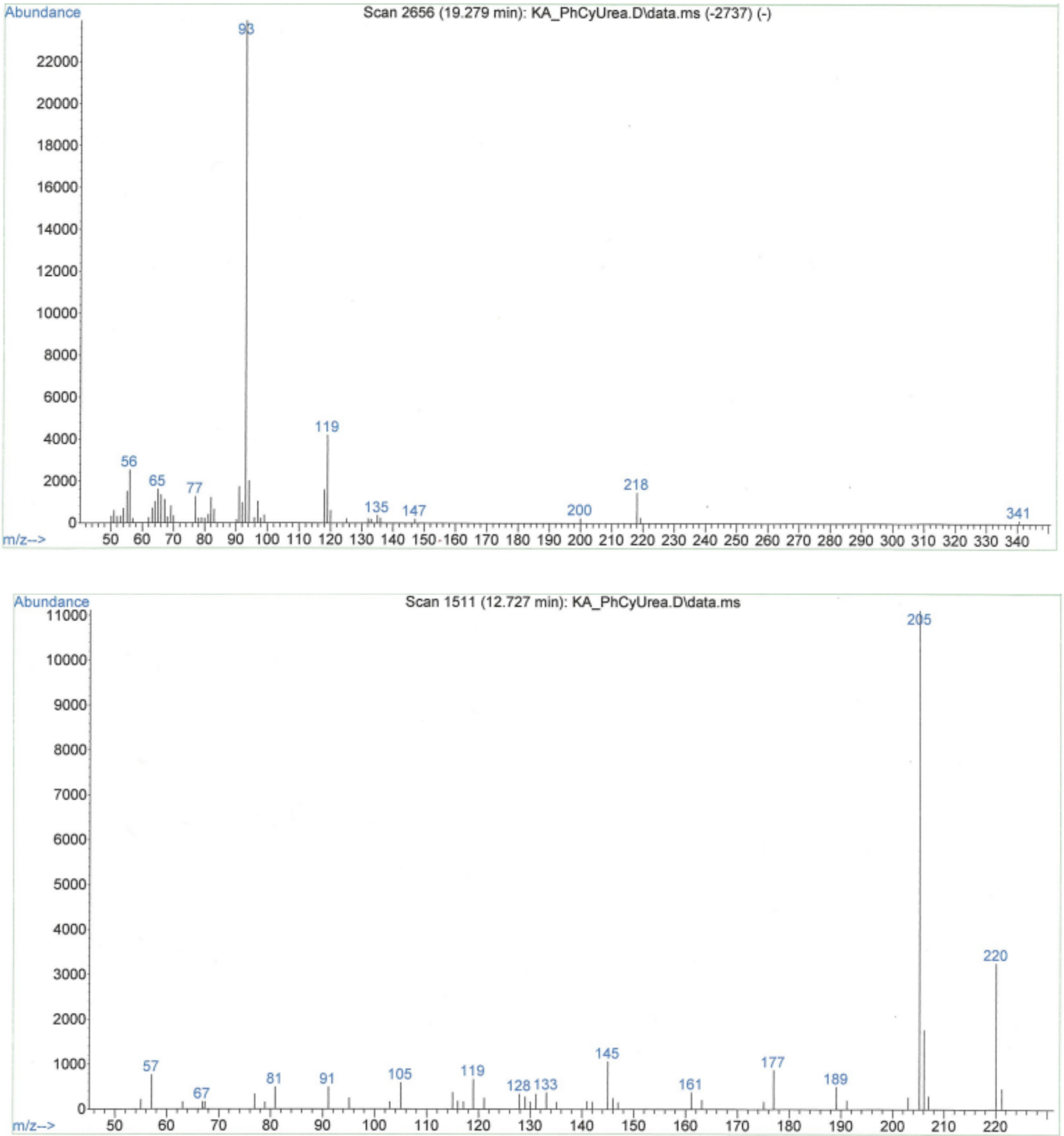


Figure S8. Two m/z peaks observed by GC/MS analysis of 1-phenyl-3-cyclohexylurea. The parent peak of 218 matches the molecular weight of the compound (top), which is pure as synthesized by ^{1}H and ^{13}C NMR. The m/z 220 peak appears to be a decomposition product formed upon introduction of the urea complex to the GC column.

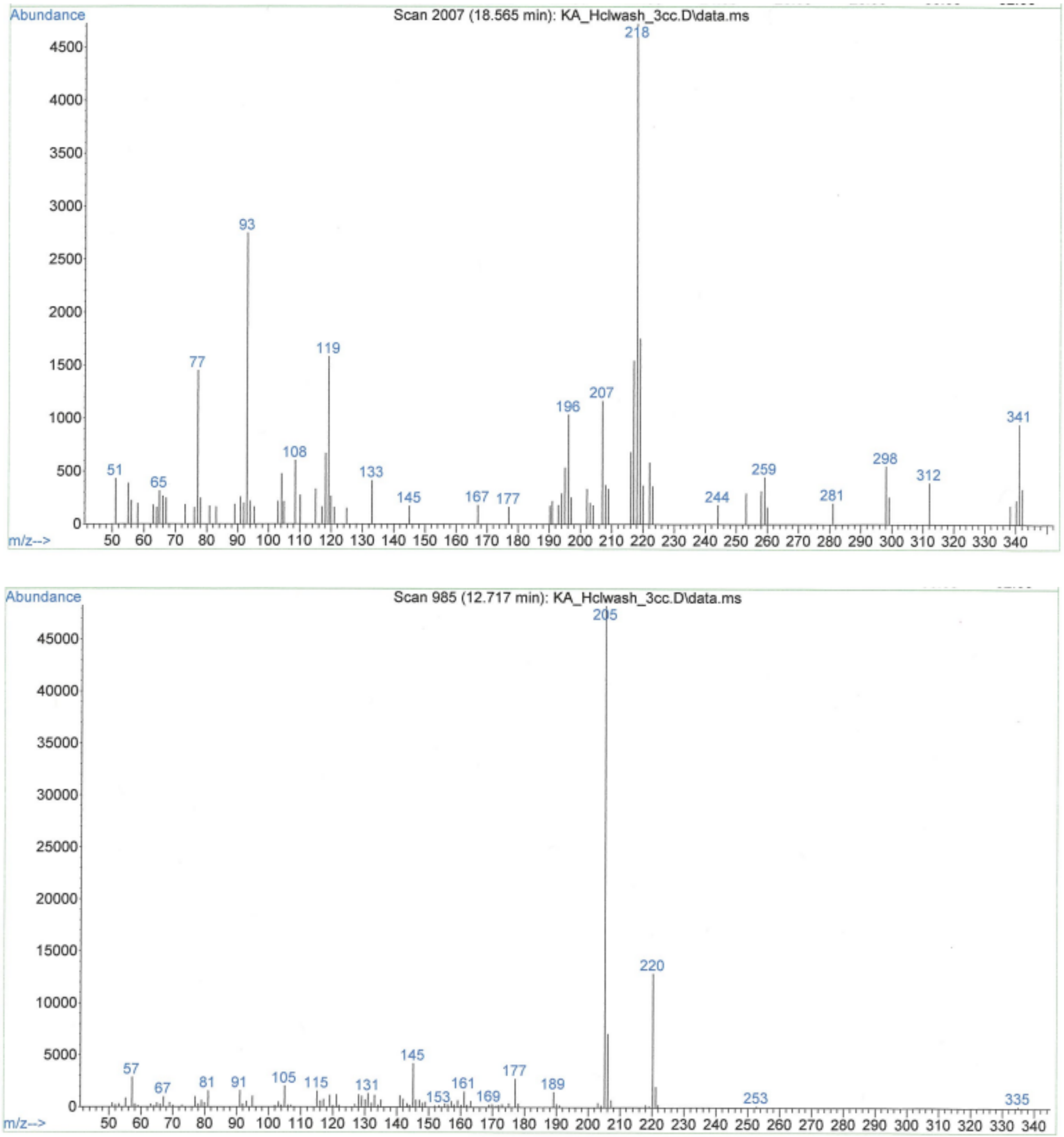


Figure S9. Two m/z peaks observed by GC/MS of the HCl washed of the catalyst material after a 3CC reaction. The retention times and fragmentation patterns are very similar between the two. Note that in the top spectrum, some amount of column bleed was observed which was not able to be background subtracted from the MS spectrum (i.e. m/z 341, 259, 207).

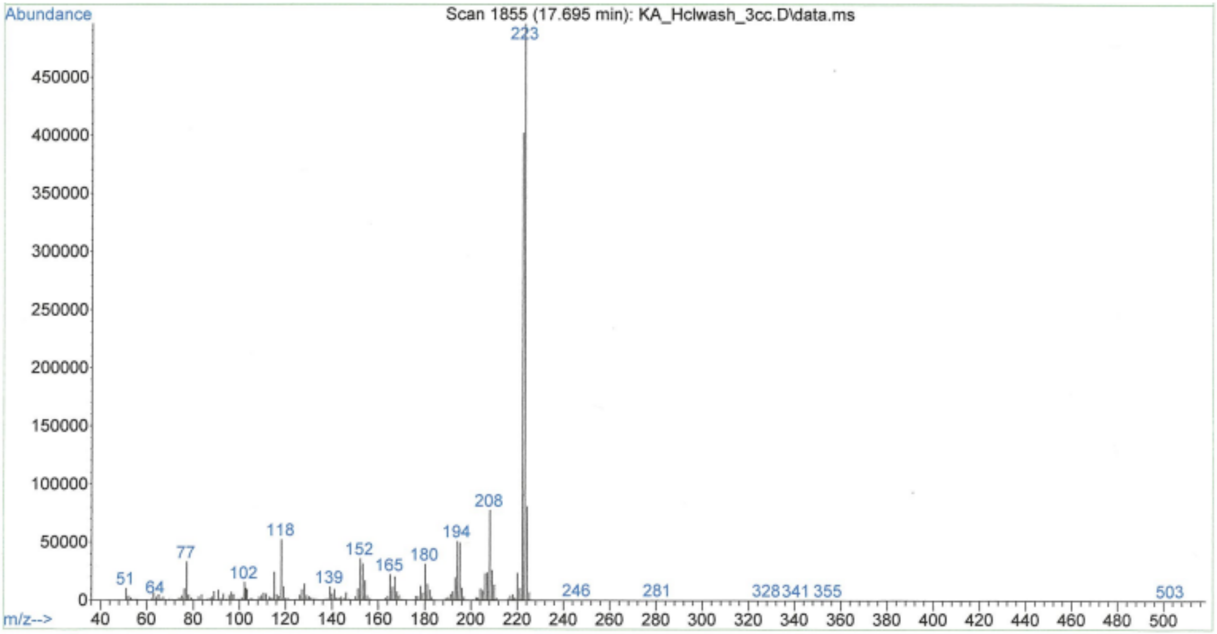
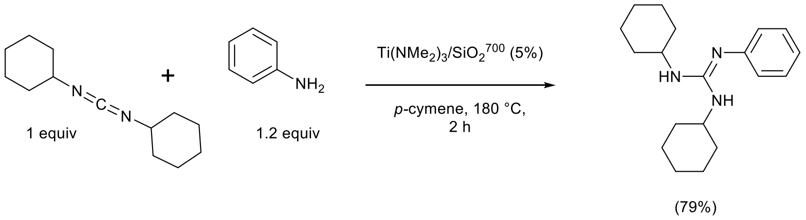


Figure S10. Additional peak observed in the GC/MS analysis of the HCl wash of used 3CC catalyst, with m/z 223 (this species is proposed to be 1,3-dicyclohexylurea).

With experimental support for formation of new complexes from the combination of anilide fragments and excess isonitrile, we turned to the literature in search of similar reactivity reports with Ti. We found a few reports of homogeneous Ti catalyst generating guanidines from carbodiimides and amines, with specific ligand platforms.[5-7] The identification of urea or urea-like species after an aqueous acid treatment of the surface suggested to us that species such as carbodiimides or guanidines may be bound to Ti. These species would bind strongly and act as good ligands with Ti(IV), which could potentially inhibit the catalyst.

To test this hypothesis, 1,3-dicyclohexylcarbodiimide, aniline, and $Ti(NMe_2)_3/SiO_2^{700}$ were combined in pressure tube, as a solution in *p*-cymene, and heated at 180 °C. After 1 h, a large amount of the coupled product (guanidine) was observed by GCMS, with small peaks observed correlating to the starting materials. The reaction was repeated on a catalytic scale, following the conditions shown in the scheme below. This provided the guanidine in 79% isolated yield. The guanidine product matched previously reported characterization of the product by NMR (^{1}H and ^{13}C).[7]

Scheme S1. Catalytic synthesis of substituted guanidine utilizing heterogeneous titanium catalyst.



The same reaction shown in the scheme above was also performed with the addition of 0.2 equiv of CyNC, and inhibition of the guanidine formation was noted. Thus, it appears that the addition of isonitrile to the catalyst material with aniline and carbodiimide (a likely combination of compounds present in the crude reaction solution of a 3CC) prevents this catalytic turnover to the guanidine. While this experiment did not provide direct confirmation for the original hypothesis, a lack of guanidine in the 3CC reaction solution cannot rule out the formation of carbodiimide-like species, since isonitrile is inhibitory of the guanylation reaction.

ICP-OES Details for $Ti(NMe_2)_3/SiO_2^{700}$ and Used Precatalyst

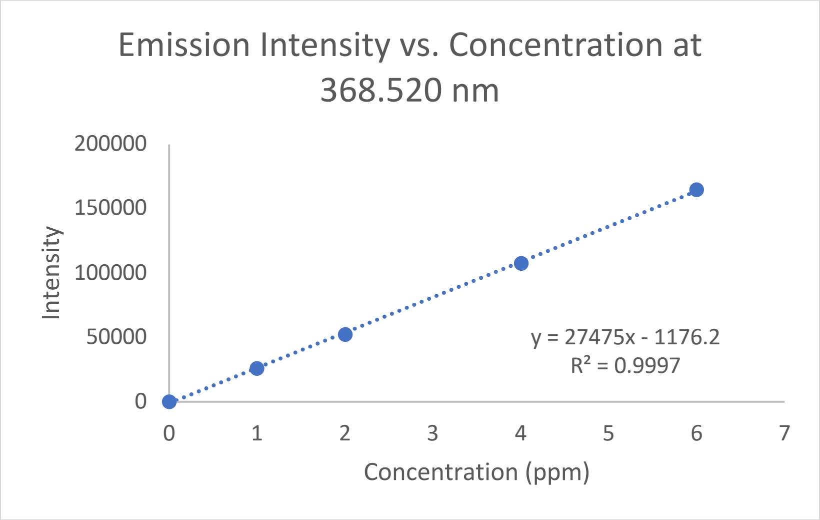


Figure S11. Typical Calibration Curve for ICP-OES Intensity vs. Std Ti Concentration (PPM)

Table S2. Experimental Determination of Ti content (wt%) via ICP-OES Measurement of Digests

Sample Type	Mass (mg)	OES Intensity (368.52 nm)	Avg. Calibrated ppm Ti	Mg Ti in sample	Avg. wt%	Std. Error	Species Avg.	Total error
Ti^{700} (as prepared)	102.0	66832	2.47	1.51	1.517	0.042	1.50	0.07
	92.6	58294	2.16	1.46	1.461	0.044		
	69.1	45497	1.695	1.06	1.534	0.043		
Used Ti^{700}	188.0[a]	148384	4.21	2.72	1.441	0.032	-	-
	82.3[b]	39476	0.969	1.21	1.480	0.041	-	-

[a] $Ti(X)_3/SiO_2^{700}$ used for hydroamination catalysis. [b] $Ti(X)_3/SiO_2^{700}$ used for iminoamination catalysis.

Table S3. Estimated Ti wt% for Different SiO_2^{700}-bound Ti Species

Sample Type	Estimated wt% Ti (± error)
as-prepared $Ti(NMe_2)_3/SiO_2^{700}$	1.46 (0.12)
$Ti(X)_3/SiO_2^{700}$ after iminoamination	1.46-1.35 (0.11)

Table S2 shows the ICP-OES analysis for titanium content in the catalyst material, both as-prepared and catalyst after use in both hydroamination and iminoamination catalysis. Table S3 shows the predicted wt% values of titanium based on the surface-site titrations, correlating to the 0.00031 mol/g SiO_2^{700}. Good agreement is achieved with the titration predicted and ICP-OES-observed titanium content in the $Ti(NMe_2)_3/SiO_2^{700}$ precatalyst. Note that for the used-variants, a range of possible wt% values is listed for the titanium content. This is because after use in catalysis, the types of ligands on the titanium are different from the three NMe_2 ligands in the precatalyst. The difference in the effective molecular weight of each titanium site will then contribute differently to the overall mass of the silica material, and consequently stands to change the wt% titanium present. (Not the same as actual loss of titanium metal atoms from the surface.)

For hydroamination, this could be three anilide ligands on titanium, for example, or the hydroamination product bound to the metal. In the iminoamination reactions, there are even more possibilities for combinations of ligands bound to each titanium site before and after the reaction. Possible ligands include anilides, isonitriles, the iminoamination product itself (a “nacnac” ligand), or even hydroamination or formamidine byproducts. Thus, the wt% titanium content expected for several different speciation on the surface were calculated and a range of the likely possibilities is given. Both used variants are within error of this range, so statistically the titanium content before and after catalysis are indistinguishable.

References

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