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Multicomponent Pyrazole Synthesis from Alkynes, Nitriles, and Titanium Imido Complexes via Oxidatively Induced N–N Bond Coupling

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Abstract

Pyrazoles are an important class of heterocycles found in a wide range of bioactive compounds and pharmaceuticals. Pyrazole synthesis often requires hydrazine or related reagents where an intact N–N bond is conservatively installed into a pyrazole precursor fragment. Herein, we report the multicomponent oxidative coupling of alkynes, nitriles, and Ti imido complexes for the synthesis of multisubstituted pyrazoles. This modular method avoids potentially hazardous reagents like hydrazine, instead forming the N–N bond in the final step via oxidation-induced coupling on Ti. The mechanism of this transformation has been studied in-depth through stoichiometric reactions of the key diazatitanacyclohexadiene intermediate, which can be accessed

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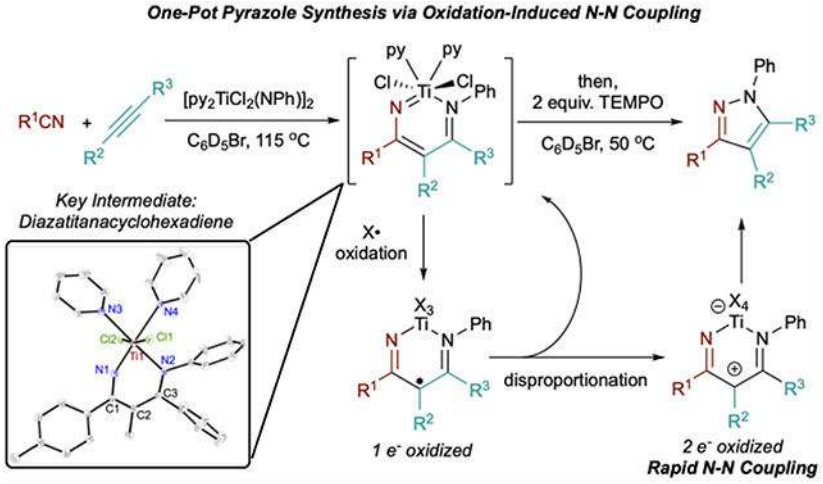
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13173.
Full experimental and computational details, including Figures S1-S109 and Tables S1 and S2 (PDF) CIF files for 5a, 6a, 7a, 7b, 9a, 10a, and S1 (ZIP)

via multicomponent coupling of Ti imidos with nitriles and alkynes, ring opening of 2-imino-2*H*-azirines, or direct metalation of 4-azadiene-1-amine derivatives. The critical transformation in this reaction is the 2-electron oxidation-induced N–N coupling on Ti. This is a rare example of formal N–N coupling on a metal center, which likely occurs through an electrocyclic mechanism analogous to a Nazarov cyclization. Conveniently, these 2-electron-oxidized diazatitanacyclohexadiene intermediates can be accessed via disproportionation of the 1-electron-oxidized species, which allows utilization of weak oxidants such as TEMPO

Graphical Abstract



INTRODUCTION

Pyrazoles are an important class of N–N-bond-containing heterocycles found in flagship pharmaceuticals such as Eliquis, Viagra, Celebrex, and Acomplia.[1–3] Multisubstituted pyrazoles are most commonly synthesized via the Knorr condensation of hydrazines onto 1,3-diketones[4–6] or through a 1,3-dipolar cycloaddition of hydrazones with alkynes or electron-deficient alkenes after autoxidation.[7–15] Direct N–N bond formation is an attractive alternative to these classical methods, as it would remove the need to use potentially toxic and/or explosive hydrazine reagents. However, N–N bond-forming methods are limited, particularly those proceeding through formal reductive elimination at a transition metal center. This is due to the unfavorable thermodynamics of N–N bond reductive elimination, which results in a weak N–N bond at the expense of two strong metal–N bonds. Despite this challenge, there are a few elegant examples of late transition metal facilitated N–N bond reductive eliminations: (1) Cu-catalyzed or -mediated synthesis of pyrazoles from nitriles and enamines (Figure 1a),[16,17] as well as a few related transformations[18–22] and (2) a stoichiometric example featuring a binuclear Ni complex which couples triazabicyclodecene ligands after oxidation with hypervalent iodine reagent PhICl2 (Figure 1b).[23] In the pyrazole examples, the aromaticity gained provides driving force to overcome the otherwise weak N–N bond (approximately 24 kcal/mol for the parent pyrazole[24]). In the binuclear Ni example, generation of high-valent metal centers makes reductive elimination more favorable. Oxidatively induced reductive elimination is a common strategy employed in late-transition-

metal organometallic chemistry to overcome otherwise challenging couplings.[25–32] Moreover, increasing the oxidation state of the system as a whole has been shown to increase the electrophilicity of the *ligands* toward nucleophilic coupling.33 Other aerobically triggered reductive eliminations have been reported for the synthesis of hydrazines and azoarenes,34 and there is also an example of air oxidation of a d^0 yttrium triamide complex that liberates aminyl radicals competent for N–N coupling.35

Our group has produced several examples of early transition metal-catalyzed oxidative aminations of alkynes for the synthesis of pyrroles,[36–40] which proceeds through an electrocyclic reductive elimination to form a C–N bond from an azatitanacyclohexadiene intermediate (Figure 1c, bottom right).[41] We envisioned that reaction of an analogous diazatitanacyclohexadiene[42,43]–formed from the reaction between a nitrile and the common azatitanacyclobutene intermediate[44–54]–could result in a formal N–N bond reductive elimination to produce multisubstituted pyrazoles, either through catalytic turnover with azobenzene as an oxidant or by further reaction with an exogenous oxidant (Figure 1c, bottom left). Herein, we report an example of oxidation-induced N–N bond reductive elimination, yielding pyrazoles from diazatitanacyclohexadienes (Figure 1c, top). These diazatitanacyclohexadienes can be generated from the coupling of an alkyne and a nitrile with a Ti imido complex, providing a practical and simple multicomponent [2+2+1] route to pyrazoles. Mechanistic studies indicate that N–N coupling is triggered by 2-electron oxidation of the diazatitana- cyclohexadiene, which generates an intermediate that can undergo electrocyclic ring closure in analogy to a Nazarov-type cyclization.

RESULTS AND DISCUSSION

Multicomponent Coupling for the Synthesis of Pyrazoles

Initial catalytic multicomponent coupling attempts of azobenzene, alkynes, and nitriles catalyzed by $[py_2TiCl_2(NPh)]_2$, were met with limited success. For example, reaction of *p*-tolunitrile, 3-hexyne, and azobenzene for 20 h at 145 °C yields 16% of the desired 4,5-diethyl-*N*-phenyl-3-*p*-tolylpyrazole (l) in addition to 57% *N*-phenyl-3-hexanimine (2) and 9% 2,3,4,5-tetraethyl-*N*-phenylpyrrole (3) (Figure 2). Although the yield of 1 is lower than the catalyst loading, we were able to demonstrate catalytic turnover using a labeled azobenzene, ArNNAr (Ar = *p*-$(CF_3O)C_6H_4$), which showed incorporation of both Ph (from the precatalyst) and Ar into the pyrazole product (Table S2).

A potential mechanism for the multicomponent catalytic reaction was computed in analogy to our previous multicomponent synthesis of pyrroles (Figure 3). Computations indicate that the key intermediate diazatitanacyclohexadiene **IM5-pyz** is very stable ($\Delta G = -17.4$ kcal/mol relative to $py_3TiCl_2(NPh)$) and the barrier to N–N reductive elimination (TS3-pyz 47.1 kcal/mol from **IM5-pyz**) is overwhelmingly high. In fact, ^1H NMR monitoring of the reaction shows the formation of a new species consistent with the structure of **IM5-pyz** at 90% yield relative to catalyst within 10 min, suggesting the stability of **IM5-pyz** is inhibitive for productive catalysis. While the formation of 1a demonstrates that diazatitanacyclohexadiene **IM5-pyz** or another analogous species is capable of N–N coupling, we suspect that the high barrier to ring closure likely facilitates competitive acid/base chemistry to occur, ultimately leading to hydroamination. In fact, protonated

diazatitanacycles crystallize from the reaction mixture (see Supporting Information). Thus, unlike previous examples of Ti-catalyzed nitrene transfer, PhNNPh may not be a strong enough oxidant to drive productive N–N bond-forming catalysis.

Diazatitanacyclohexadiene Synthesis

We next synthesized several diazatitanacyclohexadiene model complexes in order to study potential routes to productive N–N bond formation with other oxidants beyond PhNNPh (Figure 4). Protonolysis of TiCl2(NMe2)2 with a 4-azadiene-1-amine (H_2ADA) (4a) gives ($HNMe_2$)$TiCl_2$(ADA^{Ph}) (5a) in 46% isolated yield. Reaction of H_2ADA (4a, 4b) with $TiCl_4(THF)_2$ in THF followed by the addition of 2 equiv of LiHMDS (HMDS = hexamethyldisilazide) produces the dinuclear species $[TiCl_2(ADA)]_2$ (6a, 6b), which is bridged through the imido ligands. Treatment of 6a and 6b with pyridine generates py_2TiCl_2(ADA) (7a, 7b) in 30% crystallized yield. The X-ray crystal structures for 5a and 7a are shown in Figure 4. 5a, 7a, and 7b all have similar solid-state metrics and contain a titanium vinylimido with a pendent imine donor. For example, 7a has a Ti1–N1 distance of 1.768(1) Å, indicative of Ti–N imido multiple bonding, and a Ti1–N2 distance of 2.126(1) Å, indicative of a Ti–N imine dative bond. These bond lengths are consistent with the computed values for **IM5-pyz** (Figure 3, bottom), where Ti1–N1 and Ti–N2 were computed to be 1.71701 and 2.10562 Å, respectively. Further reactions were carried out with 7a and 7b because the $HNMe_2$ ligand in 5a can potentially participate in deleterious acid/base reactions.

Diazatitanacyclohexadiene Oxidation

Although 7a and 7b are both Ti^{IV}, we hypothesized that ligand-based oxidation could increase the electrophilicity of N_α and promote N–N coupling in analogy to late transition metal-based oxidations that induce reductive elimination. In fact, several oxidants promote facile, room temperature N–N coupling with 7a and 7b (Table 1). Reaction of 7a and 7b with 2 equiv of TEMPO resulted in 80% isolated yield of the N–N coupled pyrazole product **1a** or **1b** after 2 h (Table 1, entry 1), respectively. When the reaction is performed with 1 equiv of TEMPO, a 1:1 mixture of unreacted **7a** and pyrazole **1a** is observed, which is indicative of a net 2-electron stoichiometry requirement for the reaction (Table 1, entry 2). Likewise, hypervalent iodine reagents $PhICl_2$, $PhI(TFA)_2$, and $PhI(OAc)_2$ all resulted in good yields of **1a** or **1b** (Table 1, entries 3–5). Interestingly, oxidation of **7a** by $PhI(OAc)_2$ (Table 1, entry 5) results in an initial mixture of **1a** with a kinetic azirine product (**8a**), which slowly converts to **1a** over time. Intermediacy of **8a** could indicate potential free nitrene reactivity[55–57] or transmetalation to I, but control experiments rule out these possibilities (Figures S90 and S96). The intermediacy of **8a** was not evident in any other reaction. Other oxidants also engender productive N–N coupling, including $FcPF_6$ (Fc = Cp_2Fe^+) and even O_2, albeit in lower yields. Prolonged exposure of **7a** to PhNNPh even at elevated temperatures (up to 145 °C) did not furnish tractable amounts of **1a**, consistent with early catalytic attempts. Thermolysis of **7a** in the absence of any oxidant also only led to trace amounts of **1a**. N–N bond coupling was not observed when reacting with several common oxidants such as I_2, NBS, $NOBF_4$, and Me_3NO, instead leading to intractable mixtures.

In Situ Multicomponent Pyrazole Synthesis

One-pot multicomponent synthesis via alkynes and nitriles is an attractive, unrealized, and simple route to pyrazoles. Given that diazatitanacycles have been observed as long-lived intermediates in our initial catalytic reaction attempts, it seemed plausible that they could be generated *in situ* by reaction of an alkyne and nitrile with a Ti imido and then oxidized to generate the desired pyrazole product in a one-pot procedure (Table 2). Indeed, diazatitanacycles analogous to **7a** and **7b** can be synthesized in 81% in *situ* yield (^{1}H NMR) by reaction of $[py_2TiCl_2(NPh)]_2$ with an excess of *p*-tolunitrile (6 equiv; 3 equiv with respect to [Ti]) and 3-hexyne (6 equiv) in C_6D_5Br after 1 h at 115 °C (Table 2, entry 1). C_6D_5Br solvent was chosen because it is an affordable-to-access polar NMR solvent, and was successful for our previous [2+2+1] pyrrole cyclizations.[41] Addition of TEMPO after diazatitanacyclohexadiene formation, followed by heating at 50 °C for 2 h affords pyrazole **1** in 75% yield with respect to $[py_2TiCl_2(NPh)]_2$ (98% yield with respect to **IM5-pyz**). Based off of this result, comparative reactions were next carried out at a 3:3:1 and 1:1:1 stoichiometry of benzonitrile, 3-hexyne, and Ti=NR (Table 2, entries 2 and 3). While the 1:1:1 stoichiometry results in a lower conversion to the metallacyclic intermediate (Figures S54 and S57), **1b** is still generated in 56% overall yield with respect to alkyne (Table 2, entry 3). This reaction could be performed at 1 mmol scale, resulting in 65% yield of **1b** (see Supporting Information). Inferring that the alkyne and nitrile fragments may often be the more precious components of this reaction, we next briefly explored the scope of this reaction at the 1:1:1 stoichiometry. In all cases, the desired pyrazole products were furnished in moderate to good yield. This method can tolerate both electron-rich and electron-poor nitriles (entries 3–5). *p*-(Trifluoromethyl)benzonitrile affects a slightly lower yield (49%) which is explained by detectable amounts of titanacycle decomposition (entry 5). Alkyl nitriles (entries 6–8) are also effective coupling partners in the reaction; however, the yield of diazatitanacycle oxidation is poor when coupling acetonitrile to 1-phenyl-1-propyne (entry 8). 1-Phenyl-1-propyne couples with both acetonitrile and benzonitrile, affording the 5-methyl-4-phenyl regioisomers selectively (entries 8 and 9); notably, 5-alkyl-3-arylpyrazoles are challenging to access via Knorr pyrazole synthesis due to the regioselectivity of the hydrazine condensation step. Tetraarylpyrazoles, which have shown the enhancement of aggregation-induced emission,[58,59] are accessible in 37% in *situ* yield for pyrazole **1j** (entry 11) or 42% isolated yield when diphenylacetylene (**1k**) is used (see Supporting Information). This scope demonstrates that multisubstituted pyrazoles can be accessed directly and generally in a single step through multicomponent coupling of Ti imidos, while avoiding prerequisite hydrazine or hydrazine-derived coupling partners. Conveniently, $[py_2TiCl_2(NPh)]_2$ and derivatives thereof can be prepared in a single pot from $TiCl_4(THF)_2$, and demonstrated benchtop-compatible Ti imido generation.[60] Thus, access to these multicomponent coupling reactions does not require specialized equipment or protocols.

Mechanistic Studies of N–N Coupling

N–N coupling on Ti could plausibly occur through one (or more) of three possible oxidation states–either the “default” oxidation state, 1-electron-oxidized, or 2-electron-oxidized (Figure 5, top). In order to determine the system oxidation state that triggers N–N coupling

on Ti, we sought to conduct N–N coupling reactions with the entire redox series. Previous work in our group has shown that Cp_2Ti(BTMSA) (BTMSA = bis(trimethylsilyl)acetylene)[61–65] rapidly ring-opens 2*H*-azirines at the C–N bond.[66] Thus, we hypothesized 2-imino-2*H*-azirine **8a**–an isomer of pyrazole **1a**–could react with a Ti^{II} source to give a diazatitanacyclohexadiene in the "default" oxidation state. By extension of this logic, reacting 2-imino-2*H*-azirines with Ti^{III} and Ti^{IV} precursors could allow for interrogation of 1- and 2-electron-oxidized diazatitana- cyclohexadiene species, respectively.

The reaction of Ti^{II}, Ti^{III}, and Ti^{IV} precursors with the 2-imino-2*H*-azirine **8a** is shown in Figure 5. Reaction of **8a** and Cp_2Ti(BTMSA) rapidly gives the expected diazatitanacyclohexadiene $Cp_2Ti(ADA^{Ph})$ (**9a**) in 89% yield (Figure 5, reaction II). Interestingly, XRD analysis of **9a** (Figure 6) shows a Til–N1 bond distance of 1.857(l) Å and a Til–N2 distance of 2.12l(l) Å, indicating an iminyl-enamide bonding description for this complex, contrasting the vinylimidoimine resonance form in complexes **5a, 7a,** and **7b** (Figure 4). Consistent with earlier results with **7a** and **7b**, no N–N coupling occurs from **9a** in this oxidation state.

Having shown that Ti^{II} reacts cleanly with **8a** to give diazatitanacyclohexadiene **9a**, we moved to investigate the in *situ* formation of a diazatitanacycle radical via radical ring opening of **8a** by $TiCl_3(THF)_3$ (Figure 5, reaction III) A benzene solution of **8a** reacts instantaneously with a benzene slurry of $TiCl_3(THF)_3$ yielding a 1:1 mixture of pyrazole **1a** and presumably the "default" oxidation state diazatitanacycle, $(THF)_xTiCl_2(ADA^{Ph})$ (**7a-0e**$^-$). Addition of 2 equiv of pyridine generates **7a** with the gradual precipitation of a yellow solid presumed to be $(py)_2TiCl_4$. The formation of equal parts pyrazole **1a, 7a**, and $TiCl_4$ strongly suggests the initial formation of diazatitanacycle radical $TiCl_3(ADA^{Ph\cdot})$ (**7a-1e**$^-$), followed by disproportionation into the "default" oxidation state and the 2-electron-oxidized species **7a-2e**$^-$, which then couples to form pyrazole.

Given the disproportionation reactivity with Ti^{III}, we then tested the reactivity of 2-imino-2*H*-azirines with Ti^{IV} (Figure 5, reaction IV). Treatment of azirine **8a** with $TiCl_4(THF)_2$ generates an unidentified intermediate species, which upon heating to 50 °C results in conversion to **1a** as the major product. Alper demonstrated that $TiCl_4$ will ring open 2*H*-azirines, in which γ-chlorination occurs after C–N bond cleavage.[67] By analogy, 2-imino-2*H*-azirines likely undergo similar reactivity to form **7a-Cl-2e**$^-$, which can then undergo N–N coupling upon chloride loss. Consistent with this mechanism, there are examples of late transition metal-catalyzed 2-acyl-2*H*-azirine or 2-imino-2*H*-azirine rearrangements to isoxazoles or pyrazoles, respectively, that may proceed through similar vinyl-nitrenoid intermediates.[68–71]

Reactivity of $Cp_2Ti(ADA^{Ph})$ (9a) with $PhICl_2$

The 2*H*-azirine ring-opening redox series in Figure 5 strongly suggests that N–N coupling to form pyrazoles occurs through the 2-electron-oxidized diazatitanacycle of the form **7a-2e**$^-$. We next aimed to synthesize analogues of the **7a-2e**$^-$ intermediate and observe their direct N–N coupling reactivity. We hoped that the stability imbued by the titanocene moiety in **9a** would allow for isolation of an intermediate in the $PhICl_2$ oxidations of

diazatitanacyclohexadienes. Mixing a dark claret C_6D_6 solution of **9a** with $PhICl_2$ at room temperature immediately furnishes a bright yellow solution, yielding 10a quantitatively (Figure 6), which exists as two isomers. The solid-state structure of **10a** (Figure 6) reveals chlorination of Ti and the C_γ position of the diazatitanacyclohexadiene ring. **10a** is a "2-electron-oxidized" organic moiety, similar to the proposed azirine ring-opened product from $TiCl_4(THF)_2$ **7a-Cl-2e**$^-$ (Figure 5, reaction IV) and Alper's earlier observations of γ-chlorination. However, steric encumbrance imposed by the Cp rings in **10a** likely prevents imine coordination to Ti. Interestingly, **9a** does not react with TEMPO, which may indicate that reaction of TEMPO with **7a** initially requires coordination to Ti.

Refluxing **10a** in C_6D_6 for 22 h gives pyrazole **1a** and Cp_2TiCl_2 as the major products (Figure 6), consistent with 2-imino-2*H*-azirine ring-opening by $TiCl_4(THF)_2$. The slower rate of decomposition of 1**0a** into pyrazole compared to the reaction of **8a** and $TiCl_4$ is likely due to the hindered approach of the imine during N–N coupling. Further, cyclic voltammetry of **9a** features a quasi-reversible 1-electon oxidation at –0.55 mV vs $Fc^{0/+}$ which exhibits fully reversible behavior at scan rates ≥200 mV/s (Figure 7). A linear dependence of i_{pa} on $\nu^{1/2}$ was observed, consistent with a mass-transfer-limited process. This suggests that the quasi-reversibility of **9a** oxidation at low scan rates arises from a chemical event coupled to oxidation, which, based on the 2-imino-2*H*-azirine reactivity above, is likely related to disproportionation of the 1-electron-oxidized $Cp_2Ti(ADA^{Ph\bullet})$ en route to **1a** formation. Notably, no other current deflection is observed in the anodic sweep before oxidation of the supporting electrolyte at ~700 mV.

Discussion of the Mechanism of Oxidatively Induced N–N Coupling Mediated by Ti

We propose the mechanism for N–N coupling in Figure 8 based on the stoichiometric oxidations of **7a,b,** the 2*H*-azirine **8a** ring-opening reactivity with various Ti oxidation states, and the reactivity and electrochemistry of **9a**. First, multicomponent coupling of a Ti imido with an alkyne and nitrile via the previously established [2+2]/insertion mechanism[44,49] gives diazatitanacycle **A**, arbitrarily considered to be in the "default" oxidation state of this system. As demonstrated in the series of redox experiments above (Figure 5, reaction II), **A** can also be accessed via ring-opening of 2-imino-2*H*-azirines by a Ti^{II} precursor such as $Cp_2Ti(BTMSA)$. The barrier for N–N reductive elimination from **A** is too high, facilitating entry into competitive decomposition pathways. Single-electron oxidation of **A** leads to the 1-electron-oxidized diazatitanacycle **B**, which is unstable. From **B**, there are two possible reaction pathways: (1) disproportionation to **A** and 2-electron-oxidized **C**, which undergoes rapid N–N coupling to form **1** and a TiX_4 coproduct, or (2) further oxidation to **D**, as seen in the oxidation of **9a** to **10a** by $PhICl_2$. The reaction of **8a** with $TiCl_3(THF)_3$, which results in 50% N–N coupled **1a** and 50% of the "default" oxidation state **7a** (Figure 5, reaction III), provides evidence for disproportionation. Further, weak oxidants such as TEMPO or $FcPF_6$ result in product formation despite an inability to oxidize **7a** by two electrons, indicating that a disproportionation mechanism is likely in play.

Although **D** is also 2-electron-oxidized like **C**, C–X dissociation to **C** is likely necessary for rapid N–N coupling to occur. Evidence for this can be seen in several reactions. For example, reaction of $TiCl_4(THF)_2$ with **8a** (Figure 5, reaction IV) results in full conversion

to **1a**, but the reaction is slower than that of $TiCl_3(THF)_3$ and requires heat to drive it to completion. Based on work from Alper, reaction IV likely generates an intermediate analogous to **D**. Thus, the major difference between the oxidized diazatitanacycles in reactions III and IV is the presence of an extra equivalent of Cl^- in IV; indicating that dissociation of halide from **D** to make the carbocationic diazatitanacycle **C** is likely kinetically relevant. Further evidence for the role of X^- dissociation from **D** may also be seen in the overall yields with hypervalent iodine oxidants presented in Table 1: reactions with anion equivalents that would be poor leaving groups (e.g., OAc^-) generally result in lower yields than more weakly coordinating anion equivalents and/or better leaving groups (Cl^-, $O_2CCF_3^-$).

Based on the above evidence, the 2-electron-oxidized diazatitanacycle C is likely responsible for rapid N–N bond formation, which depending on oxidant strength can be accessed either through disproportionation of a 1-electron-oxidized species or directly through 2-electron oxidation. We have previously established in related [2+2+1] pyrrole syntheses that C–N bond reductive elimination from a 6-membered azatitanacycle proceeds through an electrocyclic mechanism. Here, oxidation of the diazatitanacycle should make the α-N significantly more electrophilic, prompting ringclosure in analogy to a Nazarov-like electrocyclization (Figure 9). The kinetic slowdown in the presence of coordinating anions is further evidence for an electrocyclic mechanism: intermediate **C**, with full π-conjugation, undergoes rapid reaction, whereas intermediate **D** lacks the conjugated π-system requisite for electrocyclization.

CONCLUSION

In summary, we have shown that simple titanium imido complexes are capable of selective coupling with alkynes and nitriles to generate diazatitanacyclohexadienes, which can be oxidized under mild conditions to generate pyrazoles in good yield. By exploring an electrochemical series of 2-imino-2*H*-azirine ring openings with Ti^{II}, Ti^{III}, and Ti^{IV}, we have demonstrated that Ti-mediated N–N coupling occurs from 2-electron-oxidized diazatitanacyclohexadienes via a potentially electrocyclic process. While oxidatively induced reductive elimination has been extensively explored, the concept of d^0 transition metals mediating oxidatively induced couplings through ligand-centered oxidations may be a general strategy for accessing new reactivity and myriad new types of metal- mediated bond couplings, particularly via these types of electrocyclic pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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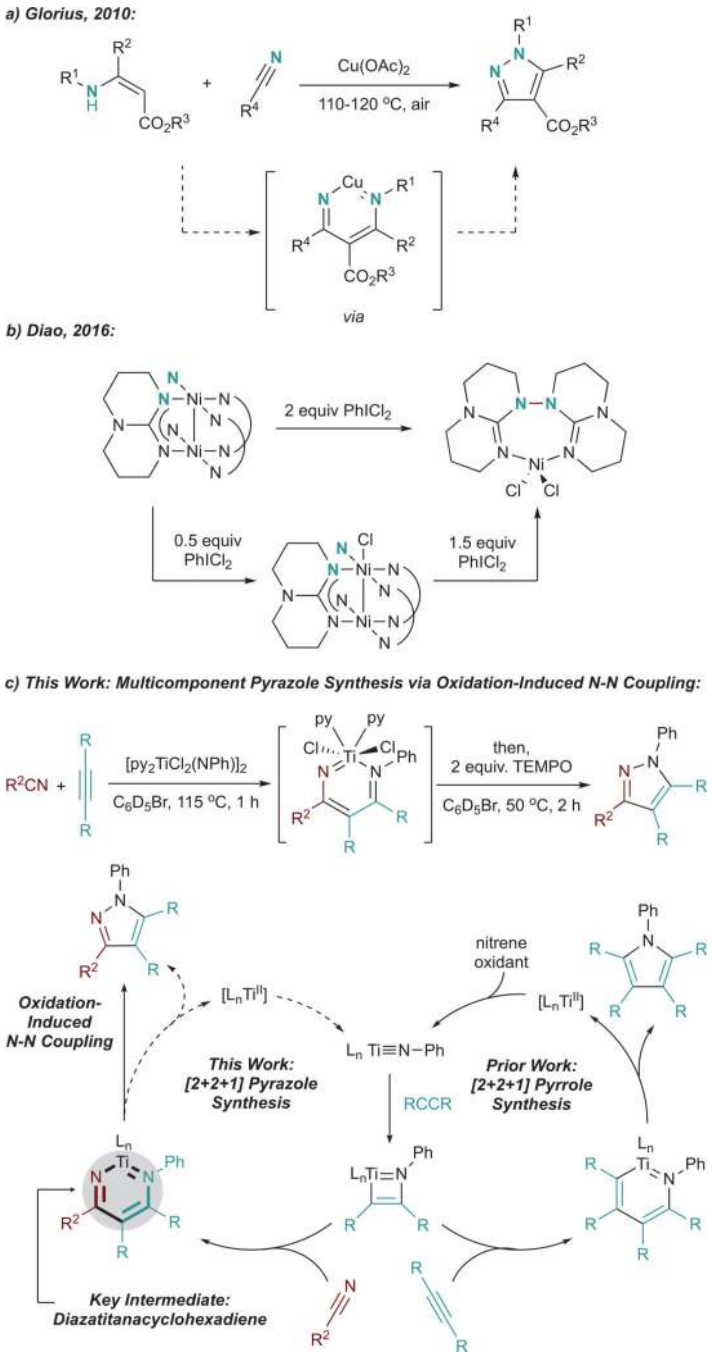


Figure 1.

(a) Cu-catalyzed oxidation-induced formal N–N reductive elimination for the synthesis of pyrazoles from electron-poor enamines and nitriles. (b) Ni-mediated N–N bond reductive elimination. (c) Formal [2+2+1] multicomponent synthesis of pyrazoles via oxidation-induced N–N coupling, and a proposed catalytic cycle for pyrazoles compared to the previously reported [2+2+1] synthesis of pyrroles.

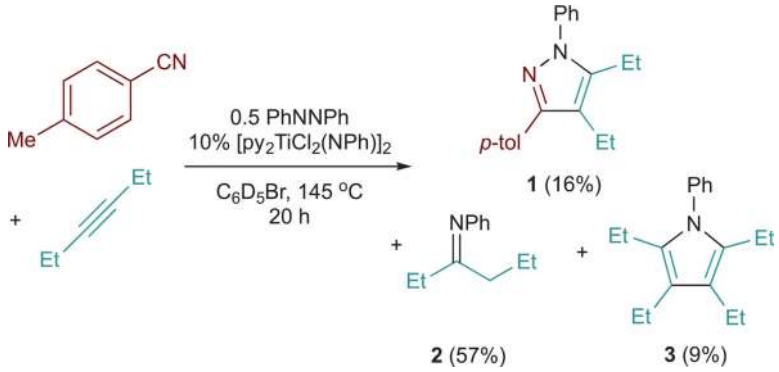


Figure 2.

Multicomponent coupling of p-tolunitrile, 3-hexyne, and azobenzene catalyzed by $py_2TiCl_2(NPh)$.

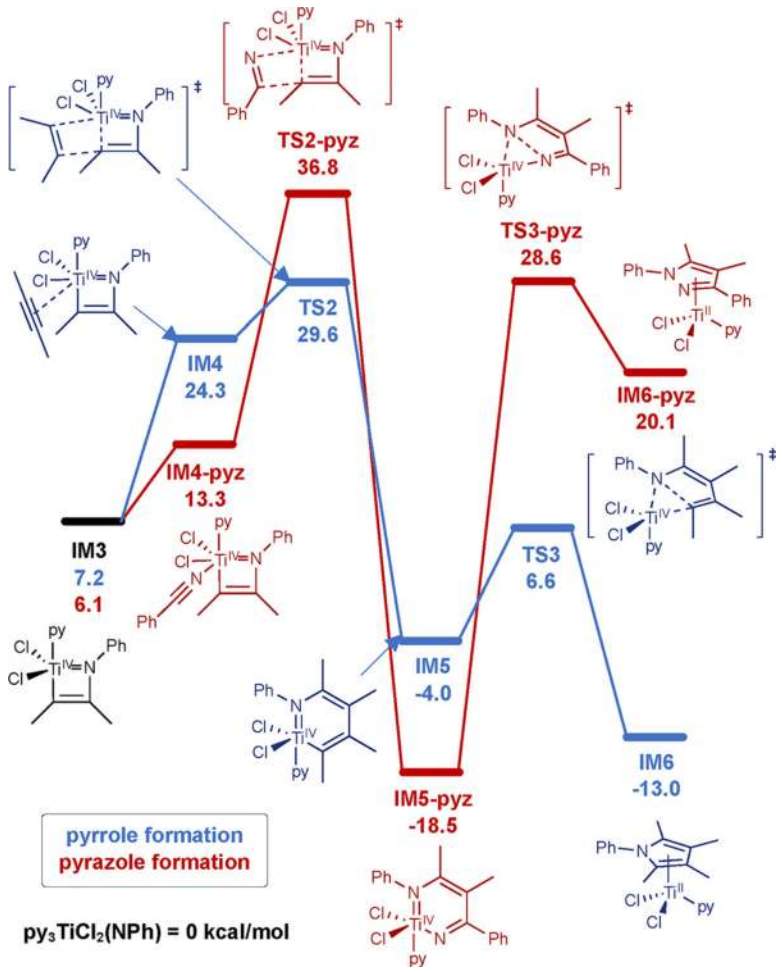


Figure 3.

Computed cycle for pyrazole formation via direct N–N bond coupling (M06/6–311G(d,p)/SMD, 145 °C, C_6D_5Br) compared to C–N bond formation in the analogous multicomponent pyrrole synthesis (M06/6–311G(d,p)/SMD, 115 °C, PhCF3) by Ti imido catalysts. Pyrrole computations and intermediate labels are adapted from ref 37. All free energies are referenced to py3TiCl2(NPh) = 0.0 kcal/mol.

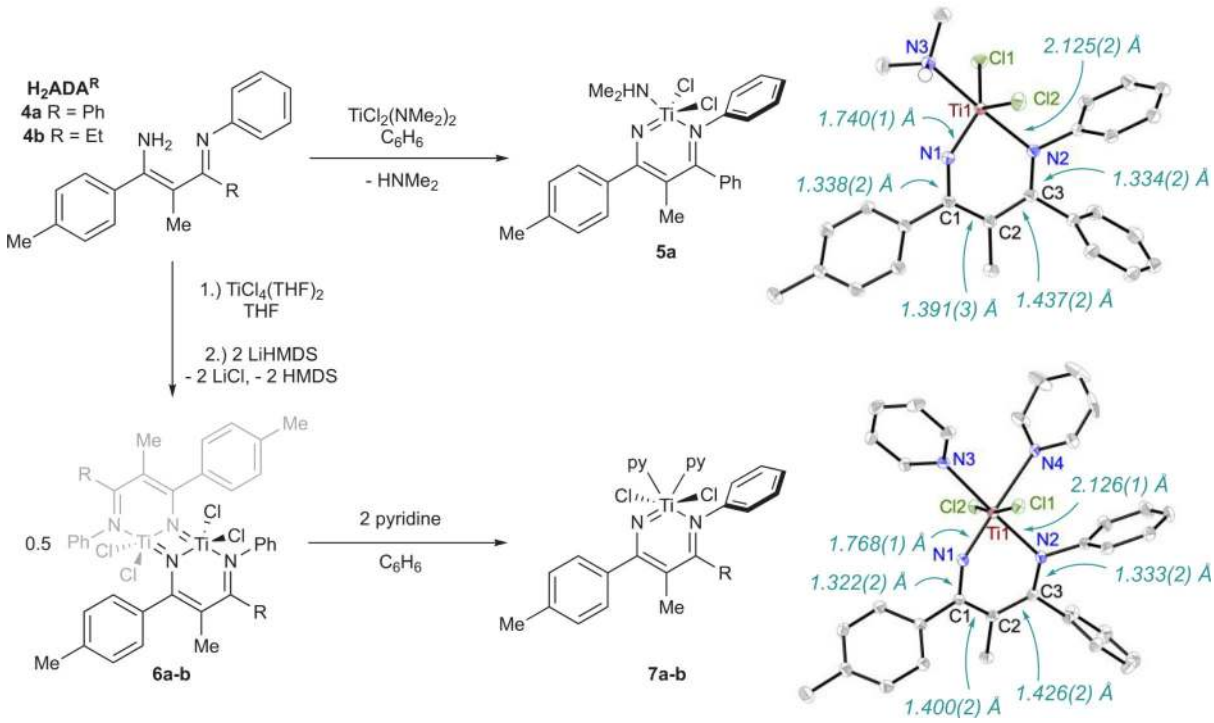


Figure 4.

Syntheses of diazatitanacyclohexadienes **5a, 7a,** and **7b** and ORTEP diagrams of **5a** and **7a**. Thermal ellipsoids are drawn at 50% probability and hydrogen atoms omitted for clarity. Full crystallographic data for **5a, 7a,** and **7b** is available in the Supporting Information.

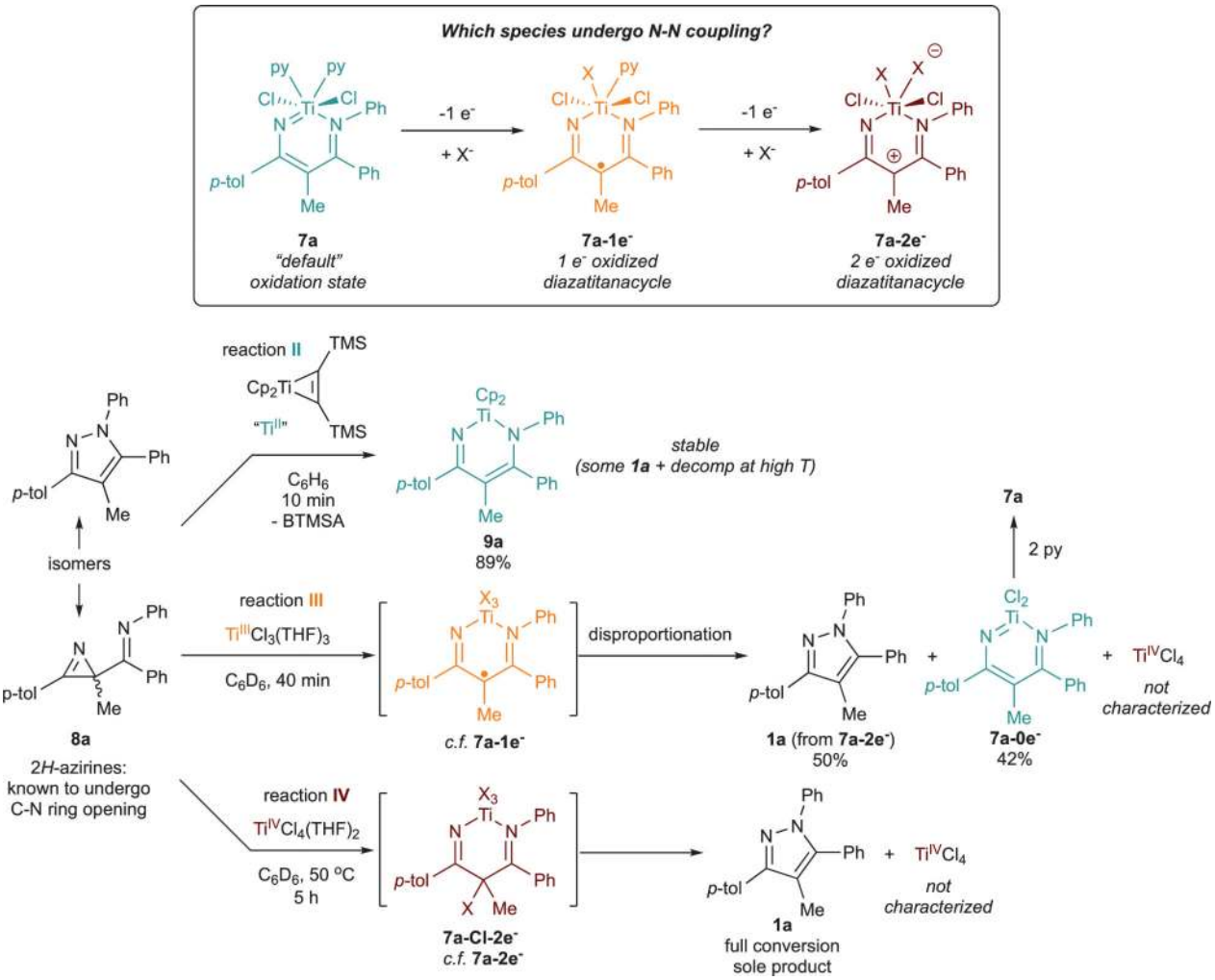


Figure 5.

Reaction of **8a** with a series of Ti complexes spanning Ti^{II}, Ti^{III}, and Ti^{IV} oxidation states.

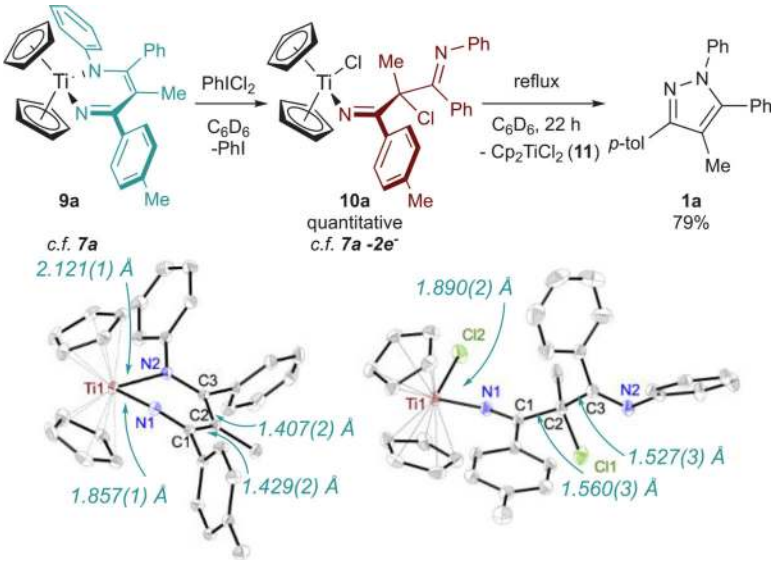


Figure 6.

Oxidation of **9a** to **10a** by $PhICl_2$ followed by thermal elimination of Cp_2TiCl_2 to give **1a**, and ORTEP diagrams of **9a** and **10a**. Thermal ellipsoids are drawn at 50% probability, and hydrogen atoms are omitted for clarity. One crystallographically independent molecule of **10a** and a solvent Et_2O have also been omitted. Full crystallographic data is available in the Supporting Information, including CIF files.

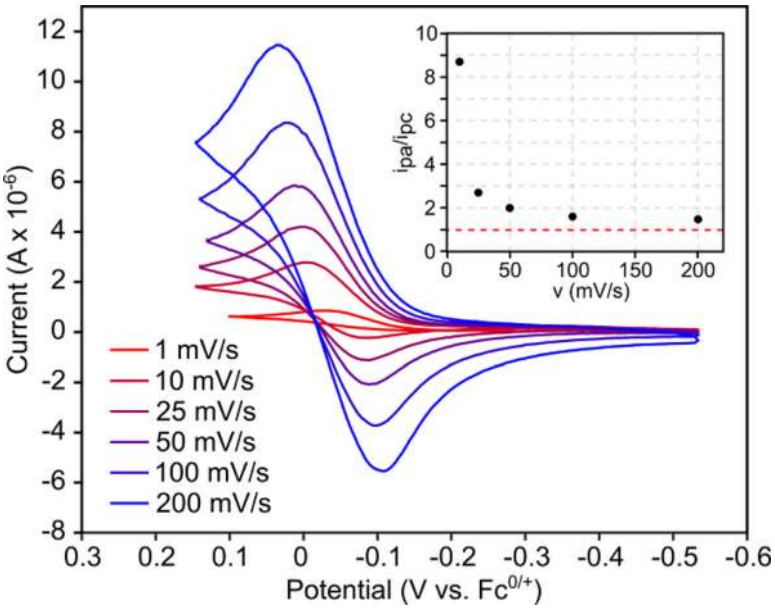


Figure 7.

Cyclic voltammogram of **9a** (DCM solvent, 3.5 mM **9a**, 0.1 M NBu4BPh4) at scan rates 1–200 mV/s (red-blue). Inset displays i_{pa}/i_{pc} as a function of scan rate.

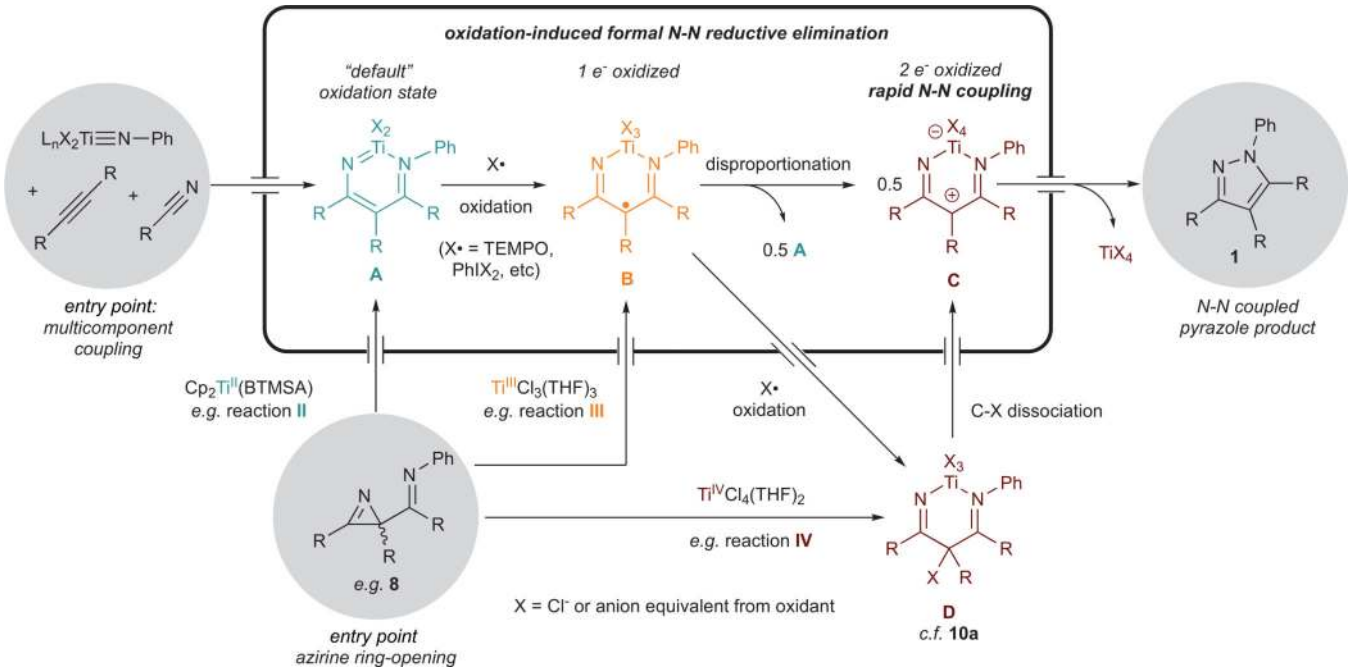


Figure 8.
Proposed mechanism for pyrazole formation from diazatitanacyclohexadienes.

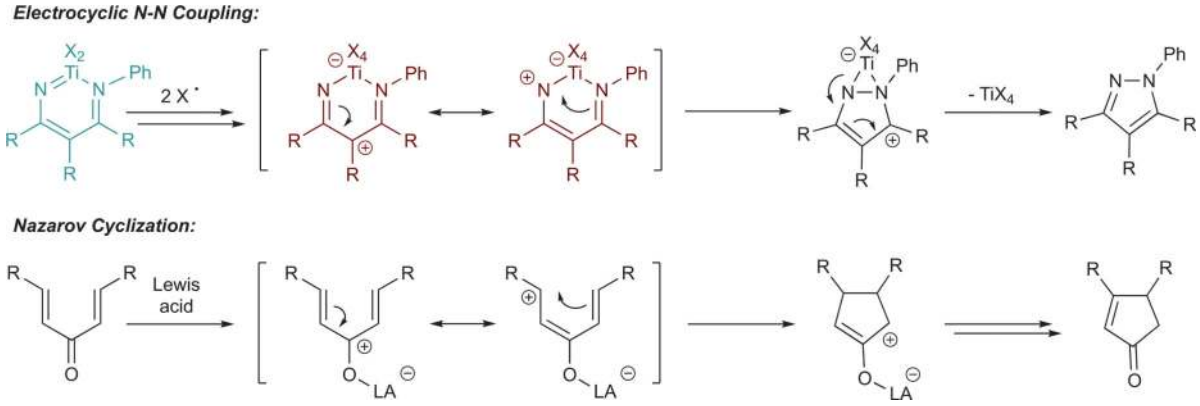
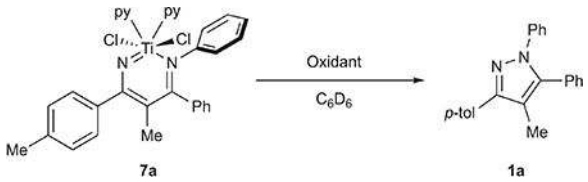


Figure 9.

Analogy between electrocyclic N–N coupling and the electrocyclic Nazarov cyclization of dienones.

Table 1.

Oxidation of 7a with Various Oxidants[a]



7a **1a**

entry	oxidant	time (h)	*T* (°C)	yield (%)
1	TEMPO (2 equiv)	2	50	87(80[b])
2	TEMPO (1 equiv)	2	50	40
3[c]	$PhICl_2$	3	rt	70
4[c]	$PhI(O_2CCF_3)_2$	3	rt	76
5[c]	$PhI(OAc)_2$	3	rt	44
6	$FcPF_6$ (2 equiv)	16	rt	32
7	$FcPF_6$(2 equiv)	70	rt	50
8	O_2(1 atm)	3	60	17

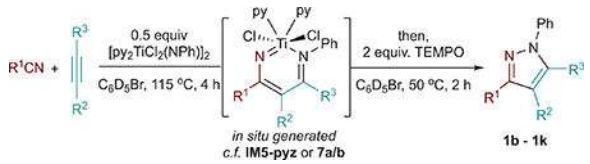
[a]Conditions: **7a** (0.02 M), oxidant (1–2 equiv), 0.5 mL of benzene. Yields are determined *in situ* via ^{1}H NMR against internal TMB standard.

[b]Isolated yield.

[c]Yields are determined via ^{1}H NMR against internal TCE standard added after the reaction.

Table 2.

Substrate Scope of One-Pot *In Situ* Pyrazole Synthesis from Alkynes and Nitriles[a]



entry	R^1	R^2	R^3	product	yield (%)
1[b]	4-Me-C_6H_4	Et	Et	**1**	75[c]
2[b]	Ph	Et	Et	**1b**	79[c]
3	Ph	Et	Et	**1b**	56
4	4-MeO-C_6H_4	Et	Et	**1c**	52
5	4-CF_3-C_6H_4	Et	Et	**1d**	49
6	^{i}Pr	Et	Et	**1e**	54
7	Me	Et	Et	**1f**	43
8	Me	Ph	Me	**1g**	28
9	Ph	Ph	Me	**1h**	54
10	Ph	Me	Me	**1i**	52
11	Ph	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	**1j**	37

[a]Conditions: 0.025 mmol of $[py_2TiCl_2(NPh)]_2$, 0.05 mmol (2 equiv) of alkyne, 0.05 mmol (2 equiv) of nitrile, 0.5 mL of PhBr, 115 °C, 4h; yields with respect to alkyne are determined *in situ* via ^{1}H NMR against internal 1,3,5-trimethoxybenzene standard.

[b]Conditions: 0.025 mmol of $[py_2TiCl_2(NPh)]_2$, 0.15 mmol (6 equiv) of alkyne, 0.15 mmol (6 equiv) of nitrile, 0.5 mL of PhBr, 115 °C, 1 h.

[c]Yields reported with respect to $[py_2TiCl_2(NPh)]_2$, which is the limiting reagent under condition B.