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α-Diimine synthesis *via* titanium-mediated multicomponent diimination of alkynes with C-nitrosos†

Connor W. Frye, Dominic T. Egger, Errikos Kounalis, Adam J. Pearce, Yukun Cheng and Ian A. Tonks*

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α-Diimines are commonly used as supporting ligands for a variety of transition metal-catalyzed processes, most notably in α-olefin polymerization. They are also precursors to valuable synthetic targets, such as chiral 1,2-diamines. Their synthesis is usually performed through acid-catalyzed condensation of amines with α-diketones. Despite the simplicity of this approach, accessing unsymmetrical α-diimines is challenging. Herein, we report the Ti-mediated intermolecular diimination of alkynes to afford a variety of symmetrical and unsymmetrical α-diimines through the reaction of diazatitanacyclohexadiene intermediates with C-nitrosos. These diazatitanacycles can be readily accessed *in situ via* the multicomponent coupling of Ti≡NR imidos with alkynes and nitriles. The formation of α-diimines is achieved through formal [4 + 2]-cycloaddition of the C-nitroso to the Ti and γ-carbon of the diazatitanacyclohexadiene followed by two subsequent cycloreversion steps to eliminate nitrile and afford the α-diimine and a Ti oxo.

Introduction

α-Diimines (1,4-diaza-1,3-dienes) are widely used as ligands for organometallic complexes,[1,2] perhaps most notably in Brookhart-type catalysts for α-olefin polymerization.[3–5] The α-diimine ligand scaffold has proven to be remarkably versatile due to its facile stereoelectronic tunability.[6–9] For example, modifications to the backbone and *N*-aryl substituents of α-diimines can exert control over the molecular weight and microstructure of α-olefin polymers by attenuation of chain walking processes.[1,10] As ligands, they are often redox non-innocent, which allows for richer and more complex redox processes.[11–14] α-Diimines are also precursors to valuable chiral 1,2-diamines through asymmetric hydrogenation,[15,16] or to *N*-heterocyclic carbene (NHC) ligands through cyclization with paraformaldehyde and subsequent deprotonation.[17–20]

Typically, α-diimines are synthesized through condensation of α-diketones and amines. Despite the apparent simplicity of this approach, accessing unsymmetrical α-diimines through stepwise condensations is synthetically challenging due to poor chemoselectivity.[21] Furthermore, since imine formation is reversible, attempts at sequential selective condensations can result in complex mixtures (for example, see Fig. 1A and S95–S98†). Imines are also notoriously difficult to isolate because they are prone to hydrolysis, making methods that generate product mixtures impractical. Highlighting this problem, although amine condensation with glyoxal to afford α-diimines is a common route to symmetric NHCs, examples of

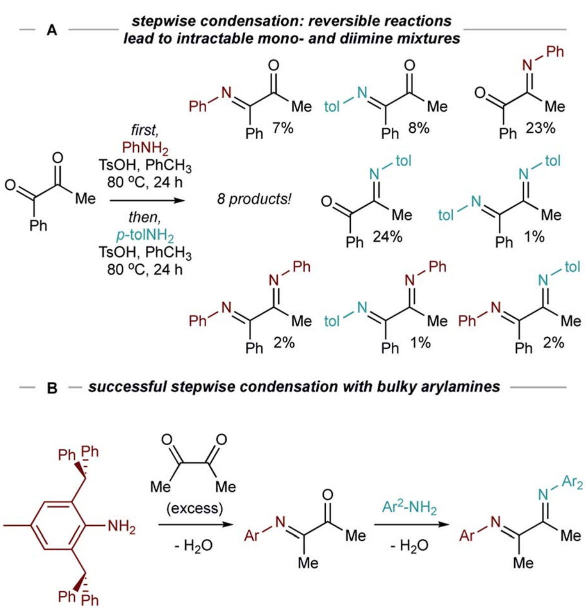

Fig. 1 Challenges and current strategies for unsymmetric α-diimine synthesis.

Department of Chemistry, University of Minnesota – Twin Cities, 207 Pleasant St SE, Minneapolis, Minnesota 55455, USA. E-mail: itonks@umn.edu

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unsymmetric NHCs synthesized *via* condensation with glyoxal are rare.[19,22,23]

There are comparatively few examples of unsymmetrical α-diimines, and these are mostly limited to modification of *N*-aryl substituents, usually involving very sterically encumbered groups,[3,9,24] rather than substituents on the backbone (Fig. 1B),[11,25] although there are several examples from aldimine cross coupling.[26,27] Selective trapping of unsymmetrical diimines *via* cyclization has also recently been reported.[28] Given this methodology gap, developing a route to unsymmetrical α-diimines from simple feedstocks would provide a useful tool for the development of more diverse ligand scaffolds and pharmaceutically relevant building blocks.[3,15,16] Our group has reported several examples of Ti-catalyzed oxidative functionalizations of alkynes for the synthesis of multisubstituted *N*-heterocycles that overcome limitations of classical condensation reactions.[29–32] We envisioned that a complementary synthetic route to unsymmetrical α-diimines could be achieved through Ti-mediated oxidative diimination of alkynes. Examples of alkyne diamination or diimination are scarce[33–36] despite many reports of alkene diamination.[37–42] To the best of our knowledge, there is only a single example of a multicomponent intermolecular alkyne diamination[43] and no examples of alkyne diimination. Nevertheless, there are several elegant examples of alkyne difunctionalizations[44] using Ti including alkyne carboamination[45–47] and iminoamination[48] that provide motivation for further exploring Ti-catalyzed or -mediated diamination/diimination.

Previously, we reported that diazatitanacyclohexadienes (prepared from the multicomponent coupling of Ti imidos, alkynes, and nitriles) could undergo oxidation-induced N–N coupling to yield pyrazoles (Fig. 2, top).[32] In the interest of further expanding the utility of this unique intermediate, we have begun examining its reactivity with various group transfer reagents. Herein, we report the intermolecular diimination of alkynes by Ti imidos and C-nitrosos to afford unsymmetrical α-diimines (Fig. 2, bottom). This diimination reaction proceeds through a cascading sequence of formal cycloaddition and retrocycloaddition reactions from this key diazatitanacyclohexadiene intermediate. This approach is a useful strategy for synthesizing unsymmetrical α-diimines, which are challenging to access through traditional condensation reactions.

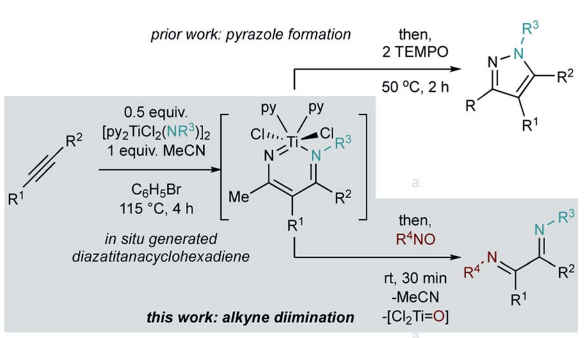


Fig. 2 *In situ* generated diazatitanacyclohexadiene intermediates. (top) Previous work on oxidative N–N coupling to pyrazoles; (bottom) intermolecular diimination of alkynes (this work).

Results and discussion

Addition of C-nitrosos to diazatitanacyclohexadienes

Addition of PhNO (**2a**) to diazatitanacycle **1** resulted in rapid, near-quantitative formation of α-diimine **3a** (81% by ^{1}H NMR) with the concomitant formation of *p*-tolunitrile (Fig. 3). It is proposed that this occurs through [4 + 2]-cycloaddition of PhNO to the Ti and γ-carbon of the ligand backbone, followed by [4 + 2]-retrocycloaddition to eliminate *p*-tolunitrile, and a second cycloreversion to afford **3a** and a Ti═O species (*vide infra*).

The scope of the C-nitroso reactants examined is shown in Table 1. Conveniently, nitrosoarenes can be readily prepared from the corresponding aniline *via* Oxone® oxidation.[49] In most cases, the α-diimine products were obtained in very good isolated yields (70% to 85%).

Use of sterically demanding nitrosos **2b** and **2c** resulted in good yields of **3b** and **3c** (77% and 76%), which are commonly used as bulky α-diimine substituents.[3] This method tolerates both electron-poor (**3d–3f**) and electron-rich (**3g–3i**) *para*-substituted (**3d–3i**) nitrosoarenes, as well as *ortho*-substituted (**3j–3l**) nitrosoarenes (**3l** is formed in a 6 : 1 ratio with its enamine tautomer). The reaction also proceeds cleanly with aliphatic nitrosos: 2-methyl-2-nitrosopropane **2n** gives a mixture of *tert*-butyl substituted α-diimine **3n** and its enamine tautomer in a 3.75 : 1 ratio (71%). Similarly, 1-nitrosoadamantane **2o** afforded α-diimine **3o** and its enamine tautomer in a 3.13 : 1 ratio (70%). While the yield of the reaction was mostly consistent irrespective of nitrosoarene substituent, there were a couple of exceptions. For the reaction with electron-rich **2i**, the formation of α-diimine **3i** (49% yield by ^{1}H NMR) was accompanied by the formation of unidentified side products that precluded isolation. Also, the reaction with 2-nitrosopyridine **2m** yielded only a small amount of **3m** by ^{1}H NMR (20%) relative to the amount of *p*-tolunitrile byproduct (85%).

In situ multicomponent diimine synthesis

Diazatitanacycles such as **1** can be synthesized *via* the multicomponent coupling of Ti imidos, alkynes, and nitriles.[32] With this strategy, one-pot alkyne diiminations were carried out (Fig. 4 and Table 2).

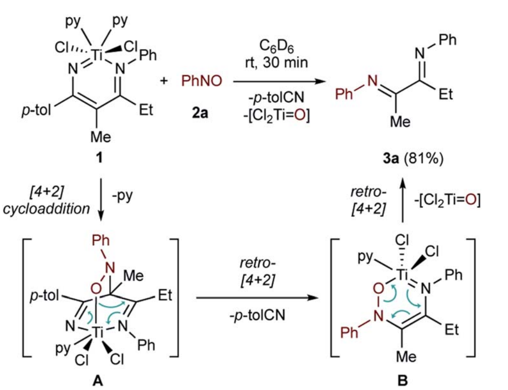
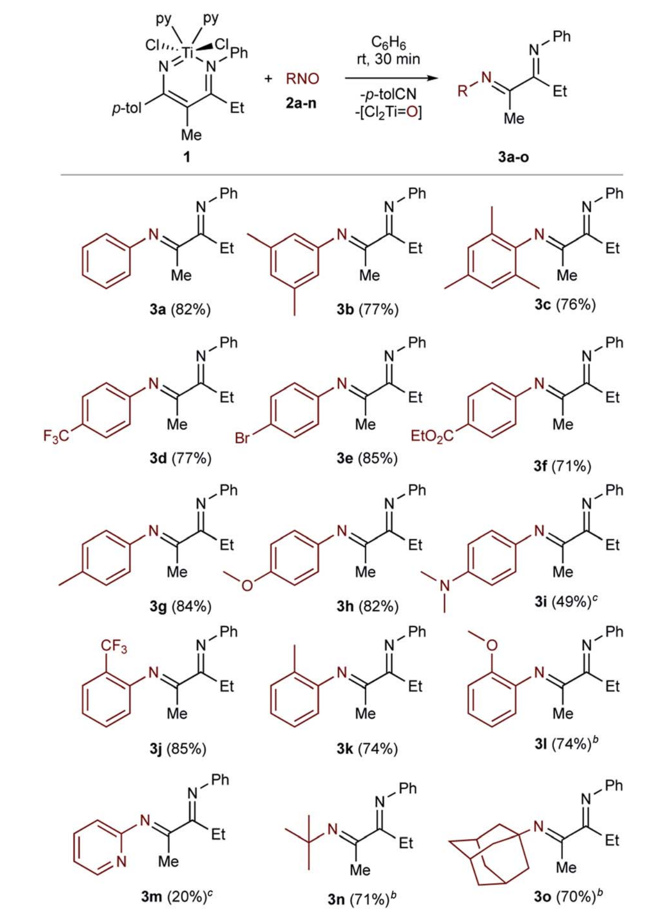


Fig. 3 Reaction of a C-nitroso with **1** yields an α-diimine **3a** *via* a sequence of cycloaddition/retrocycloaddition steps.

Table 1 Substrate scope of the addition of C-nitrosos to **1**[a]



[a] Conditions: **1** (0.2 mmol), **2a–o** (0.2 mmol, 1 equiv.), 3 mL C_6H_6, N_2 atmosphere (glovebox). Isolated yields. [b] Mixture of imine/enamine tautomers. See ESI for enamine characterization. [c] ^{1}H NMR yield *vs.* 1,3,5-trimethoxybenzene internal standard = 0.2 M.

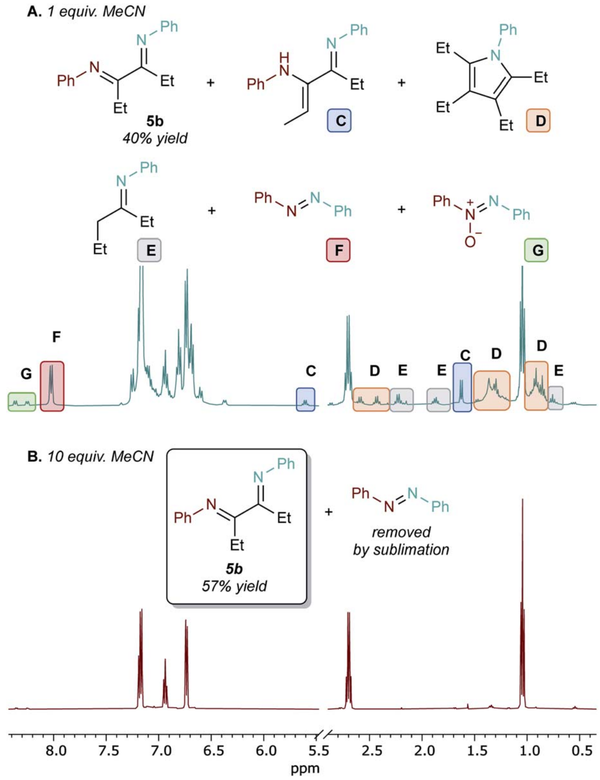


Fig. 4 Comparison of synthesis of **5b** using (A) 1 equiv. or (B) 10 equiv. MeCN.

In an initial experiment, reactions with 1 equiv. MeCN led to moderate yields of **5b** (40%) from reaction of **4b** and PhNO (Fig. 4A). MeCN was chosen over *p*-tolCN (the formal nitrile component from the reactions in Table 1) because of the easier removal of MeCN *in vacuo*. However, several species from competing side reactions also formed that were difficult to separate from the desired product given the instability of diimines towards hydrolysis: pyrrole (**D**, 5%) from insertion of a second equivalent of alkyne;[29] imine from the hydroamination of 3-hexyne (**E**, 6%); and azobenzene (**F**, 12%) from direct metathesis of PhNO with leftover Ti imido.[50,51] Using excess MeCN (10 equiv.) suppressed these competing side reactions (Fig. 4B) and led to cleaner formation of the product, with azobenzene as the predominant side-product after removal of volatiles. Conveniently, basic aqueous extraction can remove the Ti byproducts, and azobenzene can be easily removed by sublimation—avoiding the need to perform column chromatography on the sensitive products.

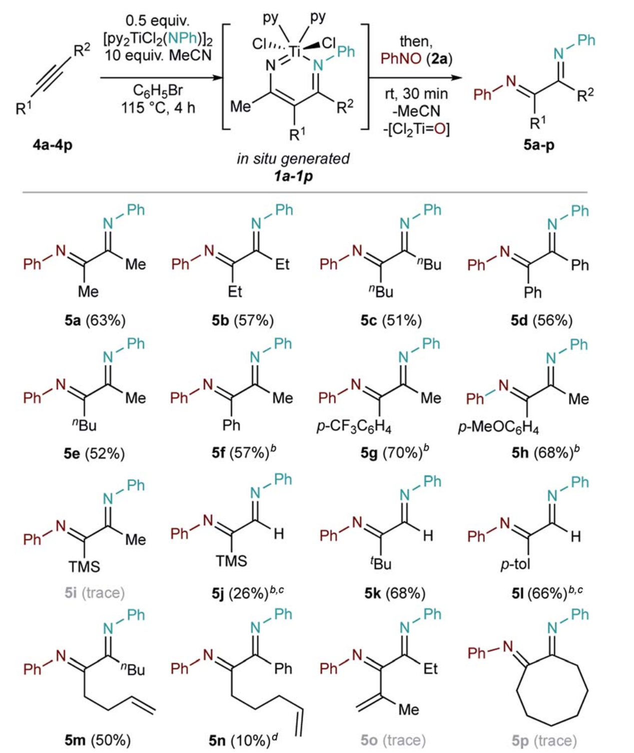
Based on this result, the scope of one-pot oxidative alkyne diimination with $[py_2TiCl_2(NPh)]_2$ and PhNO was examined (Table 2, **5a–5p**). Here, the α-diimine yields are ultimately determined by the yield of *in situ* formed diazatitanacycle **1a–1p**, as the subsequent oxidations are near-quantitative. Symmetrical internal alkynes with both alkyl and aryl substituents formed the respective α-diimines (**5a–5d**) in good isolated yields (51% to 63%).

Unsymmetrical internal alkyne **4e** resulted in the formation of a single α-diimine isomer (**5e**) in a 52% yield. In contrast, α-diimines **5f–5h** give complex ^{1}H and ^{13}C NMR spectra, presumably due to formation of multiple imine stereoisomers. Analysis of **5f** by NOESY (Fig. S53 and 54†) showed that chemical exchange occurs between each of these isomers by the presence of EXSY cross-peaks. Additionally, GC-MS revealed only one peak corresponding to the mass of **5f** (Fig. S55†).

Imines are well-known to undergo rapid equilibrium between *E*/*Z* isomers through inversion (also called the lateral shift mechanism) in nonpolar solvents.[52] Confirmation that the complex spectra of **5f–5h** were a result of stereoisomer equilibration was obtained through further reaction of the isomer mixtures. For example, reaction of the **5f** isomeric mixture with $ZnCl_2$ resulted in 93% yield of α-diimine adduct **6f** (Fig. 5). The identities of diimines **5g** and **5h** were similarly confirmed *via* $ZnCl_2$ coordination (see ESI†).

Terminal alkynes **4j–4l** were also examined. Trapping Ti≡NR + terminal alkyne [2 + 2] cycloadducts is challenging: terminal alkynes typically react faster to form pyrrole or alkyne trimerization products.[53] Nevertheless, **5k** was obtained cleanly in a 68% yield, while **5j** and **5l** were obtained as a mixture of

Table 2 Substrate scope of one-pot *in situ* diimine synthesis from alkynes, imidos, and C-nitrosos[a]



[a] Conditions: 0.2 mmol (0.5 equiv.) $[py_2TiCl_2(NPh)]_2$, 0.4 mmol (1 equiv.) alkyne, 4.0 mmol (10 equiv.) MeCN, 4 mL PhBr, 115 °C, 4 h, N_2 atmosphere (glovebox); then, 0.4 mmol (1 equiv.) PhNO, rt, 0.5 h. Isolated yields. [b] Mixture of stereoisomers. [c] Yield corrected for minor pyrrole impurities. [d] GC-FID yield (*vs.* 1,3,5-trimethoxybenzene standard).

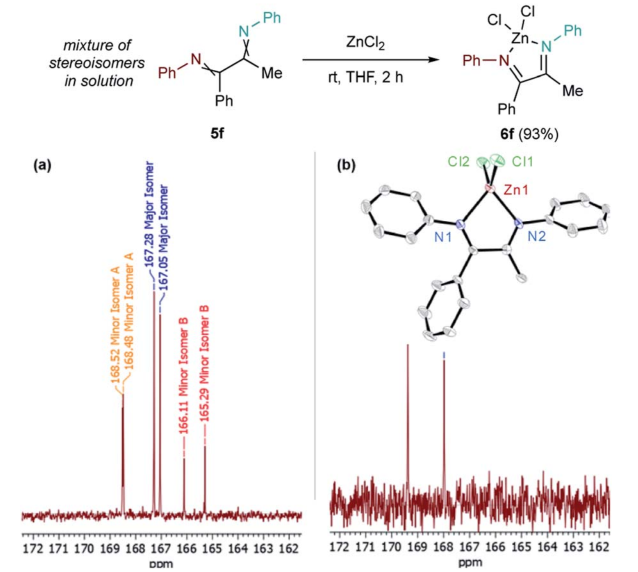


Fig. 5 Top: reaction of stereoisomeric mixture **5f** with $ZnCl_2$ results in convergence to **6f**. Bottom: ^{13}C NMR imine region of (a) **5f** (C_6D_6) and (b) **6f** ($CDCl_3$). Inset: crystal structure of **6f** showing half of the asymmetric unit with cocrystallized solvent and hydrogens omitted for clarity.

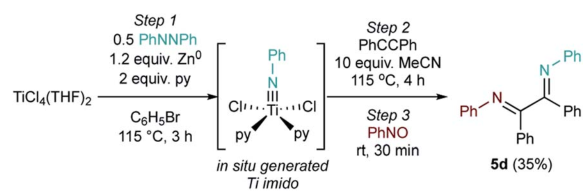


Fig. 6 Telescoped one-pot synthesis of **5d** from $TiCl_4(THF)_2$.

stereoisomers with small pyrrole impurities (2.4% and 12% pyrrole, respectively).

1,5-Enyne **4m** allows for clean formation of **5m** (50%), while 1,6-enyne **4n** results in formation of **5n** (10%) as **a** mixture with competing carboamination[47] products (6%). Here, the shorter linker of **4m** compared to **4n** prevents the intramolecular alkene insertion that would lead to carboamination. Conjugated enyne **4o** yielded only trace **5o**, while cyclooctyne **4p** predominantly formed alkyne trimer and pyrrole, with only a trace amount of **5p**.

5d was also synthesized *via* a telescoped *in situ* route from $TiCl_4(THF)_2$, azobenzene, and Zn^0 powder with only a moderate decrease in yield (Fig. 6). We have previously shown that this strategy is a benchtop-compatible approach to other Ti oxidative amination reactions.[54] This one-pot approach facilitates the *in situ* formation of diazatitanacycle intermediates such as **1** without the need for specialized equipment, making the synthesis of both α-diimines and pyrazoles[32] more operationally simple.

Given that diazatitanacyclohexadiene intermediate formation is regioselective,[32,55–57] this method could be used to prepare regioisomeric α-diimines through different combinations of alkynes, imidos, and nitrosos (Fig. 7). For example, reaction of **4k** with $[py_2TiCl_2(Np\text{-tol})]_2$ imido gives **5q** (41%), while its regioisomer **5r** can be synthesized by using **2g** and $[py_2TiCl_2(NPh)]_2$ (44%). Another regioisomer **5s** can be prepared from $[py_2TiCl_2(N^tBu)]_2$ with a 50% yield of diimine stereoisomers, albeit with a small pyrrole impurity (4% yield).

Together, these reaction scopes demonstrate that a wide range of both symmetric and unsymmetric α-diimines can be accessed directly through a one-pot multicomponent reaction with a variety of Ti imidos, alkynes, and C-nitrosos.

Proposed mechanism for intermolecular diimination

A plausible mechanism and accompanying DFT calculations for the formation of **5a** from **1a** (**IM1**) and PhNO (**2a**) are shown in Fig. 8. The *in situ* formation of **IM1** from Ti imidos, alkynes, and nitriles through alkyne/imido [2 + 2]-cycloaddition and nitrile insertion has been previously established.[32,58–60] The formal [4 + 2] cycloaddition of PhNO to **IM1** occurs in a stepwise fashion. First, O-coordination of PhNO to Ti yields **IM3**. From **IM3**, the nucleophilic, electron-rich γ-carbon in the metallacycle backbone[61] attacks the electrophilic N of coordinated PhNO, generating bicyclic **IM4**. This process can be further visualized using IBO analysis (Fig. 8a): coordination of PhNO results in a puckering of the γ-C orbital toward the N of coordinated PhNO.

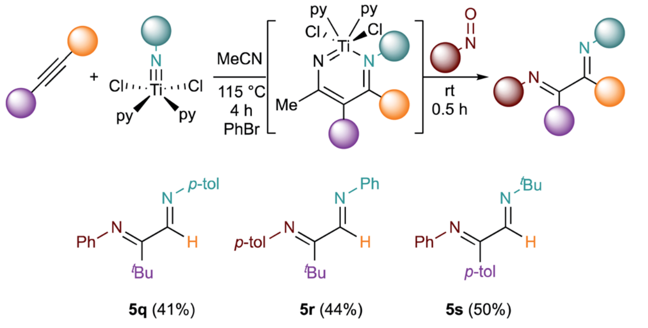


Fig. 7 Modular strategy for the synthesis of α-diimine regioisomers.

Subsequently the new N–C σ-bond is formed in **IM4**, with simultaneous rearrangement of the Ti–N and N–O π-bonds to a new N–C π-bond and O lone pair, respectively.

The tendency of C-nitrosos to undergo Diels–Alder-type cycloaddition reactions is well known,[62,63] but examples of this process with metallacycles are scarce.[64,65] Titanium β-diketiminate complexes, which differ from diazatitanacyclohexadienes by a degree of unsaturation, have also been observed to undergo [4 + 2]-cycloaddition with ketenes.[66,67]

IM4 then undergoes rate-determining (12.6 kcal mol^{-1}) retro-[4 + 2] cycloaddition to extrude nitrile, forming azaoxatitanacycle **IM5**. The retrocycloadditive nature of **TS2** can also be visualized by IBO calculations (Fig. 8b), which show the elimination of nitrile by the breaking of C–C and Ti–N σ-bonds in **IM4** and the formation of three new N–C, C–C, and Ti–N π-bonds in **IM5**. Further IBO analysis is provided in Fig. S100.† A similar tandem [4 + 2]-cycloaddition-cycloreversion process to eliminate nitriles has also been proposed in the synthesis of phosphinines.[68] **IM5** then undergoes a haptotropic shift following loss of the coordinated nitrile (**IM6**) generating η^2-(N,O)-bound **IM7**. Finally, N–O bond cleavage results in exothermic formation of a Ti═O species with the bound α-diimine product **IM8**.[69] Cycloreversions of group IV heterometallacycles to yield M = X (M = Ti, Zr; X= O, N) are well-precedented.[70–75]

Ultimately, nitrile serves as a promoter in the *in situ* reactions—first forming the key diazatitanacycle intermediate, and then being eliminated prior to product formation. Alternatively, instead of undergoing a [4 + 2]-cycloaddition, a nitroso could directly insert into the [2 + 2] alkyne/Ti≡NR cycloadduct, bypassing the need for nitrile. Indeed, C-nitrosos undergo insertions with Ti and Zr metallacycles.[76,77] However, a nitrile-free control reaction resulted in exclusive formation of azobenzene through metathesis of the Ti imido with PhNO (Fig. 9), making this route unlikely.[50,51]

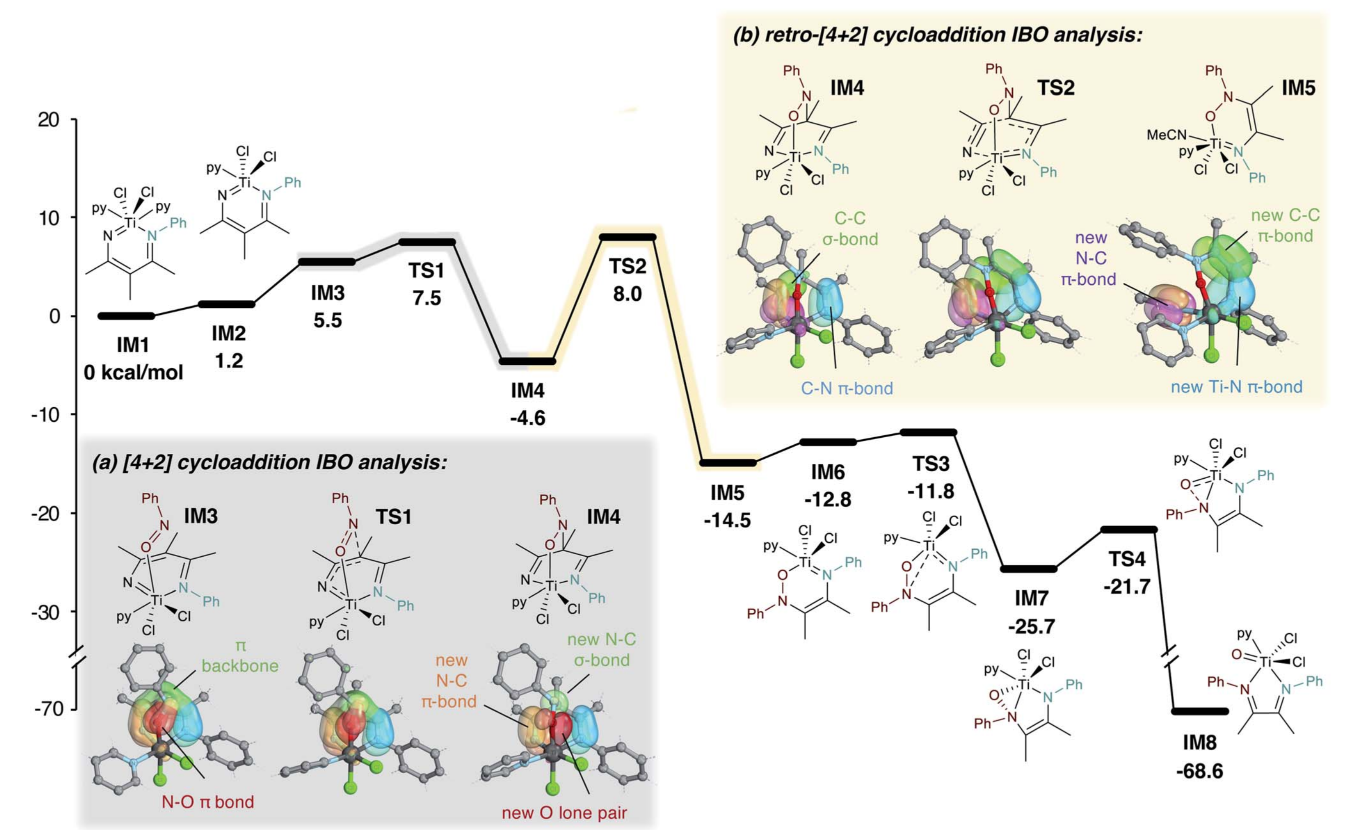


Fig. 8 Computed pathway for diimine formation (M06/6-311G(d,p)/SMD, 25 °C, C_6H_5Br). All free energies are referenced to IM1 = 0.0 kcal mol^{-1}. (a) Intrinsic bond orbitals (IBOs) showing [4 + 2] cycloaddition between NO π-bond (red) orbital of coordinated PhNO and π-backbone (green orbital) of IM3. (b) IBOs showing rearrangement of IM4 to IM5 *via* retro-[4 + 2] cycloaddition.

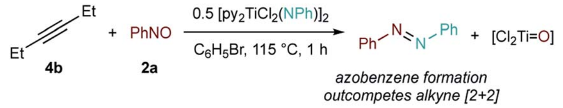


Fig. 9 Direct reaction of nitrosos with Ti imidos and alkynes results in formation of azobenzene.

Conclusions

In summary, we have demonstrated a one-pot multicomponent synthesis of α-diimines by the diimination of alkynes by Ti imidos and C-nitrosos. This reaction likely occurs by [4 + 2]-cycloaddition of a nitroso to the Ti and γ-carbon of a diazatitanacyclohexadiene intermediate, followed by two subsequent cycloreversion steps to eliminate nitrile and afford the α-diimine and Ti═O. This is an attractive route to complex, unsymmetrical α-diimines that are difficult to obtain through classical condensation reactions, providing new strategies for ligand synthesis,[3,18,20] and generally adding to the library of alkyne difunctionalization reactions. Efforts are ongoing to make this cycloaddition–retrocyclization strategy generalizable to other difunctionalizations.

Author contributions

CWF: experimental data collection and analysis, computational analysis; DTE: computational analysis; EK: computational analysis; AJP: experimental data collection and analysis; YC: experimental data collection and analysis; IAT: project direction and all authors contributed to the writing, editing, and revision of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 L. K. Johnson, C. M. Killian and M. Brookhart, New Pd(II)- and Ni(II)-Based Catalysts for Polymerization of Ethylene and α-Olefins, *J. Am. Chem. Soc.*, 1995, **117**, 6414–6415.
2 N. G. Léonard and P. J. Chirik, Air-Stable α-Diimine Nickel Precatalysts for the Hydrogenation of Hindered, Unactivated Alkenes, *ACS Catal.*, 2018, **8**, 342–348.
3 F. Wang and C. Chen, A continuing legend: the Brookhart-type α-diimine nickel and palladium catalysts, *Polym. Chem.*, 2019, **10**, 2354–2369.
4 Z. Chen and M. Brookhart, Exploring Ethylene/Polar Vinyl Monomer Copolymerizations Using Ni and Pd α-Diimine Catalysts, *Acc. Chem. Res.*, 2018, **51**, 1831–1839.
5 S. D. Ittel, L. K. Johnson and M. Brookhart, Late-Metal Catalysts for Ethylene Homo- and Copolymerization, *Chem. Rev.*, 2000, **100**, 1169–1204.
6 F.-S. Liu, H.-B. Hu, Y. Xu, L.-H. Guo, S.-B. Zai, K.-M. Song, H.-Y. Gao, L. Zhang, F.-M. Zhu and Q. Wu, Thermostable α-Diimine Nickel(II) Catalyst for Ethylene Polymerization: Effects of the Substituted Backbone Structure on Catalytic Properties and Branching Structure of Polyethylene, *Macromolecules*, 2009, **42**, 7789–7796.
7 J. L. Rhinehart, L. A. Brown and B. K. Long, A Robust Ni(II) α-Diimine Catalyst for High Temperature Ethylene Polymerization, *J. Am. Chem. Soc.*, 2013, **135**, 16316–16319.
8 S. Sa, M. Jeon and S. Y. Kim, Controlling branch distribution of polyethylenes by steric tuning of Ni α-diimine complexes based on phenanthrenequinone, *J. Mol. Catal. A: Chem.*, 2014, **393**, 263–271.
9 S. Dai, S. Zhou, W. Zhang and C. Chen, Systematic Investigations of Ligand Steric Effects on α-Diimine Palladium Catalyzed Olefin Polymerization and Copolymerization, *Macromolecules*, 2016, **49**, 8855–8862.
10 L. Guo, S. Dai, X. Sui and C. Chen, Palladium and Nickel Catalyzed Chain Walking Olefin Polymerization and Copolymerization, *ACS Catal.*, 2016, **6**, 428–441.
11 N. Muresan, C. C. Lu, M. Ghosh, J. C. Peters, M. Abe, L. M. Henling, T. Weyhermöller, E. Bill and K. Wieghardt, Bis(α-diimine)iron Complexes: Electronic Structure Determination by Spectroscopy and Broken Symmetry Density Functional Theoretical Calculations, *Inorg. Chem.*, 2008, **47**, 4579–4590.
12 K. A. Kreisel, G. P. A. Yap and K. H. Theopold, Synthesis, Characterization, and Electronic Structure of Diimine Complexes of Chromium, *Inorg. Chem.*, 2008, **47**, 5293–5303.
13 H. Nishiyama, H. Ikeda, T. Saito, B. Kriegel, H. Tsurugi, J. Arnold and K. Mashima, Structural and Electronic Noninnocence of α-Diimine Ligands on Niobium for Reductive C–Cl Bond Activation and Catalytic Radical Addition Reactions, *J. Am. Chem. Soc.*, 2017, **139**, 6494–6505.
14 K. Mashima, Redox-Active α-Diimine Complexes of Early Transition Metals: From Bonding to Catalysis, *Bull. Chem. Soc. Jpn.*, 2020, **93**, 799–820.
15 M. Shimizu, M. Kamei and T. Fujisawa, Stereocontrol in the reduction of 1,2-diimine with an oxazaborolidine catalyst.

Highly stereoselective preparation of (*R*,*R*)-1,2-diphenylethylenediamine, *Tetrahedron Lett.*, 1995, **36**, 8607–8610.

16 X. Zhu and H. Du, A Highly Stereoselective Metal-Free Hydrogenation of Diimines for the Synthesis of Cis-Vicinal Diamines, *Org. Lett.*, 2015, **17**, 3106–3109.

17 M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, An overview of N-heterocyclic carbenes, *Nature*, 2014, **510**, 485–496.

18 L. Hintermann, Expedient syntheses of the N-heterocyclic carbene precursor imidazolium salts IPr·HCl, IMes·HCl and IXy·HCl, *Beilstein J. Org. Chem.*, 2007, **3**, 22.

19 P. Queval, C. Jahier, M. Rouen, I. Artur, J.-C. Legeay, L. Falivene, L. Toupet, C. Crévisy, L. Cavallo, O. Baslé and M. Mauduit, Multicomponent Synthesis of Unsymmetrical Unsaturated N-Heterocyclic Carbene Precursors and Their Related Transition-Metal Complexes, *Angew. Chem., Int. Ed.*, 2013, **52**, 14103–14107.

20 S. Li, F. Yang, T. Lv, J. Lan, G. Gao and J. You, Synthesis of unsymmetrical imidazolium salts by direct quaternization of N-substituted imidazoles using arylboronic acids, *Chem. Commun.*, 2014, **50**, 3941–3943.

21 M. Jeon and S. Y. Kim, Ethylene Polymerizations with Unsymmetrical (α-Diimine)nickel(II) Catalysts, *Polym. J.*, 2008, **40**, 409–413.

22 L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz and V. César, Synthetic Routes to N-Heterocyclic Carbene Precursors, *Chem. Rev.*, 2011, **111**, 2705–2733.

23 A. Dumas, R. Tarrieu, T. Vives, T. Roisnel, V. Dorcet, O. Baslé and M. Mauduit, A Versatile and Highly Z-Selective Olefin Metathesis Ruthenium Catalyst Based on a Readily Accessible N-Heterocyclic Carbene, *ACS Catal.*, 2018, **8**, 3257–3262.

24 V. Rosar, A. Meduri, T. Montini, P. Fornasiero, E. Zangrando and B. Milani, The contradictory effect of the methoxy-substituent in palladium-catalyzed ethylene/methyl acrylate cooligomerization, *Dalton Trans.*, 2018, **47**, 2778–2790.

25 S. K. Ellandula, C. Opoku Amoako, J. T. Mague and P. Chandrasekaran, Crystal structure of unsymmetrical [alpha]-diimine palladium(II) complex cis-[{ArN=C(Me)-(Et)C=NAr}PdCl2] [Ar = 2,6-(iPr)2C6H3], *Acta Crystallogr., Sect. E: Crystallogr. Commun.*, 2017, **73**, 1148–1150.

26 C. Kison and T. Opatz, Synthesis of Highly Substituted Unsymmetrical 1,2-Diamines, 1,2-Diimines, Imidazolium Salts and Imidazolylidenes by Aldimine Cross-Coupling, *Synthesis*, 2006, **2006**, 3727–3738.

27 C. Kison, N. Meyer and T. Opatz, An Aldimine Cross-Coupling for the Diastereoselective Synthesis of Unsymmetrical 1,2-Diamines, *Angew. Chem., Int. Ed.*, 2005, **44**, 5662–5664.

28 J. Wang, X. Cheng, Y. Liu and J. Zhang, Multicomponent Synthesis of Unsymmetrical 4,5-Disubstituted Imidazolium Salts as N-Heterocyclic Carbene Precursors: Applications in Palladium-Catalyzed Cross-Coupling Reactions, *J. Org. Chem.*, 2021, **86**, 6278–6288.

29 Z. W. Gilbert, R. J. Hue and I. A. Tonks, Catalytic formal [2 + 2 + 1] synthesis of pyrroles from alkynes and diazenes *via* Ti^{II}/Ti^{IV} redox catalysis, *Nat. Chem.*, 2015, **8**, 63.

30 A. N. Desnoyer, X. Y. See and I. A. Tonks, Diverse Reactivity of Diazatitanacyclohexenes: Coupling Reactions of 2*H*-Azirines Mediated by Titanium(II), *Organometallics*, 2018, **37**, 4327–4331.

31 E. P. Beaumier, A. J. Pearce, X. Y. See and I. A. Tonks, Modern applications of low-valent early transition metals in synthesis and catalysis, *Nat. Rev. Chem.*, 2019, **3**, 15–34.

32 A. J. Pearce, R. P. Harkins, B. R. Reiner, A. C. Wotal, R. J. Dunscomb and I. A. Tonks, Multicomponent Pyrazole Synthesis from Alkynes, Nitriles, and Titanium Imido Complexes *via* Oxidatively Induced N–N Bond Coupling, *J. Am. Chem. Soc.*, 2020, **142**, 4390–4399.

33 J. Zeng, Y. J. Tan, M. L. Leow and X.-W. Liu, Copper(II)/Iron(III) Co-catalyzed Intermolecular Diamination of Alkynes: Facile Synthesis of Imidazopyridines, *Org. Lett.*, 2012, **14**, 4386–4389.

34 V. Dwivedi, R. Kumar, K. Sharma, B. Sridhar and M. S. Reddy, Copper-Promoted Regioselective Intermolecular Diamination of Ynamides: Synthesis of Imidazo[1,2-*a*]pyridines, *ACS Omega*, 2017, **2**, 2770–2777.

35 C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, Heteroaromatic imidazo[1,2-*a*]pyridines synthesis from C–H/N–H oxidative cross-coupling/cyclization, *Chem. Commun.*, 2012, **48**, 11073–11075.

36 J. Li and L. Neuville, Copper-Catalyzed Oxidative Diamination of Terminal Alkynes by Amidines: Synthesis of 1,2,4-Trisubstituted Imidazoles, *Org. Lett.*, 2013, **15**, 1752–1755.

37 K. Muñiz and C. Martínez, Development of Intramolecular Vicinal Diamination of Alkenes: From Palladium to Bromine Catalysis, *J. Org. Chem.*, 2013, **78**, 2168–2174.

38 D. E. Olson, J. Y. Su, D. A. Roberts and J. Du Bois, Vicinal Diamination of Alkenes under Rh-Catalysis, *J. Am. Chem. Soc.*, 2014, **136**, 13506–13509.

39 Y. Zhu, R. G. Cornwall, H. Du, B. Zhao and Y. Shi, Catalytic Diamination of Olefins *via* N–N Bond Activation, *Acc. Chem. Res.*, 2014, **47**, 3665–3678.

40 K. Muñiz, L. Barreiro, R. M. Romero and C. Martínez, Catalytic Asymmetric Diamination of Styrenes, *J. Am. Chem. Soc.*, 2017, **139**, 4354–4357.

41 Z. Tao, B. B. Gilbert and S. E. Denmark, Catalytic, Enantioselective *syn*-Diamination of Alkenes, *J. Am. Chem. Soc.*, 2019, **141**, 19161–19170.

42 S. Minakata, H. Miwa, K. Yamamoto, A. Hirayama and S. Okumura, Diastereodivergent Intermolecular 1,2-Diamination of Unactivated Alkenes Enabled by Iodine Catalysis, *J. Am. Chem. Soc.*, 2021, **143**, 4112–4118.

43 J. D. Selby, C. D. Manley, M. Feliz, A. D. Schwarz, E. Clot and P. Mountford, New ligand platforms for developing the chemistry of the Ti=N–NR_2 functional group and the insertion of alkynes into the N–N bond of a Ti=N–NPh_2 ligand, *Chem. Commun.*, 2007, 4937–4939.

44 M. Manßen and L. L. Schafer, Titanium catalysis for the synthesis of fine chemicals – development and trends, *Chem. Soc. Rev.*, 2020, **49**, 6947–6994.

45 F. Basuli, H. Aneetha, J. C. Huffman and D. J. Mindiola, A Fluorobenzene Adduct of Ti(IV), and Catalytic Carboamination to Prepare α,β-Unsaturated Imines and Triaryl-Substituted Quinolines, *J. Am. Chem. Soc.*, 2005, **127**, 17992–17993.

46 F. Basuli, B. Wicker, J. C. Huffman and D. J. Mindiola, Understanding the role of an easy-to-prepare aldimine–alkyne carboamination catalyst, $[Ti(NMe_2)_3(NHMe_2)][B(C_6F_5)_4]$, *J. Organomet. Chem.*, 2011, **696**, 235–243.

47 Z. W. Davis-Gilbert, L. J. Yao and I. A. Tonks, Ti-Catalyzed Multicomponent Oxidative Carboamination of Alkynes with Alkenes and Diazenes, *J. Am. Chem. Soc.*, 2016, **138**, 14570–14573.

48 C. Cao, Y. Shi and A. L. Odom, A Titanium-Catalyzed Three-Component Coupling To Generate α,β-Unsaturated β-Iminoamines, *J. Am. Chem. Soc.*, 2003, **125**, 2880–2881.

49 B. Priewisch and K. Rück-Braun, Efficient Preparation of Nitrosoarenes for the Synthesis of Azobenzenes, *J. Org. Chem.*, 2005, **70**, 2350–2352.

50 S. C. Dunn, N. Hazari, A. R. Cowley, J. C. Green and P. Mountford, Synthesis and Reactions of Group 4 Imido Complexes Supported by Cyclooctatetraene Ligands, *Organometallics*, 2006, **25**, 1755–1770.

51 S. A. Blum and R. G. Bergman, Nitro and Nitroso Metathesis Reactions with Monomeric Zirconium Imido Complexes, *Organometallics*, 2004, **23**, 4003–4005.

52 D. Y. Curtin, E. J. Grubbs and C. G. McCarty, Uncatalyzed *syn-anti* Isomerization of Imines, Oxime Ethers, and Haloimines, *J. Am. Chem. Soc.*, 1966, **88**, 2775–2786.

53 X. Y. See, E. P. Beaumier, Z. W. Davis-Gilbert, P. L. Dunn, J. A. Larsen, A. J. Pearce, T. A. Wheeler and I. A. Tonks, Generation of Ti^{II} Alkyne Trimerization Catalysts in the Absence of Strong Metal Reductants, *Organometallics*, 2017, **36**, 1383–1390.

54 Z. W. Davis-Gilbert, K. Kawakita, D. R. Blechschmidt, H. Tsurugi, K. Mashima and I. A. Tonks, *In situ* Catalyst Generation and Benchtop-Compatible Entry Points for Ti^{II}/Ti^{IV} Redox Catalytic Reactions, *Organometallics*, 2018, **37**, 4439–4445.

55 J. I. Seeman, Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin–Hammett Winstein–Holness kinetics, *Chem. Rev.*, 1983, **83**, 83–134.

56 H.-C. Chiu, X. Y. See and I. A. Tonks, Dative Directing Group Effects in Ti-Catalyzed [2 + 2 + 1] Pyrrole Synthesis: Chemo- and Regioselective Alkyne Heterocoupling, *ACS Catal.*, 2019, **9**, 216–223.

57 Y. Cheng, C. K. Klein and I. A. Tonks, Synthesis of pentasubstituted 2-aryl pyrroles from boryl and stannyl alkynes *via* one-pot sequential Ti-catalyzed [2 + 2 + 1] pyrrole synthesis/cross coupling reactions, *Chem. Sci.*, 2020, **11**, 10236–10242.

58 K. Kawakita, B. F. Parker, Y. Kakiuchi, H. Tsurugi, K. Mashima, J. Arnold and I. A. Tonks, Reactivity of terminal imido complexes of group 4–6 metals: Stoichiometric and catalytic reactions involving cycloaddition with unsaturated organic molecules, *Coord. Chem. Rev.*, 2020, **407**, 213118.

59 A. D. Schofield, A. Nova, J. D. Selby, A. D. Schwarz, E. Clot and P. Mountford, Reaction Site Diversity in the Reactions of Titanium Hydrazides with Organic Nitriles, Isonitriles and Isocyanates: $Ti{=}N_\alpha$ Cycloaddition, $Ti{=}N_\alpha$ Insertion and N_α–N_β Bond Cleavage, *Chem.–Eur. J.*, 2011, **17**, 265–285.

60 M. Manßen, S. de Graaff, M.-F. Meyer, M. Schmidtmann and R. Beckhaus, Direct Access to Titanocene Imides *via* Bis(η^5:η^1-penta-fulvene)titanium Complexes and Primary Amines, *Organometallics*, 2018, **37**, 4506–4514.

61 J. Barluenga, C. d. Pozo and B. Olano, Reactions of *N*-Unsubstituted 4-Amino-1-azadienes Towards Electrophiles, *Synthesis*, 1996, **1996**, 133–140.

62 S. Carosso and M. J. Miller, Nitroso Diels–Alder (NDA) reaction as an efficient tool for the functionalization of diene-containing natural products, *Org. Biomol. Chem.*, 2014, **12**, 7445–7468.

63 B. Maji and H. Yamamoto, Catalytic Enantioselective Nitroso Diels–Alder Reaction, *J. Am. Chem. Soc.*, 2015, **137**, 15957–15963.

64 J. R. Bleeke, P. V. Hinkle and N. P. Rath, Synthesis, Structure, Spectroscopy, and Reactivity of a Metallathiabenzene, *Organometallics*, 2001, **20**, 1939–1951.

65 R. L. Holland and J. M. O'Connor, Nitroso Compounds Serve as Precursors to Late-Metal η^2(N,O)-Hydroxylamido Complexes, *Organometallics*, 2009, **28**, 394–396.

66 F. Basuli, J. C. Huffman and D. J. Mindiola, Reactivity at the β-Diketiminate Ligand Nacnac- on Titanium(IV) (Nacnac- = $[Ar]NC(CH_3)CHC(CH_3)N[Ar]$, Ar = $2,6\text{-}[CH(CH_3)_2]_2C_6H_3$). Diimine-alkoxo and Bis-anilido Ligands Stemming from the Nacnac-Skeleton, *Inorg. Chem.*, 2003, **42**, 8003–8010.

67 F. Basuli, B. C. Bailey, L. A. Watson, J. Tomaszewski, J. C. Huffman and D. J. Mindiola, Four-Coordinate Titanium Alkylidene Complexes:Synthesis ,Reactivity ,and Kinetic Studies Involving the Terminal Neopentylidene Functionality, *Organometallics*, 2005, **24**, 1886–1906.

68 N. Avarvari, P. Le Floch, L. Ricard and F. Mathey, 1,3,2-Diazaphosphinines and -Diazaarsinines as Precursors for Polyfunctional Phosphinines and Arsinines, *Organometallics*, 1997, **16**, 4089–4098.

69 L. Becker, F. Strehler, M. Korb, P. Arndt, A. Spannenberg, W. Baumann, H. Lang and U. Rosenthal, Unusual Nitrile–Nitrile and Nitrile–Alkyne Coupling of Fc–C≡N and Fc–C≡C–C≡N, *Chem.–Eur. J.*, 2014, **20**, 3061–3068.

70 G. D. Kortman, M. J. Orr and K. L. Hull, Synthesis and Reactivity of Dioxazirconacyclohexenes: Development of a Zirconium–Oxo-Mediated Alkyne–Aldehyde Coupling Reaction, *Organometallics*, 2015, **34**, 1013–1016.

71 T. T. Nguyen, G. D. Kortman and K. L. Hull, Synthesis, Cycloaddition, and Cycloreversion Reactions of Mononuclear Titanocene–oxo Complexes, *Organometallics*, 2016, **35**, 1713–1725.

72 K. M. Doxsee and J. K. M. Mouser, Titanium-mediated synthesis of conjugated dienes, *Tetrahedron Lett.*, 1991, **32**, 1687–1690.
73 J. L. Polse, R. A. Andersen and R. G. Bergman, Cycloaddition and Cycloreversion Reactions of a Monomeric Ti(IV) Oxo Complex with Terminal and Internal Alkynes. A Reversible Oxametallacyclobutene/Hydroxoacetylide Interconversion, *J. Am. Chem. Soc.*, 1995, **117**, 5393–5394.
74 R. T. Ruck, R. L. Zuckerman, S. W. Krska and R. G. Bergman, Carboamination: Additions of Imine C=N Bonds Across Alkynes Catalyzed by Imidozirconium Complexes, *Angew. Chem., Int. Ed.*, 2004, **43**, 5372–5374.
75 T. A. Hanna, A. M. Baranger, P. J. Walsh and R. G. Bergman, Formation of .alpha,beta.-Unsaturated Imines and Successful Trapping of Oxozirconocene in a [4 + 2] Azaoxametallacyclohexene Retrocycloaddition, *J. Am. Chem. Soc.*, 1995, **117**, 3292–3293.
76 K. M. Doxsee, J. J. J. Juliette, T. J. R. Weakley and K. Zientara, Nitrosoarene and nitrosoalkane insertion reactions of titanacyclobutenes, *Inorg. Chim. Acta*, 1994, **222**, 305–315.
77 M. Nakamoto and T. D. Tilley, Reactions of Zirconacyclopentadienes with Nitrosobenzene. Characterization of Zirconacycle Intermediates and Formation of *N*-Phenylpyrroles, *Organometallics*, 2001, **20**, 5515–5517.