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Bis(imido)vanadium(V)-Catalyzed [2+2+1] Coupling of Alkynes and Azobenzenes Giving Multisubstituted Pyrroles

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Abstract

The combination of $\text{VCl}_3(\text{THF})_3$ and *N,N*-bis(trimethylsilyl)aniline (**1a**) is an efficient catalyst for the [2+2+1] coupling reaction of alkynes and azobenzenes, giving multisubstituted pyrroles. A plausible reaction mechanism involves the generation of a mono-(imido)vanadium(III) species as an initiation step, where **1a** served as an imido source with concomitant release of 2 equiv of ClSiMe_3 , followed by a reaction with azobenzene to form a catalytically active bis(imido)-vanadium(V) species via $\text{N}=\text{N}$ bond cleavage.

Multisubstituted pyrroles are synthetically valuable heteroaromatic compounds in terms of their versatility as building blocks of pharmaceuticals,¹ natural products,² functional materials,³ and dyes.⁴ Although cyclocondensation reactions such as the Paal–Knorr⁵ and Hantzsch⁶ reactions are well-established routes for synthesizing multisubstituted pyrroles, transition-metal-catalyzed multicomponent coupling reactions have been recently investigated as potent alternatives.⁷ Among them, the [2+2+1] cycloaddition reaction of alkynes and primary amines is attractive because many alkynes and primary amines are commercially available or easily synthesized.⁸ As shown in Scheme 1, AgBF_4 catalyzed the oxidative coupling of activated alkynes and primary amines in the presence of stoichiometric amounts of iodobenzene diacetate (Scheme 1a),^{8g} $\text{Cu}(\text{OAc})_2$ combined with Cs_2CO_3 under O_2 catalyzed the coupling of 2-butyndioate and primary amines (Scheme 1b),^{8c} and PdCl_2 combined with super-stoichiometric amounts of CuCl and Na_2CO_3 catalyzed the coupling of diarylalkynes and primary amines (Scheme 1c).^{8d} In these [2+2+1] cycloaddition reactions, activated alkynes bearing ester groups and stoichiometric amounts of oxidant and base were inevitably required.

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Supporting Information

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NMR characterization of complex **7** and the coupling products; full experimental details regarding the kinetic study (PDF)

X-ray crystallographic data for complex **7** (CIF)

Notes

The authors declare no competing financial interest.

Recently, we reported a formal [2+2+1] coupling of alkynes and azobenzenes that was catalyzed by (imido)titanium complexes, either preformed or *in situ* generated from $\text{TiCl}_4(\text{THF})_2$ and reductant (Scheme 1d).⁹ In an effort to expand the classes of catalysts and utility of this type of oxidative coupling, we herein report that vanadium complexes facilitate the [2+2+1] coupling of alkynes and azobenzenes, where an *in situ* generated catalyst system of $\text{VCl}_3(\text{THF})_3$ combined with *N,N*-bis(trimethylsilyl)aniline (**1a**) showed the best catalytic activity (Scheme 1e). Furthermore, we confirmed that an *in situ* generated mono(imido)vanadium(III) intermediate cleaves the $\text{N}=\text{N}$ double bond of azobenzene to give a bis(imido)vanadium(V) active species, which is responsible for the catalytic reaction, in contrast to the previously reported mono(imido)titanium(IV) active species for the Ti(II)/Ti(IV) catalytic cycle. These results highlight that diverse catalyst metals, architectures, and oxidation states can potentially play a role in complex, oxidative heterocycle-forming reactions.¹⁰

We have proposed that the previous Ti catalyst system for the [2+2+1] pyrrole formation reaction involved an (imido) titanium as the catalytically active species.⁹ Accordingly, we sought to find another effective catalyst system by varying transition metal chlorides upon activation by *N,N*-bis-(trimethylsilyl)aniline (**1a**), since some imido complexes of early transition metals have been synthesized by treating metal chlorides with **1a** with concomitant loss of 2 equiv of ClSiMe_3 .^{9b,11} Thus, we searched for the best catalyst system for [2+2+1] pyrrole formation by reacting 5-decyne (**2a**) and azobenzene (**3a**) in the presence of various metal chlorides (10 mol %) and **1a** (10 mol %) in *o*-dichlorobenzene at 170 °C for 16 h.

The results of our initial catalyst screening are summarized in Table 1. The [2+2+1] coupling product, *N*-phenyl-2,3,4,5-tetra(*n*-butyl)pyrrole (**4aa**), was obtained in 23% yield with $\text{TiCl}_3(\text{THF})_3$ and **1a**, whereas the yield of **4aa** was 4% for $\text{TiCl}_4(\text{THF})_2$ and **1a** (entries 1 and 2);¹² both reactions produced a small amount of alkyne cyclotrimerization product, hexa(*n*-butyl)benzene. In contrast, $\text{VCl}_3(\text{THF})_3$ quantitatively gave **4aa** without any contamination of hexa(*n*-butyl)benzene (entry 3). $\text{CrCl}_3(\text{THF})_3$ and $\text{MnCl}_2(\text{THF})_{1.5}$ resulted in no reaction (entries 4 and 5). In the absence of **1a**, the reactivity of $\text{VCl}_3(\text{THF})_3$ was significantly suppressed, giving **4aa** in 9% yield (entry 6). Among other early transition metal chlorides we screened in Table S1, WCl_6 showed moderate catalytic activity to give **4aa** in 65% yield.

Noteworthy was that the yield of **4aa** by a preformed (imido)vanadium(V) complex, $\text{V}(=\text{NPh})\text{Cl}_3$, was sensitively affected by the addition of **1a**: in the presence of **1a**, $\text{V}(=\text{NPh})\text{Cl}_3$ produced **4aa** in quantitative yield, whereas in the absence of **1a**, $\text{V}(=\text{NPh})\text{Cl}_3$ resulted in poor yield of **4aa** (entries 7 and 8). This result indicates that the formation of bis(imido)vanadium(V) species may be important for catalysis (*vide infra*). Bulkiness of the substituent on the imido group of the precatalyst was another factor to control the catalytic yield: $\text{V}(=\text{N}^t\text{Bu})\text{Cl}_3/\textbf{1a}$ showed high yield, while bulkier $\text{V}(=\text{N}(2,6\text{-}i\text{-Pr}_2\text{C}_6\text{H}_3))\text{Cl}_3/\textbf{1a}$ resulted in significantly lower yield (entries 9 and 10). We thus selected $\text{VCl}_3(\text{THF})_3/\textbf{1a}$ as the best catalytic system for further substrate scope.¹³

With the best catalytic system in hand, we explored the scope and limitations of alkynes for the vanadium-catalyzed pyrrole synthesis with **3a** in C₆D₅Br, and the results of the NMR yields are shown in Table 2. Coupling reactions of symmetrical aliphatic alkynes such as 3-hexyne (**2b**) and 4-octyne (**2c**) afforded the corresponding pyrroles **4ba** and **4ca** in 74% and 92% yield, respectively (entries 1 and 2), whereas the yield of **4da** from diphenylacetylene (**2d**) and **3a** was low (entry 3). The unsymmetrical alkyne, 4-methyl-2-pentyne (**2e**), produced a mixture of **4ea**, **5ea**, and **6ea** in 54% total yield with the ratio of 72:17:11 for the regioisomers (entry 4). When 1-phenyl-1-propyne (**2f**) was used as a substrate, the corresponding regioisomers of **4fa** and **5fa** were formed in the ratio of 53:47 in 34% total yield (entry 5). Regioselectivity of this reaction is assumed to be derived from the electronic effect of **2f**.^{9c} In contrast, good steric control of the regioselectivity was observed when 1-trimethylsilyl-1-hexyne (**2g**) was applied to the reaction, in which the single regioisomer **4ga** was obtained in 42% yield (entry 6). Reaction with a bulky terminal alkyne, *tert*-butylacetylene (**2h**), also afforded the single regioisomer **4ha** in 53% yield (entry 7), whereas all three regioisomers of **4ia**, **5ia**, and **6ia** were detected by using *n*-butylacetylene (**2i**) (entry 8); both terminal alkynes **2h** and **2i** produced significant amounts of alkyne cyclotrimerization byproducts, even in the presence of excess amount of azobenzene in the case of **2i**.¹⁴ We further tested the effect of various additives for synthesizing **4aa**: ether, iodoarene, nitrile, amide, and triarylphosphine (1 equiv with respect to **3a**) were tolerated in the reaction, an improved scope compared to the original Ti system (Table S4).¹⁵

We next examined the effect of the *para*-substituents of azobenzenes. The coupling reaction with 4,4'-dimethoxyazo-benzene (**3b**) or 4,4'-dimethylazobenzene (**3c**) afforded the corresponding pyrroles **4ab** and **4ac** in 66% and 69% yield, whereas reaction with 4,4'-dibromoazobenzene (**3d**) or 4,4'-bis(trifluoromethoxy)azobenzene (**3e**) resulted in the formation of **4ad** or **4ae** in 91% and 94% yield, respectively (Table S5). Hammett analysis of the catalytic reaction using **3a–e** revealed that the reaction rate was accelerated by the electron-withdrawing substituents ($\rho = 1.97$, Figure S38), being in good accordance with the tendency observed for the Ti-catalyzed system.^{9d,15} In addition, a good positive correlation was observed between the initial reaction rate and reduction potentials of azobenzenes, indicating that the reduction potential of azobenzenes is significant to determine the reaction rate (Figure S40).¹⁵

To gain insight into a reaction mechanism, we carried out a kinetic study for pyrrole formation under the optimized reaction conditions where the catalyst was *in situ* generated by treating VCl₃(THF)₃ with **1a** and analyzed the resulting data by variable time normalization analysis.¹⁶ The obtained rate law is provided in eq 1. The reaction obeyed a second-order with respect to the concentration of VCl₃(THF)₃, which was in sharp contrast to the half-order rate dependence on the catalyst concentration for the Ti-catalyzed system,^{9d} suggesting the involvement of a dimeric vanadium species for azobenzene N=N double-bond cleavage. For the substrates, we found a first-order rate dependence for the concentration of 5-decyne, while the dependency of the concentration of azobenzene was slightly deviated from a first-order rate, being 0.8.

$$\text{Rate} \propto [\text{VCl}_3(\text{THF})_3]^2 [5\text{-decyne}] [\text{azobenzene}]^{0.8} \quad (1)$$

During the catalytic reaction, an imidovanadium(III) species is assumed to be responsible for the N=N bond cleavage, giving a bis(imido)vanadium(V) species. We thus examined an *in situ* generated “V(=NPh)Cl” species for the catalytic reaction. V(=NPh)Cl₃ was treated with an organosilicon reducing reagent, *Si*-Me₄-DHP,¹⁷ in the presence of **2a** and **3a** in C₆D₅Br, giving “V(=NPh)Cl”. The stoichiometry of this reaction was clarified by the observation of 2 equiv of ClSiMe₃ and 1 equiv of 2,3,5,6-tetramethylpyrazine (Me₄-pyrazine) by ¹H NMR analysis (Figure S44).¹⁵ Subsequent treatment of the reaction mixture at 145 °C for 20 h resulted in the formation of **4aa** in 91% yield, indicating that a similar imidovanadium(III) species may be generated from VCl₃(THF)₃ and **1a** in the reaction mixture.

We further examined the reaction of the *in situ* generated imidovanadium(III) species “V(=NPh)Cl” with **3a** in toluene at 80 °C, followed by subsequent addition of PMe₃ to trap a bis(imido)vanadium complex, V(=NPh)₂Cl(PMe₃)₂ (**7**), in 63% yield (eq 2). In this reaction, half an equivalent of **3a** with

(2)

respect to V(=NPh)Cl₃ was consumed. The molecular structure of **7** was confirmed by NMR and single-crystal X-ray diffraction analysis (Figure 1).¹⁸ Complex **7** catalyzed the pyrrole formation in the presence of B(C₆F₅)₃ as a phosphine scavenger in 88% yield (eq 3), clearly indicating that the

(3)

bis(imido)vanadium(V) species is a catalytically relevant species. We also found that complex **7** was generated by treating VCl₃(THF)₃ with **1a** in the presence of **3a** in C₆D₅Br at 145 °C followed by addition of PMe₃.¹⁵

On the basis of the kinetic study and the control experiments, we propose a plausible catalytic cycle for the vanadium-catalyzed [2+2+1] coupling of 5-decyne (**2a**) and azobenzene (**3a**) (Scheme 2). Reaction of $\text{VCl}_3(\text{THF})_3$ with **1a** generates an on-cycle mono(imido)vanadium(III) species **A** together with a release of 2 equiv of ClSiMe_3 under the reaction conditions. The V(III) species **A** reductively cleaves the $\text{N}=\text{N}$ double bond of **3a** upon reaction with half an equivalent of **3a**, giving a bis(imido)vanadium species **B**,¹⁹ presumably through a dimerization process similar to that proposed for the Ti system.^{9d,e} This is consistent with the second-order rate dependence on the concentration of the catalyst and the requirement of the imido ligand for showing high catalytic activity. In addition, formation of **B** is consistent with the generation of **7** after exposure of $\text{VCl}_3(\text{THF})_3$ to **1a** and **3a** under the reaction conditions and trapping with PMe_3 . One of two $\text{V}=\text{N}$ moieties in **B** reacts with alkyne via [2+2] addition to form an azavanadacyclobutene **C**.²⁰ Next, subsequent insertion of the second alkyne into the $\text{V}-\text{C}$ bond affords an azavanadacyclohexadiene intermediate **D**. The formation of azametallacyclohexadienes from imidometal complexes and alkynes was already noted for molybdenum,^{21b} tungsten,^{21b} titanium,^{21a} and zirconium^{21c} complexes. After the second insertion, reductive elimination from **D** forms the corresponding pyrrole and mono(imido)vanadium(III) species **E**, in which the low-valent vanadium center might be stabilized by the coordination of generated pyrrole.²² Odom and co-workers observed the similar reductive elimination from azamolybda- or azatungstacyclohexadiene, giving pyrrole derivatives^{21b}. Finally, the pyrrole is dissociated to regenerate a mono(imido)vanadium(III) species **A**. In fact, no reaction was observed for complex **7** and 3-hexyne (**2b**) at room temperature in the presence of $\text{B}(\text{C}_6\text{F}_5)_3$, while we only found the formation of *N*-phenyl-2,3,4,5-tetraethylpyrrole (**4ba**) without any intermediates such as **C**, **D**, and **E** upon heating. Based on the kinetic study, the mono(imido)vanadium(III) **A** is the resting state for generating catalytically active bis(imido) vanadium **B** via a bimetallic mechanism, and further reaction of **B** with 1 equiv of alkyne is the rate-determining step in this catalytic reaction. The key differences between this V-catalyzed reaction and the previous Ti-catalyzed reaction is low-valent species as a resting state during this catalytic cycle, which is consistent with the relative reducing ability of Ti(II) and V(III).

In summary, we have demonstrated catalytic [2+2+1] pyrrole formation from alkynes and azobenzenes by $\text{VCl}_3(\text{THF})_3$ upon activation with **1a** as an imido source. Control experiments and kinetic studies provided a plausible reaction mechanism, in which bis(imido)vanadium(V) species is assumed to be a catalytic active species. Bimetallic activation of azobenzene by a mono(imido)vanadium(III) species is a key step in the catalytic cycle, as evidenced by the observation of the second-order rate dependence on the concentration of the catalyst. Further development of this vanadium-catalyzed pyrrole formation reaction is ongoing in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1) (a). Bhardwaj V; Gumber D; Abbot V; Dhiman S; Sharma P Pyrrole: A Resourceful Small Molecule in Key Medicinal Heteroaromatics. *RSC Adv.* 2015, 5, 15233.(b)Baumann M; Baxendale IR; Ley SV; Nikbin N An Overview of the Key Routes to the Best Selling 5-Membered Ring Heterocyclic Pharmaceuticals. *Beilstein J. Org. Chem* 2011, 7, 442. [PubMed: 21647262]
- (2). Walsh CT; Garneau-Tsodikova S; Howard-Jones AR Biological Formation of Pyrroles: Nature's Logic and Enzymatic Machinery. *Nat. Prod. Rep* 2006, 23, 517. [PubMed: 16874387]
- (3). Novák P; Müller K; Santhanam KSV; Haas O Electrochemically Active Polymers for Rechargeable Batteries. *Chem. Rev* 1997, 97, 207. [PubMed: 11848869]
- (4). Loudelt A; Burgess K BODIPY Dyes and Their Derivatives: Syntheses and Spectroscopic Properties. *Chem. Rev* 2007, 107, 4891. [PubMed: 17924696]
- (5) (a). Knorr L Synthese von Furfuranderivaten aus dem Diacethbernsteinsäureester. *Ber. Dtsch. Chem. Ges* 1884, 17, 2863.(b)Paal C Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Ber. Dtsch. Chem. Ges* 1884, 17, 2756.
- (6). Hantzsch A Neue Bildungsweise von Pyrrollderivaten. *Ber. Dtsch. Chem. Ges* 1890, 23, 1474.
- (7) Representative reviews for multicomponent pyrrole formation: (a). Estévez V, Villacampa M, Menéndez JC Recent Advances in the Synthesis of Pyrroles by Multicomponent Reactions. *Chem. Soc. Rev* 2014, 43, 4633. [PubMed: 24676061] (b)Gulevich AV; Dudnik AS; Chernyak N; Gevorgyan V Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev* 2013, 113, 3084. [PubMed: 23305185] (c)Estévez V; Villacampa M; Menéndez JC Multicomponent Reactions for the Synthesis of Pyrroles. *Chem. Soc. Rev* 2010, 39, 4402. [PubMed: 20601998]
- (8) Selected examples of [2+2+1] pyrrole formation: (a). Matsui K, Shibuya M, Yamamoto Y Synthesis of Pyrroles via Ruthenium-catalyzed Nitrogen-transfer [2+2+1] Cycloaddition of α,ω -Diyne Using Sulfoximines as Nitrene Surrogates. *Commun. Chem* 2018, 1, 21.(b)Chong Q; Xin X; Wang C; Wu F; Wan B Synthesis of Polysubstituted Pyrroles via Ag(I)-mediated Conjugate Addition and Cyclization Reaction of Terminal Alkynes with Amines. *Tetrahedron* 2014, 70, 490.(c)Zhang L; Wang X; Li S; Wu J Synthesis of Pyrrole-2,3,4,5-tetracarboxylates via a Copper-catalyzed Reaction of Amine with But-2-ynedioate. *Tetrahedron* 2013, 69, 3805.(d)Chen X; Li X; Wang N; Jin J; Lu P; Wang Y Palladium-Catalyzed Reaction of Arylamine and Diarylacetylene: Solvent-Controlled Construction of 2,3-Diarylindoles and Pentaarylpyrroles. *Eur. J. Org. Chem* 2012, 2012, 4380.(e)Chen X; Jin J; Wang Y; Lu P Palladium-Catalyzed Synthesis of 7,9-Diaryl-8-*H*-acenaphtho[1,2-*c*]-pyrroles and Their Application in Explosives Detection. *Chem. - Eur. J* 2011, 17, 9920. [PubMed: 21796693] (f)Wu T-C; Tai C-C; Tiao H-C; Kuo M-Y; Wu Y-T Nickel-Catalyzed, Cascade Cycloadditions of 1-Ethynyl-8-halonaphthalenes with Nitriles: Synthesis, Structure, and Physical Properties of New Pyrroloarenes. *Chem. - Eur. J* 2011, 17, 1930. [PubMed: 21274944] (g)Liu W; Jiang H; Huang L One-Pot Silver-Catalyzed and PIDA-Mediated Sequential Reactions: Synthesis of Polysubstituted Pyrroles Directly from Alkynoates and Amines. *Org. Lett* 2010, 12, 312. [PubMed: 20000625] (h)Yamamoto Y; Kinpara K; Saigoku T; Takagishi H; Okuda S; Nishiyama H; Itoh K Cp*RuCl-Catalyzed [2+2+2] Cycloadditions of α,ω -Diyne with Electron-Deficient Carbon-Heteroatom Multiple Bonds Leading to Heterocycles. *J. Am. Chem. Soc* 2005, 127, 605. [PubMed: 15643884]

- (9) (a). Chiu H-C; See XY; Tonks IA Dative Directing Group Effects in Ti-Catalyzed [2+2+1] Pyrrole Synthesis: Chemo- and Regioselective Alkyne Heterocoupling. *ACS Catal* 2019, 9, 216.(b)Davis-Gilbert ZW; Kawakita K; Blechschmidt DR; Tsurugi H; Mashima K; Tonks IA In Situ Catalyst Generation and Benchtop-Compatible Entry Points for Ti^{II}/Ti^{IV} Redox Catalytic Reactions. *Organometallics* 2018, 37, 4439.(c)Chiu H-C; Tonks IA Trimethylsilyl-Protected Alkynes as Selective Cross-Coupling Partners in Titanium-Catalyzed [2+2+1] Pyrrole Synthesis. *Angew. Chem., Int. Ed* 2018, 57, 6090.(d)Davis-Gilbert ZW; Wen X; Goodpaster JD; Tonks IA Mechanism of Ti-Catalyzed Oxidative Nitrene Transfer in [2+2+1] Pyrrole Synthesis from Alkynes and Azobenzene. *J. Am. Chem. Soc* 2018, 140, 7267. [PubMed: 29763560] (e)Guo J; Deng X; Song C; Lu Y; Qu S; Dang Y; Wang Z-X Differences between the Elimination of Early and Late Transition Metals: DFT Mechanistic Insights into the Titanium-catalyzed Synthesis of Pyrroles from Alkynes and Diazenes. *Chem. Sci* 2017, 8, 2413. [PubMed: 28451348] (f)Davis-Gilbert ZW; Hue RJ; Tonks IA Catalytic Formal [2+2+1] Synthesis of Pyrroles from Alkynes and Diazenes via Ti^{II}/Ti^{IV} Redox Catalysis. *Nat. Chem* 2016, 8, 63. [PubMed: 26673265]
- (10). Beaumier EP; Pearce AJ; See XY; Tonks IA Modern Applications of Low-valent Early Transition Metals in Synthesis and Catalysis. *Nat. Rev. Chem* 2019, 3, 15.
- (11) Selected examples of using N,N-bis(trimethylsilyl)aniline derivatives as an imido source: (a). Benito JM, de Jesús E, de la Mata FJ, Flores JC, Gómez R, Gómez-Sal P Carbosilane Dendrimers Containing Peripheral Cyclopentadienyl Niobium- and Tantalum-imido Complexes. *J. Organomet. Chem* 2006, 691, 3602.(b)Antiñolo A; Dorado I; Fajardo M; Garcés A; Kubicki MM; López-Mardomingo C; Otero A; Prashar S Synthesis and Reactivity of New Mono- and Dinuclear Niobium and Tantalum Imido Complexes: X-ray Crystal Structure of $[Ta(\eta^5-C_5H_4SiMe_3)Cl_2\{\mu-C_6Me_4-4-(N(SiMe_3)_2)\}]$. *J. Organomet. Chem* 2006, 691, 1361.(c)Pennington DA; Horton PN; Hursthouse MB; Bochmann M; Lancaster SJ Synthesis and Catalytic Activity of Dinuclear Imido Titanium Complexes: the Molecular Structure of $[Ti(NPh)Cl(\mu-Cl)(THF)_2]_2$. *Polyhedron* 2005, 24, 151.(d)Antiñolo A; Dorado I; Fajardo M; Garcés A; López-Solera I; López-Mardomingo C; Kubicki MM; Otero A; Prashar S Synthesis, Structural Characterisation and Reactivity of New Dinuclear Monocyclopentadienyl Imidoniobium and -tantalum Complexes – X-ray Crystal Structures of $[Nb(\eta^5-C_5H_4SiMe_3)Cl_2]_2(\mu-1,4-NC_6H_4N)$, $[Ta(\eta^5-C_5Me_5)Cl_2]_2(\mu-1,4-NC_6H_4N)$ and $[Ta(\eta^5-C_5Me_5)(CH_2SiMe_3)_2]_2(\mu-1,4-NC_6H_4N)$. *Eur. J. Inorg. Chem* 2004, 2004, 1299.(e)Antiñolo A; Dorado I; Fajardo M; Garcés A; Kubicki MM; López-Mardomingo C; Otero A Synthesis and Structural Characterisation of New Organo-diimido Tantalum and Niobium Complexes. *Dalton Trans* 2003, 910.(f)Benito JM; de Jesús E; de la Mata FJ; Flores JC; Gómez R; Gómez-Sal P Arylimido Niobium(V) Complexes: Mononuclear and Dendritic Derivatives. *J. Organomet. Chem* 2002, 664, 258.(g)Dorado I; Garcés A; López-Mardomingo C; Fajardo M; Rodríguez A; Antiñolo A; Otero A Synthesis and Structural Characterization of New Organo-diimido and Organo-imido Niobium and Titanium Complexes. *J. Chem. Soc., Dalton Trans* 2000, 2375.
- (12). Titanium chloride/**1a** catalyzed the pyrrole formation in over 70% yield under higher concentration of the substrates (**2a**) = 2.4 M, (**3a**) = 0.4 M)..
- (13). Effects of additional reaction parameters such as solvent, temperature, other metal chlorides, and other additives were included in the Supporting Information.
- (14). The result of the three-component coupling reaction is shown in the Supporting Information.
- (15). See the Supporting Information.
- (16) (a). Burés JA Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem., Int. Ed* 2016, 55, 2028.(b)Burés J Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem., Int. Ed* 2016, 55, 16084.
- (17) (a). Tsurugi H; Mashima K A New Protocol to Generate Catalytically Active Species of Group 4–6 Metals by Organosilicon-Based Salt-Free Reductants. *Chem. - Eur. J* 2019, 25, 913. [PubMed: 30047181] (b)Saito T; Nishiyama H; Kawakita K; Nechayev M; Kriegel B; Tsurugi H; Arnold J; Mashima K Reduction of $(^tBuN=)NbCl_3(py)_2$ in a Salt-Free Manner for Generating Nb(IV) Dinuclear Complexes and Their Reactivity toward Benzo[c]cinnoline. *Inorg. Chem* 2015, 54, 6004. [PubMed: 26017157] (c)Saito T; Nishiyama H; Tanahashi H; Kawakita K; Tsurugi H; Mashima K 1,4-Bis(trimethylsilyl)-1,4-diaza-2,5-cyclo-hexadienes as Strong Salt-Free

Reductants for Generating Low-Valent Early Transition Metals with Electron-Donating Ligands. *J. Am. Chem. Soc.* 2014, 136, 5161. [PubMed: 24597916]

- (18) (a). La Pierre HS; Arnold J; Toste FD Z-Selective Semihydrogenation of Alkynes Catalyzed by a Cationic Vanadium Bisimido Complex. *Angew. Chem., Int. Ed* 2011, 50, 3900.(b)La Pierre HS; Minasian SG; Abubekero M; Kozimor SA; Shuh DK; Tylliszczak T; Arnold J; Bergman RG; Toste FD Vanadium Bisimide Bonding Investigated by X-ray Crystallography, ^{51}V and ^{13}C Nuclear Magnetic Resonance Spectroscopy, and V $L_{3,2}$ -Edge X-ray Absorption Near-Edge Structure Spectroscopy. *Inorg. Chem* 2013, 52, 11650. [PubMed: 24024833]
- (19) (a). Milsmann C; Turner ZR; Semproni SP; Chirik PJ Azo N=N Bond Cleavage with a Redox-Active Vanadium Compound Involving Metal-Ligand Cooperativity. *Angew. Chem., Int. Ed* 2012, 51, 5386.(b)Komuro T; Matsuo T; Kawaguchi H; Tatsumi K Synthesis of a Vanadium(III) Tris(arylthiolato) Complex and Its Reactions with Azide and Azo Compounds: Formation of a Sulfenamide Complex via Cleavage of an Azo N=N Bond. *Inorg. Chem* 2005, 44, 175. [PubMed: 15651859]
- (20). DeWith J; Horton AD; Orpen AG Unusual [2+2] Cycloaddition Adducts of an Imidovanadium Complex with Alkynes and Ethene: Conversion to η^3 -1-Azaallyl and Ethenyl Complexes. *Organometallics* 1993, 12, 1493.
- (21) (a). Vujkovic N; Ward BD; Maisse-François A; Wadepohl H; Mountford P; Gade LH Imido-Alkyne Coupling in Titanium Complexes: New Insights into the Alkyne Hydroamination Reaction. *Organometallics* 2007, 26, 5522.(b)Lokare KS; Ciszewski JT; Odom AL Group-6 Imido Activation by a Ring-Strained Alkyne. *Organometallics* 2004, 23, 5386.(c)Walsh PJ The Synthesis and Reactivity of Zirconium-Nitrogen Double and Single Bonds. Ph.D. Thesis, University of California, Berkeley, 1990.
- (22) (a). Glueck DS; Wu J; Hollander FJ; Bergman RG Monomeric (Pentamethylcyclopentadienyl)iridium Imido Compounds: Synthesis, Structure, and Reactivity. *J. Am. Chem. Soc* 1991, 113, 2041.(b)Kuhn N; Horn E-M; Zauder E; Bläser D; Boese R Stable Sandwich Complexes with Pentamethylpyrrole Ligands. *Angew. Chem., Int. Ed. Engl* 1988, 27, 579.(c)Huttner G; Mills OS Übergangsmetallkomplexe cyclischer π -Liganden, III. Kristall- und Molekülstruktur von Tricarbonyl(N-methyl-pyrrol)-chrom(0). *Chem. Ber* 1972, 105, 301. (d)Öfele K; Dotzauer E $\text{Cr}(\text{CO})_3$ - π -komplexe von Pyrrol und Pyrrolderivaten. *J. Organomet. Chem* 1971, 30, 211.

Figure 1.
Molecular structure of complex **7** with 30% thermal ellipsoids. All hydrogen atoms are omitted for clarity.

Coupling Reactions of Alkynes and Primary Amines

Coupling Reactions of Alkynes and Azobenzenes

This Work **Scheme 1.**

Transition-Metal-Catalyzed [2+2+1] Pyrrole Formation Reactions

Scheme 2.

Plausible Reaction Mechanism for Vanadium-Catalyzed [2+2+1] Coupling of Alkynes and Azobenzenes

Table 1.

Catalyst Screening ^a

entry	cat.	additive	yield [%] ^b
1	$\text{TiCl}_3(\text{THF})_3$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	23
2	$\text{TiCl}_4(\text{THF})_2$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	4
3	$\text{VCl}_3(\text{THF})_3$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	>99 (71) ^c
4	$\text{CrCl}_3(\text{THF})_3$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	trace
5	$\text{MnCl}_2(\text{THF})_{1.5}$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	n.d. ^d
6	$\text{VCl}_3(\text{THF})_3$		9
7	$\text{V}(\text{=NPh})\text{Cl}_3$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	>99
8	$\text{V}(\text{=NPh})\text{Cl}_3$		6
9	$\text{V}(\text{=N}^t\text{Bu})\text{Cl}_3$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	98
10	$\text{V}(\text{=N}(2,6\text{-}^i\text{Pr}_2\text{C}_6\text{H}_3))\text{Cl}_3$	$\text{PhN}(\text{SiMe}_3)_2$ (1a)	33

^a Reaction conditions: **2a**, 3.00 mmol; **3a**, 0.500 mmol; $o\text{-C}_6\text{H}_4\text{Cl}_2$, 2.5 mL.

^b Determined by GC using pentadecane (internal standard).

^c Isolated yield.

^d Not detected.

Table 2.

Scope and Limitations of Alkynes ^a

entry	alkyne	yield [%](4:5:6) ^b
1	$\text{R}^1 = \text{R}^2 = \text{Et}$ (2b)	74
2	$\text{R}^1 = \text{R}^2 = n\text{Pr}$ (2c)	92
3	$\text{R}^1 = \text{R}^2 = \text{Ph}$ (2d)	16 ^c
4	$\text{R}^1 = \text{Me}$, $\text{R}^2 = i\text{Pr}$ (2e)	54 (72:17:11)
5	$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$ (2f)	34 (53:47:0)
6 ^d	$\text{R}^1 = \text{SiMe}_3$, $\text{R}^2 = n\text{Bu}$ (2g)	42 (100:0:0)
7	$\text{R}^1 = \text{H}$, $\text{R}^2 = t\text{Bu}$ (2h)	53 (100:0:0)
8 ^e	$\text{R}^1 = \text{H}$, $\text{R}^2 = n\text{Bu}$ (2i)	17 (53:35:12)

^aReaction conditions: **2**, 0.988 mmol; **3a**, 0.165 mmol; $\text{C}_6\text{D}_5\text{Br}$, 0.5 mL.

^bNMR yield based on **3a** using 1,3,5-trimethoxybenzene (internal standard).

^cIsolated yield.

^dFor 40 h.

^eThe reaction was performed using 1 equiv of **2i** and 6 equiv of **3a**.