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Oxidant-Free Direct Coupling of Internal Alkynes and 2-Alkylpyridine via Double C−H Activations by Alkylhafnium Complexes

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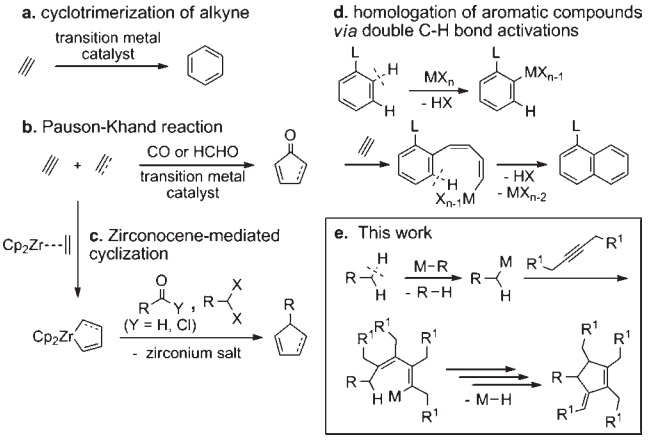
Supporting Information

ABSTRACT: We have developed a novel oxidant-free direct cross-coupling reaction of 2,6-lutidine and internal alkynes leading to five-membered carbocyclic compounds mediated by nonmetallocene cationic hafnium alkyl complexes. Mechanistic studies of the coupling reaction showed that the reaction begins with C(sp^3)−H bond activation via σ-bond metathesis, after which the coordinatively unsaturated hafnium center mediates further insertion, migration, and β-H elimination reactions to give five-membered carbocycles from readily available substrates.

The development of new methods for selective syntheses of functionalized carbocycles with a controlled configuration has been extensively studied because of the presence of these skeletons in biologically relevant compounds.[1,2] Transition-metal-mediated intermolecular cyclization reactions of readily available starting materials, such as simple alkynes, are a straightforward method for constructing small carbocycles in comparison with the intramolecular cyclization of complexed dienes, enynes, or diynes. The [2 + 2 + 2] cyclotrimerization of alkynes is an attractive and elegant synthetic method for producing polysubstituted arenes, and a large number of excellent procedures have been developed (Scheme 1a).[3] As an exceptional strategy for constructing five-membered carbocyclic compounds, the transition-metal-catalyzed Pauson−Khand cyclization reaction produces a wide variety of five-membered cyclopentenones or cyclopentadienones from alkynes, alkenes, and carbon monoxide (Scheme 1b).[4] Another notable method of forming five-membered carbocycles is the five-membered zirconametallacycle-mediated coupling reaction with aldehydes, acid chlorides, or 1,1-dihalo compounds (Scheme 1c).[5] Although multiple activation of C(sp^2)−H bonds followed by a cyclization reaction resulting in the homologation of aromatic compounds (Scheme 1d) has recently attracted interest,[6] the direct cross-coupling reaction of alkanes with 2 equiv of alkynes involving double C(sp^3)−H bond activation is an efficient and favorable pathway for preparing five-membered cyclic compounds (Scheme 1e). Catalytic and stoichiometric direct cross-coupling approaches require oxidants to eliminate the preactivation of the substrates.[6−8] From the point of view of environmentally benign synthesis, the oxidant-free catalytic direct cross-coupling reaction is highly desirable; however, the development of a catalytic protocol for such a transformation remains challenging, although a stoichiometric and stepwise oxidant-free direct cross-coupling reaction by a cationic zirconocene-mediated method has been reported.[9,10]

Scheme 1. Synthesis of Five- and Six-Membered Carbocycles Using Readily Available Alkynes



We recently developed a rational strategy for synthesizing coordinatively unsaturated group 4 metal alkyl complexes via an insertion reaction of the metal−carbon bond into the C═N bond of α-diimine ligands.[11] As an extension of this methodology to *N*,*N*′-bis(arylmethylene)ethylenediamine (β-diimine), we studied the reaction of the β-diimine ligands with $Hf(CH_2Ph)_4$ and found that alkylation of one of the two C═N bonds as well as ortho C(sp^2)−H bond activation of one of two aromatic rings of the ligand afforded a dibenzylhafnium complex with a β-diimine-derived dianionic (*N*,*N*,*C*)-tridentate ligand. Such an electron-deficient, coordinatively unsaturated metal center was anticipated to serve as a necessary platform to assist σ-bond metathesis and direct cross-coupling reactions. Herein we report the first example of an oxidant-free catalytic direct cross-coupling reaction, in which the hafnium complex bearing the (*N*,*N*,*C*)-tridentate ligand catalyzes the coupling reaction of 2 equiv of various alkynes with a 2-alkylpyridine derivative to give five-membered carbocyclic compounds (Scheme 1e). Subsequent acid-catalyzed isomerization to give the pentasubstituted cyclopentadienes clearly revealed the usability of this novel direct cross-coupling reaction for the synthesis of multisubstituted cyclopentadienes as precursors of various cyclopentadienyl ligands. The mechanism of this novel catalytic transformation was revealed by isolation of the hafnium complex corresponding to each reaction step.

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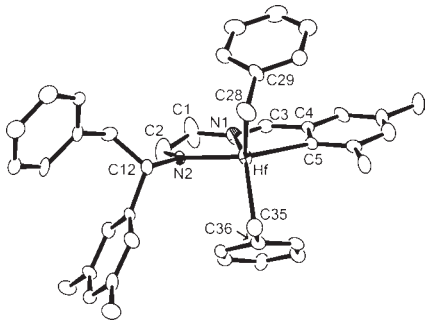
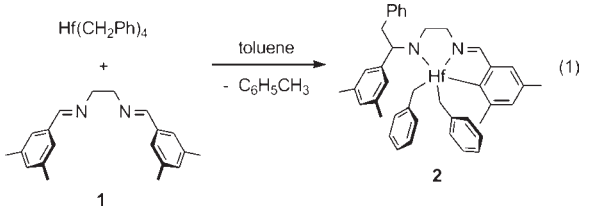


Figure 1. Molecular structure of complex **2**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Hf−N1, 2.271(8); Hf−N2, 2.072(7); Hf−C5, 2.338(9); Hf−C28, 2.244(10); Hf−C29, 2.739(11); Hf−C35, 2.253(11); Hf−C36, 2.810(12); C28−Hf−C35, 110.2(4); Hf−C28−C29, 91.8(6); Hf−C35−C36, 95.8(7).

Treatment of $Hf(CH_2Ph)_4$ with β-diimine ligand **1** in toluene produced dibenzyl complex **2** in 80% yield (eq 1):



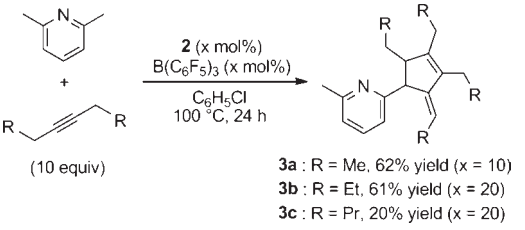
During the course of the reaction, two consecutive reactions proceeded to give complex **2** with an (*N*,*N*,*C*)-tridentate ligand: (1) the insertion reaction of one benzyl group into one of the two C═N moieties of **1** to form a hafnium−amido bond and (2) cyclometalation of one aromatic ring bound to the nitrogen atom of the ligand via activation of the C−H bond with release of toluene, giving a Hf−C(aromatic) bond. Such an intramolecular $C(sp^2)$−H bond activation at one of the ortho positions of the aromatic substituent by an early-transition-metal alkyl group has been reported previously.[12] In the ^{1}H NMR spectrum of **2**, the methylene proton signals of $HfCH_2Ph$ were observed as two AB*q* resonances at δ_H 2.34 and 2.88 (^2J = 10.7 Hz) and δ_H 2.42 and 2.80 (^2J = 11.3 Hz), and ABX signals corresponding to the methylene and methine protons of the $NCHCH_2Ph$ moiety were observed at δ_H 3.55, 3.73, and 5.30 (^2J = 12.6 Hz, ^3J = 3.6 and 10.4 Hz). The ^{13}C NMR spectrum of **2** displayed a signal assignable to one C═N group at δ_C 175.0. It was noteworthy that a downfield-shifted resonance due to the cyclometalated carbon was observed at δ_C 199.5.[12,13] The molecular structure of **2** was clarified by X-ray analysis (Figure 1).

The system of **2** and $B(C_6F_5)_3$ catalyzed the coupling reaction of 1 equiv of 2,6-lutidine with 2 equiv of the internal alkynes 3-hexyne, 4-octyne, and 5-decyne in chlorobenzene at 100 °C for 24 h to give the corresponding products **3a**−**c** (Scheme 2), accompanied by the release of H_2. This is the first example of an oxidant-free catalytic direct cross-coupling reaction, in sharp contrast to the previously reported catalytic direct cross-coupling reactions catalyzed by late-transition-metal catalysts, which require the addition of oxidants or bases to the reaction medium.[7,8]

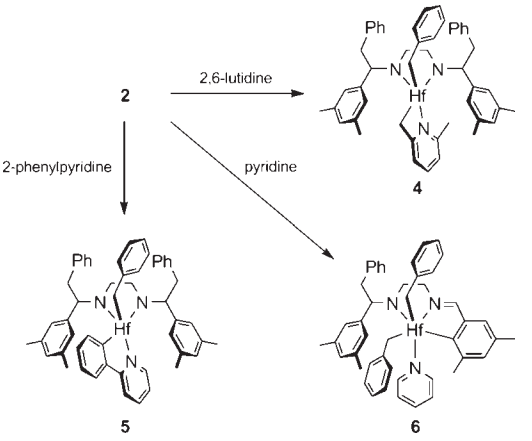
To elucidate the reaction mechanism, we performed the reaction of **2** with several heteroaromatic substrates (Scheme 3). Heating a mixture of **2** and 2,6-lutidine in toluene at 60 °C for 24 h resulted in selective activation of one benzylic $C(sp^3)$−H bond of 2,6-lutidine to form the {η^2-(*C*,*N*)-(6-methylpyrid-2-yl)-methyl}hafnium complex **4**. In the ^{1}H NMR spectrum, the resonance for the imine proton was not present, and signals assignable to two $NCHCH_2Ph$ groups were observed. Also, the signal for the cyclometalated carbon disappeared, and a signal for $Hf\text{-}CH_2(C_5H_3N{-}CH_3\text{-}6)$ appeared at δ_C 62.0. Similarly, heating a toluene solution of **2** in the presence of 2-phenylpyridine at 60 °C for 22 h gave cyclometalated product **5** in 94% yield through the formation of an dianionic (*N*,*N*)-bidentate ligand. X-ray analysis of **5** revealed the overall molecular structure (Figure 2a), indicating a large structural difference between the starting complex **2** and the product **5**: the Hf−C(aromatic) bond of **2** was cleaved by the abstraction of the H atom of the ortho C−H bond of phenylpyridine via σ-bond metathesis to form {η^2-(*C*,*N*)-2-pyridylphenyl}hafnium, and a spontaneous migration insertion of one benzyl group bound to the Hf atom in the C═N moiety of the ligand backbone afforded a dianionic (*N*,*N*′)-diamide ligand of **5**. In contrast, treatment of **2** with excess pyridine afforded **6**, in which pyridine is simply coordinated to the metal center, and no C−H bond activation was observed (Figure 2b).

Pyridine-directed C−H bond-activated complexes **4** and **5** were used as catalysts for the coupling reaction. Both **4** and **5** were inactive for the reaction involving further alkyne insertion; however, the combination of complex **4** and $B(C_6F_5)_3$, which was used as a cocatalyst for generating cationic alkyl species, became an active catalyst for the coupling reaction. Thus, we examined the 1:1 reaction of **4** with $B(C_6F_5)_3$, which resulted in cationic complex **7**. The molecular structure determination of **7** revealed that $B(C_6F_5)_3$ abstracted the bridged carbon atom of the {η^2-(*C*,*N*)-(6-methylpyrid-2-yl)methyl}hafnium moiety to form a borate anion coordinated to the cationic hafnium center through the nitrogen atom of the pyridine ring (Figure 3). The hafnium atom

Scheme 2. Direct Cross-Coupling Reaction of 2,6-Lutidine and Internal Alkynes



Scheme 3. Reactions of 2 with Heteroaromatic Substrates



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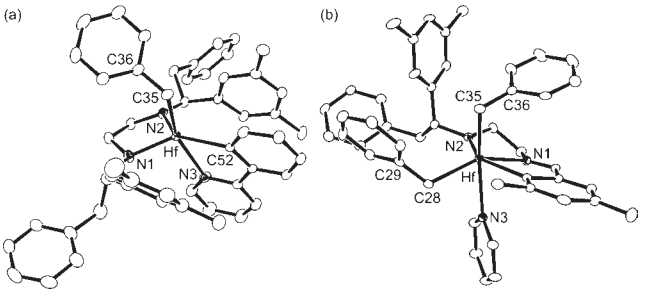


Figure 2. Molecular structures of complexes (a) **5** and (b) **6**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg) for **5**: Hf−N1, 2.043(3); Hf−N2, 2.050(4); Hf−N3, 2.349(4); Hf−C35, 2.339(6); Hf−C52, 2.381(3); Hf−C35−C36, 116.5(4). For **6**: Hf−N1, 2.304(3); Hf−N2, 2.075(3); Hf−N3, 2.463(3); Hf−C28, 2.302(3); Hf−C35, 2.280(3); Hf−C28−C29, 119.6(2); Hf−C35−C36, 104.9(2).

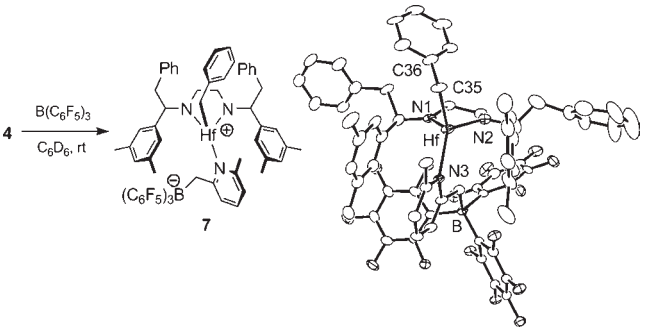


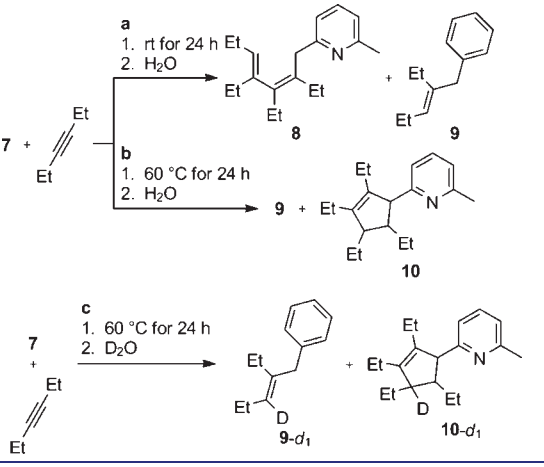
Figure 3. Synthesis and molecular structure of zwitterionic complex **7**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Hf−N1, 1.998(7); Hf−N2, 2.007(6); Hf−N3, 2.282(5); Hf−C35, 2.287(12); Hf−C35−C36, 115.2(8).

adopts a tetrahedral geometry involving coordination by two nitrogen atoms of the diamido ligand, one nitrogen atom of the pyridine unit, and one carbon atom of the benzyl group. The Hf−N1 and Hf−N2 distances are 1.988(7) and 2.007(6) Å, respectively, which are typical for observed σ-bonded hafnium−nitrogen bonds, whereas the Hf−N3 bond length of 2.282(5) Å is consistent with the coordination of the pyridyl nitrogen atom to the hafnium atom.[12c,14] In the ^{19}F NMR spectrum of **7**, resonances of the fluorine atoms of the C_6F_5 group were observed at δ −131.7, −165.1, and −167.9, indicating the formation of the four-coordinate borate anion in solution.

We conducted further controlled experiments by hydrolysis. The reaction of **7** with 3-hexyne at room temperature was quenched by hydrolysis after 24 h, and the products were analyzed by GC−MS and NMR measurements, which revealed the formation of 2-methyl-6-[(2*Z*,4*E*)-2,3,4-triethylhepta-2,4-dienyl]pyridine (**8**), a 1:2 coupling product of 2,6-lutidine and 3-hexyne, and (*E*)-(2-ethylpent-2-enyl)benzene (**9**), which is the product of 1:1 coupling of the benzyl group and 3-hexyne (Scheme 4a). In contrast, when the same reaction of **7** and 3-hexyne was conducted at 60 °C for 24 h, hydrolysis afforded **9** and the cyclized product **10** (Scheme 4b). Quenching the reaction mixture with D_2O resulted in the formation of **9**-d_1 and **10**-d_1 (Scheme 4c). The formation of **10**-d_1 indicates that the hafnium atom was attached to the 2,3,4,5-tetraethylcyclopent-2-enyl ring at the 4-position.

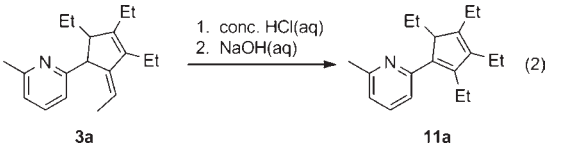
On the basis of the experimental results outlined in Figure 3 and Scheme 4, we propose the catalytic cycle shown in Scheme 5. In the first step, 1 equiv of alkyne inserts into the Hf−C bond of **7** to form a vinylhafnium intermediate, which is converted to

Scheme 4. Reaction of 7 with 3-Hexyne



{η^2-(*C*,*N*)-(6-methylpyrid-2-yl)methyl}hafnium (**A**) and alkenylborate. Second, the alkyne reacts with **A** to form a dienylhafnium intermediate **B**. The Hf atom migrates to the benzylic position via σ-bond metathesis to give **C**, and subsequent insertion of the Hf−C bond into the tethered alkene moiety produces the cyclopentenylhafnium intermediate **D**. The Hf atom shifts to the 2-position of the cyclopentenyl ring to form another cyclopentenylhafnium intermediate **E** through the η^3 coordination mode, and the coupling product **3** is obtained after β-H elimination. Finally, the hafnium hydride **F** reacts with 2,6-lutidine via σ-bond metathesis to regenerate the catalytically active {η^2-(*C*,*N*)-(6-methylpyrid-2-yl)methyl}hafnium species **A** along with H_2.

Cyclopentene **3a** was successfully converted to pentasubstituted cyclopentadiene **11a** by the addition of concentrated HCl(aq) (eq 2):



(2)

Cyclopentadienes are valuable precursors for generating cyclopentadienyl anions, which are widely used as supporting ligands in d-element, f-element, and main-group organometallic complexes.[15] Thus, this coupling methodology is a candidate method for rapid access to multisubstituted cyclopentadienyl ligands.

We have demonstrated a coupling reaction of 2,6-lutidine and internal alkynes leading to five-membered carbocyclic compounds mediated by a nonmetallocene cationic alkylhafnium complex as a first example of an oxidant-free direct cross-coupling reaction. Formally, the methyl group of 2,6-lutidine becomes a C1 source of the [2 + 2 + 1] cyclization reaction through the activation of two C−H bonds of the methyl group, and the double C−H activation on the same carbon atom is a new strategy for generating C1 sources for various coupling reactions. Mechanistic studies of the coupling reaction have suggested that C(sp^3)−H bond activation via σ-bond metathesis is the first step of the reaction. The coordinatively unsaturated metal center can mediate further insertion, migration, and β-H elimination reactions to produce five-membered carbocycles from readily available substrates. Further applications of early-transition-metal alkyl complexes for C−H bond activation and direct cross-coupling reactions are being developed in our laboratory.

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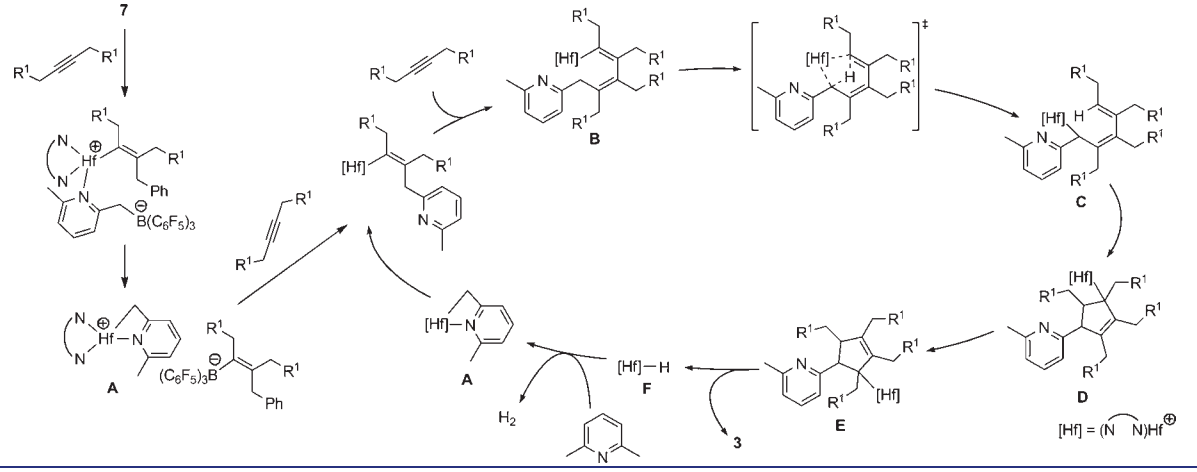
Scheme 5. Plausible Reaction Mechanism for the Direct Cross-Coupling Reaction of 2,6-Lutidine and Internal Alkynes



■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, selected 1D and 2D NMR spectra, and crystallographic data for complexes **2** and **5**−**7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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