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Group 4 Diarylmetallocenes as Bespoke Aryne Precursors for Titanium-Catalyzed [2 + 2 + 2] Cycloaddition of Arynes and Alkynes

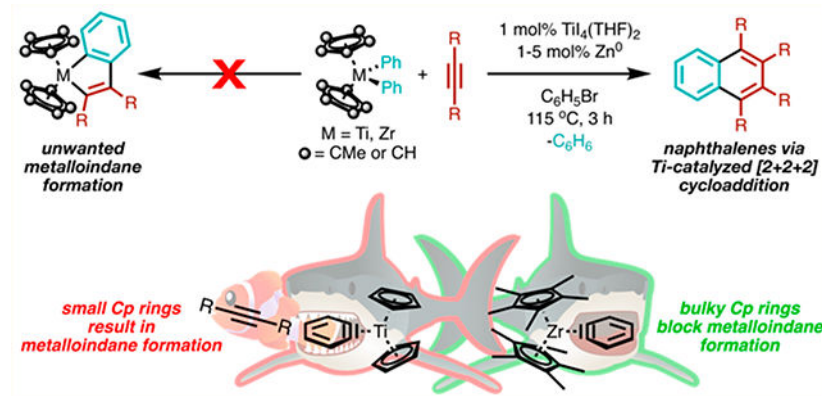
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Abstract

Despite the ubiquity of reports describing titanium (Ti)-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes, the incorporation of aryne into this potent manifold has never been reported. The in situ generation of aryne often requires fluoride, which instead will react with the highly fluorophilic Ti center, suppressing productive catalysis. Herein, we describe the use of group 4 diarylmetallocenes, $\text{Cp}^{\text{R}}_2\text{M}\text{Ar}_2$ ($\text{Cp}^{\text{R}} = \text{C}_5\text{H}_5, \text{C}_5\text{Me}_5$; $\text{M} = \text{Ti}, \text{Zr}$), as aryne precursors for the Ti-catalyzed synthesis of substituted naphthalenes via coupling with 2 equiv of an alkyne. Fair-to-good yields of the desired naphthalene products could be obtained with 1% catalyst loadings, which is roughly an order of magnitude lower than similar reactions catalyzed by palladium or nickel. Additionally, naphthalenes find broad applications in the electronics, photovoltaics, and pharmaceutical industries, urging the discovery of more economic syntheses. These results indicate that aryne transfer from a $\text{Cp}^{\text{R}}_2\text{M}(\eta^2\text{-aryne})$ complex to another metal is a viable route for the introduction of aryne fragments into organometallic catalytic processes.

Graphical Abstract



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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b01082. Spectroscopic (NMR) and quantitative GC-FID data (PDF)

INTRODUCTION

Titanium (Ti) is an attractive substitute to expensive noble metals owing to its natural abundance, low toxicity, and high activity in a number of synthetically relevant bond-forming reactions.^{1–3} Our laboratory has an ongoing interest in leveraging the reactivity of multiple valence states of Ti toward the modular assembly of complex small molecules.^{4–13} While Ti^{II} intermediates have been invoked in a multitude of catalytic and stoichiometric transformations, historically the chemistry of low-valent Ti species is weighted toward alkyne cycloaddition reactions such as alkyne cyclotrimerization.¹⁴ Alkyne cyclotrimerization is a powerful synthetic tool that allows the rapid construction of aromatic hydrocarbons through the formation of three bonds in one pot.

Naphthalenes and phenanthrenes have important applications in pharmaceuticals,¹⁵ photovoltaics,¹⁶ and the design of functional electronic materials.¹⁷ Moreover, substituted naphthalenes exhibit a myriad of biologically relevant activities including anticancer, antidepressant, antiinflammatory, antiviral, and antihypertensive activities.¹⁵ For example, Naproxen, marketed as Aleve, is a nonsteroidal antiinflammatory drug (NSAID) that is very commonly prescribed for the treatment of arthritis (Figure 1).

The synthesis of naphthalenes via formal [2 + 2 + 2] cycloaddition requires the engagement of key metallacyclic intermediates with an in situ generated reactive aryne substrate. Fast generation and capture of a stoichiometric aryne reagent is essential for selective trimerization. Modern techniques for the in situ generation of arynes have turned toward fluoride-based activators, which enjoy mild reaction conditions and easily accessible aryne precursors (Figure 2, top).¹⁸ These methods avoid the use of strong reductants such as magnesium(0) or organolithiums, synthetically elaborate aryne precursors such as those employed in the hexadehydro Diels–Alder (HDDA) reaction,¹⁹ or thermally activated substrates such as diazonium salts, which can pose serious operational hazards.²⁰

While catalytic synthesis of naphthalenes and phenanthrenes has been achieved using palladium (Pd),^{21–23} nickel (Ni),²⁴ and rhodium²⁵ (Figure 2, middle), analogous reactivity with Ti has never been reported. The prohibitive fluorophilicity of Ti [Ti–F bond dissociation energy (BDE) = 138 kcal/mol],^{26,27} which makes in situ aryne generation with fluoride incompatible with most potential Ti catalysts, likely contributes to this conspicuous absence. Considering the ubiquity of Ti-mediated trimerization reactions and the high catalytic activity reported therein, we were inspired to design aryne precursors that could be safely activated under conditions compatible with Ti.

The thermolysis and prolific ensuing insertion chemistry of group 4 diarylmetallocenes is well-established (Figure 3).^{28,29} This chemistry is proposed to proceed via a putative aryne–metallocene adduct, which is formed via β -abstraction under relatively mild conditions (~80 °C). This aryne adduct can then be intercepted by a variety of unsaturated small molecules including alkynes, alkenes, nitriles, CO₂, N₂O, and N₂.^{30–32}

The aryne intermediate can be stabilized via the addition of L-type ligands³³ or C–H activation of the cyclopentadienyl ligands.^{32,34} Given this rich chemistry, we hypothesized that this putative benzyne adduct could serve as an aryne coupling partner via transfer from

the metallocene fragment to a catalytic metal center. Unlike other aryne generation methods, we speculated that this simple and safe thermal generation of arynes would be compatible with Ti-mediated catalysis.

Herein, we report the investigation of group 4 diarylmetallocenes as aryne precursors for the catalytic synthesis of substituted naphthalenes (Figure 2, bottom). Good yields of naphthalene products could be obtained with catalyst loadings as low as 1%, which is an order of magnitude lower than similar reactions catalyzed by Pd^{21–23} or Ni.²⁴ Overall, our experiments demonstrate that aryne transfer from a Cp^R₂M(η^2 -aryne) complex to another metal is a viable route for the introduction of aryne fragments into organometallic catalytic processes.

RESULTS AND DISCUSSION

Model Reactions

We began our investigation by choosing a suitable model reaction (Table 1). Diphenylacetylene was chosen as the alkyne coupling partner owing to the low proclivity toward self-cyclotrimerization and the high symmetry expected for the desired naphthalene products. Diphenyltitanocene was chosen as an initial benzyne precursor owing to its ease of synthesis. All reactions were carried out in the presence of stoichiometric or catalytic amounts of titanium tetrahalide catalyst precursors and zinc(0) (Zn⁰), along with equimolar amounts of diphenylacetylene and a metallocene benzyne precursor. Access to the active Ti^{II} catalytic species is proposed to occur via the initial reduction of titanium tetrahalide to Ti^{III} by Zn⁰ followed by disproportionation to Ti^{II} and Ti^{IV}.³⁵ The product yields were determined by quantitative gas chromatography flame ionization detection (GC-FID) with respect to an internal standard (trimethoxybenzene).

Under stoichiometric conditions, diphenyltitanocene served as a suitable benzyne precursor and generated 1,2,3,4-tetraphenylnaphthalene (**2**) in near-quantitative yields (Table 1, entry 1). However, under catalytic conditions, the quantitative formation of metalloindane species **3** was observed (Table 1, entry 2). This suggests that interception of the putative metallocene–benzyne adduct with diphenylacetylene is kinetically competitive to productive catalysis. Prolonged thermolysis of metalloindane **3** in the presence of additional diphenylacetylene does not afford naphthalene **2**, demonstrating that **3** is likely an off-cycle thermodynamic sink. We considered that increasing the steric bulk of the Cp rings (Cp = cyclopentadiene) on the titanocene might suppress the formation of parasitic metalloindane species such as **3**. However, the substitution of Cp₂TiPh₂ for Cp*₂TiPh₂ (Cp* = pentamethylcyclopentadiene) led to no product formation (Table 1, entry 3). Cp*₂TiPh₂ is known to favor Ti–C bond homolysis to form phenyl radical rather than β -abstraction to afford the desired benzyne adduct and benzene.³⁶

Bearing in mind that the zirconium (Zr)–phenyl (Ph) bonds in Cp*₂ZrPh₂ (BDE ~ 75 kcal/mol) have a higher BDE than analogous Ti–Ph bonds (BDE ~ 67 kcal/mol),³⁷ we were prompted to consider Cp*₂ZrPh₂ as a benzyne precursor in the hopes of promoting β -abstraction over extrusion of the phenyl radical. Indeed, using Cp*₂ZrPh₂ as the benzyne precursor, **2** was delivered in 71% yield with no detectable amount of **3** (Table 1, entry 4).

Reactions using a 1:2 stoichiometry of $\text{Cp}^*_2\text{ZrPh}_2$ and diphenylacetylene afforded **2** in slightly lower yields, likely owing to decomposition of the incipient Zr–benzyne complex (entry 5). Control reactions conducted in the absence of catalytic Ti or Zn (Table 1, entries 8 and 9) showed no formation of **2**. Other TiX_4 precatalysts (Table 1, entries 6 and 7) only afforded trace amounts of **2**, demonstrating the importance of iodide ligands to catalysis. We have previously observed that TiI_4 -based precatalysts are significantly more productive for alkyne trimerization than TiCl_4 -based precatalysts,⁷ likely due to the decreased donor ability of iodide (I^-) compared to chloride (Cl^-).³⁸ Reactions performed at lower temperatures (80 or 100 °C) afforded no naphthalene product; however, evolution of stoichiometric amounts of benzene signaled that β -hydrogen abstraction of $\text{Cp}^*_2\text{ZrPh}_2$ did occur. Moreover, low-valent Ti is competent for trimerization under mild conditions.³⁹ Thus, the high reaction temperature may be more readily associated with the barrier for the generation of an active Ti^{II} species. Notably, **2** is furnished in good yield at 1 mol % catalyst loading, while similar reactions employing Ni or Pd catalysts require 10 mol % catalyst loading to achieve comparable yields. This highlights the inherent advantage of utilizing Ti-based catalyst systems.

^1H NMR spectra of catalytic reactions show decomposition of $\text{Cp}^*_2\text{Zr}^{\text{II}}$ to multiple ill-defined species. In order to ascertain whether any of these species are catalytically competent, the cycloaddition of tetraphenylnaphthalene was attempted using catalytic amounts of $\text{Cp}^*_2\text{ZrCl}_2/\text{Zn}$. This system did not afford tractable amounts of naphthalene product. Similarly, attempts to catalyze the cyclotrimerization of 3-hexyne with $\text{Cp}^*_2\text{ZrCl}_2/\text{Zn}$ were also unsuccessful. These observations suggest that $\text{Cp}^*_2\text{Zr}^{\text{II}}$ -borne species are likely not involved in promoting cycloaddition catalysis.

Alkyne Scope

With optimized reaction conditions in hand, we set out to explore the scope of the alkyne coupling partner. We hypothesized that only alkynes with sufficient steric bulk could engage in productive catalysis by avoiding the formation of parasitic metallocene species. A simple structure–activity relationship was developed in order to qualitatively correlate the alkyne steric size to reactivity. While several models for substituent size have been developed,^{40–45} A values proved sufficient. The A values for both alkyne substituents were summed to give a “composite A value” and plotted against the total yield of naphthalene products formed under catalytic conditions (Figure S20).

Alkynes with composite A values of below 4 delivered naphthalene products in zero or very poor yield (Table 2, alkynes **1a–1f**). These reactions were dominated by formation of the corresponding metallocenes **7a–7f**. In the cases of 3-hexyne (Table 1, alkyne **1a**) and 4-octyne (Table 1, alkyne **2a**), alkylated benzenes formed via alkyne trimerization were observed in low yields (~10%).

Composite A values between 4 and 6 appear necessary but are not sufficient to furnish naphthalene products **4–6** in acceptable yields (Table 2, alkynes **1f–1m**). The product selectivity for asymmetric alkynes appears entirely substrate-biased in accordance with literature precedent.^{21–24} Notably, slight changes to the steric profile of the alkyne coupling partner can substantially affect the catalytic performance. While phenylpropyne affords the

metalloindane complex **7f** as the exclusive product (Table 2, alkyne **1f**), phenylhexyne furnished the metalloindane complex **7g** in a substantially lower yield and produced both naphthalene and trimer products in comparable yields (~15%; Table 2, alkyne **1g**). The difference in the *A* values between Me and ^tBu is only 0.1 kcal/mol, illustrating how even small steric perturbations can manifest in observable differences in the catalytic performance.

A substrate screen utilizing para-substituted diarylalkynes shows a slight yield dependence on the electronic character of the alkyne (Table 2, alkynes **1i–1k**). More electron-rich alkyne coupling partners deliver naphthalene products in higher yields. Alkynes with composite *A* values exceeding 6 did not convert under the reaction conditions (Table 2, alkyne **1n**) likely owing to the steric strain associated with the formation of metallacyclic intermediates. While limited in overall scope, the reactivity of the alkyne coupling partners appears to be more closely governed by the steric rather than electronic properties of the alkyne. Although the reaction yields delivered by productive alkynes are moderate, the relatively high turnover numbers are encouraging, and current work is directed toward developing more robust catalytic systems.

Only trace amounts of benzyne homocoupled products could be detected in the reactions with any alkynes. Thermolysis of Cp*₂ZrPh₂ in the absence of alkyne or catalyst also only affords trace yields of benzyne homocoupling products. This stands in contrast to other synthetically relevant metal–benzyne adducts of ruthenium,⁴⁶ Pd,^{21–23} and Ni,²⁴ where benzyne coupling products such as biphenylene or triphenylene are furnished in more substantial yields. Additionally, Ti species generated during catalysis do not appear to promote the formation of metalloindane byproducts. The propensity of alkynes to form metalloindanes is identical in the presence or absence of catalytic Ti.

Proposed Mechanism

Synthetic success with a fairly unusual benzyne precursor prompted us to consider the mechanistic aspects of the ensuing catalytic reaction. The most likely pathway for naphthalene synthesis is as follows (Figure 4): after generation of an active Ti^{II} species (**I**) by the Zn reductant, 2 equiv of alkyne undergo oxidative coupling to yield a titanacyclopentadiene (**II**). Next, the titanacyclopentadiene reacts with the in situ generated Zr–benzyne adduct, either via transmetalation of the benzyne to Ti or direct [4 + 2] cycloaddition of Zr–benzyne to the diene fragment. The resulting bound arene can either then dissociate to regenerate the reduced Ti^{II} species **I** or undergo associative displacement by alkyne to generate **II**. We favor **II** over titanaindane (Figure 4a) formation owing to the observed product and byproduct selectivity: catalysis results in the formation of only naphthalenes and a small amount of hexasubstituted benzene as a consequence of alkyne cyclotrimerization. In principle, a titanaindane intermediate (or a Ti–benzyne adduct) could result in the formation of phenanthrene or triphenylene byproducts, neither of which are observed.

We were prompted to interrogate the role of Zn during catalysis because the ZnX₂ byproduct of Ti reduction could facilitate either transmetalation or act as a Lewis acid—in either case possibly impacting how naphthalenes are formed. We previously reported the generation of

Ti^{II} trimerization catalysts through the alkyne-triggered reduction of titanium imidos⁷ instead of Zn reduction of titanium halides. Conducting the coupling reaction with equimolar amounts of Cp*₂ZrPh₂ and PhCCPh in the presence of 10% py₃TiI₂(NPh) and 3-hexyne afforded naphthalene **2** in 60% yield (Figure 5). 3-Hexyne was chosen as a sacrificial alkyne owing to its high reactivity in the formation of the requisite pyrrole catalyst activation product. The formation of **2** in the absence of Zn demonstrates that Zn is “innocent”—not likely participating as a transmetalation agent or Lewis acid during the catalytic synthesis of naphthalenes.

Thus, benzyne incorporation into titanacyclopentadiene **II** likely occurs via direct engagement of the Zr–benzyne adduct with Ti, through either transmetalation (Figure 4c) or direct [4 + 2] cycloaddition with **II** (Figure 4d). Thermolysis of Cp*₂ZrPh₂ in the presence of furan and cyclohexadiene as benzyne traps yielded no products from free benzyne capture (Figure 4c). Instead, only the tuck-in complex **V** (Figure 6) was observed. Identical benzyne trap experiments were conducted with Cp₂TiPh₂, which cannot form a tuck-in complex, but still no products assignable to free benzyne capture were detected. Notably, the Zr tuck-in complex **V** does not exhibit evidence of interconversion to the benzyne adduct **IV** up to 90 °C;³² however, a small yet reactive population of the benzyne adduct may be responsible for direct transmetalation from Zr to Ti. How the bulky zirconocene fragment may hinder formation of the requisite transition state(s) needed for transmetalation remains a lingering question.

In order to determine whether the Cp*₂Zr benzyne adduct **IV** is indeed a relevant species during catalysis, we examined substituted aryne coupling partner **8** as an isomerization probe to detect the intermediacy of an aryne complex (Figure 7). Metallocene aryne complexes that can be stabilized via C–H activation of the Cp* ring (as in **V**) are expected to “proton walk” via the successive protonation of an incipient aryne intermediate (Figure 7).³⁴ By measurement of the product distribution, the aryne adduct isomer of Cp*₂Zr(C₆H₃Me) can be implicated as an on-cycle species in catalysis if isomerization occurs. Indeed, after complex **8** was subjected to the catalytic reaction conditions, a ~2:1 mixture of 6-methyl-1,2,3,4-tetraphenylnaphthalene (**9**) and 5-methyl-1,2,3,4-tetraphenylnaphthalene (**10**) was afforded in 64% yield. The formation of naphthalene **10** can only arise following isomerization via an aryne adduct and thus implicates the intermediacy of a complex such as **IV** during catalysis (Figure 6). Notably, thermolysis of **8** shows almost immediate scrambling of the tolyl group to an equimolar mixture of ortho-, meta-, and para-substituted analogues of **V** (Figure S21), demonstrating that isomerization is energetically facile and not dictated by Cp* ring sterics. This isomerization behavior is consistent with the observed reactivity of the analogous Cp₂Zr(tolyl)₂ complex.⁴⁷

Overall, the mechanistic data are most consistent with the direct engagement of a Zr–aryne adduct with a titanacyclopentadiene to afford the observed naphthalene products. Future work is focused on elucidating the fine details of this transmetalation event and how it may affect or effect product selectivity.

CONCLUSIONS

$\text{Cp}^*_2\text{ZrPh}_2$ was employed as a benzyne precursor in a Ti-catalyzed formal [2 + 2 + 2] cycloaddition of aryne and alkynes to form highly substituted naphthalene products. Bulky Cp^* rings were required to suppress the formation of parasitic metalloindane byproducts. A screen of potential alkyne coupling partners showed that formation of the desired naphthalene products is best correlated to alkyne steric rather than electronic properties. The product selectivity toward naphthalenes over other potential coupling products including triphenylenes or phenanthrenes suggests a mechanism in which a titanacyclopentadiene is intercepted by a Zr–benzyne adduct. An isomerization probe substrate, **8**, was designed to interrogate this possibility. The product distribution arising from this substrate implicates isomerization through a Zr–aryne adduct during productive catalysis.

While the yields of naphthalene products are modest, the relatively low catalyst loading—nearly an order of magnitude lower than comparable systems with Ni or Pd—is encouraging. The high oxo- and fluorophilicity of Ti could be circumvented with an unusual aryne precursor, demonstrating a novel way to introduce aryne fragments into organometallic catalytic processes. Future work is directed toward expanding the scope of reactions that incorporate these metallocene-born arynes in the hopes of assembling more complex small molecules and understanding the mechanistic implications of aryne transmetalation in catalysis.

EXPERIMENTAL SECTION

General Considerations

All air- and moisture-sensitive compounds were manipulated in a glovebox under a N_2 atmosphere. Benzene, pentane, diethyl ether (Et_2O), tetrahydrofuran (THF), and toluene were sparged with ultrahigh-purity argon and dried via passage through drying columns using a solvent purification system from Pure Process Technologies. All solvents were stored over 4 Å molecular sieves. $\text{C}_6\text{D}_5\text{Br}$ was dried over CaH_2 and distilled before use. All high-boiling liquid reagents were freeze–pump–thawed three times, brought into the glovebox, diluted in hexanes or Et_2O , passed through activated basic alumina, pumped dry in vacuo, and checked by ^1H NMR in CDCl_3 to ensure the dryness. 1,2-Bis(4-*tert*-butylphenyl)ethyne,⁴⁸ bis(4-methoxyphenyl)ethyne,⁴⁹ bis(4-trifluoromethylphenyl)ethyne,⁵⁰ Cp_2TiPh_2 ,³⁶ $\text{Cp}^*_2\text{TiPh}_2$,³⁶ $\text{Cp}^*_2\text{ZrPh}_2$,³² and *p*-tolyllithium⁵¹ were prepared according to reported procedures. ^1H and ^{13}C NMR spectra were collected on a Bruker Avance III HD NanoBay 400 MHz spectrometer. Chemical shifts are reported with references of the residual protiosolvent impurity: ^1H (s, 7.26 ppm for CHCl_3), ^{13}C (t, 77.16 ppm for CDCl_3). GC-FID was performed using an Agilent 7890 series gas chromatograph system (HP-5 column, 30 m length, 0.32 mm inside diameter, 0.25 μm film thickness; temperature program = 50 °C for 1.5 min, 20 °C/min to 290 °C, and held for 6.5 min) equipped with a Polyarc reactor for quantitative C detection.

General Procedure for Catalytic Reactions

In an N₂-filled glovebox, a vial was charged with Cp*₂ZrPh₂ (25.8 mg, 0.05 mmol, 1 equiv), alkyne (0.05 mmol, 1 equiv), TiI₄(THF)₂ (0.350 mg, 0.0005 mmol, 0.01 equiv), C₆D₅Br (0.5 mL), and trimethoxybenzene (8.4 mg, 0.05 mmol, 1 equiv) as an internal standard. The reaction mixture was transferred into an NMR tube charged with Zn (0.1–0.3 mg, 0.0015–0.0030 mmol, 0.03–0.05 equiv). The reaction was heated at 115 °C for 3 h in a preheated oil bath outside the glovebox. After being cooled to ambient temperature, the reaction was concentrated in vacuo, and the resulting residue was dissolved in ethyl acetate (EtOAc) and passed over a plug of silica. Reactions using tetramethylsilane–alkynes that afforded naphthalene products were concentrated in vacuo and mixed with 10 mL of 2 M HCl in methanol. After the mixture was stirred for 2 h, it was diluted by 20 mL of deionized water and extracted by EtOAc (3 × 15 mL). The organic layer was washed with brine and dried by MgSO₄. All reactions were analyzed by ¹H NMR in a CDCl₃ solvent, and spectra containing naphthalene products were compared to literature examples.^{24,52–58} NMR samples were then diluted with dichloromethane (CH₂Cl₂) and analyzed by GC-FID. Product yields were determined by quantitative GC-FID.

Synthesis of 8

A solution of *p*-tolyllithium (68 mg, 0.69 mmol, 3 equiv) in THF (2 mL) was added dropwise to a stirring solution of Cp*₂ZrCl₂ (100 mg, 0.23 mmol, 1 equiv) in Et₂O (5 mL) at –30 °C. The reaction was allowed to warm to room temperature and stirred for 6 h, affording a hazy orange solution. CH₂Cl₂ (0.5 mL) was added dropwise to quench the remaining organolithium species. The reaction solvent was removed in vacuo, and the resulting residue was extracted into Et₂O and filtered over Celite. The solution was concentrated to quarter volume and left to stand in the freezer overnight. The resulting white precipitate was collected and washed with hexanes (3 × 2 mL). **8** was isolated as a white microcrystalline powder (yield: 78 mg, 63%). ¹H NMR (400 MHz, CDCl₃): δ 7.11 (d, 2H, t, ³J_{H–H} = 7.4 Hz, tolyl H), 6.97–6.91 (m, 6H), 2.26 (s, 6H, tolyl Me), 1.64 (s, 30H, Cp*–Me). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 189.1 (s, 2C, Zr C), 136.7 (s, 2C, tolyl Me), 134.11 (s, 2C, *o*-tolyl C), 133.0 (s, 2C, *o*-tolyl C), 126.9 (s, 1C, *m*-tolyl C), 126.6 (s, 1C, *m*-tolyl C), 120.3 (s, 2C, *m*-tolyl C), 21.3 (s, 2C, tolyl Me), 12.3 (s, 10C, Cp* Me). Anal. Calcd for C₃₄H₄₄Zr: C, 75.08; H, 8.15. Found: C, 75.38; H, 8.21.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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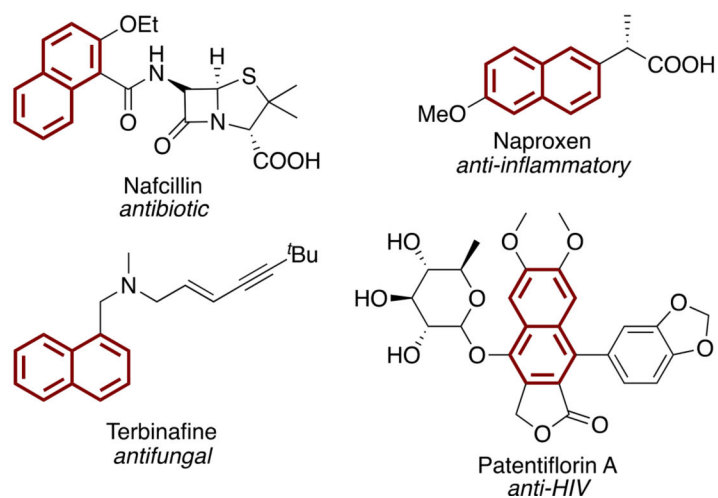
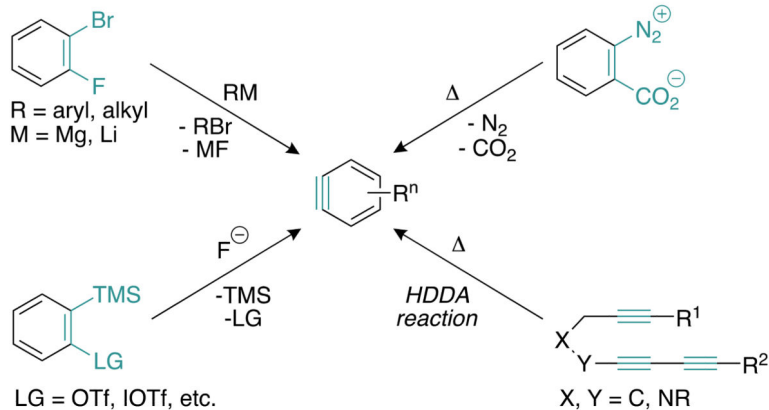
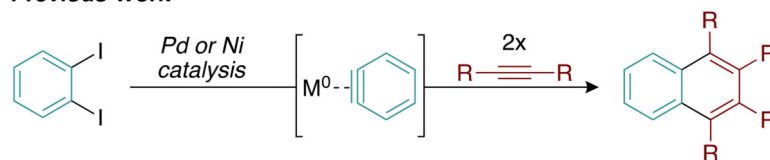


Figure 1.
Examples of naphthalene cores in drug molecules.

Common Methods for In Situ Generation of Arynes



Previous Work



This Work

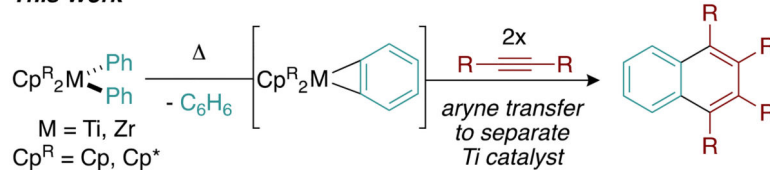


Figure 2. Modern methods of in situ aryne generation.

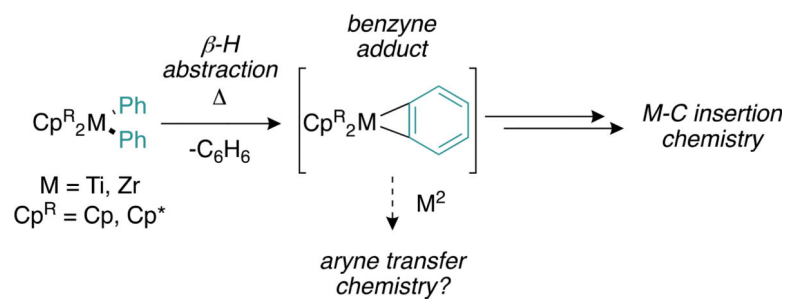
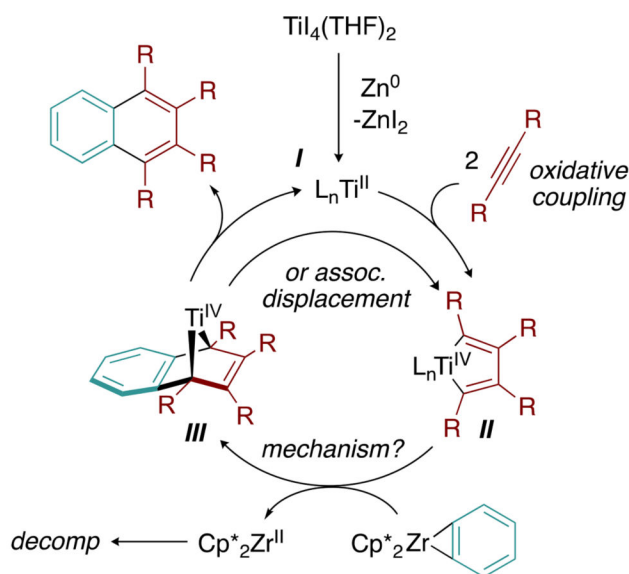
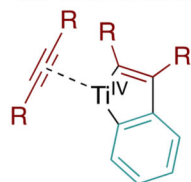


Figure 3. Group 4 diarylmetallocenes undergo β -hydrogen abstraction, leading to aryne adducts that can be intercepted via insertion.



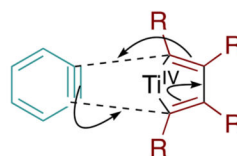
possible mechanisms of benzyne incorporation:

a. coordination-insertion via titanaindane



ruled out - no overincorporation of benzyne (phenanthrenes)

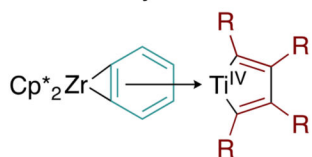
b. [4+2] cycloaddition via free benzyne



ruled out - no observed products w/ benzyne traps

most likely pathways

c. transmetalation through π system



d. [4+2] cycloaddition via zirconocene-benzyne adduct

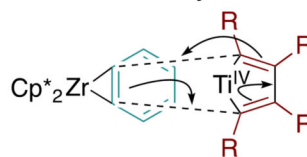


Figure 4. Plausible mechanism for the formation of naphthalene products from aryne/alkyne cyclization.

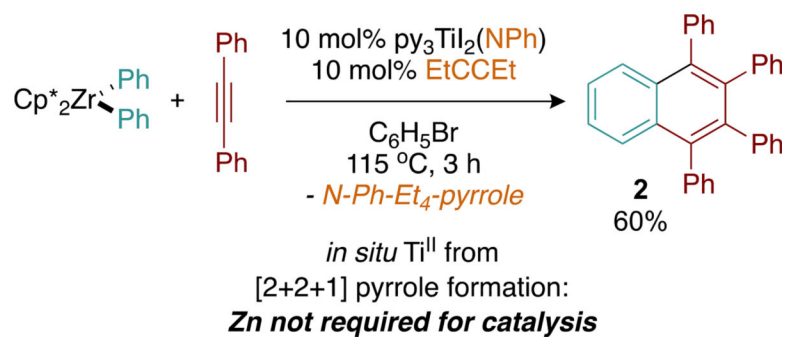


Figure 5. Zn-free reactions yield significant amounts of 2, indicating that Zn is not critically important for catalysis.

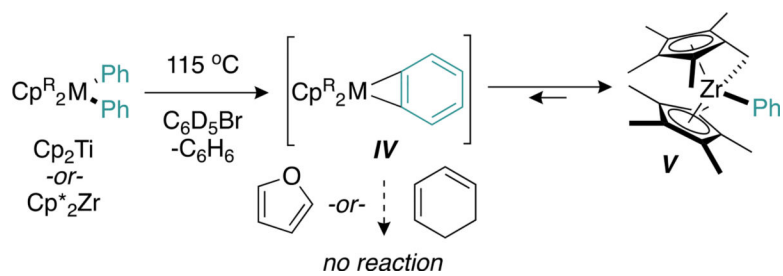


Figure 6. Free benzyne trap experiments led only to formation of the tuck-in complex **V**.

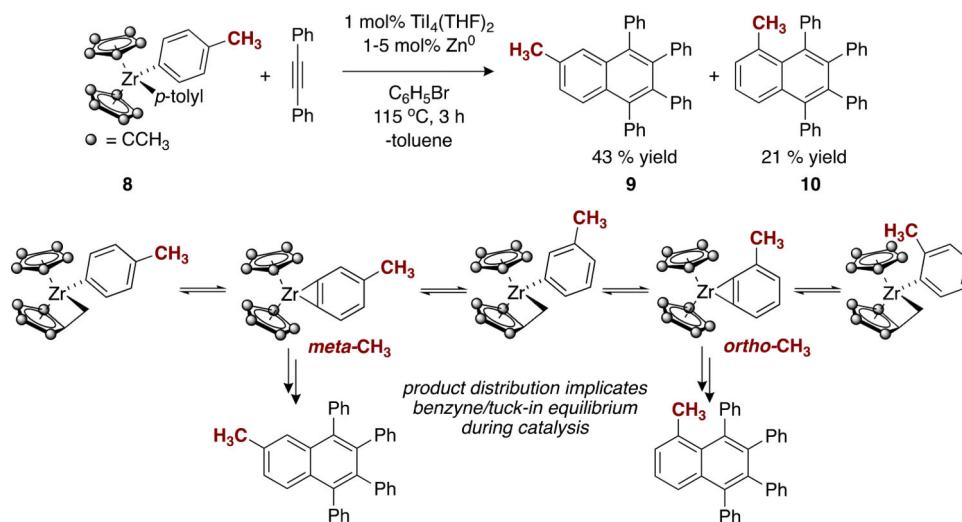


Figure 7.
 Formation of **10** implicating isomerization through a Zr–aryne adduct.

Table 1.

Screening of Reaction Conditions^a

$\text{Cp}^{\text{R}2}\text{M} + \text{Ph-C}\equiv\text{C-Ph} \xrightarrow[\text{-C}_6\text{H}_6]{\text{1 mol\% catalyst, 1 mol\% Zn}^0, \text{C}_6\text{H}_5\text{Br, 115 }^\circ\text{C, 3 h}}$

entry	$\text{Cp}^{\text{R}2}\text{M}^b$	catalyst	% yield 2 ^c	% yield 3 ^d
1	Cp_2Ti	$\text{TiI}_4(\text{THF})_2^e$	>95	0
2	Cp_2Ti	$\text{TiI}_4(\text{THF})_2$	0	>95
3	Cp^*_2Ti	$\text{TiI}_4(\text{THF})_2$	0	0
4	Cp^*_2Zr	$\text{TiI}_4(\text{THF})_2$	71	0
5	Cp^*_2Zr	$\text{TiI}_4(\text{THF})_2^f$	55	0
6	Cp^*_2Zr	$\text{TiBr}_4(\text{THF})_2$	trace	0
7	Cp^*_2Zr	$\text{TiCl}_4(\text{THF})_2$	trace	0
8	Cp^*_2Zr	$\text{TiI}_4(\text{THF})_2^g$	0	0
9	Cp^*_2Zr	none	0	0

^aReaction conditions: metallocene (0.05 mmol), diphenylacetylene (0.05 mmol), catalyst (0.05–0.0005 mmol of Ti), Zn^0 (0.05–0.0005 mmol), 0.5 mL of $\text{C}_6\text{H}_5\text{Br}$, 115 °C, 3 h.

^b Cp = cyclopentadiene; Cp^* = pentamethylcyclopentadiene.

^cDetermined by quantitative GC-FID with respect to an internal standard (1,3,5-trimethoxybenzene).

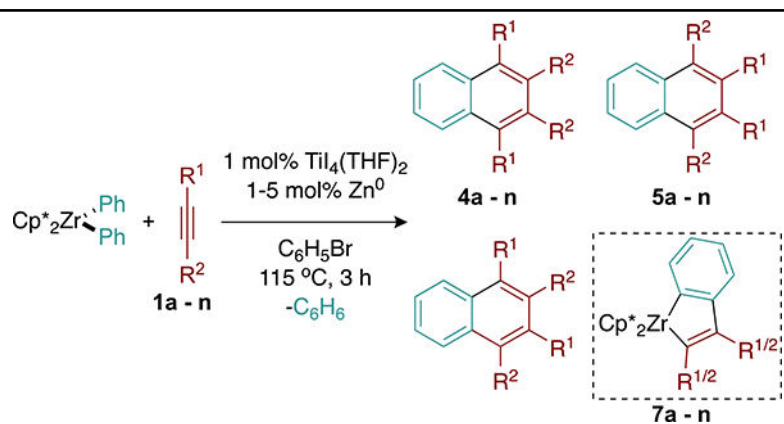
^dDetermined by ^1H NMR with respect to an internal standard (1,3,5-trimethoxybenzene).

^eReaction conducted with 100 mol % $\text{TiI}_4(\text{THF})_2$.

^fReaction conducted with 0.1 mmol of diphenylacetylene.

^gReaction conducted in the absence of Zn^0 .

Table 2.

Alkyne Partner Substrate Scope^a

	R^1, R^2	% yield 4:5:6 ^b	% yield 7 ^c	% yield trimer ^d	A value ^e
1a	Et, Et	5	86	8	3.5
1b	ⁿ Pr, ⁿ Pr	4	88	9	3.6
1c	TMS, H	0	>95	0	2.5
1d	Ph, H	0	>95	0	3.0
1e	ⁱ Pr, Me	0	>95	0	3.9
1f	Ph, Me	0	>95	0	4.7
1g	Ph, ⁿ Bu	0:4:10	19	16	4.8
1h	Ph, Ph	71	0	24	6.0
1i	<i>p</i> -CF ₃ Ph, <i>p</i> -CF ₃ Ph	64	0	19	6.0
1j	<i>p</i> -OMe-Ph, <i>p</i> -OMe-Ph	78	0	15	6.0
1k	<i>p</i> - ^t BuPh, <i>p</i> - ^t BuPh	76	0	22	6.0
1l	Ph, TMS	8:14:26	0	0	5.5
1m	ⁿ Bu, TMS	0:34:31	0	0	4.3
1n	Me, ^t Bu	0	0	0	6.6

^a Reaction conditions: metallocene (0.05 mmol), alkyne (0.05 mmol), catalyst (0.0005 mmol of Ti), Zn^0 (0.0005 mmol), 0.5 mL of $\text{C}_6\text{H}_5\text{Br}$, $115\text{ }^\circ\text{C}$, 3 h. Cp* = pentamethylcyclopentadiene.

^b Determined by quantitative GC-FID with respect to an internal standard (1,3,5-trimethoxybenzene).

^c Determined by ¹H NMR with respect to an internal standard (1,3,5-trimethoxybenzene).

^d % yield of all alkyne cyclotrimer regioisomers; determined by ¹H NMR with respect to an internal standard (1,3,5-trimethoxybenzene).

^e Sum of both alkyne substituent A values.