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# In Situ Catalyst Generation and Benchtop-Compatible Entry Points for $Ti^{II}/Ti^{IV}$ Redox Catalytic Reactions

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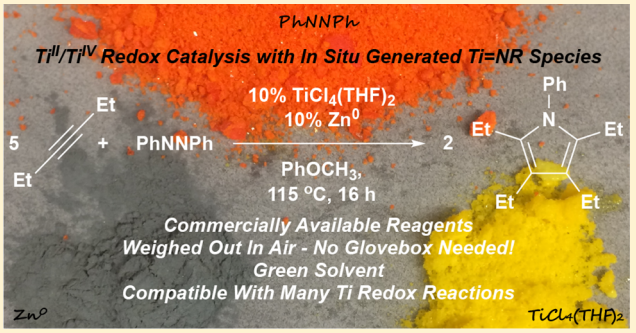
Supporting Information

**ABSTRACT:** The development of several in situ generated catalyst systems for Ti-catalyzed oxidative nitrene transfer reactions is reported. The simplest and widely applicable catalyst system, $TiCl_4(THF)_2/Zn^0$, can be set up on the benchtop under air. This system uses commercially available reagents and can be used as an entry point for $Ti^{II}/Ti^{IV}$ multicomponent redox reactions for the synthesis of pyrroles, α,γ-unsaturated imines, α,β-unsaturated imines, cyclopropylimines, and arenes.




## INTRODUCTION

Over the past several decades, there has been a large effort toward developing new reactions using less toxic and earth-abundant transition metals.[1] Titanium represents an excellent source for new catalysis research as it is the second most earth-abundant transition metal and generally considered to be nontoxic.[2,3] Its differential reactivity (e.g., [2 + 2] cycloaddition and electrocyclization) compared to that of the first-row late transition metals (e.g., groups 9 and 10) allows for the development of new complementary chemistry. Despite these apparent advantages, titanium is still underutilized in the development of "base metal" catalysis. This is partially due to the fact that late transition metal catalysts (e.g., $PdCl_2(PPh_3)_2$ or [(TMEDA)Ni(*o*-tolyl)Cl]) are often air-stable and easy to handle.[4] In contrast, many simple titanium precursors are air- and moisture-sensitive and can be difficult to handle; nonetheless, a number of elegant and useful titanium-catalyzed reactions have been developed.[5]

Recently, we developed a suite of new titanium-catalyzed oxidative C−N bond coupling reactions for the synthesis of pyrroles,[6] α,γ-unsaturated imines,[7,8] and cyclopropylimines,[7] mediated by a formal $Ti^{II}/Ti^{IV}$ redox couple (Figure 1). Although these reactions have all utilized relatively simple titanium imido precatalysts, these precatalysts all require synthesis and storage under stringent air- and moisture-free conditions.[9] In order to make this oxidative $Ti^{II}/Ti^{IV}$ manifold more broadly usable, we aimed to develop a simple route of entry to allow for benchtop chemistry without the need for a glovebox or any precatalyst synthesis.

In this vein, we were inspired by myriad examples of Ti-catalyzed reductive coupling reactions where simple reductants (Grignard reagents, alkyl lithiums, Zn, Mn) have been used to accomplish both two-electron reductions (via β-H abstraction of Ti-alkyls)[10] or one-electron reductions (via Zn or Mn reduction coupled with weak acid).[11] The desired criteria for our catalyst system include being (1) benchtop-stable, solid Ti precursors that can be weighed out in air and (2) benchtop-stable, solid reductants or reductant solutions that can be

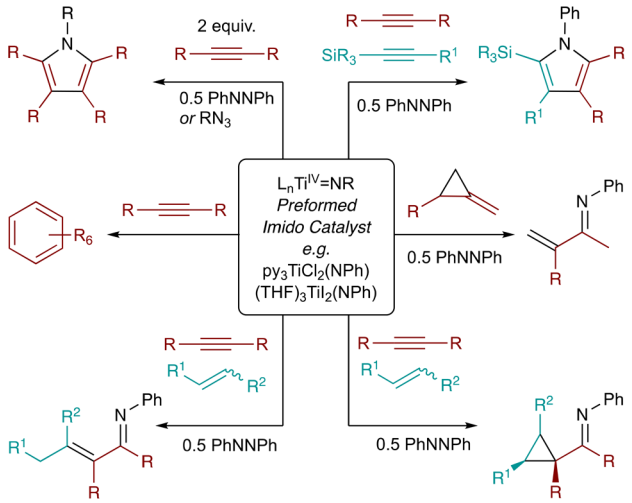



**Figure 1.** Divergent oxidative C−N and C−C bond coupling reactions enabled by Ti imido catalysts.

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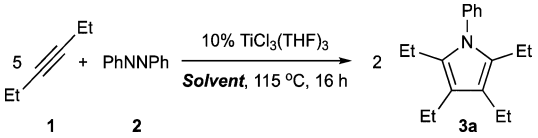
handled via simple syringe/Schlenk technique. We also aimed to investigate reagents that are both commercially available and inexpensive. Herein, we report several in situ generated and benchtop-compatible systems for Ti-catalyzed oxidative nitrene transfers via $Ti^{II}/Ti^{IV}$ couples, including the optimization and substrate scope of a particularly convenient to use $TiCl_4(THF)_2/Zn^0$ combination.

## RESULTS AND DISCUSSION

We began our investigations by attempting [2 + 2 + 1] pyrrole synthesis from 3-hexyne and azobenzene with 10% $TiCl_3(THF)_3$ as a catalyst. $TiCl_3(THF)_3$ was chosen as the starting point because it has been shown to disproportionate into $TiCl_2(THF)_4$ and $TiCl_4(THF)_2$ at 150−200 °C in the solid state,[12] and we envisioned that a solvated disproportionation may occur at lower temperatures—potentially providing access to an on-cycle low-valent $Ti^{II}$ species needed to cleave azobenzene en route to Ti imido formation.[13] Satisfyingly, reaction of 5 equiv of 3-hexyne (**1**) with azobenzene (**2**) and 10% $TiCl_3(THF)_3$ at 115 °C gave modest yields of the expected 2,3,4,5-tetraethyl-1-phenyl-1*H*-pyrrole (**3a**) across an array of polar aromatic solvents (Table 1). These reactions

**Table 1. Solvent Scope of $TiCl_3(THF)_3$-Catalyzed [2 + 2 + 1] Pyrrole Formation**[a]




| solvent | NMR yield | conversion[b] (%) |
|---|---|---|
| bromobenzene | 43 | 80 |
| toluene | 57 | 97 |
| anisole | 41 (72)[c] | 74 (>99)[c] |
| α,α,α-trifluorotoluene | 40 | >99 |
| *o*-dichlorobenzene | 62 | >99 |

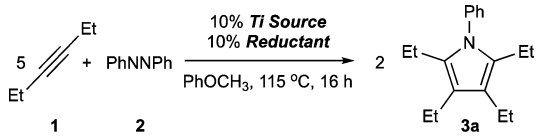
[a]Conditions: 0.19 mmol azobenzene, 0.96 mmol 3-hexyne, 0.019 mmol $TiCl_3(THF)_3$, 0.1 mmol trimethoxybenzene as internal standard in 0.5 mL of solvent at 115 °C. [b]% Consumption of azobenzene. [c]0.038 mmol $TiCl_3(THF)_3$.

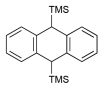
proceeded at roughly half the rate of reactions catalyzed by preformed $[py_2TiCl_2(NPh)]_2$, indicating that approximately half of the Ti in these in situ activated reactions sits as inactive $TiCl_4(THF)_2$—consistent with a disproportionation mechanism of activation. Although these reactions were modestly yielding, they were all plagued by hydroamination side reactions presumably resulting from radical reactions of $TiCl_3(THF)_3$ or Lewis acid/base reactions of $TiCl_4(THF)_2$.

Given the demonstration of $TiCl_3(THF)_3$ disproportionation as a route into $Ti^{II}/Ti^{IV}$ chemistry, we next sought to further optimize catalytic pyrrole formation by screening various reductants in combination with $TiCl_3(THF)_3$ and several $Ti^{IV}$ sources ($TiCl_4(THF)_2$, $Ti(O^iPr)_4$, and $TiF_4(THF)_2$) (Table 2)—envisioning that in situ reduction by an additive would result in more active catalyst than the inherent 50% maximum from disproportionation. Although anisole was not the most effective solvent in the initial solvent screen, we chose to optimize these reactions in anisole because it is a green solvent.[14]

For these in situ reductions, we first explored adding $^n$BuLi and EtMgBr, which are commonly used as two-electron

**Table 2. Yields ($^1$H NMR) of [2 + 2 + 1] Pyrrole Synthesis with Various Reductants and Ti Precursors**[a]




| Red. | $TiCl_3(THF)_3$ | $TiCl_4(THF)_2$ | $Ti(O^iPr)_4$ | $TiF_4(THF)_2$ |
|---|---|---|---|---|
| - | 41 | 0 | 0 | 0 |
| *n*-BuLi | 9 | 78 | trace | 4 |
| EtMgBr | 13 | 0 | trace | 24 |
| $Mg^0$ | 69 | trace | trace | 0 |
| $Al^0$ | 56 | 0 | 0 | 0 |
| $Mn^0$ | 66 | 0 | 0 | 0 |
| $Zn^0$ | 89 | 95 | 0 | 0 |
|  | 88 | 69 | 0 | 0 |
|  | 34 | 79 | 0 | 7 |
|  | - | trace | - | - |

[a]Conditions: 0.19 mmol azobenzene, 0.96 mmol 3-hexyne, 0.019 mmol $TiCl_3(THF)_3$, 0.019 mmol reductant, and 0.09 mmol trimethoxybenzene as internal standard in 0.5 mL of PhOMe at 115 °C.

reductants of $Ti^{IV}$ in reductive coupling reactions.[15,16] Neither of these experiments resulted in productive catalytic reactivity with $TiCl_3(THF)_3$, likely due to deleterious direct reaction with $TiCl_3(THF)_3$ instead of the desired reaction with in situ disproportionated $TiCl_4(THF)_2$.[15c] Consistent with this hypothesis, reaction of $^n$BuLi with $TiCl_4(THF)_2$ results in a high yield (78%) of pyrrole, indicating that direct two-electron reduction of $TiCl_4(THF)_2$ is a viable route to catalyst activation. Interestingly, reactions with EtMgBr were significantly worse than those with $^n$BuLi, although discrepancies between organomagnesium and organolithium reagents for titanium reductions have been previously observed.[15]

Next, we examined $Mg^0$, $Al^0$, $Mn^0$, and $Zn^0$ metal powders as reductants. None was effective for $Ti(O^iPr)_4$ or $TiF_4(THF)_2$, whereas $Zn^0$ was remarkably effective with $TiCl_4(THF)_2$, giving 95% yield of **3a** under standard screening conditions—the highest of any examined reducant/precatalyst combination. Additionally, the $TiCl_4(THF)_2/Zn^0$ reaction is virtually free of side products, unlike reactions with $TiCl_3(THF)_3$. Interestingly, although $Mg^0$, $Al^0$, and $Mn^0$ failed for all $Ti^{IV}$ precursors, their reaction with $TiCl_3(THF)_3$ resulted in slight increases in pyrrole yield over reactions without added reductant. Based on the failed in situ reduction of $Ti^{IV}$ precursors with these reductants, these modest yield increases with $TiCl_3(THF)_3$ may be related to slow electron transfer kinetics or to impurity scrubbing effects; however, the precise effect remains unclear.

Similar results are also seen with organosilane reductants 1-methyl-3,6-bis(trimethylsilyl)-1,4-cyclohexadiene and 2,5-dimethyl-1,4-bis(trimethylsilyl)-1,4-dihydropyrazine,[17] which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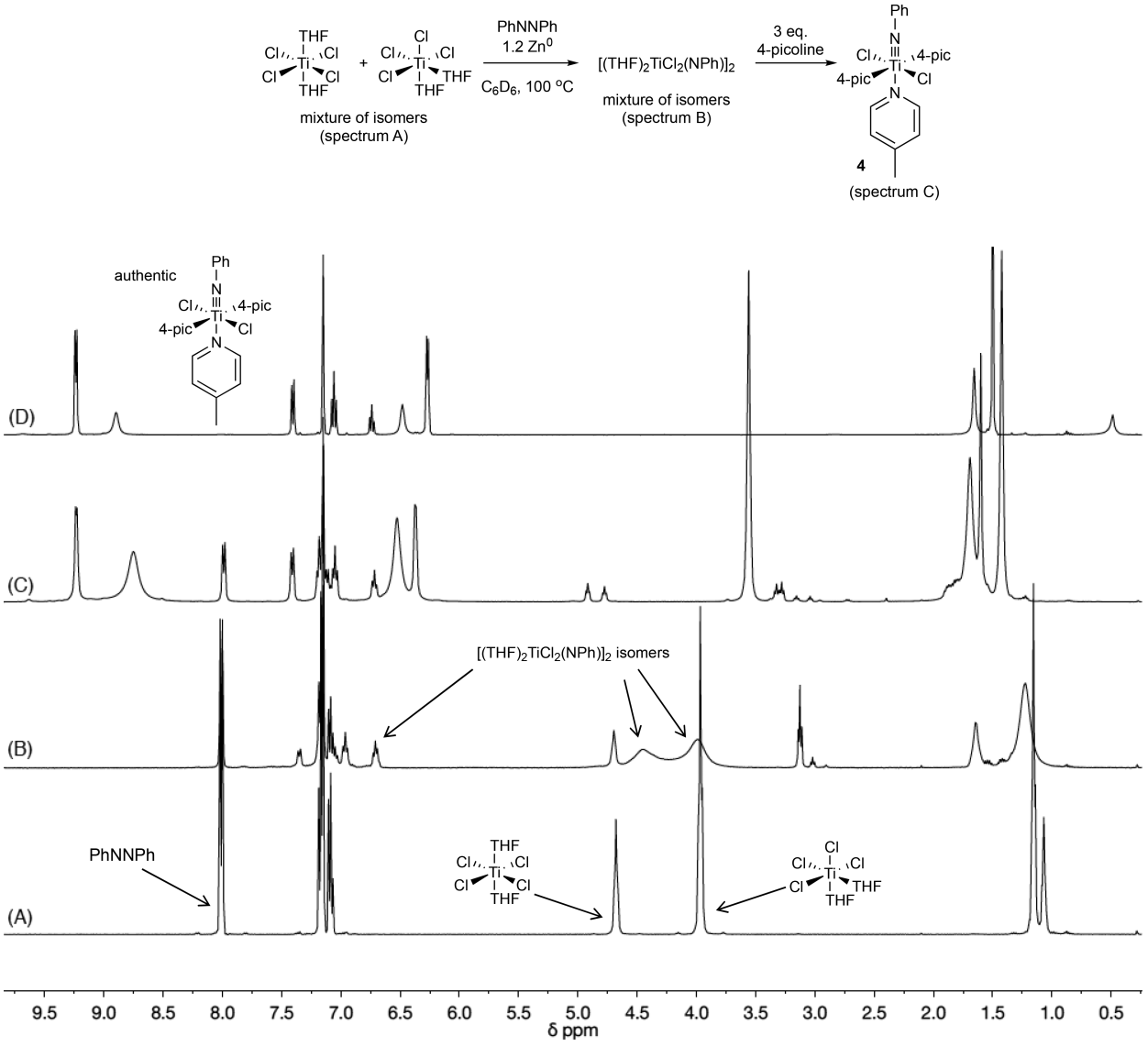


**Figure 2.** $^1$H NMR spectra of the reaction between $TiCl_4(THF)_2$, 0.5 equiv of PhNNPh, and 1.2 equiv of $Zn^0$ in $C_6D_6$: (A) $t$ = 0 h; (B) $t$ = 3 h at 100 °C; (C) after heating and addition of 3 equiv of 4-picoline; (D) authentic $(4\text{-picoline})_3TiCl_2(NPh)$ **4**.

are effective for the in situ reduction of $TiCl_3(THF)_3$ and $TiCl_4(THF)_2$ precatalysts but not for $Ti(O^iPr)_4$ or $TiF_4(THF)_2$. The advantage of these reductants is that the byproducts, TMSCl and simple arenes (toluene, 2,5-dimethylpyrazine), can easily be removed from the reaction in vacuo. Interestingly, the air-stable silane reductant 9,10-bis(trimethylsilyl)-9,10-dihydroanthracene failed to yield any product upon reaction with $TiCl_4(THF)_2$, likely because it is a weaker reductant than the other two silanes examined.[17a,18]

An investigation of the stoichiometric reduction of $TiCl_4(THF)_2$ with $Zn^0$ in the presence of azobenzene provides insight into how these in situ reductions occur, and how the catalyst enters the catalytic cycle (Figure 2). Heating $TiCl_4(THF)_2$ with 0.5 equiv of PhNNPh and 1.2 equiv of $Zn^0$ dust in $C_6D_6$ at 100 °C results in complete conversion of the $TiCl_4(THF)_2$ to a mixture of two isomeric $[(THF)_2TiCl_2(NPh)]_2$ species (Figure 2B). This mixture can be converted to a single species, $(4\text{-picoline})_3TiCl_2(NPh)$ (**4**), upon addition of 3 equiv of 4-picoline (Figure 2C). The NMR of this in situ generated **4** matches well with an independently synthesized sample of **4** (Figure 2D). Thus, the overall mechanism of activation for these in situ reductions is through the formation of a Ti═NR imido active species from the reaction of reduced Ti with PhNNPh.

We propose that the initial reaction of reduced Ti with azobenzene occurs via a $Ti^{III}$ intermediate (Figure 3). This conclusion is based on several observations: (1) $Zn^0$ is not a strong enough reductant ($E_0$ = −0.76 V) to directly reduce $TiCl_4$ to $TiCl_2$ ($E_0$ = −1.62 V);[19] (2) previous studies have shown that coordination of redox-active ($\pi$-accepting) substrates to $Ti^{III}$ can promote further reduction to $Ti^{II}$;[19] and (3) $^1$H NMR studies indicate that azobenzene does not displace THF in $TiCl_4(THF)_2$ (Figure 2A). Thus, it is likely that the overall mechanism of formation of Ti═NR from in situ reduction occurs through the mechanism outlined in Figure 3: first, single-electron reduction of $TiCl_4(THF)_2$ to $TiCl_3(THF)_n$ by $Zn^0$, then PhNNPh coordination to $TiCl_3(THF)_n$, followed by a second reduction by $Zn^0$ to form $(\eta^2\text{-PhNNPh})TiCl_2(THF)_n$, and finally disproportionation of $(\eta^2\text{-PhNNPh})TiCl_2(THF)_n$ to $(NPh)TiCl_2(THF)_n$.

This two-electron manifold is in contrast to the typical one-electron manifolds commonly encountered with in situ


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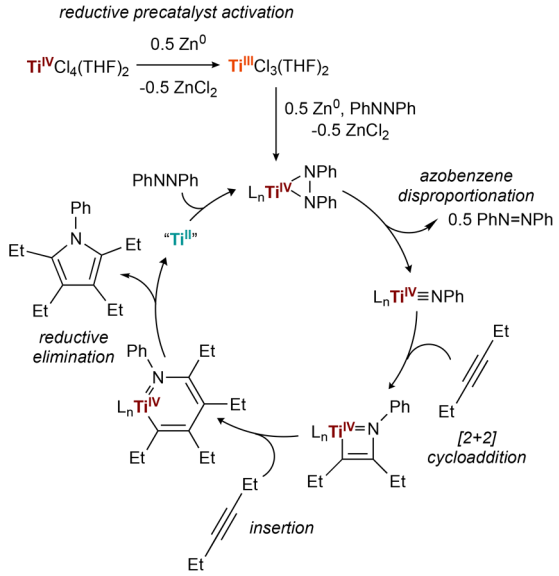


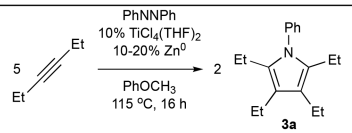
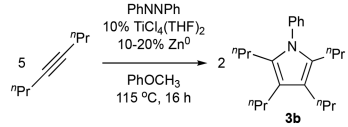
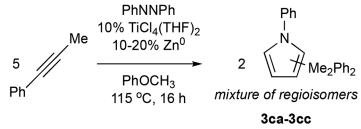
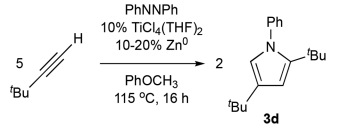
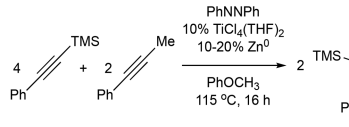
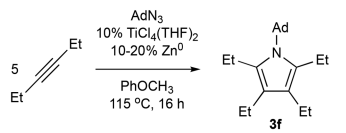
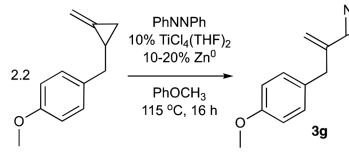
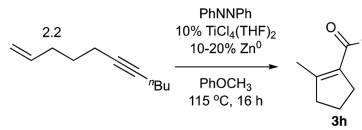
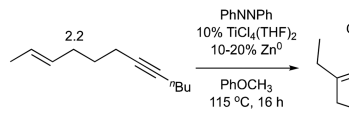
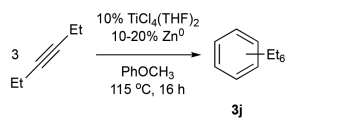

**Figure 3.** Activation of $TiCl_4(THF)_2$ by $Zn^0$ and entrance into catalytic cycle for the synthesis of pyrroles.

generated reduced Ti systems. For example, $Cp_2TiX$-based reagents/intermediates are well-established in a diverse array of single-electron reactions (e.g., epoxide ring opening, ring-forming reactions, and HAT reactions), which commonly use either Mn or Zn alongside a weak acid.[5b,11] The ability to access the two-electron manifold is likely an effect of having weakly donating halide ligands on Ti in combination with strongly $\pi$-accepting substrates.[5b] Interestingly, many common metal reductants used in Ti-mediated reactions (e.g., Al, Mn, Mg) fail for the [2 + 2 + 1] pyrrole synthesis; this may be due to over-reduction of the Ti intermediates, metal salt complex formation (e.g., $[Mg(THF)_6][TiCl_5THF]$ or $(TiCl_3)_3AlCl_3$), or kinetically slow reductions under these conditions.[20]

Having identified several in situ generated catalytic systems for Ti-catalyzed nitrene transfer, we next sought to explore the "benchtop" compatibility and scope of reactions catalyzed by the $TiCl_4(THF)_2/Zn^0$ catalyst combination. This system was chosen for further exploration because it gave the highest yield for **3a** in our initial studies and also because $TiCl_4(THF)_2$ is a commercially available, bench-stable solid: it can be weighed out in air and stored in a desiccator, obviating the need for a glovebox or other specialized air-free equipment. Likewise, we have found that the reaction is relatively insensitive to the quality/age/oxidized impurities of the $Zn^0$ (see Supporting Information), making it an ideal reductant for benchtop protocols.

In these studies (Table 3), we examined several Ti-catalyzed nitrene transfer reactions under rigorously air-free glovebox conditions, as well as "benchtop" conditions where all solid materials were loaded under air before being purged with $N_2$. Quite remarkably, all Ti-catalyzed [2 + 2 + 1] pyrrole syntheses are equally effective under both sets of conditions: internal and terminal alkynes (entries 1–4) both result in high yields of pyrrole products with regioselectivity similar to that of previously reported catalysts,[6a] and heterocoupling reactions[6b] (entry 5) also proceed in high yield with excellent selectivity. The benchtop reaction with 3-hexyne has also been scaled to greater than 2 g with no loss of fidelity. The terminal alkyne $^t$BuCCH gave a slightly lower yield under benchtop conditions (entry 4). For the other Ti-catalyzed nitrene transfer reactions

**Table 3. Benchtop and Air-Free Yields of Ti-Catalyzed Nitrene Transfer Reactions from 10% $TiCl_4(THF)_2$/10–20% $Zn^0$ in Situ Catalyst Generation**[a]

| Entry | Reaction | Yield[a] (Air[b]) |
|---|---|---|
| 1 |  | 95 (95) |
| 2 |  | 93 (95) |
| 3 |  | 88 (83) |
| 4 |  | 60 (40) |
| 5[c] |  | 74 (73) |
| 6[d] |  | 61 (-) |
| 7[e] |  | 42[f] (-) |
| 8[e] |  | 63[f,g] (-) |
| 9[e] |  | 64[f,g] (-) |
| 10 |  | 63[h] (-) |

[a]Condition A: 0.19 mmol azobenzene, 0.95 mmol alkyne, 0.019 mmol $TiCl_4THF_2$, 0.019 mmol $Zn^0$, 0.1 mmol trimethoxybenzene as internal standard in 0.5 mL of anisole at 115 °C in an NMR tube; yields calculated with respect to PhNNPh. [b]Condition B: all solid reagents were weighed out and loaded into the reaction vessel in air before being purged with $N_2$; 0.55 mmol azobenzene, 2.74 mmol alkyne, 0.054 mmol $TiCl_4THF_2$, 0.110 mmol $Zn^0$ in 2 mL of anisole. Trimethoxybenzene was added after being heated for 16 h as external standard. Yields calculated with respect to PhNNPh. [c]0.38 mmol MeCCPh and 0.77 mmol TMSCCPh (condition A), 1.1 mmol



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**Table 3. continued**

MeCCPh and 2.2 mmol TMSCCPh (condition B). [d]1.0 mmol alkyne (condition A), 2.8 mmol alkyne (condition B), 0.2 mmol $AdN_3$ (condition A), 0.56 mmol $AdN_3$ (condition B) used instead of PhNNPh. [e]0.42 mmol substrate (condition A), 1.2 mmol substrate (condition B). [f]$TiCl_4(THF)_2$, PhNNPh, and $Zn^0$ were preheated for 1 h before addition of substrate. [g]Yields were obtained after hydrolysis in 2 M HCl. [h]0.95 mmol 3-hexyne (conditions A), 2.74 mmol (conditions B).

(entry 6, azide coupling for pyrrole synthesis;[6d] entry 7, oxidative ring-opening amination;[8] entries 8 and 9, oxidative carboamination[7]) as well as alkyne trimerization[6e] (entry 10), the in situ air-free protocol resulted in good yields in all cases, but the benchtop reactions were unsuccessful, presumably due to catalyst decomposition from advantageous water. These results highlight the sensitive nature of the transient low-valent Ti intermediates—even subtle changes in the rates of catalysis and/or the structure of reagents/stabilizing ligands can impact the robustness of the reaction protocol.

In summary, we have reported several new in situ catalyst systems for Ti-catalyzed nitrene transfer reactions. $Zn^0$ is a particularly effective reductant for $TiCl_4(THF)_2$ and $TiCl_3(THF)_3$ precatalysts, yielding low-valent Ti species that can easily enter nitrene transfer catalytic cycles through oxidation by azobenzene. Remarkably, these in situ $Zn^0$ reductions can be carried out under "benchtop" conditions, eliminating the need for specialized air-free equipment.

## EXPERIMENTAL SECTION

**General Considerations.** All air- and moisture-sensitive compounds were manipulated in a glovebox under a nitrogen atmosphere or on a nitrogen Schlenk line. Solvents for air- and moisture-sensitive reactions were vacuum distilled from sodium benzophenone ketyl ($C_6D_6$) or $CaH_2$ (PhOMe, $C_6H_5Br$, *o*-$Cl_2C_6H_4$) or predried on a Pure Process Technology solvent purification system (hexanes, PhMe, $CH_2Cl_2$, $PhCF_3$). Azobenzene was purchased from TCI America and purified by flash chromatography using hexanes before grinding the isolated product in a mortar and pestle and drying in vacuo. $TiCl_3(THF)_3$,[21] $TiF_4(THF)_2$,[22] and $TiCl_4(THF)_2$[23] were prepared according to literature procedure. $Ti(OiPr)_4$ was purchased from Sigma-Aldrich and used with no further purification. 3-Hexyne, 1-phenyl-1-propyne, 4-octyne, and 3,3-dimethyl-1-butyne were purchased from Sigma-Aldrich. Undec-1-en-6-yne,[7] (*E*)-dodec-2-en-7-yne,[7] 1-methoxy-4-((2-methylenecyclopropyl)methyl)benzene,[8] trimethyl(phenylethynyl)silane,[6b] 1-methyl-3,6-bis(trimethylsilyl)-1,4-cyclohexadiene,[17a] and 2,5-dimethyl-1,4-bis(trimethylsilyl)-1,4-dihydropyrazine[17b] were prepared following literature procedure. All liquid substrates were freeze−pump−thawed three times, brought into a glovebox, and passed through activated basic alumina before being stored at −35 °C. PhOMe used outside the glovebox for benchtop reactions was stored over $CaH_2$ or 4 Å molecular sieves (can be used filtered or unfiltered). 3-Hexyne used outside the glovebox for benchtop reactions was stored over activated basic alumina (to dry and scrub out polar impurities) and filtered prior to use.

$^1H$, $^{13}C$, HMBC, and No-D NMR spectra were recorded on Bruker Avance III 500 MHz, Bruker Avance III HD 500 MHz, or Bruker Avance 400 MHz spectrometers. Chemical shifts are reported with respect to residual protio-solvent impurity for $^1H$ (s, 7.16 ppm for $C_6D_5H$; s, 7.27 for ppm of $CHCl_3$), and solvent carbons for $^{13}C$ (t, 128.39 ppm for $C_6D_6$) and No-D NMR[24] were referenced to 1,3,5-trimethoxybenzene (s, 6.02 ppm).

**Example Reaction Solvent Scope (Table 1).** Azobenzene (35 mg, 0.19 mmol, 1.0 equiv), 3-hexyne (78.8 mg, 0.95 mmol, 5.0 equiv), 1,3,5-trimethoxybenzene (15 mg, 0.1 mmol, as internal standard), and $TiCl_3(THF)_3$ (7.0 mg, 0.019 mmol, 0.1 equiv) were loaded into a 4 mL scintillation vial. To this vial was added 0.5 mL of desired solvent; the reaction was sealed with a Teflon screw cap, removed from the glovebox, and heated for 16 h at 115 °C in an oil bath. The reaction mixture was then cooled to room temperature and loaded into an NMR tube, and the No-D $^1H$ NMR spectrum was collected.

**Example Reaction Optimization (Table 2).** *Example for $Zn^0$ Powder:* Azobenzene (140 mg, 0.76 mmol), 3-hexyne (315 mg, 3.84 mmol), and 1,3,5-trimethoxybenzene (60 mg, 0.36 mmol, as internal standard) were added to a 2 mL volumetric flask and diluted to 2 mL with anisole to make a stock solution. $TiCl_4(THF)_2$ (6.3 mg, 0.019 mmol), $TiCl_3(THF)_3$ (7.0 mg, 0.019 mmol), $TiF_4(THF)_2$ (5.1 mg, 0.019 mmol), and $Ti(OiPr)_4$ (5.4 mg, 0.019 mmol) were each added to separate NMR tubes, and then $Zn^0$ (1.2 mg, 0.019 mmol) and 0.5 mL of the stock solution were added to each NMR tube. The NMR tubes were then sealed and removed from the glovebox, and $t$ = 0 h No-D $^1H$ NMR spectra were taken. The NMR tubes were then heated for 16 h at 115 °C in an oil bath. The NMR tubes were then cooled to room temperature, and No-D $^1H$ NMR spectra were taken at $t$ = 16 h.

**Synthesis of $[Ti(NPh)Cl_2(4\text{-picoline})_3]$ (4).** Compound **4** was prepared following a modification of the literature procedure for the preparation of $[Ti(NPh)Cl_2(THF)_2]_2$.[19b] In a glovebox, $TiCl_4$ (200 mg, 1.05 mmol, 1.0 equiv) was added to a 20 mL scintillation vial equipped with a stir bar and diluted with 2 mL of $CH_2Cl_2$. To this was added dropwise a solution of 1,1,1-trimethyl-*N*-phenyl-*N*-(trimethylsilyl)silanamine (250.4 mg, 1.05 mmol, 1.0 equiv) in 2 mL of $CH_2Cl_2$. The vial was then sealed with a Teflon screw cap and heated to 60 °C for 1 h. The vial was then cooled to room temperature, diluted with 5 mL of hexanes, and filtered on a fine porosity fritted glass funnel. The black solid was then washed with 3 × 3 mL of hexanes and transferred back to a 20 mL scintillation vial and dissolved in 10 mL of $CH_2Cl_2$. Next, 0.338 mL of 4-picoline (324 mg, 3.47 mmol, 3.3 equiv) was then added dropwise. The reaction mixture was then stirred overnight, filtered through a pipet plug of Celite, layered with hexanes, and precipitated in a −35 °C freezer. The solid was collected on a fine porosity fritted glass funnel, washed with hexanes, and dried in vacuo to give the title compound as a tan powder, 354 mg (69.0% yield). $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$, ppm: 9.25 (d, $^3J_{HH}$ = 6.5 Hz, 4H, *o*-4-picoline-*H*), 8.91 (s, 2H, *axial o*-4-picoline-*H*), 7.41 (d, $^3J_{HH}$ = 7.3 Hz, 2H, *o*-NPh-*H*), 7.07 (t, $^3J_{HH}$ = 7.7 Hz, 2H, *m*-NPh-*H*), 6.75 (t, $^3J_{HH}$ = 7.4 Hz, 1H, *p*-NPh-*H*), 6.49 (s, 2H, *axial m*-4-picoline-*H*), 6.28 (d, $^3J_{HH}$ = 5.6 Hz, 4H, *m*-4-picoline-*H*), 1.67 (s, 3H, *axial* 4-picoline-$CH_3$), 1.51 (s, 6H, 4-picoline-$CH_3$). $^{13}C$ NMR (101 MHz, $C_6D_6$) $\delta$, ppm: 160.8, 151.9, 151.2, 150.4, 147.6, 128.9, 128.7, 125.0, 124.7, 122.5, 20.9, 20.8.

**Example Substrate Scope Experiment (Table 3, Condition A).** *Example for 3-Hexyne:* Azobenzene (35 mg, 0.19 mmol, 1.0 equiv), 1,3,5-trimethoxybenzene (15 mg, 0.1 mmol, as internal standard), $TiCl_4(THF)_2$ (6.3 mg, 0.019 mmol, 0.1 equiv), and $Zn^0$ (1.2 mg, 0.019 mmol, 0.1 equiv) were added as solids to an NMR tube, and then 3-hexyne (78.8 mg, 0.95 mmol, 5.0 equiv) and 0.5 mL of PhOMe were added. The NMR tube was then sealed and removed from the glovebox, and a $t$ = 0 h No-D $^1H$ NMR spectrum was taken. The NMR tube was then heated for 16 h at 115 °C in an oil bath. The NMR tube was then cooled to room temperature, and a No-D $^1H$ NMR spectrum was taken at $t$ = 16 h.

**Example Substrate Scope Experiment (Table 3, Condition B).** *Example for 3-Hexyne:* Azobenzene (100 mg, 0.55 mmol, 1 equiv), $TiCl_4(THF)_2$ (18.0 mg, 0.054 mmol, 0.1 equiv), and $Zn^0$ (6.8 mg, 0.11 mmol, 0.2 equiv) were weighed out on the benchtop and added to a 100 mL Schlenk flask under air. The flask was then stoppered with a rubber septum and purged with $N_2$. To this were then added via syringe 2 mL of anisole (predried over molecular sieves or $CaH_2$) and then 0.31 mL of 3-hexyne (225 mg, 2.74 mmol, 5 equiv). The septum was then replaced with a reflux condenser fitted with a $N_2$ inlet, and the flask was heated to 115 °C overnight. The reaction vessel was then allowed to cool to room temperature, and 1,3,5-trimethoxybenzene (60 mg, 0.36 mmol) was added as an


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internal standard. A 0.5 mL aliquot of the reaction mixture was loaded into an NMR tube, and a No-D $^1$H NMR spectrum was collected.

**Scale-Up Synthesis of 2,3,4,5-Tetraethyl-1-phenyl-1*H*-pyrrole (Condition B).** Azobenzene (1.0 g, 5.5 mmol, 1 equiv), $TiCl_4(THF)_2$ (183 mg, 0.55 mmol, 0.1 equiv), and $Zn^0$ (35 mg, 0.55 mmol, 0.1 equiv) were weighed out on the benchtop and added to a 100 mL Schlenk flask under air. The flask was then stoppered with a rubber septum and purged with $N_2$. To this were then added via syringe 10 mL of anisole and then 3.11 mL of 3-hexyne (2.25 g, 27.4 mmol, 5 equiv). The septum was then replaced with a reflux condenser fitted with a $N_2$ inlet, and the flask was heated to 115 °C overnight. The reaction vessel was then cooled to 40 °C and dried in vacuo. The dark red solid was extracted into minimal hexanes, loaded onto a silica column, and eluted with a 1−5% EtOAc/hexanes gradient. 1.77 g (64% yield) of 2,3,4,5-tetraethyl-1-phenyl-1*H*-pyrrole was collected as a pale yellow oil. Spectral data matched literature.[6a] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$, ppm: 7.48−7.43 (m, 2H, *m*-Ph-*H*), 7.42−7.36 (m, 1H, *p*-Ph-*H*), 7.29 (d, $^3J_{HH}$ = 7.0 Hz, 2H, *o*-Ph-*H*), 2.50 (q, $^3J_{HH}$ = 7.5 Hz, 4H, $-CH_2CH_3$), 2.40 (q, $^3J_{HH}$ = 7.5 Hz, 4H, $-CH_2CH_3$), 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 6H, $-CH_2CH_3$), 0.87 (t, $^3J_{HH}$ = 7.5 Hz, 6H, $-CH_2CH_3$).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00474.

Optimization of $Zn^0$ sources, NMR spectra corresponding to entries in Tables 1−3, and scale-up reaction of 2,3,4,5-tetraethyl-1-phenyl-1*H*-pyrrole (PDF)

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Z.W.D.-G., K.K., and D.C.B. carried out the initial reaction screens. Z.W.D.-G. optimized the reactions, carried out the substrate scope experiments, and carried out the mechanistic experiments. H.T., K.M., and I.A.T. conceived of and directed the research project. Z.W.D.-G. and I.A.T. wrote the manuscript. All authors participated in the editing and revision of the manuscript.

### Notes

The authors declare no competing financial interest.

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