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On the Mechanism of Ti-Catalyzed Oxidative Nitrene Transfer in [2+2+1] Pyrrole Synthesis from Alkynes and Azobenzene

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ABSTRACT: A combined computational and experimental study on the mechanism of Ti-catalyzed formal [2+2+1] pyrrole synthesis from alkynes and aryl diazenes is reported. This reaction proceeds through a formally Ti^{II}/Ti^{IV} redox catalytic cycle as determined by natural bond orbital (NBO) and intrinsic bond orbital (IBO) analysis. Kinetic analysis of the reaction of internal alkynes with azobenzene reveals a complex equilibria involving Ti=NPh monomer/dimer equilibrium, Ti=NPh + alkyne [2+2] cycloaddition equilibrium, along with azobenzene and pyridine inhibition equilibria prior to rate determining 2nd alkyne insertion. Computations support this kinetic analysis and provide insights in the structure of the active species in catalysis, the roles of solvent, and provide a new mechanism for regeneration of the Ti imido catalyst via disproportionation. Reductive elimination from a 6-membered azatitanacyclohexadiene species to generate pyrrole-bound Ti^{II} is surprisingly facile, and occurs through a unique electrocyclic reductive elimination pathway similar to a Nazarov cyclization. The resulting Ti^{II} species are stabilized through backbonding into the π^* of the pyrrole framework, although solvent effects also significantly stabilize free Ti^{II} species that are required for pyrrole loss and catalytic turnover. Further computational and kinetic analysis reveals that in complex reactions with unsymmetric alkynes, the resulting pyrrole regioselectivity is driven primarily by steric effects for terminal alkynes and inductive effects for internal alkynes.

1. INTRODUCTION

Ti is an ideal metal for sustainable catalysis—earth abundant, environmentally benign and easily recycled.¹⁻² Considering these properties, Ti catalysis is underutilized in organic method development compared to the earth abundant first row late transition metals (Fe, Co, Ni).³⁻⁵ Two significant challenges in designing early transition metal-catalyzed reactions are the oxophilicity of the metals and the thermodynamic stability of their highest oxidation states. In fact, Ti-catalyzed reactions involving a formal oxidation state change at the metal center (*i.e.* Ti^{II}/Ti^{IV}) are quite rare.⁵

We recently reported a Ti-catalyzed oxidative nitrene transfer reaction that we speculated proceeds through a formally Ti^{II}/Ti^{IV} catalytic cycle: the [2+2+1] coupling of alkynes with diazenes to yield multisubstituted pyrroles.⁶ In our initial report, we proposed the mechanism shown in Figure 1: first, a Ti imido complex **1** undergoes [2+2] cycloaddition with an alkyne to form an azatitanacyclobutene **2**, identical to the first step of Ti-catalyzed alkyne hydroamination.⁷⁻⁹ Next, **2** inserts a second equivalent of alkyne to yield an azatitanacyclohexadiene **3**, which then undergoes reductive C-N coupling to yield the pyrrole product and a Ti^{II} species **4**. **4** could be reoxidized *via* coordination of azobenzene to form an η^2 -hydrazido complex **5**, which

disproportionates to regenerate **1** and 0.5 equiv azobenzene. Previous computational work by Wang¹⁰ confirmed the feasibility of this overall mechanistic picture through DFT calculations at the Mo6-L/6-311++G(d,p)/PCM level of theory with geometries obtained in the gas phase at the B3LYP/6-31G(d,p) level of theory. Wang suggested that the mechanism proceeds through an unconventional elimination pathway that requires azobenzene coordination to release pyrrole, ostensibly avoiding discrete formally Ti^{II} intermediates.

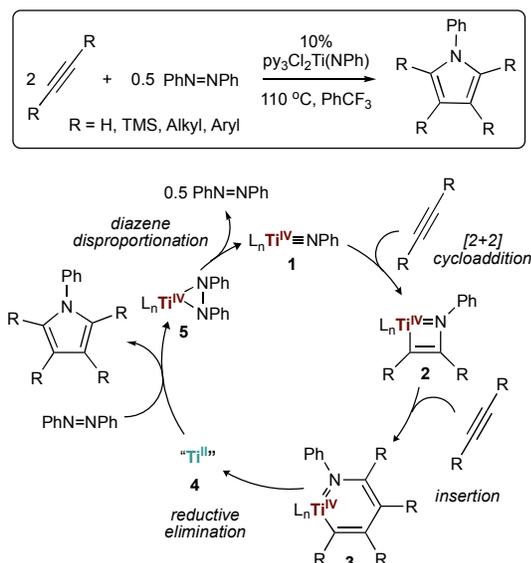


Figure 1. Proposed mechanism of Ti-catalyzed formal [2+2+1] cycloaddition of alkynes with azobenzene.

We are interested in developing a deeper experimental and theoretical understanding of the mechanism of this reaction in order to design new Ti-catalyzed nitrene transfer reactions, and further understanding the requirements for catalytic turnover in low-valent early transition metal-catalyzed processes. In particular, we are interested in understanding (1) the structure of the active species in catalysis and the role of catalyst structure in reactivity; (2) the kinetic interplay between the two steps involving alkyne cycloaddition and insertion; (3) how and why C-N reductive elimination occurs; and (4) the role of azobenzene in C-N reductive elimination and catalyst reoxidation.

Herein, we report a detailed kinetic and computational study on the Ti-catalyzed formal [2+2+1] pyrrole synthesis. The main kinetic manifold of the reaction involves two equilibria, a Ti imido monomer/dimer equilibrium followed by a [2+2] alkyne/Ti imido cycloaddition equilibrium. Geometry optimization of intermediates in solvent turns out to be critical to uncovering several important details of the catalytic cycle. Additionally, we perform an exhaustive DFT analysis to determine which ligands are active during the catalytic cycle and find that coordinatively unsaturated complexes have the lowest transition state barriers. By using these geometries and a combination of Intrinsically Bonding Orbitals (IBOs)¹¹⁻¹² and Natural Bond Orbitals (NBOs),¹³ we show that this reaction proceeds through a true reductive elimination pathway, where discrete “Ti^{II}”-like species are present. NBOs have previously been used successfully in Ti compounds to describe bonding in Ti-imido complexes.^{7b} This reductive elimination occurs via a surprising electrocyclic pathway similar to the Nazarov cyclization. The resulting Ti^{II} pyrrole species is stabilized through backbonding into the pyrrole π^* system, but

stabilizing solvent interactions also allow for facile pyrrole dissociation. This mechanistic knowledge has also been extended into a combined computational and physical organic study of the stereoelectronic effects on the regioselectivity of unsymmetrical alkyne couplings, revealing that sterics predominantly control the selectivity of terminal alkyne reactions, while inductive effects dominate for internal unsymmetrical alkynes such as phenylpropyne.

2. METHODS

2.1 Experimental Methods. All air- and moisture-sensitive compounds were manipulated in a glovebox under a nitrogen atmosphere. Solvents for air- and moisture-sensitive reactions were vacuum transferred from sodium benzophenone ketyl (C₆D₆) or CaH₂ (CDCl₃, C₆D₁₂, C₇D₈) or pre-dried on a Vacuum Atmospheres Solvent Purification System (hexanes, toluene, benzene, THF, Et₂O, DCM, and TFT). Solvents were stored over CaH₂ and filtered through dry basic alumina before use. Azobenzene was purchased from TCI America (100 g). Commercial azobenzene is typically contaminated with 0-5% methanol and nitrobenzene; flash chromatography using hexanes and grinding the isolated product in a mortar and pestle before drying *in-vacuo* yields analytically pure azobenzene. C₆D₅Br was prepared following literature procedure.¹⁴ [py₂TiCl₂(N^tBu)]₂ and py₃TiCl₂(N^tBu) were prepared according to literature procedure.¹⁵ All liquid alkynes were freeze pump-thawed three times, brought into the glove box and passed through activated basic alumina before being stored at -35 °C. ¹H, ¹³C, ¹⁵N, HMBC, HSQC, NOE and No-D NMR spectra were recorded on Varian INOVA 500 MHz, 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 C₆D₅H; s, 7.27 for ppm CHCl₃), solvent carbons for ¹³C (t, 128.39 ppm for C₆D₆; t, 77.16 ppm for CDCl₃), referenced to tetrachloroethane (s, 5.53 ppm) or trimethoxybenzene (s, 6.02 ppm) in C₆D₅Br. Full experimental details and kinetic traces are available in the Supporting Information.

2.2 Computational methods Geometry optimizations were performed using the Gaussian 09 program version doi.¹⁶ Unless otherwise noted, all calculations were formed using the Mo6 functional,¹⁷ the 6-31G(d,p) basis set,¹⁸ the ultrafine grid, and the SMD solvation model¹⁹ in the experimentally used solvent PhCF₃ ($\epsilon = 9.18$). Calculations performed for symmetric alkynes used the superfine grid. All geometries were characterized by frequency analysis calculations to be minima (without imaginary frequency) or transition states (having only one imaginary frequency). The refined energies were corrected to free energies at 383.15K and 1 atm. Intrinsic bond orbital (IBO) calculations were performed in MOLPRO 2015.1²⁰ using Mo6/def2-TZVP.²¹ Density fitting was employed to accelerate calculations in MOLPRO

using the def2-TZVP JK-fitting basis set. Molecular and orbital depictions were made using the IBOView program.¹¹⁻¹² For NBO calculations the NBO 5.G¹³ program was used and the d orbital occupation numbers were generated following the protocol in ref. 22.

3. RESULTS AND DISCUSSION

3.1 Experimental Studies and Kinetic Analysis.

First, we set out to determine the kinetic robustness of the reaction of 4-octyne with azobenzene catalyzed by $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ by *in-situ* ¹H NMR same-excess analysis.²³⁻²⁴ The dimeric catalyst $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ was chosen due to greater solubility over previously-reported $\text{py}_3\text{TiCl}_2(\text{NR})$ species, and because formation of N^tBu pyrrole products then provides information on the amount of catalyst activation. In experiment 1, 0.44 mmol azobenzene and 2.3 mmol 4-octyne were reacted with 0.04 mmol $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$. In experiment 2, 0.34 mmol azobenzene and 1.77 mmol 4-octyne were reacted with 0.04 mmol $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$. Overlay of these two reactions produces good overlapping kinetic traces indicating no catalyst decomposition and no significant catalyst induction period caused by the N^tBu group (Figure 2).

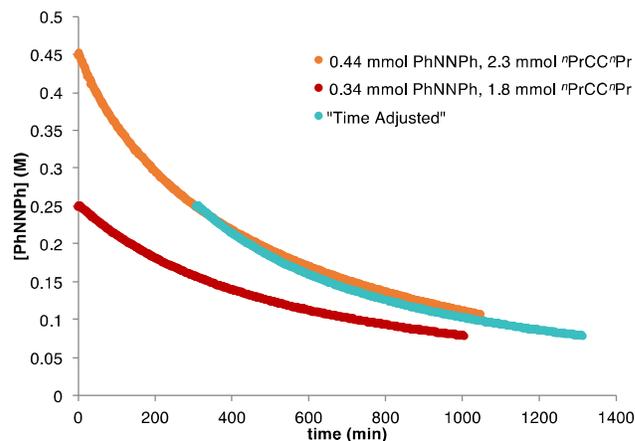
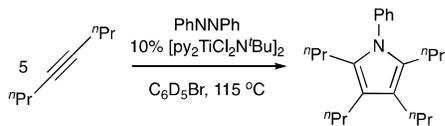


Figure 2. Same-excess experiments of $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ -catalyzed pyrrole formation from 4-octyne and azobenzene indicates no catalyst decomposition or product inhibition. Reaction Conditions: Exp 1: 0.44 mmol PhNNPh and 2.3 mmol 4-octyne were reacted with 0.04 mmol $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ in 0.5 mL $\text{C}_6\text{D}_5\text{Br}$ at 115 °C. In Exp 2, 0.34 mmol PhNNPh and 1.77 mmol 4-octyne were reacted with 0.04 mmol $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ in 0.5 mL $\text{C}_6\text{D}_5\text{Br}$ at 115 °C.

Having established that this catalyst system is well-behaved, we next sought to determine the rate law using Variable Time Normalization Analysis (VTNA) of each individual component of the reaction.²⁷⁻²⁸ In VTNA experiments, the time scale is normalized as a time integral (approximated *via* the trapezoid rule) of one component of the reaction to remove the kinetic effect of that component from the reaction profile.²⁷ By systematically varying concentrations of each component, one can rapidly construct

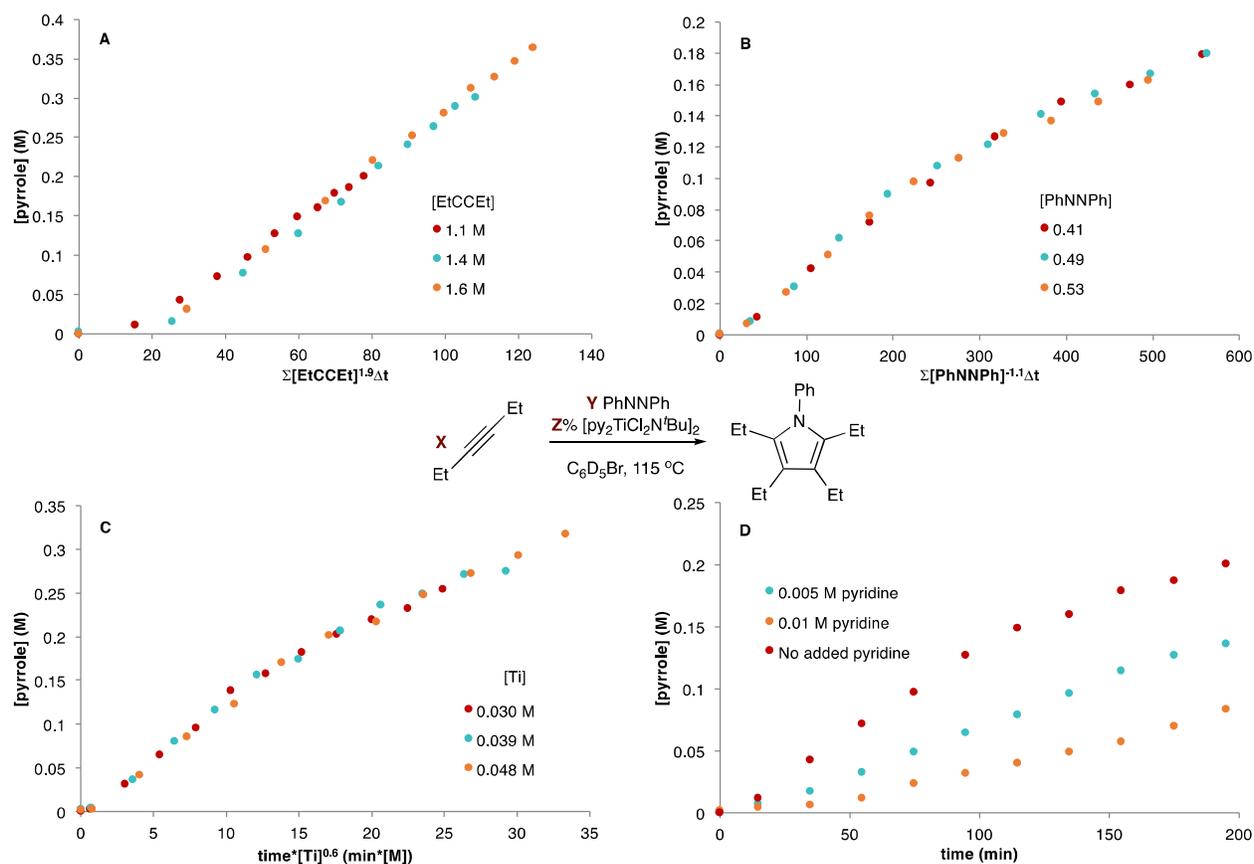


Figure 3. Best-fit rate law determination of $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ -catalyzed pyrrole formation from 3-hexyne and azobenzene via variable time normalization analysis (VTNA). Full reaction conditions can be found in Table S1.

graphical overlays that indicate component order. The VTNA overlay plots of each component of the reaction of 3-hexyne with azobenzene catalyzed by $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ (catalyst, 3-hexyne, azobenzene, pyridine) are presented in Figure 3, and the approximate derived rate law is provided in eq. 1.

$$\text{rate} = k \frac{[\text{Ti}]^{0.5}[\text{3-hexyne}]^2}{[\text{PhNNPh}][\text{pyridine}]} \quad (1)$$

The half-order dependence on $[\text{Ti}]$ indicates a monomer-dimer equilibrium and that at this concentration the bulk of catalyst is dimerized.²⁵⁻²⁶ This is consistent with many other Ti-catalyzed reactions involving Ti imido intermediates such as such as alkyne hydroamination, wherein bridged imidos are often off-cycle resting states.²⁹⁻³⁴ Unlike hydroamination reactions, however, the Ti dimer species is *on cycle* in [2+2+1] catalysis, as azobenzene cleavage requires dimerization (*vide infra*). The reaction is first-order inhibited by $[\text{PhNNPh}]$, indicating that productive catalyst reoxidation by PhNNPh is kinetically unimportant, and instead that PhNNPh can inhibit catalysis through competitive binding with alkyne at one or more points along the catalytic cycle. As a result, the second order dependence on $[\text{3-hexyne}]$ indicates that either second alkyne insertion or reductive elimination is rate-determining. Taken together, this rate law indicates a likely Ti

monomer/dimer equilibrium prior to reversible [2+2] imido+alkyne cycloaddition followed by irreversible, rate determining 3-hexyne 2nd insertion or reductive elimination. (Figure 4). The specific step(s) at which pyridine and azobenzene inhibits catalysis cannot be experimentally determined, since the inhibition could potentially occur at any Ti intermediate prior to the rate-determining step.

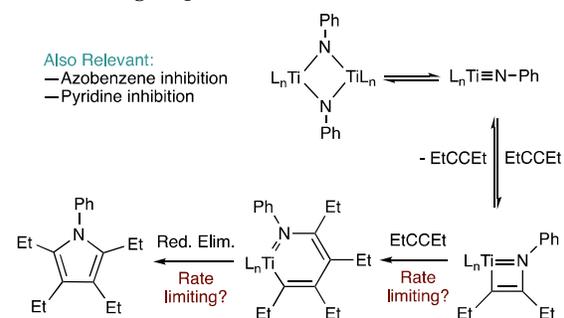


Figure 4. Kinetically relevant steps of Ti-catalyzed 3-hexyne pyrrole formation proposed from rate law data.

Given the initial mechanistic insights above, we next turned to computation to more deeply examine the mechanism. First, we wanted to determine the number and type of L donor ligands bound to the active species at each step in the catalytic cycle: the rate law indicates an inhibition by pyridine and azobenzene, but it is unclear at

1 what stage this occurs. One could envision pyridine,
2 alkyne, or azobenzene coordinated to the Lewis acidic
3 metal during catalysis. Additionally, we were interested in
4 probing the steps of catalysis that are not kinetically
5 observable (reductive elimination and diazene
6 disproportionation) to determine at a fundamental level
7 how and why this unique Ti^{II}/Ti^{IV} mechanism takes place.

8 **3.2 DFT analysis of the mechanism and effects of**
9 **Ligands.** We first examined the energetics of the
10 catalytic reaction of 2-butyne with azobenzene to
11 determine the rate-determining step in the mechanism
12 and the effects of different ligands on the individual steps.
13 The precatalyst py₃TiCl₂(NPh) can potentially undergo
14 dissociation of pyridines such that 1, 2, or no pyridine
15 ligands are bound; furthermore, 2-butyne or azobenzene
16 could also act as a ligand. Therefore, we performed a
17 series of calculations such that we can isolate what
18 ligands are most probably bound to Ti for each
19 intermediate and transition state over the course of the
20 reaction. In general, there is no significant barrier with
21 the addition or removal of a pyridine ligand or alkyne;
22 however, the same cannot be said about the addition of
23 azobenzene, as we discuss later in this section.

24 Figure 5 shows the free energy profile for the formation of
25 N-phenyl tetraethylpyrrole from 2-butyne. Dissociation
26 of one pyridine from py₃TiCl₂(NPh) (CAT) to **IM₁** is
27 favorable by 8.2 kcal/mol in PhCF₃, while the removal of
28 two pyridines is roughly thermoneutral. However,
29 liberation of all 3 pyridines to generate a naked 3-
30 coordinate complex, binding of 2-butyne, and binding of
31 azobenzene are all shown to be unfavorable. Therefore,
32 at the start of the catalytic cycle Ti is likely to be
33 coordinated to one or two pyridines. This is consistent
34 with ¹H NMR spectroscopic evidence that shows that the
35 pyridine *trans* to the imido is already in coordination
36 equilibrium at room temperature; thus, at elevated
37 temperature more complex pyridine coordination
38 equilibria are likely involved.
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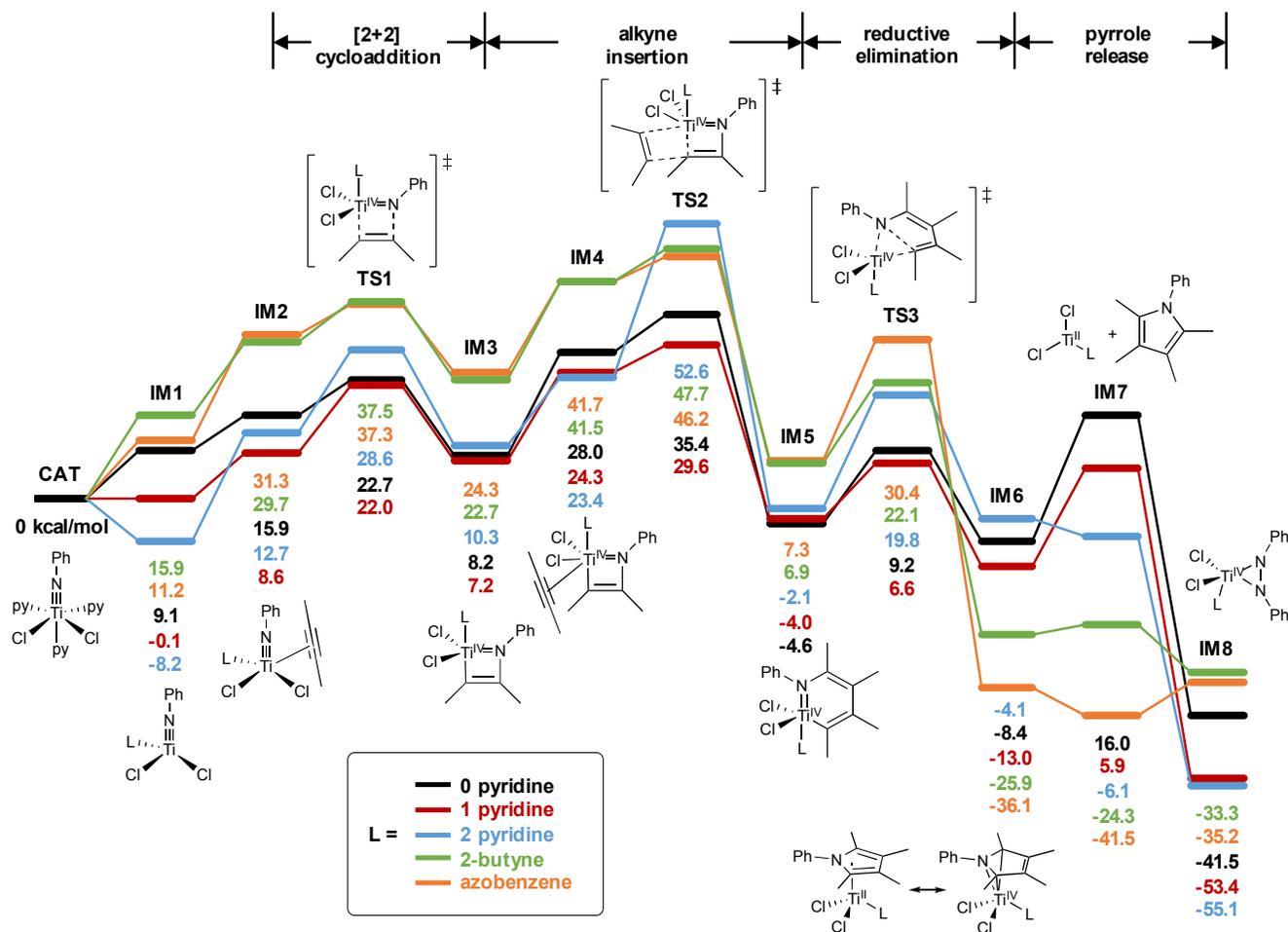


Figure 5. Free energy profile for the formation of N-phenyl tetramethylpyrrole from 2-butyne, azobenzene and $\text{py}_3\text{TiCl}_2(\text{NPh})$. The reaction pathway is calculated using L = None (black), 1 pyridine (red), 2 pyridines (blue), 2-butyne (green), and azobenzene (orange). The geometries for all ligand combinations are provided in the Supporting Information. The free energy profile to close the catalytic cycle from IM8 to CAT' can be found in Figure 11.

After pyridine loss, 2-butyne can then coordinate to Ti to make **IM2**, which is an endergonic process for all possible ligand combinations. As the catalyst coordinates to the π -bond of the alkyne, the lowest energy **IM2** structure contains only one pyridine to minimize steric effects. This species then reacts through [2+2] cycloaddition to the imido Ti=N bond through **TS1**, with a barrier of 13.6 kcal/mol (assuming 1 bound pyridine) to form azatitanacyclobutene (**IM3**). The relative free energy differences between 0, 1, or 2 pyridines bound to **IM3** are relatively small, suggesting that all of these complexes may play a role during the cycloaddition step. Likewise, coordination of the second equivalent of 2-butyne to **IM4** can readily occur with either 0 or 1 pyridine.

The 2-butyne insertion transition state **TS2** proves to be the rate-determining step. Unlike previous steps where several ligand combinations were energetically feasible, this step has significant free energy differences between the different ligand combinations, strongly suggesting that the catalyst has a single pyridine ligand during **TS2**. The reaction barrier is 5.3 kcal/mol compared to **IM4**, 29.6 kcal/mol compared to the starting catalyst while being exergonic to form azatitanacyclohexadiene **IM5** by 33.6 kcal/mol. This also accounts for the observed inhibition by azobenzene and pyridine, since coordination of either of these species significantly raises the energy of all species through **TS2**.

Next, C-N reductive elimination from **IM5** occurs to form a Ti^{II}-bound pyrrole **IM6**. Remarkably, despite forming a formally Ti^{II} species, the formation of **IM6** has a relatively small barrier of 10.6 kcal/mol for the single pyridine bound catalyst and is exergonic. We discuss this step in detail in Section 3.3 to show how it is likely that a true Ti^{II} intermediate is formed at this stage of the catalytic cycle.

The next step is release of the pyrrole product to form **IM7**. Surprisingly, we find that even with a single pyridine ligand the energy required to dissociate the pyrrole is only 18.9 kcal/mol, significantly lower than the rate determining step. This suggests that the formation of Ti^{II} is readily accessible.

Since **IM6** with bound azobenzene is significantly lower in energy than all other ligands, we examined this step in greater detail. It is clear from Figure 5 that azobenzene being bound to Ti prior to **IM6** is significantly unfavorable for productive catalysis, consistent with the kinetic inhibition observed experimentally. Therefore, to proceed over **TS3** to form **IM6** the catalyst must have either 0 or 1 bound pyridine ligands. However, after the reductive elimination, an azobenzene could bind to **IM6** to aid in pyrrole release via associative displacement as suggested by Wang.¹⁰ Therefore, we calculated the barrier for associative displacement of pyrrole by azobenzene, shown in Figure 6 as **TS4**.

Figure 6 compares direct pyrrole release to form Ti^{II} with azobenzene coordination to dissociate pyrrole, which would ostensibly avoid a discrete formally Ti^{II} intermediate through direct electron transfer from pyrrole to azobenzene. Our calculations suggest that the pathway requiring azobenzene binding has a transition state barrier of 23.1 kcal/mol compared to only 18.9 kcal/mol for direct pyrrole dissociation. These results are in direct contrast to previous calculations from the Wang group, who proposed a “redox neutral” associative interchange mechanism that was predicated on azobenzene coordination prior to pyrrole release to avoid discrete, free Ti^{II} intermediates.¹⁰ We believe the inclusion of solvent polarization effects within our geometry optimizations leads to the differences in conclusions: other groups have optimized Ti catalysts in implicit solvation and have found good agreement with experimental kinetics.³⁵ Additionally, we have found experimentally that stoichiometric pyrrole production (and subsequent catalytic alkyne cyclotrimerization by Ti^{II}) is possible in the absence of azobenzene.³⁶ Taken together, this suggests that azobenzene binding for pyrrole release is not a requirement for [2+2+1] pyrrole synthesis, and that free Ti^{II} intermediates are plausible under catalytic conditions.

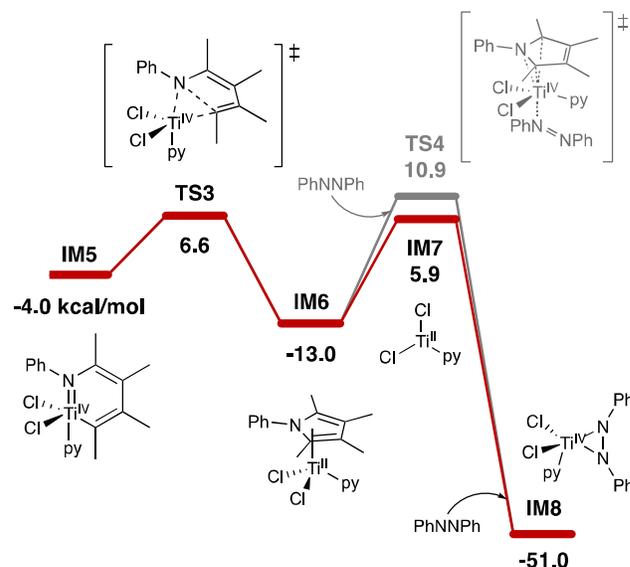


Figure 6. Comparing the free energy required to dissociate pyrrole from Ti^{II} to the transition state barrier for azobenzene binding to the Ti-pyrrole complex. Direct pyrrole dissociation from Ti^{II} in **IM6** is the lower energy pathway.

Finally, **IM7** is reoxidized by binding azobenzene to form **IM8**. **IM8** is best described as a Ti^{IV} hydrazido²⁻ species wherein the electron pair from the Ti^{II} has been fully backdonated into the N-N π^* of azobenzene (*vide infra*), as shown in Figure S114c. Overall, the catalytic production of N-phenyl tetraethylpyrrole is exergonic by 55.1 kcal/mol with a barrier of 29.6 kcal/mol if the most

energetically favorable ligands are used, which is a reasonable barrier for the 110 °C temperature.

In order to further validate the computationally-derived energy values, we carried out Arrhenius analysis on the reaction of 4-octyne with azobenzene catalyzed by $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$. Figure 7 shows the Arrhenius-like plot for 4-octyne giving an activation enthalpy of 16.3 ± 0.6 kcal/mol. Computationally, the activation enthalpy from **CAT** to **TS2** for 4-octyne is 21.1 kcal/mol; therefore, this represents relative good agreement between our DFT model and the experimental result.

The overall rate constant in an Eyring equation³⁷ type form is:

$$k = \kappa \left(\frac{k_b T}{h} \right) e^{\frac{\Delta S^\ddagger}{k_b}} e^{-\frac{\Delta H^\ddagger}{k_b T}}$$

where ΔH^\ddagger and ΔS^\ddagger is the change in enthalpy and entropy, from **CAT** to **TS2**, κ is the transmission coefficient, h is Plank's constant, k_b is Boltzmann's constant. By using the experimentally-measured rates and our DFT calculations for the enthalpy (21.1 kcal/mol) and entropy (18.8 cal/mol K), we can then extract that κ is 0.017. The small transmission coefficient shows that this reaction occurs in the high-friction regime of Kramer theory,³⁸ showing that solvent viscosity likely plays a role in the kinetics. There is a large geometry change that occurs from **TS2** to **IM5**, yet a small geometry change between **IM4** and **TS2**; therefore, there is a relatively large solvent reorganization required after the transition state to proceed to products, which leads to a small transmission coefficient.

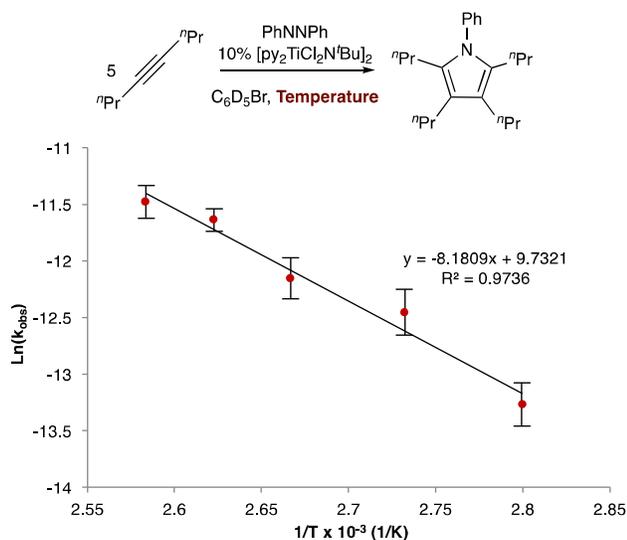


Figure 7. Arrhenius-like plot of the reaction of 4-octyne with azobenzene catalyzed by $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$. Reaction conditions can be found in Table S7.

3.3 Mechanism and NBO/IBO analysis of C-N reductive elimination. Our calculations show that dissociation of pyrrole from Ti^{II} intermediates is more favorable than azobenzene binding to the Ti^{II} -pyrrole

complex. But the question remains if formal reduction occurs during C-N bond formation, or if the pyrrole acts as a fully redox active ligand through bilateral donation and back-donation, obviating the need for charge distribution onto Ti. Therefore, we calculated the Natural Bond Orbitals (NBO) and performed Intrinsic Bond Orbitals (IBOs) analysis to gain insight into this step.

In complicated binding situations involving noninnocent ligands and covalent metal-ligand bonding, formal oxidation state assignment from first principles or DFT calculations can become ambiguous or arbitrary—after all, oxidation state is merely a formalism used to describe extreme ends of a spectrum of bonding. However, it is often useful to describe systems in terms of *relative* oxidation/reduction. D'Acchioli *et. al.* suggested using the d-orbital occupations²² based on NBO theory instead of atomic charge to infer to the natural oxidation state of a transition metal,³⁹ since simple changes to the primary covalent coordination sphere (*i.e.* changing from alkoxide to amide) can dramatically impact the computed charge on the metal. Therefore, we use both Natural Bond Orbitals (NBO) and Intrinsic Bond Orbitals (IBOs) to argue that C-N bond formation from **IM5** to **IM6** occurs through a formal +4/+2 reductive elimination.

The results of $3d_z^2$ NBO orbital occupation calculations for all pyrrole-forming steps of the catalytic cycle (assuming 1 bound pyridine) are listed in Table 1, with the full list of all *d*-orbitals in Table S8. All of the *d* orbital occupations remain mostly constant throughout the reaction except for the $3d_z^2$ orbital occupation. By analyzing the $3d_z^2$ orbital and relating the occupation of this orbital to the formal oxidation state for compounds with known oxidation states, we can infer the oxidation state for all intermediates. As a benchmark for Ti^{II} complexes, the $3d_z^2$ values for TiCl_2 , $[\text{TiCl}_4]^{2-}$, TiCl_2py_2 , and TiCl_2py_4 were found to range between 0.65 to 0.82. As a benchmark for Ti^{IV} complexes, **IM1-IM5** and TiCl_4 were calculated to have $3d_z^2$ values between 0.29 to 0.44. Therefore, intermediates with $3d_z^2$ values closer to 0.4 can be assigned a formal +4 oxidation state and closer to 0.6 a +2 oxidation state.

From this analysis, we assign **IM5** a formal +4 oxidation state ($3d_z^2 = 0.44$) and **IM6** a formal +2 oxidation state ($3d_z^2 = 0.61$). However, the $3d_z^2$ occupation of 0.61 is on the lower end of occupation for Ti^{II} , which does suggest strong bilateral donation and back-donation into the pyrrole π^* . This backdonation can be seen in the calculated bond lengths of the pyrrole in **IM6**, where C1-N, C4-N, and C4-C3 are elongated (Figure 8). Similarly, the $3d_z^2$ value (0.64) for TiCl_2py_4 , which can also backdonate into the ligand framework, is also on the lower end of " Ti^{II} " occupation. Interestingly, **TS3**, the C-N bond-forming step, has a $3d_z^2$ of 0.54 suggesting that the 2-electron reduction is happening through this transition state. **IM7** is assigned a +2 oxidation state before the

catalysts binds with azobenzene, after which it returns to the +4 oxidation state in **IM8**.

Table 1. The occupation number of the $3dz^2$ orbital compared with the formal oxidation state of the Ti atom in the complex. Species labels match with structures in Figure 5. This analysis suggests that complexes with an occupation number closer to 0.4 should be assigned the formal +4 state, and complexes with an occupation number closer to 0.6 should be assigned the formal +2 state.

Species	Occupation numbers ($3dz^2$ orbital)	Formal Oxidation State
IM1	0.31	+4
IM2	0.30	+4
TS1	0.35	+4
IM3	0.38	+4
IM4	0.37	+4
TS2	0.40	+4
IM5	0.44	+4
TS3	0.54	+2/+4
IM6	0.61	+2
IM7	0.72	+2
IM8	0.38	+4
TiCl₂	0.82	+2
[TiCl₄]²⁻	0.77	+2
TiCl₂py₂	0.68	+2
TiCl₂py₄	0.65	+2
TiCl₄	0.29	+4

Further evidence for the reductive elimination mechanism is obtained through intrinsic bond orbital (IBO) analysis. By obtaining IBOs along the reaction coordinate, the continuous rearrangement of IBOs can be correlated to electron flows and bond rearrangements, and then expressed by the curved arrow formalism.^{11,12} By construction, a minimal number of IBOs change their nature during a reaction, to make it clear and straightforward to analyze the mechanism and identify electron flow.

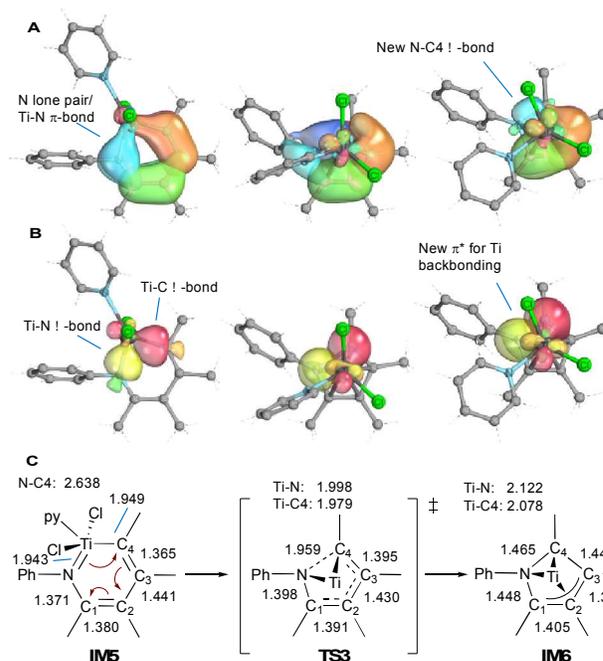


Figure 8. IBOs of the reactant (L, **IM5**), transition state (M, **TS3**) and product (R, **IM6**) in the reductive elimination step. IBOs show (A) the lone pair on the N atom/Ti-N π -bond in **IM5** (blue orbital) rotates and attacks C₄ to form the new C-N σ bond in an electrocyclic fashion; (B) orbital rotation for π backbonding with Ti; and (C) an arrow pushing diagram of the reductive elimination along with calculated bond lengths (in Å).

Figure 6 shows the IBOs for the reductive elimination step from **IM5** to **IM6**. Figure 6a shows that the lone pair on the N atom in **IM5** (blue orbital) rotates and attacks C₄ to form the new C-N σ bond in an electrocyclic fashion, similar to how a C-C bond is formed in a Nazarov cyclization of divinylketones.⁴⁰ Simultaneously the orange orbital (π bond on C₁ and C₂) and the magenta orbital (π bond on C₃ and C₄) simply shift during the reductive elimination and become localized on C₁, C₂, and C₃. Concurrent with electrocyclization, Figure 6b shows the fate of the Ti-C and Ti-N σ -bonding orbitals. As the electrocyclization takes place, these two orbitals rotate perpendicular to the forming pyrrole ring, becoming the basis for a π backbonding interaction with Ti. The net result of this electron movement (Figure 6c) is to generate a bound pyrrole whose binding can be described as an η^3 -allyl interaction between C₁, C₂, C₃ and Ti, and a strong π backbonding interaction between Ti, N, and C₄. This bonding picture is consistent with the calculated bond lengths in **IM6**, where C₁-C₂ and C₂-C₃ are average (~1.4 Å), while C₃-C₄, C₄-N, and N-C₁ are elongated (~1.45 Å) compared to normal pyrrole bond lengths.

This electrocyclic reductive elimination is unique, and provides an important piece of data on C-X (X \neq H) reductive eliminations on Ti: direct M-C σ reductive coupling on Ti is virtually unknown; it appears as though in almost all cases Ti organometallics would energetically

prefer H abstraction,⁴¹⁻⁴² radical decomposition,⁴³ substitution,⁴⁴ or electrocyclization to classical 2-electron reductive elimination pathways seen with late transition metals. In fact, in our previous report on Ti-catalyzed alkyne/alkene/nitrene coupling, direct C-N bond forming was never observed.⁴⁵ Since these systems had semi-saturated ring systems, they are unable to undergo electrocyclization and instead access alternative reductive pathways. Similarly, the Ti-catalyzed Pauson-Khand reaction, an example of apparent C-C direct reductive coupling, may instead proceed through a related π -electrocyclization-type pathway.⁴⁶⁻⁴⁷

3.4 Solvent effects on the mechanism and rate. Next, the effect of solvents on the rate of catalysis was examined by varying the solvent dielectric from 2.03 (C_6D_{12}) to 10.5 ($C_2H_4Cl_2$), and the data summarized in Figure 9. There is a strong correlation between rate and dielectric constant, with high dielectric solvents ($C_2H_4Cl_2$, C_6D_5Br , $PhCF_3$) yielding fast, productive catalysis and low dielectric solvents (cyclohexane, C_6D_6 , C_6F_6) performing poorly. Additionally, there is no obvious arene coordination or other solvent coordination effect to the rate since

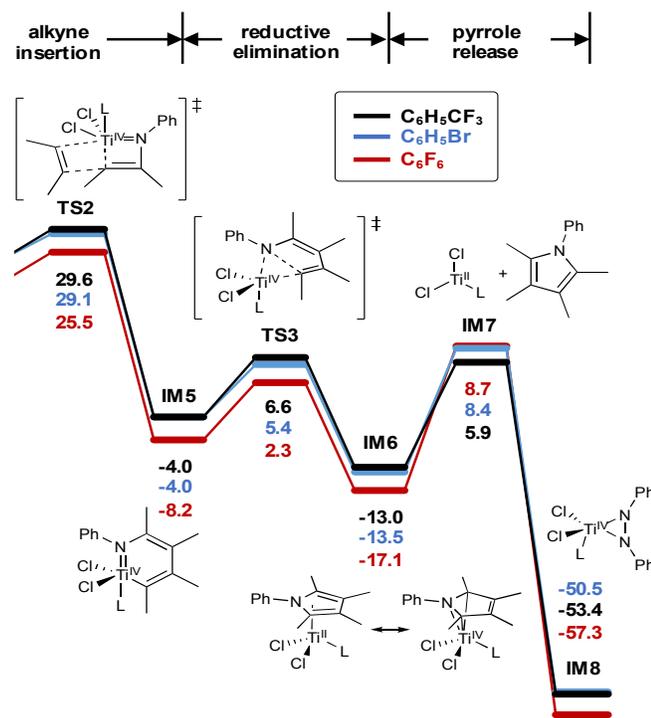


Figure 10. The free energy profile for the alkyne insertion, reductive elimination, and pyrrole release step in $PhCF_3$ (black), C_6F_6 (red), and C_6D_5Br (blue).

Curiously, the data shows that $PhCF_3$, $C_2H_4Cl_2$, and C_6D_5Br all have very similar rates, despite the fact that C_6D_5Br 's dielectric constant is only 5.4, while $PhCF_3$ and $C_2H_4Cl_2$ are 9.18 and 10.5, respectively. This step function behavior in the rate suggests a deeper mechanistic feature in the role of the solvent; therefore, we performed

$C_2H_4Cl_2$, C_6D_5Br , and $PhCF_3$ all have similar rates.

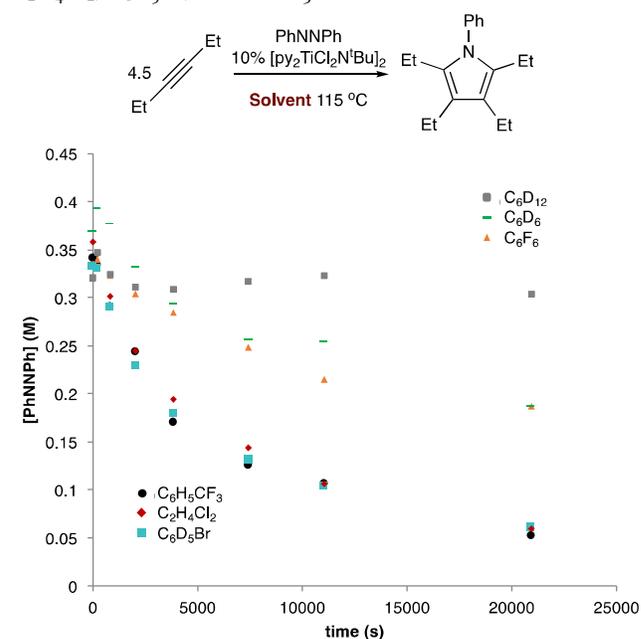


Figure 9. Solvent screen of $[py_2TiCl_2N^tBu]_2$ -catalyzed pyrrole formation from 3-hexyne and azobenzene. Reaction conditions can be found in the Figure S34.

calculations on a subset of these solvents to probe the effect of dielectric constant on the rate.

Figure 10 shows the calculated catalytic cycle for 3 of the experimentally used solvents, $PhCF_3$, C_6D_5Br and C_6F_6 . Overall, the catalytic picture looks largely the same, with **TS2** being the highest overall energy of the catalytic cycle. However, contrary to experimental expectations, the free energy difference between **CAT** and **TS2** actually *increases* with increasing dielectric constant with barriers of 29.6, 29.1, and 25.5 kcal/mol barriers for $PhCF_3$, C_6D_5Br and C_6F_6 , respectively. Since the **TS2** barrier controls the rate, this data suggests that the increase in the barrier with high dielectric constant is contrary to experiment. Given that we are using an implicit solvation model, the associated errors with such a model can certainly lead to 3-5 kcal/mol errors.⁴⁸ Furthermore, as discussed in the Supporting Information, we only changed the dielectric constant of the solvent and ignored other changes in the solvent such as the thermal expansion coefficient or the surface tension at interface. Additionally, we showed that this reaction takes place in the high friction regime of Kramer rate theory; therefore, the solvent viscosity, which was not taken into effect here, plays a role in the kinetics. Therefore, the discrepancy between our calculations and experiments could be from not including these effects.

Despite this, an interesting trend can be seen which might suggest why experimentally the reaction rate increases with dielectric constant. The free energy difference between **IM6** and **IM7** is increasing with

1 decreasing dielectric constant, going from 18.9 (PhCF₃) to
2 21.9 (C₆D₅Br) to 25.8 kcal/mol for C₆F₆. This data shows
3 that high dielectric constant solvents are able to more
4 adequately stabilize free Ti^{II} species. Therefore, it could
5 be that in C₆F₆ slower ligand dissociation rates at various
6 steps of catalysis may play a role in kinetically relevant
7 equilibria or related processes.

8 Additionally, it is important to note how sensitive these
9 calculations are to fully relaxing the geometries in the
10 associated solvent. We also performed single-point
11 energy calculations in these three solvents using PhCF₃
12 solvent-optimized geometries (Figure S11). Using this
13 simplified protocol, there is a dramatically higher energy
14 difference between **IM6** and **IM7**, which would lead to
15 the inaccurate conclusion that the free energy difference
16 between **IM6** and **IM7** was becoming the rate-
17 determining step for C₆F₆. This further demonstrates the
18 large role solvent plays in the dissociation of pyrrole.
19 Additionally, the differences between Figure 10 and Figure
20 S11 emphasize the need for careful computations in the
21 description of solvent effects.
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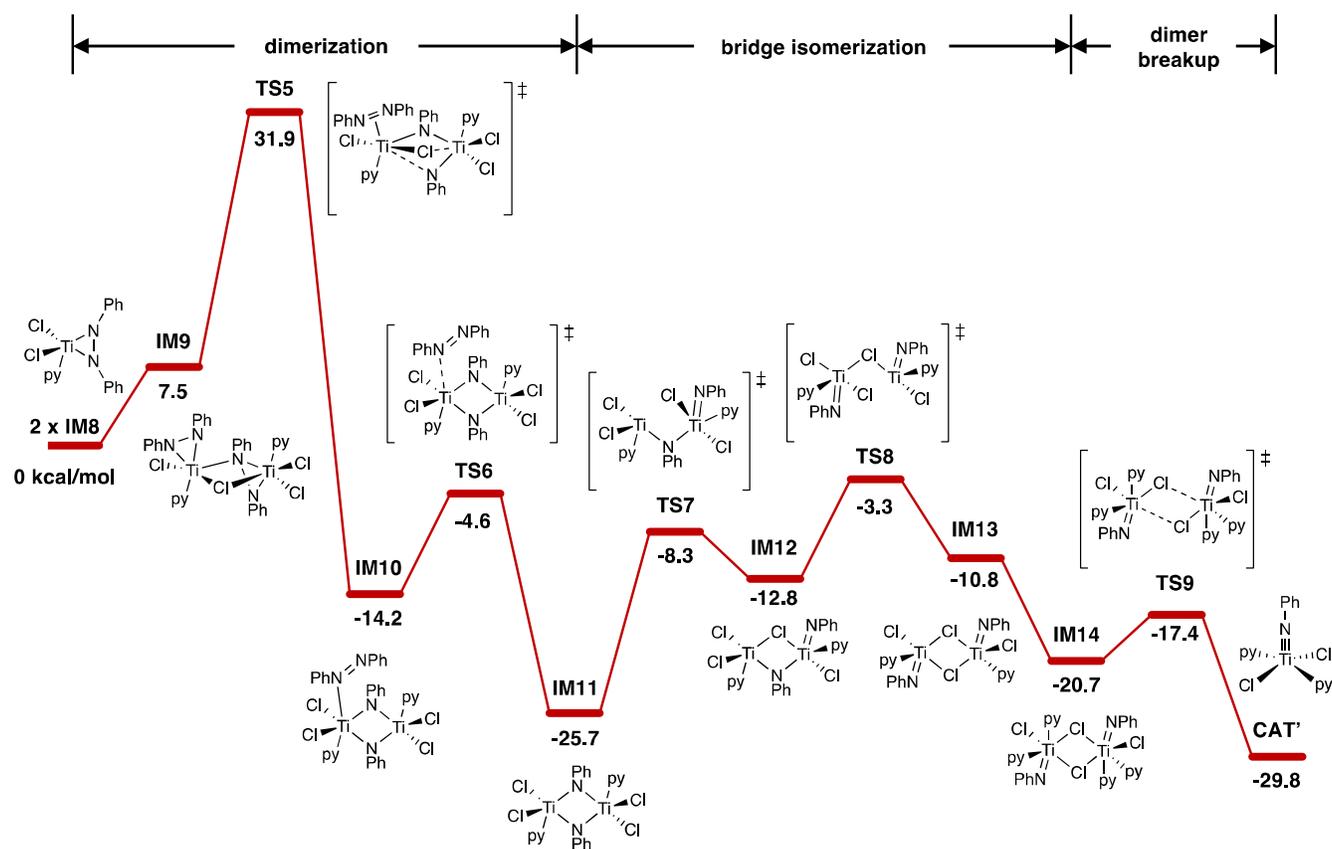


Figure 11. Free energy profile for the regeneration of the Ti imido catalyst via disproportionation.

3.5 Mechanism for regeneration of the catalyst via disproportionation.

Next, we computed the regeneration of the active Ti imido (CAT') from the η^2 -hydrazido adduct IM8. Previously, we hypothesized that this reaction proceed through a dimerization process to make a bridged Ti_2N_4 6-membered metallacycle that would then eject azobenzene and regenerate 2 Ti imidos in a *retro*-[2+2+2] reaction. However, we were unable to experimentally interrogate this mechanism because simple ligand loss from model complexes was rate-limiting.

The computed mechanism for regeneration of the Ti imido catalyst is shown in Figure 11. We were unable to locate a reaction pathway that proceeded through the originally proposed *retro*-[2+2+2].⁶ Here, we start with two IM8 complexes with one pyridine on each complex since pyrrole release likely occurs with one pyridine (*vide supra*). For convenience, we reset the energy scale to zero here, but IM8 is actually -53.4 kcal/mol relative to the starting catalyst; therefore, we do not expect, nor is experimentally observed, that any step in the regeneration pathway to be rate determining. Two equivalents of IM8 first dimerize through one chlorine atom and one azobenzene to form IM9. Next, IM9 then reacts to break the bridging azobenzene N-N bonds through TS5,

forming an unsymmetric *bis* imido-bridged four-membered ring IM10 where the non-reacted azobenzene remains coordinated to one Ti. This dimerization pathway is consistent with previous crossover studies which indicated no azobenzene N-N scrambling during catalysis.⁶ Subsequently, there is a reaction barrier of 9.6 kcal/mol to liberate this azobenzene to generate IM11, a bridging imido dimer. These species are often the resting states in other Ti imido-catalyzed reactions such as hydroamination,²⁹⁻³⁴ and in fact this species is close in energy to CAT'.

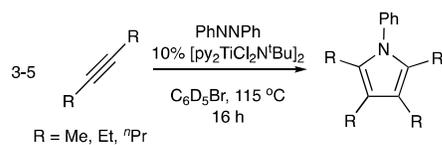
There are multiple energetically accessible pathways from IM11 to CAT', we show the lower energy pathway here and a secondary pathway in the Supporting Information (Figure S112), which uses different regioisomers. The pathway shown here involves first gearing the imido-bridge dimer IM11 to a chloro-bridged dimer IM13 (the experimental crystal structures of $[TiCl_2(NC_6H_4Me)py_2]_2$ and $[TiCl_2(NC_6F_5)py_2]_2$ are chloro-bridged^{29b}) in contrast direct splitting of IM11 as proposed by the Wang group.¹⁰ In this chloro-bridged splitting pathway, IM11 first isomerizes by overcoming a 17.4 kcal/mol barrier in TS7 to move from a *bis* imido-bridge to a mixed imido/chloro-bridge IM12. Next, the second isomerization takes place, this time only requiring 9.5 kcal/mol of energy through TS8 to form *bis* chloro-

bridged **IM13**. At this point, barrierless addition of pyridines forms a coordinatively saturated **IM14**, which is exergonic by 9.9 kcal/mol. Finally, the dimer **IM14** breaks through a small 3.3 kcal/mol barrier to regenerate 2 equivalents of **CAT'**.

Regardless of how the dimer dissociates, the free energy difference between **IM11** and **CAT'** is relatively small, suggesting an equilibrium of the dimer and monomer under catalytic conditions. This matches the experimentally observed rate order of [Ti]^{0.5}.

3.6 Alkyne Effects on Reaction Kinetics and Regioselectivity. Next, the effect of alkyne substitution on the reaction kinetics and product regioselectivity was explored. First, we experimentally examined the rates of 3-hexyne vs 4-octyne (Table 2) to explore any steric differences on reaction rate, and compared these to the computationally-derived relative rates of 2-butyne, 3-hexyne, and 4-octyne. 2-butyne was not tested experimentally because its low boiling point precludes precise concentration measurements at the elevated reaction temperature. It was found that there was a small observable experimental rate difference between 3-hexyne and 4-octyne. Although Et and ⁿPr groups have similar A-values, their ligand repulsion energies (E_r) and steric values (E_s) are quite different, which appears to have some small influence on rate-determining 2nd insertion (**TS2**).⁴⁹ Consistent with this observation, there is only a small computed energy difference between **TS2** for the 3 internal alkyne substrates. The experimental k_{obs} difference between 3-hexyne and 4-octyne correlates to a free energy difference of 1.4 kcal/mol, which is in excellent agreement with the computational result of 1.4 kcal/mol. Further computational analysis of the complete catalytic cycle also indicates only small changes in energies between 2-butyne, 3-hexyne, and 4-octyne for other intermediates and transition states (Figure S113).

Table 2. Alkyne substituent effects on the rate of [2+2+1] pyrrole synthesis.



R =	K _{obs} × 10 ⁵	A ^b	E _S ^c	E _R ^d	ΔG [‡] TS ₂ (Calc) ^e
Me	-	1.7	0	17	29.1
Et	5.97 ± 0.4	2.1	0.08	34	27.1
ⁿ Pr	0.980 ± 0.07	2.1	0.31	36	28.5
Et vs ⁿ Pr ΔΔG [‡] from K _{obs} : 1.4 kcal/mol			Et vs ⁿ Pr ΔΔG [‡] from calcs: 1.4 kcal/mol		

^a Reaction conditions can be found in the Supporting Information. Et = S43, Pr = S64. ^b Steric A value;⁵⁰ ^c Taft steric parameter;⁴⁹ ^d Steric value;⁴⁹ ^e Mo6/6-311g(d,p)/SMD/ultrafine grid in C₆H₅Br. ΔG[‡] TS₂ is the energy difference between **CAT** and **TS2**.

Unsymmetrical alkynes introduce a new layer of complexity: there are 3 possible regioisomeric products that result from 2 azatitanacyclobutene intermediates (**IM3**) and 4 azatitanacyclohexadiene intermediates (**IM5**). The selectivities for several unsymmetrical alkynes are shown in Table 3.⁶ Given these results, we were interested in determining the exact pathways through which products were formed, since the 2,4-substituted head-to-tail coupled product **H** could be formed through multiple routes (Figure 13, *vide infra*). Based on our initial computational and kinetic results, formation of **IM3** is in most cases reversible, while **IM5** is irreversible. Thus, in order to understand the origin of selectivity, the equilibrium constants and each individual 2nd insertion rate must be known. As such, we embarked on full kinetic and computational analysis of the selectivity manifold of several unsymmetrical alkynes.

Table 3. Product distribution of pyrrole formation with various unsymmetric alkynes. Taken from ref. 6.

R ¹ , R ²	G	H	I
H, ⁿ Bu	0.13	1	0.13
H, ^t Bu	0	1	0
H, Ph	0	1	0.25
Me, Ph	0.45	1	0.91

For the purposes of experimentally examining the kinetics of unsymmetrical reactions, phenylpropyne (PhCCMe) derivatives were selected. PhCCMe was determined as the best candidate for kinetic analysis because terminal alkynes are typically plagued by alkyne trimerization side reactions.⁶ Again we turned to VTNA to determine the rate equation of the reaction of PhCCMe with azobenzene and [py₂TiCl₂N^tBu]₂. The VTNA reactions (Figure 12) give a rate equation consistent with the computational analysis (eq. 2). In this case, [PhCCMe] is still second order at low concentrations and both [PhNNPh] and [pyridine] were still found to give first order inhibition of the reaction. [Ti] is still 0.5 order, indicating that a change in the alkyne substrate has, unsurprisingly, little effect on the catalyst monomer-dimer equilibrium. However, at high [PhCCMe] the order changes to [PhCCMe]^{1.5} (Figure S40). This change in the rate order indicates that at high

concentration of PhCCMe there is population of [2+2] cycloadduct **IM₃** in equilibrium with **IM₁**. Consequently, this perturbs the rate law from rigorous second order. This is in contrast to 3-hexyne, which under all tested conditions is second order.

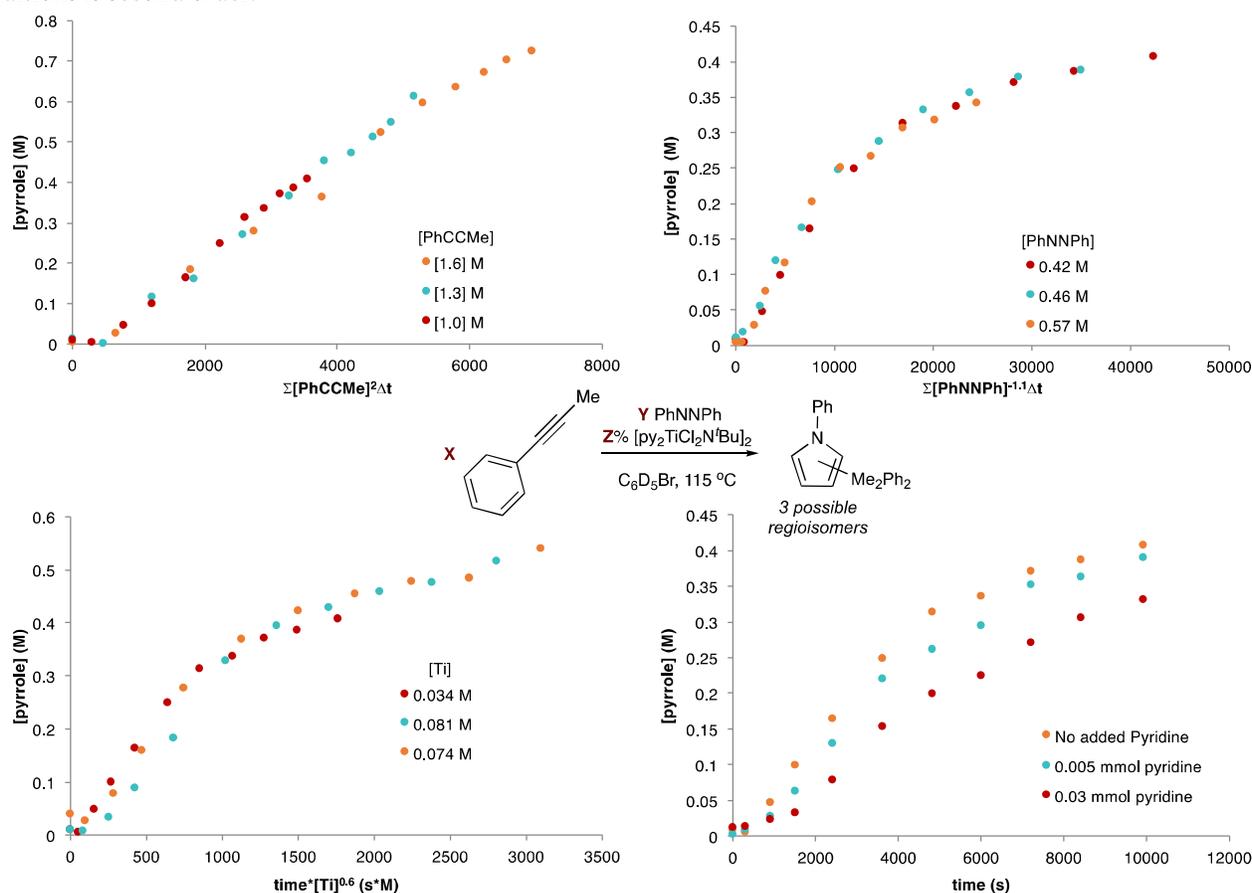


Figure 12. Best-fit rate law determination of $[\text{py}_2\text{TiCl}_2\text{N}^t\text{Bu}]_2$ -catalyzed pyrrole formation from phenylpropyne and azobenzene via variable time normalization analysis (VTNA). Reaction conditions can be found in Table S3.

Next, the catalytic cycle from precatalyst through **IM₅** (immediately after irreversible, rate determining 2nd alkyne insertion) was calculated for 3 unsymmetric terminal alkynes, ⁿBuCCH, ^tBuCCH, and PhCCH. The energies of all selectivity-relevant species are presented in the selectivity manifold in Figure 13. Full computational details and selectivity determination for these three alkynes are available in the Table S9.

For ⁿBuCCH, there is very little preference for forming either [2+2] regioisomer **IM_{3A}** (electronically favored) or **IM_{3B}**, (sterically favored). Despite the fact that it may seem counterintuitive that Ti would be the sterically “small” fragment of the Ti=NPh unit, the 2 Cl ligands provide little spatial hindrance to [2+2] cycloaddition in **TS₁** in comparison to the Ph on the imido. In the alkyne insertion step, **TS₂**, going from **IM₃** to **IM₅**, there is a small ($\Delta\Delta G^\ddagger = 1.4$ kcal/mol) preference for 1,2 insertion from **IM_{3A}** (**TS_{2AD}**, going to **IM_{5D}**), and little preference ($\Delta\Delta G^\ddagger = 0.1$ kcal/mol) for either 1,2- (**TS_{2BF}**) or 2,1-

(**TS_{2BE}**) insertion from **IM_{3B}**. As a result, all possible pathways are kinetically accessible, leading to a distribution of **G**, **H**, and **I** that agrees well with experimental data. Product **H** is the major product because the lowest energy pathway (**IM_{3A}** to **IM_{5D}**) and the second lowest energy pathway (**IM_{3B}** to **IM_{5E}**) both lead to **H**.

^tBuCCH regioselectivity is dominated by sterics. Both [2+2] cycloaddition pathways are energetically accessible >100 °C, but there is a huge kinetic preference ($\Delta\Delta G^\ddagger = 7.2$ kcal/mol) as well as a thermodynamic preference ($\Delta G = 4.5$ kcal/mol) for formation of the sterically favored **IM_{3B}** due to the increased size of ^tBu vs. ⁿBu.⁵⁰ In the 2nd insertion step from favored **IM_{3B}**, there is a large steric preference for 2,1-insertion over 1,2-insertion ($\Delta\Delta G^\ddagger = 6.1$ kcal/mol for **TS_{2BE}** over **TS_{2BF}**), and as a result ^tBuCCH produces solely **H**.

Finally, PhCCH again has a slight kinetic and thermodynamic preference for the formation of the

sterically-preferred **IM**_{3B} over **IM**_{3A}. Additionally, there is a low-energy pathway for sterically-preferred 2,1-insertion in the second step (**TS**_{2BE}) leading to **IM**_{5E} and ultimately onto **H**, which is the experimentally-determined major product. However, the computational selectivity significantly favors formation of **I**. This is because **TS**_{2BF} converges to a lowest-energy state that has an arene π -stacking interaction. Since our simplistic rate theory does not take ensemble averages into account, the contribution of other, non-stacked close-in-energy states to the ensemble partition function at high temperature is missed, disproportionately increase the rate of forming **IM**_{5F} that yields product **I**. Nonetheless, excluding this pathway the computational pathways and selectivities for all three alkynes match experimental data well.

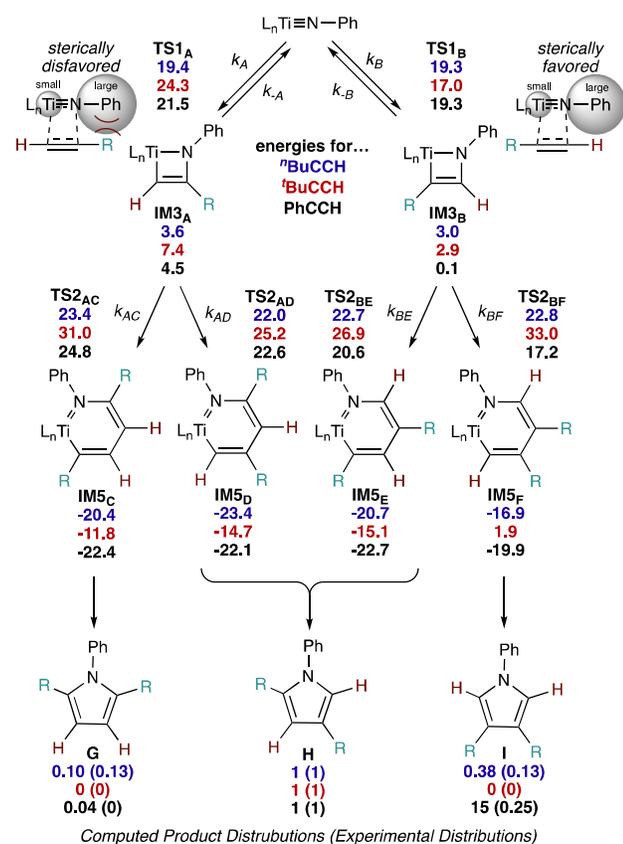


Figure 13. Reaction pathways leading to 3 regioisomeric pyrroles from unsymmetrical terminal alkynes. $L_n = pyCl_2$ for all calculated structures. Full details are available in Table S9. Calculated transition state and intermediate energies are presented below each structure. All energies are in kcal/mol and reported with respect to $py_3TiCl_2(NPh) = 0.0$ kcal/mol. Product distributions are standardized against **H**. Experimental ratios were taken from ref 6.

Next, we computationally investigated the regioselectivity of reactions with PhCCMe (Figure 14). Unlike in the terminal alkynes, [2+2] cycloaddition is most influenced by electronic effects of the alkyne substituents: electronically favored **IM**_{3L} is both kinetically and thermodynamically favored over **IM**_{3K}, and as a result

product **Q** is made in lowest quantity since it can only originate from **IM**_{3K}. Interestingly, much like with ^tBuCCH, there is again little kinetic preference for the regioselectivity of 2nd insertion, leading to significant quantities of both **R** and **S**.

In summary, the regioselectivity of pyrrole formation in terminal alkynes is driven primarily by sterics, where the degree of selectivity is dependent on the size and nature of the alkyne functional group. In contrast, for an internal alkyne such as phenylpropyne where the steric bias is not as obvious, inductive effects have a larger impact on product distribution.⁵¹ Ironically, the head-to-tail coupled product (**H** or **R**) is the major product no matter whether sterics or electronics is the controlling selectivity factor. This unfortunate phenomenon is a function of the bifurcating selectivity manifold wherein 2 different pathways can later merge to give a common product.

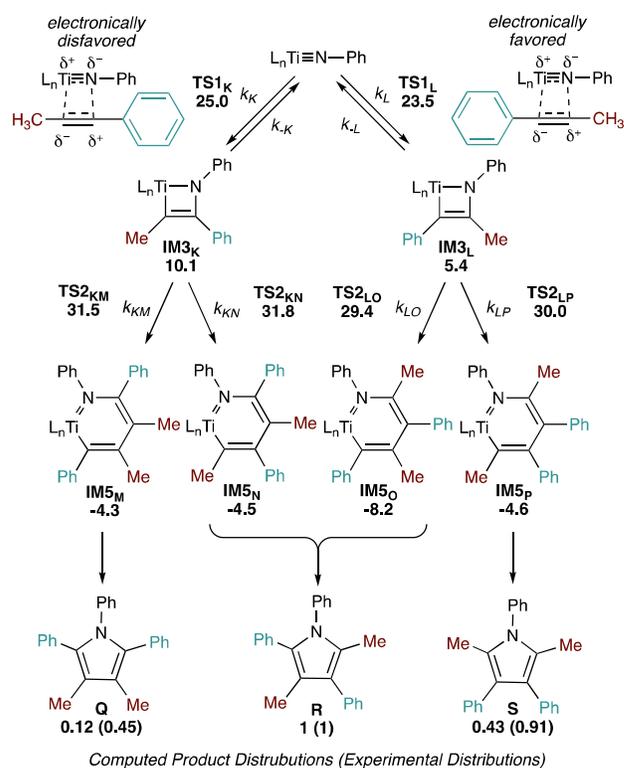


Figure 14. Reaction pathways leading to 3 regioisomeric pyrroles from phenylpropyne alkynes. $L_n = pyCl_2$ for all calculated structures. Full details are available in Table S9. Calculated transition state and intermediate energies are presented below each structure. All energies are in kcal/mol and reported with respect to $py_3TiCl_2(NPh) = 0.0$ kcal/mol. Product distributions are standardized against **R**. Experimental ratios were taken from ref 6.

3.7 Phenylpropyne Substitution Effects and Hammett Analysis. Given the computational result of the importance of inductive effects in PhCCMe regioselectivity, we next carried out Hammett analysis

using various *para*-substituted phenylpropyne derivatives to determine the transition state electronic effects on the rate of reactivity and regioselectivity. A survey of 5 different phenylpropynes indicates a very strong linear correlation between rate and electron donicity (Figure 15). This correlation most likely stems from the increased Lewis basicity of the alkyne, which leads to an increased rate of coordination to Ti, which should assist in both [2+2] cycloaddition and 1,2-alkyne insertion.⁵²

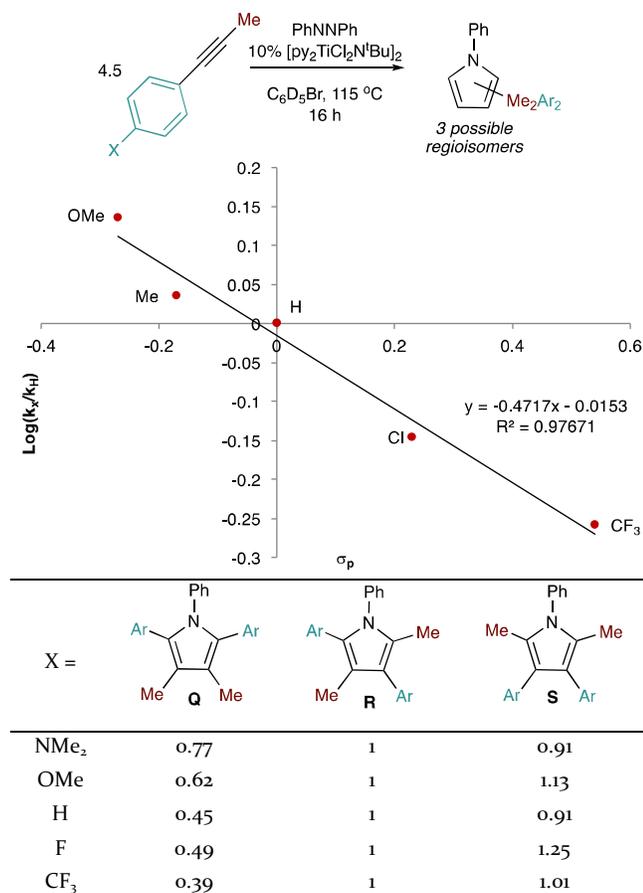


Figure 15. Top: Hammett plot of various *para*-substituted phenylpropynes. Bottom: product distribution of regioisomers as a function of *p*-substitution. All product ratios are standardized against **R**. Reaction conditions are available in Table S5.

Analysis of the regioselectivity in electronically different phenylpropynes reveals an interesting trend in regioselectivity: decreasing electron density on the alkyne decreases the formation of 3,4-dimethyl-1,2,5-triphenylpyrrole **Q** relative to the other two regioisomers (Figure 15, bottom). We propose that this result indicates that there is a bias against formation of the electronically disfavored azitanacyclobutene intermediate, **K**. This is consistent with a picture in which electron-withdrawing groups on the phenyl ring stabilize partial negative charge buildup on the carbon adjacent to the phenyl ring in **TS_{1L}**, and likewise *destabilize* positive charge buildup on carbon

in **TS_{1K}** (Figure 16). It is difficult to interpret the effects this may have on the insertion or reductive elimination steps, since the electronic effect now influences the partial charges on both the reactive intermediate (**IM_{3K}** or **IM_{3L}**) as well as the alkyne.

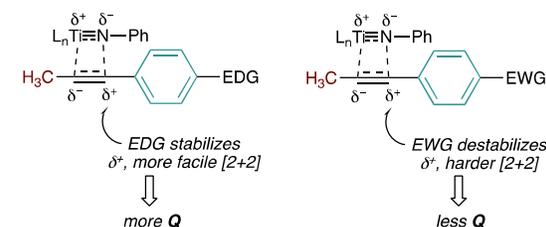


Figure 16. Partial charge explanation for donor effects in arylpropyne regioselectivity.

3.8 Catalyst Effects on Reaction Kinetics and Regioselectivity. Next, we investigated simple anionic ligand changes on the catalyst using Cl, Br, and I to probe electronic and steric effects based on ligand donor parameters (LDP) previously generated for early transition metals.⁵³⁻⁵⁴ These values allow direct comparison between different ligand sets based on their donor-ability (LDP) and steric contributions (%Vol) to the metal center. A general periodic trend can be seen (Table 4): the larger, poorer donor ligand I is significantly faster than the smaller, stronger donor ligand Cl. Interestingly, the rate effect of changing the X ligand is significantly smaller than simply using a *bis*(pyridine) catalyst [py₂TiCl₂N^tBu]₂ instead of py₃TiCl₂N^tBu. Since the data is only three points, we chose not to over interpret this data and assign a fitted model to determine the relative contribution of LDP vs. %BurV.⁵⁵

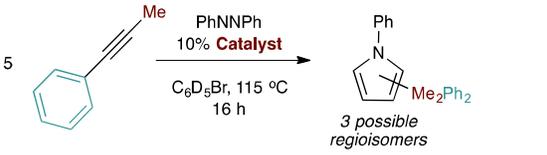
Table 4. Ligand donor parameter (LDP) effects on the rate of py₃TiX₂N^tBu-catalyzed pyrrole formation from 3-hexyne and azobenzene. Reaction conditions can be found in Table S6.

Catalyst	K _{obs} x 10 ⁵	LDP ^a	%BurV ^b
py ₃ TiCl ₂ N ^t Bu	0.42 ± 0.17	15.05	16.8
py ₃ TiBr ₂ N ^t Bu	0.97 ± 0.17	15.45	18.1
py ₃ TiI ₂ N ^t Bu	2.34 ± 0.11	15.80	19.2
[py ₂ TiCl ₂ N ^t Bu] ₂	5.97 ± 0.4	15.05	16.8

^aLigand donor parameter.⁵³⁻⁵⁴ ^b% Buried volume from SambVca.⁵⁶

Further analysis of these catalyst effects on phenylpropyne pyrrole regioselectivity yields an increase in the selectivity for 2,5-dimethyl-1,3,4-triphenylpyrrole **S** and decreasing selectivity for **Q** when moving from Cl to I (Table 5). We propose a compounding electronic and steric effect on the reaction mechanism to achieve this selectivity. We hypothesize that the initial [2+2] is primarily governed by increased electrophilicity of the titanium center/polarization of the Ti imido favoring **TS₁** and **IM₃**. This is in agreement with the Hammett results with substituted arylpropynes. Steric effects then contribute for the insertion step, where the larger iodide ligands disfavor putting the sterically encumbered aryl group α to Ti relative to the smaller chloride ligands.

Table 5. X-type ligand effects on product distribution from phenylpropyne. All product ratios are standardized against **R**. Reaction conditions can be found in Table S6.



Catalyst	Q	R	S
py ₃ TiCl ₂ N ^t B _u	0.45	1	0.91
py ₃ TiBr ₂ N ^t B _u	0.22	1	1.21
py ₃ TiI ₂ N ^t B _u	0.14	1	1.41

3.9 Azobenzene effects on reaction kinetics. Due to the inverse order in [azobenzene] we hypothesized that altering the electronics or sterics of the diazene could potentially lead to a change in rate. Seven *p*-substituted aryldiazenes were tested to generate the Hammett plot shown in Figure 17 (top). A linear correlation was found between strong EDG (OMe) to weakly EWG (F), giving a general decrease in reaction rate. We hypothesize this decrease in rate is due to decreased Lewis acidity of the metal center containing a more electron rich imido ligand, which should inhibit alkyne binding. Interestingly, strongly EWG groups (Cl, OCF₃) do not fall within this trend. Typically large deviations in Hammett plots would indicate a change in mechanism or a change in the RDS;⁵⁷⁻⁵⁸ however, VTNA of (*p*-F₃COPh)₂N₂ showed an identical rate equation to the parent azobenzene. Due to the complexity of this reaction and the fact that NR species are involved in many steps leading up to the rate determining step, it is difficult to determine the cause of this large deviation for strongly EWGs.

To further investigate the ability of the diazene to affect the reaction rates, we compared 4 different *o*-substituted

diazenes (H, Me, Et, and *i*-Pr) yielding the Taft plot shown in Figure 17 (bottom). Changing from H to Me causes a large decrease in rate, but further increases yield only moderate additional slowdown. As was the case in the azobenzene Hammett, the overall decrease in rate is most likely due to increased steric bulk at the metal center inhibiting alkyne coordination events such as [2+2] cycloaddition and 2nd insertion.

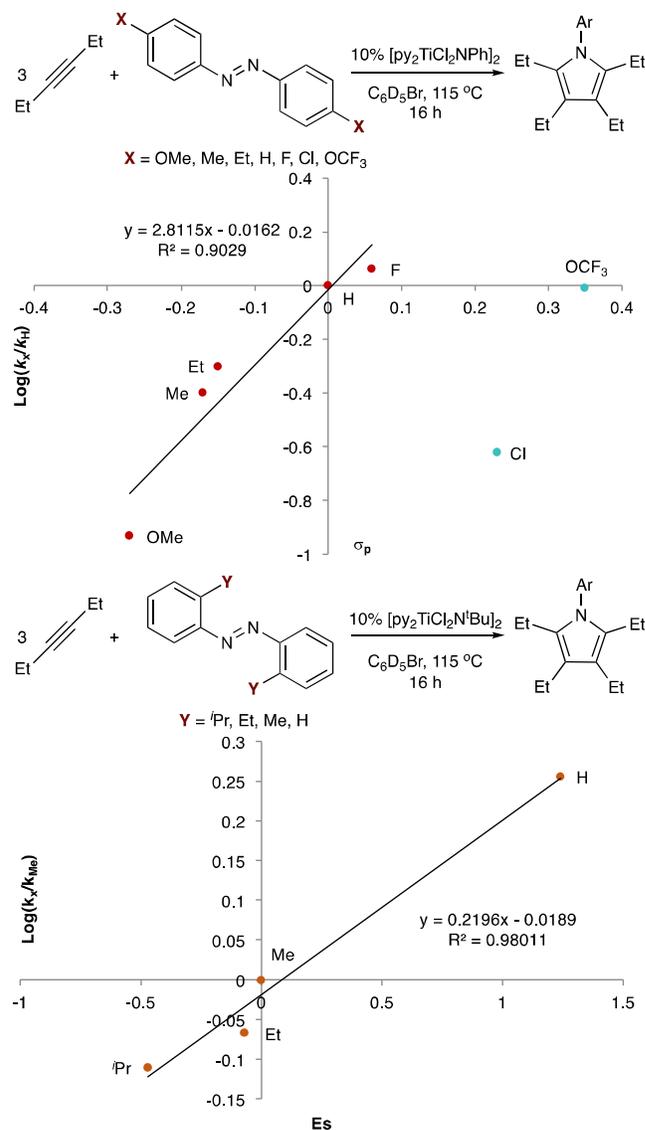


Figure 17. Hammett (top) and Taft (bottom) plots of substituted diazenes. Reaction conditions can be found in Table S4.

4. CONCLUSION

In conclusion, experiment and theory have shown that Ti-catalyzed [2+2+1] synthesis of pyrroles from alkynes and aryl diazenes proceeds through a unique electrocyclic reductive elimination mechanism. The crux of this mechanism is that low valent Ti^{II} intermediates can be stabilized both through backdonation into the reaction products and by solvent effects. In all cases, 2nd alkyne insertion into a titanacyclobutene is rate determining,

although complex equilibria prior to the rate determining step can significantly alter the reaction rate and selectivity. Importantly, computational analysis has allowed us to separate out the stereoelectronic effects that influence reaction selectivity in each step involving alkyne reactivity ([2+2] cycloaddition and 1,2-insertion), which will allow for the new development of ligands and catalysts capable of controlling regioselectivity of multisubstituted pyrrole synthesis. Additionally, a key feature of this reaction is that there is no single reaction component that is critical in stabilizing intermediates or transition states throughout the catalytic cycle, indicating that it should be possible to translate this type of reactivity beyond simple pyrrole synthesis and into more broad classes of oxidative catalysis.

ASSOCIATED CONTENT

Supporting Information

Full experimental, kinetic, and computational details are provided in the supporting information (PDF).

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