

Communication

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Oxidative Coupling with Zr(IV) Supported by a Non-Innocent Anthracene-Based Ligand: Application to the Catalytic Cotrimerization of Alkynes and Nitriles to Pyrimidines

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Supporting Information Placeholder

ABSTRACT: We report the synthesis and reactivity of Zr complexes supported by a 9,10-anthracenediyl-linked bisphenoxide ligand, L. $Zr^{IV}LBn_2$ (1) undergoes facile photolytic reduction with concomitant formation of bibenzyl and $Zr^{IV}L(THF)_3$ (2), which displays a two-electron reduced anthracene moiety. Leveraging ligand-stored reducing equivalents, 2 promotes the oxidative coupling of internal and terminal alkynes to isolable zirconacyclopentadiene complexes, demonstrating the reversible utilization of anthracene as a redox reservoir. With diphenylacetylene under CO, cyclopentadienone is formed stoichiometrically. 2 is competent for the catalytic formation of pyrimidines from alkynes and nitriles. Mechanistic studies suggest that selectivity for pyrimidine originates from preferred formation of an azazirconacyclopentadiene intermediate, which reacts preferentially with nitriles over alkynes.

The use of redox-active ligands has expanded the reaction toolkit for chemists, mediating challenging multi-electron chemical transformations not usually observed in their absence.1 At early metals such as Zr, for which redox-neutral processes like olefin polymerization are prevalent, redox-active ligands can facilitate new reactivity.² Typically, transformations involving redox non-innocent ligands result in formal changes of the ligand redox state without substantial changes in ligand coordination mode. Ligands that may change coordination environment around the metal are expected to result in more facile reactivity if adapted to the electronic and steric demands of the metal center. Our group and others have demonstrated the utility of labile and redox non-innocent pendant arene ligands in the development of new chemical reactivity, including CO cleavage and coupling, metal phosphide formation and coupling, metal nitride CO coupling, cross-coupling chemistry, and CO₂ activation.³ In most of these systems, the arene ligands are based on substituted benzene, requiring very negative potentials for formal reduction. Due to a smaller loss of aromaticity in its π -system,⁴ anthracene displays a more accessible reduction potential,⁵ allowing for formation of a dianionic state that coordinates metal ions at the bridgehead



Figure 1. Non-innocent anthracene moiety facilitating reductive elimination.

positions,⁶ though such transition metal complexes are very rare.⁷ We envisioned that the anthracene motif will promote novel reactivity by functioning as a reductively non-innocent ligand at milder potentials than benzene, facilitating redox chemistry at the pendant arene. Additionally, the formation of new bonds to the metal filling coordination sites opened during reactions such as reductive elimination is expected to facilitate reaction turnover and catalysis (Figure 1).

Syn-9,10-anthracenediyl-linked bisphenol (LH₂) was synthesized from commercially available starting materials in six steps (see SI). Protonolysis of tetrabenzyl zirconium (ZrBn₄) with LH₂ provides bisbenzyl complex 1. Single-crystal X-ray diffraction (XRD) studies (Figure 2) reveal long distances between Zr and the anthracene group which correlate with the C-C distances in the arene to suggest no significant interaction of the metal with the anthracene π -system.

Toward promoting reductive elimination from 1, photolysis was investigated. After 18 h irradiation, ¹H NMR spectroscopy shows the loss of the benzylic signal in 1, and the formation of Scheme 1. Synthesis and reactivity of bisphenoxide zirconium complexes with pendant anthracene





Figure 2. Solid-state structures of **1**, **2**, and **3a** and central ring bond metrics of **1** and **2**. Bond distances in Å. Thermal ellipsoids shown at 50% probability. Solvent molecules and hydrogen atoms omitted for clarity.

bibenzyl and a new species, **2** (Scheme 1). The solid-state structure of **2** (Figure 2) shows coordination to Zr of the two phenoxide donors, three THF molecules and the anthracene linker. The anthracene motif binds in an η^4 fashion via C1, C2, C7, and C8, with Zr–C distances in the range of 2.432(1)–2.525(1) Å indicative of strong interactions. These are slightly longer than the Zr-benzyl distances in **1** (2.257(2)-2.272(2) Å). Significant lengthening of the C1–C2, C1–14, C7–C8 and C8–C9 bonds suggests disruption of aromaticity in the arene. Overall, the structural parameters observed are consistent with a two-electron reduced anthracene motif.^{6a-e} Although oxidatively or photolytically induced C–C reductive eliminations have been reported at Zr(IV),^{2d,8} such transformations are rare, and the reduced metal species can undergo undesired side reactivity such as CH activation.^{8e}

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Complex 2, although formally displaying a Zr(IV) center, stores two reducing equivalents in the anthracene motif. The possibility of 2 performing anthracene-based redox chemistry was investigated towards the oxidative cyclometallation of alkynes, a reaction with precedent for Zr(II).⁹ Heating a solution of 2 with diphenylacetylene (two equiv.) at 90 °C led to a redto-yellow color change and formation of a 1:2 Zr:alkyne species (3a) by ¹H NMR spectroscopy. The solid-state structure of 3a shows the formation of a zirconacyclopentadiene by the oxidative coupling of two alkynes with two reducing equivalents originating from the ligand (Figure 2). Within the zirconacyclopentadiene ring, localized double bonds at C58–C59 (1.357(2) Å) and C60–C61 (1.354(3) Å) are observed.

With examples of both reductive and oxidative C-C bond formation involving redox at the pendant anthracene, we probed substrates with potential for regeneration of a masked Zr(II) complex. Extended heating of 3a in the presence of excess diphenylacetylene did not effect further reactivity, likely due to steric constraints. Treatment of in situ-generated 3a with CO at 90 °C results in the formation of a new major species assigned as 4, a 1:1 adduct between zirconium and a tetraphenylcyclopentadienone (CPD) molecule (Scheme 1). Independent synthesis by mixing one equiv. CPD with 2, resulting in a matching ¹H NMR spectrum, support this assignment. The synthesis of cyclopentadienones via [2+2+1] coupling of two alkynes and CO has been reported but is limited to mid-to-late transition metal complexes.¹⁰ CO insertion into zirconacyclopentadiene has not been reported, to our knowledge, though related systems involving CO-alkyne chemistry are known for Zr.11 Conceptually related, the catalytic aza-Pauson-Khand reaction involving Ti-imido complexes and alkynes to afford pyrroles, with diazenes acting as a nitrene source has been reported.¹² Although turnover was not achieved for CPD formation, this reaction demonstrates that coupling of three substrates is possible, with

an overall process that requires both oxidation and reduction of the anthracene moiety.

To examine if a sterically more open zirconacyclopentadiene promotes further reactivity, terminal alkyne phenylacetylene was tested. Addition of phenylacetylene (two equiv.) to **2** in benzene at room temperature led to a rapid red-to-yellow color change. The new species (**3b**) was assigned as a zirconacyclopentadiene complex structurally analogous to **3a** (¹H NMR spectroscopy). Coupling of terminal alkynes by zirconium is rare, ¹³ primarily attributed to incompatibility of the acidic acetylenic proton with low-valent Zr(II) species and/or precursors.¹⁴

Heating **3b** in benzene to 90 °C in the presence of excess phenylacetylene did not result in further insertion. However, heating of **3b** in the presence of one equiv. of *p*-tolunitrile (TolCN) and two equiv. of phenylacetylene led to the almost complete consumption of TolCN after one hour, with complex **3b** still present (¹H NMR spectroscopy). GC-MS analysis showed the formation of a mixture of homo- and heterotrimerized products, suggesting that **2** may be a competent precatalyst for the cotrimerization of alkynes and nitriles.

To further investigate this reactivity, benzonitrile and phenylacetylene were chosen as model substrates. A mixture of alkyne was heated at 90 °C with excess nitrile (7.5 equiv.), to disfavor alkyne trimerization,¹⁵ in the presence of 5 mol% of 2. After two hours, highly selective formation of 2,4,6-triphenylpyrimidine (6a) was observed, in 53% yield (Table 1, entry 1). GC-MS and NMR analysis showed no detectable formation of triphenylbenzene or triphenyltriazine, and less than 2% of triphenylpyridine. Pyrimidines feature in a wide variety of active pharmaceuticals and natural products, and as ligands in coordination complexes.¹⁶ Syntheses of pyrimidines via the highly efficient and atom-economical [2+2+2] cycloaddition route¹⁷ have been scarce.¹⁸ This has been attributed to the difficulty in incorporation of multiple nitrogen atoms via cycloaddition due to the more reactive nature of alkynes compared to nitriles,¹⁹ even when employing the nitrile as solvent.²⁰ Of those, many are either stoichiometric or require high catalyst loadings (20%),^{18d-g} the use of nitriles as a solvent,^{18h,18i} or tethered alkyne-nitrile substrates.^{18j} The observation of catalytic cycloaddition involving a nitrile is particularly notable for an early metal. Although there are several systems for pyridine synthesis based on Zr in combination with Ni²¹ or Cu,²² and Ti,²³ these reactions are not catalytic, likely due to the strong binding of the nitrogen moiety to the highly Lewis acidic metal center. For the present catalyst, the propensity of the anthracene moiety to accept reducing equivalents is proposed to facilitate reductive cyclization, promoting turnover.

Increasing the reaction temperature to 105 °C in toluene led to quantitative yields of **6a**, with longer reaction times leading

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to triazine formation after alkyne substrate has been consumed (Table 1, entries 2 and 3). The nitrile excess can be reduced without appreciable loss in selectivity, but results in slower conversions (entries 4 and 5). At 2:1 PhCN:PhCCH, high selectivity for pyrimidine (94%) is retained, albeit with a lower yield of ~80% (entry 6). Notably, even excess alkyne (1:5 PhCN:PhCCH), the pyrimidine is favored over pyridine. Catalyst loading can be lowered to 3 mol%, while providing similarly high yields and selectivities after five hours (entry 8). Control experiments ran with simple Zr complexes (ZrBn4, ZrCl4 and ZrBn2Cl2) reduced by Mg(THF)3(anthracenide), or with KC8 or photolytically in the presence of anthracene, did not result in catalysis (see SI).

Using the optimized conditions (Table 1, entry 4), the scope of pyrimidine synthesis was explored (Table 2). Internal dialkyl alkyne 5-decyne provides **6b** quantitatively, while diphenylacetylene is not competent. Terminal alkyl alkynes (Table S1) did not produce any cotrimerized products detectable by GC-MS, with the exception of trimethylsilylacetylene, which quantitatively afforded **6c**. A variety of nitriles were also found to be competent for catalysis (Table 2, **6d**, **6e** and **6f**) though arylnitriles with O or N-containing substituents and alkyl nitriles (Table S2) did not lead to cyclotrimerized products. Addition of an equimolar amount of acetonitrile to PhCN under optimized conditions completely shuts down generation of **6a**, suggesting that it acts as a strong inhibitor, likely through competitive binding to the metal.

To gain insight into the mechanistic basis of product selectivity, the synthesis of azazirconacycle **5**, a potential catalytic intermediate, was targeted. Addition of two equiv. TolCN followed by one equiv. PhCCH to **2** results in the formation of azazirconacycle **5**. XRD studies took advantage of the distinct aryl groups to unambiguously assign N-coordination to Zr and 2,4-diaryl substitution (Figure S37). Although we could not rule out the initial reversible formation of a nitrile-nitrile coupled complex²⁴ of the type previously reported for group IV metals,²⁵ in the presence of both nitrile and alkyne, complex **5** is the major Zr product. Stoichiometric reactions carried out from the isolated (aza)zirconacycles, **3b** and **5**, provide insight into catalytically relevant pathways (Scheme 2). Reaction of **3b** or **5** at

Table 1. Cycloaddition of phenyl acetylene with benzonitrile under various conditions

PhCi (1 equ	CH + PhCN - .iv.)	2 toluene 105 °C	Ph N P P	Ph Ph N N h P a 6	h h	² h / N N / F 6	Ph N Ph a"	
enti	ry [2]/mol	nitrile	time/h	^a PhCCH	^{b,c} se	^{b,c} selectivity/%		
	%	(equiv.)		consumed/ %	6a	6a'	6a"	
1 ^d	5	7.5	2	53	98	2	nd	
2	5	7.5	1	>99	59	1	40	
3	5	7.5	0.5	>99	99	1	nd	
4	5	6	1	>99	99	1	nd	
5	5	3	5	98	97	3	nd	
6	5	2	8	79	95	5	nd	
7	5	0.2	8	7	55	45	nd	
8	3	6	5	95	98	2	nd	

^abased on GC-MS analysis, averaged over 2 runs; ^bbased on ¹H NMR integration, averaged over 2 runs; ^cnd: not detected by GC-MS; ^drun at 90 °C in benzene

 Table 2. Substrate scope of cycloaddition of alkynes with nitriles to pyrimidines



aisolated yields averaged over 2 runs

90 °C with PhCN results in pyridine or pyrimidine formation, respectively, while neither complex reacts in the presence of additional PhCCH (*vide supra*). GC-MS analysis of the reaction of **5** with PhCN showed predominantly the formation of pyrimidine with mixed aryl substituents, with minor formation of 2,4,6-triphenylpyrimidine and 6-phenyl-2,4-di(tolyl)pyrimidine, indicating that the coupling of alkyne and nitrile is reversible, but is slow relative to pyrimidine formation. Based on the selectivity in catalysis, pathway B is strongly favored over pathway A, leading to the high selectivities observed. The preference for the formation of **5** rather than **3b** from a mixture of nitrile and alkyne is likely due to the precoordination of nitrile. The small amount of pyridine byproduct results from the formation of **3b** as a minor component through Pathway A.

In summary, we have synthesized and characterized a series of zirconium complexes supported by a bisphenoxide ligand displaying a 9,10-anthracenediyl motif. The ligand exhibits both redox non-innocence and hemilability, facilitating twoelectron chemistry at a Zr(IV) center such as the photolytic reductive elimination of bibenzyl, oxidative coupling of unsaturated organic substrates such as alkynes and nitriles and **Scheme 2. Stoichiometric reactions involving catalytically relevant species.**



their subsequent reductive elimination to CPD or N-containing heterocycles. We have demonstrated an efficient Zr-catalyzed three-component [2+2+2] cycloaddition of alkynes and arylnitriles to selectively afford tri- and tetra-substituted pyrimidines. The catalyst displays excellent selectivity even without the use of excess nitrile. The ability of this Zr catalyst to turnover, in contrast to other early metal systems is proposed to stem from the ability of the anthracene motif to promote redox chemistry and product dissociation. Given the established efficient stoichiometric oxidative coupling chemistry characteristic of Zr,^{9b,26} the development of new types of catalysis based on it is of interest for a variety of applications.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the synthesis of LH₂, complexes 1-5, detailed characterization data, supplementary figures (PDF) and crystallographic details (CIF) for complexes 1, 2, 3a, and 5. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

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